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Universitäts-Kinderspital beider Basel

Chronic cardiac ischemia: engineered cardiac tissues as therapy and as in vitro models | To find the maple sirup, trace the heavy glucose in the snow | Brazil

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Chronic cardiac ischemia: engineered cardiac tissues as therapy and as *in vitro* models from Anna Marsano



To find the maple sirup, **trace the heavy glucose in the snow** from Jordan Löliger



Research Day



Brazil from Luana Sella Motta Maia



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IMPRESSUM

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EDITORIAL



Radek Skoda Leiter DBM

Liebe Leserinnen und Leser

Passend zur endlich einziehenden wärmeren Jahreszeit liegt nun auch die Frühjahrsausgabe der DBM Facts vor Ihnen. Die letzten Monate standen im Zeichen sich verändernder Verhältnisse im Spital- und Forschungsumfeld: Die Spitalfusion zwischen den basellandschaftlichen Spitälern und dem Universitätsspital Basel zu einem Universitätsspital Nordwest hat wichtige Hürden genommen und ist auf gutem Weg. Die Neugründung des Institute of Molecular and Clinical Ophthalmology Basel (IOB), eine Kooperation des USB, der Universität Basel und Novartis, schafft eine neue Plattform für translationale Forschung, zu der auch das DBM enge Verbindungspunkte hat und die die Forschungslandschaft in Basel bereichern wird. Wir wünschen Hendrik Scholl und seinen co-Chairs viel Erfolg bei der Realisierung ihrer Vision. Ganz herzlich begrüssen wir im Kreis der Forschungsgruppenleiter Gregor Hutter, der seine SNF-Förderprofessur per 1. Mai 2018 antritt, und wünschen ihm viel Erfolg!

Der Besuch des Advisory Boards im Januar war wieder einmal eine gute Möglichkeit, unsere Organisation und Forschungsaktivitäten aus einem anderen Blickwinkel beurteilen zu lassen und hat uns wertvolle Anregungen gegeben (Seite 11).

In dieser Ausgabe stellt uns Anna Marsano die Forschungsschwerpunkte ihrer Gruppe «Cardiac Surgery and Engineering» vor (ab Seite 2). Jordan Löliger lässt uns an seinem Forschungsaufenthalt in Montreal teilhaben (ab Seite 8), bevor ab Seite 14 die neuesten Publikationen aus dem DBM folgen. Luana Sella Motta Maia nimmt uns mit in ihre Heimat Brasilien und stimmt uns ein auf die schönsten Wochen im Jahr (ab Seite 30).

Eine spannende Lektüre wünscht Ihnen Radek Skoda

Dear Readers,

The spring issue of DBM Facts that lies before you is perfectly suited to the warmer time of year that has finally arrived. The last few months have been characterised by changes in the hospital and research fields: The fusion of the Basel Land hospitals and the University Hospital Basel to form the "Universitätsspital Nordwest" has overcome important hurdles and is well under way. The formation of the Institute of Molecular and Clinical Ophthalmology Basel (IOB), a collaboration between the USB, the University of Basel and Novartis, establishes a new platform for translation research to which the DBM has close ties and which will enrich the research landscape in Basel. We wish Hendrik Scholl and his co-chairs every success in the realisation of their vision. We welcome Gregor Hutter, who takes up his SNSF professorship on May 1st 2018, to the rank of research group leader and wish him every success!

The visit of the Advisory board in January was, yet again, a good opportunity to see our organisation and research activities through other eyes and has given us valuable suggestions (page 11).

In this issue Anna Marsano introduces us to the research foci of her group, "Cardiac Surgery and Engineering" (from page 2). Jordan Löliger lets us take part in his research visit to Montreal (from page 8) before we move on to the latest publications from the DBM on page 14. Luana Sella Motta Maia brings us to her native Brazil and sets us up for the most beautiful weeks of the year (from page 30).

I hope you all find this an interesting read Radek Skoda

Chronic cardiac ischemia: engineered cardiac tissues as therapy and as *in vitro* models

Introduction

Chronic myocardial ischemia causes progressive deterioration of cardiac function often leading to end-stage heart failure. After an infarction, in the myocardial areas exposed to low-blood-perfusion, cardiomyocytes adapt their metabolism and de-differentiate toward a fetal-like phenotype in order to survive (namely, hibernating myocardium). The endogenous response establishes collateral arteries (by arteriogenesis) distal to the blockage and surgical revascularization strategies (e.g. coronary artery bypass graft, respectively) aim to restore the macrocirculation: however, often the net result is not resolutive leaving some patients with still a microcirculation dysfunction due to a rarefaction of capillary networks in the affected tissues¹. These patients plus those who are not good candidates for surgery (e.g. because of age/morbidity issues) would clearly benefit from an additional angiogenic/repair therapy to both 1. restore the dysfunctional microcirculation² and 2. rescue the damaged cardiomyocytes³. Specific induction of microvascular networks and release of cardioprotective factors in these hypo-perfused areas might be crucial to preserve cardiomyocyte survival and rescue their contraction capability in order to improve the overall cardiac function^{3,4}.

In the past 15-20 years angiogenic cell-based therapies hold a great potential for the treatment of chronic cardiac ischemia and heart failure condition. The-first-generation adult stem cell therapies typically relied on the use of a single cell type, often delivered by intra-myocardial injection⁴. Cardiac progenitors and adult stem cells have been the most investigated cells. Cardiac stem or myogenic progenitor cells mainly aim to restore the loss of cardiomyocyte of the whole damaged infarcted area, but their real contribution to differentiate into functional and integrated cardiomyocytes is still questionable and plays a minor role⁵. On the other hand, adult stem cells have been in clinical testing since early 2000s, but their beneficial effects are still controversial⁵ mainly due to the type of cells used and their low *in vivo* survival/homing. The

next-generation-cell-therapy aims to 1. combine more than one single cell type, 2. exploit mainly the therapeutic potential of the cell secretome 3. improve the in vivo cell delivery system. Along these lines, ongoing basic science and preclinical studies focus on the enhancement of stem cell secretome profile (e.g. by hypoxia). Delivery of cells following in vitro organization into tissue structures (i.e., engineered tissues) was instead recently shown to offer superior control over the targeted area and enhance the implanted cell survival, thereby sustaining the delivery of the target signals⁷. As it concerns the choice of the cell type, adipose tissue-derived mesenchymal stromal cells (ASC) have been recently identified as a very promising cell source candidate for cardiac regeneration⁵. More recently, freshly isolated adipose tissue-derived stromal vascular fraction (SVF) cells have been extensively investigated for their possible intra-operative direct application and for their heterogeneous composition. Compared to ASC, which consist almost exclusively of mesenchymal stromal cells after monolayer-expansion, freshly isolated SVF cells also include the endothelial/mural mature and progenitor cells conferring them with a possibly superior vasculogenic potential and a broader range of factor and cytokine release. SVF has been demonstrated to be singularly capable of generating a vascular-like network in vitro, and also to have a role in the stabilization of microvasculature and of the cardiac function in an established infarct heart model⁸.

The *first main research program* of my group is to develop repair therapies based on engineered tissues. For this purpose, human adipose tissue-derived stromal vascular fraction (SVF) cells are used thanks to their broad range of pro-angiogenic released factors. The working hypothesis is that *in vitro* controlled perfusion-based culture induces SVF cells to organize themselves in 3D tissue structures with a high cardiac regenerative potential by significantly enhancing their proangiogenic/cardioprotective paracrine-effects. The *second main program* of my group is to develop *in vitro* functional cardiac disease models to investigate processes of myocardial repair/regeneration in pathological-like conditions (e.g. ischemia, fibrosis). Main current research aims

(i) Engineered patches for treatment of chronic cardiac ischemia

Our ultimate goal is to generate a cell-based patch with an enhanced repair potential, particularly focused to induce angiogenesis, to rescue hibernating myocardium and restore its function in a chronic ischemic tissue. This goal is pursued by using a 3D cell culture in perfusion-based bioreactors to particularly promote the growth of the vascular cell subpopulation of the human heterogeneous adipose tissue-derived SVF (*Figure 1*)^{9,10}. The working hypothesis is that the perfusion culture might modulate the SVF composition to generate engineered tissues with an enhanced *in vitro secretome therapeutic potential* (in particular the angiogenic and cardioprotective ones).

Compared to other perfusion-culture systems, our bioreactors allow direct-flow through the scaffold-pores and combine the cell seeding with culture, leading to a future automation of the patch-production process (in collaboration with Tissue Engineering Group, I. Martin-A. Scherberich). We recently observed that culture condition could, on its o wn, modulate the initial composition of freshly isolated SVF cells in order to generate patches composed by cell population enriched for endothelial/ mural cells (Figure 2A)⁹. Moreover, in dynamic culture the endothelial cells form complex elongated capillary-like structure in vitro covered by basement membrane, positive for laminin (Figure 2B). The so generated engineered tissues function as angiogenic niches capable to remarkably accelerate the angiogenesis and supporting the formation of blood vessels by human origin grafted cells upon *in vivo* implantation (Figure 2C)⁹.

To unveil the main paracrine-driven mechanisms at the base of the repair process, functional *in vitro* cardiac models are, along with *in vivo* ischemic rat heart models,





Scheme representing the generation of SVF cell-based patches.

also implemented to rigorously investigate the cardiomyocyte response in the absence of the confounding effects of the multiple endogenous secreted factors upregulated by ischemia.

