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A tale without a tail: novel functions for lipid-anchored adhesion molecules in cardiovascular disease and cancer | Có chí thì nên: Where there is a will, there is a way | First Year International

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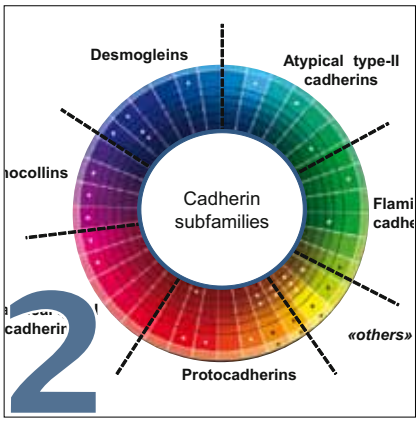
Departement Biomedizin Basel



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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

2011 geht mit raschen Schritten dem Ende entgegen. In der letzten Ausgabe dieses Jahres steht die wissenschaftliche Tätigkeit des Labors "Signal Transduction" im Mittelpunkt. Thérèse Resink und Maria Philippova gewähren uns einen vertieften Einblick in die Komplexität der T-Cadherin-Forschung (ab Seite 2). Eine Aufgabe ganz anderer Art hat sich Regine Landmann gestellt, als sie vor zwei Jahren begann, ein Labor für Mikrobiologie am "National Hospital of Tropical Diseases" in Hanoi mit aufzubauen. Was daraus geworden ist, erfahren Sie ab Seite 8. Die neuesten Publikationen aus dem DBM finden Sie anschliessend ab Seite 15. Weihnachtlich-winterlich wird es dann ganz jahreszeitgemäss in der zweiten Hälfte des Newsletters: Das Christfest in Spanien, Curling, grosse Pakete für kleine Menschen und vieles andere mehr. Möge für jede und jeden etwas dabei sein!

Nach zehn Jahren als Leiter DF und später DBM werde ich ab Januar bis Ende August 2012 ein Sabbatical in Boston machen und mich in dieser Zeit ausschliesslich der Forschung widmen. Während meiner Abwesenheit werden die Geschicke des DBMs in den Händen von Peter Meier-Abt liegen, der sich in dankenswerter Weise bereit erklärt hat, die Leitung des DBMs ad interim zu übernehmen.

Frohe Festtage und einen guten Rutsch in ein gesundes und glückliches 2012!

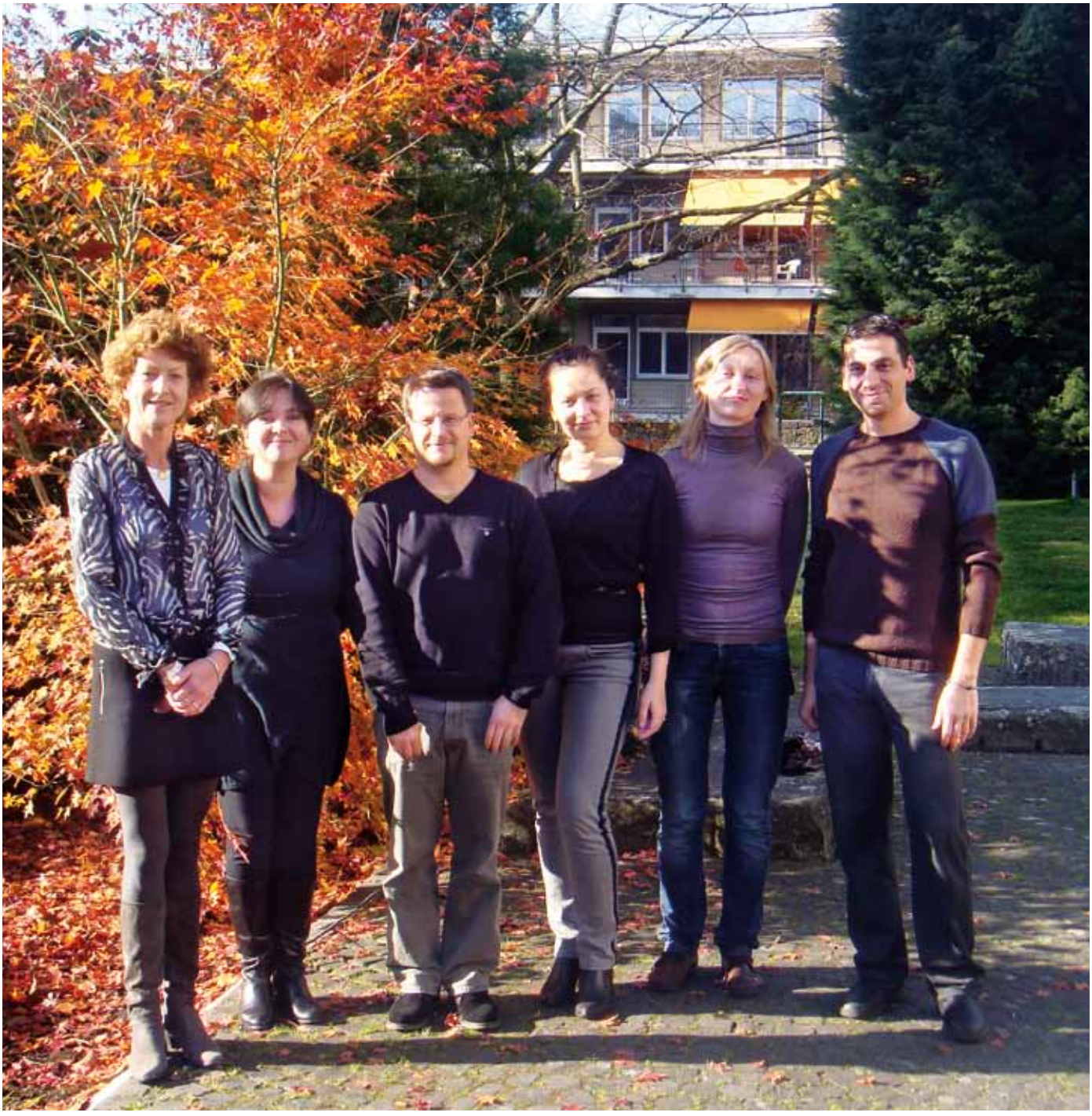
Dear readers

The end of 2011 is fast approaching. In the last edition for this year the focus is on the scientific activities of the Signal Transduction laboratory. Thérèse Resink and Maria Philippova impart a deeper understanding of the complexity of T-Cadherin research (from page 2 onward). A completely different sort of mission is confronted by Regine Landmann, who, two years ago, began the establishment of a laboratory for microbiology at the National Hospital of Tropical Diseases in Hanoi. What became of it can be discovered from page 8 onward. The latest publications of the DBM can be found from page 15 onward. The second half of this newsletter is filled with seasonal Christmassy and wintery topics: Christmas celebration in Spain, curling, large packets for little people, and lots more. There is sure to be something for everyone there!

After ten years as the director of the DF and then the DBM I am going to take a sabbatical in Boston from January till the end of August 2012 where I will be devoting my time to research. During my absence the fate of the DBM lies in the hands of Peter Meier-Abt who has thankfully agreed to take over the direction of the DBM in the interim.

Wishing you all happy holidays and a healthy and happy start to 2012!

A tale without a tail: novel functions for lipid-anchored adhesion molecules in cardiovascular disease and cancer



The group "Signal Transduction". From left to right: Therese Resink, Maria Philippova, Dennis Pfaff, Kseniya Maslova, Agne Petuskaite, Emmanouil Kyriakakis

1. The cadherin superfamily of adhesion molecules: T-cadherin, an ugly duckling in the herd

Precise spatial and temporal regulation of cell-cell and cell-extracellular matrix adhesive contacts is crucial to accurate execution of complex biological processes that occur during embryonic development and the controlled growth and turnover of adult tissues. Four major groups of cell surface adhesion proteins have been described: integrins, immunoglobulins, selectins and cadherins. Cadherins, a major component of intercellular adherens junctions, represent a superfamily comprising more than 100 members. The majority can be divided into six subfamilies defined upon protein domain composition, genomic structure and phylogenetic analysis of protein sequence but outlyer cadherins also exist (Fig. 1A). Classical type-1 cadherins typically comprise an extracellular domain containing 5 tandem cadherin repeats, a single membrane-spanning domain and a cytoplasmic tail (Fig. 1B). Cadherin-based cell-cell contacts are formed via calcium-dependent ligation between extracellular domains of same-type cadherins (i.e. homophilic interactions). Cytoplasmic domains of cadherins interact with cytoplasmic proteins such as catenins which mediate anchorage to the cytoskeleton and ensure strong mechanical cell-cell coupling (Fig. 1B).

T-cadherin (T-cad), also known as H-cadherin or cadherin 13, represents a striking exception to the general principle of cadherin domain structure: it possesses the 5 tandem repeat ectodomain structure of type-I cadherins but lacks transmembrane and cytoplasmic domains and is attached to the plasma membrane via a lipid glycosylphosphatidylinositol (GPI) anchor (Fig. 1B). T-cad was so named because of its "t"runcation. The "tailless" character of T-cad suggests that its functions and mechanisms of signal transduction are very different from those of classical cadherins. Unfortunately, very few laboratories have studied T-cad in a dedicated manner. Here we give an overview of our efforts toward delineating the functions and mechanisms of action of T-cad in vascular and tumor biology.

2. T-cadherin in vascular biology: a reparative modulator

T-cad is expressed on endothelial and smooth muscle cells of vascular tissue with prominent upregulation in coronary arteries during atherosclerosis and restenosis and in tumor microvessels. In contrast to type-1 cadherins, T-cad is not present in adherens junctions of quiescent cells but expressed globally on the apical surface and translocates to the leading edge of migrating cells.

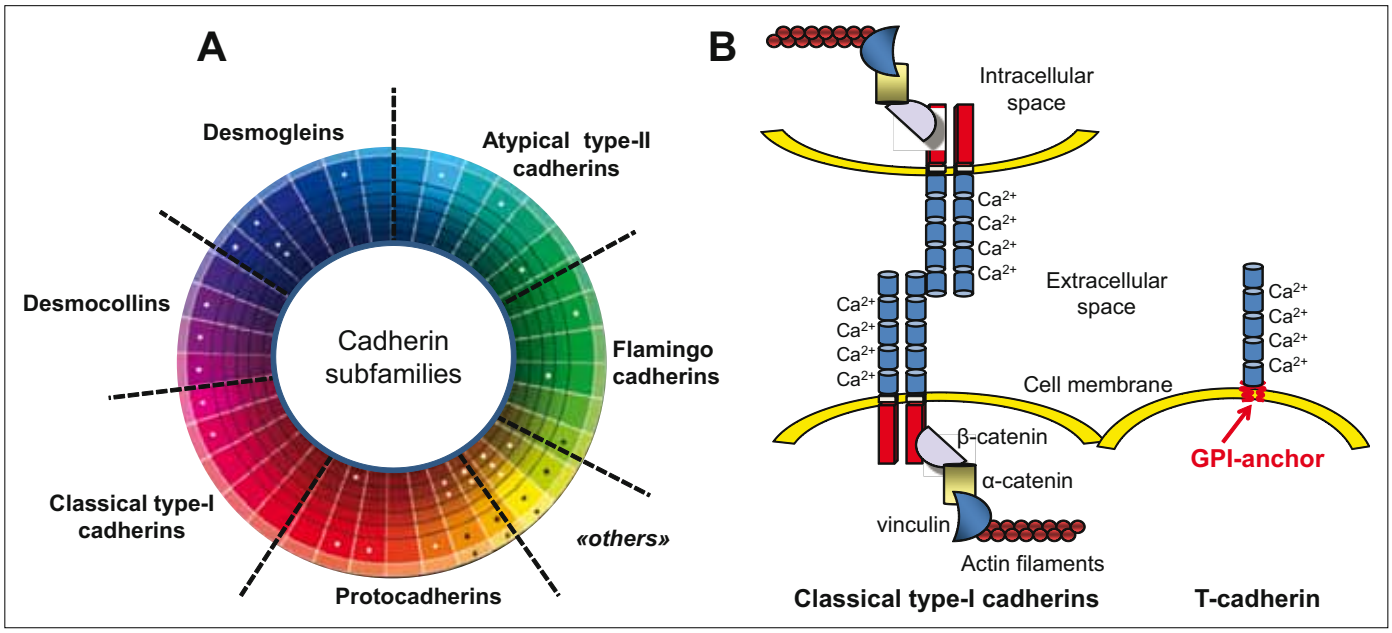


Figure 1. (A) Phylogenetic diversity of the cadherin superfamily. (B) Domain structure comparison between classical type 1 cadherins (with extracellular, transmembrane and cytoplasmic domains) and T-cadherin (with extracellular domain and GPIanchorage to the plasma membrane).

