DBM FACTS

Periodisches Informationsblatt des Departementes Biomedizin
Universität Basel, Universitätsspital Basel und
Universitäts-Kinderspital beider Basel

"Balancing immunity: Autoimmunity, immunosuppression, Infection and Vaccination" | Christmas in Romania | Wiehnacht z' Basel

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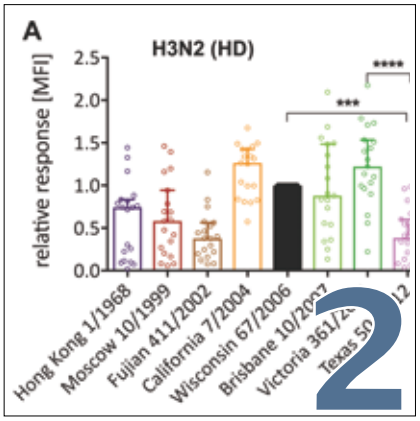
Departement Biomedizin Basel



"Balancing immunity: Autoimmunity, immunosuppression, Infection and Vaccination"
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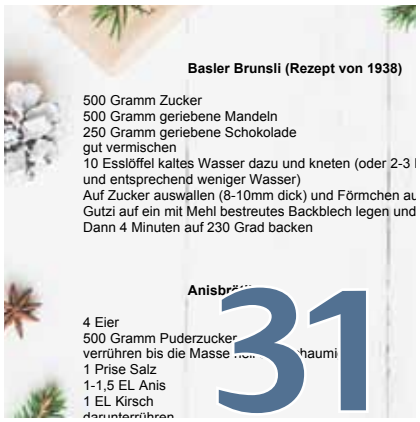

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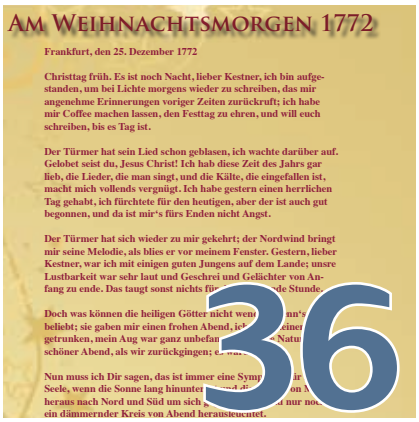

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UNI BASEL

EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Mit guten Nachrichten möchten wir 2017 zu Ende gehen lassen: Volker Spindler hat am 1. Oktober 2017 die Professur für Anatomie angetreten und wird ab Januar 2018 sein Forschungslabor "Cell Adhesion" am DBM aufbauen. Lukas Jeker wurde vom Universitätsrat per 1. Oktober 2017 zum Assistenzprofessor für Experimentelle Transplantationsimmunologie und Nephrologie gewählt und wird seine Forschungsgruppe "Molecular Immune Regulation" in neuer Funktion weiterführen. Jan Gründemann wird am 1. Januar 2018 seine SNF-Förderprofessur und damit seine Tätigkeit als Forschungsgruppenleiter des Labors "Sensory processing and behaviour" aufnehmen. Wir wünschen allen viel Erfolg! Am 20. November 2017 wurde Primo Schär zum neuen Dekan der Medizinischen Fakultät gewählt. Wir gratulieren Primo herzlich und wünschen ihm viel Erfolg und gutes Gelingen! Bei der Vergabe von Projekten durch das Swiss Personalized Health Network (SPHN) hat die Allianz Zürich-Basel sehr gut abgeschnitten: Mit Adrian Egli und Momo Bentires-Alj werden zwei der insgesamt sieben Projekte von Mitgliedern des DBM koordiniert. Wir wünschen allen Beteiligten eine gute und fruchtbare Zusammenarbeit!
In dieser Ausgabe stellt uns Christoph Berger sein Forschungsgebiet der "Translational Immunology" vor (ab Seite 2). Anschliessend folgen die neuesten Publikationen aus dem DBM (Seite 10). Weihnachtlich geht es weiter: Dieses Mal in den Osten, mit Andrei-Dragos Costache erleben wir die Festtage in Rumänien (Seite 32), Manuela Bernasconi führt uns mit Grossmutters Rezepten in die Basler Weihnachtsbäckerei ein (Seite 31), für die Kleinen und Grossen gibt es weihnachtliche Unterhaltung ab Seite 40. Nach Kälte und Besinnlichkeit zieht es uns mit Rachel Mak'Ayengo zum Abschluss dann in wärmere Gefilde, wo kenianische Lebensfreude uns erwartet (Seite 38).
Ich möchte allen danken, die im zu Ende gehenden Jahr täglich ihr Bestes gegeben und sich für das Wohlergehen des DBM eingesetzt haben. Nur gemeinsam werden wir die Herausforderungen der Zukunft meistern.

Schöne Festtage!

Dear Readers,

We finish off 2017 with some good news: Volker Spindler took up the position of Professor of Anatomy on October 1st 2017 and will start to build his "Cell Adhesion" research lab at the DBM in January 2018. On October 1st the university board named Lukas Jeker as Assistant Professor of Experimental Transplant Immunology and Nephrology and he will continue as head of his "Molecular Immune Regulation" research group in this new role. Jan Gründemann will take up his SNF professorship on January 1st 2018 and with it his position as head of the "Sensory Processing and Behaviour" research group. We wish them all every success! On November 20th 2017 Primo Schär was chosen as the new Dean of the Medical Faculty. We heartily congratulate Primo and which him good look and every success! The Zürich-Basel alliance fared very well in the distribution of projects by the Swiss Personalized Health Network (SPHN). Between Adrian Egli and Momo Bentires-Alj two of the seven projects will be lead by members of the DBM. We wish all of the participants successful collaborations!
In this issue Christoph Berger introduces us to his "Translational Immunology" research group (page 2). Following this are the latest publications from the DBM (page 10). After that things take on a festive theme: this time we go East and learn about the Romanian festivities from Andrei-Dragos Costache (page 32), Manuela Bernasconi introduces us to Basel Christmas baking with her Grandmother's recipes (page 31), and a Christmas story for both young and old starts on page 40. After the cold and the contemplation, Rachel Mak'Ayengo brings us to warmer climes where the Kenyan zest for life awaits us (page 38).
I would like to thank all of you who have given their best every day during the last year and who are committed to the well-being of the DBM. It is only together that we will master the challenges of the future.

Happy holidays!

"Balancing immunity: Autoimmunity, immunosuppression, Infection and Vaccination"

Introduction

In the Translational Immunology Lab, we are studying human adaptive immunity in the context of autoimmune disease and vaccination. With a strong tie to the clinical immunology and rheumatology clinic at the University Hospital Basel, our research projects are motivated by clinical questions and executed on patient samples. Our main goal is to better understand individual patient outcomes.

The human autoimmune disease we are studying is called Giant Cell Arteritis (GCA). GCA is an autoimmune vasculitis of unknown etiology. Disease manifests as an inflammatory syndrome and ischemic symptoms resulting from stenosis of inflamed arteries (i.e. vision loss or stroke). There is strong evidence that T cells play an important role in disease induction and/or maintenance: (i) the histology shows dramatic infiltration of CD4 T cells; (ii) genetic studies demonstrate an association of disease susceptibility and specific MHC class II alleles (e.g. a recent European GWAS study we contributed to Carmona FD et al. 2017); and (iii) the strict tissue specificity to larger arteries suggests an antigen specific immune response against an antigen only expressed in these vessels. Given that no animal model of the disease exists, translational studies are needed to unravel disease pathogenesis to generate hypothesis for potential personalized biomarkers and novel treatment approaches. To address such translational research questions, we have established a large, prospective single-center GCA cohort (Basler Riesenzellarteriitis Kohorte; BARK). This is a joint-effort, involving clinical immunology, rheumatology, angiology, nuclear medicine, vascular surgery and pathology. We collect peripheral blood cells, biopsy material, and plasma. Combined with the available clinical data (routine laboratory, imaging, clinical pathology) we can put our immunological findings in context of the individual clinical presentation. To date we have included more than 160 patients. This puts us in the position to address key questions including (i) the identification of clinically and immunologically distinct patient subsets that might benefit from individualized treatment strategies, (ii) probing the usefulness of immunological biomarkers in disease monitoring and towards personalized treatment strategies, and (iii) the identification of potential immunological targets in GCA. More personalized treatment strategies are needed, as therapeutic immunosupression is a balancing-act between 'too little' with the risk of relapses, or 'too much' with potentially life threatening infections *(Berger CT et al. 2015)*.

Indeed, respiratory infections are amongst the most frequent and relevant complications of the immunosuppressive treatment of autoimmune diseases. This is especially true for GCA, as the patients are typically > 60 years old (median age in our cohort 73 years), thus also affected by immunosenescence. Vaccination can reduce morbidity of vaccine preventable infections including influenza. Yet, immunosuppressed elderly subjects show substantially reduced vaccine responses. This led to our interest in characterizing how individual factors – including a compromised immune system – impacts the vaccine response to seasonal influenza vaccination. Influenza vaccination is unique in terms that: (i) annual vaccination is recommended to adapt to newly circulating strains, and (ii) it's almost inevitable that subjects are also repeatedly exposed to natural virus which shapes immunity as well. Since different vaccine strains at times only differ in few amino acids, the response to a related strain may reflect a boosted response to a pre-existing variant response. How this is affected in immunosuppressed subjects is still ill understood.

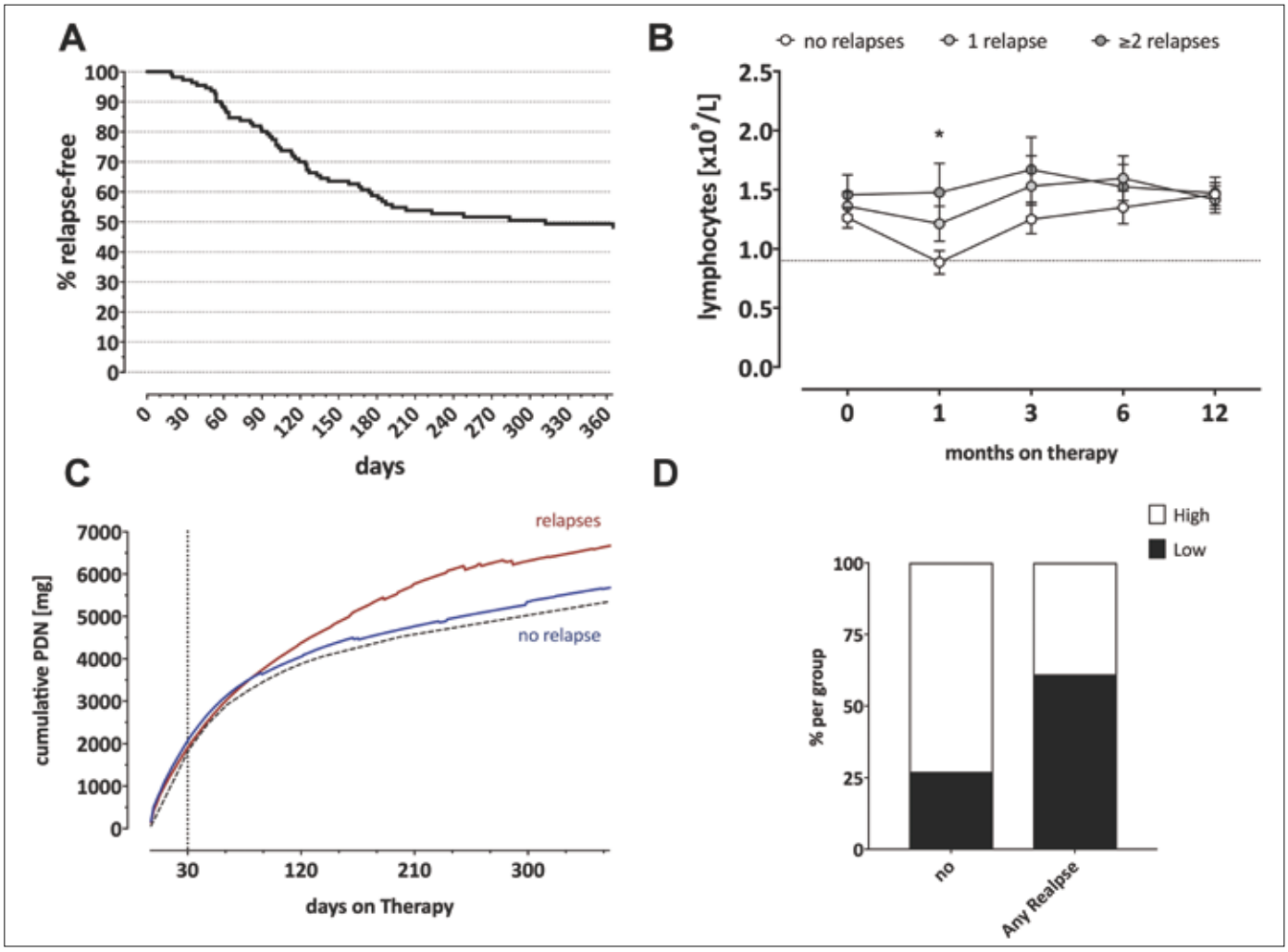


Fig. 1 – Predictors of relapse in patients with Giant cell arteritis. Data from our prospective GCA cohort: about half of the patients experience a disease flare/relapse, when the immunosuppressive therapy is tapered (A). Those without relapse had lower lymphocyte counts (i.e. were lymphocytopenic) after one month of therapy (B). This was not due to a higher cumulative steroid dose in those without relapses (blue line) at that time-point (vertical dotted line at day 30). Dotted curve indicates the recommended doses by the European league against rheumatism (EULAR) (C). Flow cytometry based assessment of glucocorticoid receptor (GCR) expression on T cells. Relapses had a high % of subjects with lower level expression (black) than those without relapses (D).