(ii) In vitro functional cardiac models

Functional *in vitro* biomimetic cardiac models are a valid tool to predict the therapeutic implanted cell/paracrine potential, drastically decreasing the number of animals used for the *in vivo* studies. In recent years, my group aimed to generate functional engineered contractile 3D micro- and macro-scale cardiac models by using key biophysical stimuli.

Direct perfusion of the culture medium through the cardiac constructs is employed to mimic the highly dense capillary network present in the myocardium to ensure the *cardiomyocyte survival* in vitro in several mm-thick engineered cardiac or skeletal muscle constructs¹¹⁻¹³.

Electrical and mechanical stimuli are the most investigated physiological stimuli, known to enhance the cardiomyocyte maturation and ultra-structural organization^{14,15} during 2D/3D cell culture.

Recently, we exploited the organ-on-a-chip technology to obtain a fine micro-environmental control over the mechanical stimulation to reproducibly engineer func-



Figure 2.

Angiogenic potential of SVF-based patches generated in static or dynamic (perfusion) condition:

A. In vitro flow cytometry-based quantification of the two specific SVF subpopulations: the pericyte and endothelial progenitor and mature cells together presented as fold of increase over the fresh SVF population (red line at 1).

B. In vitro immunofluorescence analysis for endothelial cells (CD31 in red) and basal lamina (laminin in grey) and cell nuclei (DAPI in blue). C. Immunofluorescence analysis for endothelial cells (VE-Cadherin in red), implanted human cells (HuNu in green) and cell nuclei (DAPI in blue) of SVF-patches after 28 days in vivo.

The image is adapted from Cerino G et al., Scientific Reports, 2017.

tional 3D cardiac micro-tissues. *Functional engineered cardiac micro-tissues* were reproducibly generated by both neonatal rat and human inducible-pluripotent stem cell-derived cardiomyocytes¹⁶ (healthy cardiac tissue model) and by rat cardiac fibroblasts (scar model)¹⁷.

Macro-scale automated bioreactor-based systems for the culture of cardiac tissue-engineered tissues have also been developed (*Figure 3A-B*). This innovative bioreactor design is capable, in its most advanced operational mode, of (i) applying physiological or pathologic stimuli, (ii) monitoring *in real-time* both the milieu parameters (e.g. oxygen tension, pH, temperature) and the progress in mechanical stiffness of the engineered cardiac tissues,



Figure 4.

Automated bioreactor for mechanical stimulation. A. Picture of the bioreactor, illustrating all the components: a. culture chamber; b. linear motor and position transducer; c. T, O2, CO2, pH and force sensors. B. Picture of 3-mm-thick cardiac construct (ring shape 12 mm outer diameter) during mechanical loading. In collaboration with Politecnico of Torino, Italy.



Figure 3. Functional engineered cardiac micro-tissues. Graphical abstracts of engineered micro-tissues resembling either a contractile cardiac tissue (Marsano A et al. Lab on a Chip 2016) or a cardiac scar formation (Occhetta P and Isu G, et al. Integrative Bology, 2018). In collaboration with the Politecnico of Milano, Italy.

and (iii) adapting the stimulation to their actual maturation stage during the entire culture time.

Future perspectives

As a long-term vision, we aim to engineer functional contractile patches with high angiogenic/repair potential to be used as myocardial substitutes which in addition to rescuing the hibernating myocardium could also substitute the irrevocably damaged cardiac tissue. To this end, we aim, in the future, to co-culture the human SVF (with high angiogenic potential) with a clinically relevant parenchymal cell source (e.g. already differentiated human induced-pluripotent stem cell-derived cardiomyocytes) to generate contractile cardiac engineered substitutes.

We also aim to reduce the use of animal ischemic heart models to validate the therapeutic effects of our treatment by optimizing and developing new human functional in vitro 3D models.

Anna Marsano



Portrait – The Cardiac Surgery and Engineering Group: in the second row from left to right: Dr Vladislav Borisov, Professor Martin Grapow, Professor Friedrich Eckstein, Dr Anna Marsano, Dr Giuseppe Isu, Francesca Carminati (master student), Alessia Pisanu (master student); in the first row from left to right: Diana Robles Diaz (researcher assistant), Laia Gili Sole' (PhD student), Deborah Fusco (master student), Emanuela Vitale (visiting PhD student).

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To find the maple syrup, trace the heavy glucose in the snow

Dear DBM-Members!

My name is Jordan and I am a MD-PhD student in the immunobiology group of Christoph Hess. We are active in the field of immunometabolism and specifically focus on how metabolism supports aspects of T cell biology, as well as how metabolic changes in the microenvironment impact T cell functionality. An emerging technique in the metabolism field is stable isotope tracer analysis (SITA). Thereby, the fate of stable isotope tracers (often ¹³C-labeled glucose) can be determined by mass spectrometry. Christoph gave me the opportunity to get introduced to this technique by sending me to one of our collaborators in Montreal. To make sure I would not spend all of my time bathing in the sun, he sent me to the harshest winter I ever experienced.

Lab: My three-month placement was with the group of Russell Jones at McGill University in Montreal, Canada. The lab was situated in the Goodmann Cancer Research Center, which is the big round building if one looks from the city's mountain "Mont Royal" in the direction of downtown (Fig. 1). There I worked mainly with Eric Ma (Fig. 2a), a senior PhD student in the group, who took great care of me. Together we analyzed some human samples I brought with me and I learnt the SITA workflow. I was able to make the most of my stay with some pre-



Fig. 1: View from Mont Royal on downtown Montreal. I was located in the round building at the foot of the mountain.





Fig. 2: A. Eric Ma, my main man and me in the lab. B. Our playground: metabolomics core facility with four different mass spectrometers.

emptive hands-on mass spectrometry experience with the help and patience of Urs Duthaler and the generosity of Stephan Krähenbühl from clinical pharmacology group at the DBM. I could not have had better support and I would like to take this opportunity to thank all of them.

While working with Eric and speaking with other PhD students, I realized, that we are quite privileged to do a PhD at the DBM: Canadian PhDs have high debts from their studies, work very long hours and finish in 5-7 years. I was also surprised by how lucky we are with our infrastructure and facilities. For instance, there was one cell sorter



Fig. 3: A. Typical Montreal staircase to my flat and my bike. B. Swiss dinner with my flat mates and my girlfriend at the end of my stay

at the whole cancer center and obviously, it was booked for months in advance. Only in terms of department wide availability of mass spectrometers, do we lag behind significantly.

Life in Montreal: I was very lucky to get the best Airbnb in town. My flat had the typical Montreal staircase, was well located in the "Village" and I was able to go everywhere by bike (Fig. 3a). I lived together with David (Quebecois), Romain (French) and Veejey (Mauritian) (Fig. 3b) and thanks to them I felt right at home very quickly. In my flat and in most parts of Montreal, they speak French and it took me some time until I got used to their accent. Only in the "McGill bubble", the area around McGill University, do people speak English. Montreal has great food from every corner of the world, lots of bars, live-music and street-art etc.

Winter: During my first skype call, my flatmates said to me: "Ahh you are Swiss, so you are used to -25°C", which was wrong of course. Just after Christmas, the tempera-

ture dropped to these levels and so gave my girlfriend a warm welcome when she arrived to visit me. But we would not let this deter us! We put on every piece of clothing we had and discovered the city in more detail, traveled around a bit and enjoyed the winter wonderland (Fig. 4). One of the highlights was probably skating the 7km long frozen river through Ottawa, passing below



Fig. 4: Exploring beautiful Montreal at -25°C



Fig. 5: A. Skating on the frozen river through Ottawa. B. NHL game



bridges (Fig. 5a) and observing people going to work on their skates. We also went to watch an NHL game in Canada's capital, where the Ottawa-Senators had a devastating loss of 8:2 against the Chicago-Blackhawks (Fig. 5b).

Escape winter: A lot of Canadians go to Central America to evade winter. Because it is relatively close, and thanks to my great boss, I was able to travel to Nicaragua as well. It gave me a chance to heat up again a bit before coming back to Basel. It was very unreal to experience a 60 degree temperature difference within just a few hours.

There Marius, my Swiss friend, and I rented some motocross bikes and discovered the country on dirt roads (Fig. 6). We spent our days on volcanos, in volcanos (diving lagoons) and at the beach while eating rice with beans three times a day. But after a huge flight, Managua-Miami-Montreal-Zürich, I was very happy to be back home again.

Conclusion: To sum up, if anybody has the possibility to spend some months abroad to do some research, do it! I had a great time, made new friends, saw how other labs work and learned a new technique. Montreal, I definitely will come back, but next time during summer!





Fig. 6: Heating up again in Nicaragua

DBM Research Day 2018

Fotos: Frank Neumann



Packed auditorium



Jim Norman ...



... and Ivo Touw in conversation



Paying attention (from left to right): Karl-Heinz Krause, Radek Skoda, Christian Rosenmund, Bernard Malissen and Jim Norman



Thomas Gasser, Andrea Schenker-Wicki and Werner Kübler during final discussions (from left to right)

Dissertationen

Am 28. September 2017 konnte **Elvis Ajuh** von der Forschungsgruppe "Transplantation and Clinical Virology" (Departement Biomedizin Petersplatz) seine Dissertation mit Erfolg beenden. Er befasste sich in seiner Dissertation mit dem Thema: "Functional Characterization of the Non-Coding Control Region of Human Polyomaviruses".

