DBM FACTS

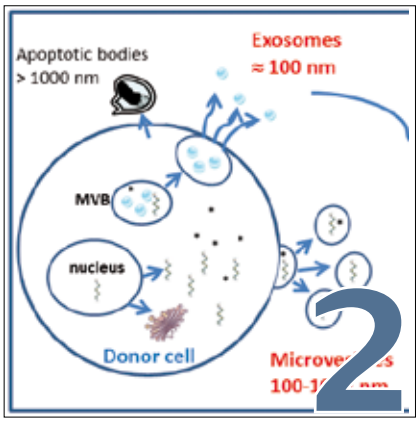
Periodisches Informationsblatt des Departementes Biomedizin
Universität Basel, Universitätsspital Basel und
Universitäts-Kinderspital beider Basel

Multiple Sclerosis: Molecular and immunological analysis – Interplay between basic and clinical research | Into the deep | Tere tulemast Eestisse! / Welcome to Estonia!

2 | 17

INHALT CONTENTS

Departement Biomedizin Basel



Multiple Sclerosis: Molecular and immunological analysis – Interplay between basic and clinical research
from Raija Lindberg, Tobias Derfuss and Jens Kuhle

DBM Scientific Spring Retreat 2017

Into the deep
from Corina Kohler

Tere tulemast Eestisse! / Welcome to Estonia!
from Aleksei Suslov

IMPRESSUM

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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Leider muss ich mit zwei traurigen Nachrichten beginnen: Am 6. August 2017 ist Antonius G. Rolink, Forschungsgruppenleiter am DBM und Professor für Immunologie, unerwartet verstorben (Nachruf auf Seite 26) und am 5. April 2017 mussten wir von Fritz R. Bühler, ehemaliger Leiter des Departement Forschung (Vorläufer des DBM), Abschied nehmen (Nachruf auf Seite 26). Wir vermissen diese zwei starken Persönlichkeiten, die beide das DBM mit geprägt haben.
Ein Schwerpunkt der vorliegenden Ausgabe ist die Forschung des Labors «Clinical Neuroimmunology». Raija Lindberg, Tobias Derfuss und Jens Kuhle stellen uns neue Entwicklungen zum Verständnis der Krankheitsentstehung und Therapie der Multiplen Sklerose (MS) vor. Das Hauptaugenmerk liegt auf nicht-kodierenden RNAs (miRNAs) mit regulatorischen Funktionen in Immunzellen, therapeutischen Antikörpern, welche die Funktion von Immunzellen verändern und Biomarkern, die es erlauben, den Verlauf der MS und die Wirksamkeit der Therapie zu verfolgen (ab Seite 2).
Es folgen 27 Publikationen, die Auskunft über unsere erfolgreiche wissenschaftliche Arbeit seit der letzten Ausgabe geben (ab Seite 11).
Doch das DBM ist nicht nur Wissenschaft – das DBM ist auch die Vielfalt der Menschen, die dort arbeiten. Ganz saisongemäss, wie das Titelbild schon zeigt, nehmen uns drei Mitarbeitende mit an Orte, die eine ganz besondere Bedeutung für sie haben. Geniessen Sie die Spätsommertage mit Corina Kohler, die für ihr Leben gern auf den Malediven taucht (Seite 29), Aleksei Suslov, der uns seine Heimat Estland zeigt (Seite 32) und Duvini De Silva, die uns mit nach Sri Lanka und Singapur nimmt (Seite 35).

Viel Spass bei der Lektüre!

Dear Readers

I must begin with two items of sad news: Antonius G. Rolink, research group leader at DBM and Professor for Immunology, unexpectedly passed away on August 6, 2017 (see page 26) and Fritz R. Bühler, former head of the Department of Research (predecessor of the DBM) left us on April 5, 2017 (page 26). We will miss these two strong personalities, who made important contributions to the DBM.
The research of the Clinical Neuroimmunology laboratory is one of the main foci of the current edition. Raija Lindberg, Tobias Derfuss and Jens Kuhle introduce us to new developments in the understanding of the symptoms and therapy of multiple sclerosis (MS). The main focus is on non-coding RNAs (miRNAs) that have regulatory functions in immune cells, therapeutic antibodies, that alter the function of immune cells and biomarkers, that can be used to track the progress of the disease and the efficacy of the therapy (page 2 onward).
Following this are 27 publications that highlight the successes in our scientific studies since the last edition (page 11 onward).
However, the DBM is not just science. The DBM is also the diversity of people that work there. In a very seasonal manner, as has already been depicted in the cover image, we are travelling with three of our co-workers to places that have a very special meaning to them. Enjoy late summer days in the Maldives with Corina Kohler, who loves to go scuba diving there (page 29). Aleksei Suslov shows us his homeland Estonia (page 32) and Duvini De Silva transports us to Sri Lanka and Singapore (page 35).

Happy Reading!

