DBM FACTS

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Universität Basel, Universitätsspital Basel und
Universitäts-Kinderspital beider Basel

Immunological Tolerance: A fine line between self-protection and self-destruction | Natural Killer Cell Immunity after Transplantation | DBM Postdoc Club

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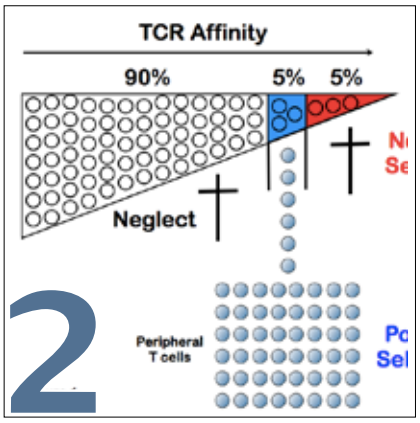
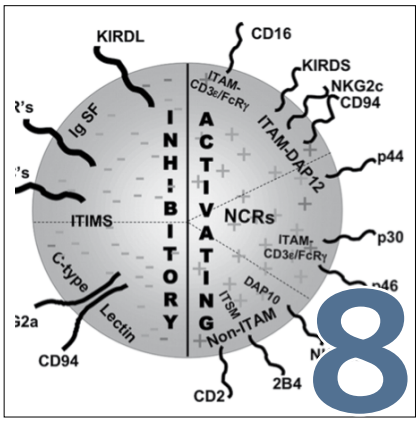
Departement Biomedizin Basel



Immunological Tolerance: A fine line between self-protection and self-destruction
from Ed Palmer



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EDITORIAL

Peter Meier-Abt
Head a.i.

Liebe Leserinnen und Leser

Mit dem frischen Grün liegt nun auch die Frühlingsausgabe der DBM Facts vor Ihnen und bietet mir die Möglichkeit, Ihnen allen herzlich für die freundliche Aufnahme am DBM zu danken. Nach fast 100 Tagen im Amt kann ich von einem lebendigen Research Day mit einem aufmerksamen Scientific Advisory Board (SAB), von kollegialen DBM Leitungssitzungen, von interessanten Diskussionen mit verschiedenen FGLs, von motivierten DBM Stabsmitgliedern, von initiativen PhD- und PostDoc-Clubs und von erfreulichen Fortschritten in der Raumplanung berichten. Ganz besonders wichtig ist mir eine transparente Kommunikation mit allen DBM Mitarbeiterinnen und Mitarbeitern. Zudem ist es mir ein grosses Anliegen, dass das Departement geordnet weiterläuft. Sobald wir den definitiven Bericht des SAB erhalten haben, werden wir über allfällig notwendige Massnahmen allgemeiner Art berichten. Bereits jetzt ist klar, dass die Schaffung eines konziseren "DBM Graduate Student Program" eine hohe Priorität haben wird.
Raphael Guzman hat am 1. Dezember 2011 seine Tätigkeit als stv. Chefarzt der Neurochirurgie aufgenommen und in diesem Jahr mit dem Aufbau seiner Forschungsgruppe "Brain Ischemia and Regeneration" am DBM begonnen. Seit dem 1. März 2012 verstärkt Frank Neumann als Assistent der Departementsleitung den Stab des DBMs. Beiden viel Erfolg und ein herzliches Willkommen!
In dieser Ausgabe erfahren wir von Ed Palmer mehr über Immunological Tolerance (ab Seite 2). Martin Stern entführt uns dann in die Welt der klinischen Forschung im Bereiche der Transplantationsimmunologie. In seinem Artikel erläutert er die Bedeutung von "Natural Killer Cells" im Kontext der hämatopoetischen Stammzell-Transplantation (ab Seite 8). Die neuesten Publikationen aus dem DBM finden Sie anschliessend ab Seite 19.
Doch das Leben besteht nicht nur aus Wissenschaft: Wer seinen Urlaub noch nicht gebucht hat, bekommt ab Seite 30 die besten Tipps aus erster Hand. Sandra Feliciano, Imane Möst Azzouzi und Elissavet Paraskevopoulou stellen uns die schönsten Plätze ihrer Heimat vor.
Aber auch von Bällen im Aus, japanischen Bierparties und indischen Frühlingsfesten gibt es viel zu erzählen.

Viel Spass bei der Lektüre und frohe Ostern!
Peter Meier-Abt

Dear Readers

With the arrival of fresh green outdoors the spring issue of DBM Facts is here and it offers me the possibility to thank you all for the very friendly acceptance at the DBM. After almost 100 days in office I can tell you about a lively Research Day with an attentive Scientific Advisory Board (SAB), about helpful DBM board meetings, interesting discussions with various research group leaders, motivated DBM staff, about proactive PhD- and PostDoc-Clubs and about pleasing developments in spatial planning. It is particularly important to me to maintain transparent communication with all members of the DBM. Furthermore, it is of great importance to me that the department continues to run in a well ordered manner. As soon as we receive the definitive report from the SAB we will inform you of all of the measures necessary. It is already clear that the development of a concise DBM Graduate Student Program should have highest priority.
On 1st December Raphael Guzman took up his position as Deputy-Head of Department of Neurosurgery and this year he has started to develop his research group "Brain Ischemia and Regeneration" at the DBM. Since the 1st March 2012 Frank Neumann has bolstered the staff of the DBM as assistant to the department administration. We welcome them both and wish them every success!
In this issue we learn more about Immunological Tolerance from Ed Palmer (on Page 2). Martin Stern then brings us into the world of clinical research in the field of transplantation immunology. In his article he elucidates the importance of "Natural Killer Cells" in the context of hematopoietic stem cell transplantation (on page 8). The latest publications from the DBM can be found on page 19.
However, life does not just consist of science: for those who have not yet booked their holidays there are great first hand tips from page 30 on. Sandra Feliciano, Imane Möst Azzouzi and Elissavet Paraskevopoulou introduce the most beautiful places from their home countries.
And finally there is also a lot to tell about Japanese beer parties and Indian spring festivals.

Happy reading and a happy Easter!
Peter Meier-Abt

Immunological Tolerance: A fine line between self-protection and self-destruction

Laboratory of Transplantation Immunology and Nephrology: (from left to right) Claudia Petit, Carolyn King, Denise Bielmann Bussar, Virginie Galati-Fournier, Marina Beaufils Hugot, Barbara Hausmann, Simone Keck, Lena Wyss, Ed Palmer, Sabrina Köhli (missing Rosmarie Lang, Celine Osswald, Regan Geissmann, Doris Lutz, Ondrej Stepanek)

The road not taken: Bench to Bedside

When I arrived in the DBM a little over 10 years ago, I had an opportunity to change the direction of my research. Given my background in biology and medicine (MD PhD) and a new job within the Department of Transplantation Immunology and Nephrology, it seemed like a good chance to bring what I knew from the lab to approach the clinical problem of preventing rejection of transplanted organs. In talking to the clinicians (Jürg Steiger, Michael Dickenmann, Stefan Schaub, Gil Thiel), I received an accelerated course in transplantation medicine and I tried to imagine the essential thing or parameter one had to understand to prevent graft rejection.

The more I got into it, the more I realized that there is no single most important parameter that controls whether a transplanted organ is rejected. As with many things in medicine, there are many factors controlling whether or not a transplant is well tolerated. This is the primary challenge of clinical research — trying to sort out all the variables in a patient population. Very little of my training had prepared me for this. In fact, I had actively pursued a career in basic science to avoid the hornets' nest of variability and unknown factors, which determine a clinical outcome. I couldn't see how I would be able to sort out the most important thing in transplantation medicine, when there are so many important things. If I had started down this road, I would have become a mediocre human immunologist at best; I had neither the head nor enough clinical experience to do it well. I had also invested so much of my career into understanding how the immune system avoids autoimmunity (self-tolerance); it would be a shame to stop.

So after two or three years of considering clinically relevant research, I decided to remain a basic scientist. Although, the bench to bedside thing isn't for me, I sometimes have a bad conscience about it, especially working in the Departments of Transplantation Immunology and Biomedicine. Nevertheless, by extending our basic understanding of immunological tolerance, we might contribute to a better understanding of transplantation medicine.

The road taken: Trying to understand the basics of T cell tolerance

Background

You are not born with a mature immune system and your body has to generate T lymphocytes from bone marrow precursors that mature in your thymus. (The thymus is an organ that is located in your chest above your heart.) Developing T cells start out as thymocytes and they are selected based on how well they recognize the proteins (self-antigens) in your body (Figure 1). Thymocytes whose antigen receptors bind self-antigens with low affinity (white cells) die because they fail to generate a survival and differentiation signal. We call this death by neglect. Thymocytes with medium affinity antigen receptors for HLA molecules (blue cells) are triggered to generate a survival and differentiation signal. This process is called positive selection and this generates a population of thymocytes that will develop into mature T cells and populate your lymph nodes and spleen. These are the CD4 and CD8 T cells, which are important for generating a protective immune response to infectious organisms like bacteria, viruses and fungi. (These are also the T cells responsible for the cellular rejection of transplanted organs.) The thymus has an additional important function. Thymocytes recognizing self-antigens with high affinity antigen receptors would potentially generate auto-reactive T cells, capable of killing us (red cells). Fortunately, these cells are removed from the body by negative selection; for this reason, most of us have a repertoire of peripheral T cells that is capable of responding to foreign invaders, but tolerant of our own tissues and cells. Even a small failure of negative selection can lead to the development of an autoimmune disease, such as diabetes, multiple sclerosis or rheumatoid arthritis.

Positive vs. negative selection: What determines this cell fate decision?

How does the developing thymocyte know whether it is destined for positive or negative selection? In a series of time consuming experiments over a 7 year span, Dieter (Didi) Naeher, Mark Daniels and Barbara Hausmann identified antigens, which were just at the threshold where negative selection is initiated. They did this for three different TCRs and found that in each case, the threshold antigen had the same affinity for their respective TCR. This threshold affinity has the following characteristics: K_D = 6 μM and a t1/2 = 2 s. From these results, there seems to be a clear rule to sort out positive and negative selection. When the thymocyte's TCR has an affinity for a self-antigen, which is higher than the threshold affinity (t1/2 > 2s), the receptor will generate a negative selection signal and the thymocyte undergoes apoptosis. In this way, autoimmune T cells are eliminated even before they exit the thymus.

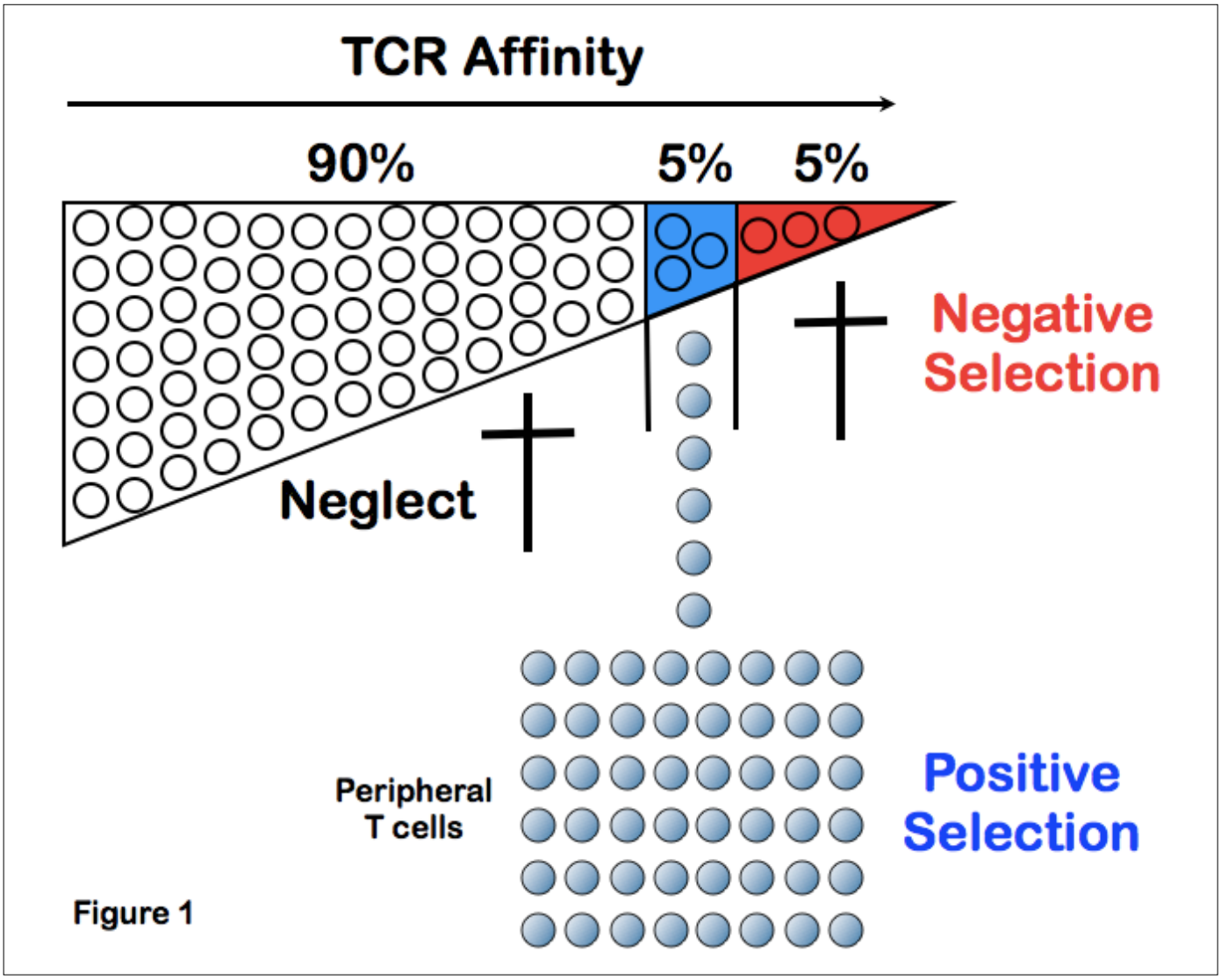


Figure 1

The next issue we tried to settle was how the TCR actually measures antigen affinity. What does the TCR actually sense when it binds an antigen? It's not easy to trigger a thymocyte or a T cell because the kinase (lck) that initiates a TCR signal is on a separate molecule called the co-receptor (CD4 or CD8). To initiate a signal the antigen has to bring the TCR and the co-receptor together and this requires a certain amount of time. By carrying out some simple mathematical modeling, Didi Naeher and I estimated the minimum time required to generate a TCR signal that initiates negative selection. For thymocytes in the CD8 lineage, a self-antigen has to remain bound to the TCR for 4 seconds to start a negative selection signal. During this time, the TCR collides with and properly aligns with a kinase-carrying co-receptor molecule. Once this happens, the kinase can phosphorylate the activation motifs within the TCR/CD3 complex. Many people have contributed or are continuing to contribute to this major effort in the lab including past lab members, Didi Naeher, Mark Daniels and Michel Mallaun and current lab members, Carolyn King, Marina Hugot-Beaufils, Barbara Hausmann, Virginie Galati and Rosmarie Lang.