Am 30. Oktober 2017 stellte sich **Sime Brkic** von der Forschungsgruppe "Cell and Gene Therapy" (Departement Biomedizin Hebelstrasse) den Fragen des Dissertationskomitees. Der Titel seiner Dissertation hiess: "Molecular regulation of intussusceptive angiogenesis by ephrinB2/EphB4 signaling and its therapeutic potential".

Seit dem 15. Dezember 2017 darf sich **Julie Gamart** von der Forschungsgruppe "Developmental Genetics" (Departement Biomedizin Mattenstrasse) Frau Dr. nennen. Sie befasste sich in ihrer Doktorarbeit mit dem Thema: "SMAD4: a Multifunctional Regulator of Limb Bud Initiation and Outgrowth".

Mit der Doktorprüfung am 18. Dezember 2017 schloss Julia Manzetti von der Forschungsgruppe "Transplantation and Clinical Virology" (Departement Biomedizin Petersplatz) erfolgreich ihre Dissertationszeit ab. Das Thema ihrer Doktorarbeit lautete: "BK Polyomavirus replication in primary human renal tubular epithelial cells: Factors of early and late viral life cycle as determinants of kidney disease".

Am 19. Dezember 2017 stellte sich **Chiara Stüdle** von der Forschungsgruppe "Tissue Engineering" (Departement Biomedizin Hebelstrasse) den Fragen des Dissertationskomitees. Der Titel ihrer Dissertation hiess: "Towards osteochondral regeneration with human bone marrow derived mesenchymal stromal cells in a functionalized hydrogel system". Am 11. Januar 2018 konnte **Pradeep Sherkhane** von der Forschungsgruppe "Developmental Neurobiology and Regeneration" (Departement Biomedizin Pestalozzistrasse) seine Dissertation mit Erfolg beenden. Er befasste sich in seiner Dissertation mit dem Thema: "Calcium Extrusion Mechanisms and Dendritic Development of Cerebellar Purkinje Cells".

Am 28. Februar 2018 konnte **Tanja Blumer** von der Forschungsgruppe "Hepatology" (Departement Biomedizin Hebelstrasse) ihre Dissertation mit Erfolg beenden. Sie befasste sich in ihrer Dissertation mit dem Thema: "Negative regulation of the IFN lambda induced JAK-STAT signaling and development of PDX models from fresh human HCC biopsies".

Am 1. März 2018 stellte sich **Sébastien Pigeot** von der Forschungsgruppe "Tissue Engineering" (Departement Biomedizin Hebelstrasse) den Fragen des Dissertationskomitees. Der Titel seiner Dissertation hiess: "Hypertrophic cartilage engineering for human bone and bone marrow regeneration".

Seit dem 9. März 2018 darf sich **Giacomo Della Verde** von der Forschungsgruppe "Myocardial Research" (Departement Biomedizin Hebelstrasse) Herr Dr. nennen. Er befasste sich in seiner Doktorarbeit mit dem Thema: "Role of fms-like tyrosine kinase 3 (flt3) in cardiac health and disease ".

Auszeichnungen

Venia docendi verliehen

In ihrer Sitzung am 7. März 2018 hat die Regenz der Universität Basel Bettina Wölnerhanssen von der Forschungsgruppe "Clinical Pharmacology" (Departement Biomedizin Hebelstrasse) die Venia docendi für Experimentelle Medizin verliehen. Sie ist damit befugt, den Titel einer Privatdozentin zu führen.

Jakub Zmajkovic erhält Bruno Speck Award 2018

Für die Publikation "A Gain-of-function Mutation in EPO in Familial Erythrocytosis" Zmajkovic J, Lundberg P, Nienhold R, Torgersen ML, Sundan A, Waage A, Skoda RC, published in N Engl J Med. 378:924-930 (2018) erhält Jakub Zmajkovic von der Forschungsgruppe Experimental Hematology (Departement Biomedizin Hebelstrasse) im Namen des Steering Committee of the Basel Stem Cell Network (BSCN) und der Stiftung für Hämatologische Forschung in Basel den Bruno Speck Award 2018 für Klinische Forschung. Der Preis wird ihm im Rahmen des Jahrestreffens des BSCN übergeben.

Pfizer Forschungspreis an Bénédict Fallet und Kerstin Narr

Bénédict Fallet und Kerstin Narr, beide von der Forschungsgruppe "Transplantation and Clinical Virology" (Departement Biomedizin Petersplatz), sind von der Stiftung Pfizer Forschungspreis für ihre Publikation: Benedict Fallet, Kerstin Narr, Yusuf I. Ertuna, Melissa Remy, Rami Sommerstein, Karen Cornille, Mario Kreutzfeldt, Nicolas Page, Gert Zimmer, Florian Geier, Tobias Straub, Hanspeter Pircher, Kevin Larimore, Philip D. Greenberg, Doron Merkler and Daniel D. Pinschewer Interferon-driven deletion of antiviral B cells at the onset of chronic infection

Science Immunology (2016), doi: 10.1126/sciimmunol. aah6817 mit dem renommierten Medizin-Forschungspreis in der Kategorie "Infektiologie, Rheumatologie und Immunologie" ausgezeichnet worden.

Das DBM gratuliert ganz herzlich!

PUBLICATIONS

«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. Department of Biomedicine and University of Basel affiliation must be mentioned in authors list as published by 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 focussing on original publications. 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 June, 30, 2018.

The New England Journal of Medicine

TH NEW ENGLAND

378;10 nejm.org March 8, 2018 IF 72.406

A Gain-of-Function Mutation in EPO in Familial Erythrocytosis

Jakub Zmajkovic, M.Sc., Pontus Lundberg, Ph.D., Ronny Nienhold, Ph.D., Maria L. Torgersen, Ph.D., Anders Sundan, Ph.D., Anders Waage, M.D., Ph.D., and Radek C. Skoda, M.D.

Summary

Familial erythrocytosis with elevated erythropoietin levels is frequently caused by mutations in genes that regulate oxygen-dependent transcription of the gene en-coding erythropoietin (EPO). We identified a mutation in EPO that cosegregated with disease with a logarithm of the odds (LOD) score of 3.3 in a family with autosomal dominant erythrocytosis. This mutation, a single-nucleotide deletion (c.32delG), introduces a frame-

shift in exon 2 that interrupts translation of the main EPO messenger RNA (mRNA) transcript but initiates excess production of erythropoietin from what is normally a noncoding EPO mRNA transcribed from an alternative promoter located in intron 1. (Funded by the Gebert Rüf Foundation and others.)

From the Department of Biomedicine, Experimental Hematology, University Hospital Basel and University of Basel (J.Z., P.L., R.N., R.C.S.), and Diagnostic Hematology, University Hospital Basel (P.L.), Basel, Switzerland; and the Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology (M.L.T., A.S., A.W.), and the Department of Hematology St. Olavs Hospital (A.W.) — both in Trondheim, Norway, Address reprint requests to Dr. Skoda at radek.skoda@unibas.ch or to Dr. Waage at anders.waage@ ntnu.no.

Immunity

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Interleukin-33-Activated Islet-Resident Innate Lymphoid Cells Promote Insulin Secretion through Myeloid Cell Retinoic Acid Production

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Summary

Pancreatic-islet inflammation contributes to the failure of β cell insulin secretion during obesity and type 2 diabetes. However, little is known about the nature and function of resident immune cells in this context or in homeostasis. Here we show that interleukin (IL)-33 was produced by islet mesenchymal cells and enhanced by a diabetes milieu (glucose, IL-1 β , and palmitate). IL-33 promoted β cell function through islet-resident group 2 innate lymphoid cells (ILC2s) that elicited retinoic acid (RA)-producing capacities in macrophages and dendritic cells via the secretion of IL-13 and colony-stimulating factor 2. In turn, local RA signaled to the β cells to increase insulin secretion. This IL-33-ILC2 axis was activated after acute $\boldsymbol{\beta}$ cell stress but was defective during chronic obesity. Accordingly, IL-33 injections rescued islet function in obese mice. Our findings provide evidence that an immunometabolic crosstalk between islet-derived IL-33. ILC2s, and myeloid cells fosters insulin secretion.

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Mitochondria-Endoplasmic Reticulum Contact Sites Function as Immunometabolic Hubs that Orchestrate the Rapid Recall Response of Memory CD8⁺ T Cells

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Summary

Glycolysis is linked to the rapid response of memory CD8⁺ T cells, but the molecular and subcellular structural elements enabling enhanced glucose metabolism in nascent activated memory CD8⁺ T cells are unknown. We found that rapid activation of protein kinase B (PKB or AKT) by mammalian target of rapamycin complex 2 (mTORC2) led to inhibition of glycogen synthase kinase 3 β (GSK3 β) at mitochondria-endoplasmic reticulum (ER) junctions. This enabled recruitment of hexokinase I (HK-I)

to the voltage-dependent anion channel (VDAC) on mitochondria. Binding of HK-I to VDAC promoted respiration by facilitating metabolite flux into mitochondria. Glucose tracing pinpointed pyruvate oxidation in mitochondria, which was the metabolic requirement for rapid generation of interferon- γ (IFN- $\gamma)$ in memory T cells. Subcellular organization of mTORC2-AKTGSK3 β at mitochondria-ER contact sites, promoting HK-I recruitment to VDAC, thus underpins the metabolic reprogramming needed for memory CD8⁺ T cells to rapidly acquire effector function.