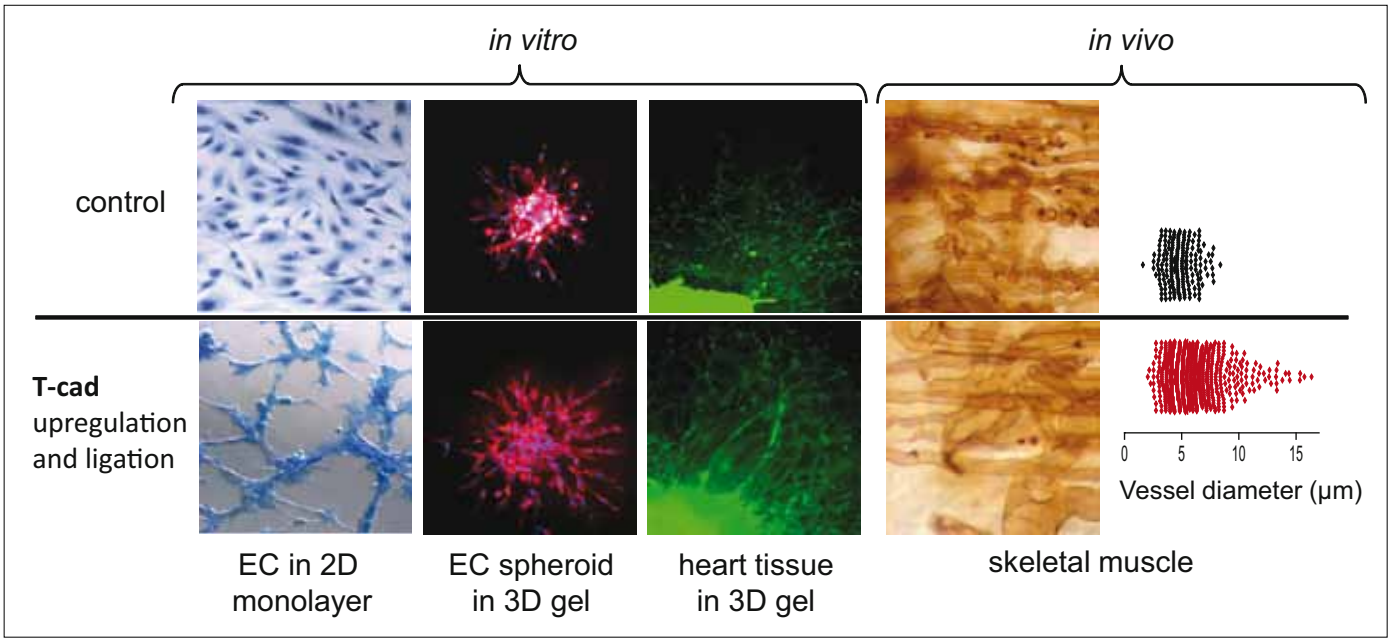


Figure 2. T-cad upregulation and ligation facilitates angiogenesis. Pro-angiogenic properties of T-cad are demonstrable in different in vitro systems. In vivo proangiogenic effects of T-cad after implantation of myoblast clones expressing T-cad or not into murine posterior auricular muscle are evident as increased vessel diameters (performed in collaboration with Dr. Andrea Banfi, Cell and Gene Therapy group, Departments of Biomedicine and of Surgery).

T-cad has important pro-angiogenic and pro-survival functions in endothelial cells: upregulation and ligation of T-cad promotes cell proliferation, motility, angiogenesis *in vitro* and *in vivo* (Fig. 2) as well as resistance to various types (oxidative, endoplasmic reticulum) of stress. We consider T-cad as a modulator of reparative behaviour of vascular cells in cardiovascular disorders.

3. Security guard fail: loss of T-cadherin and cellular layer integrity open gates to cancer invasion?

T-cad expression has been immunohistochemically demonstrated in many tissues, heterogeneous in origin and function. We noticed two major expression patterns. The first is characterized by thin polarized protruding structures, which under the orchestrated control of various guidance molecules, organize themselves into cellular nets united by the same function into a "community" (such as extending axons, endothelial cells of growing vessels or the net of vascular smooth muscle cells in the subintimal area of the vessel). The second is characterized by single cellular layers delineating borders of distinct structural tissue units (such as different sclerotomes in the embryo, intestinal villi, basal keratinocyte cell layer, endothelial lining). Hence, we have hypothesized that the "functional predestination" of T-cad is the control of tissue architecture through both "guiding" navigation of moving structures or segregation of functional tissue compartments and "guarding" integrity of functionally connected tissue layers. In the adult organism, failure to maintain integrity of the tissue architecture and to restrict cells from traversing into surrounding areas can result in cancer progression.

We recently initiated investigations on involvement of T-cad in progression of non-melanoma skin cancers, such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Expression of T-cad in the healthy skin is a perfect example of a restricted layer pattern: it is present only in basal layer keratinocytes (Fig. 3A,B), characterized by proliferative activity necessary for the constant renewal of the outer dermal layer. Specimens of BCC which are highly proliferative but non-invasive and remain *in situ* (Fig. 3C) display high T-cad levels. In SCC T-cad expression is variably downregulated (Fig. 3D,E), appearing to occur in association with acquisition of the invasive tumor phenotype. Fig. 3D illustrates loss of T-cad expression occurring in a region where tumor cells are starting to invade the dermis. We believe that in the basal keratinocyte layer T-cad plays a role similar

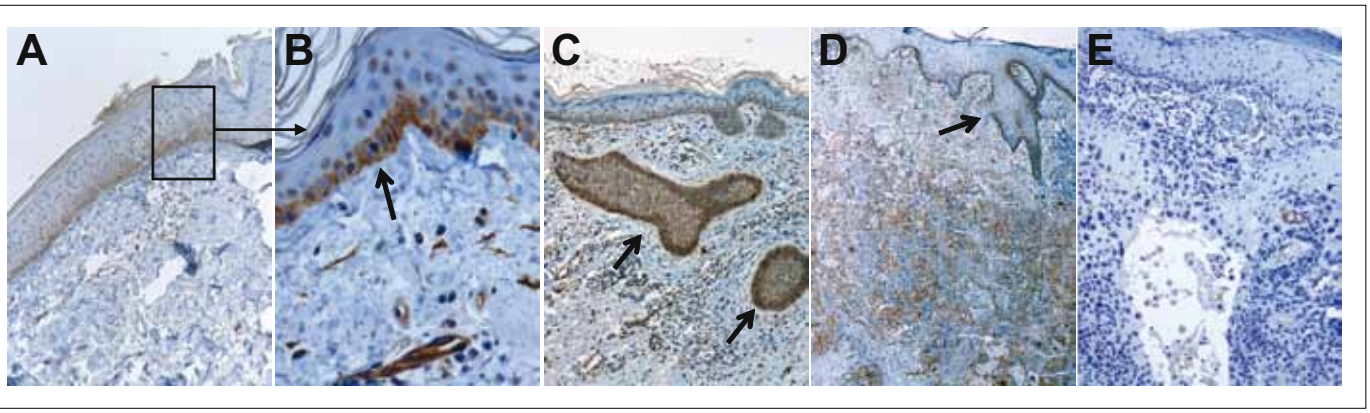


Figure 3. T-cad expression in skin. (A, B) In healthy skin T-cad expression (brown) is restricted to the basal keratinocyte layer (arrow). (C) High T-cad levels in nodular BCC (arrow). (D) Local loss of T-cad expression at the invasive front of SCC (arrow). (E) Complete downregulation of T-cad in advanced poorly differentiated SCC (were performed in collaboration with Prof. Stanislaw A. Buechner, Blumenrain 20, Basel).

to that during embryonic development: it not only limits proliferation rates of actively growing cellular layers but also controls their spatial orientation and restricts motility. When this "guard" function is faulty the "gates" open and affected cells are free to travel into neighbouring tissues. This hypothesis is supported by *in vitro* data showing that T-cad silencing leads to tumor spheroid expansion and invasion whereas overexpression preserves spheroid compaction and reduces invasion (Fig. 4A,B). Actin staining in monolayer cultures (Fig. 4C) clearly shows the distinct phenotypes of SCC after T-cad silencing (elongated, promigratory) and T-cad overexpression (spread, poorly motile).

4. The double-edged sword of T-cad loss and gain in cancer: what actually happens *in vivo*?

We used a murine xenograft model, with subcutaneous implantation of Matrigel-embedded SCC, to examine how T-cad expression affects tumor cell behaviour *in vivo.* The outcome was completely unexpected: both silencing and overexpression of T-cad promoted tumor expansion (Fig. 5A). This paradox was explained by distinct mechanisms controlling tumor expansion (Fig. 5B). T-cad silencing increased SCC proliferation via EGF receptor-dependent mechanisms. T-cad overexpression promoted intratumoral angiogenesis, attributable to the fact that T-cad-overexpressing SCC produce

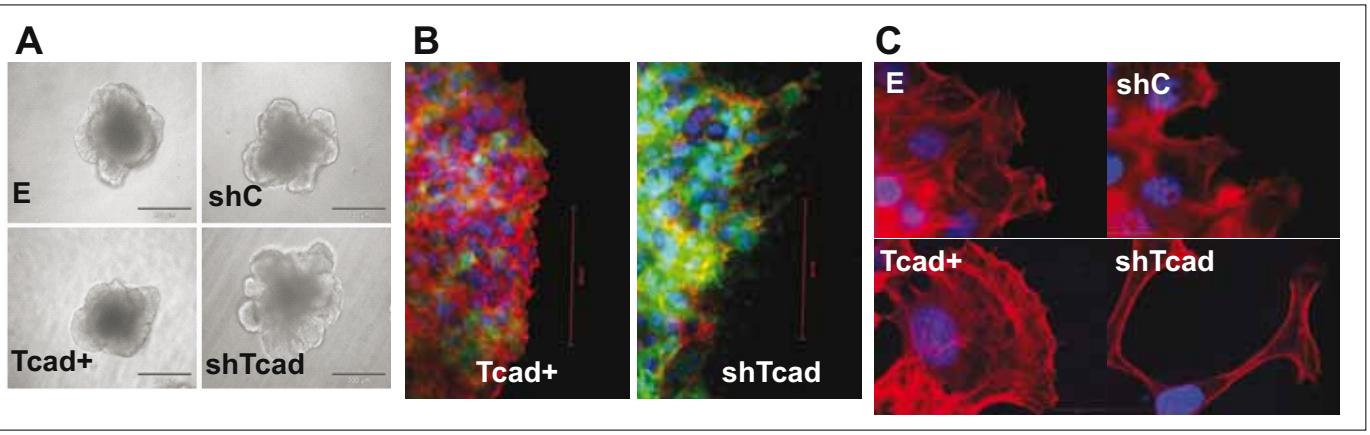


Figure 4. T-cad overexpression suppresses and silencing promotes expansion/invasion of SCC spheroids in 3D matrix. A431 cells stably transduced with lentivectors carrying T-cad gene (T-cad+) or T-cad shRNA (shTcad) or control empty (E) and scrambled shRNA (shC) vectors were cotransduced to express GFP. Spheroids were prepared and embedded in 3D gel matrix Matrigel, incubated for 36 hrs and examined by phase contrast microscopy (A) or confocal microscopy after fixation, actin cytoskeleton (TRITC-phalloidin, red) and nuclei (Hoechst, blue) (B). T-cad overexpression makes the spheroid front compact while silencing converts it to invasive phenotype. (C) TRITC-phalloidin staining in monolayer cultures shows phenotype (compact, spread after T-cad overexpression but elongated, promigratory after T-cad silencing).