(A) Giant Cell Arteritis – towards a molecular understanding of pathogenesis

A1) Prediction of refractory, relapsing disease course using clinical and immunological data (Marc Bigler, Ph. Fuchs, Cédrine Küng)

GCA treatment consists in immunosuppression with (high-dose) glucocorticoids (GC), that needs to be maintained over months. Very recently steroid-sparing therapy with a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R) has been approved in the US and Europe. What is striking in GCA, is that in 50-60% of the patients therapy is highly effective and after treatment is tapered, they remain in remission even years after therapy was stopped (i.e. a monophasic autoimmune disease). Others have a diametrically opposed outcome: they respond poorly to treatment, their disease flares ('relapse') repeatedly when treatment is reduced, and symptoms reoccur over years. To test whether the clinical manifestation, the immunological presentation at baseline, and/or genetic factors might predict who will respond poorly, we stratified the patients of our cohort (n=113 with available follow up data) based on whether they experienced a relapse ('relapsers') or not. In our cohort 50% had at least one relapse, defined as reappearance of clinical symptoms and/or systemic inflammation while on therapy (Figure 1A). The majority of the relapses occurred 3 months after treatment start, which is the time the steroid dose is tapered below 20mg/d, i.e. a reduced immunosuppression. Looking at clinical or immunological features

that associate with relapses after three months, we found that those with low lymphocytes after 1 month on therapy were protected from relapses (Figure 1B). A plausible explanation would be that the patients without relapses were treated more intensively, and the lymphocyte count acts as a surrogate for the level of immunosuppression. The cumulative steroid dose (i.e. total amount of GC/prednisone the patient has been taking) was, however, comparable between relapsers and those that remained in remission (Figure 1C). Still, the lymphocyte count suggested more intensive treatment response in those without subsequent relapses. We are therefore now interested in host factors that associate with a stronger response to GC. The obvious thing to look at is the glucocorticoid receptor (GCR), since its expressed on all immune cells. Genetic polymorphisms that associate with heightened or reduced signaling have been described. We first analyzed GCR expression levels using flow cytometry (Bigler MB, PLOSOne 2015). There is strong heterogeneity in the expression levels. Indeed, we found that relapsers more often had a low-level GCR expression phenotype compared to non-relapsers (Figure 1D). From our participation in a European GWAS study looking for risk genes for GCA *(Carmona FD, Am J Hum Genet. 2017)*, we could check in a subset of our study for genetic polymorphisms in the GCR gene that associate with relapsing disease course. In our preliminary analysis, we found a potential candidate SNP (i.e. several SNPs in high linkage disequilibrium) and are now extending the genotyping of this genetic variant to the whole cohort. A genetic predictor of relapse (alone or in combination with other factors (e.g. degree of lymphocytopenia after 1 month)) would provide a rational for personalized treatment strategies such as early aggressive therapy in high risk or shorter treatment duration for low risk patients.

A2) The search for potentially self-reactive T cells and their target in Giant cell arteritis (Marc Bigler, Julia Hirsiger)

Although a large body of evidence suggests that an antigen specific CD4 T cell response is important in GCA, the potential immunological targets remain elusive. These could derive from a self-protein in the vessel wall or a pathogen with blood vessel tropism, such as some Herpes viruses. Recently, Varicella Zoster Virus (VZV) has been suggested as a potential pathogen important in GCA pathogenesis. While some studies detected VZV antigen in the arteries of patients, many others found no pathogen. If T cells recognize a specific antigen/pathogen, we hypothesized that we should be able to detect expanded antigen-specific T cell populations. In our lab, we chose a two-way approach to identify clonally expanded T cell populations by: (i) studying the peripheral blood T cell compartment by testing for aorta – or VZV-specific T cell responses, and (ii) applying an unsupervised analysis of the clonal composition of T cells directly in the inflamed artery (Figure 2).

(i) Antigen-specific peripheral blood CD4 T cells in untreated GCA

We tested the reactivity of peripheral blood T cells against different antigens (Figure 2). As a potential self-antigen source, we included protein extracts from aortic tissue of a vasculitic aorta. Given the proposed association of GCA with VZV, we also tested against VZV antigen (vaccine virus and an immunodominant glycoprotein). T cells from GCA patients showed slightly reduced IFN-γ responses to aortic tissue and VZV compared to healthy blood donors. However, patients with polymyalgia rheumatica (PMR) (= another inflammatory disease that clinically and immunologically mimics GCA with exception of vasculitis) showed comparable T cell reactivity patterns as GCA patients, arguing against peripheral VZV specific T cells being pathogenic in vasculitis (Bigler MB and Hirsiger J et al. 2017). Whether reduced levels of VZV reactive T cells favors VZV reactivation and thereby impacts disease pathogenesis remains open.

(ii) Identifying clonally expanded T cell populations in the inflammed artery and tracking them in the blood

Given the very strict tissue tropism of GCA – i.e. large arteries – our second approach focuses on the site of inflammation (Figure 2). For the detection of clonally expanded T cells in the inflammatory lesions we will perform NGS of tissue extracted genetic material from artery biopsies and analyze the T cell receptor (TCR) repertoire. We hypothesized that the interrogation of the infiltrating cells for clonally expanded T cells could identify an individual (i.e. each patient has another dominant

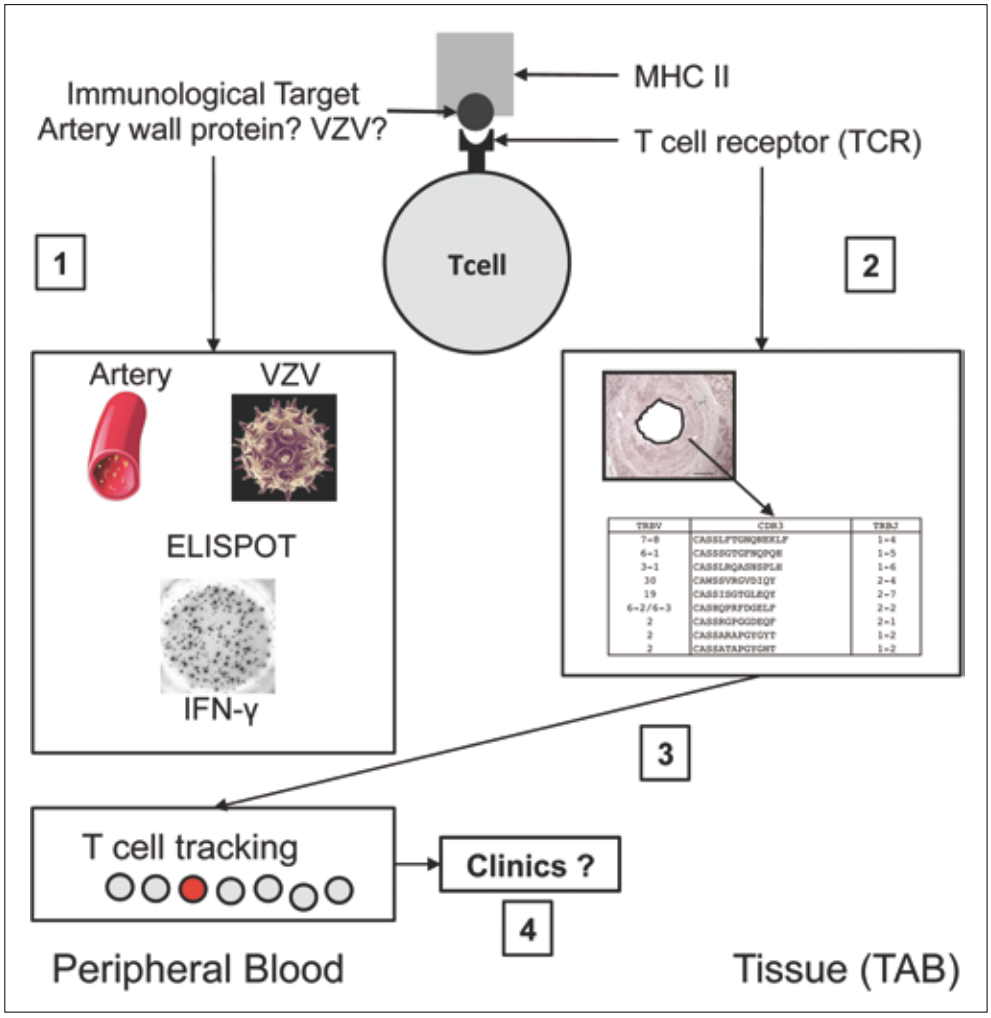


Fig. 2: T cell target discovery approach. (1) Using Elispot we screened for T cells reactive to artery wall proteins or VZV proteins. Compared to healthy controls, T cells of GCA patients were less reactive (Bigler MB and Hirsiger J et al. 2017). (2) The second approach focuses on the clonal repertoire analysis of T cells of the inflammatory lesions of GCA. We aim to detect dominant (i.e. presumably antigen specific) clones. (3) These will then be searched for in the peripheral blood of the patient. (4) Finally, their frequency will be linked to disease activity.

TCR clone), or shared T cell clone (i.e. same clone shared between different patients – so called 'public TCR or clones'). Moreover, public TCR sequences could be expressed in reporter cell lines to screen for the ligand of the pathogenic TCR using peptide libraries. By correlating peripheral blood clonal frequencies with disease activity, their relevance in disease pathogenesis can be assigned, and their value to serve as biomarker for immunosuppressive treatment-stewardship defined.

A3) The role of Autoantibodies in Diagnosing GCA or its Complications (Anne Kistner, Marc Bigler)

Few studies investigated the role of humoral immunity in GCA. B cells are mostly absent in the tissue inflammation. In contrast to other autoimmune diseases – such as multiple sclerosis, rheumatoid arthritis or systemic lupus – B cell depleting therapies work poorly in GCA. However, in a recent study, auto-antibodies against specific isoforms of the intracellular regulatory 14-3-3 protein have been proposed as biomarkers in large-vessel vasculitis (LVV), i.e. GCA and Takayasu's arteritis (TA). This was concluded from a study conducted in patients with aortic aneurysm due to LVV, i.e. patients with a late complication of vasculitis. Leveraging our prospective GCA cohort, we explored, whether anti-14-3-3 antibodies are already present 'at GCA diagnosis', which would underpin their potential usefulness as biomarkers/autoantibodies for the diagnosis and monitoring of treatment. The presence of disease specific autoantibodies similarly to other autoimmune diseases (e.g. systemic lupus, ANCA vasculitis) would facilitate diagnosis of GCA. To test this, antibodies against three isoforms of 14-3-3 (γ, ε, and ζ) were measured in 48 GCA, three TA patients, and 42 controls (including non-inflammatory and inflammatory diseases). We applied a multiplexed bead-based immunoassay and immunoprecipitation assays *(Kistner A et al. 2017)*. The positivity threshold for the presence of anti-14-3-3 antibodies was defined based on results in young healthy controls. Anti-14-3-3 IgG antibodies were compared between GCA patients

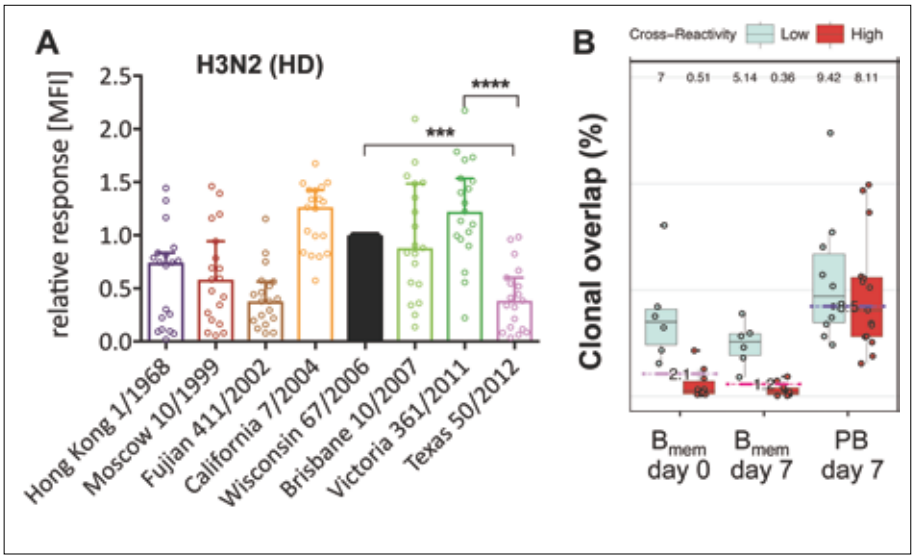


Fig. 3 – Influenza H3N2 cross-binding profiles and BCR repertoire analysis. IgG cross-binding of healthy subjects (n=24) vaccinated with H3N2/Wisconsin in 2007/2008 was assessed against strains circulation in the previous or following years. Strain specific responses were normalized to the vaccine strain response. Between the Victoria and Texas strain more than 50% of the IgG response was lost in some individuals (A). (B) The clonal (CDRH3) percent overlap between different vaccines is shown. Memory B cells (day 0 and 7) and vaccine induced plasma blasts (PB, CD19^{pos}IgD^{neg}CD38^{high}) were FACS sorted. Memory B cell repertoires of individuals with low cross-reactivity (light blue) are less diverse that those of individuals showing high cross-strain cross-reactivity (red).

and controls to assess their diagnostic performance as a biomarker, and related to the immunohistopathology of artery explants. Antibodies against all three 14-3-3 isoforms were detected in GCA patients as well as in age-matched inflammatory and non-inflammatory controls. Amongst LVV patients, detection of antibodies targeting 14-3-3 ε and ζ was associated with more severe disease, specifically stroke or aortitis. Thus, we could conclude that detection of antibodies against 14-3-3 proteins at the time of GCA diagnosis was not disease-specific. However, their presence at high levels in LVV with stroke, aortitis and – in a previous study – with aneurysm formation may indicate their value as potential biomarkers for extensive tissue destruction.