Multiple Sclerosis: Molecular and immunological analysis – Interplay between basic and clinical research

INTRODUCTION

Multiple Sclerosis is a disease that combines the complexities of structure and function of the central nervous system with the complexity of our innate and adaptive immune system. Genetic and environmental factors trigger different pathophysiological processes, including autoimmune inflammation, demyelination, axonal damage and respective counter regulatory and repair mechanisms that all together contribute to the disease phenotype. Patients display a great variety of symptoms, different disease courses and response to therapies is poorly predictable. Despite recent progress in developing new treatments that target the immune response in different ways, the disease mechanisms are still poorly understood. MS is considered to be an autoimmune disorder mediated by autoreactive T cells. However, the efficacy of recent B cell targeted therapies support the involvement of B lymphocytes in MS pathogenesis. On the other hand, the cell to cell communication between various immune cells and neuronal cells is largely unknown in MS. Furthermore, there is still an unmet need for biomarkers for disease prognosis and treatment responses for a better management of MS. Our research is embedded in the setting of a large MS Clinic that is leading in the development of novel therapies (Hauser et al., 2017; Kappos et al., 2016; Kappos et al., 2015; Montalban et al., 2017) and follows large long term cohorts of people with MS (Disanto et al., 2016). In these prospective cohorts, participants are systematically phenotyped by standardized neurological and neuropsychological assessment, standard and advanced neuroimaging, neurophysiology and biobanking of cerebrospinal fluid (CSF) and blood samples.

We focus on the following main research lines: 1) gene expression analysis, including extracellular regulators of the immune response, 2) B cell and antibody role in the pathogenesis, diagnosis and treatment of MS and other neuroinflammatory diseases, 3) search for biomarkers for disease prognosis and treatment response.

1. CELLULAR AND EXTRACELLULAR REGULATORS OF MS

MicroRNAs (miRNAs) are small non-coding RNA molecules, which modulate gene-expression of >50% of all protein-encoding genes, and are key regulators of a wide variety of biological processes, e.g. cell proliferation, differentiation, apoptosis and organ development. Our cellular miRNA studies in immune cells from MS patients have revealed distinct expression profiles compared with those in healthy volunteers. Notably, we have shown the deregulation of miR-17-92 and miR-106b-25 clusters in $CD4^+$ T lymphocytes and B cells from MS patients. A pathway analysis of potential target genes of miR-17 indicated that the PI3K/Akt pathway was one of the most affected. The PI3K family of lipid kinases regulates different stages of lymphocyte development, activation and survival. Two molecules, PI3KR1, PI3K regulatory subunit 1 and PTEN, an inhibitor of PI3K, were deregulated in stimulated lymphocytes in our study (Lindberg et al., 2010; Sievers et al., 2012). We have also shown that various current treatments of relapsing-remitting MS have diverse effects on miRNA expression.

MiRNAs are not only intracellular molecules, but they are also found in various body fluids, like serum, plasma, CSF, urine and tears. MiRNAs can be bound with