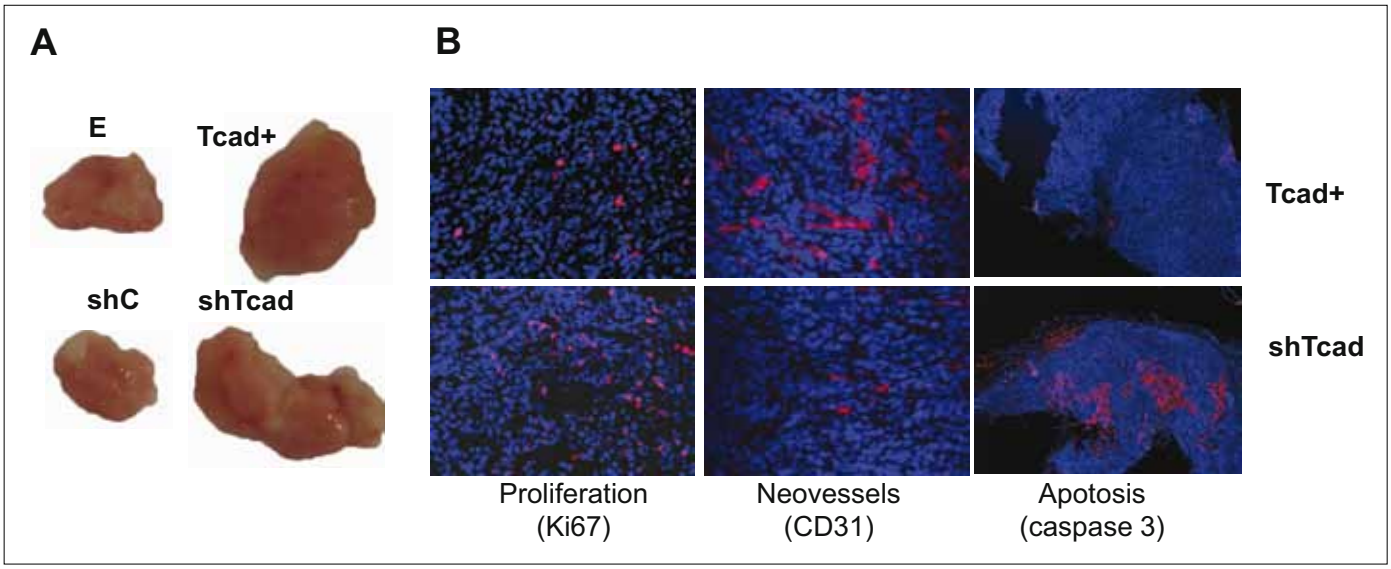


Figure 5. Effects of T-cad on SCC xenograft development. (A) Both T-cad overexpression (T-cad+) and silencing (shTcad) promote SCC growth in vivo as compared to control (E and shC) tumors. (B) Tcad+ tumors (vs shTcad) exhibit a lower proliferation index, a higher rate of intratumoral angiogenesis and lower apoptosis index (specific antigens (red), nuclei (blue)). Animal experimentation was performed in collaboration with Dr. Giandomenica Iezzi, Oncology Surgery group, Departments of Biomedicine and of Surgery.

increased amounts of VEGF-A, VEGF-C and VEGF-D, favouring ingrowth of blood and lymphatic vessels, thereby improving oxygen and nutrient delivery to the xenograft and reducing apoptosis. Thus T-cad effects *in vivo* are pleiotropic, going far beyond simple "local" control of cell growth and motility and involving interplay between different cell types.

5. Who's covering your tail? How does lipid-anchored T-cad transmit outward-inward signals?

We have identified several intracellular signaling targets of T-cad including Akt/GSK3β/mTOR in endothelial cells, Erk1/2-p38MAPK in SCC cells, and small Rho GTPases in both endothelial cells and SCC. However, one important question remains unsolved: how does a cell surface lipid-anchored protein that does not possess either a transmembrane domain or a cytoplasmic tail transmit a signal across the plasma membrane to its cytoplasmic targets?

T-cad, like GPI-anchored proteins, locates to highly dynamic, sterol- and sphingolipid-enriched microdomains termed membrane lipid rafts. Proximity to signal effector molecules also resident within raft domains is presumed to be the basis of signal transmission by GPI-linked proteins/receptors. In endothelial cells, T-cad associates with at least three proteins (integrin β3, integrin-linked kinase and chaperon protein Grp78/BiP) that enable T-cad to signal via Akt andGSK3β.

Importantly, growth factor receptors are also among proteins locating in lipid rafts. Fine tuning of receptor activation is often achieved by their rapid redistribution into various plasma membrane domains including lipid rafts or by internalization, allowing fast association of the receptor with various scaffolds and adaptors or signal attenuation. T-cad appears to function as an auxiliary "negative" regulator of growth factor receptor activity. In SCC T-cad regulates lipid raft localization of EGF receptor (EGFR): when T-cad is lost EGFR is released from raft domains, resulting in increased EGF-stimulated proliferation and motility. This action of T-cadherin in SCC may be relevant to other malignancies displaying concomitant T-cadherin loss and enhanced EGFR activity. In endothelial cells T-cad directly interacts with insulin receptor (IR) in lipid rafts and probably also with its close homologue, insulin-growth factor receptor (IGF-1R): upregulation of T-cad attenuates insulin-induced signals and angiogenic responses. T-cad expression in the endothelium normally favours reparative cell survival and angiogenesis during cardiovascular stress. However, its ability to attenuate IR signalling has implications for development of vascular insulin resistance, mani-

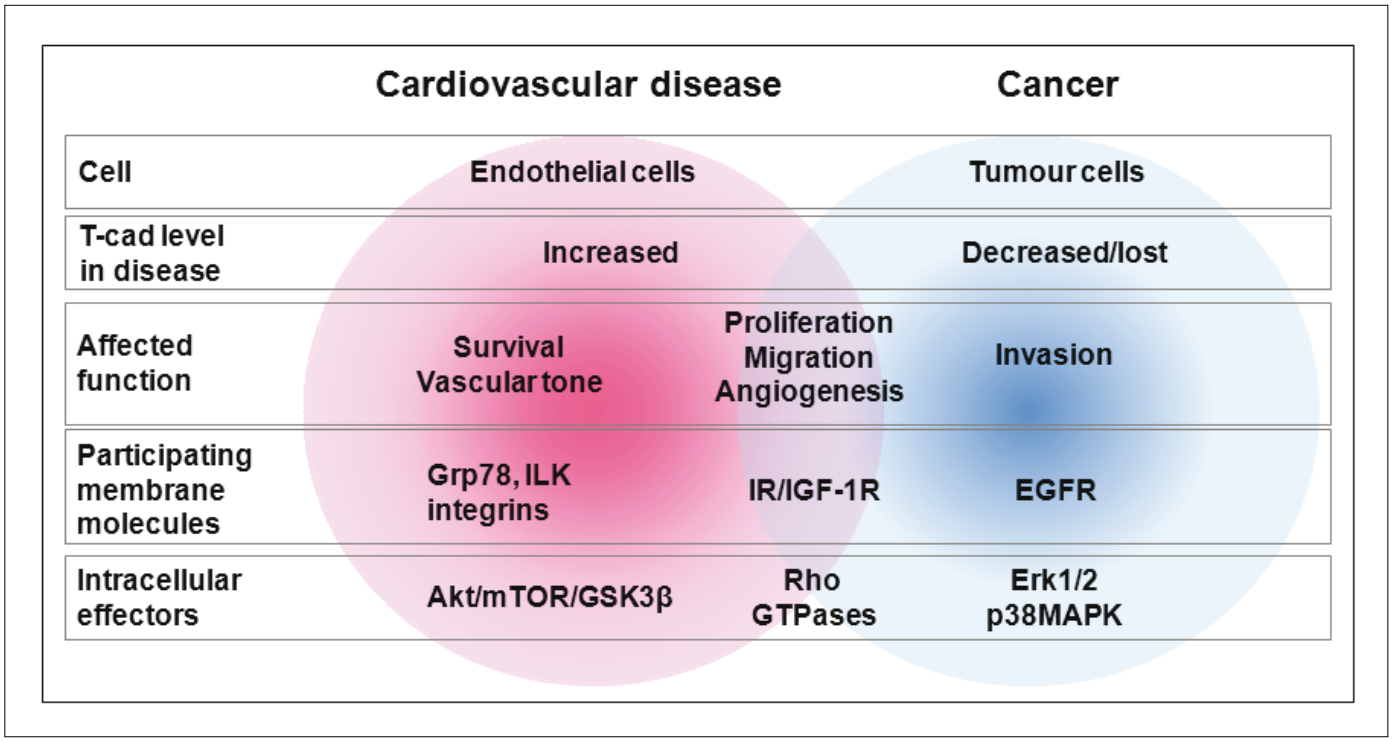


Figure 6. Current knowledge on T-cad function and involved molecules in the fields of vascular and tumor biology. Behavioural consequences of disease-associated alterations in T-cad, involved membrane molecules and signaling effectors are depicted.

fest as endothelial dysfunction, constriction, impaired insulin-dependent angiogenesis and wound healing.

Does the ability of T-cad to modulate activity of different growth factor receptors explain the multi-functionality of T-cad in different tissues and disease states? Is this an evolving paradigm?

6. General principles of T-cad functions and mechanisms: merging information from cardiovascular and cancer fields

Figure 6 provides a schematic overview of what we now know about T-cad in the contexts of cardiovascular disease and cancer. It illustrates how pieces of information from different fields of research might fit within one jigsaw puzzle that will eventually define general principles underpinning T-cad-dependent regulation of cellular functions in health and disease.

Our ongoing studies address how T-cad bridges cancer and vascular disease (abnormal angiogenesis and vascular complications of metabolic disorders). Does T-cad expression on blood and lymphatic endothelial cells and/or tumor cells influence not only tumor growth but also metastatic potential of tumor cells? Does T-cad also modulate IR/IGF-1R activity in tumor cells? This could have implications for cancer progression in association with metabolic disease: loss of T-cad expression on tumor cells may enhance insulin/IGF-1-associated tumorigenesis during diabetes/hyperinsulinemia.

Maria Philippova and Therese Resink

Declaration of Love to Vietnam:

Có chí thì nên

Where there is a will, there is a way

For the past two years, after the official retirement as a group leader of Infection biology at DBM, Regine Landmann has participated in a microbiological laboratory development project in Hanoi. Here, she describes the setting of the work, her contribution in the laboratory and what she gets in return from the people and the country.

Oxford University Clinical Research Unit (OUCRU) and National Hospital of tropical Diseases (NHTD) in Hanoi

For almost two decades, the **Oxford University Clinical Research Unit (OUCRU**, www.oucru.org) as part of the Oxford Centre for Tropical Medicine, has been developing the infrastructure and capacity to perform clinical trials and basic scientific research in Vietnam, as well as in Laos and Thailand. OUCRU units were first established in 1991 in Ho Chi Minh City. In February 2006, an OUCRU office in Hanoi was opened with support from the National Hospital for Tropical Diseases (NHTD) and the Welcome Trust. More recently, OUCRU has been approved by the Vietnamese Ministry of Health (MOH) as a Non-Governmental-Organisation.

The **OUCRU** unit Hanoi is located within NHTD, with one office for 12 people and 2 laboratories for molecular biology, cell culture and FACS work. OUCRU Hanoi is currently led by Heiman Wertheim (NL), a clinical microbiologist. He is supported by a Swedish Infectious Disease Specialist – the only western person speaking fluent Vietnamese – and an Australian immunologist. With grants from the Welcome Trust and different foundations, OUCRU supports 12 Vietnamese staff (master students, technicians, 1 PhD student, administrative staff). The main research projects of OUCRU are dengue immuno-pathogenesis, malaria transmission, tuberculosis therapy, in particular in HIV patients, *Streptococcus Suis* meningitis, *Klebsiella Pneumoniae* pneumonia, and antibiotic resistance against *Acinetobacter,* which is the most frequent microorganism in intensive care.

National Hospital of tropical Diseases (NHTD) in Hanoi

Vietnam is a densely populated country with 90 Million people and 8 times the surface of Switzerland. **NHTD** is one of three large infectious disease hospitals in the whole

OUCRU group

country and the only tertiary infectious disease hospital in Hanoi, and it receives patients from all over North Vietnam. Together with most other national hospitals, NHTD is located in Bach Mai, the largest hospital campus in the southern, poorer part of Hanoi. It has about 250 beds and 5 units in 5 floors of the building shown. a) Outpatients/emergency care, b) Intensive care c) Hepatitis, d) General infectious diseases, e) Viral and parasitic infectious diseases. The laboratory unit serves the whole hospital and comprises 4 units with about 30 employees: Clinical chemistry, molecular diagnostics, hematology and microbiology/parasitology. A high number of doctors (> 30 per unit, more men than women) are responsible of patient care. 5 older doctors (1 woman) lead the clinical units. An enthusiast young clinical microbiologist is responsible for the laboratory as a part-time (50%) job! The hospital director is a very potent doctor with tight connections to the ministry of health (MOH). NHTD is as a teaching hospital linked to Hanoi Medical University, which was founded in 1902 by the French and first led by the famous Yersin (discoverer of the bacterium causing the plague). there are many students around in the hospital at all times.