(B) Functional and molecular profiling of the influenza vaccine response (Marc Bigler, Simon Egli)

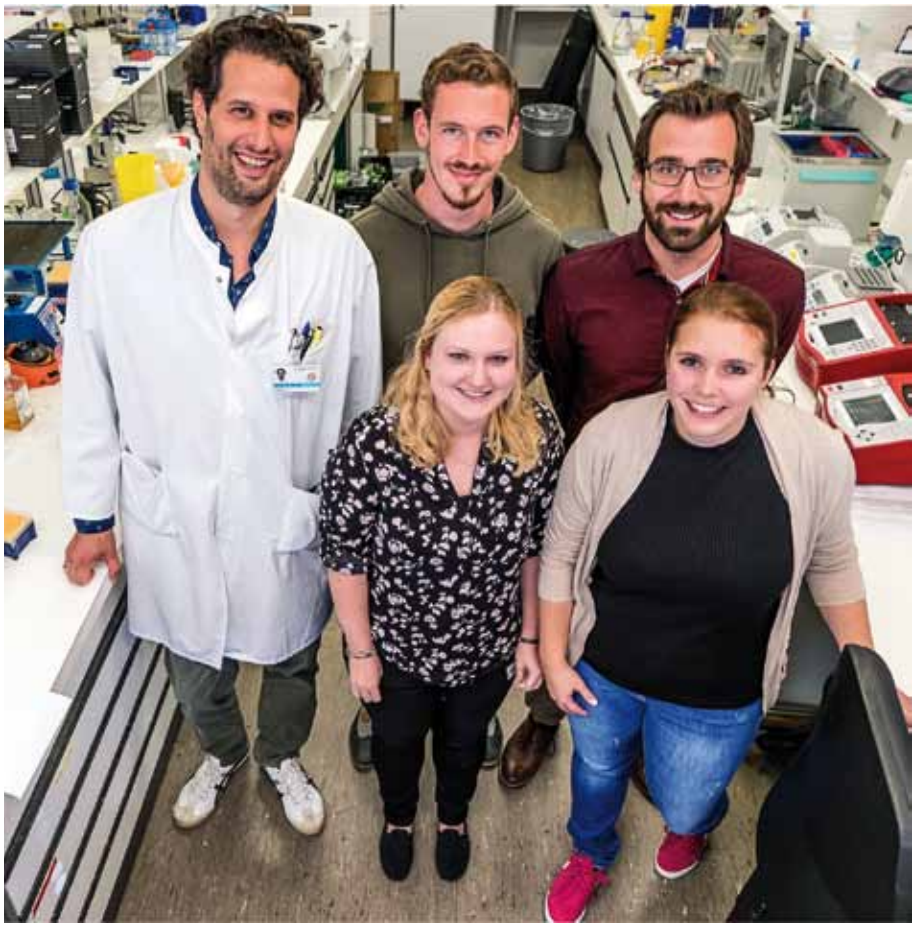
Patients with autoimmune disease are treated with immunosuppressive drugs, making them prone to infections *(Fuchs P and Bigler MB et. al. in preparation, Berger CT et al. 2015, Berger CT et al. 2017)*. We therefore vaccinate them against vaccine preventable infections including influenza and pneumococcal disease. Pathogens with a high mutation rate continuously adapt to evade host immunity. In the case of influenza, single point mutations ('antigenic drift') occur continuously, while recombination of two independent strains ('antigenic shift') happens rarely, but typically results in pandemics. Amongst other factors, antigenic drift is responsible for the efficacy of the influenza vaccine being far from perfect. Moreover, the immune response is quantitatively reduced in subjects with a dysregulated immune system such as the elderly and immunosuppressed.

Over the past three years, we were therefore interested how individual factors – including a compromised immune system – impact the vaccine response to seasonal influenza vaccination. Influenza vaccination is unique since seasonal vaccination is recommended to adapt to newly circulating or antigenically drifted strains. The adapted vaccine strains may differ in as little as a few amino acids. Therefore, we hypothesize that depending on the preexisting immunity the response to antigenically related strains may be dominated by a recall response to a preexisting variant, rather than a *de novo* response.

Indeed, we found evidence that immune response to the seasonal influenza vaccination is strongly impacted by the vaccine preparation and preexisting immunity *(Berger CT et al. 2015, Bigler MB and Egli SE, in preparation)*. We therefore hypothesized, that repeated exposure to very similar antigens (i.e., the seasonal flu vaccine strains) boosts the preexisting immunity, yet might interfere with the emergence of antibodies against mutated epitopes, i.e. the antigenic changes between two vaccinations. To test this, we took advantage of samples of a prospective influenza vaccine cohort from 10 years ago. We studied the cross-reactivity of the vaccine induced response using a multiplexed immune assay with 13 different hemagglutinin (HA) specificities. Indeed, our data indicated that the influenza IgG vaccine response cross-recognizes various previously and subse-

quently circulating strains (Figure 3A). This cross-reactive response was, however, narrow and vulnerable to viral escape. Specifically, vaccinated subjects showed almost no response to one given variant – the Texas strain – which was circulated several years later. The Texas strain only differed by five amino acids to the Victoria strain that was well-recognized by the IgG response (Figure 3A). This suggests that the immune response must have been dominated by an epitope where Texas and Victoria differ. We observed, however, substantial inter-individual differences with regards to the extent of cross-reactivity of the vaccine response. While in some a broad variety of viruses is recognized and viral escape is compensated to a certain extent, others have a skewed response targeting a limited number of epitopes on the virus making them prone to escape by the virus. This gave us the opportunity to compare the composition of the B cell memory compartment ('BCR repertoire') of those with broader vs. more limited cross-reactivity (Figure 3B). Intriguingly, those with limited cross-reactivity had a skewed BCR repertoire, suggesting a role of the previous exposure history to vaccination or natural infection. Influenza viruses infect 5 to 10% of all adults each year. Consequently, the majority of humans have a history of repeated previous contact with the virus. Due to the retrospective nature of this study (no information on vaccination status or previous infection history), we were not able to pinpoint the cause of the narrowed immune response. We aim to close this gap by currently expanding on our findings in a *prospective vaccination study* (ARIVA, **A**ntibodies in **R**epeated **I**nfluenza **VA**ccination) to assess the impact of repeated vaccination with antigenically related strains on the functional and molecular vaccine response. This will provide us with further insights, how the individual cumulative exposure history of natural influenza contacts and/or vaccination shapes the influenza-specific adaptive immune memory. Moreover, by including immune dysregulated subjects (such as elderly patients, patients on steroids or IL-6 cytokine blockade from our GCA cohort), we will be able to study how different treatment strategies impact the functional and molecular immune response to seasonal influenza vaccination.

Christoph Berger



Portrait - Translational Immunology Group. From left to right: Christoph Berger, Marc Bigler (PhD Student), Julia Hirsiger (Master Student Biology), Philipp Fuchs (Master Student Medicine), Cédrine Küng (Master Student Medicine).

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Dissertationen

Am 14. August 2017 konnte **Anna Steinert** von der Forschungsgruppe "Gastroenterology" (Departement Biomedizin Hebelstrasse) ihre Dissertation mit Erfolg abschliessen. Sie befasste sich in ihrer Doktorarbeit mit dem Thema: "Regulation and Function of the Interleukin 19 in Intestinal Immunity."

Auszeichnungen

Ernennung zu Titularprofessoren

Der Universitätsrat genehmigte am 25. Oktober 2017 die von der Regenz beschlossene Ernennung folgender Titularprofessoren: **PD Dr. Martin Grapow** von der FG Cardiac Surgery and Engineering (DBM Hebelstrasse) für Herzchirurgie und **PD Dr. Nina Khanna** von der FG Infection Biology (DBM Hebelstrasse) für Infektiologie.

SGDV- Posterpreis an Elias Imahorn

An der 99. Jahresversammlung der Schweizerischen Gesellschaft für Dermatologie und Venereologie (SGDV) in Bern vom 7.–9. September 2017 hat **Elias Imahorn** von der Forschungsgruppe "Dermatology" (DBM Hebelstrasse) den "Prof. U.W. Schnyder Posterpreis für Genodermatosen" für das Poster "A cell culture model for epidermodysplasia verruciformis will help to elucidate the pathomechanism of the disease" erhalten.

Das DBM gratuliert ganz herzlich!

Und weil es so schön war, alle Jahre wieder:

Cell Host & Microbe | Cell Host & Microbe | 22, 354–365, September 13, 2017 | IF 14,946

Interferon-γ-Driven iNOS: A Molecular Pathway to Terminal Shock in Arenavirus Hemorrhagic Fever

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Summary

Arenaviruses such as Lassa virus (LASV) cause hemorrhagic fever. Terminal shock is associated with a systemic cytokine storm, but the mechanisms are ill defined. Here we used HLA-A2-expressing mice infected with a monkey-pathogenic strain of lymphocytic choriomeningitis virus (LCMV-WE), a close relative of LASV, to investigate the pathophysiology of arenavirus hemorrhagic fever (AHF). AHF manifested as pleural effusions, edematous skin swelling, and serum albumin loss, culminating in hypovolemic shock. A characteristic cytokine storm included numerous pro-inflammatory cytokines and nitric oxide(NO) metabolites. Edema formation and terminal shock were abrogated in mice lacking inducible nitric oxide synthase (iNOS), although the cytokine storm persisted. iNOS was upregulated in the liver in a T cell and interferon-γ (IFN-γ)-dependent fashion. Accordingly, blockade of IFN-γ or depletion of T cells repressed hepatic iNOS and prevented disease despite unchecked high-level viremia. We identify the IFN-γ-iNOS axis as an essential and potentially druggable molecular pathway to AHF-induced shock.

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Constitutive high expression of protein arginine methyltransferase 1 in asthmatic airway smooth muscle cells is caused by reduced microRNA-19a expression and leads to enhanced remodeling

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Abstract

Background: In asthma remodeling airway smooth muscle cells (ASMCs) contribute to airway wall thickness through increased proliferation, migration, and extracellular matrix deposition. Previously, we described that protein arginine methyltransferase 1 (PRMT1) participates in airway remodeling in pulmonary inflammation in E3 rats. Objective: We sought to define the asthma-specific regulatory mechanism of PRMT1 in human ASMCs.

Methods: ASMCs from healthy subjects and asthmatic patients were activated with platelet-derived growth factor (PDGF)–BB. PRMT1 was localized by means of immunohistochemistry in human lung tissue sections and by means of immunofluorescence in isolated ASMCs. PRMT1 activity was suppressed by the pan-PRMT inhibitor AMI-1, signal transducer and activator of transcription 1 (STAT1) was suppressed by small interfering RNA, and extracellular signal-regulated kinase (ERK) 1/2 mitogen-activated protein kinase (MAPK) was suppressed by PD98059. MicroRNAs (miRs) were assessed by using real-time quantitative PCR and regulated by miR mimics or inhibitors.

Results: PRMT1 expression was significantly increased in lung tissue sections and in isolated ASMCs of patients with severe asthma. PDGF-BB significantly increased PRMT1 expression through ERK1/2 MAPK and STAT1 signaling in control ASMCs, whereas in ASMCs from asthmatic patients, these proteins were constitutively expressed. ASMCs from asthmatic patients had reduced miR-19a expression, causing upregulation of ERK1/2 MAPK, STAT1, and PRMT1. Inhibition of PRMT1 abrogated collagen type I and fibronectin deposition, cell proliferation, and migration of ASMCs from asthmatic patients.

Conclusions: PRMT1 is a central regulator of tissue remodeling in ASMCs from asthmatic patients through the pathway: PDGF-BB–miR-19a–ERK1/2 MAPK and STAT1. Low miR-19a expression in ASMCs from asthmatic patients is the key event that results in constitutive increased PRMT1 expression and remodeling. Therefore PRMT1 is an attractive target to limit airway wall remodeling in asthmatic patients.

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Mutations in signal recognition particle *SRP54* cause syndromic neutropenia with Shwachman-Diamond–like features

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Shwachman-Diamond syndrome (SDS) (OMIM #260400) is a rare inherited bone marrow failure syndrome (IBMFS) that is primarily characterized by neutropenia and exocrine pancreatic insufficiency. Seventy-five to ninety percent of patients have compound heterozygous loss-of-function mutations in the Shwachman-Bodian-Diamond syndrome *(SBDS)* gene. Using trio whole-exome sequencing (WES) in an *SBDS*-negative SDS family and candidate gene sequencing in additional *SBDS*-negative SDS cases or molecularly undiagnosed IBMFS cases, we identified 3 independent patients, each of whom carried a de novo missense variant in *SRP54* (encoding signal recognition particle 54 kDa). These 3 patients shared congenital neutropenia linked with various other SDS phenotypes. 3D protein modeling revealed that the 3 variants affect highly conserved amino acids within the GTPase domain of the protein that are critical for GTP and receptor binding. Indeed, we observed that the GTPase activity of the mutated proteins was impaired. The level of *SRP54* mRNA in the bone marrow was 3.6-fold lower in patients with *SRP54*-mutations than in healthy controls. Profound reductions in neutrophil counts and chemotaxis as well as a diminished exocrine pancreas size in a *SRP54*-knockdown zebrafish model faithfully recapitulated the human phenotype. In conclusion, autosomal dominant mutations in *SRP54*, a key member of the cotranslation protein-targeting pathway, lead to syndromic neutropenia with a Shwachman-Diamond–like phenotype.

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Genome-wide mapping of genetic determinants influencing DNA methylation and gene expression in human hippocampus

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Emerging evidence emphasizes the strong impact of regulatory genomic elements in neurodevelopmental processes and the complex pathways of brain disorders. The present genome-wide quantitative trait loci analyses explore the cis-regulatory effects of single-nucleotide polymorphisms (SNPs) on DNA methylation (meQTL) and gene expression (eQTL) in 110 human hippocampal biopsies. We identify *cis*-meQTLs at 14,118 CpG methylation sites and *cis*-eQTLs for 302 3'-mRNA transcripts of 288 genes. Hippocampal *cis*-meQTL-CpGs are enriched in flanking regions of active promoters, CpG island shores, binding sites of the transcription factor CTCF and brain eQTLs. Cis-acting SNPs of hippocampal meQTLs and eQTLs significantly overlap schizophrenia-associated SNPs. Correlations of CpG methylation and RNA expression are found for 34 genes. Our comprehensive maps of *cis*-acting hippocampal meQTLs and eQTLs provide a link between disease-associated SNPs and the regulatory genome that will improve the functional interpretation of non-coding genetic variants in the molecular genetic dissection of brain disorders.