What's the origin of autoimmune disease?

This is a difficult question to answer, but it's likely that most of them involve a breakdown of T cell tolerance in some way. Barbara Hausmann, Carolyn King and Sabrina

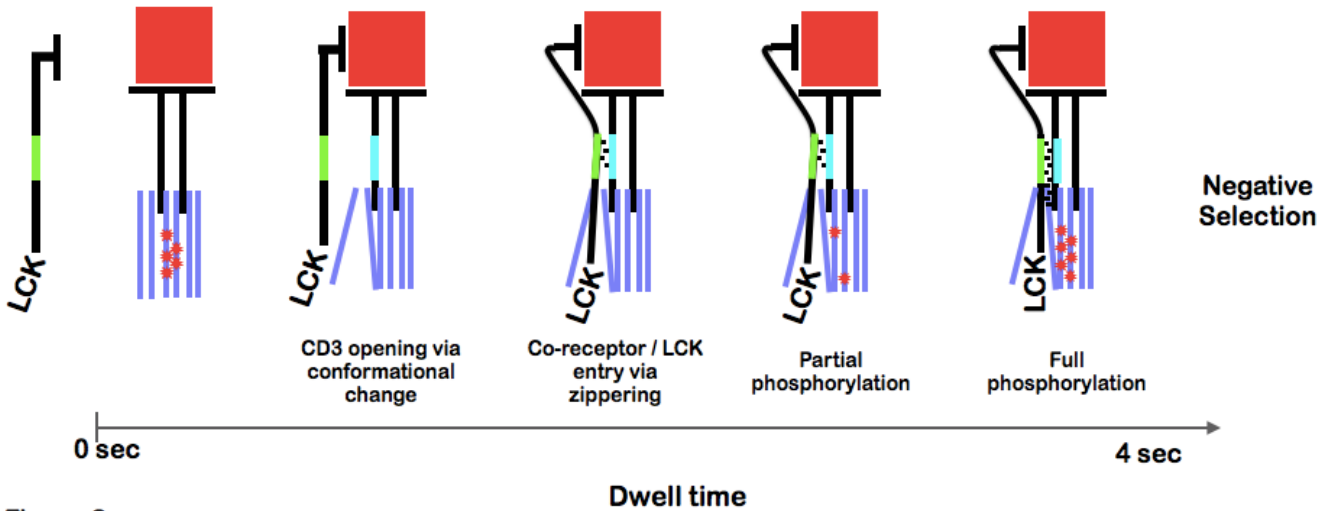


Figure 2

Köhli used a model of experimental autoimmune diabetes where we intentionally "broke" tolerance by injecting mice with T cells reactive to an antigen expressed in their pancreatic β cells. When these T cells were activated, the pancreatic β cells were destroyed and the animals became diabetic. Interestingly, the intolerant T cells have to be triggered with a high affinity antigen (i.e. an antigen that binds the TCR longer than 4 seconds). This makes sense since patients suffering from autoimmune diseases, likely harbor high affinity autoimmune T cells that "escaped" negative selection. These "illegal" cells most likely have initiated the autoimmune disease. Carolyn King showed that T cells responding to high affinity antigens enter into asymmetric cell division, which results in a proximal and distal daughter T cell. It's the proximal daughter T cell that actually causes the experimental autoimmune diabetes (Figure 3). Based on these interesting findings, Carolyn is now looking at the role of asymmetric cell division during the differentiation of CD4 T cells. Sabrina Köhli is trying to answer the question of whether autoimmunity comes from a few high affinity T cells escaping negative selection or from the chronic stimulation of threshold affinity T cells. Ondrej Stepanek has just joined the lab and plans to study how antigen affinity affects the strength of the T cell – APC synapse.

Regulatory T cells: T cells dancing to a different tune

Most peripheral T cells can be activated to participate in an immune response. Once activated, they are called effector T cells and they promote an immune response in many different ways. Regulatory T cells (Tregs), on the other hand, limit the immune response (Figure 4). Mice and patients that lack regulatory T cells, have massive infiltrations of T cells in their organs and die at an early age. One idea is that regulatory T cells are generated to compensate for defects in negative selection that are likely to occur. Still, the question of how regulatory T cells are generated and how they function to maintain tolerance is still not completely understood. We started in this area a few years ago and are making some progress. Carolyn King's early work suggested that the generation of regulatory T cells in the thymus is a side-product of negative selection. This implies that Tregs express high affinity self-reactive TCRs. Lena Wyss is pursing this idea by testing whether high affinity self-reactive T cells exist among regulatory T cells. Another question that has not been completely addressed is how the TCR transmits a signal in a Treg compared to an effector T cell. Using mice that we bred for this purpose, Céline Osswald is taking on this project. Finally, Tregs play an important role in maintaining lymphocyte homeostasis in the intestinal mucosa. Simone Keck has

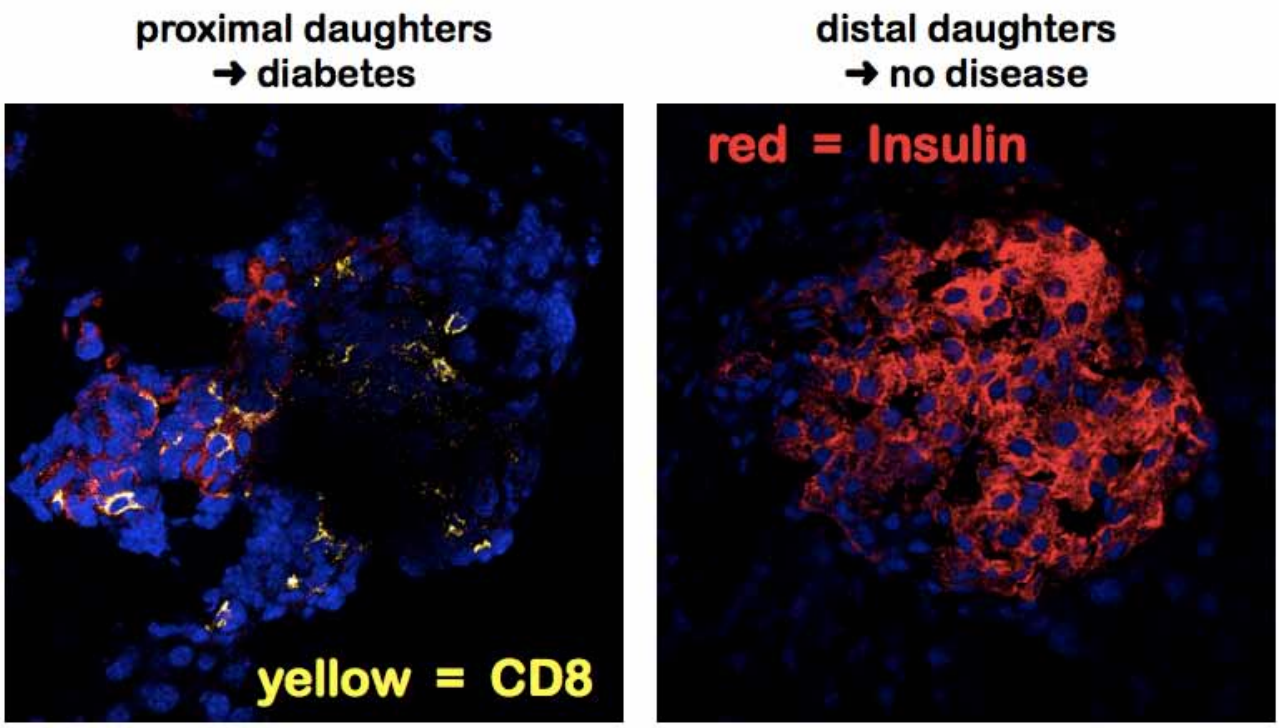


Figure 3

been working on the role of intestinal epithelial cells (enterocytes) in controlling T cell responsiveness in the mucosal environment.

Conclusion

From this brief description, you can see that we are a diverse group, working in diverse areas, but we're all fascinated by the different mechanisms the immune system uses to avoid autoimmunity. As basic biology is the foundation of clinical medicine, I hope that what we are doing in the lab will eventually contribute to a deeper understanding of transplantation medicine. It's a pleasure to be working in the Departments of Trans-

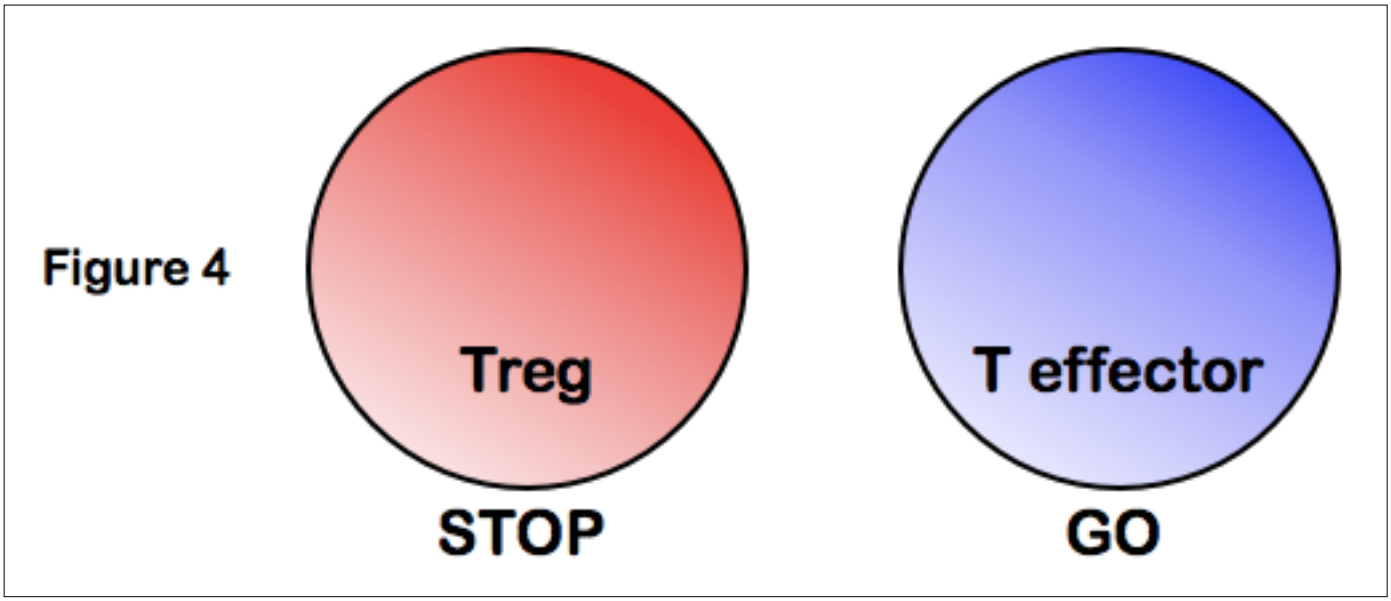


Figure 4

plantaion Immunology and Nephrology and Biomedicine. They have offered us generous financial and technical support and a friendly atmosphere. Of the things that I've worked on during my career, I'm most proud of what we have achieved here in the DBM.

Ed Palmer

Publications:

Schrum A. G., Gil, D., Dopfer, E. P., Wiest, D. L., Turka, L. A., Schamel, W. W. A. & Palmer, E. (2007) High-sensitivity detection and quantitative analysis of native protein-protein interactions and multiprotein complexes by flow cytometry. Sci STKE, 2007 (389).

Naeher, D., Daniels, M. A., Hausmann, B., Guillaume, P., Luescher, I. & Palmer, E. (2007) A constant affinity threshold for T cell tolerance. J Exp Med, 204 (11), 2553-2559.

Gil, D., Schrum, A. G., Daniels, M. A. & Palmer, E. (2008) A role for CD8 in the developmental tuning of antigen recognition and CD3 conformational change. J Immunol, 180 (6), 3900-3909.

Mallaun, M., Naeher, D., Daniels, M. A., Yachi, P. P., Hausmann, B., Luescher, I. F., Gascoigne, N. R. J. & Palmer, E. (2008) The T cell receptor's α-chain connecting peptide motif promotes close approximation of the CD8 co-receptor allowing efficient signal initiation. J Immunol, 180 (12), 8211-8221.

Palmer, E. & Naeher, D. (2009) Affinity threshold for thymic selection through a T-cell receptor-co-receptor zipper. Nat Rev Immunol, 9 (3), 207-213.

Teixeiro, E., Daniels, M. A., Hamilton, S. E., Schrum, A. G., Bragado, R., Jameson, S. C. & Palmer, E. (2009) Different T cell receptor signals determine CD8+ memory versus effector development. Science, 323 (5913), 502-505.

Mallaun, M. Zenke, G., and Palmer, E. (2010) A discrete affinity-driven elevation of ZAP-70 kinase activity initiates negative selection. J Receptors and Signal Transduct. Res. , 30 (6), 430-443.