Patient admittance

Among the most striking features of NHTD are its contrasts: its rapid development and at the same time its lack of adaptation. At every one of my bimonthly visits I find locations changed, expanded, small daily tasks considerably improved; this happens through the clever initiative of individuals. Other major things remain controlled by the MOH and are unchangeable, e.g. a system of patient ID and of laboratory information management (LIMS) is still missing. Every order for the laboratory and every result is written by hand into large books; these are identical in the whole country. There are very few persons trained in microbiology, and there is no dialogue between laboratory specialists and clinicians. Progress in knowledge among technicians and laboratory doctors is very slow. Technicians are taught handcraft without any explanation, since they lack a basic technician training. Accordingly, complex machines brought in by international aid often remain unused.

My work in OUCRU and NHTD

I had been in biomedical research for 31 years. As an MD, I wanted to finish my career with work, which is closer to, and directly useful for, patients. Two factors contributed to transform the wish into a concrete plan:

Boattrip

through my daughter Lucretia, who had been working repeatedly in Vietnam, I developed an interest in this country. In 2008, while on a visit to Lucretia, I met Heiman Wertheim, the head of OUCRU, whom I knew from earlier staphylococcal work. After a one-hour meeting my plans were set:

1) Development of a rapid and easy diagnostic test for *Streptococcus suis,* which can be applied in the country side.

2) Development of the clinical microbiological laboratory to international standards.

My work is thus initiated by OUCRU, realized in NHTD, and serves to improve research at OUCRU by advancing the microbiological diagnostics of the patients, who are included in their studies.

Progress after 2 years is slow, since procedures, which are done routinely in Switzerland need a long introduction and training in Vietnam, but it is visible:

Project 1: *Streptococcus suis* causes severe systemic infection in adults exposed to infected pigs or after consumption of undercooked pig products. It is the most frequent cause of bacterial meningitis in Vietnam. *S. suis* is often misdiagnosed, due to lack of awareness and improper testing. OUCRU contributes with clinical, microbiological and PCR diagnosis to the improved detection and reporting of *S. suis* cases, and thus fostered the issue of guidance to all hospitals in Vietnam on diagnosis, treatment and prevention of *S. suis* by the Ministry of Health. However 80% of people live in the countryside with limited medical care and resources, where PCR diagnostics are impossible. Therefore we set up an ELISA for detection of *S. suis* antigen in urine. By

now antibodies are available and a sensitive and specific test has been developed. All that remains is to scale up the antibody production and to render the test field-compatible.

Project 2: First aim: accompany and shape the earlier planned structural improvements. This was the easy part, everyone was happy to support the reorganisation, because it strongly ameliorated working conditions. We moved and reinstalled everything ourselves. On this occasion I learnt how each individual Vietnamese can intensely engage himself into a task serving the group. At all times there was a lot of laughter, shouting and music.

Second aim: Teaching of good clinical laboratory practice: I asked for support by WHO and last October held a 3-day theoretical and practical course on a) collection and processing of samples, and b) SOPs for bacteriological analyses of stool, blood, and sputum including mycobacteria. A student of OUCRU translated my lectures into Vietnamese *ad hoc.* It was great fun with lots of photos, thanking of high MOH officials and awarding of certificates. The young people in the laboratory have become good friends and we go for lunch together in the market every day. What a pleasure and a new experience, BUT quality of work did not improve after that, knowledge remained on paper.

Third aim: Teaching daily practice of microbiological tests and of quality control. This is the hard part because of language problems and of actual methods, which may not identify the right germ. Under the premise that the microbiological diagnoses are correct, the major pathogens are HIV, hepatitits B and C, mycobacteria, *Klebsiellae, Streptococcus suis, Acinetobacter* in ventilated patients, *Penicillium marneffei* in HIV patients, and we see also *Plasmodium falciparum, Burkholderia pseudomallei,* tetanus, and cholera epidemics in summer. With the help of two young doctors and a lot of good will from the technicians' side, I can transfer and improve practice and knowledge. Every morning it is a great joy to go to the laboratory, since many are smart and eager practical learners. We look forward to going on together.

Fourth aim: Set up a correct antibiotic resistance testing system. First I set up a database to register the results, which, according to MOH guide lines, still have to be kept handwritten in books. The database which was updated with results since 2009 in hundreds of hours of technicians' work (!), allowed me to see the major pathogens diagnosed. After knowing the multitude of antibiotics distributed by the clinicians, a dialogue between clinicians and microbiology diagnostics started. Due to the great help of the Swedish Infectious disease colleague, an evidence-based choice of antibiotics and antibiotic resistance testing is being initiated.

And this is where I now am. After about 6 months of work in total, distributed over 2 years, we are optimistic to contribute a little bit to the quality of microbiological diagnostics to the benefit of the patients and the research at NHTD.

Hanoi and its people through the seasons

My enthusiasm for Vietnam has been transformed into admiration and love. Why?
Hanoi is a beautiful city with a lively old town and a rich French heritage e.g. in form of baguette bakeries, of alleys of trees in all streets and elegant architecture, BUT the climate is difficult, in winter humid, 10°C, grey (no heating); in summer 35° to 45°C and heavy rains with flooded streets; only early spring and late autumn are agreeable for a European.

1) People are joyful: Since I spend hours among the OUCRU and the NHTD teams, I have the privilege to immerge deeply into habits of a young, educated Vietnamese middle social class: they are loud and chat a lot about money, clothes, marriage and mobile phones. They laugh much more than we do. They are polite, but straight forward, good and bad habits are openly addressed. They are very enduring and struggle for survival under all conditions. e.g. they ride through flooded streets by motorbike, which then fails, they continue walking, arrive soaked at work, and find it normal! Most people I know have a much more difficult life than we have, but never complain: "where there is a will, there is a way". They live for the here and now.

Regine's residental neighbourhood

2) Contrasts are surprising: poor and rich, rapid cars and slow bikers, hard-working women buying vegetables at 5 am on the market, cooking for the whole family and driving long ways to work and idle men sitting a whole day behind a pile of second hand phones. Housing of families in a French 19th century palace and in one room of simple wooden homes. Eating phó in the street and exquisite fish in a beautiful restaurant with lotus flowers. Bustling traffic in the city and grazing buffalos in the field. Active and sleeping during the day: at 9 am there is a full outpatient department with busy nurses and doctors, at 1 pm doctors and nurses everywhere sleeping on chairs or on tables.

3) The language is interesting and life is colourful: Private Vietnamese lessons twice a week made it clear, that Vietnamese is very difficult to learn, but beautiful and rich. I can read everything, but still only understand spoken bits and numbers; even with a 1000 word vocabulary, Vietnamese don't understand me, because of my inadequate pronunciation. More importantly, the teacher introduces me into the secrets of Hanoian behaviour and has become a good friend. Through the lessons I learnt that truth has a different meaning than in Switzerland, depending on the context and the person addressed, there are so many modalities to express a simple observation; therefore reality has many faces. Together with the joyful Buddhism, where offers for family and luck are made on many days and in any place (at home or in a pagoda), life is very colourful.

4) The country is beautiful. Thousands of kilometres of untouched beach, tropical woods on steep hills, large tea and rice plantations, picturesque karst mountains,

Typical vietnamese food: Turtles

romantic scenes: women bare foot and with Vietnamese hats in the rice fields. I have seen very little and I hope to see more when my work is done.

My everyday life in Hanoi

Dropped alone on a chilly, grey day of January 2010 in this bustling city with bikes, motorbikes, and young people all around, was a pretty challenging experience at the age of 63. I had no orientation about the location of my flat in the city of 3 million, and immediately realized that, except for the few members of the OUCRU team, no one speaks English, neither in the street nor in the hospital. The welcome in the hospital was puzzling, "sorry, we are reconstructing". I started as a silent observer in a chaotic laboratory surrounding. I felt like a dog, that had to explore its surroundings by nose. I saw: 1) hundreds of patients and families in the hospital area, waiting, sleeping outside; 2) severely ill patients carried outdoor on weak metal stretchers; 3) families bringing a modest meal: *phó,* the noodle soup and *rau muông,* the vegetable morning glory to the in-patients 4) packed wards with 2 patients per bed; and 5) a technician bringing an open microbiology plate with bacteria to me in the corridor, look: *"Streptococcus suis."*

When leaving the hospital in the evening, I came along street restaurants and vendors with an incredible variety of seafood, fish and vegetables, fruits and flowers. I progressively ate more Vietnamese food, except for turtles and picky pork, for worms and snails; the latter I fear because we had many vibiro paramemolyticus cases in the hospital, and these bacteria live in snails. Since it was Tet (new years) time, light chains were everywhere and people were shopping big golden and red parcels.

Every weekend I spent walking for hours through the streets and markets, visiting the museums and bookshops to learn about Hanoi.

During the next visits I started doing sports with Vietnamese women, which is more fun than in Switzerland, otherwise socializing is not easy.

I read the biography of Ho Chi Minh, this being a key of understanding Vietnamese history, and many translated books from Vietnamese authors. The diary of the American Vietnam war by Sang Thuy Tram "Letzte Nacht träumte ich vom Frieden" I would recommend to every reader interested into this country.

Now, after 8 trips, I feel as if I am coming home when I arrive in Hanoi. I look forward to Vietnamese food, I have a pleasure greeting the same bread and vegetable seller around the corner from my flat and I feel happy, when I open the door to the laboratory with its friendly people.

Regine Landmann

Dissertationen

Mit der Doktorprüfung am 30. September 2011 schloss **Uta Helmrich** von der Forschungsgruppe Cell and Gene Therapy (ICFS/Departement Biomedizin USB) erfolgreich ihre Dissertationszeit ab. Das Thema ihrer Doktorarbeit lautete: "VEGF-expressing mesenchymal stem cells for improved angiogenesis in regenerative medicine – a bone tissue engineering approach".

Am 20. Oktober 2011 stellte sich **Sinan Güven** von der Forschungsgruppe Tissue Engineering (ICFS/Departement Biomedizin USB) dem Dissertationskomitee. Der Titel seiner Dissertation lautete: "Towards clinical translation of upscaled osteogenic grafts using human adipose tissue progenitors".

Seit dem 1. November 2011 darf sich **Estelle Hirzel** von der Forschungsgruppe Clinical Pharmacology (Departement Biomedizin USB) Frau Dr. nennen. Sie befasste sich in ihrer Doktorarbeit mit dem Thema: "Characterization of human bone marrow derived mesenchymal stem cells as a model for in vitro adipocytes studies".

Am 29. November 2011 konnte **Corina Kohler** von der Forschungsgruppe Gyn. Oncology (Departement Biomedizin USB) ihre Dissertation mit Erfolg beenden. Sie befasste sich in ihrer Dissertation mit dem Thema "Cell-free DNA in the Circulation as a Potential Biomarker for Breast Cancer".

Beförderungen

Venia docendi für Andreas Jehle

Die Regenz der Universität Basel hat in ihrer Sitzung am 28. September 2011 Andreas Jehle von der Forschungsgruppe Molecular Nephrology (Departement Biomedizin USB) die Venia docendi für Nephrologie erteilt. Er ist nun befugt, den Titel eines Privatdozenten zu führen.

Thierry Girard zum Titularprofessor ernannt

Der Universitätsrat der Universität Basel hat in seiner Sitzung vom 20. Oktober 2011 die Ernennung von Thierry Girard von der Forschungsgruppe Perioperative Patient Safety (Departement Biomedizin USB) zum Titularprofessor für Anästhesie genehmigt.

Preise

Swiss Bridge-Award an Jürg Schwaller

Jürg Schwaller von der Forschungsgruppe Childhood Leukemia (Departement Biomedizin USB) hat den diesjährigen Forschungspreis der Swiss Bridge-Stiftung erhalten. Als einer von drei Preisträgern erhält er 175'000 CHF für sein Projekt zur Erforschung der akuten Mixed-Lineage-Leukämie. Die Preisverleihung fand am 25. Oktober 2011 in Zürich statt.

Herzliche Gratulation an alle!

Zwei Preise an Forschungsgruppe Hepatology

Gleich zwei Preise durfte die Forschungsgruppe Hepatology (Departement Biomedizin USB) an der Jahrestagung der Schweizerischen Gesellschaft für Gastroenterology in Empfang nehmen. Michael Dill erhielt den Junior Hepatology Prize, dotiert mit 7'500 CHF, für seine Publikation in Gastroenterology 2011; 140:1021-1031, Zuzanna Makowska den Forschungspreis ebenfalls in Höhe von 7'500 CHF für ihre Publikation in Hepatology 2011; 53 (4): 1171-80.