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Cocapture of cognate and bystander antigens can activate autoreactive B cells

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Autoantibodies against myelin oligodendrocyte glycoprotein (MOG) are associated with autoimmune central nervous system diseases like acute disseminated encephalomyelitis (ADEM). For ADEM, it is speculated that a preceding infection is the trigger of the autoimmune response, but the mechanism connecting the infection to the production of MOG antibodies remains a mystery. We reasoned that the ability of B cells to capture cognate antigen from cell membranes, along with small quantities of coexpressed "bystander" antigens, might enable B-cell escape from tolerance. We tested this hypothesis using influenza hemagglutinin as a model viral antigen and transgenic, MOG-specific B cells. Using flow cytometry and live and fixed cell microscopy, we show that MOG-specific B cells take up large amounts of MOG from cell membranes. Uptake of the antigen from the membrane leads to a strong activation of the capturing B cell.When influenza hemagglutinin is also present in themembrane of the target cell, it can be cocaptured with MOG by MOG-specific B cells via the B-cell receptor. Hemagglutinin and MOG are both presented to T cells, which in turn are activated and proliferate. As a consequence, MOG-specific B cells get help from hemagglutinin-specific T cells to produce anti-MOG antibodies. In vivo, the transfer of MOG-specific B cells into recipient mice after the cocapture of MOG and hemagglutinin leads to the production of class-switched anti-MOG antibodies, dependent on the presence of hemagglutinin-specific T cells. This mechanism offers a link between infection and autoimmunity.

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Cell Reports

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β Cell-Specific Deletion of the IL-1 Receptor Antagonist Impairs β Cell Proliferation and Insulin Secretion

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Summary

Interleukin-1 receptor antagonist (IL-1Ra) is elevated in the circulation during obesity and type 2 diabetes (T2D) but is decreased in islets from patients with T2D. The protective role of local IL-1Ra was investigated in pancreatic islet β cell (β IL-1Ra)-specific versus myeloid-cell (myeloIL-1Ra)-specific IL-1Ra knockout (KO) mice. Deletion of IL-1Ra in β cells, but not in myeloid cells, resulted in diminished islet IL-1Ra expression. Myeloid cells were not the main source of circulating IL-1Ra in obesity. β IL-1Ra KO

mice had impaired insulin secretion, reduced β cell proliferation, and decreased expression of islet proliferation genes, along with impaired glucose tolerance. The key cell-cycle regulator E2F1 partly reversed IL-1 β -mediated inhibition of potassium channel *Kir6.2* expression and rescued impaired insulin secretion in IL-1Ra knockout islets. Our findings provide evidence for the importance of β cell-derived IL-1Ra for the local defense of β cells to maintain normal function and proliferation.

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Notch2 Signaling Maintains NSC Quiescence in the Murine Ventricular-Subventricular Zone

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Summary

Neurogenesis continues in the ventricular-subventricular zone (V-SVZ) of the adult forebrain from quiescent neural stem cells (NSCs). V-SVZ NSCs are a reservoir for new olfactory bulb (OB) neurons that migrate through the rostral migratory stream (RMS). To generate neurons, V-SVZ NSCs need to activate and enter the cell cycle. The mechanisms underlying NSC transition from quiescence to activity are poorly understood. We show that Notch2, but not Notch1, signaling conveys quiescence to V- SVZ NSCs by repressing cell-cycle-related genes and neurogenesis. Loss of Notch2 activates quiescent NSCs, which proliferate and generate new neurons of the OB lineage. Notch2 deficiency results in accelerated V-SVZ NSC exhaustion and an aging-like phenotype. Simultaneous loss of Notch1 and Notch2 resembled the total loss of Rbpj-mediated canonical Notch signaling; thus, Notch2 functions are not compensated in NSCs, and Notch2 is indispensable for the maintenance of NSC quiescence in the adult V-SVZ.

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ONCOIMMUNOLOGY

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The T cell repertoire in tumors overlaps with pulmonary inflammatory lesions in patients treated with checkpoint inhibitors

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Abstract

Cancer immunotherapy with antibodies targeting immune checkpoints such as the PD-1/PD-L1 pathway have emerged as breakthrough treatment for multiple solid tumors with high response rates and durable remissions. Despite the benefit for patients and encouraging safety profile, severe inflammatory reactions are observed in some patients. Such immune-related adverse events (irAEs) frequently lead to temporary or permanent cessation of the treatment and require systemic immunosuppression yet underlying mechanisms of irAEs are not known in detail. Here, we describe the T cell-mediated immune reaction in irAE lesions of four patients that developed pneumonitis during therapy with a PD-1 blocking antibody. Immunohistochemical analysis was performed to map the environment of the inflammatory lesions. Tumor infiltrating T cell clones were identified by sequencing the T cell receptor, and comparison with clones from peripheral blood or secondary lymphoid organs. A significant overlap of clones infiltrating irAE lesions and tumors was found. The most prevalent clones were also expanded in peripheral blood, but only a minor fraction of clonal overlap was found. Our findings suggest that irAE lesions in patients under PD-1 blockade are infiltrated by T cells with similar specificity as tumor-infiltrating T cells. These results raise the possibility that the immune response is elicited in these patients against antigens shared by the tumor and distant organs affected by irAEs.

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Dimethyl fumarate influences innate and adaptive immunity in multiple sclerosis

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Abstract

Introduction: The mode of action of dimethyl fumarate (DMF), an immunomodulatory treatment for relapsing-remitting multiple sclerosis (RRMS), has not yet been fully elucidated. While in-vitro experiments and animal studies suggest effects on immune cell survival, proliferation, migration and oxidative stress response, corresponding observations from human studies are lacking. This study aims to characterize ex-vivo and in-vivo effects in a cohort of DMF treated RRMS patients.

Methods: Blood samples were collected from twenty well-characterized RRMS patients at baseline and after 3, 6 and 12 months of DMF treatment and an age- and gender-matched cohort of 20 healthy individuals at 0 and 3 months. Leukocyte subpopulations, immunoglobulin levels and cytokine secretion were measured. T cells were assessed for their levels of reactive oxygen species (ROS), metabolic status and their proliferative capacity. Levels of antioxidants were determined in serum by mass spectrometry. Responses of monocyte activation markers as well as NFkB and MAPK pathways to DMF were analysed.

Results: Upon DMF treatment, all lymphocyte subpopulations dropped significantly over the course of 12 months with cytotoxic and effector T cells being affected most significantly. DMF induced cell death and inhibited proliferation of T cells in-vitro. Interestingly, this anti-proliferative effect decreased under treatment. In-vivo DMF treatment led to decreased T cell glycolysis and higher turn-over of antioxidants. In line with these results a significant increase of cytosolic ROS levels after 3 months treatment was detected in T cells. In-vitro DMF treatment reduced NFkB (p65) translocation to the nucleus and MAPK (p38) levels decreased upon stimulation with monomethyl fumarate (MMF) in-vitro and ex-vivo. Consequently, the expression of co-stimulatory molecules like CD40 and CD150 was decreased in antigen presenting cells both in-vitro and ex-vivo.

Conclusion: This study translates knowledge from in-vitro and animal studies on DMF into the clinical setting. Our data suggest that DMF not only alters lymphocyte composition, but also has profound effects on proliferation and induces oxidative stress in T cells. It also acts on innate immunity by reducing the activation status of antigen presenting cells (APCs) via NFkB and MAPK inactivation.

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Mechanisms of hepatotoxicity associated with the monocyclic β -lactam antibiotic BAL30072

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Abstract

BAL30072 is a new monocyclic β -lactam antibiotic under development which provides a therapeutic option for the treatment of severe infections caused by multi-drug-resistant Gram-negative bacteria. Despite the absence of liver toxicity in preclinical studies in rats and marmosets and in single dose clinical studies in humans, increased transaminase activities were observed in healthy subjects in multiple-dose clinical studies. We, therefore, initiated a comprehensive program to find out the mechanisms leading to hepatocellular injury using HepG2 cells (human hepatocellular carcinoma cell line), HepaRG cells (inducible hepatocytes derived from a human hepatic progenitor cell line), and human liver microtissue preparations. Our investigations demonstrated a concentration- and timedependent reduction of the ATP content of BAL30072- treated HepG2 cells and liver microtissues. BAL30072 impaired oxygen consumption by HepG2 cells at clinically relevant concentrations, inhibited complexes II and III of the mitochondrial electron transport chain, increased the production of reactive oxygen species (ROS), and reduced the mitochondrial membrane potential. Furthermore, BAL 30072 impaired mitochondrial fatty acid metabolism, inhibited glycolysis, and was associated with hepatocyte apoptosis. Co-administration of N-acetyl-L-cysteine partially protected hepatocytes from BAL30072-mediated toxicity, underscoring the role of oxidative damage in the observed hepatocellular toxicity. In conclusion, BAL30072 is toxic for liver mitochondria and inhibits glycoly-

sis at clinically relevant concentrations. Impaired hepatic mitochondrial function and inhibition of glycolysis can explain liver injury observed in human subjects receiving long-term treatment with this compound. **Keywords** Monocyclic β -lactams · Mitochondrial toxicity · Glycolysis · Reactive oxygen species (ROS) · Hepatotoxicity

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BSO	Buthionine sulphoximine
CYP	Cytochrome P450
DILI	Drug-induced liver injury
DMSO	Dimethylsulfoxide
DPBS	Dulbecco's phosphate buffered saline
ECAR	Extracellular acidification rate

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Opioid-induced inhibition of the human 5-HT and noradrenaline transporters *in vitro*: link to clinical reports of serotonin syndrome

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BACKGROUND AND PURPOSE Opioids may inhibit the 5-HT transporter (SERT) and the noradrenaline transporter (NET). NET inhibition may contribute to analgesia, and SERT inhibition or interactions with 5-HT receptors may cause serotonergic toxicity. However, the effects of different opioids on the human SERT, NET and 5-HT receptors have not been sufficiently studied.