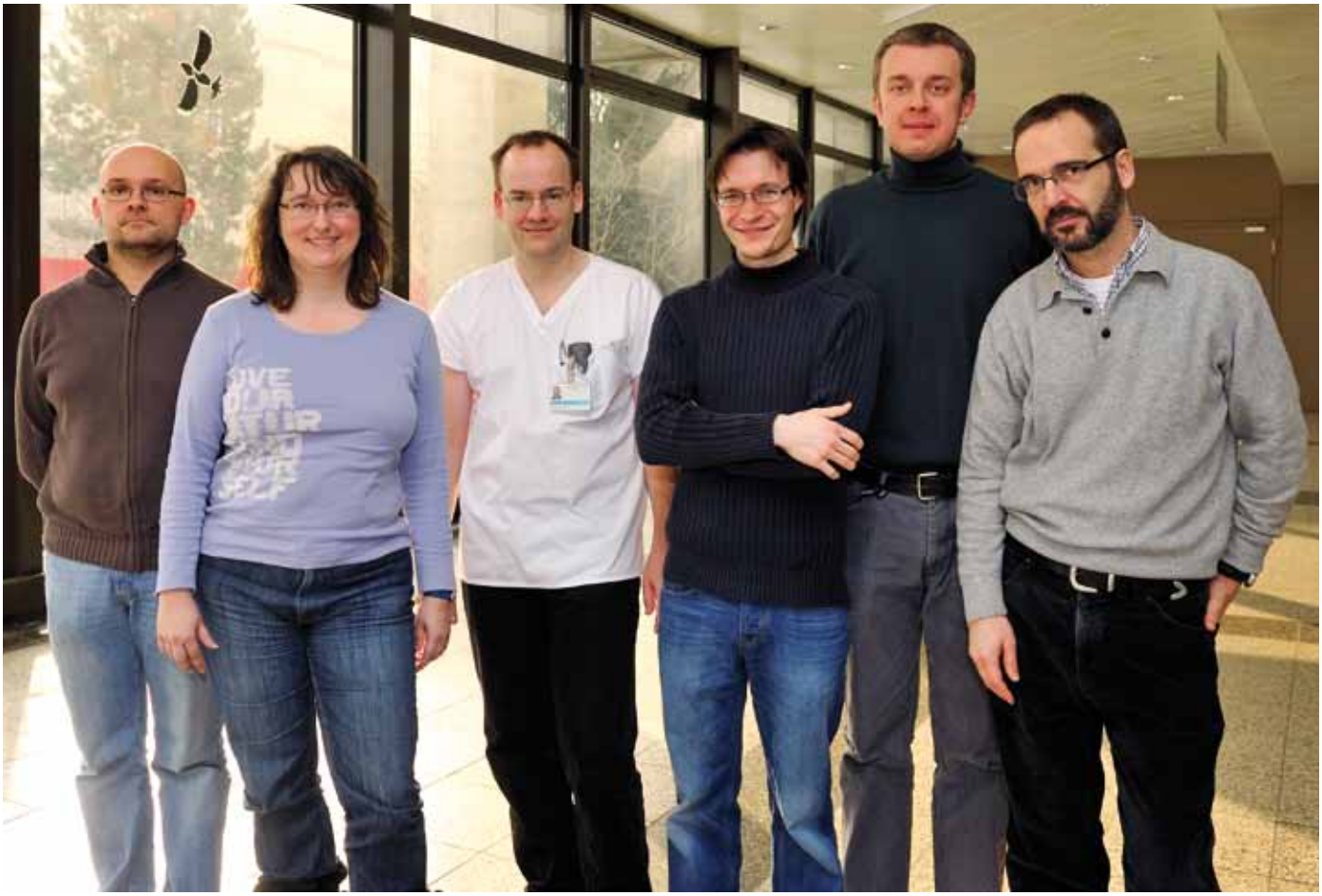
Schrum, A. G., Gil, D., Turka, L. A. and Palmer, E. (2011) Physical and Functional Bivalency Observed Among TCR/CD3 Complexes Isolated From Primary T Cells, J. Immunol. 187 : 870-8

Carolyn G. King, Sabrina Koehli, Barbara Hausmann, Matthias Schmaler, Dietmar Zehn, Ed Palmer, Induction of tissue pathology driven by asymmetric T cell division, under review 2011.

Natural Killer Cell Immunity after Transplantation

Background

Over the past five decades, the transplantation of hematopoietic stem cells after myeloablative radio-/chemotherapy to treat tumors of the lymphohematopoietic system has developed from experimental procedure to standard of care. Initially, the function of the transplanted cells was uniquely interpreted as a "replacement tissue" supplanting the patients' bone marrow which is destroyed by the supralethal chemo-/radiotherapy preceding the transplant. In the 1980s it was first discovered that patients suffering from graft-versus-host disease (GvHD) – i.e. the immune rejection of recipient tissue by donor lymphocytes co-transplanted in the graft – showed a lower risk of disease relapse after transplantation compared to patients not developing GvHD. These observations suggested that the donor immune system might contribute to the elimination of tumor cells in the process of stem cell transplantation. In the 1990s, this concept was confirmed by the successful treatment with donor lymphocyte infusions



Laboratory of Immunotherapy: (from left to right) Grzegorz Terszowski, Karin Schmitter, Martin Stern, Laurent Schmied, Karol Czaja, Asensio Gonzalez

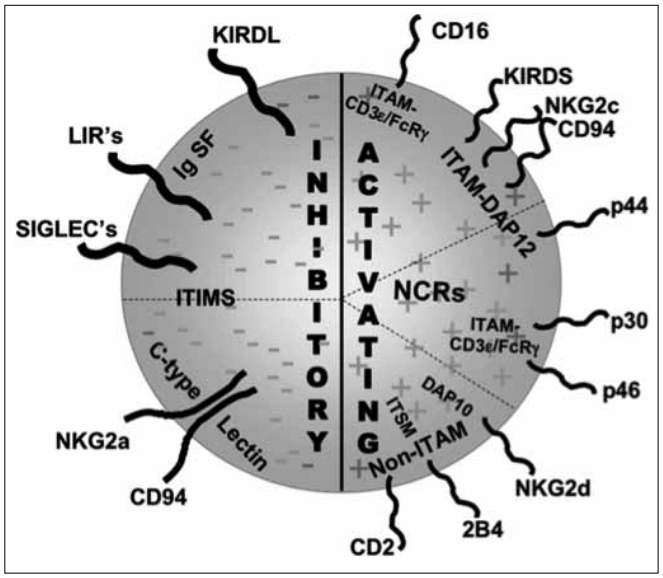


Figure 1: NK cells express a variety of cell surface markers which can elicit negative or positive signals. The negative signal generating/inhibitory molecules include the Ig superfamily molecules such as the killer cell Ig-like receptors with long cytoplasmic tails (KIRxDL), lymphocyte inhibitory receptors (LIRs) and sialic acid binding Ig-like lectins (SIGLECs), and the C-type lectin receptors, which include NKG2a/CD94 heterodimer. The positive signal generating/activating receptors include the ITAM-bearing molecules CD16, p30, p44, and p46; the NKG2c/CD94 heterodimer, KIRDS; and 3) the non-ITAM bearing receptors CD2, NKG2D, and 2B4

in patients developing disease relapse after stem cell transplantation. Both beneficial (graft-versus-tumor) and detrimental (graft-versus-host-disease) effects of donor immunity against patient cells were attributed to T-lymphocytes co-transplanted with the graft, due to the substantial reduction of both types of reactions, if graft products were depleted of T-cells.

Over the past 10–15 years, many studies have shown that Natural Killer (NK) cells are also involved in immunity both against residual tumor cells and against pathogens in patients undergoing stem cell transplantation. Most importantly, the beneficial effects attributed to NK cells appear to occur without the risk for graft-versus-host disease, a fact that makes these cells uniquely suitable for adoptive immunotherapy.

Natural killer (NK) cells reside in the bone marrow, spleen and peripheral blood where they comprise approximately 10% of peripheral blood lymphocytes. Unlike B- and T-lymphocytes, NK cells do not express clonally rearranged receptors to detect antigens. Instead, activation is regulated by integration of signaling from germline encoded activating and inhibitory cell surface receptors. These include inhibitory receptors for HLA class I antigens, and activating receptors such as DNAM-1, NKG2D and natural cytotoxicity receptors (NCRs). Inhibitory receptors for self HLA include Killer cell Immunoglobulin-like Receptors (KIR), the lectin-like receptor NKG2A, and LIR1/ILT-2 (Figure 1). Upon interaction with target cells expressing activating ligands, lack of engagement of inhibitory receptors results in predominance of activating signaling and target cell lysis. These systems form the basis of the "missing self" recognition and exemplify the mechanisms of the immune system to counteract HLA down-regulation induced by tumors and viral infection to escape T-cell recognition.

While initial data derived from clonally expanded NK cells had suggested that every NK cell expresses at least one inhibitory receptor for self MHC, more recent analyses in mice and humans have shown that subsets of NK cells do not express inhibitory receptors for self HLA. The mechanism of tolerance in this subset is not completely understood. However, growing evidence exists for a role of KIR-HLA interactions in "licensing" of NK cells in a manner that only NK cells expressing inhibitory receptors for self HLA acquire full functional competence. The ligands for inhibitory KIRs are HLA class I antigens. The main inhibitory KIR/HLA pairs are KIR2DL1 recognizing HLA-C antigens with a lysine at position 80 (e.g. HLA-C 2, 4, 5, 6); KIR2DL2 and KIR2DL3 recognizing HLA-C antigens with asparagine at position 80 (e.g. HLA-C 1, 3, 7, 8) and KIR3DL1 recognizing HLA-B antigens with Bw4 specificity (e.g. HLA B5, 13, 17, 27). KIR3DL2 has been shown to recognize HLA-A3 and A11 expressed on target cells in vitro depending on the peptide presented; its significance in vivo remains unclear. KIR2DL4 recognizes HLA-G, an atypical class I antigen expressed on decidual cells and is implicated in the maintenance of tolerance against fetal-derived placental tissue. KIR3DL3 and KIR2DL5 are still orphan receptors.

KIR ligand mismatching in haploidentical HSCT

Haploidentical stem cell transplantation is the transfer of hematopoietic stem cells from a donor that shares half of the HLA antigens with the patients, and is typically a first-degree relative (i.e. father, mother, sibling,

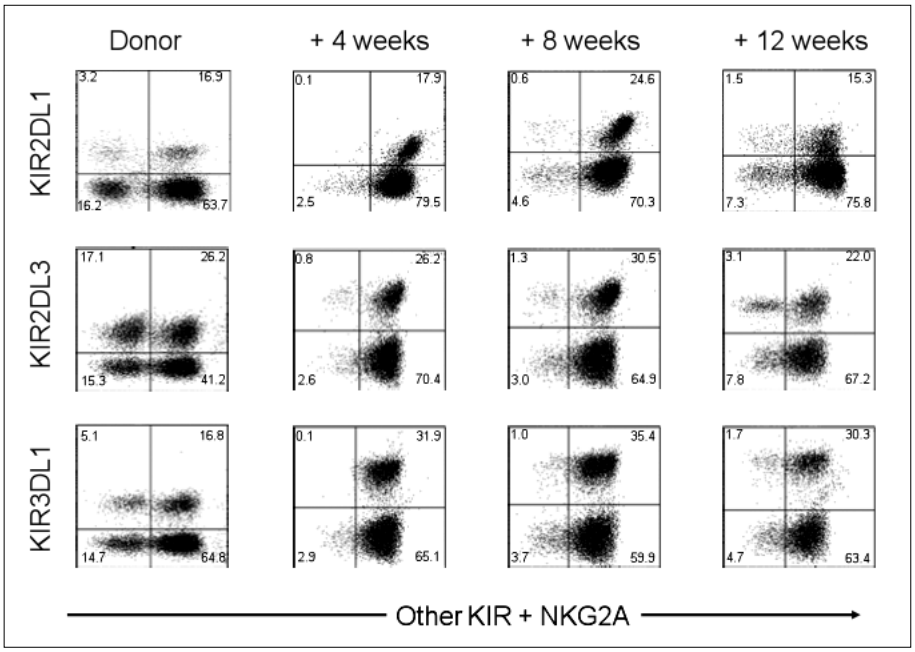


Figure 2: KIR/NKG2A repertoire of natural killer cells of donor and patient after haploidentical HSCT. Whereas the donor possessed all three KIR ligands, the patient lacked the HLA-C1 ligand for KIR2DL3. KIR2DL3+/other KIR-/NKG2A- NK cells (second row, upper left quadrant) are therefore alloreactive against the patient's malignant cells and are found at a frequency of 17.1% in the donor, and at frequencies of 0.8%, 1.3% and 3.1% at 4, 8, and 12 weeks post-transplant in the patient, respectively.

or child). Haploidentical HSCT is carried out if a fully or almost fully matched donor is not available. Due to the multiple HLA mismatches between donor and patients, patients are at high risk of T-cell mediated graft-versus-host disease. This procedure is therefore always accompanied by rigorous depletion of T-cells *ex vivo* (by magnetic sorting) *in vivo* (by co-administration of a T-cell depleting antibody such as alemtuzumab). T-cell depletion leads to loss of beneficial T-cell mediated graft-versus-tumor effects, which in some cases can be compensated for by natural killer cells (1). Especially in the case of a KIR ligand mismatch, i.e. in the setting when a donor but not a patient carries a KIR ligand, a subset of NK cells produced from the graft after transplantation will become alloreactive and eliminate residual leukemic cells. While early research had indicated that the NK cell KIR repertoire after transplantation immediately resembles that of the stem cell donor, more recent investigations have shown that the potentially alloreactive NK cell subset after transplantation is in fact much lower than in the donor (Figure 2) (2). An additional observation that emerged from these studies was that the reconstitution of alloreactive NK cell clones was dependent of the type of KIR involved, with alloreactive NK cells expressing the KIR2DL2/3 receptors recovering at a much earlier timepoint than the remaining KIR (Figure 3A). When correlating these data with the survival of acute leukemia patients transplanted from a haploidentical donor, we observed that patients transplanted from a donor mismatched for the ligand of a KIR with early reconstitution showed significantly better survival and less leukemia relapse compared to patients transplanted from a donor mismatched for a KIR ligand with late reconstitution or from a KIR ligand matched donor (Figure 3B). These data clearly point to the importance of NK cells in this type of transplantation and to the relative benefit associated with the early occurrence of alloreactive NK cells.