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 January 31, 2012.

Nature Medicine nature medicine 30 October 2011, doi:10.1038/nm.2513 IF 25,4

Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells

Helga Ellingsgaard[1], Irina Hauselmann[1], Beat Schuler[2], Abdella M Habib[3], Laurie L Baggio[4], Daniel T Meier[1], Elisabeth Eppler[5], Karim Bouzakri[6], Stephan Wueest[7], Yannick D Muller[8], Ann Maria Kruse Hansen[9], Manfred Reinecke[5], Daniel Konrad[7], Max Gassmann[2], Frank Reimann[3], Philippe A Halban[6], Jesper Gromada[10], Daniel J Drucker[4], Fiona M Gribble[3], Jan A Ehses[11] & Marc Y Donath[1]

Exercise, obesity and type 2 diabetes are associated with elevated plasma concentrations of interleukin-6 (IL-6). Glucagon-like peptide-1 (GLP-1) is a hormone that induces insulin secretion. Here we show that administration of IL-6 or elevated IL-6 concentrations in response to exercise stimulate GLP-1 secretion from intestinal L cells and pancreatic alpha cells, improving insulin secretion and glycemia. IL-6 increased GLP-1 production from alpha cells through increased proglucagon (which is encoded by GCG) and prohormone convertase 1/3 expression. In models of type 2 diabetes, the beneficial effects of IL-6 were maintained, and IL-6 neutralization resulted in further elevation of glycemia and reduced pancreatic GLP-1. Hence, IL-6 mediates crosstalk between insulin-sensitive tissues, intestinal L cells and pancreatic islets to adapt to changes in insulin demand. This previously unidentified endocrine loop implicates IL-6 in the regulation of insulin secretion and suggests that drugs modulating this loop may be useful in type 2 diabetes.

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The EMBO Journal | 6 September 2011, doi: 10.1038/emboj.2011.319 | IF 10,1

Transcription factor Dlx2 protects from TGFβ-induced cell-cycle arrest and apoptosis

Mahmut Yilmaz*, Dorothea Maaß*, Neha Tiwari, Lorenz Waldmeier, Petra Schmidt, François Lehembre, Gerhard Christofori

Acquiring resistance against transforming growth factor β (TGFβ)-induced growth inhibition at early stages of carcinogenesis and shifting to TGFβ's tumour-promoting functions at later stages is a pre-requisite for malignant tumour progression and metastasis. We have identified the transcription factor distal-less homeobox 2 (Dlx2) to exert critical functions during this switch. Dlx2 counteracts TGFβ-induced cell-cycle arrest and apoptosis in mammary epithelial cells by at least two molecular mechanisms: Dlx2 acts as a direct transcriptional repressor of TGFβ receptor II (*TGFβRII*) gene expression and reduces canonical, Smad-dependent TGFβ signalling and expression of the cell-cycle inhibitor $p21^{CIP1}$ and increases expression of the mitogenic transcription factor c-Myc. On the other hand, Dlx2 directly induces the expression of the epidermal growth factor (EGF) family member betacellulin, which promotes cell survival by stimulating EGF receptor signalling. Finally, Dlx2 expression supports experimental tumour growth and metastasis of B16 melanoma cells and correlates with tumour malignancy in a variety of human cancer types. These results establish Dlx2 as one critical player in shifting TGFβ from its tumour suppressive to its tumour-promoting functions.

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PNAS | October 18, 2011, vol. 108, no. 42 | IF 9,7

PI3Kγ within a nonhematopoietic cell type negatively regulates diet-induced thermogenesis and promotes obesity and insulin resistance

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Obesity is associated with a chronic low-grade inflammation, and specific antiinflammatory interventions may be beneficial for the treatment of type 2 diabetes and other obesity-related diseases. The lipid kinase PI3Kγ is a central proinflammatory signal transducer that plays a major role in leukocyte chemotaxis, mast cell degranulation, and endothelial cell activation. It was also reported that PI3Kγ activity within hematopoietic cells plays an important role in obesity-induced inflammation and insulin resistance. Here, we show that protection from insulin resistance, metabolic inflammation, and fatty liver in mice lacking functional PI3Kγ is largely consequent to their leaner phenotype. We also show that this phenotype is largely based on decreased fat gain, despite normal caloric intake, consequent to increased energy expenditure. Furthermore, our data show that PI3Kγ action on diet-induced obesity depends on PI3Kγ activity within a nonhematopoietic compartment, where it promotes energetic efficiency for fat mass gain. We also show that metabolic modulation by PI3Kγ depends on its lipid kinase activity and might involve kinase-independent signaling. Thus, PI3Kγ is an unexpected but promising drug target for the treatment of obesity and its complications.

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PNAS PNAS Sept. 2011, doi:10.1073/pnas.1110118108 IF 9,7

Structural reorganization of the antigen-binding groove of human CD1b for presentation of mycobacterial sulfoglycolipids

Luis F. Garcia-Alles[1,2], Anthony Collmann[3], Cees Versluis[4], Buko Lindner[5], Julie Guiard[1,2], Laurent Maveyraud[1,2], Emilie Huc[1,2], Jin S. Im[6], Sebastiano Sansano[3], Thérèse Brando[1,2], Sylviane Julien[1,2], Jacques Prandi[1,2], Martine Gilleron[1,2], Steven A. Porcelli[6], Henri de la Salle[7,8,9], Albert J. R. Heck[4], Lucia Mori[3,10], Germain Puzo[1,2], Lionel Mourey[1,2], and Gennaro De Libero[3]

The mechanisms permitting nonpolymorphic CD1 molecules to present lipid antigens that differ considerably in polar head and aliphatic tails remain elusive. It is also unclear why hydrophobic motifs in the aliphatic tails of some antigens, which presumably embed inside CD1 pockets, contribute to determinants for T-cell recognition. The 1.9-Å crystal structure of an active complex of CD1b and a mycobacterial diacylsulfoglycolipid presented here provides some clues. Upon antigen binding, endogenous spacers of CD1b, which consist of a mixture of diradylglycerols, moved considerably within the lipid-binding groove. Spacer displacement was accompanied by F′ pocket closure and an extensive rearrangement of residues exposed to T-cell receptors. Such structural reorganization resulted in reduction of the A′ pocket capacity and led to incomplete embedding of the methyl-ramified portion of the phthioceranoyl chain of the antigen, explaining why such hydrophobic motifs are critical for T-cell receptor recognition. Mutagenesis experiments supported the functional importance of the observed structural alterations for T-cell stimulation. Overall, our data delineate a complex molecular mechanism combining spacer repositioning and ligandinduced conformational changes that, together with pocket intricacy, endows CD1b with the required molecular plasticity to present a broad range of structurally diverse antigens.

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Clinical Infectious Diseases Clinical Infectious Diseases Aug.18, 2011, 1058-4838 IF 8,1

John Cunningham Virus Antibody and Viremia as Predictors of Progressive Multifocal Leukoencephalopathy in HIV-1– Infected Individuals

Raphael P Viscidi[1,*], Nina Khanna[2,3], Chen S. Tan[4,5], Xiuhung Li[6], Lisa Jacobson[6], David B Clifford[7], Avindra Nath[8], Joseph B. Margolick[9], Keerti V Shah[9], Hans H Hirsch[2,3,*], Igor J Koralnik[4,5,*]

We examined whether prediagnostic John Cunningham virus (JCV) antibodies and viremia are predictors of progressive multifocal leukoencephalopathy (PML) in 83 PML cases and 240 human immunodeficiency virus (HIV) diseasematched controls. JCV viremia was not predictive of PML, but some patients showed higher anti-JCV immunoglobulin G (IgG) responses 6 months prior to diagnosis.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by lytic infection of oligodendrocytes with John Cunningham polyomavirus (JCV). PML occurs in immunosuppressed individuals with AIDS or hematological malignancies, transplant recipients, and patients treated with immunomodulatory medications for autoimmune diseases [1–3].

Clinically useful predictors for PML are lacking. We therefore performed nested case-control studies within the Multicenter-AIDS and the Swiss-HIV (human immunodeficiency virus) cohort studies (MACS and SHCS) to examine whether JCV-specific virological and serological markers are predictors of PML.

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Tissue Engineering | Tissue Engineering | Part A, Vol. 17, Numbers 17 and 18, 2011 IF 4,6

The Survey on Cellular and Engineered Tissue Therapies in Europe in 2009

Ivan Martin, Ph.D.[1], Helen Baldomero, B.Sc.[2], Chiara Bocelli-Tyndall, Ph.D.[3], Ineke Slaper-Cortenbach, Ph.D.[4], Jakob Passweg, M.D.[2], Alan Tyndall, M.D.[3]

Thanks to the coordinated efforts of four major scientific organizations, this report describes the ''novel cellular therapy'' activity in Europe for the year 2009. Fifty teams from 22 countries reported data on 814 patients using a dedicated survey, which were combined to additional 328 records reported by 55 teams to the standard European Blood and Marrow Transplantation (EBMT) database. Indications were cardiovascular (37%; 64% autologous), graft-vs.-host disease (27%; 7% autologous), musculoskeletal (17%; 98% autologous), epithelial/parenchymal (8%; 73% autologous), autoimmune (9%; 84% autologous), or neurological diseases (3%; 50% autologous). Autologous cells were used predominantly for cardiovascular (42%) and musculoskeletal (30%) disorders, whereas allogeneic cells were used mainly for graft-vs.-host disease (58%) and cardiovascular (30%) indications. Reported cell types were mesenchymal stem/stromal cells (MSC) (46%), hematopoietic stem cells (27%), chondrocytes (7%), keratinocytes (5%), dermal fibroblast (13%), and others (2%). In 59% of the grafts, cells were delivered after expansion; in 2% of the cases, cells were transduced. Cells were delivered intraorgan (46%), on a membrane or gel (29%), intravenously (16%) or using 3D scaffolds (8%). As compared to last year, the number of teams adopting the dedicated survey was 1.7-fold higher, and, with few exceptions, the collected data confirmed the captured trends. This year's edition specifically describes and discusses the use of MSC for the treatment of autoimmune diseases, due to the scientific, clinical, and economical implications of this topic.

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Plos One | PLoS one | May 2011, Vol. 6, Issue 5, e20142 IF 4,4

Meningothelial Cells React to Elevated Pressure and Oxidative Stress

Xiaorong Xin[1]*, Bin Fan[1]*, Josef Flammer[1], Neil R. Miller[2], Gregor P. Jaggi[3], Hanspeter E. Killer[3], Peter Meyer[1], Albert Neutzner[1]

Abstract

Background: Meningothelial cells (MECs) are the cellular components of the meninges enveloping the brain. Although MECs are not fully understood, several functions of these cells have been described. The presence of desmosomes and tight junctions between MECs hints towards a barrier function protecting the brain. In addition, MECs perform endocytosis and, by the secretion of cytokines, are involved in immunological processes in the brain. However, little is known about the influence of pathological conditions on MEC function; e.g., during diseases associated with elevated intracranial pressure, hypoxia or increased oxidative stress.
Methods: We studied the effect of elevated pressure, hypoxia, and oxidative stress on immortalized human as well as primary porcine MECs. We used MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) bioreduction assays to assess the proliferation of MECs in response to treatment and compared to untreated control cells. To assess endocytotic activity, the uptake of fluorescently labeled latex beads was analyzed by fluorescence microscopy.
Results: We found that exposure of MECs to elevated pressure caused significant cellular proliferation and a dramatic decrease in endocytotic activity. In addition, mild oxidative stress severely inhibited endocytosis.
Conclusion: Elevated pressure and oxidative stress impact MEC physiology and might therefore influence the microenvironment of the subarachnoid space and thus the cerebrospinal fluid within this compartment with potential negative impact on neuronal function.

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Plos One PLoS one June 2011, Vol. 6, Issue 6, e21338 IF 4,4

Mannose-Binding Lectin Deficiency Is Associated With Smaller Infarction Size and Favorable Outcome in Ischemic Stroke Patients

Michael Osthoff[1,*], Mira Katan[2,3,*], Felix Fluri[3], Philipp Schuetz[6], Roland Bingisser[4], Ludwig Kappos[3], Andreas J. Steck[3], Stefan T. Engelter[3], Beat Mueller[5], Mirjam Christ-Crain[2], Marten Trendelenburg[1]

Abstract

Background: The Mannose-binding lectin (MBL) pathway of complement plays a pivotal role in the pathogenesis of ischemia/reperfusion (I/R) injury after experimental ischemic stroke. As comparable data in human ischemic stroke are limited, we investigated in more detail the association of MBL deficiency with infarction volume and functional outcome in a large cohort of patients receiving intravenous thrombolysis or conservative treatment.