EXPERIMENTAL APPROACH We determined the potencies of different opioids to inhibit the SERT and NET *in vitro* using human transporter-transfected HEK293 cells. We also tested binding affinities at $5 \cdot HT_{1A'}$ 5-HT_{2A} and 5-HT_{2C} receptors. Additionally, we assessed clinical cases of the serotonin syndrome associated with each opioid reported by PubMed and a World Health Organization database.

KEY RESULTS Dextromethorphan, I(R)-methadone, racemic methadone, pethidine, tramadol and tapentadol inhibited the SERT at or close to observed drug plasma or estimated brain concentrations in patients. Tapentadol was the most potent NET inhibitor. Pethidine, tramadol, I(R)-methadone, racemic methadone, dextromethorphan and *O*-desmeth-yltramadol also inhibited the NET. 6-Monoacetylmorphine, buprenorphine, codeine, dihydrocodeine, heroin, hydrocodone, hydromorphone,

morphine, oxycodone and oxymorphone did not inhibit the SERT or NET. Fentanyl interacted with $5-HT_{1A}$ receptors and methadone, pethidine and fentanyl with $5-HT_{2A}$ receptors, in the lowmicromolar range. Opioidsmost frequently associated with the serotonin syndrome are tramadol, fentanyl, tapentadol, oxycodone, methadone and dextromethorphan.

CONCLUSIONS AND IMPLICATIONS Some synthetic opioids interact with the SERT and NET at potentially clinically relevant concentrations. SERT inhibition by tramadol, tapentadol, methadone, dextromethorphan and pethidine may contribute to the serotonin syndrome. Direct effects on $5-HT_{1A}$ and/or $5-HT_{2A}$ receptors could be involved with methadone and pethidine.

Abbreviations DAT, dopamine transporter; ICSR, Individual Case Safety Report; MDMA, 3,4-methylenedioxymethamphetamine; NET, noradrenaline transporter; SERT, 5-HT transporter

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Advanced Healthcare Materials

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Scaffold Composition Determines the Angiogenic Outcome of Cell-Based Vascular Endothelial Growth Factor Expression by Modulating Its Microenvironmental Distribution

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Delivery of genetically modified cells overexpressing Vascular Endothelial Growth Factor (VEGF) is a promising approach to induce therapeutic angiogenesis in ischemic tissues. The effect of the protein is strictly modulated by its interaction with the components of the extracellular matrix. Its therapeutic potential depends on a sustained but controlled release at the microenvironmental level in order to avoid the formation of abnormal blood vessels. In this study, it is hypothesized that the composition of the scaffold plays a key role in modulating the binding, hence the therapeutic effect, of the VEGF released by 3D-cell constructs. It is found that collagen sponges, which poorly bind VEGF, prevent the formation of localized hot spots of excessive concentration, therefore, precluding the development of aberrant angiogenesis despite uncontrolled expression by a genetically engineered population of adipose tissue-derived stromal cells. On the contrary, after seeding on VEGF-binding egg-white scaffolds, the same cell population caused aberrantly enlarged vascular structures after 14 d. Collagen-based engineered tissues also induced a safe and efficient angiogenesis in both the patch itself and the underlying myocardium in rat models. These findings open new perspectives on the control and the delivery of proangiogenic stimuli, and are fundamental for the vascularization of engineered tissues/organs.

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<u>Neuropharmacology</u>

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GABA_B receptor subtypes differentially regulate thalamic spindle oscillations

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Abstract

Following the discovery of GABA_B receptors by Norman Bowery and colleagues, cloning and biochemical efforts revealed that GABA_B receptors assemble multi-subunit complexes composed of principal and auxiliary subunits. The principal receptor subunits GABA_{B1a}, GABA_{B1b} and GABA_{B2} form two heterodimeric GABA_{B(1a,2)} and GABA_{B(1b,2)} receptors that can associate with tetramers of auxiliary KCTD (K⁺ channel tetramerization domain) subunits. Experiments with subunit knock-out mice revealed that GABA_{B(1b,2)} receptors activate slow inhibitory postsynaptic currents (sIP-SCs) while GABA_{B(1a,2)} and GABA_{B(1b,2)} and GABA_{B(1a,2)} receptors and inhibit glutamate release. Both GABA_{B(1a,2)} and GABA_{B(1b,2)} receptors can serve as autoreceptors and inhibit GABA release. Auxiliary KCTD subunits regulate the duration of sIPSCs and scaffold effector channels at the receptor. GA

 BA_{B} receptors are well known to contribute to thalamic spindle oscillations. Spindles are generated through alternating burst-firing in reciprocally connected glutamatergic thalamocortical relay (TCR) and GABAergic thalamic reticular nucleus (TRN) neurons. The available data implicate postsynaptic GABA_B receptors in TCR cells in the regulation of spindle frequency. We now used electrical or optogenetic activation of thalamic spindles and pharmacological experiments in acute slices of knock-out mice to study the impact of GABA_{B(11,2)} and GABA_{B(11,2)} receptors on spindle oscillations. We found that selectively GABA_{B(11,2)} heteroreceptors at TCR to TRN cell synapses regulate oscillation strength, while GABA_{B(11,2)} receptors control oscillation frequency. The auxiliary subunit KCTD16 influences both oscillation strength and frequency, supporting that KCTD16 regulates network activity through GABA_{B(11,2)} and GABA_{B(11,2)} receptors.

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Neurosurgery

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Intended Near-Total Removal of Koos Grade IV Vestibular Schwannomas: Reconsidering the Treatment Paradigm

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BACKGROUND: The goals of treating Koos grade IV vestibular schwannomas are to relieve brainstem compression, preserve or restore neurological function, and achieve long-term tumor control while minimizing tumor- and treatment-related morbidity.

OBJECTIVE: To propose a treatment paradigminvolving the intentional near-total removal of Koos grade IV vestibular schwannomas, in which a small amount of residual tumor is not dissected off the cisternal portion of the facial nerve. Patients are then followed by a wait-and-scan approach. Any subsequent volumetric progression of the residual tumor is treated with radiosurgery.

METHODS: This is a case series of 44 consecutive unselected patients who underwent intended near-total resection of a Koos grade IV vestibular schwannoma through a retrosigmoid approach from January 2009 to December 2015. Pre- and postoperative volumetric analyses were performed on routine magnetic resonance imaging sequences (constructive interference in steady state and gadolinium-enhanced T1-weighted sequence).

RESULTS: The mean preoperative tumor volume was 10.9 cm³. The mean extent of resectionwas 89%. At the last clinical follow-up, facial nerve

functionwas good [House and Brackmann (HB) I-II] in 89%, fair (HB III) in 9%, and poor (HB IV-VI) in 2% of the patients. At the last radiological follow-up, the residual tumor had become smaller or remained the same size in 84% of patients. Volumetric progression was negatively correlated with the original extent of resection and positively correlated with post-operative residual tumor volume (P = .01, P < .001, respectively).

CONCLUSION: Intended near-total removal results in excellent preservation of facial nerve function and has a low recurrence rate. Any progressive residual tumor may be treated by radiosurgery.

KEY WORDS: Vestibular schwannoma, Koos grade IV, Intended near-total resection, Facial nerve preservation surgery, Facial nerve outcome

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The Journal of Immunology

A Immunology

2018, 200: 2489–2501 IF 4.587

Highly Efficient and Versatile Plasmid-Based Gene Editing in Primary T Cells

Kornete M¹, Marone R¹, Jeker LT².

Adoptive cell transfer is an important approach for basic research and emerges as an effective treatment for various diseases, including infections and blood cancers. Direct genetic manipulation of primary immune cells opens up unprecedented research opportunities and could be applied to enhance cellular therapeutic products. In this article, we report highly efficient genome engineering in primary murine T cells using a plasmid-based RNA-guided CRISPR system. We developed a straightforward approach to ablate genes in up to 90% of cells and to introduce precisely targeted single nucleotide polymorphisms in up to 25% of the transfected primary T cells. We used gene editing–mediated allele switching to quantify homology-directed repair, systematically optimize experimental parameters, and map a native B cell epitope in primary T cells. Allele switching of a surrogate cell surface marker can be used to enrich cells, with successful simultaneous editing of a second gene of interest. Finally, we applied the approach to correct two disease-causing mutations in the *Foxp3* gene. Repairing the cause of the scurfy syndrome, a 2-bp insertion in *Foxp3*, and repairing the clinically relevant Foxp3^{k276x} mutation restored Foxp3 expression in primary T cells.