Adoptive immunotherapy with NK cell donor lymphocyte infusions

To improve on the early NK cell immune reconstitution, administration of purified NK cell products has been proposed several years. The University Hospital Basel was among the first to explore this approach and could show in a prospective trial that production of highly purified NK cell products is feasible and safe, as long as stringent T-cell depletion is guaranteed (3). Outcome of patients treated with NK DLI was however not improved compared to those of patients treated with haploidentical HSCT alone. In collaboration with the Experimental Hematology laboratories, an NK cell expansion protocol was developed which allows expansion of NK cell products up to 100 fold along with a strong increase in cytolytic potential. A study in which these expanded NK cell products are administered after haploidentical transplantation for patients with leukemia is underway and

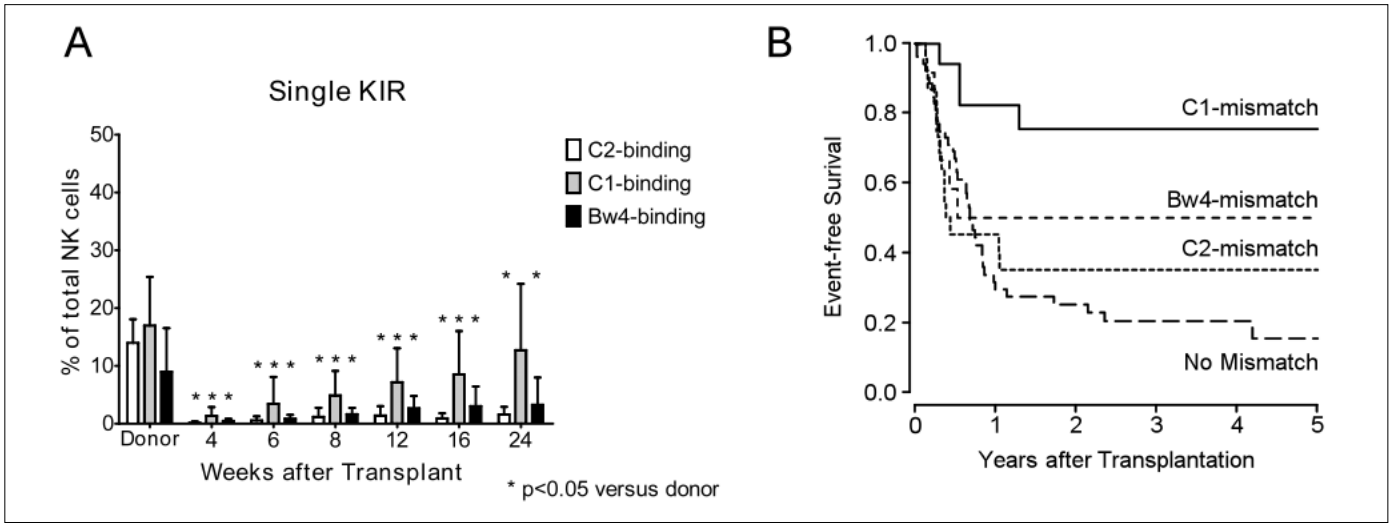


Figure 3: A: Temporal evolution of the frequencies single KIR expressing NK cells as percentage of total NK cells shows a skewed repertoire with slow reconstitution of single KIR expressing subsets. Reconstitution is fastest for C1-binding KIR, followed by Bw4 binding KIR and C1-binding KIR. This is mirrored in survival curves of patients stratified by type of KIR ligand mismatch, with best survival seen in patients transplanted from a donor KIR ligand mismatched for a receptor that reconstitutes early after transplantation.

a second study where NK cell DLI will be administered to patients treated with autologous stem cell transplantation for plasma cell myeloma will start recruiting patients in the next months.

Activating KIR genes and their contribution to immunity against cytomegalovirus

In contrast to the well-defined biology of inhibitory KIR, the function of activating KIR has remained largely elusive. While all individuals carry the genes for inhibitory KIR receptors - indicating that they are necessary for NK cell function – KIR haplotypes are highly variable regarding activating KIR gene content. In Caucasians, roughly 25% of healthy donors do not carry activating KIR genes. Analyses in HSCT recipients have convincingly demonstrated a survival advantage for patients transplanted from a donor carrying activating KIR genes. A reduced rate of viral infection (most importantly a reduction in cytomegalovirus reactivation) is partly responsible for this, suggesting that viral proteins might be ligands for activating KIR. No other viral ligands for activating KIR have been described so far and the association of activating KIR with protection from cytomegalovirus has not grown beyond the stage of epidemiological data.

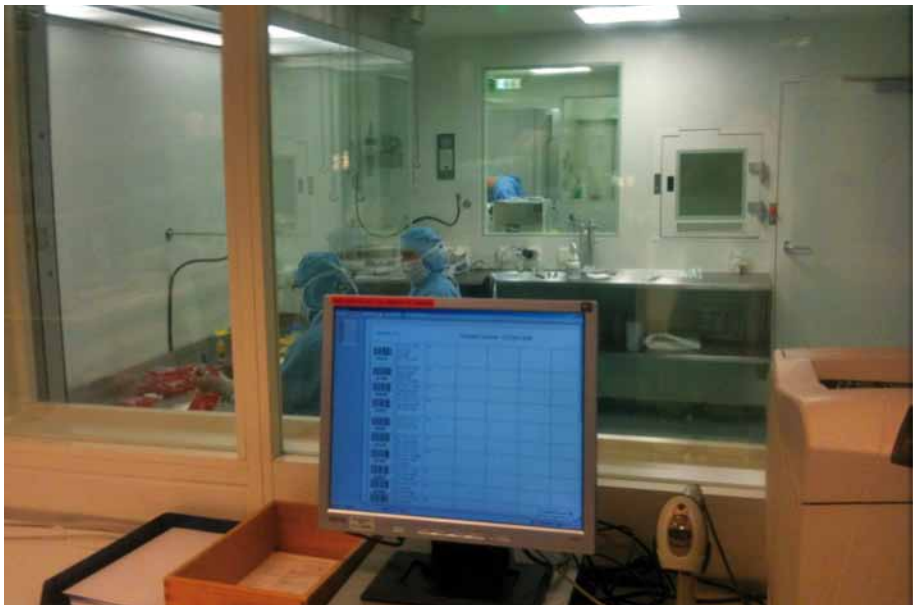


Figure 4: View of the Good Manufacturing Practice (GMP) room at Basel University Hospital, where NK cell and other cellular products for clinical use are produced.

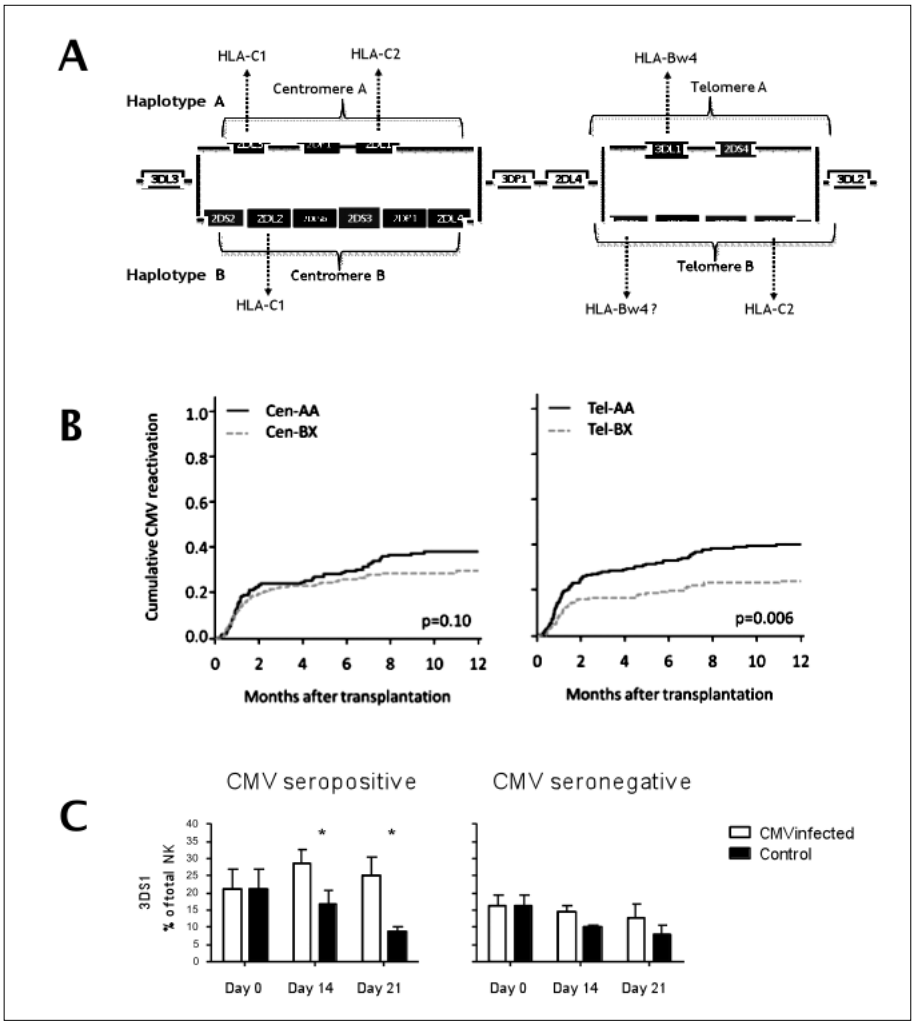


Figure 5: A) Organization of the KIR complex. The framework KIR genes are in white, the activating KIR genes are in grey and the inhibitory KIR genes are in black. The HLA-C1, C2 and HLA-Bw4 cognate ligands of the inhibitory KIRs are depicted. KIR A haplotypes have a fixed number of KIR gene, KIR haplotypes B have variable gene content. B) Adjusted cumulative incidence of CMV infection after kidney transplantation in patients carrying at least on group B gene (BX) or only group A genes (AA) centromeric (left panel) or telomeric (right panel) of KIR2DL4. C) Significant alteration to the NK cell repertoire after co-culture with CMV infected fibroblasts. NK cells expressing KIR3DS1 proliferate. Alterations in response to CMV-infected fibroblasts are restricted to patients previously infected with CMV as documented by anti-CMV IgG positivity.

Our own studies in patients receiving kidney transplantation showed a significant protection from CMV reactivation in patients carrying activating KIR genes (4). In a combined analysis with patients transplanted in Geneva, we could further map the locus of resistance to the telomeric part of the KIR gene complex, which may contain the activating receptors KIR2DS1, KIR2DS5, and KIR3DS1 (5). As linkage disequilibrium between these genes is high, population-based studies are unlikely to further identify a single locus of resistance. Using an in vitro model of CMV infection, we therefore aimed to quantify changes in the NK cell repertoire occurring in NK cells when co-cultured with CMV infected fibroblasts. In this model, expression of the activating KIR3DS1 was significantly up-regulated in NK cells exposed to CMV. Interestingly, this expansion was not seen for other activating KIR receptors and occurred exclusively in patients carrying IgG antibodies against CMV as a marker of previous infection with the virus. In further experiments we are now attempting to elucidate how KIR3DS1 interacts with CMV infected target cells. Moreover the specific protection from CMV reactivation in patients carrying KIR3DS1 and other activating KIR genes is being validated in a collaborative project involving the Swiss Transplant Cohort Study involving several hundred recipients of lung, heart, liver, and kidney allografts. The aim of these studies is to identify populations of patients at particularly high or low risk of CMV reactivation after transplantation which might benefit from an individualized approach to CMV prophylactic and preemptive treatment strategies.

Outlook and conclusions

NK cells have in the past 20 years gained a lot of interest in the context of hematopoietic stem cell transplantation. While many aspects of NK cell biology in this setting are still poorly understood, donor selection criteria in HLA-mismatched transplantation includes the po-

tential of a donor to generate alloreactive NK cells post-transplant. Retrospective studies showing a survival advantage for patients transplanted from an HLA-identical donor carrying activating KIR receptors (6) have led to large prospective trials underway which aim to preferentially recruit stem cell donors with a beneficial activating KIR gene profile. While these are exciting time for researchers interested in NK cells, much work remains to be performed to unravel the many ways in which NK cells influence the transplant outcome.

Acknowledgements

I would like to thank all current and past members of my group, our collaborators in the Department of Biomedicine for help and useful discussions, as well as all collaborators from the clinic providing us with patient samples. Special thanks go to Andreas Buser and his team at Bluspendezentrum for supporting us in many ways. I am grateful to SNF, the «Stiftung für Hämatologische Forschung», the «Stiftung für Krebsbekämpfung», the «Stiftung für Infektionskrankheiten», the «Freiwillige Akademische Gesellschaft», the «Novartis Stiftung für Medizinisch-Biologische Forschung», and Oncosuisse for generous grant support.

Martin Stern

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Impressionen vom Abschlussmeeting des Advisory Boards am 20. Januar 2012

Nach dem Research Day und dem Besuch bei den Forschungsgruppen gab es viel zu diskutieren …


Brigitta Stockinger


Kathryn Wood


Peter Meier-Abt


Ed Constable


Paolo Bianco

… und mitzuschreiben …


Jürg A. Schifferli


Conrad E. Müller

Fotos:
Mathias Mangold
(www.sublim.ch)

… unter den strengen Augen von Greg Lemke …


Greg Lemke

… aber am Ende waren alle zufrieden.


Werner Kübler

Christoph Beglinger

INTRODUCING DEPARTMENT OF BIOMEDICINE POSTDOC CLUB:

HOW CAN WE IMPROVE OUR COMMUNICATION AND NETWORKING?

Postdoc, such a tricky word! This term refers to both the position and the person holding it. Although they are sometimes referred to as students, they really are employees in reality. In addition to outstanding scientific skills, their position requires development and application of teaching, management, networking, writing and leadership skills. While PhD students and tenured scientists have a well-defined career goal or track, postdocs often find themselves in an intermediate position with a very ambiguous perspective. Generally, at least one postdoctoral position is crucially needed to move up on the academic career ladder. Often several postdoc positions may be required before acquiring a tenured position, which however is by no means guaranteed.

Therefore, a postdoc often finds himself asking: "What is – or should be – my next step?"
The Department of Biomedicine (DBM) employs more than 80 postdoc fellows and senior scientists, which are distributed over several floors and buildings. Additionally, the University of Basel consists of several institutes including the Biozentrum, Friedrich Miescher Institute and Swiss Tropical and Public Health Institute. Moreover, Basel is a key European center for the pharmaceutical, chemical and biotechnological industries, with more than 900 life science-oriented companies in the region. Such a unique environment seems ideally suited for synergism and collaboration through multidisciplinary research and knowledge transfer. Nonetheless, structural opportunities for networking within and between institutes are scarce.

To address these questions, we have founded a volunteer-based association called DBM Postdoc Club (PDC). The activities of this association aim to provide its members:

1) Hints for career development and orientation
2) An informal platform for networking

Each postdoctoral or senior scientist joining the department of biomedicine automatically becomes a member of the DBM PDC. Membership is free of charge, and members receive updates on upcoming events through email or the PDC website: **http://postdoc.dfusb.unibas.ch.**
PhD students are warmly encouraged to participate in the organized career seminars.