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miR-1199-5p and Zeb1 function in a double-negative feedback loop potentially coordinating EMT and tumour metastasis

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Epithelial tumour cells can gain invasive and metastatic capabilities by undergoing an epithelial–mesenchymal transition. Transcriptional regulators and post-transcriptional effectors like microRNAs orchestrate this process of high cellular plasticity and its malignant consequences. Here, using microRNA sequencing in a time-resolved manner and functional validation, we have identified microRNAs that are critical for the regulation of an epithelial–mesenchymal transition and of mesenchymal tumour cell migration. We report that miR-1199-5p is downregulated in its expression during an epithelial–mesenchymal transition, while its forced expression prevents an epithelial–mesenchymal transition, tumour cell migration and invasion in vitro, and lung metastasis in vivo. Mechanistically, miR-1199-5p actsina reciprocal double-negative feedback loop with the epithelial–mesenchymal transition transcription factor Zeb1. This function resembles the activities of miR-200family members, guardians of an epithelial cell phenotype. However, miR-1199-5p and miR-200 family members share only six target genes, indicating that, besides regulating Zeb1 expression, they exert distinct functions during an epithelial–mesenchymal transition.

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The Interplay Between Neutrophils and CD8+ T Cells Improves Survival in Human Colorectal Cancer

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Abstract

Purpose: Tumor infiltration by different T lymphocyte subsets is known to be associated with favorable prognosis in colorectal cancer. Still debated is the role of innate immune system. We investigated clinical relevance, phenotypes, and functional features of colorectal cancer–infiltrating CD66b+ neutrophils and their crosstalk with CD8+ T cells.

Experimental Design: CD66b+ and CD8+ cell infiltration was analyzed by IHC on a tissue microarray including >650 evaluable colorectal cancer samples. Phenotypic profiles of tissue-infiltrating and peripheral blood CD66b+ cells were evaluated by flow cytometry. CD66b+/CD8+ cells crosstalk was investigated by in vitro experiments.

Results: CD66b+ cell infiltration in colorectal cancer is significantly associated with increased survival. Interestingly, neutrophils frequently colocalize with CD8+ T cells in colorectal cancer. Functional studies indicate that although neutrophils are devoid of direct antitumor potential, coculture with peripheral blood or tumor-associated neutrophils (TAN) enhances CD8+ T-cell activation, proliferation, and cytokine release induced by suboptimal concentrations of anti-CD3 mAb. Moreover, under optimal activation conditions, CD8+ cell stimulation in the presence of CD66b+ cells results in increasing numbers of cells expressing CD45RO/CD62L „central memory" phenotype. Importantly, combined tumor infiltration by CD66b+ and CD8+ T lymphocytes is associated with significantly better prognosis, as compared with CD8+ T-cell infiltration alone.

Conclusions: Neutrophils enhance the responsiveness of CD8+ Tcells to T-cell receptor triggering. Accordingly, infiltration by neutrophils enhances the prognostic significance of colorectal cancer infiltration by CD8+ T cells,suggesting that they might effectively promote antitumor immunity.

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Transcriptional response to hepatitis C virus infection and interferon-alpha treatment in the human liver

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Abstract

Hepatitis C virus (HCV) is widely used to investigate host–virus interactions. Cellular responses to HCV infection have been extensively studied *in vitro*. However, in human liver, interferon (IFN)-stimulated gene expression can mask direct transcriptional responses to infection. To better characterize the direct effects of HCV infection *in vivo*, we analyze the transcriptomes of HCV-infected patients lacking an activated endogenous IFN system. We show that expression changes observed in these patients predominantly reflect immune cell infiltrates rather than cell-intrinsic pathways. We also investigate the transcriptomes of patients with endogenous IFN activation, which paradoxically cannot eradicate viral infection. We find that most IFN-stimulated genes are induced by both recombinant IFN therapy and the endogenous IFN system, but with lower induction levels in the latter, indicating that the innate immune response in chronic hepatitis C is too weak to clear the virus. We show that coding and non-coding transcripts have different expression dynamics following IFN treatment. Several microRNA primary transcripts, including that of miR-122, are significantly down-regulated in response to IFN treatment, suggesting a new mechanism for IFN-induced expression fine-tuning.

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Pancreatic α Cell-Derived Glucagon-Related Peptides Are Required for β Cell Adaptation and Glucose Homeostasis

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Summary

Pancreatic α cells may process proglucagon not only to glucagon but also to glucagon-like peptide-1 (GLP-1). However, the biological relevance of paracrine GLP-1 for β cell function remains unclear. We studied effects of locally derived insulin secretagogues on β cell function and glucose homeostasis using mice with α cell ablation and with α cell-specific GLP-1 deficiency. Normally, intestinal GLP-1 compensates for the lack of α cell-derived GLP-1. However, upon aging and metabolic stress, glucose tolerance is impaired. This was partly rescued with the DPP-4 inhibitor sitagliptin, but not with glucagon administration. In isolated islets from these mice, glucose-stimulated insulin secretion was heavily impaired and exogenous GLP-1 or glucagon rescued insulin secretion. These data highlight the importance of α cell-derived GLP-1 for glucose homeostasis during metabolic stress and may impact on the clinical use of systemic GLP-1 agonists versus stabilizing local α cell-derived GLP-1 by DPP-4 inhibitors in type 2 diabetes.

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Silent synapses generate sparse and orthogonal action potential firing in adult-born hippocampal granule cells

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Abstract

In adult neurogenesis young neurons connect to the existing network via formation of thousands of new synapses. At early developmental stages, glutamatergic synapses are sparse, immature and functionally 'silent', expressing mainly NMDA receptors. Here we show in 2-to 3-week-old young neurons of adult mice, that brief-burst activity in glutamatergic fibers is sufficient to induce postsynaptic AP firing in the absence of AMPA receptors. The enhanced excitability of the young neurons lead to efficient temporal summation of small NMDA currents, dynamic unblocking of silent synapses and NMDA-receptor-dependent AP firing. Therefore, early synaptic inputs are powerfully converted into reliable spiking output. Furthermore, due to high synaptic gain, small dendritic trees and sparse connectivity, neighboring young neurons are activated by different distinct subsets of afferent fibers with minimal overlap. Taken together, synaptic recruitment of young neurons generates sparse and orthogonal AP firing, which may support sparse coding during hippocampal information processing.

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Ontogenic Identification and Analysis of Mesenchymal Stromal Cell Populations during Mouse Limb and Long Bone Development

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Summary

Bone-derived mesenchymal stromal cells (MSCs) differentiate into multiple lineages including chondro-and osteogenic fates and function in establishing the hematopoietic compartment of the bone marrow. Here, we analyze the emergence of different MSC types during mouse limb and long bone development. In particular, PDGFRα^{pos}SCA-1^{pos} (PαS) cells and mouse skeletal stem cells (mSSCs) are detected within the PDGFRα^{pos}CD51^{pos} (PαCD51) mesenchymal progenitors, which are the most abundant progenitors in early limb buds and developing long bones until birth. Long-bone-derived PαS cells and mSSCs are most prevalent in newborn mice, and molecular analysis shows that they constitute distinct progenitor populations from the earliest stages onward. Differential expression of CD90 and CD73 identifies four PαS subpopulations that display distinct chondro-and osteogenic differentiation potentials. Finally, we show that cartilage constructs generated from CD90^{pos} PαS cells are remodeled into bone organoids encompassing functional endothelial and hematopoietic compartments, which makes these cells suited for bone tissue engineering.

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PI3Kγ activity in leukocytes promotes adipose tissue inflammation and early-onset insulin resistance during obesity

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The phosphoinositide 3-kinase γ (PI3Kγ) plays a major role in leukocyte recruitment during acute inflammation and has been proposed to inhibit classical macrophage activation by driving immunosuppressive gene expression. PI3Kγ plays an important role in diet-induced obesity and insulin resistance. In seeking to determine the underlying molecular mechanisms, we showed that PI3Kγ action in high-fat diet–induced inflammation and insulin resistance depended largely on its role in the control of adiposity, which was due to PI3Kγ activity in a nonhematopoietic cell type. However, PI3Kγ activity in leukocytes was required for efficient neutrophil recruitment to adipose tissue. Neutrophil recruitment was correlated with proinflammatory gene expression in macrophages in adipose tissue, which triggered insulin resistance early during the development of obesity. Our data challenge the concept that PI3Kγ is a general suppressor of classical macrophage activation and indicate that PI3Kγ controls macrophage gene expression by non–cell-autonomous mechanisms, the outcome of which is context-dependent.

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Engineered, axially-vascularized osteogenic grafts from human adipose-derived cells to treat avascular necrosis of bone in a rat model

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Abstract

Background: Avascular necrosis of bone (AVN) leads to sclerosis and collapse of bone and joints. The standard of care, vascularized bone grafts, is limited by donor site morbidity and restricted availability. The aim of this study was to generate and test engineered, axially vascularized SVF cells-based bone substitutes in a rat model of AVN. Methods: SVF cells were isolated from lipoaspirates and cultured onto porous hydroxyapatite scaffolds within a perfusion-based bioreactor system for 5 days. The resulting constructs were inserted into devitalized bone cylinders mimicking AVN-affected bone. A ligated vascular bundle was inserted upon subcutaneous implantation of constructs in nude rats. After 1 and 8 weeks in vivo, bone formation and vascularization were analyzed. Results: Newly-formed bone was found in 80% of SVF-seeded scaffolds after 8 weeks but not in unseeded controls. Human ALU + cells in the bone structures evidenced a direct contribution of SVF cells to bone formation. A higher density of regenerative, M2 macrophages was observed in SVF-seeded constructs. In both experimental groups, devitalized bone was revitalized by vascularized tissue after 8 weeks. Conclusion: SVF cells-based osteogenic constructs revitalized fully necrotic bone in a challenging AVN rat model of clinically-relevant size. SVF cells contributed to accelerated initial vascularization, to bone formation and to recruitment of pro-regenerative endogenous cells.

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When patients fail UNAIDS' last 90 – the "failure cascade" beyond 90-90-90 in rural Lesotho, Southern Africa: a *prospective cohort study*

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Abstract

Introduction: HIV-infected individuals on first-line antiretroviral therapy (ART) in resource-limited settings who do not achieve the last "90" (viral suppression) enter a complex care cascade: enhanced adherence counselling (EAC), repetition of viral load (VL) and switch to second-line ART aiming to achieve resuppression. This study describes the "failure cascade" in patients in Lesotho.

Methods: Patients aged ≥16 years on first-line ART at 10 facilities in rural Lesotho received a first-time VL in June 2014. Those with VL ≥80 copies/mL were included in a cohort. The care cascade was assessed at four points: attendance of EAC, result of follow-up VL after EAC, switch to second-line in case of sustained unsuppressed VL and outcome 18 months after the initial unsuppressed VL. Multivariate logistic regression was used to assess predictors of being retained in care with viral resuppression at follow-up.

Results: Out of 1563 patients who underwent first-time VL, 138 (8.8%) had unsuppressed VL in June 2014. Out of these, 124 (90%) attended EAC and 116 (84%) had follow-up VL (4 died, 2 transferred out, 11 lost, 5 switched to second-line before follow-up VL). Among the 116 with follow-up VL, 36 (31%) achieved resuppression. Out of the 80 with sustained unsuppressed VL, 58 were switched to second-line, the remaining continued first line. At 18 months' follow-up in December 2015, out of the initially 138 with unsuppressed VL, 56 (41%) were in care and virally suppressed, 37 (27%) were in care with unsuppressed VL and the remaining 45 (33%) were lost, dead, transferred to another clinic or without documented VL. Achieving viral resuppression after EAC (adjusted odds ratio (aOR): 5.02; 95% confidence interval: 1.14–22.09; $p = 0.033$) and being switched to second-line in case of sustained viremia after EAC (aOR: 7.17; 1.90–27.04; $p = 0.004$) were associated with being retained in care and virally suppressed at 18 months of follow-up. Age, gender, education, time on ART and level of VL were not associated.

Conclusions: In this study in rural Lesotho, outcomes along the "failure cascade" were poor. To improve outcomes in this vulnerable patient group who fails the last "90", programmes need to focus on timely EAC and switch to second line for cases with continuous viremia despite EAC.

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5-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (PQR309), a Potent, Brain-Penetrant, Orally Bioavailable, Pan-Class I PI3K/mTOR Inhibitor as Clinical Candidate in Oncology

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Abstract

Phosphoinositide 3-kinase (PI3K) is deregulated in a wide variety of human tumors and triggers activation of protein kinase B (PKB/Akt) and mammalian target of rapamycin (mTOR). Here we describe the preclinical characterization of compound 1 (PQR309, bimiralisib), a potent 4,6-dimorpholino-1,3,5-triazine-based pan-class I PI3K inhibitor, which targets mTOR kinase in a balanced fashion at higher concentrations. No off-target interactions were detected for 1 in a wide panel of protein kinase, enzyme, and receptor ligand assays. Moreover, 1 did not bind tubulin, which was observed for the structurally related 4 (BKM120, buparlisib). Compound 1 is orally available, crosses the blood-brain barrier, and displayed favorable pharmacokinetic parameters in mice, rats, and dogs. Compound 1 demonstrated efficiency in inhibiting proliferation in tumor cell lines and a rat xenograft model. This, together with the compound's safety profile, identifies 1 as a clinical candidate with a broad application range in oncology, including treatment of brain tumors or CNS metastasis. Compound 1 is currently in phase II clinical trials for advanced solid tumors and refractory lymphoma.