Methodology/Principal Findings: In a post hoc analysis of a prospective cohort study, admission MBL concentrations were determined in 353 consecutive patients with an acute ischemic stroke of whom 287 and 66 patients received conservative and thrombolytic treatment, respectively. Stroke severity, infarction volume, and functional outcome were studied in relation to MBL concentrations at presentation to the emergency department. MBL levels on admission were not influenced by the time from symptom onset to presentation ($p = 0.53$). In the conservative treatment group patients with mild strokes at presentation, small infarction volumes or favorable outcomes after three months demonstrated 1.5 to 2.6-fold lower median MBL levels ($p = 0.025$, $p = 0.0027$ and $p = 0.046$, respectively) compared to patients with more severe strokes. Moreover, MBL deficient patients (<100 ng/ml) were subject to a considerably decreased risk of an unfavorable outcome three months after ischemic stroke (adjusted odds ratio 0.38, $p<0.05$) and showed smaller lesion volumes (mean size 0.6 vs. 18.4 ml, $p = 0.0025$). In contrast, no association of MBL concentration with infarction volume or functional outcome was found in the thrombolysis group. However, the small sample size limits the significance of this observation.

Conclusions: MBL deficiency is associated with smaller cerebral infarcts and favorable outcome in patients receiving conservative treatment. Our data suggest an important role of the lectin pathway in the pathophysiology of cerebral I/R injury and might pave the way for new therapeutic interventions.

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Plos One PLoS one June 2011, Vol. 6, Issue 6, e21433 IF 4,4

Discordant Gene Expression Signatures and Related Phenotypic Differences in Lamin A-and A/C-Related Hutchinson-Gilford Progeria Syndrome (HGPS)

Martina Plasilova[1], Chandon Chattopadhyay[2,3], Apurba Ghosh[2], Friedel Wenzel[1], Philippe Demougin[4], Christoph Noppen[5], Nathalie Schaub[1], Gabor Szinnai[6], Luigi Terracciano[7], Karl Heinimann[1]

Abstract

Hutchinson-Gilford progeria syndrome (HGPS) is a genetic disorder displaying features reminiscent of premature senescence caused by germline mutations in the *LMNA* gene encoding lamin A and C, essential components of the nuclear lamina. By studying a family with homozygous *LMNA* mutation (K542N), we showed that HGPS can also be caused by mutations affecting both isoforms, lamin A and C. Here, we aimed to elucidate the molecular mechanisms underlying the pathogenesis in both, lamin A-(sporadic) and lamin A and C-related (hereditary) HGPS. For this, we performed detailed molecular studies on primary fibroblasts of hetero-and homozygous *LMNA* K542N mutation carriers, accompanied with clinical examinations related to the molecular findings. By assessing global gene expression we found substantial overlap in altered transcription profiles (13.7%; 90/657) in sporadic and hereditary HGPS, with 83.3% (75/90) concordant and 16.7% (15/90) discordant transcriptional changes. Among the concordant ones we observed down-regulation of *TWIST2*, whose inactivation in mice and humans leads to loss of subcutaneous fat and dermal appendages, and loss of expression in dermal fibroblasts and periadnexial cells from a $LMNA^{K542N/K542N}$ patient further confirming its pivotal role in skin development. Among the discordant transcriptional profiles we identified two key mediators of vascular calcification and bone metabolism, *ENPP1* and *OPG,* which offer a molecular explanation for the major phenotypic differences in vascular and bone disease in sporadic and hereditary HGPS. Finally, this study correlates reduced *TWIST2* and *OPG* expression with increased osteocalcin levels, thereby linking altered bone remodeling to energy homeostasis in hereditary HGPS.

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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.
Key Words: Swyer syndrome, 46,XY complete gonadal dysgenesis, SRY, gonadal mosaicism, HMG domain, c.347T>C.

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Journal of Cellular Physiology Cellular Physiology 227: 88–97, 2012 IF 3,9

Enhanced Chondrocyte Proliferation and Mesenchymal Stromal Cells Chondrogenesis in Coculture Pellets Mediate Improved Cartilage Formation

Chitrangada Acharya[1,*], Adetola Adesida[1,2,*], Paul Zajac[1], Marcus Mumme[1], Jens Riesle[3], Ivan Martin[1], and Andrea Barbero[1]

In this study, we aimed at investigating the interactions between primary chondrocytes and mesenchymal stem/stromal cells (MSC) accounting for improved chondrogenesis in coculture systems. Expanded MSC from human bone marrow (BM-MSC) or adipose tissue (AT-MSC) were cultured in pellets alone (monoculture) or with primary human chondrocytes from articular (AC) or nasal (NC) cartilage (coculture). In order to determine the reached cell number and phenotype, selected pellets were generated by combining: (i) human BM-MSC with bovine AC, (ii) BM-MSC from HLA-A2+ with AC from HLA-A2-donors, or (iii) human green fluorescent protein transduced BM-MSC with AC. Human BM-MSC and AC were also cultured separately in transwells. Resulting tissues and/or isolated cells were assessed immunohistologically, biochemically, cytofluorimetrically, and by RT-PCR. Coculture of NC or AC (25%) with BM-MSC or AT-MSC (75%) in pellets resulted in up to 1.6-fold higher glycosaminoglycan content than what would be expected based on the relative percentages of the different cell types. This effect was not observed in the transwell model. BM-MSC decreased in number (about fivefold) over time and, if cocultured with chondrocytes, increased type II collagen and decreased type X collagen expression. Instead, AC increased in number (4.2-fold) if cocultured with BM-MSC and maintained a differentiated phenotype. Chondro-induction in MSC–chondrocyte coculture is a robust process mediated by two concomitant effects: MSC-induced chondrocyte proliferation and chondrocyte-enhanced MSC chondrogenesis. The identified interactions between progenitor and mature cell populations may lead to the efficient use of freshly harvested chondrocytes for ex vivo cartilage engineering or in situ cartilage repair.

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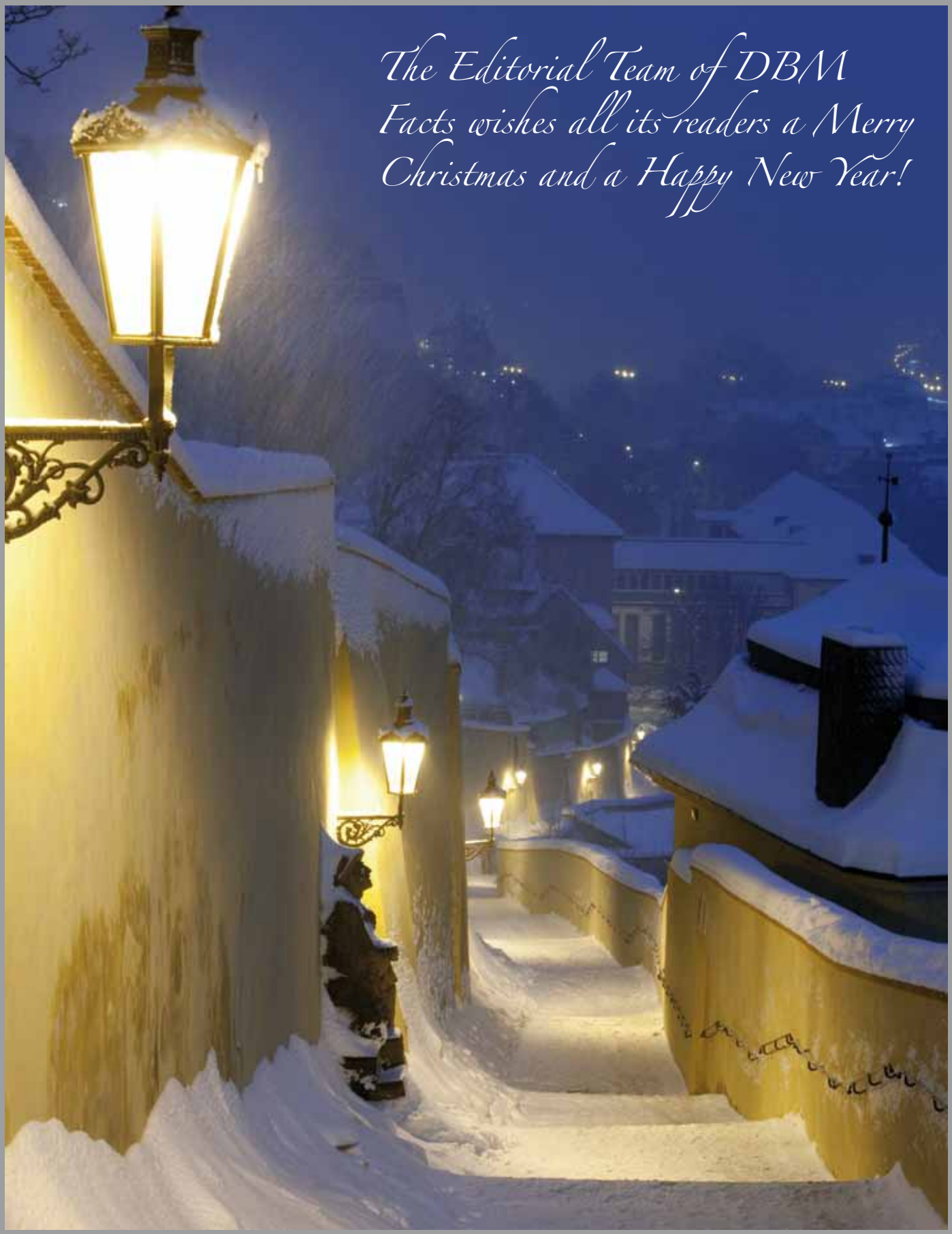

Prague (narrow stairway from hradcany castle with gas laterns during heavy snowfall)

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Ronja Ellingsgaard
Geboren am 21.10.2011

Herzlich willkommen, allerseits!

Das DBM gratuliert ganz herzlich!

Emelie Geissmann-Raff
Geboren am 09.11.2011

CHRISTMAS IN SPAIN

From mid November Spanish cities showcase cosy displays. The main streets illuminate, their shops filled with customers. In the countryside the days are short, evenings dark and long. There is not much to do in the fields... Christmas is coming. In many homes and on the squares of municipalities a *Belén* is placed, a miniature representation of the birth of Christ with shepherds, angels, domestic animals and other characters, including the *Reyes Magos* (the Three Kings of Orient) who, according to legend, came to Bethlehem to worship the newly born. Many people coming to the city to shop make a passing visit to the *Belén*. Next to it, traditionally children and adults come together to sing *villancicos* (carols) accompanied by tambourines and rustic drums. Although today the custom is seldom practiced in cities, in small towns and villages groups of children still roam the streets singing carols and asking from house to house for candy or some coins, comparable to the night of Halloween.

King Balthazar during the Cabalgata de Reyes in Navarra

The season's festivities loudly kick off the morning of December 22 with the biggest national raffle of the year, the *lotería de Navidad* (Christmas lottery). It is broadcasted live on national TV to every home, shopping center, bar, hair salon, small grocery kiosk and public space of any kind. Virtually everybody participates, either alone or with family, friends or, very often, with colleagues from work, all rather nervously awaiting the announcement of *El Gordo* (the big prize). By lunchtime, everybody knows where it went and considerable sums have been distributed to communities and entire villages. No matter what your luck was this year, for the next two weeks gifts and cards will be exchanged among family and friends, patrons will bestow an *aguinaldo* (gift consisting

of foodstuffs, sweets, wine, and champagne) on lucky employees, and there is time ahead for merriment and surprises. And anyway, the season's official closure comes with yet another big raffle on January 6: the *lotería del niño* (kids' lottery).