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Biochemical Pharmacology

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Cathepsin S inhibition suppresses autoimmune-triggered inflammatory responses in macrophages

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Abstract

In several types of antigen-presenting cells (APCs), Cathepsin S (CatS) plays a crucial role in the regulation of MHC class II surface expression and consequently influences antigen (Ag) presentation of APCs to CD4+ T cells. During the assembly of MHC class II-Ag peptide complexes, CatS cleaves the invariant chain p10 (Lip10) - a fragment of the MHC class IIassociated invariant chain peptide. In this report, we used a selective, high-affinity CatS inhibitor to suppress the proteolytic activity of CatS in lymphoid and myeloid cells. CatS inhibition resulted in a concentrationdependent Lip10 accumulation in B cells from both healthy donors and patients with systemic lupus erythematosus (SLE). Furthermore, CatS inhibition led to a decreased MHC class II expression on B cells, monocytes, and proinflammatory macrophages. In SLE patient-derived peripheral blood mononuclear cells, CatS inhibition led to a suppressed secretion of IL-6, TNF α , and IL-10. In a second step, we tested the effect of CatS inhibition on macrophages being exposed to patient-derived autoantibodies against C1q (anti-C1q) that are known to be associated with severe lupus nephritis. As shown previously, those SLE patient-derived high-affinity anti-C1q bound to immobilized C1q induce a proinflammatory phenotype in macrophages. Using this human in vitro model of autoimmunity, we found that CatS inhibition reduces the inflammatory responses of macrophages as demonstrated by a decreased secretion of proinflammatory cytokines, the downregulation of MHC class II and CD80. In summary, we can show that the used CatS inhibitor is able to block Lip10 degradation in healthy donor- and SLE patient-derived B cells and inhibits the induction of proinflammatory macrophages. Thus, CatS inhibition seems to be a promising future treatment of SLE.

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Scientific Reports

SCIENTIFIC **REPORTS**

(2018) 8:636 IF 4.259

Over-expression of a retinol dehydrogenase (SRP35/DHRS7C) in skeletal muscle activates mTORC2, enhances glucose metabolism and muscle performance

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SRP-35 is a short-chain dehydrogenase/reductase belonging to the DHRS7C dehydrogenase/ reductase family 7. Here we show that its over-expression in mouse skeletal muscles induces enhanced muscle performance in vivo, which is not related to alterations in excitationcontraction coupling but rather linked to enhanced glucose metabolism. Over-expression of SRP-35 causes increased phosphorylation of Akt₅₄₇₃, triggering plasmalemmal targeting of GLUT4 and higher glucose uptake into muscles. SRP-35 signaling involves RAR α and RAR γ (non-genomic effect), PI3K and mTORC2. We also demonstrate that all-trans retinoic acid, a downstream product of the enzymatic activity of SRP-35, mimics the effect of SRP-35 in skeletal muscle, inducing a synergistic effect with insulin on AKT_{s473} phosphorylation. These results indicate that SRP-35 affects skeletal muscle metabolism and may represent an important target for the treatment of metabolic diseases.

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Scientific Reports

SCIENTIFIC REPORTS

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Targeting Insulin-Like Growth Factor-I and Extracellular Matrix Interactions in Melanoma Progression

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Insulin-like growth factor (IGF)-I binds to the ECM protein vitronectin (VN) through IGF binding proteins (IGFBPs) to enhance proliferation and migration of skin keratinocytes and fibroblasts. Although evidence exists for the role of individual components of the complex (IGF-I, IGFBP-3 and VN), the cellular functions stimulated by these proteins together as a complex remains un-investigated in melanoma cells. We report here that the IGF-I:IGFBP-3:VN trimeric complex stimulates a dosedependent increase in the proliferation and migration of WM35 and Sk-MEL28 melanoma cells. In 3D Matrigel™ and hydrogel cultures, both cell lines formed primary tumor-like spheroids, which increased in size in a dose-dependent man

ner in response to the trimeric complex. Furthermore, we reveal IGFBP-3:VN protein complexes in malignant melanoma and squamous cell carcinoma patient tissues, where the IGFBP-3:VN complex was seen to be predominantly tumor cell-associated. Peptide antagonists designed to target the binding of IGF-1:IGFBP-3 to VN were demonstrated to inhibit IGF-1:IGFBP- 3:VN-stimulated cell migration, invasion and 3D tumor cell growth of melanoma cells. Overall, this study provides new data on IGF:ECM interactions in skin malignancies and demonstrates the potential usefulness of a growth factor:ECM-disrupting strategy for abrogating tumor progression.

Journal of Biological Chemistry

BC BIOLOGIC

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SOCS1 is an inducible negative regulator of interferon λ (IFN- λ)–induced gene expression *in vivo*

Blumer T¹, Coto-Llerena M¹, Duong FHT^{1*}, Heim MH^{1,2*}.

Abstract

Type I (α and β) and type III (λ) interferons (IFNs) are induced upon viral infection through host sensory pathways that activate IFN regulatory factors (IRFs) and nuclear factor kB. Secreted IFNs induce autocrine and paracrine signalling through the JAK-Stat pathway leading to the transcriptional induction of hundreds of IFN stimulated genes (ISGs), amongst them sensory pathway components such as cGAS, STING, RIG-I, MDA5 and the transcription factor IRF7 that enhance the induction of IFN α s and IFN λ s. This positive feedback loop enables a very rapid and strong host response, which at some point has to be controlled by nega-

tive regulators to maintain tissue homeostasis. Type I IFN signalling is controlled by the inducible negative regulators suppressor of cytokine signalling 1 (SOCS1), SOCS3 and ubiquitinspecific peptidase 18 (USP18). The physiological role of these proteins in IFN λ signalling has not been clarified. Here we used knockout cell lines and mice to show that IFN λ signalling is regulated by SOCS1, but not by SOCS3 or USP18. These differences were the basis for distinct kinetic properties of type I and III IFNs. We found that IFN α signalling is transient and becomes refractory after hours, whereas IFN λ provides a long-lasting ISG induction.

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JVH

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In vivo analysis at the cellular level reveals similar steatosis induction in both hepatitis C virus genotype 1 and 3 infections

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Summary

Steatosis is a frequent histological feature of hepatitis C virus (HCV) infection. Cohort studies of patients with chronic hepatitis C identified HCV genotype 3 (HCV GT3) as the prevalent steatotic genotype. Moreover, Huh- 7 cells over- expressing HCV GT3 core protein accumulate more triglyceride in larger lipid droplets than cells expressing core proteins of other HCV genotypes. However, little is known about the relationship of steatosis and HCV infection at the cellular level in vivo. In this study, we used highly sensitive multiplex in situ hybridization methodology together with lipid staining to investigate HCV- induced lipid droplet accumulation at the cellular level in liver biopsies. Consistent with previous reports, histological steatosis grades were significantly higher in GT3 compared to GT1 infected livers, but independent of viral load. Using nile red lipid stainings, we observed that the frequency of lipid droplet containing cells was similar in HCV GT1- and HCV GT3- infected livers. Lipid droplet formation preferentially occurred in HCV- infected cells irrespective of the genotype, but was also observed in noninfected cells. These findings demonstrate that the main difference between GT1- and GT3- induced steatosis is the size of lipid droplets, but not the number or relative distribution of lipid droplets in infected vs uninfected hepatocytes. **Keywords**

Adipophillin, hepatitis C virus, lipid droplet, liver steatosis, perilipin 2

E-Mail: stefan.wieland@unibas.ch, markus.heim@unibas.ch Wieland and Heim equally contributed to this study.

Toxicology

Toxicology

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Mechanisms of mitochondrial toxicity of the kinase inhibitors ponatinib, regorafenib and sorafenib in human hepatic HepG2 cells

Franziska Paech^{a,b}, Cécile Mingard^{a,b}, David Grünig^{a,b}, Vanessa F. Abegg^{a,b}, Jamal Bouitbir^{a,b,c}, Stephan Krähenbühl^{a,b,c,*}

Abstract

Previous studies have shown that certain kinase inhibitors are mitochondrial toxicants. In the current investigation, we determined the mechanisms of mitochondrial impairment by the kinase inhibitors ponatinib, regorafenib, and sorafenib in more detail. In HepG2 cells cultured in galactose and exposed for 24 h, all three kinase inhibitors investigated depleted the cellular ATP pools at lower concentrations than cytotoxicity occurred, compatible with mitochondrial toxicity. The kinase inhibitors impaired the activity of different complexes of the respiratory chain in HepG2 cells exposed to the toxicants for 24 h and in isolated mouse liver mitochondria exposed acutely. As a consequence, they increased mitochondrial production of ROS in HepG2 cells in a timeand concentration-dependent fashion and decreased the mitochondrial membrane potential concentration-dependently. In HepG2 cells exposed for 24 h, they induced mitochondrial fragmentation, lysosome content and mitophagy as well as mitochondrial release of cytochrome c, leading to apoptosis and/or necrosis. In conclusion, the kinase inhibitors ponatinib, regorafenib, and sorafenib impaired the function of the respiratory chain, which was associated with increased ROS production and a drop in the mitochondrial membrane potential. Despite activation of defense measures such as mitochondrial fission and mitophagy, some cells were liquidated concentration- dependently by apoptosis or necrosis. Mitochondrial dysfunction may represent a toxicological mechanism of hepatotoxicity associated with certain kinase inhibitors.

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Psychopharmacology

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Direct comparison of the acute subjective, emotional, autonomic, and endocrine effects of MDMA, methylphenidate, and modafinil in healthy subjects

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Abstract

Rationale 3,4-Methylenedioxymethamphetamine (MDMA) is used recreationally and investigated as an adjunct to psychotherapy. Methylphenidate and modafinil are psychostimulants that are used to treat attentiondeficit/hyperactivity disorder and narcolepsy, respectively, but they are also misused as cognitive enhancers. Little is known about differences in the acute effects of equally cardiostimulant doses of these stimulanttype substances compared directly within the same subjects.

Methods We investigated the acute autonomic, subjective, endocrine, and emotional effects of single doses of MDMA (125 mg), methylphenidate (60 mg), modafinil (600 mg), and placebo in a double-blind, crossover study in 24 healthy participants. Acute drug effects were tested using psychometric scales, the Facial Emotion Recognition Task (FERT), and the Sexual Arousal and Desire Inventory (SADI).