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Sesn2 gene ablation enhances susceptibility to gentamicin-induced hair cell death via modulation of AMPK/mTOR signaling

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The process of gentamicin-induced hair cell damage includes the activation of oxidative stress processes. Sestrins, as stress-responsive proteins, protect cells against oxidative stress. Sestrins, particularly Sestrin-2, suppress excessive reactive oxygen species (ROS) accumulation and inhibit mammalian target of rapamycin complex 1 (mTORC1). Thus, we addressed the role of Sestrin-2 in the regulation of sensory hair cell survival after gentamicin exposure. Here, we show that Sestrins were expressed in the inner ear tissues, and Sestrin-2 immunolocalized in sensory hair cells and spiral ganglion (SG). The expression of Sestrin-2 was unchanged, and later downregulated, in gentamicin-treated explants from wild-type mice *in vitro*. Compared with wild-type mice, Sestrin-2 knockout mice exhibited significantly greater hair cell loss in gentamicin-treated cochlear explants. Significant downregulation of phosphorylation of AMP-activated protein kinase alpha (AMPKα) and upregulation of the 70-kDa ribosomal protein S6 kinase (p70S6K) were measured in wild-type cochlear explants exposed to gentamicin compared with their untreated controls. Such regulatory effect was not observed between explants from untreated and gentamicin-treated knockout mice. The gentamicin effect on mTOR signaling was rapamycin-sensitive. Thus, our data provide evidence that Sestrin-2 plays an important role in the protection of hair cells against gentamicin, and the mTOR signaling pathway appears to be modulated by gentamicin during hair cell death.

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Differential interactions between Notch and ID factors control neurogenesis by modulating Hes factor autoregulation

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Abstract

During embryonic and adult neurogenesis, neural stem cells (NSCs) generate the correct number and types of neurons in a temporospatial fashion. Control of NSC activity and fate is crucial for brain formation and homeostasis. Neurogenesis in the embryonic and adult brain differ considerably, but Notch signaling and inhibitor of DNA-binding (ID) factors are pivotal in both. Notch and ID factors regulate NSC maintenance; however, it has been difficult to evaluate how these pathways potentially interact. Here, we combined mathematical modeling with analysis of single-cell transcriptomic data to elucidate unforeseen interactions between the Notch and ID factor pathways. During brain development, Notch signaling dominates and directly regulates Id4 expression, preventing other ID factors from inducing NSC quiescence. Conversely, during adult neurogenesis, Notch signaling and Id2/3 regulate neurogenesis in a complementary manner and ID factors can induce NSC maintenance and quiescence in the absence of Notch. Our analyses unveil key molecular interactions underlying NSC maintenance and mechanistic differences between embryonic and adult neurogenesis. Similar Notch and ID factor interactions may be crucial in other stem cell systems.

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Tissue glycomics distinguish tumour sites in women with advanced serous adenocarcinoma

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In the era of precision medicine, the tailoring of cancer treatment is increasingly important as we transition from organ-based diagnosis towards a more comprehensive and patient-centric molecular diagnosis. This is particularly the case for highgrade serous adenocarcinomas of the ovary and peritoneum, which are commonly diagnosed at an advanced stage, and collectively treated and managed similarly. We characterized the *N*-and *O*-glycome of serous ovarian (OC) and peritoneal cancer (PC) tissues using PGC-LC-ESI-IT-MS/MS profiling and validated the discriminatory glycans and their corresponding glyco-gene expression levels using cell lines and transcriptomic data from 232 patients. Overall, the *N*-and *O*-glycan repertoires of both cancer types were found to comprise mostly of α2,6-sialylated glycan structures, with the majority of *N*-glycans displaying the biantennary mono-and disialylation as well as bisecting-type biantennary glycans. The MS profiling by PGC-LC also revealed several glycan structural isomers that corresponded to LacdiNAc-type (GalNAcβ1-4GlcNAc) motifs that were unique to the serous ovarian cancers and that correlated with elevated gene expression of *B4GALNT3* and *B4GALNT4* in patients with serous cancer. Statistical evaluation of the discriminatory glycans also revealed 13 *N*-and 3 *O*-glycans ($P < 0.05$) that significantly discriminated tumour-sampling sites, with LacdiNAc-type *N*-glycans (*m/z* 1205.0^{2-} and *m/z* 1059.4^{2-}) being associated with ovarian-derived cancer tissue and bisecting GlcNAc-type (*m/z* 994.9^{2-})and branched *N*-glycans (*m/z* 1294.0^{2-} and *m/z* 1148.4^{2-}) upregulated at the metastatic sites. Hence, we demonstrate for the first time that OC and PC display distinct molecular signatures at both their glycomic and transcriptomic levels. These signatures may have potential utility for the development of accurate diagnosis and personalized treatments.

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The hyaluronan-mediated motility receptor RHAMM promotes growth, invasiveness and dissemination of colorectal cancer

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Abstract

In colorectal cancer (CRC), RHAMM is an independent adverse prognostic factor. The aim of the study was therefore to investigate on the role of RHAMM as a potential direct driver of cell proliferation and migration in CRC cell lines and to identify pathways dependent on RHAMM in human CRC.

Proliferation, cell cycle alterations and invasive capacity were tested in two RHAMM- and control- knockdown CRC cell lines by flow cytometry and *in vitro* assays. Tumorigenicity and metastasis formation was assessed in immunodeficient mice. RNA-Seq and immunohistochemistry was performed on six RHAMM+/– primary CRC tumors.

In vitro, silencing of RHAMM inhibited CRC cell migration and invasion by 50% ($p<0.01$). *In vivo*, RHAMM knockdown resulted in slower growth, lower tumor size ($p<0.001$) and inhibition of metastasis ($p<0.001$). Patients with RHAMM-high CRC had a worse prognosis ($p=0.040$) and upregulated pathways for cell cycle progression and adhesion turnover.

RHAMM overexpression is correlated with increased migration and invasion of CRC cells, leads to larger, fast growing tumors, and its downregulation essentially abolishes metastasis in mouse models. RHAMM is therefore a promising therapeutic target in all CRC stages as its inhibition affects growth and dissemination of the primary CRC as well as the metastases.

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Strengthening HIV therapy and care in rural Tanzania affects rates of viral suppression

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Objectives: To assess viral suppression rates, to assess prevalence of acquired HIV drug resistance and to characterize the spectrum of HIV-1 drug resistance mutations (HIV-DRM) in HIV-1-infected patients in a rural Tanzanian HIV cohort.

Methods: This was a cross-sectional study nested within the Kilombero and Ulanga Antiretroviral Cohort. Virological failure was defined as HIV-1 RNA ≥ 50 copies/mL. Risk factors associated with virological failure and with the development of HIV-DRM were assessed using logistic regression.

Results: This study included 304 participants with a median time on ART of 3.5 years (IQR = 1.7–5.3 years); 91% were on an NNRTI-based regimen and 9% were on a boosted PI-based regimen. Viral suppression was observed in 277/304 patients (91%). Of the remaining 27 patients, 21 were successfully genotyped and 17/21 (81%) harboured ≥ 1 clinically relevant HIV-DRM. Of these, 13/17 (76.5%) had HIV-1 plasma viral loads of > 1000 copies/mL. CD4 cell count < 200 cells/mm^3 at the time of recruitment was independently associated with a close to 8-fold increased odds of virological failure [adjusted OR (aOR) = 7.71, 95% CI = 2.86–20.78, $P < 0.001$] and with a > 8-fold increased odds of developing HIV-DRM (aOR = 8.46, 95% CI = 2.48–28.93, $P = 0.001$).

Conclusions: High levels of viral suppression can be achieved in rural sub-Saharan Africa when treatment and care programmes are well managed. In the absence of routine HIV sequencing, the WHO-recommended threshold of 1000 viral RNA copies/mL largely discriminates virological failure secondary to HIV-DRM.

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The Stimulation of Macrophages with TLR Ligands Supports Increased IL-19 Expression in Inflammatory Bowel Disease Patients and in Colitis Models

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IL-19, a member of the IL-10 cytokine family that signals through the IL-20 receptor type I (IL-20Rα:IL-20Rβ), is a cytokine whose function is not completely known. In this article, we show that the expression of *IL19* in biopsies of patients with active ulcerative colitis was increased compared with patients with quiescent ulcerative colitis and that colitis was attenuated in IL-19– deficient mice. The disruption of the epithelial barrier with dextran sodium sulfate leads to increased IL-19 expression. Attenuated colitis in IL-19–deficient animals was associated with reduced numbers of IL-6–producing macrophages in the inflamed colonic lamina propria. Microbial-driven expression of IL-19 by intestinal macrophages may contribute to the pathogenesis of inflammatory bowel disease.

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Polo-Like Kinase 2 is Dynamically Regulated to Coordinate Proliferation and Early Lineage Specification Downstream of Yes-Associated Protein 1 in Cardiac Progenitor Cells

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Background–Recent studies suggest that adult cardiac progenitor cells (CPCs) can produce new cardiac cells. Such cell formation requires an intricate coordination of progenitor cell proliferation and commitment, but the molecular cues responsible for this regulation in CPCs are ill defined.

Methods and Results–Extracellular matrix components are important instructors of cell fate. Using laminin and fibronectin, we induced two slightly distinct CPC phenotypes differing in proliferation rate and commitment status and analyzed the early transcriptomic response to CPC adhesion (<2 hours). Ninety-four genes were differentially regulated on laminin versus fibronectin, consisting of mostly downregulated genes that were enriched for Yes-associated protein (YAP) conserved signature and TEA domain family member 1 (TEAD1)-related genes. This early gene regulation was preceded by the rapid cytosolic sequestration and degradation of YAP on laminin. Among the most strongly regulated genes was polo-like kinase 2 (*Plk2*). *Plk2* expression depended on YAP stability and was enhanced in CPCs transfected with a nuclear-targeted mutant YAP. Phenotypically, the early downregulation of *Plk2* on laminin was succeeded by lower cell proliferation, enhanced lineage gene expression (24 hours), and facilitated differentiation (3 weeks) compared with fibronectin. Finally, overexpression of Plk2 enhanced CPC proliferation and knockdown of Plk2 induced the expression of lineage genes.

Conclusions–Plk2 acts as coordinator of cell proliferation and early lineage commitment in CPCs. The rapid downregulation of Plk2 on YAP inactivation marks a switch towards enhanced commitment and facilitated differentiation. These findings link early gene regulation to cell fate and provide novel insights into how CPC proliferation and differentiation are orchestrated.

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Pharmacokinetics and Pharmacodynamics of Lisdexamfetamine Compared with D-Amphetamine in Healthy Subjects

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Rationale: Lisdexamfetamine is a prodrug of D-amphetamine used for the treatment of attention-deficit/hyperactivity disorder (ADHD). Lisdexamfetamine is thought to have a prolonged pharmacokinetic profile compared with oral D-amphetamine, possibly associated with lower drug liking and a lower risk of oral misuse. However, differences in the pharmacokinetics and pharmacodynamics of lisdexamfetamine and D-amphetamine have not been directly compared.

Methods: Equimolar doses of D-amphetamine (40 mg) and lisdexamfetamine (100 mg), and placebo were administered in 24 healthy subjects in a randomized, double-blind, placebo-controlled, cross-over study. Plasma concentrations of amphetamine, subjective effects, and vital signs were repeatedly assessed. The pharmacokinetic parameters were determined using compartmental modeling.

Results: The increase in plasma concentrations of amphetamine had a 0.6 ± 0.6 h (mean ± SD) longer lag time and reached peak levels 1.1 ± 1.5 h later after lisdexamfetamine administration compared with D-amphetamine administration, but no differences in maximal concentrations or total exposure (AUC) were found between the two treatments. Consistent with the pharmacokinetics, the subjective and cardiovascular stimulant effects of lisdexamfetamine also occurred later compared with D-amphetamine. However, no differences in peak ratings of potentially abuse-related subjective drug effects (e.g., drug liking, drug high, stimulation, happy, well-being, and self-confidence) were observed after lisdexamfetamine administration compared with D-amphetamine administration. Lisdexamfetamine and D-amphetamine also produced similar peak increases in mean arterial blood pressure, heart rate, body temperature, pupil size, and adverse effects.

Conclusion: The pharmacokinetics and pharmacodynamics of lisdexamfetamine are similar to D-amphetamine administered 1h later. Lisdexamfetamine is likely associated with a similar risk of oral abuse as D-amphetamine. The study was registered at ClinicalTrials.gov (NCT02668926).

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Hepatocellular Toxicity Associated with Tyrosine Kinase Inhibitors: Mitochondrial Damage and Inhibition of Glycolysis

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Tyrosine kinase inhibitors (TKIs) are anticancer drugs with a lesser toxicity than classical chemotherapeutic agents but still with a narrow therapeutic window. While hepatotoxicity is known for most TKIs, underlying mechanisms remain mostly unclear. We therefore aimed at investigating mechanisms of hepatotoxicity for imatinib, sunitinib, lapatinib and erlotinib *in vitro*. We treated HepG2 cells, HepaRG cells and mouse liver mitochondria with TKIs (concentrations 1–100 μM) for different periods of time and assessed toxicity. In HepG2 cells maintained with glucose (favoring glycolysis), all TKIs showed a time-and concentration-dependent cytotoxicity and, except erlotinib, a drop in intracellular ATP. In the presence of galactose (favoring mitochondrial metabolism), imatinib, sunitinib and erlotinib showed a similar toxicity profile as for glucose whereas lapatinib was less toxic. For imatinib, lapatinib and sunitinib, cytotoxicity increased in HepaRG cells induced with rifampicin, suggesting formation of toxic metabolites. In contrast, erlotinib was more toxic in HepaRG cells under basal than CYP-induced conditions. Imatinib, sunitinib and lapatinib reduced the mitochondrial membrane potential in HepG2 cells and in mouse liver mitochondria. In HepG2 cells, these compounds increased reactive oxygen species production, impaired glycolysis, and induced apoptosis. In addition, imatinib and sunitinib impaired oxygen consumption and activities of complex I and III (only imatinib), and reduced the cellular GSH pool. In conclusion, imatinib and sunitinib are mitochondrial toxicants after acute and longterm exposure and inhibit glycolysis. Lapatinib affected mitochondria only weakly and inhibited glycolysis, whereas the cytotoxicity of erlotinib could not be explained by a mitochondrial mechanism.