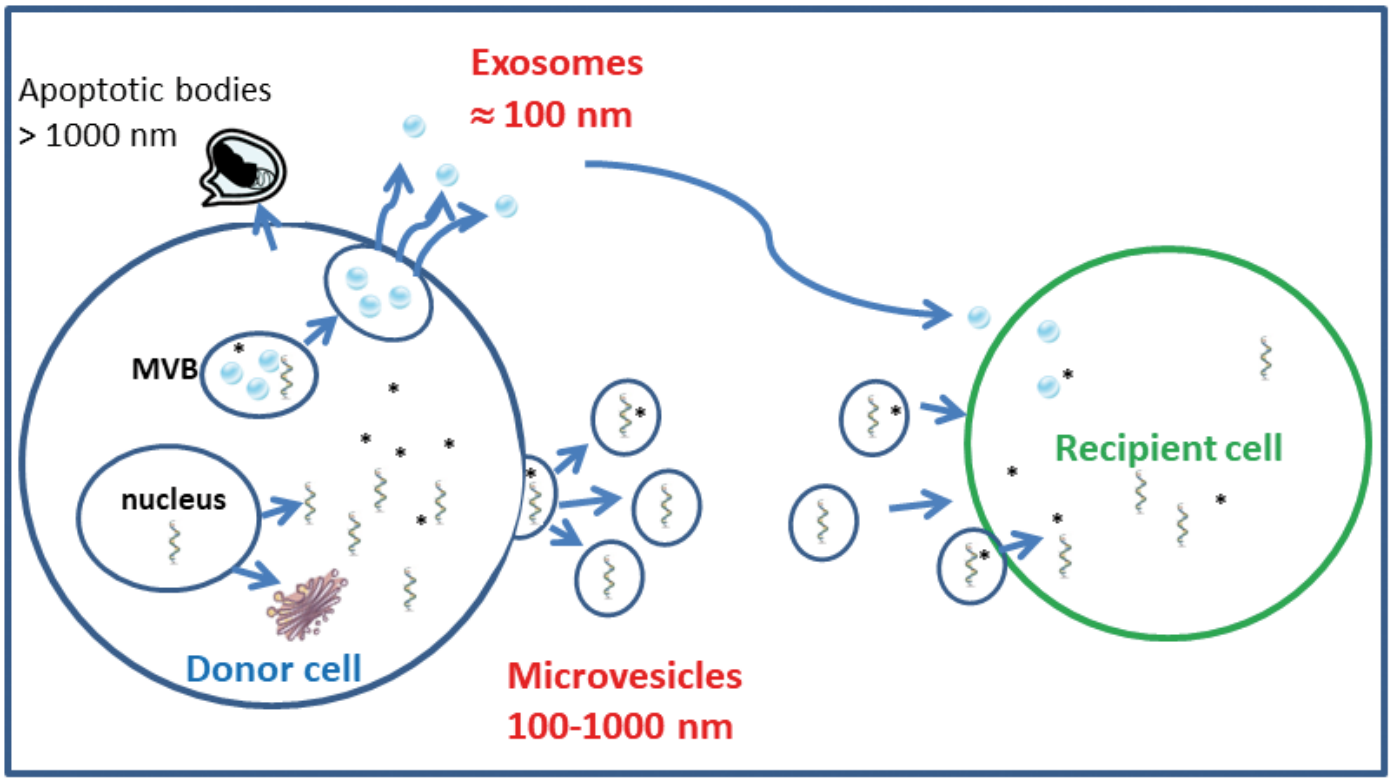

Figure 1. Cell-to-cell communication via extracellular vesicles (EVs). There are three main subgroups of EVs, namely exosomes, microvesicles and apoptotic bodies, which differ in their size, origin and release pathways. Exosomes, with a diameter less than 100 nm, are formed intracellularly in multivesicular bodies (MVB) and are secreted, when these MVBs fuse with plasma membrane. Microvesicles are particles with a diameter of 100 to 1000 nm, which are released by budding of the plasma membrane. EVs carry various molecules, e.g. RNA, DNA, lipids and proteins.

proteins and lipids, and they can be stored in the extracellular vesicles (EVs) (Fig. 1), which protects them from endogenous RNAse activity. EVs have recently emerged as potent mediators for signaling and immune modulation upon delivery of their molecular cargo. They have been investigated as biomarkers in oncology and vascular diseases. Increased release of EVs has been described to be associated to active phases of several neurological disorders; including MS. EVs can be released by various cell types, e.g. endothelial cells, platelets, monocytes, lymphocytes, neutrophils and erythrocytes. Recent studies have shown that EVs are also released by CNS cells, e.g. oligodendrocytes, myeloid cells and astrocytes. However, very little is known about the role of EVs in intercellular communication and in immune regulation in MS.

Our main research focus is the characterization and the functional analysis of EVs in MS. We aim at characterizing EVs derived from CSF and serum of MS patients with various disease courses and healthy volunteers. Furthermore, we are studying microRNA/RNA expression and protein content, e.g. cytokines, chemokines and signaling molecules in EVs. Characterization of molecular cargo of EVs will provide better insights to their role in intercellular communication and signaling pathways and thus also their possible involvement in immune pathogenesis of MS.

2. B CELL AND ANTIBODY ROLE IN THE PATHOGENESIS, DIAGNOSIS AND TREATMENT OF MS AND OTHER NEUROINFLAMMATORY DISEASES

All effective MS therapies affect the immune system, and most affect many different cell types, which limits their usefulness as clues to the cause of the disease. One exception are anti-CD20 antibodies, that specifically deplete B cells, and strongly suppress disease activity in many patients. With this as a starting point, we are trying to understand how B cells might be involved. One obvious possibility is autoantibodies; there are several diseases in which antibodies directly cause neurological symptoms, for example myasthenia gravis, where antibodies against the acetylcholine receptor interfere with the transmission of nerve impulses to muscles. However, despite decades of research,

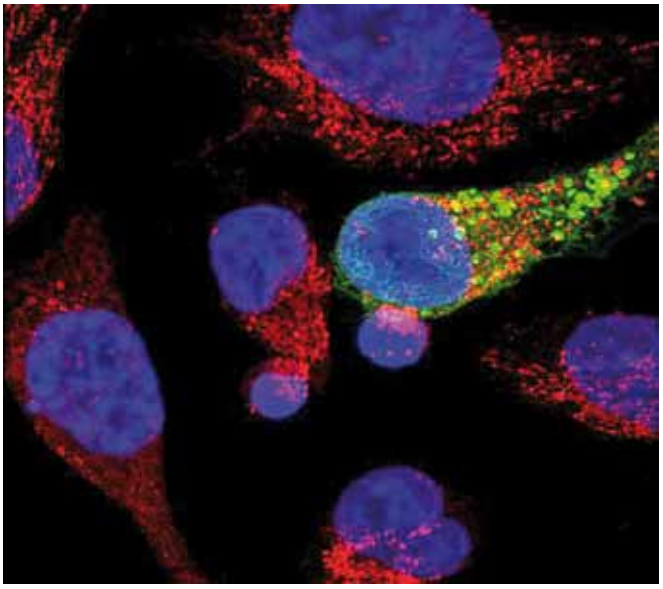

Figure 2. Immunofluorescence micrograph showing the interaction between a B cell and an epithelial cell expressing the B cell's cognate antigen. The large nuclei, labeled with DAPI (blue) belong to adherent epithelial cells, and the small nuclei belong to transgenic mouse B cells, whose immunoglobulin receptor recognises the extracellular domain of Myelin Oligodendrocyte Glycoprotein (MOG), a membrane protein normally expressed in myelin. The epithelial cell in the middle right of the frame expresses a fusion protein of MOG and green fluorescent protein (green), and the preparation is immunolabeled to show LAMP1 (red), which is highly expressed in lysosomes. At the contact between the MOG-GFP-expressing epithelial cell and the B cell, the B cell's lysosomes are polarised towards the antigen-expressing epithelial cell.

no autoantibodies have been clearly associated with MS. It was reported in 2012 that antibodies against the potassium channel KIR4.1 were found in sera from about half of all patients with MS and not from other donors (Srivastava et al., 2012), but we and others have disputed this result (Pröbstel et al., 2016).