Activities: Career Seminars
In order to facilitate the career development and orientation of DBM scientists (PhD and Postdocs), we organize monthly career seminars. Taking place in an informal and interactive setting, we will discuss a variety of topics covering the crucial scientific and soft skills that are required for successful career development. To facilitate career orientation, the PDC invites interesting speakers from academia, government and industry. Thus far, successful seminars have been held on CV writing, SNF Professorship, clinical trial management and success in academia. As we seek to promote networking opportu-

nities with the DBM, the career seminars are followed by an apéro at which PDC members can get to know each other and converse over a glass of wine, a cold beer, or some orange juice.

Activities: Social Events

In order to promote networking within the DBM, we will organize two social events per year to take a break and have some fun. The first one will take place in Spring 2012, and will be a "multicultural postdoc get-together". We will ask the participants to bring a dish, which is typical to their country. Complimentary drinks will be offered by the DBM PDC. A poll will be posted prior to the event, to help us estimate the number of participants. So, do not hesitate to reserve your place ASAP!
Another idea that we think will be highly appreciated, and which will soon take place, is the "language lunch". These lunches aim to help those who would like to practice their foreign languages or, for newcomers, learn the basics. Once a month, a date and language will be fixed and announced. We invite all the native or fluent speakers for a unique teaching experience. If you are interested do not miss these great opportunities for networking and language practice!

Activities: Basel Postdoc Network Retreat

An interesting challenge is to develop a networking platform for postdoctoral scientists of the academic and industrial research institutes in the Basel area. Toward this goal, the DBM PDC is a co-founder and member of the Basel Postdoc Network. Currently, academic partners include the DBM, Biozentrum, FMI and Swiss TPH, while Novartis Institute of Biomedical Research and Roche constitute the industrial partners. Every postdoc or senior scientist is warmly encouraged to join this network through LinkedIn (http://www.linkedin.com/). Participants will be informed about scheduled activities and can directly interact with other group members of the whole network.

DBM PDC committee (from left to right): Emmanouil Kyriakakis, Jeroen Geurts, Ceylan Eken, Adam Papadimitropoulos and Varaprasad Kolla.

The Basel Postdoc Network is currently organizing a 3-day retreat event, which will take place from 15–17 August 2012 at the Mercure Classic Hotel in Leysin, VD. The program will include oral and poster presentations, career development workshops as well as social events. More details will be announced soon at the dedicated webpage of the retreat (http://postdocretreat.biozentrum.unibas.ch). We are looking forward to your participation at "(y)our event" with great enthusiasm!

Financial support: DBM PDC has successfully acquired financial support of 5000 CHF for 2012. Funding was requested in order to maintain and expand its activities. The perseverance and contribution of Mrs. Heidi Hoyermann with regard to this issue has to be acknowledged.

Steering committee: Every club needs a structure and the same holds true for the DBM PDC.

- Chairman is Varaprasad Kolla (Prenatal Medicine, Lab 416, kollap@uhbs.ch)
- Treasurer is Emmanouil Kyriakakis (Signal Transduction, Lab 316, Emmanouil.Kyriakakis@unibas.ch)
- Deputy Chairman and coordinator of the Basel Postdoc Network is Adam Papadimitropoulos (Tissue Engineering, Lab 422, papadimitropoulosa@uhbs.ch)

- Event organizer and webmaster is Ceylan Eken (Immunonephrology, Lab 414, ceylan.eken@unibas.ch)
- Communication issues are dealt with by Jeroen Geurts (Osteoarthritis Research Center, GeurtsJ@uhbs.ch)

The current committee will be finishing their first term Late 2012. An annual meeting will be held to elect the committee for 2013. Do not hesitate to volunteer for a position and strengthen your CV

The DBM Postdoc Club committee hopes for a continuation of the current enthusiasm and support of its members and is looking forward to an exciting year in science and networking! Feel free to contact the committee any time for questions and suggestions.

DBM Postdoc Club Basel

Dissertationen

Mit der Doktorprüfung am 26. März 2011 schloss **Ila Geigenfeind** von der Forschungsgruppe Integrative Biology (Departement Biomedizin Pestalozzistrasse) erfolgreich ihre Dissertationszeit ab. Das Thema ihrer Doktorarbeit lautete: "On the Biology and Epidemiology of the Feral Pigeon (Columbia livia)".

Am 21. Dezember 2011 stellte sich **Jonas Sieber** von der Forschungsgruppe Molecular Nephrology (Departement Biomedizin Hebelstrasse) dem Dissertationskomitee. Der Titel seiner Dissertation lautete: "Regulation of Podocyte Survival and Endoplasmic Reticulum Stress by Fatty Acids and its Modification by Stearoyl-CoA Desaturases and Cyclic AMP".

Seit dem 25. Januar 2012 darf sich **Pankaj Shende** von der Forschungsgruppe Cardiobiology (Departement Biomedizin Hebelstrasse) Herr Dr. nennen. Er befasste sich in seiner Doktorarbeit mit dem Thema: "Dissecting the roles of mTORC1 and mTORC2 in the mouse heart".

Herzliche Gratulation an alle!

Leben ohne Impactfactor

Letztens erzählte mir eine Nachbarin, die als Biologin bei Roche arbeitet, auf dem Nachhauseweg, dass sie vor kurzem bei einem Bewerbungsgespräch dabei gewesen sei, in dem der Kandidat, bevor er seinen Namen nannte, den Anwesenden den Impactfactor seiner letzten Publikation mitteilte. Traurig gehe ich nach Hause und bin froh daheim zu sein. Hier bin ich sicher, hier kann mich keiner nach meinem Impactfactor fragen. Denn wenn mich einer fragt, kann ich keinen angeben. Ich habe keinen und unsere Familie hatte auch noch nie einen. Wo bekomme ich nur einen Impactfactor her? Ich könnte einen fragen, der einen hat. Vielleicht teilt er ja mit mir, aber dann ist seiner nur noch die Hälfte wert und er wird nicht mehr zum Bewerbungsgespräch eingeladen und hat dann keine Chance mehr, seinen Impactfactor zu erhöhen. Ich könnte jemanden heiraten mit hohem Impactfactor, dann könnte ich sagen, mein Mann hat einen hohen Impactfactor. Die Idee ist nicht neu, aber ich hätte immer noch keinen eigenen. Ich gebe ein Inserat auf: IF gesucht. Daraufhin erhalte ich eine DVD mit einer sehr menschlichen, sehr britischen Komödie aus dem Jahr 1968 mit dem Titel «IF», Regie Lindsay Anderson, eine ziemlich sentimentale Gedichtsammlung mit dem Namen «IF» sowie eine Grammatik über Bedingungssätze im Englischen (If...) ... schlaflose Nächte folgen. Weit und breit kein Impactfactor in Sicht. Per Zufall treffe eine Freundin und erzähle ihr von meinem Problem. Sie fragt mich, ob meine Grossmutter keinen Rat wisse. Sie habe doch immer für jede Lebenslage einen guten Rat parat. In der Tat zitiere ich meine Grossmutter gern und häufig. Mir fällt es wie Schuppen von den Augen: Oma wird zitiert! Und hat damit einen Impactfactor! Und was würde Oma auf gut Kölsch antworten, würde sie nach ihm gefragt: «Et jitt kei grösser Leid, als wat der Minsch sich selvs andät». Kompetenz lässt sich nun mal nicht in Zahlen ausdrücken.

Heidi Hoyermann

Selected publications by DBM members

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

1. The first author, last author or corresponding author (at least one of them) is a member of the DBM.
2. The DBM affiliation must be mentioned in the authors list as it appeared in the journal.
3. The final version of the article must be available (online pre-publications will be included when the correct volume, page numbers etc. becomes available).

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

If you wish that your article will appear in the next issue of DBM Facts please submit a pdf file to the Departmental Assistant, Manuela Bernasconi: manuela.bernasconi@unibas.ch

Deadline for the next issue is April 30, 2012.

The Journal of Cell Biology JCB Vol. 195 No. 7 1171–1184 IF9,9

Neuregulin/ErbB regulate neuromuscular junction development by phosphorylation of α-dystrobrevin

Nadine Schmidt[1], Mohammed Akaaboune[2], Nadesan Gajendran[1], Isabel Martinez-Pena y Valenzuela[2], Sarah Wakefield[1], Raphael Thurnheer[3], and Hans Rudolf Brenner[1]

Neuregulin (NRG)/ErbB signaling is involved in numerous developmental processes in the nervous system, including synapse formation and function in the central nervous system. Although intensively investigated, its role at the neuromuscular synapse has remained elusive. Here, we demonstrate that loss of neuromuscular NRG/ErbB signaling destabilized anchoring of acetylcholine receptors (AChRs) in the postsynaptic muscle membrane and that this effect was caused by dephosphorylation of A-dystrobrevin1, a component of the postsynaptic scaffold. Specifically, in mice in which NRG signaling to muscle was genetically or pharmacologically abolished, postsynaptic AChRs moved rapidly from the synaptic to the perisynaptic membrane, and the subsynaptic scaffold that anchors the AChRs was impaired. These defects combined compromised synaptic transmission. We further show that blockade of NRG/ErbB signaling abolished tyrosine phosphorylation of α-dystrobrevin1, which reduced the stability of receptors in agrin-induced AChR clusters in cultured myotubes. Our data indicate that NRG/ErbB signaling maintains high efficacy of synaptic transmission by stabilizing the postsynaptic apparatus via phosphorylation of α-dystrobrevin1.

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Clinical Cancer Research | Clinical Cancer Research | January 15, 2012, 18(2); 454–464 IF7,3

Targeting Tumor-Associated Endothelial Cells: Anti-VEGFR2 Immunoliposomes Mediate Tumor Vessel Disruption and Inhibit Tumor Growth

Andreas Wicki[1,2], Christoph Rochlitz[1], Annette Orleth[1], Reto Ritschard[1], Imke Albrecht[2], Richard Herrmann[1], Gerhard Christofori[2], and Christoph Mamot[1,3]

Abstract

Purpose: Angiogenesis is a key process in tumor progression. By binding VEGF, VEGF receptor-2 (VEGFR2) is a main signaling transducer in tumor-associated angiogenesis. Accordingly, therapeutic approaches against the VEGF/VEGFR2 signaling axis have been designed. However, an efficient and specific chemotherapeutic targeting of tumor-associated endothelial cells has not yet been achieved.

Experimental Design: We have employed anti-VEGFR2 antibodies covalently linked to pegylated liposomal doxorubicin (PLD) to specifically ablate tumor-associated endothelial cells in the Rip1Tag2 mouse model of insulinoma, in the MMTV-PyMT mouse model of breast cancer, and in the HT-29 human colon cancer xenograft transplantation model.

Results: In each model, anti-VEGFR2–targeted immunoliposomes (ILs) loaded with doxorubicin (anti-VEGFR2-ILs-dox) were superior in therapeutic efficacy to empty liposomes, empty anti-VEGFR2-ILs, antibodies alone, and PLD. Efficacy was similar to that of the oral VEGFR1, -2, and -3 inhibitor PTK787. Detailed histopathologic and molecular analysis revealed a strong antiangiogenic effect of anti-VEGFR2ILs-dox, and the observed antiangiogenic therapy was significantly more efficient in reducing tumor burden in well-vascularized transgenic mouse models as compared with the less-vascularized xenograft model.

Conclusions: Anti-VEGFR2 ILs provide a highly efficient approach to selectively deplete VEGFR2expressing tumor vasculature. They offer a novel and promising anticancer strategy.

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Journal of Pathology | The Journal of Pathology | 2011; 225: 512–524 IF 7,2

Paradoxical effects of T-cadherin on squamous cell carcinoma: up-and down-regulation increase xenograft growth by distinct mechanisms

Dennis Pfaff[1], Maria Philippova[1], Emmanouil Kyriakakis[1], Kseniya Maslova[1], Katharina Rupp[1], Stanislaw A Buechner[2], Giandomenica Iezzi[3], Giulio C Spagnoli[3], Paul Erne[4], and Therese J Resink[1]

Abstract

Mechanisms underlying cutaneous squamous cell carcinoma (SCC) tumour growth and invasion are incompletely understood. Our previous pathological and *in vitro* studies suggest that cell surface glycoprotein T-cadherin (T-cad) might be a controlling determinant of the behaviour of SCC. Here we used a murine xenograft model to determine whether T-cad modulates SCC tumour progression *in vivo*. Silencing or up-regulation of T-cad in A431 (shTcad or Tcad$^+$, respectively) both resulted in increased tumour expansion *in vivo*. To explain this unanticipated outcome, we focused on proliferation, apoptosis and angiogenesis/lymphangiogenesis, which are important determinants of the progression of solid tumours *in vivo*. shTcad exhibited enhanced proliferation potential *in vitro* and *in vivo*, and their signalling response to EGF was characterizedby a higher Erk1/2:p38MAPK activity ratio, which has been correlated with more aggressive tumour growth. T-cad over-expression did not affect proliferation but staining for cleaved caspase 3 revealed a minimal occurrence of extensive apoptosis in Tcad$^+$ tumours. Immunofluoresence staining of xenograft sections revealed increased intra-tumoural total microvessel (CD31$^+$)and lymphaticvessel (LYVE-1$^+$) densities in Tcad$^+$ tumours. shTcad tumours exhibited decreased microvessel and lymphatic densities. Tcad$^+$ expressed higher levels of transcripts for *VEGF-A, VEGF-C* and *VEGF-D in vitro* and *in vivo*. Culture supernatants collected from Tcad$^+$ enhanced sprout outgrowth from spheroids composed of either microvascular or lymphatic endothelial cells, and these *in vitro* angiogenic and lymphangiogenic responses were abrogated by inclusion of neutralizing VEGF antibodies. We conclude that T-cad can exert pleiotropic effects on SCC progression; up- or down-regulation of T-cad can promote SCC tumour expansion *in vivo* but through distinct mechanisms, namely enhancement of angio/lymphangiogenic potential or enhancement of proliferation capacity.

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The Oncologist | The Oncologist | 2011;16:1698–1705 IF 5,8

Prevalence of Skin Lesions in Familial Adenomatous Polyposis: A Marker for Presymptomatic Diagnosis?