Results All active drugs produced comparable hemodynamic and adverse effects. MDMA produced greater increases in pupil dilation, subjective good drug effects, drug liking, happiness, trust, well-being, and alterations in consciousness than methylphenidate or modafinil. Only MDMA reduced subjective anxiety and impaired fear recognition and

International Journal of Molecular Sciences

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Ascorbic Acid Attenuates Senescence of Human Osteoarthritic Osteoblasts

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Abstract:

The accumulation of senescent cells is implicated in the pathology of several age-related diseases. While the clearance of senescent cells has been suggested as a therapeutic target for patients with osteoarthritis (OA), cellular senescence of bone-resident osteoblasts (OB) remains poorly explored. Since oxidative stress is a well-known inducer of cellular senescence, we here investigated the effect of antioxidant supplementation on the isolation efficiency, expansion, differentiation potential, and transcriptomic profile of OB from osteoarthritic subchondral bone. Bone chips were harvested from sclerotic and non-sclerotic regions of the subchondral bone of human OA joints. The application of 0.1 mM ascorbic acid-2-phosphate (AA) significantly increased the number of outgrowing cells and their proliferation capacity. This enhanced proliferative capacity showed a negative correlation with the amount of senescent cells and was accompanied by decreased expression of reactive oxygen species (ROS) in cultured OB. Expanded cells continued to express differentiated OB markers independently of AA supplementation and demonstrated no changes in their capacity to osteogenically differentiate. Transcriptomic analyses revealed that apoptotic, cell cycle-proliferation, and catabolic pathways were the main pathways affected in the presence of AA during OB expansion. Supplementation with AA can thus help to expand subchondral bone OB in vitro while maintaining their special cellular characteristics. The clearance of such senescent OB could be envisioned as a potential therapeutic target for the treatment of OA.

led to misclassifications of emotions as happy on the FERT. On the SADI,

only MDMA produced sexual arousal-like effects. Only MDMA produced

marked increases in cortisol, prolactin, and oxytocin. In contrast to

MDMA, methylphenidate increased subjective anxiety, and methylpheni-

date and modafinil increased misclassifications of emotions as angry on

the FERT. Modafinil had no significant subjective drug effects but signifi-

Conclusions MDMA induced subjective, emotional, sexual, and endocrine effects that were clearly distinct from those of methylphenidate

Keywords MDMA, Methylphenidate, Modafinil, Emotion recognition,

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cant sympathomimetic and adverse effects.

and modafinil at the doses used.

Sexual arousal

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Keywords: osteoblast; osteoarthritis; oxidative stress; senescence; subchondral bone; transcriptomics

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REVIEWS

Nature Reviews | Immunology

nature REVIEWS IMMUNOLOGY

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The spectrum of T cell metabolism in health and disease

Glenn R. Bantug¹, Lorenzo Galluzzi²⁻⁴, Guido Kroemer⁴⁻¹⁰ and Christoph Hess¹

Abstract

In healthy individuals, metabolically quiescent T cells survey lymph nodes and peripheral tissues in search of cognate antigens. During infection, T cells that encounter cognate antigens are activated and — in a context-specific manner — proliferate and/or differentiate to become effector T cells. This process is accompanied by important changes in cellular metabolism (known as metabolic reprogramming). The magnitude and spectrum of metabolic reprogramming as it occurs in T cells in the context of acute infection ensure host survival. By contrast, altered T cell metabolism, and hence function, is also observed in various disease states, in which T cells actively contribute to pathology. In this Review, we introduce the idea that the spectrum of immune cell metabolic states can provide a basis for categorizing human diseases. Specifically, we first summarize the metabolic and interlinked signalling requirements of T cells responding to acute infection. We then discuss how metabolic reprogramming of T cells is linked to disease.

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Nature Reviews | Neurology

REVIEWS NEUROLOGY

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Congenital myopathies: disorders of excitation–contraction coupling and muscle contraction

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Abstract

The congenital myopathies are a group of early-onset, non-dystrophic neuromuscular conditions with characteristic muscle biopsy findings, variable severity and a stable or slowly progressive course. Pronounced weakness in axial and proximal muscle groups is a common feature, and involvement of extraocular, cardiorespiratory and/or distal muscles can implicate specific genetic defects. Central core disease (CCD), multiminicore disease (MmD), centronuclear myopathy (CNM) and nemaline myopathy were among the first congenital myopathies to be reported, and they still represent the main diagnostic categories. However, these entities seem to belong to a much wider phenotypic spectrum. To date, congenital myopathies have been attributed to mutations in over 20 genes, which encode proteins implicated in skeletal muscle Ca²⁺ homeo-

stasis, excitation–contraction coupling, thin–thick filament assembly and interactions, and other mechanisms. *RYR1* mutations are the most frequent genetic cause, and CCD and MmD are the most common subgroups. Next-generation sequencing has vastly improved mutation detection and has enabled the identification of novel genetic backgrounds. At present, management of congenital myopathies is largely supportive, although new therapeutic approaches are reaching the clinical trial stage.

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Concu Maura Transplantation and Clinical Virology **Calzascia Sonia** Central Services



Das Redaktionsteam wünscht allen Hexen und Nichthexen eine Spannende Walpurgisnacht und einen wunderschönen 1. Mai!

Solution of the Christmas Logic Puzzle:

The 1m tree is at the Gertsch's home and the silver fir is decorated in blue and silver.







Gerry Brunner does the honors as the good fairy



From left to right: Mara Kornete, Heidi Hoyermann and Marianne Dölz

And the winner of the "LEGO City Mobiles Dschungel-Labor" is: Marianne Dölz, research group "Molecular Immune Regulation", who gave her present to her lab colleague Mara Kornete, who will hand over it to her little son Lukas. Have fun, Lukas!

And thank you, Marianne, we are sure the lab is in the right hands!



Brazil

The Federative Republic of Brazil is the largest country in both South America and Latin America. At 8.5 million square kilometers and with over 208 million people, it is the world's fifth-largest country by area and the sixth most populous. Bounded by the Atlantic Ocean on the east, it has a coastline of 7,491 kilometers. The most famous city is Rio de Janeiro, the most populated city is São Paulo and the capital is Brasilia, which was chosen as a UNE-SCO World Heritage Site due to its modernist architecture and uniquely artistic urban planning.

History

Brazil was claimed for the Portuguese Empire in 1500, with the arrival of the Portuguese fleet. At that time, the territory had an estimated 7 million indigenous people. The transfer of the Portuguese Court to Brazil occurred on November 29, 1807 with the escape from Lisbon of Queen Maria I of Portugal, the Braganza royal family and its court of nearly 15,000 people. On March 7, 1808, the court arrived in Rio de Janeiro. In 1822, Prince Pedro declared the country's independence from Portugal and then, a month later, Prince Pedro was declared the first Emperor of Brazil. On November 15, 1889 Emperor Dom Pedro II was deposed, and Brazil became a republic.

Government

The form of government is that of a democratic federative republic, with a presidential system composed of 26 States and one Federal district. The president is both head of state and head of government of the Union and is elected for a fouryear term, with the possibility of re-election for a second successive term. States have autonomous administrations, collecting their own taxes, but also receive taxes collected by the Federal government.

Economy

Brazil is the largest economy in Lat-

cludes agriculture, industry, and a wide range of services. It's the third largest exporter of agricultural products in the world, being a large producer of wheat and the largest producer of coffee for the last 150 years. Major export products include aircraft, electrical equipment, automobiles, ethanol, textiles, footwear, iron ore, steel, coffee, orange juice, soybeans and corned beef. Unfortunately, corruption in Brazil costs almost \$41 billion/year.

Biodiversity and environment

Brazil's large territory comprises various different ecosystems including 60% of the Amazon rainforest, which is recognized as having the greatest biological diversity in the world, the Atlantic Forest and the Cerrado, and as a result the country sustains the greatest megadiversity. There are a wide range of weather conditions across the large area and varied topography of the country, but the climate is mostly tropical. The rich wildlife of Brazil reflects the variety of natural habitats, the number of plant and ani-





The country has a dense and complex system of rivers, including the Amazon, the world's second-longest river and the largest in terms of volume of water.

Tourism

Brazil is the main destination in South America and second in Latin America after Mexico. Natural areas are the most popular for a combination of ecotourism with leisure and recreation, mainly sun and beach, and adventure travel. Among the most popular destinations are the Amazon Rainforest, the Pantanal in the Central-West Region, and beaches and dunes in the Northeast Region.

Infrastructure

The country is also a pioneer in the search for oil in deep water, and it is from there that it extracts 73% of its reserves. Brazil obtains 88% of its electricity from hydroelectric facilities and is the world's tenth largest energy consumer with much of its energy coming from renewable sources, particularly hydroelectricity and ethanol.

Culture

The core culture of Brazil is derived from Portuguese culture, but is also strongly influenced by African, indigenous and non-Portuguese European cultures and traditions. The language is Portuguese. Some aspects of Brazilian culture were influenced by the contributions of Italian, German and other European as well Japanese, Jewish and Arabic immigrants who arrived in large numbers in the South and Southeast of Brazil during the 19th and 20th centuries. The indigenous Amerindians influenced Brazil's language and cuisine; and the Africans influenced language, cuisine, music, dance and religion.