An alternative hypothesis is that B cells cause the pathology by activating autoreactive T cells. This would explain why CD20 depletion ameliorates the disease, despite sparing the highly differentiated B cells known as plasma cells that secrete most of the antibodies found in serum. A third possibility is that B cells influence the course of the disease by secreting cytokines, for example GM-CSF, which is considered a pro-inflammatory cytokine in the context of neuroinflammation.

We are concentrating our efforts on the search for hitherto undiscovered autoantibodies, and for mechanisms that could cause the transient secretion of pathologically relevant antibodies under particular rare circumstances. One possibility is that self-reactive B cells might evade tolerance by co-capturing viral antigens along with self-antigens from infected cells that express both (Fig. 2.). In a mouse model, B cells that recognise a myelin protein can obtain such fraudulent help from influenza-specific T cells (Sanderson et al., 2017). As the search for autoantibodies is hampered by the lack of appropriate techniques, we have developed a method based on membrane antigen capture for isolating autoreactive B cells directly from patients' blood. The advantages of working with B cells rather than testing sera are that each B cell has only one specificity, while the sera contain a complicated mixture of antibodies, and that once cloned, recombinant antibodies can be prepared in large quantities. We have developed this technique in collaboration with the Egli group and scientists at the Novartis Institute of Biomedical Research and used it to clone and phenotype influenza-specific B cells from healthy donors. We are currently adapting the technique to the isolation of autoimmune B cells that recognise unknown targets on neural cell types in collaboration with the Schaeren-Wiemers and Kapfhammer groups here in Basel and Renaud Du Pasquier from the Neurology Department in Lausanne.

3. SEARCH OF BIOMARKERS FOR DISEASE PROGRESSION AND TREATMENT RESPONSE IN MS

A. PML studies – "predictive markers for side-effects"

Natalizumab is an effective drug for the treatment of relapsing-remitting MS patients. However, its use is associated with the development of progressive multifocal leukoencephalopathy (PML), a potentially fatal infection of the CNS that is caused by reactivation of the latent human JC virus (JCV). In practice, risk stratification is currently used for clinical guidance; however, additional predictive markers and a better understanding of the mechanisms of development and pathophysiology of PML are needed. Our lab has uncovered a specific effect of natalizumab on the expression of POU2AF1 and Spi-B, known transactivators of the JCV, in lymphocyte subpopulations ($CD4^+$T, $CD8^+$T and B cells) from natalizumab treated patients (Meira et al., 2014; Meira et al., 2016). Therefore, POU2AF1/Spi-B might serve as potential biomarker candidates for PML risk. Also, natalizumab-induced differential expression