One may think that this period, flanked by two big money giveaways and characterized by sheer generosity, is a commercially driven invention to stimulate the economy and to renew material fantasies of adults and children alike. This is how many people feel, although it would be naïve to extend this to everyone, as many Spaniards feel alienated and even distressed by the whole thing, people in financial trouble or ideologically opposed to its consumerism or its religious character, or those who feel devoid of anybody or anything to celebrate. But, of course, Christmas celebrations far predate the birth of the *lotería de Navidad* in 1892 and the fanfare with which it is staged today. How did this festive period become implemented and maintained in our land? Evidence exists that rites around the winter solstice were already in place in pre-Roman times to welcome the new solar year. It was December 25 in the Julian calendar when Romans used to celebrate the solstice, which corresponds with the 21st in the current Gregorian calendar. It is said that these rites probably inspired an empire interested in promoting Christianity across the provinces to establish a Christian ritual on the same dates without disturbing the pagan traditions. That is how, from the fourth century, December 25 and the following twelve days became official holidays to commemorate the birth of Christ. The last of these twelve days, January 6, is the Epiphany, which in Spain celebrates the arrival of the three Magi Kings of Orient with their presents for the newly born, although according to other church traditions the symbolism, dates and interpretations change. Soon after the fourth century, the Roman Empire lost control of Hispania which was then ruled by Visigoths, followed by Arabs. Slowly Christians regained control of the peninsula over the next eight centuries, completing their conquest in 1492 when, for the first time, a unified peninsular kingdom emerged. Through the centuries, Christmas traditions were kept alive in Christian communities alongside the traditions of Moslems and Jews, two of the most significant cultures in the region. It is likely that this plurality resulted in habits' and ideas' permeating religious persuasions and shaping the country and its traditions forever.

LOS REYES MAGOS

MERCEDES DE VELILLA

Llegad, Reyes del Oriente;
la estrella que os va guiando
ya de Belén en la gruta
fija sus destellos claros;
y cuando llenos de gozo
adoréis al niño santo,
seguid por nuevos caminos,
cruzad ligeros los campos,
y atravesad las ciudades
donde os están esperando
los pequeñuelos: dormidos,
con la sonrisa en los labios,
parece que están diciendo:
¿qué traerán los Reyes Magos?

Los adurmió la esperanza,
y en el sueño, dulce y grato,
ven agrandarse, agrandarse,
las figurillas de barro
que estaban quietas y fijas
del Nacimiento en lo alto;
y por las calles obscuras
pasáis en bullicio extraño,
en ricos mantos envueltos,
sobre los caballos blancos
y en los cestos primorosos,
que en las ventanas colgaron,
dejáis los lindos juguetes
y confites delicados,
y al toque de las trompetas,
y al trote de los caballos,
cual fantasmas de la noche
vais pasando, vais pasando.

Ya pasasteis, ya pasasteis;
¡también los tiempos pasaron!
En las sendas de la vida
atrás os fuimos dejando,
y a otros reyes ofrecimos
el corazón por esclavo:
al oro, que es rey del mundo;
al amor, que es rey tirano;
al éxito, que envanece
con su pasajero aplauso;
y cuando en alas del tiempo
también se van alejando
y en el borde del camino
tristes y solos quedamos,
¡ah! cómo entonces volvemos
los ojos a lo pasado,
buscando vuestros contornos
en el imborrable cuadro
de aquella edad venturosa
que os esperaba soñando.

Porque fuisteis la inocencia
de nuestros primeros años;
porque fuisteis la caricia
de aquella bendita man
que os colocó, cuidadosa,
del Nacimiento en lo alto,
y en el cestillo de mimbres
colocó vuestro agasajo.
¡Ah! si venís todavía
como en los tiempos lejanos,
para ser de los pequeños
el regocijo y encanto,
dejad también a los grandes
de vuestros presentes algo;
dejad también a los tristes,
para el corazón, un bálsamo,
algún consuelo en el alma
y una oración en los labios;
y al dormirnos, dulces sueños
de la infancia recordando,
tal vez una blanca sombra
nos tienda amorosos brazos,
diciéndonos, como entonces:
¡ya vienen los Reyes Magos!

But back to current times. Right after the *lotería*, people prepare for two weeks of festivities. *Nochebuena* (Christmas Eve), December 24, is a typically quiet, private celebration within the family or with close friends. Many bars and restaurants close on this night, except in the big cities, where the numbers of lone clients can be considerable. On TV, the king of Spain delivers his Christmas speech, an introspective reflection on contemporary life that probably aims at bringing hope and a positive

spirit in difficult times. Many attend *misa del Gallo* (midnight mass), a most important occasion for devout Catholics, a moment of joy and desires for universal love, peace and a better world. Next day, Christmas *(Navidad)* is the most celebrated day of the entire calendar in Spain, again a day of family reunions but in a broader sense, this time including cousins or grandparents who join for a big meal or are visited before or after it. The menu for these days varies widely according to the region. Normally, it includes an *apero* and the classical two courses of Spanish meals, for example a light *jamón* soup (cured ham soup) or a delicate dish of winter vegetables such as *cardos* (cardoons) with almond sauce, followed by an entree of either shellfish, the seasons' typical fish *besugo* (sea bream, recipe included below), fowl or roasted lamb. After the meal, an extraordinary assortment of the famous Christmas sweets is brought to the table: *turrones* of various kinds, *polvorones, mazapanes, guirlaches* (all almond-and-honey desserts of Arab origin), dried fruits such as dates, apricots or raisins, caramelized almonds and pine nuts, a real festival of sweets that makes these days so beloved especially by children. A special wine and sparkling wine are always present, as is the best crockery and cutlery, reserved in many houses for such special occasions.

Asensio's sister Ana sitting on the lap of Rey Melchior

Interestingly, the 26th of December (St. Stephan) is nearly more celebrated than Christmas itself in Catalunya, whereas in the rest of the country it is not even a festive day. Once also celebrated in the Catalan-speaking regions of Valencia and the Balearic Islands, it has been lost in these areas. The period between Christmas and New Year is an ordinary time, but activity is noticeably reduced during these days, as not only students, but also professionals, may take their winter break. Apart from shopping, by far the most popular activities during the whole season are the many special music concerts or other events of a cultural nature such as art exhibits, theatre plays, contests, and kids' activities staged in cities and villages during these days. At variance with other countries, Fools' Day is celebrated on December 28 *(día de los Inocentes)*. Everybody is allowed to deceive and to make fun of others, as far as the imagination can reach, and the media are no exception. One should keep their eyes wide open and contrast any shocking information received on that day, as really wild stories are told and embarrassing situations lived by the most gullible ones.

One week after Christmas, *Nochevieja* (New Year's eve) and *Año Nuevo* (New Year) mirror the celebrations of the previous week but with no religious content attached. Across the country, many different traditions during the day make a good excuse to go out, socialize and say goodbye to the year. Massively popular in Madrid, or more precisely in

Belén in Zaragoza

the borough of Vallecas, is the San Silvestre race, a 10-km race with thousands of amateur, professional and semi-professional runners every year. In the evening it is time for more reunions and to prepare after dinner for one of the most awaited moments, the end of the year with the original Spanish ritual of the *uvas* (grapes): people in their houses prepare 12 grapes to be eaten, one by one, during the last 12 seconds of the ending year, in tandem with 12 chimes (campanadas) broadcasted live from the *Plaza del Sol* in Madrid, with a reprise one hour later in the Canary Islands. Just seconds afterwards, bottles of champagne open, fireworks burst and a long and loud party night starts, either in typical indoors venues *(cotillón)*, out in the streets, or simply at home watching a TV show filled with humour, oldies, celebrities and champagne. Almost everyone has a memory of a *Nochevieja* as being the time of their first *borrachera* (binge drinking).

Tired of celebrations? Well, if you have kids, we are not quite yet there, as under no circumstance are they going to forget theirs. The magic night of the *Reyes Magos* (Magi Kings) on the 5th of January has been longed for for weeks by the little ones, and rightfully so: they had written and posted a personal letter to the Magi weeks, perhaps months ago, to reflect on their last year, to ponder how good they were and to demand the gifts they deserve for their good deeds. They are also warned that the Kings do not like bad children, to whom they will not hand over anything but coal. In the evening, cities organize a *cabalgata*, an exuberant parade staging the arrival of the Kings: a long march of camels, elephants, slaves, chariots throwing candy, and the three kings Melchior, Gaspar and Balthazar on their thrones, smiling through their big beards and showing the excited crowds the gifts they brought from the Orient to the children. At night, in their houses, the kids clean their shoes and carefully place them at the entrance of the house or in the living room to ensure the Kings do not miss them and they know where to place their presents. The next morning, they wake up early and run to see what the Magi have left for them. This is a day of so much excitement for them, although, due to the short vacation time left afterwards, merely one day, many families opt today to move this gift day to the beginning of the vacation period to allow them more time to enjoy their gifts.

LOS REYES MAGOS

MERCEDES DE VELILLA

Arrive, Kings of the East
the star that guides you
from the grotto of Bethlehem
sets its light flashes;
and after, filled with joy
you worship the holy child,
follow new roads,
cross swiftly the fields,
and the cities
where the little ones await
for you, asleep,
their lips smiling, like saying:
What will the Kings bring?

Hope made the children asleep
and in the dream, sweet and pleasant,
they see, enlarging,
three clay figurines
quiet and still,
at the top of the Birth;
and in the dark streets
you pass through
the mutter of strangers,
wrapped in rich robes,
on white horses
and in exquisite baskets,
hung in the windows,
you let the cute toys
and delicate confections,
and to the sound of the trumpet,
and of trotting horses,
like phantoms of the night
you pass, you pass.

You passed, you passed;
Also time passed
In the path of life
you were left behind,
and to other kings we offered
our heart as slaves:
gold, king of the world;
love, tyrannical king;
success, which puffs up
with applause, his passenger;
and when the wings of time
move also away
and at the edge of the road
sad and lonely we lay,
Ah! how we then turn
our eyes to the past,
longing for your outlines
in the indelible box
of that adventurous age
when we dreamt about you

Because you were the innocence
of our early years;
you were the caress
of that blessed hand
that carefully placed you,
at the top of the Birth,
and in the wicker basket
left your treat.
Ah! if you come yet again
as in ancient times,
joy and delight,
for the little ones,
let also to us
of your presents, something;
to the sad,
a balm for the heart,
some comfort to the soul
and a prayer to our lips;
and when we sleep,
leave us sweet dreams
of childhood, remembering,
maybe a white shadow
lovingly embracing
and telling us, as then:
the Magi are coming!

Even so, this practicality has not displaced all the emotion and fantasy associated with the arrival of the *Reyes Magos*, which is still widely and pompously celebrated year after year. The Sevillian poet Mercedes de Velilla captured in her 19th century nostalgic poem *Reyes Magos* (below) the enchantment and those much-missed emotions from childhood.

The diversity of peoples, traditions and rites that have co-habited Spain throughout her history inevitably results in a rich gamut of many other peculiar regional celebrations, notoriously in rural areas, but a comprehensive list would be overwhelming. In all, this is a remarkable time, atmospheric, kind, to express a desire to share, to socialize, to remember old times, to visit old friends, to forgive and to renew. A startling need within our individuality to communicate with others is driven by a complex mix of traditions, beliefs and a great deal of fantasy and imagination. At least that is how Christmas is generally felt in Spain, where the festive and open character of her people makes this all the more easy. *Felices Fiestas* to everyone!

Asensio Gonzalez

Besugo de Navidad

1 Sea bream (2 kg), clean, scaled
2 lemons (1 sliced, 1 juiced)
3 big potatoes, peeled and cut not too thin
1 onion, thinly sliced
1 glass white wine
virgin olive oil
bread crumbs
1 bundle parsley (minced)
4 garlic cloves, whole, peeled

1. Cut 2 or 3 slits in the side of the fish and fill each with a slice of lemon. Season with salt, pepper and a sprinkle of lemon juice. Place on baking tray lightly greased with oil.

2. Fry the potatoes in plenty of hot oil, just until they start to brown. Set aside.

3. Cover the fish with onion, wine, bread crumbs and parsley. Place in a hot oven (225 C).

4. Fry the garlic cloves in a pan with 4 tablespoons of oil until they begin to brown. At this moment remove fish from oven and (carefully) pour the fried garlic, as well as the fried potatoes over it. Put back in oven.

5. Halfway through cooking baste the fish with the liquid mixture of oil, wine and water in the pan.

Cooking time depends on fish size, but total oven time should not exceed half hour. As a guide, if the side of the fish is pricked with a needle and no liquid comes out then it is ready

Men and women with brooms

I often get teased about taking up a sport in which a broom is an essential part of the equipment. But Curling is much more than sweeping the ice, and believe it or not, it is a good work out and a lot of fun.