Bettina Burger[1,2], Nadja Cattani[1], Swantje Trueb[2], Rosaria de Lorenzo[1,2], Mauro Albertini[3], Emanuele Bontognali[3], Christoph Itin[4], Nathalie Schaub[5], Peter H. Itin[1,2], Karl Heinimann[6]

Abstract

Background and Aims. Benign skin tumors such as lipomas, fibromas, and epidermal cysts are among the extracolonic manifestations of familial adenomatous polyposis (FAP). Readily detectable by inspection, they could serve as presymptomatic diagnostic markers to identify FAP patients. We therefore prospectively determined the prevalence of cutaneous lesions in genetically confirmed adenomatous polyposis coli *(APC)* mutation carriers and assessed their potential usefulness in the identification of FAP patients.

Methods. Whole-skin examination was performed in 56 adult APC mutation carriers, compared with a control group (n = 116). In addition, FAP patients were investigated for the presence of congenital hypertrophy of the retinal pigment epithelium (CHRPE), an established clinical marker for FAP, and a detailed review of medical records was performed.

Results. Nearly half of all FAP patients (48.2%) had at least one FAP-associated skin lesion, compared with one third (34.5%) of controls. Only multiple lipomas and combined skin lesions were significantly more prevalent in *APC* mutation carriers. CHRPE was observed in 22 (43.1%) of 51 FAP patients, including 14 (37.8%) of 37 individuals with *APC* mutations outside the CHRPEassociated region between codons 311 and 1465.

Conclusions. Despite a significantly higher prevalence of multiple lipomas, occurring at younger age, and combined skin lesions in *APC* mutation carriers, the low diagnostic sensitivity of FAP-associated skin lesions precludes their use as markers for FAP in clinical practice. Based on our findings, the common CHRPE-associated region should be extended to *APC* codons 148–2043.

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Journal of Cellular and Molecular Medicine | Journal of Cellular and Molecular Medicine | Vol 16, No 1, 2012 pp. 107–117 IF 4,6

FACS-purified myoblasts producing controlled VEGF levels induce safe and stable angiogenesis in chronic hind limb ischemia

Thomas Wolff[1,2], Edin Mujagic[1,2], Roberto Gianni-Barrera[1], Philipp Fueglistaler[1,2], Uta Helmrich[1], Heidi Misteli[1,2], Lorenz Gurke[2], Michael Heberer[1,2], Andrea Banfi[1]

Abstract

We recently developed a method to control the *in vivo* distribution of vascular endothelial growth factor (VEGF) by high throughput Fluorescence-Activated Cell Sorting (FACS) purification of transduced progenitors such that they homogeneously express specific VEGF levels. Here we investigated the long-term safety of this method in chronic hind limb ischemia in nude rats. Primary myoblasts were transduced to co-express rat VEGF-A_{164} (rVEGF) and truncated ratCD8a, the latter serving as a FACS-quantifiable surface marker. Based on the CD8 fluorescence of a reference clonal population, which expressed the desired VEGF level, cells producing similar VEGF levels were sorted from the primary population, which contained cells with very heterogeneous VEGF levels. One week after ischemia induction, 12 x 10^6 cells were implanted in the thigh muscles. Unsorted myoblasts caused angioma-like structures, whereas purified cells only induced normal capillaries that were stable after 3 months. Vessel density was doubled in engrafted areas, but only approximately 0.1% of muscle volume showed cell engraftment, explaining why no increase in total blood flow was observed. In conclusion, the use of FACS-purified myoblasts granted the cell-by-cell control of VEGF expression levels, which ensured long-term safety in a model of chronic ischemia. Based on these results, the total number of implanted cells required to achieve efficacy will need to be determined before a clinical application.

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Journal of Leukocyte Biology JLB Volume 90: 929–939, November 2011 IF 4,6

IL-8-mediated angiogenic responses of endothelial cells to lipid antigen activation of iNKT cells depend on EGFR transactivation

Emmanouil Kyriakakis[1], Marco Cavallari[2], Dennis Pfaff[1], Doriano Fabbro[3], Juergen Mestan[3], Maria Philippova[1], Gennaro De Libero[2], Paul Erne[4], and Therese J. Resink[1]

Abstract

iNKT cells are a unique T cell subset, which is CD1d-restricted and specific for glycolipid antigens. In advanced atherosclerotic plaques, focal collections of inflammatory cells correlate with areas of intraplaque neovascularization. We reported recently that iNKT cells might facilitate intraplaque neovascularization by enhancing EC migration and sprouting in an IL-8-dependent manner. This study investigated the participating effector mechanisms. In ECs, CM, derived from antigen-stimulated human iNKT cells (CM+), induced up-regulation of IL-8R CXCR2 and the phosphorylation of EGFR and of multiple intracellular signaling effectors, including FAK, Src, Erk, Jnk, p38-MAPK, and STAT1 and -3. We found that a cascade of events, which were IL-8-dependent and involved EGFR activation, was responsible for signaling through FAK and Src kinases and necessary for acquisition of angiogenic morphology, migration in a two-dimensional wound assay, and sprout outgrowth in a three-dimensional model of angiogenesis in vitro. The data support that IL-8-dependent activation of angiogenic behavior in ECs, in response to activated iNKT, involves CXCR2, transactivation of EGFR, and subsequent FAK/Src signaling. We found too that activated iNKT increased VEGFR2 expression in ECs. Functional studies confirmed that EGF is the motogenic-enhancing factor in CM+ and is necessary, together with an exogenous source of VEGF, for iNKT-promoted sprout formation. EGFR inhibition may represent a novel therapeutic modality aimed at plaque stabilization through control of neovascularization within developing atherosclerotic plaques.

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Plos One PLoS one Dec. 2011, Vol. 6, Issue 12, e28563 IF 4,4

Dysferlin Interacts with Histone Deacetylase 6 and Increases alpha-Tubulin Acetylation

Sabrina Di Fulvio[1], Bilal A. Azakir[1], Christian Therrien[2], Michael Sinnreich[1,2]

Abstract

Dysferlin is a multi-C2 domain transmembrane protein involved in a plethora of cellular functions, most notably in skeletal muscle membrane repair, but also in myogenesis, cellular adhesion and intercellular calcium signaling. We previously showed that dysferlin interacts with alpha-tubulin and microtubules in muscle cells. Microtubules are heavily reorganized during myogenesis to sustain growth and elongation of the nascent muscle fiber. Microtubule function is regulated by post-translational modifications, such as acetylation of its alpha-tubulin subunit, which is modulated by the histone deacetylase 6 (HDAC6) enzyme. In this study, we identified HDAC6 as a novel dysferlin-binding partner. Dysferlin prevents HDAC6 from deacetylating alpha-tubulin by physically binding to both the enzyme, via its C2D domain, and to the substrate, alpha-tubulin, via its C2A and C2B domains. We further show that dysferlin expression promotes alpha-tubulin acetylation, as well as increased microtubule resistance to, and recovery from, Nocodazole-and cold-induced depolymerization. By selectively inhibiting HDAC6 using Tubastatin A, we demonstrate that myotube formation was impaired when alpha-tubulin was hyperacetylated early in the myogenic process; however, myotube elongation occurred when alpha-tubulin was hyperacetylated in myotubes. This study suggests a novel role for dysferlin in myogenesis and identifies HDAC6 as a novel dysferlin-interacting protein.

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Jour. of Pharmacology and Exp. Therap. | The Journal of PHARMACOLOGY And Experimental Therapeutics | 2012, Vol. 340, No. 2, 340:286–294 IF 4,0

Effects of the α_2-Adrenergic Agonist Clonidine on the Pharmacodynamics and Pharmacokinetics of 3,4-Methylenedioxymethamphetamine in Healthy Volunteers

Cedric M. Hysek, Robin Brugger, Linda D. Simmler, Marcel Bruggisser, Massimiliano Donzelli, Eric Grouzmann, Marius C. Hoener, and Matthias E. Liechti

Abstract

The mechanism of action of 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) involves the carrier-mediated and potentially vesicular release of monoamines. We assessed the effects of the sympatholytic α_2-adrenergic receptor agonist clonidine (150 μg p.o.), which inhibits the neuronal vesicular release of norepinephrine, on the cardiovascular and psychotropic response to MDMA (125 mg p.o.) in 16 healthy subjects. The study used a randomized, double-blind, placebo-controlled crossover design with four experimental sessions. The administration of clonidine 1 h before MDMA reduced the MDMA-induced increases in plasma norepinephrine concentrations and blood pressure but only to the extent that clonidine lowered norepinephrine levels and blood pressure compared with placebo. Thus, no interaction was found between the cardiovascular effects of the two drugs. Clonidine did not affect the psychotropic effects or pharmacokinetics of MDMA. The lack of an interaction of the effects of clonidine and MDMA indicates that vesicular release of norepinephrine, which is inhibited by clonidine, does not critically contribute to the effects of MDMA in humans. Although clonidine may be used in the treatment of stimulant-induced hypertensive reactions, the present findings do not support a role for α_2-adrenergic receptor agonists in the prevention of psychostimulant dependence.

Division of Clinical Pharmacology and Toxicology, Departments of Biomedicine and Internal Medicine, University Hospital and University of Basel, Basel, Switzerland (C.M.H., R.B, L.D.S., M.B., M.D., M.E.L.); Division of Clinical Pharmacology and Toxicology, University Hospital, Lausanne, Switzerland (E.G.); and Pharmaceuticals Division, Neuroscience Research, F. Hoffmann-La Roche Ltd., Basel, Switzerland (M.C.H.).

Fertility and Sterility | Fertility and Sterility | Vol. 96, No. 4, October 2011 IF 3,9

A novel missense mutation in the high mobility group domain of SRY drastically reduces its DNA-binding capacity and causes paternally transmitted 46,XY complete gonadal dysgenesis

Isabel Filges, M.D.[1], Christophe Kunz, Ph.D.[2], Peter Miny, M.D.[1], Nemya Boesch, B.Sc.[1], Gabor Szinnai, M.D., Ph.D.[4], Friedel Wenzel, M.Sc.[1], Sibil Tschudin, M.D.[3], Urs Zumsteg, M.D.[4], and Karl Heinimann, M.D., Ph.D.[1]

Objective: To investigate the familial segregation, role, and function of a novel SRY missense mutation c.347T>C in two half-sisters affected by 46,XY complete gonadal dysgenesis (CDG) compatible with a successful pregnancy outcome.

Design: Phenotypic, mutational, and functional study.

Setting: Academic research unit.

Patient(s): Two half-sisters, their common father, and 100 healthy control individuals.

Intervention(s): Chromosome, molecular cytogenetic analysis, and Sanger sequencing of the *SRY* gene in blood lymphocytes of the proband, her affected half-sister, and in inflammatory tissue of the father postmortem. Cloning and expression of high mobility group box carboxy-terminal domains of Sry and electrophoretic mobility shift assay were performed.

Main Outcome Measure(s): Not applicable.

Result(s): A novel *SRY* missense mutation c.347T>C (p.Leu116Ser) was identified in two half-sisters and segregates with the CGD phenotype. It is present in the common healthy father in a mosaic state. Functional analyses demonstrate the pathogenic effect of the mutation by a strong reduction of DNA affinity for the mutant p.Leu116Ser SRY protein.

Conclusion(s): The missense mutation c.347T>C in the high mobility group domain of *SRY* causes 46,XY CGD. Paternal gonadal mosaicism is likely to explain the familial occurrence of 46,XY CGD suggesting a de novo mutational event during the early stages of embryonic development. This novel mutation is compatible with a successful pregnancy outcome. (Fertil Steril® 2011;96:851–5. ©2011 by American Society for Reproductive Medicine.)

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European Journal of Neuroscience | EJN | Vol. 35, pp. 20–33, 2012 IF 3,6

P/Q-type and T-type calcium channels, but not type 3 transient receptor potential cation channels, are involved in inhibition of dendritic growth after chronic metabotropic glutamate receptor type 1 and protein kinase C activation in cerebellar Purkinje cells

Olivia S. Gugger[1], Jana Hartmann[2], Lutz Birnbaumer[3], and Josef P. Kapfhammer[1]

Abstract

The development of a neuronal dendritic tree is modulated both by signals from afferent fibers and by an intrinsic program. We have previously shown that chronic activation of either type 1 metabotropic glutamate receptors (mGluR1s) or protein kinase C (PKC) in organotypic cerebellar slice cultures of mice and rats severely inhibits the growth and development of the Purkinje cell dendritic tree. The signaling events linking receptor activation to the regulation of dendritic growth remain largely unknown. We have studied whether channels allowing the entry of Ca^{2+} into Purkinje cells, in particular the type 3 transient receptor potential cation channels (TRPC3s), P / Q-type Ca^{2+} channels, and T-type Ca^{2+} channels, might be involved in signaling after mGluR1 or PKC stimulation. We show that the inhibition of dendritic growth seen after mGluR1 or PKC stimulation is partially rescued by pharmacological blockade of P / Q-type and T-type Ca^{2+} channels, indicating that activation of these channels mediating Ca^{2+} influx contributes to the inhibition of dendritic growth. In contrast, the absence of Ca^{2+} -permeable TRPC3s in TRPC3-deficient mice or pharmacological blockade had no effect on mGluR1-mediated and PKC-mediated inhibition of Purkinje cell dendritic growth. Similarly, blockade of Ca^{2+} influx through glutamate receptor $\delta 2$ or R-type Ca^{2+} channels or inhibition of release from intracellular stores did not influence mGluR1-mediated and PKC-mediated inhibition of Purkinje cell dendritic growth. These findings suggest that both T-type and P / Q-type Ca^{2+} channels, but not TRPC3 or other Ca^{2+}-permeable channels, are involved in mGluR1 and PKC signaling leading to the inhibition of dendritic growth in cerebellar Purkinje cells.