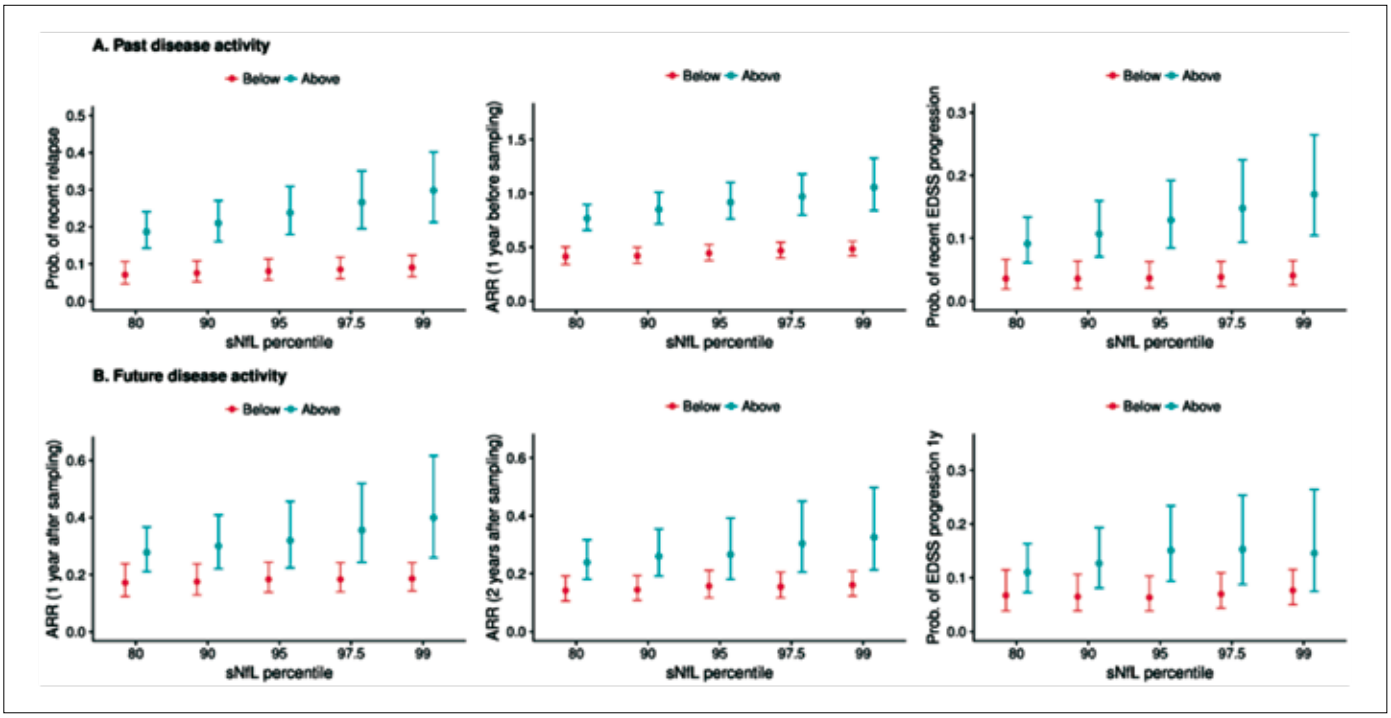

Figure 3: Model-predicted means (marginal means) and model estimates including 95% confidence intervals:
A) Probability of a recent relapse (within 60 days before sampling), ARR in the one year before sampling and probability of EDSS worsening since 6-12 months before sampling according to serum NfL percentiles.
B) ARR in the one year after sampling, ARR in the two years after sampling and probability of EDSS worsening within one year after sampling according to sNfL percentiles (Disanto et al., 2017).

of potentially regulating miRNAs (miR-126, miR-10b) has been discovered. Our lab is currently evaluating specific extracellular RNA signatures induced by natalizumab therapy that possibly contribute to PML development.

B. Tecfidera – "treatment response – mode of action"

Dimethyl fumarate (DMF, Tecfidera®) is approved as an oral treatment of MS. Its beneficial impact on disease activity was discovered through incidental observation. Being developed strictly empirically, the exact mode of action of this drug is not well understood. We collect extensive clinical data as well as bio samples (blood cells, serum, plasma, stool) from a cohort of 100 MS patients starting DMF treatment. Besides the composition of lymphocyte subtypes, also their function – for example apoptotic behaviour, proliferation, cytokine secretion, antigen presentation and response to oxidative stress – is assessed. First we aim to characterize effects of DMF that cannot only be observed in-vitro or animal models, but also in-vivo and ex-vivo in clinical use. Secondly, we try to correlate the clinical response (relapses, disease activity) with these cellular and molecular effects. The ultimate target of this study is to identify predictive markers for treatment response.

C. Design, optimization and validation of ultrasensitive Simoa bioassay

The fact that no generally accepted therapy specific for neuroprotection is available may at least partly be due to the inability to accurately quantify clinical worsening. Biofluid markers bear the advantage of measuring ongoing pathologic changes real-time, and being related to specific disease mechanisms. In MS such a biomarker would be helpful in monitoring ongoing damage and potential treatment response. The profile of a biomarker for use in routine clinical practice requires a) accessibility in blood or urine, and b) rapid, quantifiable change in function of disease activity. Until recently, no such biomarker was available.

There is increasing evidence that neuronal degeneration is a key factor in the pathogenesis of sustained neurological disability in MS and hence may also be the main driver for what we call ‚disease progression'. Neurofilaments (Nf) play an important role in maintaining neuronal size, shape, and axonal caliber. Because

Nf are exclusive products of neuronal cells, their key advantage over other biomarkers is their specificity in terms of cellular source, reflection of pathomechanism and hence signal interpretation, i.e. they are highly specific for neuronal cell damage and eventual neuronal cell death. Simoa technology for digital immunoassays has the potential to improve sensitivity significantly further compared to more conventional methods (Bacioglu et al., 2016; Kuhle J, 2017). The Simoa technology relies on single molecule arrays and the simultaneous counting of singulated capture microbeads leading to significant gain in sensitivity. We have developed and validated a Simoa assay for the Nf light chain (NfL) (Disanto et al., 2017). Using this assay in a large number of samples from the SMSC, serum NfL levels were considerably higher in patients with more active MRI or clinical disease. Patients with serum NfL levels above all healthy controls based percentiles were at higher risk of past and future relapses and EDSS worsening (Fig. 3).

The establishment of NfL as measure of ongoing neuronal loss in a routinely accessible body fluid source could potentially mark a breakthrough in the field of MS biomarkers. The close correlation of Nf levels in serum/plasma and CSF in numerous studies by others and ourselves in MS and in other neurological diseases allows to conclude from blood values on the degree of ongoing neuroaxonal injury in the CNS, and to become independent of lumbar puncture. Currently we are investigating additional large and well characterised cohorts of MS patients to extend and validate these findings in several national and international collaborations. We have access to two HD-1 analyzers (Quanterix) in the Department of Biomedicine and are actively pursuing the development of similar sensitive body fluid measures of cell signalling, inflammation and neurodegeneration.

Raija Lindberg, Tobias Derfuss and Jens Kuhle

From left to right: Simone Ritz, Helene Rossez, Heidi Bodmer, Svenya Gröbke, Franziska Koch, Natalie Rose, Ludwig Kappos, Raija Lindberg, Tobias Derfuss, Christian Barro, Nadege Lagarde, Jens Kuhle, Nicholas Sanderson, Claudia Siebers-Stober, Martin Diebold, Maria Bokalot-Meira. Missing on the photo: Anne-Catherine Lecourt.