Handicraft

The Brazilian handicraft tradition is one of the richest in the world and guarantees the livelihood of many families and communities. The Indians are the oldest craftsmen. They paint with natural pigments, weave baskets and craft pottery in addition to making garments with feathers and feathers of birds.

Music

The music of Brazil is mainly a fusion of European and African elements. Samba is recognized around the world as a symbol of Brazil and the Brazilian Carnival, which is considered one of the most popular Brazilian cultural expressions. Samba has become an icon of Brazilian national identity. It is a musical genre and dance style with its roots in Africa and the African slave trade and religious traditions. Although there were various forms of samba in Brazil with popular rhythms originating from drumming, samba as a music genre has its origins in Rio de Janeiro, the former capital of Brazil. The Bahia's Samba de Roda (dance circle) became a UNESCO Heritage of Humanity in 2005.

Cuisine

Brazilian cuisine varies greatly by region, reflecting the country's varying mix of indigenous and immigrant populations, creating a national cuisine marked by the preservation of regional differences. Feijoada is considered the country's national dish and the beverage is coffee. Cachaça is a native liquor; it's distilled from sugar cane and it's the main ingredient in the national cocktail, Caipirinha. A typical meal consists mostly of rice and beans



with beef, salad and french fries, often mixed with cassava flour (farofa). Popular snacks are coxinha and pão de queijo (cheese bread with cassava flour). The barbecue house is a very common type of restaurant all over the country. Common desserts are brigadeiros (chocolate fudge balls), goiabada (guava jam) and romeu e julieta (cheese with goiabada). Local common fruits like





açaí, cupuaçu, mango, papaya, cocoa, cashew, guava, orange, lime, passionfruit, pineapple are often juiced and used to make chocolates, popsicles and ice cream.

Sport

The most popular sport in Brazil is football. The Brazilian men's national team is ranked among the best in the world according to the FIFA World Rankings, and has won the World Cup tournament a record five times. Some sport variations have their origins in Brazil: beach football, futsal (indoor football) and futvolei (beach volley with football) emerged as variations of football. In martial arts, Brazilians developed Capoeira, Vale-tudo, and Brazilian Jiu-Jitsu. In auto-racing, three Brazilian drivers have won the Formula One world championship eight times.

Swiss influence

The Swiss were present from the first moments of the conquest of the Brazilian territory. In 1557 14 Calvinist missionaries from the canton of Geneva arrived in the bay of Guanabara. Until the 19th century, those who ventured into Brazil were Jesuit priests, mercenary soldiers and trailblazers. Between 1818 and 1819 about 2 thousand people enlisted to emigrate. Long negotiations between the Portuguese government and the canton of Fribourg defined the details of the arrival of this first large group. It was decided that the colony would be called Nova Friburgo (hand free translation- New Fribourg) in Rio de Janeiro State.





Luana Sella Motta Maia

Today: Nicholas Sanderson, Clinical Neuroimmunology

The tradition has arisen that from time to time, foreign members of the DBM write pieces for DBM Facts about the delicious dishes and merry festivals that characterise their home countries. Being from the British Isles, neither of these options is really open to me, and so I have turned to the alternative, a brief description of one of my hobbies, which is armchair epistemology. Epistemology, in the academic sense, is the study of knowledge, of how we know stuff, and armchair epistemology is the practice of lounging in bars speculating ignorantly about how we know stuff. My interest in why we think we know what we think we know was stimulated recently by a discussion with an acquaintance who is a vigourous proponent of homeopathic medicine. Homeopathy is a business based on the proposition that very low concentrations of harmful substances can heal health problems similar to the problems they would cause in higher concentrations (hereafter, "the similia principle"). However, the nature of the business is less important for the armchair epistemologist, than why my acquaintance believes that homeopathy will benefit her health, while I believe that it won't.

There were two elements to our disagreement. Firstly, I said that there is no evidence that the similia principle is true, and she said that there is evidence. This is a simple practical question of what people think of as "evidence", and I doubt that it will interest anyone much. Secondly, my response to the absence of evidence was uncompromising denial, while her response to the uncertainty was belief. "How can you be sure it doesn't work?" she asked me.

To me this is a very interesting question. How do you respond to not knowing something? There is wide variation in how knowable thing are, from the very knowable, like "How many teeth do I have?" through the partially knowable, such as "What do hedgehogs eat?" to the essentially unknowable, such as "What is the composition of the core of the Earth?" All of these questions have factual answers, and most scientists, indeed most people, would probably agree about what a convincing answer would look like. But then there is the whole imaginary universe that exists only inside the minds of humans. This is the realm of subatomic particles, the distant past, radio waves, subcellular biological processes, evolution, angels, aliens, and the similia principle. Science for the last few centuries has done an impressive job of assembling a system of imaginary entities that are so compelling as to seem real. The idea of radio waves fits so well with the observed properties of an iPhone. Plants really could be

getting their energy from the Sun. And of course, this match is no coincidence; it is a simple product of the scientist's ruthless practice of abandoning ideas that don't fit what is seen. Ideas are cheap. If your idea doesn't work, get a new one. Almost the only principle that matters in science is that new scientific ideas must be compatible with observations, and compatible with old scientific ideas.

Homeopathic remedies not only could be tested, but in fact have been, and the results are what you would expect, but there are enough medical problems in the world for which the success or failure of a treatment is not clear, and Goodness knows enough problems for which neither medicine nor pharmacology have come up with anything better, that companies selling homeopathic remedies will always be able to find a niche. "How can you be sure it doesn't work?"

I feel the same way that Bertrand Russell did about this; the possibilities for coming up with ideas about what might exist or might be true are limitless, and the fraction of them that are useful is negligible. The fact that something is not demonstrably false is no reason for thinking that it might be true. Ideas are cheap. "But what," I hear you saying, "does this have to do with me? I'm a scientist. I don't believe in that nonsensical codswallop, I know what falsifiable means."

Well, I wondered about this. Do all scientists feel the same way as Bertrand Russell? I asked eleven pseudo-randomly chosen people in the DBM (to whom I am profoundly grateful for their help) five questions, four that I hoped would represent an ascending scale of unknowableness, and one about inferential statistics. For each of the first four questions, I asked people to estimate a quantity as closely as possible, and then to tell me the range or "confidence interval" they would have to give to be sure of including the true answer.

The questions were as follows:

Question 1.

How wide are the large, open stairs (the walkable part of the stairs themselves, not the bannisters etc.) between the 0 and 1 floors of the DBM?

Question 2. How old is the Earth?

Question 3.

How much money in US dollars did the combined presidents of France, Germany, Italy, and the United States) obtain illegally in 2017?

Question 4.

How many extraterrestrial spacecraft visited our solar system during 2017?

Question 5.

Diebold et al. (2018, PMID: 28958667) report as follows: "...T regulatory cells (CD3+CD4+CD127-CD25+Foxp3+) showed a relative increase within the first three months of DMF treatment (paired t-test, p = 0.0241)." What does "p = 0.0241" mean?



Me, England , and Armchair Epistemology.

I expected that people would all be able to give quite tight confidence intervals for the first question, and as the answers became less knowable, would expand the width of their ranges accordingly. As a measure of people's confidence, I calculated the median over the 11 answers of (upper bound/lower bound), so 2-8 gives 4-fold, and 10 - 10,000 gives 1000-fold and so on.

For the first question, the confidence intervals were indeed tight, although the estimates were not accurate; the stairs are 192 cm wide, and 7/11 people gave confidence intervals starting from 2 m or more, median confidence interval size was 2-fold. Guesses for the age of the Earth were more evenly distributed around the Wikipedia value, ranging from two thousand to forty billion years, but in general individuals' uncertainty didn't reflect the population uncertainty: someone who guessed 5 million years gave a confidence interval plus or minus a few million years, while someone who guessed 8 billion, gave a confidence interval plus or minus a few billion. Median range size was 10-fold. Unlawful income of presidents was estimated between zero (only one person was this optimistic) and one trillion dollars. I am sure that nobody in the DBM knows the true figure, and indeed the median interval was 100-fold. But the most interesting question to me was the fourth one - how many UFOs. This to me is something we do know. We have never observed an extraterrestrial spacecraft visiting our solar system. Two people agreed with me and gave an estimate of zero and an interval of zero. Three other people estimated zero, five estimated between 2 and 100, and 8/10 people gave a non-zero upper limit to their

interval. The median confidence interval was only 8.5-fold, meaning that people feel they can better estimate UFO numbers than presidential trouser-pocket-filling or the age of the Earth. Why?

Back to Earth. Scientists have developed a culture, at least in writing, of being cautious. If one doesn't know, one says so, and if one can, one gives a measure of how unsure one is (one out of eleven people answered the p-value question correctly, by the way). I like this culture. I think it's important. But this caution should only be applied in the realm of the falsifiable. We don't know how much DMF affects regulatory T cell numbers, and are right to admit it. But we do know how many UFOs visit us, and whether homeopathy works, and we should say so.



My hometown, Brampton in Cumbria. Save the date

DBM Summer Symposium

Wednesday, August 22, 2018

8:00 – 13:15 Kleiner Hörsaal, ZLF, Heb<mark>els</mark>trasse 2</mark>0

Presentations by DBM postdocs, PhD students and project leaders

DBM Summer Barbecue

Wednesday, August 22, 2018

16:30 – 21:30 Kraftwerkinsel Birsfelden

For DBM members only

Für einen, der nicht weiss, welchen Hafen er ansteuern will, gibt es keinen günstigen Wind. (Seneca)

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