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Expansion of human midbrain floor plate progenitors from induced pluripotent stem cells increases dopaminergic neuron differentiation potential

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Human induced pluripotent stem cells (hiPSCs) are invaluable to study developmental processes and disease mechanisms particularly in the brain. hiPSCs can be differentiated into mature and functional dopaminergic (DA) neurons. Having robust protocols for the generation of differentiated DA neurons from pluripotent cells is a prerequisite for the use of hiPSCs to study disease mechanisms, for drug discovery, and eventually for cell replacement therapy. Here, we describe a protocol for generating and expanding large numbers of homogeneous midbrain floor plate progenitors (mFPPs) that retain efficient DA neurogenic potential over multiple passages and can be cryobanked. We demonstrate that expanded mFPPs have increased DA neuron potential and differentiate more efficiently and rapidly than progenitors generated by standard protocols. In addition, this novel method results in increased numbers of DA neurons that *in vitro* show characteristic electrophysiological properties of nigrostriatal DA neurons, produce high levels of dopamine, and integrate into host mice when grafted *in vivo*. Thus, we describe a robust method for producing human mesencephalic DA neurons from hiPSCs.

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Engineering of an *angiogenic niche* by perfusion culture of adipose-derived stromal vascular fraction cells

Giulia Cerino, Emanuele Gaudiello, Manuele Giuseppe Muraro, Friedrich Eckstein, Ivan Martin, Arnaud Scherberich & Anna Marsano

In vitro recapitulation of an organotypic stromal environment, enabling efficient angiogenesis, is crucial to investigate and possibly improve vascularization in regenerative medicine. Our study aims at engineering the complexity of a vascular milieu including multiple cell-types, a stromal extracellular matrix (ECM), and molecular signals. For this purpose, the human adipose stromal vascular fraction (SVF), composed of a heterogeneous mix of pericytes, endothelial/stromal progenitor cells, was cultured under direct perfusion flow on three-dimensional (3D) collagen scaffolds. Perfusion culture of SVF-cells reproducibly promoted *in vitro* the early formation of a capillary-like network, embedded within an ECM backbone, and the release of numerous pro-angiogenic factors. Compared to static cultures, perfusion-based engineered constructs were more rapidly vascularized and supported a superior survival of delivered cells upon *in vivo* ectopic implantation. This was likely mediated by pericytes, whose number was significantly higher (4.5-fold) under perfusion and whose targeted depletion resulted in lower efficiency of vascularization, with an increased host foreign body reaction. 3D-perfusion culture of SVF-cells leads to the engineering of a specialized milieu, here defined as an *angiogenic niche*. This system could serve as a model to investigate multi-cellular interactions in angiogenesis, and as a module supporting increased grafted cell survival in regenerative medicine.

Departments of Biomedicine and Surgery, University of Basel and University Hospital of Basel, 4031, Basel,

Scientific Reports | 7:45367 | DOI: 10.1038/srep45367 IF 4,259

Altered (neo-) lacto series glycolipid biosynthesis impairs α2-6 sialylation on *N*-glycoproteins in ovarian cancer cells

Shahidul Alam[1,2,*], Merrina Anugraham[1,*], Yen-Lin Huang[1], Reto S. Kohler[1], Timm Hettich[3], Katharina Winkelbach[1], Yasmin Grether[1], Mónica Núñez López[1], Nailia Khasbiullina[4], Nicolai V. Bovin[4], Götz Schlotterbeck[3] & Francis Jacob[1,2]

The (neo-) lacto series glycosphingolipids (nsGSLs) comprise of glycan epitopes that are present as blood group antigens, act as primary receptors for human pathogens and are also increasingly associated with malignant diseases. Beta-1, 3-*N*-acetyl-glucosaminyl-transferase 5 (B3GNT5) is suggested as the key glycosyltransferase for the biosynthesis of nsGSLs. In this study, we investigated the impact of CRISPR-*Cas9* -mediated gene disruption of *B3GNT5* (Δ*B3GNT5*) on the expression of glycosphingolipids and *N*-glycoproteins by utilizing immunostaining and glycomics-based PGC-UHPLCESI-QTOF-MS/MS profiling. Δ*B3GNT5* cells lost nsGSL expression coinciding with reduction of α2-6 sialylation on *N*-glycoproteins. In contrast, disruption of *B4GALNT1*, a glycosyltransferase for ganglio series GSLs did not affect α2-6 sialylation on N-glycoproteins. We further profiled all known α2-6 sialyltransferase-encoding genes and showed that the loss of α2-6 sialylation is due to silencing of *ST6GAL1* expression in Δ*B3GNT5* cells. These results demonstrate that nsGSLs are part of a complex network affecting *N*-glycosylation in ovarian cancer cells.

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[*] These authors contributed equally to this work.

Scientific Reports SCIENTIFIC REPORTS DOI:10.1038/s41598-017-06731-w IF 4,259

The Role of Inflammation in β-cell Dedifferentiation

Thierry M. Nordmann[1], Erez Dror[1], Friederike Schulze[1], Shuyang Traub[1], Ekaterine Berishvili[2], Charlotte Barbieux[2], Marianne Böni-Schnetzler[1] & Marc Y. Donath[1]

Chronic inflammation impairs insulin secretion and sensitivity. β-cell dedifferentiation has recently been proposed as a mechanism underlying β-cell failure in T2D. Yet the effect of inflammation on β-cell identity in T2D has not been studied. Therefore, we investigated whether pro-inflammatory cytokines induce β-cell dedifferentiation and whether anti-inflammatory treatments improve insulin secretion via β-cell redifferentiation. We observed that IL-1β, IL-6 and TNFα promote β-cell dedifferentiation in cultured human and mouse islets, with IL-1β being the most potent one of them. In particular, β-cell identity maintaining transcription factor *Foxo1* was downregulated upon IL-1β exposure. *In vivo*, anti-IL-1β, anti-TNFα or NF-kB inhibiting sodium salicylate treatment improved insulin secretion of isolated islets. However, only TNFα antagonism partially prevented the loss of β-cell identity gene expression. Finally, the combination of IL-1β and TNFα antagonism improved insulin secretion of ex vivo isolated islets in a synergistic manner. Thus, while inflammation triggered β-cell dedifferentiation and dysfunction *in vitro*, this mechanism seems to be only partly responsible for the observed *in vivo* improvements in insulin secretion.

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European Journal of Immunology European Journal of Immunology 2017. 47: 1171–1180 IF 4,227

Contact sensitizers trigger human CD1-autoreactive T-cell responses

Richard J. Betts[1,2], Adrijana Perkovic[3], Subhashree Mahapatra[4], Aurélia Del Bufalo[4], Kaddy Camara[5], Amy R. Howell[5], Silvia Martinozzi Teissier[4,*], Gennaro De Libero[1,3] and Lucia Mori[1,3,*]

Allergic contact dermatitis is a primarily T-cell-mediated inflammatory skin disease induced by exposure to small molecular-weight haptens, which covalently bind to proteins. The abundance of cutaneous T cells that recognize CD1a antigen-presenting molecules raises the possibility that MHC-independent antigen presentation may be relevant in some hapten-driven immune responses. Here we examine the ability of contact sensitizers to influence CD1-restricted immunity. Exposure of human antigen-presenting cells such as monocyte-derived dendritic cells and THP-1 cells to the prototypical contact sensitizer dinitrochlorobenzene potentiated the response of CD1a-and CD1d-autoreactive T cells, which released a vast array of cytokines in a CD1-and TCR-dependent manner. The potentiating effects of dinitrochlorobenzene depended upon newly synthesized CD1 molecules and the presence of endogenous stimulatory lipids. Further examination of a broad panel of contact sensitizers revealed 1,4-benzoquinone, resorcinol, isoeugenol, and cinnamaldehyde to activate the same type of CD1-restricted responses. These findings provide a basis for the antigen-specific activation of skin-associated CD1-restricted Tcells by smallmolecules andmay have implications forcontact-sensitizer-induced inflammatory skin diseases.

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J. Biol. Chem. ASBMB (2017) 292(43) 17928–17938 IF 4,125

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

Tanja Blumer[1,2], Mairene Coto-Llerena[1,2], Francois H. T. Duong[1,2,*], and Markus H. Heim[1,2,*]

Type I (α and β) and type III (λ) IFNs are induced upon viralinfection through host sensory pathways that activate IFN regulatory factors (IRFs) and nuclear factor κB. Secreted IFNs induce autocrine and paracrine signaling through the JAK-STAT pathway, leading to the transcriptional induction of hundreds of IFN-stimulated genes, among them sensory pathway components such as cGAS, STING, RIG-I, MDA5,and the transcription factor IRF7, which enhance the induction of IFN-αs and IFN-λs. This positive feedback loop enables a very rapid and strong host response that, at some point, has to be controlled by negative regulators to maintain tissue homeostasis. Type I IFN signaling is controlled by the inducible negative regulators suppressorof cytokine signaling 1 (SOCS1), SOCS3, and ubiquitin-specific peptidase 18 (USP18). The physiological role of these proteins in IFN-γ signaling has not been clarified. Here we used knockout cell lines and mice to show that IFN-λ signaling is regulated by SOCS1 but not by SOCS3 or USP18. These differences were the basis for the distinct kinetic properties of type I and III IFNs. We found that IFN-α signaling is transient and becomes refractory after hours, whereas IFN-A provides a long-lasting IFN-stimulated gene induction.

From the
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[*] Both authors contributed equally to this work.

J. Viral Hepatitis JVH 2017;24:662–671 IF 4,122

Hepatitis B virus covalently closed circular DNA homeostasis is independent of the lymphotoxin pathway during chronic HBV infection

M.-A. Meier[1] | A. Suslov[1] | S. Ketterer[1] | M. H. Heim[1,2] | S. F. Wieland[1]

Summary
Current treatment options for patients with chronic hepatitis B virus (HBV) infection are not curative as they are not effective in eliminating covalently closed circular DNA (cccDNA). cccDNA is a stable template for HBV transcription in the nucleus of hepatocytes and is thought to be one of the main factors responsible for HBV persistence. Recently, activation of the lymphotoxin beta receptor (LTβR) has been shown to trigger degradation of cccDNA through induction of cytidine deaminases of the APOBEC3 family in HBV cell culture model systems. To assess the presence and relevance of such mechanisms in the liver of chronically HBV- infected patients, we compared intrahepatic cccDNA levels with the expression levels of lymphotoxins and some of their target genes (eg APOBEC deaminases) in liver biopsy tissue. Our results confirm elevated gene expression levels of components of the lymphotoxin pathway including lymphotoxin alpha (LTα), lymphotoxin beta (LTβ), APOBEC3B (A3B) and APOBEC3G (A3G) in the chronically HBV- infected liver compared to uninfected liver. Furthermore, expression levels of the genes of the APOBEC deaminase family were correlated with those of LTα and LTβ gene expression, consistent with lymphotoxin- mediated upregulation of APOBEC gene expression. However, intrahepatic cccDNA and HBV replication levels were not correlated with LTα, LTβ and APOBEC gene expression. In conclusion, these results suggest that although the lymphotoxin pathway is activated in the chronically HBV- infected liver, it has no major impact on HBV cccDNA metabolism in chronic HBV infection.

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Toxicological Sciences SOT Society of Toxicology 157(1), 2017, 183–195 IF 4,081

Hepatocellular Toxicity of Imidazole and Triazole Antimycotic Agents

Patrizia Haegler[1,2], Lorenz Joerin[1,2], Stephan Krähenbühl[1,2,3], and Jamal Bouitbir[1,2,3]

Abstract

Hepatotoxicity has been described for all antimycotic azoles currently marketed. A possible mechanism involving mitochondrial dysfunction has been postulated for ketoconazole, but not for the other azoles. The aim of the current investigations was to study the toxicity of different azoles in human cell models and to find out mechanisms of their toxicity. In HepG2 cells, posaconazole and ketoconazole were cytotoxic starting at 20 and 50 μM and decreased the cellular ATP content starting at 5 and 10 μM, respectively. In HepaRG cells, cytotoxicity started at 20 and 100 μM for posaconazole and ketoconazole, respectively, and was slightly accentuated by cytochrome P450 3A4 induction with rifampicin and 1A2 with 3-methylcholantrene. Voriconazole and fluconazole were not cytotoxic. In isolated mouse liver mitochondria, ketoconazole impaired membrane potential and complex I activity, whereas the other azoles were not toxic. In HepG2 cells exposed for 24 h, both posaconazole and ketoconazole (but not fluconazole or voriconazole) decreased the mitochondrial membrane potential, impaired the function of enzyme complexes of the electron transport chain, were associated with mitochondrial superoxide accumulation, decreased mitochondrial DNA and induced apoptosis. In HepG2 cells with mitochondrial dysfunction induced by the vitamin B12 antagonist hydroxycobalamin[c-lactam], cytotoxicity and/or ATP depletion was more accentuated than in untreated cells. We conclude that ketoconazole and posaconazole are mitochondrial toxicants starting at concentrations, which can be reached in vivo. Cytotoxicity and ATP depletion are more accentuated in cells with mitochondrial damage, suggesting that preexisting mitochondrial dysfunction is a susceptibility factor for hepatotoxicity associated with these drugs.