Publications

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DBM Scientific Spring Retreat 2017

As was the case in previous years, the DBM PhD retreat proved, once again, to be a great opportunity for new and advanced PhD students alike to discuss their projects with equals and at the same time learn about the research that is done in other locations of the DBM.

This spring we ventured to the canton of St. Gallen to spend a couple of days at the beautifully located town of Quarten, where we arrived quite early in the morning. To get the students to mingle right from the beginning of the retreat, we started the day with an icebreaker game encouraging everybody to find out more about their fellows.

For the fifth edition of the retreat we made a new addition to the program and held a Mini-Symposium on the first day. The speakers were chosen from miscellaneous scientific areas and included:

Georg Keller, who explained how the mind alters our reality and how mismatches between expectation and perception are being processed in neuronal circuits.

Heinrich Leonhardt, who introduced us to the way in which DNA methylation patterns are generated and explained the complex mechanisms that are responsible for their establishment.

Polly Matzinger, who presented the story behind her Danger-Immune-Response-Model and, using only an overhead projector, inspired a very vivid and stimulating discussion.

Hugo Snippert, who showed us his findings in tracing the propagation of stem cell populations on intestinal microvilli and how they translated their findings to investigate tumor development in organoids generated from human samples.

We feel very lucky to have had the chance to hear such enthusiastic speakers and want to thank them again for making the journey. The bar for future guest speakers has been set pretty high now!

The symposium was followed by an apéro during which the students had the chance to engage in a direct conversation with the guest speakers. In our first poster session, some of the PhD students then got to present their own work before we all made our way to a bonfire set up just a bit downhill from the hotel.

The second day of the retreat was entirely dedicated to the scientific progress of the PhD students which they presented in either a talk or at the second poster session. We were truly astonished by the high quality of all the posters and presentations this year. However, public vote decided on the most outstanding ones and Inner-City vouchers, kindly sponsored by Actelion, were given to:

Best talk:	**Best poster:**
1st Julie Gamart	1st Jan Eckhardt
2nd Charlotte Navntoft	2nd Milica Vulin
3rd Sascha Fischer	3rd Virginie Tissières

So by solemnly passing on the golden pipettes to the winners, the scientific part of the retreat was officially concluded and the evening was ended with a fun quiz-session combined with (at least for some) a visit to the local pub for the last drink of the night.

Before heading back to Basel the next day, there was a chance to explore the beautiful surroundings of Lake Walenstadt either during a hike through the scenery or a boat ride on the lake.

We want to thank everybody again for participating, we really had a great group of people this year. Hopefully many of you got some new ideas for their projects and established new contacts with people from the other DBM locations.

Last, but not least, we are especially grateful for the help of Nicole Schaeren-Wiemers. We are thankful to have such a committed person supporting the activities of the PhD Club and the students of our PhD program!

We hope everyone had as much fun as we had and we would love to see many of you around for one of our other events this year or for the retreat in 2018!

Your DBM PhD-Club

Dissertationen

Am 24. April 2017 konnte **Flurina Pletscher** von der Forschungsgruppe "Gyn. Endocrinology" (Departement Biomedizin Hebelstrasse) ihre Dissertation mit Erfolg abschliessen. Sie befasste sich in ihrer Dissertation mit dem Thema: "Assessment of stem cell pluripotency using an in vitro 3D perfusion-based culture model."

Auszeichnungen

Ernennung zu Titularprofessoren

Der Universitätsrat genehmigte die von der Regenz beschlossene Ernennung folgender Titularprofessoren: **PD Dr. Andrea Barbero** von der FG Tissue Engineering (DBM Hebelstrasse) für Experimentelle Medizin und **PD Dr. Beat Kaufmann** von der FG Cardiovascular Molecular Imaging (DBM Hebelstrasse) für Kardiologie.

Susan Treves erhält FSRMM-Beitrag

Susan Treves von der FG Perioperative Patient Safety (DBM Hebelstrasse) hat von der Schweizerischen Stiftung für die Erforschung von Muskelkrankheiten (FSRMM) für ihre Arbeiten über Gemeinsamkeiten in der Pathologie kongenitaler Myopathien einen Forschungsbeitrag erhalten. Die Unterstützung beträgt für ihre Gruppe und drei andere Labors insgesamt 350'000 CHF.

Mike Recher erhält Müller-Gierok-Preis

Mike Recher von der FG Immunodeficiency (DBM Hebelstrasse) hat zusammen mit Prof. Alexander Navarini, Universitätsspital Zürich, den Preis der Müller Gierok Stiftung für die beste wissenschaftliche Arbeit im Jahr 2016 auf dem Gebiet der klinischen Allergologie gewonnen. Der Preis ist mit 10'000 CHF dotiert.

Primo Schär neues Mitglied der SAMW

Primo Schär von der FG Genome Plasticity (DBM Mattenstrasse) wurde zu einem neuen Mitglied der Schweizerischen Akademie der Medizinischen Wissenschaften (SAMW) gewählt.

Tatjana Binggeli neue Präsidentin des Gehörlosenbundes

Tatjana Binggeli von der FG Ocular Pharmacology and Physiology (DBM Hebelstrasse) ist von den Delegierten des Schweizerischen Gehörlosenbundes (SGB-FSS) zur Präsidentin gewählt worden.

Das DBM gratuliert ganz herzlich!