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Neuroscience 181 (2011) 28–39 IF 3,2

Matrix Metalloproteinases 2 and 9 in the Cochlea: expression and activity after Aminoglycoside exposition

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Abstract

The matrix metalloproteinases (MMPs) are a family of proteins involved in the remodelling and homeostasis of the extracellular matrix. These proteases have been well studied in the retina and the brain, marking their importance in neuronal cell survival and death [Chintala (2006) Exp Eye Res 82:5–12; Candelario-Jalil et al. (2009) Neuroscience 158: 983–994]. The neuroepithelia of the eye and the inner ear share common characteristics. Therefore, we hypothesized that MMPs could play a similar role in the cochlea as described in the retina. We focused on the localization and function of MMP-2 and MMP-9 in the cochlea, by determining their expression and activity under normal conditions and after cochlear damage via aminoglycoside exposition. We examined their expression in 5-day-old Wistar rat cochleas by RT-PCR, real-time PCR, and Western blot. We used immunohistochemistry to investigate their location in the cochleas of adult C57BL/6 mice. We also determined whether or not the exposure of the organs of Corti to aminoglycosides would change MMP-2 and MMP-9 expression patterns. Western blotting identified MMP-2 and MMP-9 in neonatal spiral ganglion, stria vascularis, and to a lesser extent the organ of Corti. Neonatal mRNA expression of MMP-2 was approximately equivalent in all three tissues, while MMP-9 mRNA was highest in spiral ganglion. Immunohistochemistry showed MMP-2 primarily in adult spiral ganglion neurons and inner hair cells, while MMP-9 was found mainly in spiral ganglion neurons, inner hair cells and supporting cells. Organs of Corti treated with gentamicin for 24 h showed an upregulation of MMP-2 and MMP-9 proteins, but did not show a significant upregulation of mRNA expression 3, 6, 12, 24, and 36 h after gentamicin exposure. Inhibition of MMP activity in organs of Corti incubated with an MMP inhibitor in organotypic cultures resulted in hair cell death—suggesting that a basal level of MMP activity is required for hair cell survival.

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The Editorial Team
of DBM Facts wishes
all its readers
Happy Easter!

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Frank Neumann neuer Assistent der Bereichsleitung

Am 1. März 2012 hat Frank Neumann seine Tätigkeit als Assistent der Bereichsleitung DBM begonnen. Frank hat in Basel Biologie studiert, an der Universität Genf und am ISREC promoviert und war zuletzt als Postdoc an der Rockefeller University in New York tätig.
Der reinen Forschung hat er nun den Rücken gekehrt, aber die Wissenschaftswelt nicht verlassen: Frank wird zukünftig die DBM-Leitung administrativ und organisatorisch unterstützen. Frank kommt aus der Agglomeration Basel, ist verheiratet und Vater von drei Kindern. Wir wünschen ihm viel Erfolg und Freude bei seiner neuen Tätigkeit! ***Heidi Hoyermann***

DBM Summer-Event

Dear DBM members

The fourth DBM Summer-Event will take place on Thursday, June 21, 2012.

Please reserve this date in your calendar!!!

More info will follow.

Best wishes
Manuela and Team

Congratulations

Das DBM gratuliert ganz herzlich!

Aaron Finn Bopp Limacher
Geboren am 19.01.2012

Vincent Juge
Geboren am 25.01.2012

Conor James Uaitár Baumann
Geboren am 30.01.2012

Leonidas-Ermis Kyriakakis-Buron
Geboren am 24.11.2011

Bruna Pfaff
Geboren am 19.02.2012

Herzlich willkommen, allerseits!

Rossana Barbero
Geboren am 03.12.2011

Anezka Tureckova
Geboren am 05.11.2011

COLLEAGUES RECOMMEND:

In summer 2008 my friends (Bea, Clem and Silvia) and I did a 5 days tour in Portugal.

After leaving Madrid, where we got to experience and feel the euphoria of the Spanish when they beat the then "champion of the world" Italy (sorry Bea and Silvia), we end up taking the Bus to Porto.
After a 10 hours journey, we reached Porto: It was 6 am on the 24th of June, the sun was rising but we could still feel the party atmosphere in the air. It was the end of the Sao João's Festival!
For one night in the year, the city of Porto goes absolutely wild. On this night, the entire population comes to the city center to honour John the Baptist. And they do this in the strangest way: hitting each other over the head with plastic hammers that squeak!!!

But you cannot leave Porto without visiting and tasting the famous Port wine cellars and also a must is the *Francesinha*, a cardiologist-unapproved local sandwich of ham, beef, sausage and cheese with a warm tomato-beer sauce.
After two days in Porto we drove towards the south around the coast. After a while we got to *Torreira beach*, in Murtosa. There we met José, a young surfer that ended up planning our holidays, by revealing to us some of the nicest places in Portugal. *"You definitely have to pass by Nazaré, a small fishing village, where you can see old fishing wives, dressed traditionally with the typical costumes of seven skirts covered with gold rings and necklaces. Another place to go is Peniche, the surfer's paradise, beaches with fantastic waves. At the Ilha do Baleal, just nearby, you can see the most romantic and beautiful view in whole Por-*

tugal on top of the cliffs. Before getting to Lisbon stop by Obidos, the country's prettiest medieval village, where you can visit the castle and walk through the paved streets, admire the whitewashed walls of the houses, balconies with blossoming bougainvilleas and geraniums and taste the famous Ginginha, a traditional liquor. Of course you cannot miss Lisbon, Sintra and Cascais." Jose said.
And so that's what we did: In Nazaré, across the beautiful beaches, we could see the carapaus (horse mackerel) laid out to dry. We enjoyed great food, based on the staples of Nazaré people of fish and shellfish dishes, and great wine but especially the *Licor Beirão*, the recipe for which is unknown. *Licor Beirão* can be drunk on the rocks or like Caipirinhas, the so called *Caipirão* (crushed ice, licor beirão and limes).
In the *Ilha do Baleal* we enjoyed the fantastic view José prophesied. We also had fantastic sunbaths, which can be dangerous in Portugal, due to the wind all over the Atlantic coast that can make you feel like "Marie Therèse" unable to walk after the sunburn, right Clem? :)
At the end we reached Lisbon, the city of *Fado*, the city of culture and history. You can discover it by taking the famous tram *Nr.28* which offers you the best view of the old Lisbon.

But Lisbon is more than that: the *Bairro Alto* is the center of nightlife with cosy bars, restaurants and discos.
In Lisbon you cannot miss the famous *Pastéis de Belém*. This egg tart pastry was created by Catholic nuns in the *Mosteiro dos Jeronimos*. There is no way to resist to it, even if you sit on top of them due to a lapse in memory, you will lick your fingers while eating it!

At the end of the Day the best way to discover Portugal is to do it as we did: ask a local. Portuguese people are always happy to help, to talk and believe me, language is not a problem!
Just get lost in Portugal, in its narrow streets and corners! Every narrow street will tell you a different story and every story will easily reach your heart!

Sandra Feliciano

Clem, Silvia, Bea and Sandra (from left to right)

Moroccan enchantment

The Kingdom of Morocco is a land of contrast and enchantment. *The magic of the imperial cities, the rolling dunes of the Sahara desert and the peaks of the Atlas Mountains are all sources of inspiration. Born and raised in France in a Moroccan immigrant family, I have spent most of my childhood summer holidays in north-western Morocco.* As a kid I was fascinated by the curiosity and kindness of Moroccan people who are intrigued by the outside world. They delight in welcoming foreigners or "half foreigners", as we were, into their homes to share the traditional mint tea and ask thousands of questions about the occident. In addition to this tolerant and welcoming atmosphere, where only the sun can compete with Moroccan hospitality, Morocco offers a fascinating décor made of Cherifian palaces surrounded by sumptuous gardens, Riads with their secret yards, colourful souks with delightful spice perfumes and a collection of monuments documenting a history of 2500 years. Apart from Marrakesh, the typical tourist destination, several places in Morocco are really worth a visit. For those who enjoy a bit of history, the archaeological site of Volubilis is an interesting place to go. The vestiges of this site bear witness to ten centuries of occupation, cultural traditions and lost cultures, including Libyco-Berber and Mauritanian, Roman, Christian and Arabo-Islamic. Another "must see" in Morocco is the Sahara desert. The journey to this region is an experience in itself. The way from Marrakech takes you up to the top of the high Atlas Mountains at an altitude of 2260 meters in the area known as the Tizi n'Tichka pass. Then it rapidly drops down into the region of Ouarzazate, nicknamed "The door of the desert" and famous for its studios which have hosted international film productions such as Lawrence of Arabia and Prince of Persia. When finally reaching the end of the paved road in M'hamid, it's like stepping back in time into a forgotten world, with snowy mountains on one side of the landscape and desert on the other.

Imane Möst-Azzouzi

KAVALA. NORTH GREECE.

Every step of the way through the narrow streets in the old town is steeped in history. The feeling is almost tangible at the sight of Imaret. It was used mainly as a boarding school, but now Imaret is the finest gemstone of the old town and one of the most prestigious hotels of North Greece. From there people can admire the view of the city that spreads in an amphitheatrical way. Of course, the other side of the chersonese of the old town provides an equally beautiful view of the sea and the island of Thassos.

Once in the old town the great castle, the acropolis, built in the first quarter of the 15th century, must be seen from the inside as well as from the top of the mountain across the city when it stands gloriously lighted during the night.

"Kamares", a building that immediately attracts attention, was built to bring water to the old town and with said castle are the two most well known landmarks of Kavala.

In the modern city the past is written on the walls of the old tobacco warehouses since for the most part of the 20th century tobacco trade was major business in the area.

The city hall is housed in a beautiful building that is a miniature of a Hungarian castle and was built by a Hungarian tobacco trader in 1895. The garden is full of flowers adding colour to its white walls.

The reader must be warned though that the streets of Kavala are not straight lines. It might prove a hard task to climb them, but it is rewarding, for the view from "Agios Sillas" is breathtaking. If the weather is fine Mount Athos can be seen too.

Outside the city history keeps unravelling and goes further back in time. The ancient village of Philippi, built in 356 BC by King Philip II is 20 minutes from the city center. To this day the ancient theater is still active. During the summertime musical concerts and the words of famous plays fill the night air. But there's more. The remains of the village that once gave life to people even in early Christian years must be visited as well as the archaeological museum of Philippi.

Kavala. Aka "Small Monte Carlo" by the locals due to the golden beaches within the borders of the city. One might say this is an exaggeration, but one has to visit the city to find out whether that is true or not. Whatever Kavala lacks in luxury it makes up for in authenticity. And authenticity has to be experienced.

Elissavet Paraskevopoulou

SPRING FESTIVALS OF INDIA

India is a land of great diversity. It described as a land of many religions and innumerable languages; it might well be described as a land of festivals as well. Indians love celebrating. Every little occasion from the harvesting of crops, welcoming the spring or rain, to seeing the full moon lends itself to joyous celebrations splashed with colours, music, folk dances and songs. The Indian calendar is one long procession of festivals. These are as varied in origin as they are large in number. During most of Indian festival the homes are neatly decorated, new dresses are worn for every occasion, prayers offered to Gods, and lot of sweets and goodies are cooked. Most of these festivals are common to most parts of India, however, they may be known by different names in different parts of the country. Different cultures also mean that different rituals are followed. In this article I will introduce some of the festivals of India which are celebrated between January and March to you.

Makar Sankranti is one of the most auspicious occasions for the Hindus, and is celebrated in almost all parts of the country in a myriad of cultural forms, with great devotion, fervour & gaiety. It is a harvest festival. Makar Sankranti is perhaps the only Indian festival whose date always falls on the same day every year i.e. the 14th of January.

Makar Sankranti is the day when the glorious Sun-God begins its ascendancy and entry into the Northern Hemisphere and thus it signifies an event wherein the Sun-God seems to remind their children that 'Tamaso Ma Jyotir Gamaya', may you go higher & higher, to more & more Light and never to Darkness. To Hindus, the Sun stands for knowledge, spiritual light and wisdom. Makar Sankranti signifies turning away from the darkness of delusion in which we live, and beginning to enjoy a new life with bright light within us shining brighter and brighter. We should gradually begin to grow in purity, wisdom, and knowledge, just as the Sun does from the Day of Makar Sankranti.

Sakranti – means to go from one place to another place (to change direction). It also means one meets another. The time when the sun changes direction from one constellation (of the zodiac) to another is known as Sankranti. At Sakranti time great importance is attached to Ganga snaan (bathing with waters of the river Ganges) and Surya Puja (worshipping the sun). Bathing, worshipping gods, Havan, Japa, Fasting and Charity; each of these are extremely holy deeds.

Lohri – the spring festival, dedicated to the worship of fire, is celebrated with great zeal and enthusiasm in North India. The first Lohri of a newly-wed couple and of a new born baby is considered as quite significant. Loved ones gather around the bonfire, offer their prayers to Agni, for prosperity. They enjoy the festival dancing and singing traditional folk songs around the bonfire, followed by dinner with makki ki roti and sarson ka saag.

Pongal – Makara Sakranti is called Pongal by the Tamilians, for whom it ushers in the New Year. The

day begins with Surya Pongal or sun worship. The newly harvested corn is then cooked for the first time. Joyous festivities mark the celebration in every home. Servants, farmers and the poor are fed and clothed, and given presents of money. On the next day, the cow, which is regarded as the symbol of the Holy Mother, is worshipped. Birds and animals are also fed.

Bihu – is the biggest and most important festival of the people of Assam. It is a festival which is celebrated by everyone with a lot of fun irrespective of religion, caste, creed, or any specification breaking any barriers within them and brings in a sense of solidarity and unity among all the people to celebrate in a free world. Bohaag Bihu is the most eventfully celebrated Bihu in mid-April and marks the beginning of the new agricultural season and also the new year, that is "of the Hindu calender", which is also celebrated in different states under different names. It is also called as the "festival of merriment". On this day, the cows are washed and worshipped, and are then decorated with various colourful garlands of flowers, and vegetables. The next day is called as Manuh Bihu (manuh means human) and homage is paid to elders, which is customary as well.

Maha Shivratri : Festival or the 'The Night of Shiva' is celebrated with devotion and religious fervour in honour of Lord Shiva, one of the deities of the Hindu Trinity. Shivaratri falls on the moonless 14th night of the new moon in the Hindu month of Phalgun, which corresponds to the month of February – March in the English Calendar. Celebrating the festival of Shivaratri devotees observe a day and night fast and perform ritual worship of Shiva Lingam to appease Lord Shiva.

There are various interesting legends related to the festival of Maha Shivaratri. According to one of the most popular legends, Shivaratri marks the wedding day of Lord Shiva and Parvati. Some believe that it was on the auspicious night of Shivaratri that Lord Shiva performed the 'Tandava', the dance of the primal creation, preservation and destruction. Another popular Shivratri legend stated in Linga Purana states that it was on Shivaratri that Lord Shiva manifested himself in the form of a Linga. Hence the day is considered to be extremely auspicious by Shiva devotees and they celebrate it as Mahashivaratri – the grand night of Shiva.

Various traditions and customs related to Shivaratri Festival are dutifully followed by the worshippers of Lord Shiva. Devotees observe a strict fast in honour of Shiva, and though many go on a diet of fruits and milk some do not consume even a drop of water. Devotees strongly believe that sincere worship of Lord Shiva on the auspicious day of Shivaratri absolves a person of sins and liberates him from the cycle of birth and death. Shivaratri is considered especially auspicious for women. While married women pray for the well being of their husbands, unmarried women pray for a husband like Lord Shiva, who is regarded as the ideal husband.