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Selected publications by DBM members

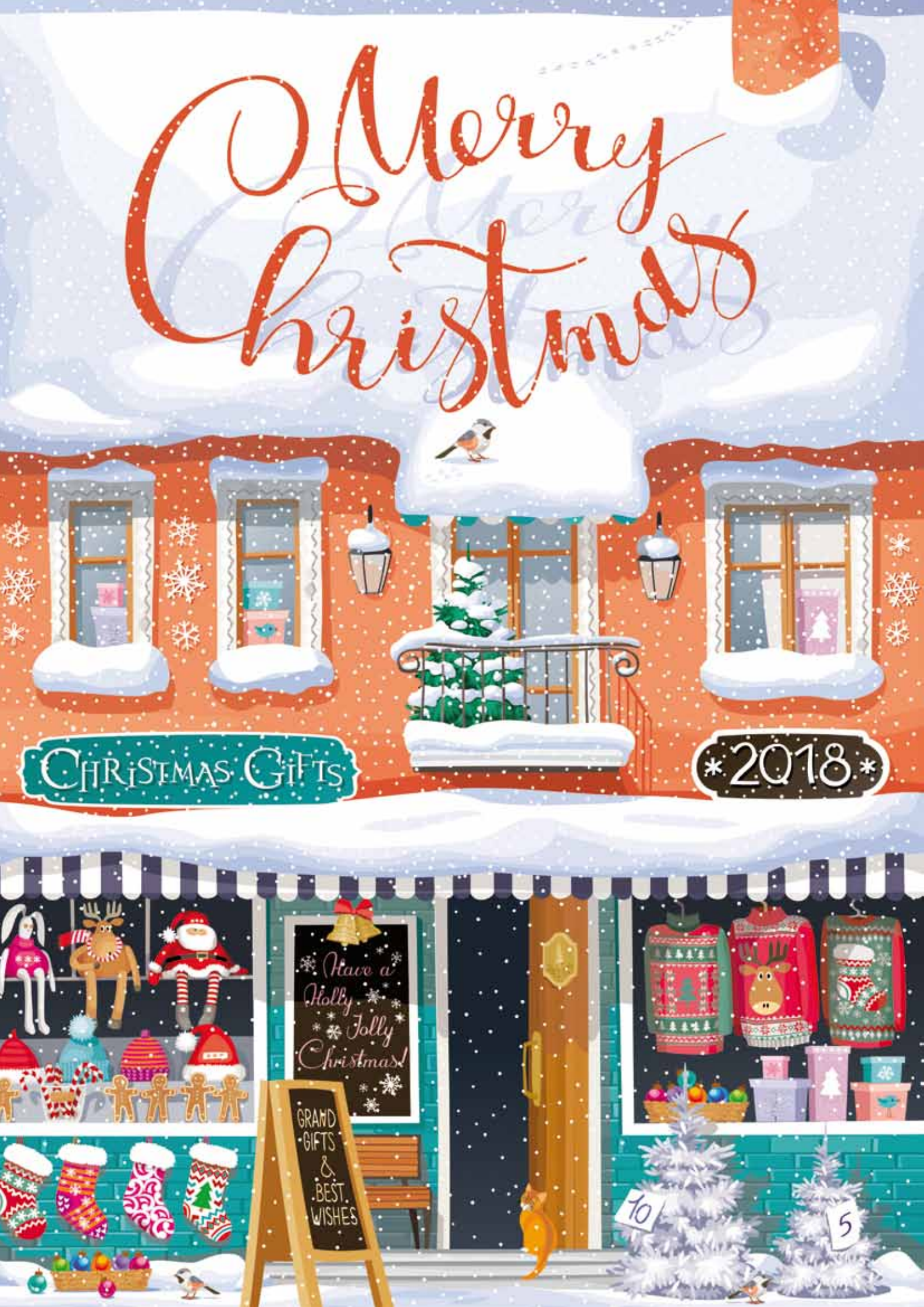
Above you can find the abstracts of recent articles published by members of the DBM. The abstracts are grouped according to the impact factor of the journal where the work appeared. To be included, the papers must meet the following criteria:

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 February 28, 2018.


Merry Christmas
CHRISTMAS GIFTS
2018
Have a Holly Jolly Christmas!
GRAND GIFTS & BEST WISHES
10
5

DEPARTEMENT BIOMEDIZIN HEBELSTRASSE

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Applied Microbiology Research
Costache Andrei-Dragos
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Lischer Mirko
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Transplantation and Clinical Virology
Wilhelm Maud
Transplantation and Clinical Virology

Department of Biomedicine Research Day

Thursday, January 19, 2018, 8:00 am – 13:20 pm
Location: Kleiner Hörsaal, Zentrum für Lehre und Forschung (ZLF)

08:00	Welcome (Radek Skoda)	
08:05 – 08:25	Gerhard Christofori	"Cancer cell plasticity in metastasis, in drug resistance and as therapeutic target"
08:35 – 08:55	Matthias Mehling	"Microfluidics-based analysis of immune cell navigation: From basic concepts to clinical samples from patients with multiple sclerosis"
09:05 – 09:25	Carolyn King	"CD4 Memory T cells: survival of the fittest"
09:35 – 09:55	Marijke Brink	"Tyrosine kinase receptor signalling in cardiac disease"
10:05 – 10:35	Raija Lindberg / Tobias Derfuss	"Defining players in Multiple Sclerosis: From B cells to extracellular microRNAs"
10:45 – 11:15	**Coffee break**	
11:15 – 11:35	Claudia Cavelti-Weder	"Role of the gastrointestinal tract's innate immune system in metabolic disease"
11:45 – 12:05	Sara Meyer	"Targeting oncogenic signaling and resistance to therapy in myeloid malignancies"
12:15 – 12:35	Eline Pecho-Vrieseling	"Do neural networks pave the way for mutant huntingtin protein spreading? A non-cell autonomous mechanism of neurodegeneration"
12:45 – 13:10	Rolf Zeller / Aimée Zuniga	"Transcriptional regulation of developmental processes by super-enhancers"
13:20	**END**	

Congratulations

Tara Mona Anette Hanser
Geboren am 11.09.2017

Raffaele Emilio Campo Müller
Geboren am 28.09.2017

Herzlich willkommen, allerseits!

Leandro Caselle Pires
Geboren am 08.09.2017

Ophelia Rae Bantug
Geboren am 30.07.2017

Das DBM gratuliert ganz herzlich!

Azmina Mohammedyaseen
Geboren am 14.09.2017

Leo Chensong Yang
Geboren am 13.08.2017

Herzlich willkommen, allerseits!

Lorenzo Calabrese Mele
Geboren am 18.11.2017

Wiehnacht z' Basel

Basler Brunsli (Rezept von 1938)

500 Gramm Zucker
500 Gramm geriebene Mandeln
250 Gramm geriebene Schokolade
gut vermischen
10 Esslöffel kaltes Wasser dazu und kneten (oder 2-3 Esslöffel Kirsch und entsprechend weniger Wasser)
Auf Zucker auswallen (8-10mm dick) und Förmchen ausstechen.
Gutzi auf ein mit Mehl bestreutes Backblech legen und über Nacht trocknen lassen. Dann 4 Minuten auf 230 Grad backen.

Anisbrötli

4 Eier
500 Gramm Puderzucker
verrühren bis die Masse hell und schaumig ist
1 Prise Salz
1-1,5 EL Anis
1 EL Kirsch
darunterrühren
500 Gramm Mehl dazusieben und zu einem Teig zusammenfügen
10 Minuten ruhen lassen
Teig auf wenig Mehl 1cm dick auswallen. Förmchen ausstechen und auf ein mit Butter eingestrichenes Backblech legen. Bei Raumtemperatur 24 Stunden trocknen lassen.
Im unteren Teil des Ofens ca. 20 Minuten backen bei 150Grad, dabei die Ofentüre nicht ganz schliessen (mit Holzkelle offen halten). Die Anisbrötli sollen hell bleiben beim Backen.

Manuela Bernasconi

Christmas in Romania

Christmas in Romania ***(Crăciunul)*** is the most expected and loved holiday of the year. It is the time when families come together in an atmosphere of joy and sacre, bliss and happiness and when all is forgiven and the children await for Santa Claus ***(Moş Crăciun)*** to bring their presents. It is also an orthodox traditional holiday, celebrated all across the country, with a few places specific for their own ways of spending it.

Advent

The period of Advent (Post) is the period when people usually refrain from eating meat or animal products and also cleanse their mind and spirit. It is basically a spiritual journey to purifying the soul, but also a good waiting period for all the treats and food accompanying the Christmas holidays, making them even more delicious. During this period, people attend religious ceremonies and pray for the loved ones or for the departed.

The Opening of the Christmas season

The Christmas holiday season begins with the Romanian National Day, on the 1st of December, when we celebrate the union of the regions: Basarabia, Bucovina, Transilvania, Banat, Maramureş, Crişana, Sătmar with the Kingdom of Romania in 1918, at the Great National Council (Marea Adunare Naţională) held in the city of Alba-Iulia, under the reign of emperor Ferdinand the 1st of Hohenzollern-Sigmaringen. It starts with the National Military Parade held both in Alba-Iulia and Bucharest, in the presence of the Romanian President in one of the two cities, by choice. It is accompanied by Romanian national anthem, specific Romanian songs, dance and food, in the presence of people wearing the national Romanian outfit.

Romanian National Day


Bukarest Christmas Market

This is the time when the Christmas markets in the cities open, welcoming the people from all around to taste the specific Christmas food (homemade sausages – ***cârnaţi***, pork specialities like ***tobă*** – which is a cleaned pork stomach filled with chunks of meat, ham and a homemade gelatin out of the boiled chicken or pork bone marrow spiced with garlic, and ***caltaboş***) accompanied by the Romanian boiled wine ***(vin fiert)***, which is made by boiling the red or white wine together with cinnamon, nutmeg, cloves, pepper and serving it hot. Of course there is also the sweets: ***scovergi*** (basically fried thin dough in a pan, served with powdered sugar), ***turtă dulce*** (gingerbread) and the most fa-

Orthodox Cathedral and Lupa capitolina, Timisoara

mous of them all, cozonac (the uniquely Romanian homemade sweet speciality; the recipe for which you will find at the end of the article). All of the big cities have their own Christmas market, the most famous of them all being in the capital, Bucharest.

Then comes the Saint Nicholas holiday ***(Moş Nicolae)*** on the 6th of December, when the children clean their shoes in the evening before, so that Moş Nicolae can come and bring them sweets, if they were nice. If not, tradition says they will receive a wooden stick called ***nuia***.

The sacrificing of the pig (Ignatul)

On the 20th of December there was an old heathen dacic tradition of sacrificing a pig in order to pray for prosperity and wealth for the year to come. The peoples` customs during the winter holidays say that this is to please the will of the Gods. It is also Saint Ignatius day. He was a follower of the orthodox belief, and it is from this that the name comes. The two opposite traditions have blended so that nowadays, no one really knows the true significance of it, and it has become more of a reason to unite the whole family under a single roof. The man of the house prepares the meat and removes the bowels, making sure that all is healthy and cleaning them properly so that they can be ready for the cooking process. The skin of the pig is cut into pieces and put in the freezer with salt so that it can be consumed later either raw or cooked as the most wanted specialty known as ***şorici***. This is the time when the food preparations begin in every house. These last until Christmas Eve, and all in all it is a very time and effort consuming tradition, which brings all of the family members together.

The Christmas

On Christmas Eve, each member of the family has a specific task: the men go out and buy the gifts and Christmas tree so they can prepare it and set it up for decoration. This is usually done by the children together with their father. The women of the house make the final meal preparations, usually the sweets. After the tasks are done and the

Colaci

house is fully decorated, the children are sent early to bed so that Moş Crăciun can come and deliver the presents.

On the day of Christmas, the children wake up excited and full of joy to open their presents and see what Moş Crăciun has brought them. The morning is also the time when the carollers come and sing about the birth of Jesus, receiving, as is tradition, ***colaci*** (homemade knot-shaped pretzels) and money. People usually keep their doors open for the carollers so that they can "embrace the news of the birth of Jesus into their homes".

The Christmas meal

The Christmas meal usually starts with a prayer, to express gratitude that the whole family is back together and able to celebrate the birth of Jesus once more. Then, the food is ready and the table is set.

Lunch starts with an appetizer: ***Piftie*** – this is only served cold and it consists of boiled meat, either pork or chicken, in a gelatin-like substance that hold the pieces of meat together, ***Tobă*** and of course ***Şorici***.

The main courses are: Sarmale – stuffed cabbage or grapevine leafs with a mix of rice, vegetables, miced meat (pork usually) and condiments, ***Cârnaţi*** – homemade sausages, ***Caltaboş*** or ***Chişcă*** – cleaned pork intestines filled with spiced minced meat and vegetables. As one can see, it is very useful to have a pig for sacrificing on Ignat Day. The food is served together with red wine, usually from homegrown vines.

As desert, the traditional ***Cozonac*** is the most awaited one. Every member of the family has a taste of it and through this, completes the Christmas spirit of the year…

Andrei-Dragos Costache

The Recipe for Cozonac

Ingredients:

<u>For the dough:</u>
- 1 kg of flour
- 50 g of fresh yeast
- 500 ml of milk
- 100 g butter
- 250 g of sugar
- 5 yolks
- a teaspoon of salt
- lemon and orange peel
- 2 vanilla sugar sachets

<u>For the filling:</u>
- 250 g ground nutmeg
- 5 egg whites
- 100 g of sugar
- 2 tablespoons of cocoa
- 1 salt of salt
- the essence of rom

<u>To spoil the cozonac:</u>
- 1 egg
- 1 teaspoon of sugar

Cozonac

How to prepare:

The flour is sieved 3 times a few hours before cooking to make it aerated.

The butter should be removed from the fridge and set at room temperature one hour before use.

Heat the milk in a pan then add the lemon and orange peel, and the vanilla sugar and mix well.

Mix the yolks and the sugar together in a separate bowl, mixing until the sugar has dissolved.

Now, we have to prepare ***Maiaua*** (the sourdough). Mix the yeast with a teaspoon of sugar until it is homogenized, add 3 tablespoons of warm milk and one tablespoon of flour, then mix a little. Place the flour in a large bowl, and in the middle of it make a nest into which the ***Maiaua*** is placed and left for 10–15 minutes. When the ***Maiaua*** has doubled in volume, add a bit of salt, the warm milk and the yolks mixed with the sugar.

Next, you will have to be armed with a lot of patience, because the success of a well-risen and very fluffy cake is in kneading. The dough must be kneaded with fists and palms, very energetically, for about 30 minutes. During the kneading, we butter our hands, so as to incorporate the butter in the dough very well.

Cover the dough and put it in a warm place for one hour. It is very important that the dough is kept in a constantly warm place, so that it will prove well. While the dough proves, we make the filling.

The whites are whisked with a pinch of salt till stiff, gradually adding the 100 g of sugar as they are being whisked.