For you to understand this you need to get the basics first. Curling is a sport where players slide heavy polished granite stones weighting almost 20 kg across a sheet of ice called a *rink* towards a circular target area. The target area or *house* is marked directly on the ice at both ends of the rink. Two teams play against each other on one rink. They take turns sliding their stones in the same direction from one end of the rink towards the house, about 35 meters away at the other end of the rink. Each team consists of 4 players sliding 2 stones each. As you might have guessed, the purpose of the game is to get your stones closer to the center of the house than your opponents. Stones that do not reach or overshoot the target area are removed immediately. The first end is completed when all players have sled their stones.

Points are scored for each stone that lies within the house and is closer to the center of the house than the closest stone of the opponent team. The game is then continued with the second *end* by playing all stones back towards the house at the other end of the rink. A game usually consists of 8 or 10 ends, depending on the competition. I have to admit that in our weekly practice we usually only play for 6 ends – this leaves us with a bit more time to get together after practice for a beer or two.

The word *curling* most likely originates from the old English verb *to curl* (drehen in German) and describes the motion of the stone when it slides across the ice on its curved path. The key technical issue of the game is the delivery of the stone. In order to induce a curved path the player needs to carefully rotate or twist the stone upon release. The rotation of the stone is also essential to keep the stone from sliding out of control. A stone that slides without rotation will get nowhere near to the spot that it was intended for. However, with a good delivery a stone can *curl around* an opposition stone or *guard* and come to rest in the center

of the house. Such a shot is called a *draw*. A shot that intends to remove other stones from the play is called a takeout and needs to be played with more speed.

To allow sliding on the ice, the sole of one curling shoe is coated with Teflon; the other one is made of non-slippery rubber. But what is it with these brooms? The curling broom, or brush, is used to influence the trajectory of the stone after it has been delivered. Sweeping the ice in the path of the stone creates a thin film of water reducing the friction beneath the stone. This allows us to increase the distance as well as to alter the curvature of the path. One of the basic strategy aspects of curling is knowing when to sweep. Therefore much of the yelling that goes on during a curling game is communication between the *sweepers* and the *skip*, who stands in the house and evaluates the path of the delivered stone. Usually the skip is the most experienced curler of the team and plays the last two, and often decisive, stones.

The sport of curling is thought to have been invented in medieval Scotland, where the climate provided good ice conditions every winter. Today, the sport is most firmly established in Canada, but is also very popular in the United States and throughout central and northern Europe. Curling has been an official sport in the Winter Olympic Games since 1998, and young teams from Asian countries like China and Japan are getting more and more competitive.

Nowadays, dedicated curling centres allow curling to be played indoors throughout the cold season or even all year round. Near Basel the Curlingzentrum Region Basel (CRB) located in Arlesheim is home to more than 500 curlers, men and women of all age. The CRB also offers a youth academy that is dedicated to getting young players into our sport. As a result of this engagement the youth teams of the CRB can compete with the best of the world. A few years ago the CRB was made accessible to wheelchair curling which enjoys great popularity.

More information about curling events and clubs in the Basel area can be found on the CRB homepage: www.curling-basel.ch

Last but not least, I would like to point out that world-class curling can be experienced from March 31 until April 8, 2012 in the St. Jakobshalle Basel during the World Men's Curling Championship. Hope to see you there!

Martin Gassmann

DBM-IT News

The DBM-iT will soon begin a new plan for 1st and 2nd level support. At that time we will distribute a circular via email. This will explain which services you can expect from us at any given time. In the future the DBM-iT must be included in the planning of certain tasks, e.g. in the purchase of complex systems (confocal microscopes etc.) by research groups or by the department. In almost all cases this will first involve the services of third parties. This could be work of a technical network or electronic nature, special hardware might have to be organised, or extra personnel resources required.

Any enquires relating to such project planning should be sent to the email address "support-dbm@unibas.ch". This email address can also be used for general enquiries when it is not possible to directly contact IT Support. However, this address should only be used in emergencies. We ask that you please always try to personally contact the relevant iT-Support first and only use this email address in emergencies.

Do you have any proposals, ideas, criticisms or questions? Please share them with us if you do. We wish to tailor our structure and services to your needs as best as possible in order to optimally serve you.

According to the URZ it is now possible for "Symantec Endpoint Protection 12" for Mac and Windows to be installed on private computers at home, with immediate effect. If you are interested in obtaining this software then please bring us a USB stick or CD and we will copy the software onto it for you. *Niklaus Vogt*

Christmas shoe boxes at the DBM

Christmas can be this beautiful! These two boxes were packed by the research group Tissue Engineering at the ICFS/DBM USB. In total 15 packets, that we know of, were collected at the DBM.

Our sincerest thanks to everyone who took part! For those who didn't, there will be another chance next year to bring some joy to the lives of children living in poverty!

First "First Year International" – the DBM greets new staff

Orientation courses are boring? That could only be the opinion of those who were unfortunately not in attendance on the 22nd November 2011, when the Department of Biomedicine opened its doors to the "First Year International" which was the first in a series of "First Year" courses that the University Hospital is offering to new staff members from a variety of career backgrounds.

Radek Skoda, as head of the DBM, opened the course in the morning with a warm welcome to all of the new arrivals to the Department of Biomedicine. He was followed by Christoph Beglinger, who, despite his overfull calendar as Dean, was able to find the time to give the attendees a personal introduction to the structure and distinctive features of the Medical Faculty of the University of Basel. Things progressed in a down to earth manner with a presentation by Thérèse Resink, research group leader of the Laboratory for Signal Transduction. Her motto: the everyday perils of working in a lab can be overcome with tolerance, common sense and a lot of humour. On this morning, she showed glimpses of her own British influenced wit, much to the enjoyment of the attendees. After the coffee break Sabrina Köhli introduced the PhD Club, by doctorates for doctorates, before Vara Prasad Kolla described the activities of the Postdoc-Club, which offers doctoral staff a plenum at the DBM. Because we can't spend all our time in ivory tower the official programme was closed with a tour through the "Humanist City of Basel" which gave everyone the chance to mix and to get to know the geography of their new home better. Those who wanted to then meet up in the Centrino to finish discussions with newly met colleagues, or just to satisfy their hunger. The DBM had shown that we are all the DBM.

Heidi Hoyermann

Christoph Beglinger

Radek Skoda

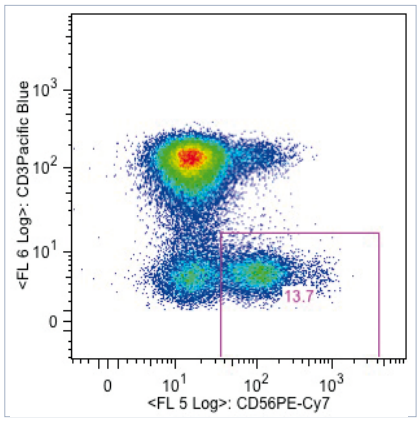
Thérèse Resink

First Year is a career specific series of courses the University Hospital of Basel is running for new staff members, organised by Human Resources and Organizational Development in cooperation with the local Human Resources administration. In this case it was organized by Thomas Reinhardt and Heidi Hoyermann.

VORSCHAU PREVIEW

In der nächsten Ausgabe . . .

... entführt uns Ed Palmer in die Welt der Transplantation Immunology

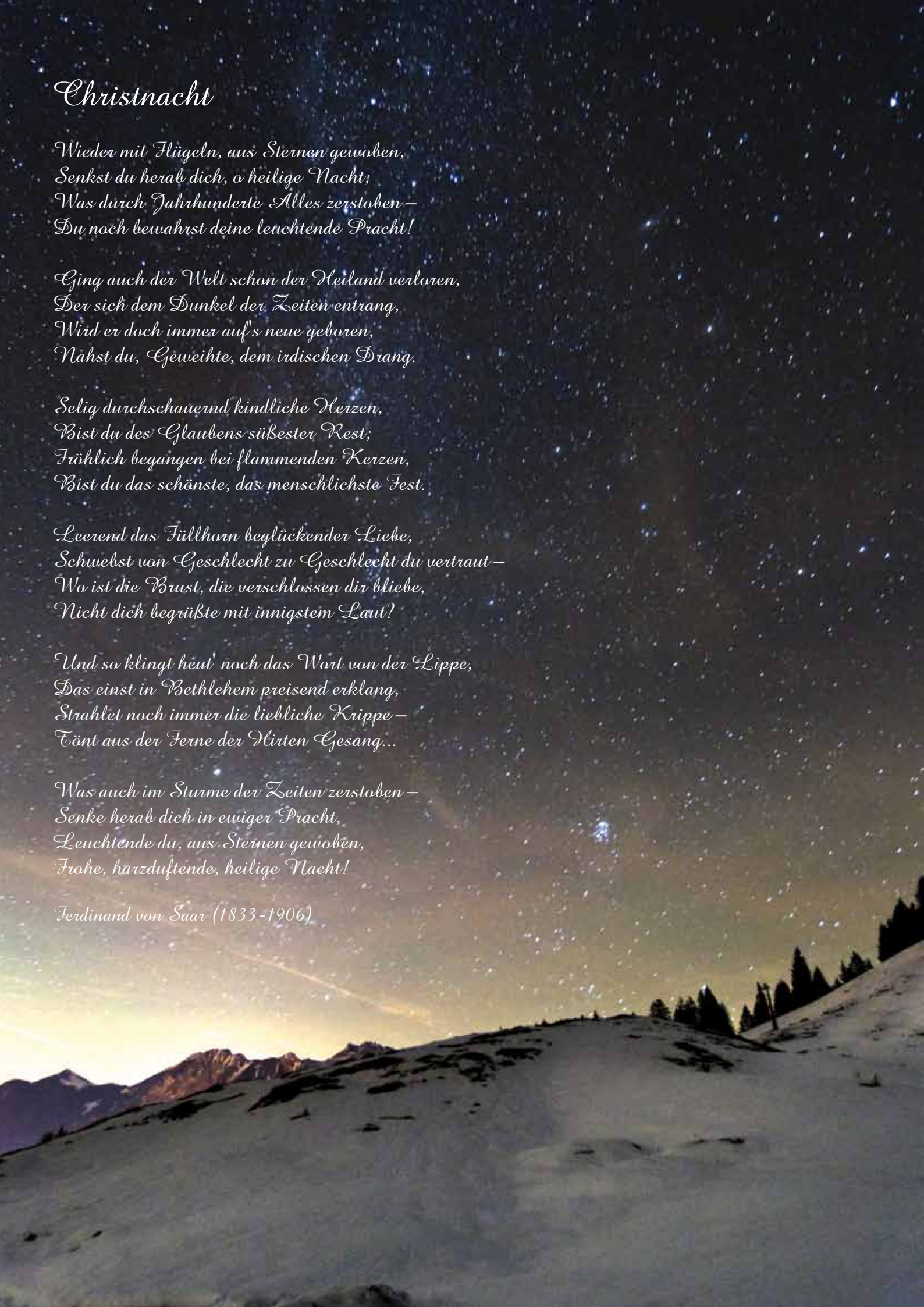


... erklärt uns Martin Stern, was Immunotherapy bedeutet

... erzählt uns Nicole Caviezel, wie spannend Volleyball sein kann

... feiern wir mit Chanchal Sur Chowdhury den Frühlingsbeginn in Indien

... geben DBM-Mitarbeitende ihre ganz persönlichen Reisetipps



Christnacht

Wieder mit Flügeln, aus Sternen gewoben,
Senkst du herab dich, o heilige Nacht;
Was durch Jahrhunderte Alles zerstoben –
Du noch bewahrst deine leuchtende Pracht!

Ging auch der Welt schon der Heiland verloren,
Der sich dem Dunkel der Zeiten entrang,
Wird er doch immer auf's neue geboren,
Nahst du, Geweihte, dem irdischen Drang.

Selig durchschauernd kindliche Herzen,
Bist du des Glaubens süßester Rest;
Fröhlich begangen bei flammenden Kerzen,
Bist du das schönste, das menschlichste Fest.

Leerend das Füllhorn beglückender Liebe,
Schwebst von Geschlecht zu Geschlecht du vertraut –
Wo ist die Brust, die verschlossen dir bliebe,
Nicht dich begrüßte mit innigstem Laut?

Und so klingt heut' noch das Wort von der Lippe,
Das einst in Bethlehem preisend erklang,
Strahlet noch immer die liebliche Krippe –
Tönt aus der Ferne der Hirten Gesang...

Was auch im Sturme der Zeiten zerstoben –
Senke herab dich in ewiger Pracht,
Leuchtende du, aus Sternen gewoben,
Frohe, harzduftende, heilige Nacht!

Ferdinand von Saar (1833-1906)