Vasant Panchami: Vasant Panchami is a Hindu festival of the spring season. 'Vasant' means spring and panchami refers to the fifth day of the Hindu lunar calendar month. Thus, Vasant Panchami refers to the Hindu spring festival that falls on the fifth day of the bright fortnight of the Hindu month of Magh. Vasant Panchami is also known a festival in honour of the goddess Saraswati, the

hindu goddess of education, learning and the fine arts (music, writing, painting, etc.). The festival is celebrated on the fifth (panch) day after the new moon (amavasaya) in the month of Magha according to the Hindu calendar (this usually occurs in late January or early February). It marks the onset of spring (vasant) according to the Hindu calendar and is marked with great gaiety and celebrations all across the northern states in India.

The colour yellow is perhaps the most prominent feature on Vasant Panchami. Yellow coloured clothes, foods (like saffron rice), flowers (mustard) and sweets (with kesar) are the traditional norm on this day. The goddess Saraswati is adorned in yellow clothes (at home or at the mandir) as yellow is considered to represent the sattva guna – characteristic of purity, prosperity and love. Kite flying is a very popular tradition observed (particularly in Haryana and Punjab) on Vasant Panchami. Children and adults alike engage in flying small and large kites and various kite-flying competitions are held across roof-tops and in playgrounds all over northern India. It is also a day for art and painting competitions, poetry recitations and music festivals all over India in honour of the goddess Saraswati – the patron of the arts.

Holi – The festival of colours is one of the most popular festivals of the country. It is celebrated during the spring season and embodies all the festivity, liveliness and exuberance of the season. Holi is the festival of young hearts. Spraying colours, dancing to traditional Holi songs, rhythmic drum beats and wild processions are the common scenes that one comes across during this festival. It symbolizes the victory of good over evil.

Holi is the festival where farmers and rural people can celebrate the prosperity and abundance in life that comes with the harvest season. The festival of colours, Holi is celebrated on the day after the full moon in early March or April every year. People smear each other's faces with coloured powder known as 'Gulal' and 'Abeer' and throw coloured water or 'Rang' on each other. Most of the people now-a-days prefer the traditionally prepared natural herbal colours that are not only fragrant but are also good for skin. People make processions on the streets that feature folk songs and dances. The 'Bhaang' (opium) drinks are very popular among people as it is the favourite festival drink. The festival of Holi has no religion ties and all celebrate it. The festival has a secular flavour.

The festival of Holi is a great time when all of families and friends get together and it can be said very simply that the fragrance of the colourful Holi symbolizes your love for everyone else. The festival of Holi is a time when all disputes and fights get dissolved in love and joy to celebrate the festival and that results in strengthening the feeling of oneness and love.

Chanchal Sur Chowdhury

Kämpfen um jeden Ball

Im Folgenden stellt Nicole Caviezel, die als Tierpflegerin in der Tierstation in der Hebelstrasse arbeitet, ihr Hobby Volleyball spielen vor. Und das einmal ganz anders - als Textform hat sie sich das Interview ausgesucht. Das Interview führte Ulrich Schneider.

Wie bist Du zum Volleyball gekommen?
Ich habe im Schulsport, da war ich 13 Jahre alt, angefangen, Volleyball zu spielen.

In welchem Verein, welcher Mannschaft und auf welcher Position spielst Du?
Beim Volleyball Club Rheindelden. Da spiele ich in der ersten Mannschaft 3. Liga. Es könnte sogar sein, dass wir diese Saison in die 2. Liga aufsteigen können. Ich bin ein Libero, das ist die Person, welche ein anderes Shirt an hat und jeweils im Rückraum spielt. Wer auch zu uns in den Verein möchte, ist herzlich willkommen, auf www.vbc-rheinfelden.ch findet man alle Informationen.

Erkläre Volleyball einem Laien.
Im Hallen-Volleyball sind sechs Personen auf dem Feld, drei am Netz und drei hinten im Rückraum. Das Ziel ist, den Ball im gegnerischen Feld auf den Boden zu spielen.

Was gefällt Dir an dieser Sportart?
Vor allem der Zusammenhalt der Mannschaft, ohne ihn läuft gar nichts. Was ich persönlich toll finde, ist, dass man um jeden Ball kämpfen muss. Egal, ob der Ball fast an der Wand ist oder am Boden.

Welche Funktion hast Du in Deinem Verein?
Ich gebe 4 x in der Woche Juniorinnen-Training, selber habe ich auch noch 2 x Training. Im Vorstand habe ich auch noch einen Platz bekommen. Dort bin ich für alle Trainer vom Volleyball Club Rheinfelden verantwortlich.

Deine grössten Erfolge?
Als ich Juniorin war, spielte ich an der Schweizer Meisterschaft mit. Mit meinen Juniorinnen habe ich schon Medaillen geholt, dieses Jahr liegt wieder eine drin.

Was wünschst Du Dir für die Zukunft?
Ein grosser Traum ist, dass ich eine hohe Juniorinnenklasse trainieren kann und natürlich, dass wir es in die 2. Liga schaffen und dort gut mithalten können.

News from the DBM-iT

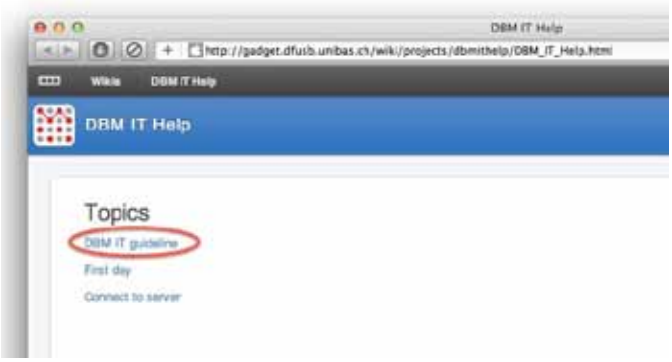
The Microsoft Exchange (Outlook) migration is progressing. The first University users will be migrated in Spring 2012. We can't tell yet when it will be our turn. The URZ recommends having the newest version of Outlook (2010 on a Windows PC, 2011 on a Macintosh) in order to use all the features properly. Mac users: please note that you must have an Intel processor and at least version 10.6 of the OS to be able to install the newest Outlook. For PC users: please note that you must have at least 256 MB RAM and 512 MB RAM graphics features. More information will follow.

All information about the IT at the DBM can be read online or downloaded as a pdf from our new web server. The address is http://gadget.dfusb.unibas.ch *(enter this address in any browser i.e. Firefox, Explorer, Safari etc.)* It is only reachable via the intranet of the unibas.ch network.

This is the screen you will see when you open our web server.

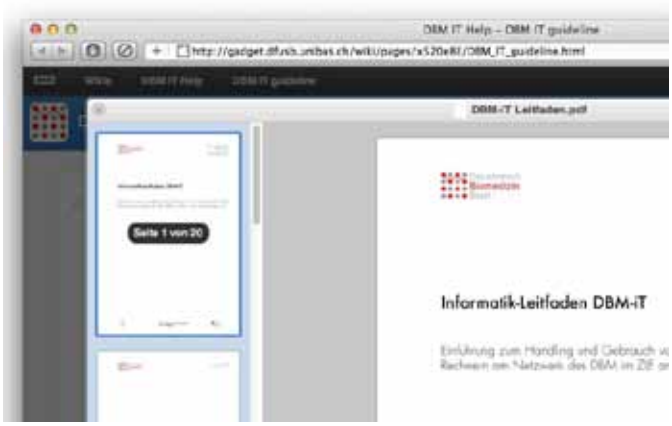
Niklaus Vogt

Click on the DBM Logo.



Here you will find our new "DBM iT Guidelines" – when you click on this you will see the next screen.

If you click the "eye"-symbol you will be able to read the "Guidelines" online. You can also download them as a pdf. Just click on the Name.



Takafumi Shimizu, Exp. Hematology

Hi everyone! My name is Takafumi Shimizu. I came from Tokyo in Japan to join the Experimental Hematology Laboratory as a post-doctoral fellow four months ago. Today, I would like to introduce the Japanese culture, life and my previous laboratory. I hope that this information will help you to enjoy a trip to or even to live in Japan, if you get an opportunity.

Japan is situated in north-eastern Asia between the North Pacific and the Sea of Japan. The area of Japan is about 380,000 square kilometres, nearly equivalent to Germany and Switzerland combined. Japan consists of four major islands, surrounded by more than 4,000 smaller islands. There are many beauty and impressive spots in many part of Japan. I think the cities of Tokyo and Kyoto are the most popular visited by tourists. I also recommend visiting both cities if you have plenty time, because both of these cities have different characters. Generically, Kyoto is one of the most traditional and is a magnificent city with a 1200 year history. You can see a lot of historical architecture and experience some of the traditional habits and cultures. In contrast, Tokyo is the bustling capital city of Japan now. The history of Tokyo extends back approximately 400 years. At the beginning Tokyo was called Edo; the history of Tokyo has seen many changes in a short time. Tokyo has now developed into an extraordinarily vibrant, exciting and fashionable modern metropolis, which still manages to reveal glimpses of its traditional past. You can enjoy a lot of things in this city, because it has many attractive spots in a small area (e.g. museums, shopping streets, historic shrines or temples or gardens, entertainment spots, dining spots, etc). The following major sightseeing spots were extremely well-received by my friends from outside Japan.

Akihabara is the most famous electronics town in Japan. Hundreds of electronics shops, ranging from tiny one man stalls specializing in a particular electronic component to large electronics retailers, line the main street and the crowded side streets around Akihabara. They offer everything from the newest computers, cameras, televisions, mobile phones, electronics parts and home appliances to second-hand goods and electronic junk. If you have the knowledge you can build your own computer for a cheap price. In more recent years,

Tokyo metropolis

Kaminari-mon in Asakusa

The Akihabara electric town

Akihabara has gained recognition as the center of Japan's otaku (diehard supporters) culture, and many shops and establishments devoted to anime, manga and idols are now dispersed among the electronic stores in the district.

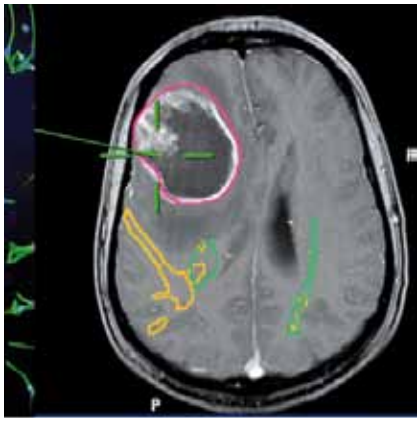
The second point is Asakusa. In contrast to Akihabara, it is a traditional sightseeing spot in Tokyo. It is also located in one of the central areas of Tokyo and is where you can experience the atmosphere of old Tokyo. The main attraction of Asakusa is Sensoji, a very popular Buddhist temple, built in the 7th century. When approaching the temple, you first enter through the famous main gate, which called Kaminari-mon (Thunder Gate), the outer gate of the temple and the symbol of Asakusa and you will find a vibrant street connecting to the temple after the gate. There are a lot of shops along the street which date back to the Edo period, and which have provided visitors with a variety of traditional, local snacks and souvenirs for centuries. In the middle of May you can enjoy one of the three major traditional festivals held in Tokyo at Asakusa. As I mentioned above, there are many attractive spots in Tokyo, you can enjoy a lot more.

The last part of my introduction relates to science. I think that the general characters of Japanese researchers are diligence, punctiliousness and being hard workers. These characters are not always true however Japanese researchers working abroad have such characters to some extent. I introduce my previous laboratory as one example, because the atmosphere and activity of laboratories is completely different in each of one. The average numbers of researchers in a laboratory is ten to twenty, but, because it has had a large grant, my previous laboratory contained about thirty researchers including students. Each of researchers had individual research themes. The start and end time of the working day is later than in Switzerland and research style is left to each individual person. Some motivated researchers work until late at night even during holidays. I'm sure some people may think they are crazy, but their activities are based on two reasons I think. One is simple intellectual curiosity, and the other is their motto that "hard-work is not sufficient but a necessary condition to achieve big work". In general a Japanese laboratory adopts a hierarchical structure consisting of four or five levels (Professor, associated or assistant Professor, post-doc fellow and so on). In order to survive in academic fields we must achieve promotions through the positions by a certain age. For this reason, the competition is very severe, just as in other countries. In addition to science we also enjoy various kinds of events in the institute, such as beer parties, soft-ball or foot-ball tournaments and so on. We gain a good connection to external or internal researchers through the events. Many foreign researchers are working in Japan now. If you get an opportunity, would you like to carry out research in Japan?

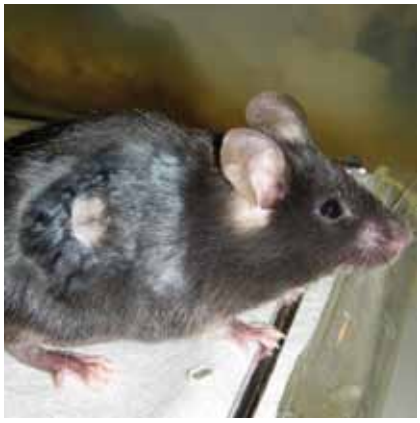
Laboratory member of stem cell therapy of Tokyo Univ. (Farewell party of 2011; Takafumi front row 3. from the right)

VORSCHAU PREVIEW

In der nächsten Ausgabe . . .



. . . erfahren wir von Luigi Mariani mehr über das Forschungsgebiet Brain Tumor Biology



. . . lernen wir mit Simona Rossi die Bedeutung der Immunoregulation kennen

. . . entführt uns Denise Berger in ihre ehemalige Wahlheimat Wien

. . . bekommen wir mit Ironwoman Brynn Kvinlaug zu spüren, was Triathlon bedeutet

. . . stellen wir die schönsten Lektüren für die Sommerferien vor

Der zurückgekehrte Storch

Der Winter zögernd schwindet hin;
Nun prangt der Storch dort beim Kamin.
Schon klappert er von stolzer Höh‘
Und steht in seinem Kleid, wie Schnee,
Mit Flügeln, schwarz, wie Ofenruss,
Doch schon auf lenzig rotem Fuss.

Karl Mayer, 1849