Auflösung Quiz

Der Hund kommt mit einer Geschwindigkeit von 512m/s in Paris an. Nach 9 Schritten überschreitet er die Schallgeschwindigkeit und kann daher den Aufschlag der Büchse nicht mehr hören und erhöht damit auch seine Geschwindigkeit nicht mehr.
Aufgrund der Vielzahl der Einsendungen werden zwei Essensbons vergeben:
Die glücklichen Gewinner sind Marie-Françoise Ritz und Pascal Lorentz.
Herzliche Gratulation!

Colon 2017; 66:692–704 IF 16,658

Dual role of tumour-infiltrating T helper17 cells in human colorectal cancer

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Abstract

Background The immune contexture predicts prognosis in human colorectal cancer (CRC). Whereas tumour-infiltrating CD8+ T cells and myeloid CD16+ myeloperoxidase (MPO)+ cells are associated with favourable clinical outcome, interleukin (IL)-17-producing cells have been reported to correlate with severe prognosis. However, their phenotypes and functions continue to be debated.

Objective To investigate clinical relevance, phenotypes and functional features of CRC-infiltrating, IL-17-producing cells.

Methods IL-17 staining was performed by immunohistochemistry on a tissue microarray including1148 CRCs. Phenotypes of IL-17-producing cells were evaluated by flow cytometry on cellsuspensions obtainedby enzymatic digestion of clinical specimens. Functions of CRC-isolated, IL-17-producing cells were assessed by in vitro and in vivo experiments.

Results IL-17+infiltrates were not themselves predictive of an unfavourable clinical outcome, but correlated with infiltration by CD8+T cells and CD16+MPO+neutrophils. Ex vivo analysis showed that tumour-infiltratingIL-17+ cells mostly consist of CD4+T helper 17(Th17) cells with multifaceted properties. Indeed, owing to IL-17 secretion, CRC-derived Th17 triggered the release of protumorigenic factors by tumour and tumour-associated stroma.However, on the other hand, they favoured recruitment of beneficial neutrophils throughIL-8secretion and, most importantly, they drove highly cytotoxic CCR5+CCR6+CD8+ T cells into tumour tissue, through CCL5 and CCL20 release. Consistent with these findings, the presence of intraepithelial, but not of stromal Th17 cells, positiv ely correlated with improved survival.

Conclusions Our study shows the dual role played by tumour-infiltrating Th17 in CRC, thus advising caution when developing new IL-17/Th17 targeted treatments.

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Deconvolution of Buparlisib's mechanism of action defines specific PI3K and tubulin inhibitors for therapeutic intervention

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BKM120 (Buparlisib) is one of the most advanced phosphoinositide 3-kinase (PI3K) inhibitors for the treatment of cancer, but it interferes as an off-target effect with microtubule polymerization. Here, we developed two chemical derivatives that differ from BKM120 by only one atom. We show that these minute changes separate the dual activity of BKM120 into discrete PI3K and tubulin inhibitors. Analysis of the compounds cellular growth arrest phenotypes and microtubule dynamics suggest that the antiproliferative activity of BKM120 is mainly due to microtubule-dependent cytotoxicity rather than through inhibition of PI3K. Crystal structures of BKM120 and derivatives in complex with tubulin and PI3K provide insights into the selective mode of action of this class of drugs. Our results raise concerns over BKM120's generally accepted mode of action, and provide a unique mechanistic basis for next-generation PI3K inhibitors with improved safety profiles and flexibility for use in combination therapies.

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Replicating viral vector platform exploits alarmin signals for potent CD8$^+$ T cell-mediated tumour immunotherapy

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Viral infections lead to alarmin release and elicit potent cytotoxic effector T lymphocyte (CTL^{eff}) responses. Conversely, the induction of protective tumour-specific CTL^{eff} and their recruitment into the tumour remain challenging tasks. Here we show that lymphocytic choriomeningitis virus (LCMV) can be engineered to serve as a replication competent, stably-attenuated immunotherapy vector (artLCMV). artLCMV delivers tumour-associated antigens to dendritic cells for efficient CTL priming. Unlike replication-deficient vectors, artLCMV targets also lymphoid tissue stroma cells expressing the alarmin interleukin-33. By triggering interleukin-33 signals, artLCMV elicits CTL^{eff} responses of higher magnitude and functionality than those induced by replication-deficient vectors. Superior anti-tumour efficacy of artLCMV immunotherapy depends on interleukin-33 signalling, and a massive CTL^{eff} influx triggers an inflammatory conversion of the tumour microenvironment. Our observations suggest that replicating viral delivery systems can release alarmins for improved anti-tumour efficacy. These mechanistic insights may outweigh safety concerns around replicating viral vectors in cancer immunotherapy.