Mix the ground nuts with 2 tablespoons of cocoa, one teaspoon of rum essence and then fold into the whisked egg whites. Fold the nuts in gently to keep the mixture fluffy.

Next prepare the two baking tins that you will use for the cozonac. Line each with baking parchment and then oil lightly.

After the dough has doubled in size, divide it into 4 equal portions. Sprinkle some flour on the table and roll out each portion of dough to form a rectangle. Spread a quarter of the filling mix over the surface of each rectangle then roll up each rectangle to enclose the filling. Twist two rolls together and the place each twisted roll pair in a prepared baking tin.

Allow the cozonac to prove again in the tins until they have doubled in volume.
Make an egg wash by beating together the egg and sugar and then brush the top of each cozonac with this mix before baking in an oven preheated to 180°C for about an hour. Avoid opening the oven during the first 20 minutes. Check the cakes with a toothpick.

Once cooked remove the cakes from the tins, sprinkle with a little water and put on them 2–3 kitchen towels, preferably cotton, and let them cool.

Enjoy!

Am Weihnachtsmorgen 1772

Frankfurt, den 25. Dezember 1772

Christtag früh. Es ist noch Nacht, lieber Kestner, ich bin aufgestanden, um bei Lichte morgens wieder zu schreiben, das mir angenehme Erinnerungen voriger Zeiten zurückruft; ich habe mir Coffee machen lassen, den Festtag zu ehren, und will euch schreiben, bis es Tag ist.

Der Türmer hat sein Lied schon geblasen, ich wachte darüber auf. Gelobet seist du, Jesus Christ! Ich hab diese Zeit des Jahrs gar lieb, die Lieder, die man singt, und die Kälte, die eingefallen ist, macht mich vollends vergnügt. Ich habe gestern einen herrlichen Tag gehabt, ich fürchtete für den heutigen, aber der ist auch gut begonnen, und da ist mir‘s fürs Enden nicht Angst.

Der Türmer hat sich wieder zu mir gekehrt; der Nordwind bringt mir seine Melodie, als blies er vor meinem Fenster. Gestern, lieber Kestner, war ich mit einigen guten Jungens auf dem Lande; unsre Lustbarkeit war sehr laut und Geschrei und Gelächter von Anfang zu ende. Das taugt sonst nichts für die kommende Stunde.

Doch was können die heiligen Götter nicht wenden, wenn‘s ihnen beliebt; sie gaben mir einen frohen Abend, ich hatte keinen Wein getrunken, mein Aug war ganz unbefangen über die Natur. Ein schöner Abend, als wir zurückgingen; es ward Nacht.

Nun muss ich Dir sagen, das ist immer eine Sympathie für meine Seele, wenn die Sonne lang hinunter ist und die Nacht von Morgen heraus nach Nord und Süd um sich gegriffen hat, und nur noch ein dämmernder Kreis von Abend herausleuchtet.

Seht, Kestner, wo das Land flach ist, ist‘s das herrlichste Schauspiel, ich habe jünger und wärmer stundenlang so ihr zugesehn hinabdämmern auf meinen Wanderungen. Auf der Brücke hielt

ich still. Die düstre Stadt zu beiden Seiten, der stilleuchtende Horizont, der Widerschein im Fluss machte einen köstlichen Eindruck in meine Seele, den ich mit beiden Armen umfasste.

Ich lief zu den Gerocks, liess mir Bleistift geben und Papier und zeichnete zu meiner grossen Freude das ganze Bild so dämmernd warm, als es in meiner Seele stand. Sie hatten alle Freude mit mir darüber, empfanden alles, was ich gemacht hatte, und da war ich‘s erst gewiss, ich bot ihnen an, drum zu würfeln, sie schlugen‘s aus und wollen, ich soll‘s Mercken schicken. Nun hängt‘s hier an meiner Wand und freut mich heute wie gestern.

Wir hatten einen schönen Abend zusammen, wie Leute, denen das Glück ein grosses Geschenk gemacht hat, und ich schlief ein, den Heiligen im Himmel dankend, dass sie uns Kinderfreude zum Christ bescheren wollen.

Als ich über den Markt ging und die vielen Lichter und Spielsachen sah, dacht ich an euch und meine Bubens, wie ihr ihnen kommen würdet, diesen Augenblick ein himmlischer Bote mit dem blauen Evangelio, und wie aufgerollt sie das Buch erbauen werde.

Hätt ich bei euch sein können, ich hätte wollen so ein Fest Wachsstöcke illuminieren, dass es in den kleinen Köpfen ein Widerschein der Herrlichkeit des Himmels geglänzt hätte. Die Torschliesser kommen vom Bürgermeister und rasseln mit den Schlüsseln.

Das erste Grau des Tags kommt mir über des Nachbarn Haus, und die Glocken läuten eine christliche Gemeinde zusammen. Wohl, ich bin erbaut hier oben auf meiner Stube, die ich lang nicht so lieb hatte als jetzt.

Johann Wolfgang von Goethe an Johann Christian Kestner

Today: Rachel Mak'Ayengo, Gastroenterology

It is my pleasure to introduce myself to you and to the DBM. I am Rachel Mak`Anyengo, a postdoctoral fellow in the Gastroenterology group. I come from Kenya, which lies in East Africa bordering Tanzania, Uganda, Ethiopia, Somalia and South Sudan. I was born and raised in Nairobi, which is the largest city in Kenya, and also happens to be the capital city. Kenya has a total of 42 tribes, and each tribe has its own language (not a dialect). This is why it is compulsory to learn the two national languages, which are Swahili and English. That way the 42 different tribes are able to communicate to each other. It is very common in Kenya that children grow up speaking 3 different languages; I personally grew up speaking Luo, English and Swahili. Luo is the third largest tribe in Kenya, who settled in west Kenya and around Lake Victoria.

I have to say that I feel quite privileged to have grown up in Kenya. As a child, I spent most of my time outside. Thanks to the wonderful weather we played on our school free days from morning to dusk, sometimes even forgetting to break for lunch. My favourite games and almost every child`s favourite games in Kenya were *kati*, which is a version of "dodge ball", *shake* and *bladder*.

Tsavo

It is not a myth but a fact, that Kenya offers some of the best safaris, with its many prestigious national parks such as Maasai Mara, Tsavo (home to elephants) and Amboseli. Maasai Mara, which has been described as the most prolific wildlife real-estate on earth, also offers the most overwhelming wild life spectacle on earth, and it was voted Africa`s leading national park at the recently held World Travel Award 2017.

To add to that, Kenya has one of the most beautiful beaches in Africa, Diani beach, where I had the privilege to celebrate my wedding. It was awarded Africa`s leading beach destination in 2017.

Insert Diani beach picture (picture of my weeding gazebo, taken on the 29th of July 2017)

The bladder

Diani beach

Tilapia meal

Being someone, whose ancestral home is Lake Victoria, my favourite dish is fried Tilapia (*Ngege* in Luo), greens and Ugali (the Kenyan version of polenta). With the influence of the 42 different tribes, Arabs at the coast and Indians, our food is very multi-cultural. Kenyan extended families gather on several occasions, mainly on weekends and public holidays, and these gatherings are associated with lots of food and drink.

I went to primary school in Homabay a town in west Kenya on the shores of Lake Victoria, and later had the privilege to join the Kenya High School, one of the most prestigious schools in Kenya. I first came into contact with German in this school and I believe that is the reason I am here today. I had the chance to be part of a school exchange programme with pupils from Kiel in Germany. It is after the exchange programme, where I had

Konstanz

Kenya High School

the chance to visit Germany, that I decided to pursue my studies in Germany.

I moved to Germany after my high school education (the 12th class), and everyone was puzzled why I would want to study in a country with such a difficult language. I could barely speak German when I moved to Germany. I practically started from scratch in Radolfzell, a small town on Lake Constance *(Bodensee)*. I strongly believe that my multi-lingual background helped me learn the language really fast.

After successfully learning the language, I applied for the pre-University *(Ausländerstudienkolleg)*, because Germany had 13 years of school and Kenya only 12. Foreign students from countries with only 12 years of school had to go through the *Ausländerstudienkolleg*, in order to be eligible to study at a German university. I successfully passed the admission test and absolved 1 year of pre-university, which I finished successfully and was able to study biological sciences at the University of Konstanz. After my studies in Konstanz, I moved to Munich and did my masters at the Ludwig-Maximillians University (LMU) Munich. My love for Munich and Bavaria in general made my decision to do my PhD at the LMU University Hospital quite easy.

I thought some change would do me good after over 5 years in Munich, and that is why I moved to Switzerland. I am very happy that I ended up at the DBM, in a lab that mainly concentrates on immunology, and especially intestinal immunology. Switzerland as a whole is moving on the first lane of scientific research and I am happy to be part of this movement. I look forward to what the future has in store for me…….

Wiesn

Christmas Logic Puzzle

- **The Gertsch family is between the family with the 2m high tree and those with the silver fir.**
- **The pine decorated in multicolour is not 1.50m high.**
- **The fourth family has a tree decorated in red and silver.**
- **The smallest tree is the Nordman fir.**
- **The Meier family have a 1.50m high silver fir.**
- **The Perlen family are next to the tree decorated in red and silver and have the largest tree.**
- **The Lehmann family have a tree that is 50cm high.**
- **The tree decorated in blue and silver is 1.50m high.**
- **The second tree is decorated with red and gold.**
- **The Norway spruce is not 50cm high.**
- **The silver fir is next to the tree decorated in red and gold and does not belong to the Perlen family.**

Questions:

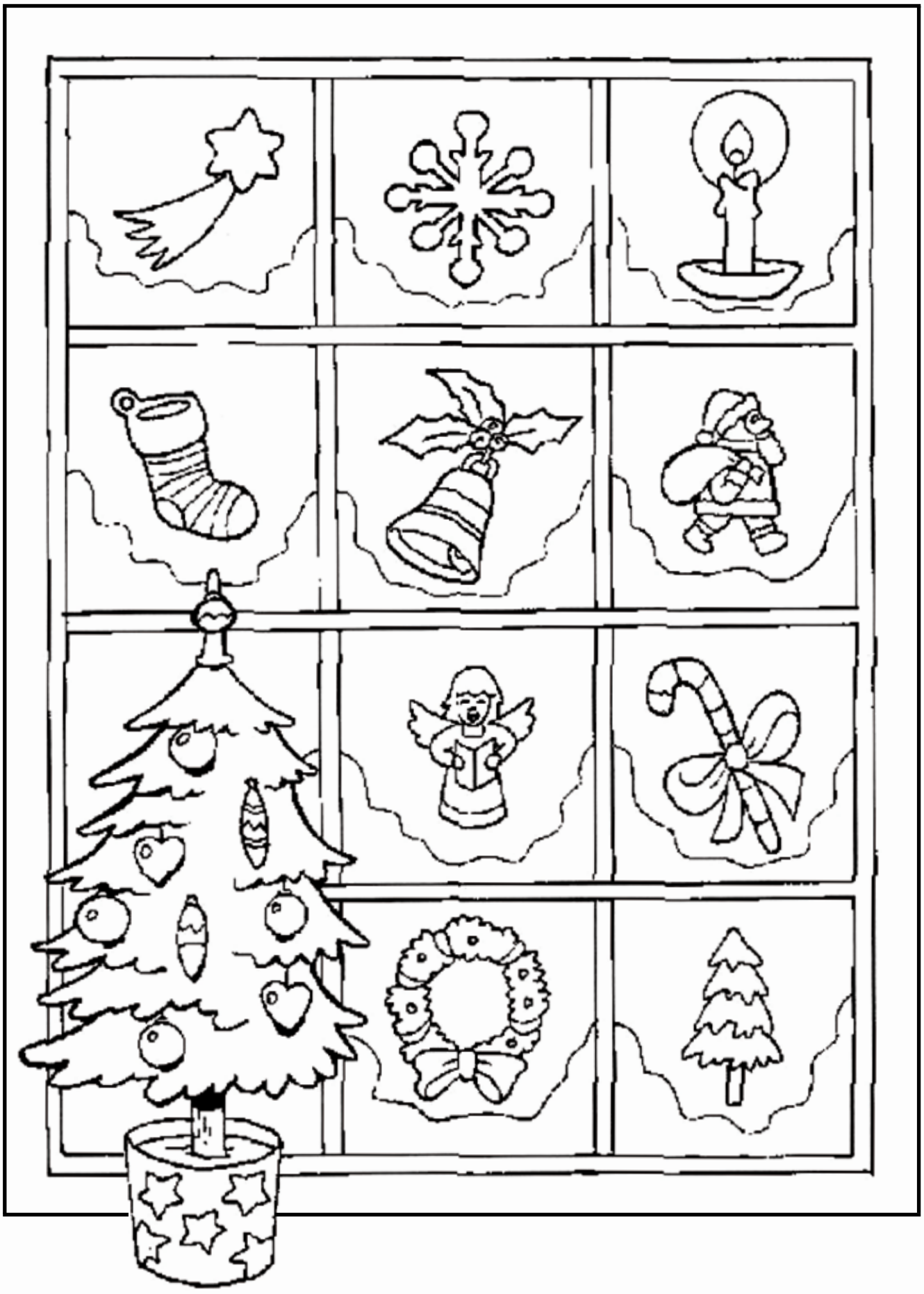
Which family has the tree that is 1m high?

What type of tree is decorated in blue and silver?

Family	**1**	**2**	**3**	**4**
Surname				
Type of tree				
Decoration colours				
Tree height				

If you would call a "LEGO City Mobiles Dschungel-Labor" your own, please send your answer to heidi.hoyermann@usb.ch.
The deadline is January 7th, 2018. If we will receive more than one right answer, we will decide by drawing lots. Much luck!

Children, please colour this Christmassy window!



O Heiliger Abend mit Sternen besät,
wie lieblich und labend dein Hauch mich umweht!
Vom Kindergetümmel, vom Lichtergewimmel
aufschau ich gen Himmel in leisem Gebet.

Karl von Gerok
(1815 – 1890)