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Engineered Extracellular Matrices as Biomaterials of Tunable Composition and Function

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Engineered and decellularized extracellular matrices (ECM) are receiving increasing interest in regenerative medicine as materials capable to induce cell growth/differentiation and tissue repair by physiological presentation of embedded cues. However, ECM production/decellularization processes and control over their composition remain primary challenges. This study reports engineering of ECM materials with customized properties, based on genetic manipulation of immortalized and death-inducible human mesenchymal stromal cells (hMSC), cultured within 3D porous scaffolds under perfusion flow. The strategy allows for robust ECM deposition and subsequent decellularization by deliberate cell-apoptosis induction. As compared to standard production and freeze/thaw treatment, this grants superior preservation of ECM, leading to enhanced bone formation upon implantation in calvarial defects. Tunability of ECM composition and function is exemplified by modification of the cell line to overexpress vascular endothelial growth factor alpha (VEGF), which results in selective ECM enrichment and superior vasculature recruitment in an ectopic implantation model. hMSC lines culture under perfusion-flow is pivotal to achieve uniform scaffold decoration with ECM and to streamline the different engineering/decellularization phases in a single environmental chamber. The findings outline the paradigm of combining suitable cell lines and bioreactor systems for generating ECM-based off-the-shelf materials, with custom set of signals designed to activate endogenous regenerative processes.

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Serum neurofilament light: a biomarker of neuronal damage in multiple sclerosis

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Abstract

Objective: Neurofilament light chains (NfL) are unique to neuronal cells, are shed to the CSF and are detectable at low concentrations in peripheral blood. Various diseases causing neuronal damage have resulted in elevated CSF concentrations. We explored the value of an ultrasensitive singlemolecule array (Simoa) serum NfL (sNfL) assay in MS.

Methods: sNfL levels were measured in healthy controls (HC, n=254) and two independent MS cohorts: (1) cross-sectional with paired serum and CSF samples (n=142); (2) longitudinal with repeated serum sampling (n=246, median (IQR) follow-up 3.1 (2.0-4.0) years). We assessed their relation to concurrent clinical, imaging and treatment parameters and to future clinical outcomes.

Results: sNfL levels were higher in both MS cohorts than in HC (p<0.001). We found a strong association between CSF NfL and sNfL (β=0.589, p<0.001). Patients with either brain or spinal (43.4 (25.2-65.3) pg/ml) or both brain and spinal gadolinium enhancing lesions (62.5 (42.7-71.4) pg/ml) had higher sNfL than those without (29.6 (20.9-41.8) pg/ml; β=1.461, p=0.005 and β=1.902, p=0.002 respectively). sNfL was independently associated with EDSS assessments (β=1.105, p<0.001) and presence of relapses (β=1.430, p<0.001). sNfL levels were lower under disease modifying treatment (β=0.818, p=0.003). Patients with sNfL levels above the 80th, 90th, 95th, 97.5th and 99th HC based percentiles had higher risk of relapses (97.5th percentile: IRR=1.94, 95%CI=1.21-3.10, p=0.006) and EDSS worsening (97.5th percentile: OR=2.41, 95%CI=1.07-5.42, p=0.034).

Interpretation: These results support the value of sNfL as a sensitive and clinically meaningful blood biomarker to monitor tissue damage and the effects of therapies in MS.

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Prominent Oncogenic Roles of EVI1 in Breast Carcinoma

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Abstract

Overexpression of the EVI1 oncogene is associated typically with aggressive myeloid leukemia, but is also detectable in breast carcinoma where its contributions are unexplored. Analyzing a tissue microarray of 608 breast carcinoma patient specimens, we documented EVI1 overexpression in both estrogen receptor–positive (ER^+) and estrogen receptor–negative (ER-) breast carcinomas. Here, we report prognostic relevance of EVI1 overexpression in triple-negative breast carcinoma but not in the HER2-positive breast carcinoma subset. In human breast cancer cells, EVI1 silencing reduced proliferation, apoptosis resistance, and tumorigenicity, effects rescued by estrogen supplementation in ER+ breast carcinoma cells. Estrogen addition restored ERK phosphorylation in EVI1-silenced cells, suggesting that EVI1 and estradiol signaling merge in MAPK activation. Conversely, EVI1 silencing had no effect on constitutive ERK activity in $HER2^+$ breast carcinoma cells. Microarray analyses revealed G-protein–coupled receptor (GPR) signaling as a prominent EVI1 effector mechanism in breast carcinoma. Among others, the GPR54-ligand KISS1 was identified as a direct transcriptional target of EVI1, which together with other EVI1-dependent cell motility factors such as RHOJ regulated breast carcinoma cell migration. Overall, our results establish the oncogenic contributions of EVI1 in ER-and HER2-negative subsets of breast cancer.

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Control of angiogenesis and host response by modulating the cell adhesion properties of an Elastin-Like Recombinamer-based hydrogel

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Abstract

The control of the in vivo vascularization of engineered tissue substitutes is essential in order to obtain either a rapid induction or a complete inhibition of the process (e.g. in muscles and hyaline-cartilage, respectively). Among the several polymers available, Elastin-Like Recombinamers (ELR)-based hydrogel stands out as a promising material for tissue engineering thanks to its viscoelastic properties, non-toxicity, and non-immunogenicity. In this study, we hypothesized that varying the cell adhesion properties of ELR-hydrogels could modulate the high angiogenic potential of adipose tissue-derived stromal vascular fraction (SVF) cells, predominantly composed of endothelial/mural and mesenchymal cells. Human SVF cells, embedded in RGD-REDV-bioactivated or unmodified ELR-hydrogels, were implanted in rat subcutaneous pockets either immediately or upon 5-day-culture in perfusion-bioreactors. Perfusion-based culture enhanced the endothelial cell cord-like-organization and the release of pro-angiogenic factors in functionalized constructs. While in vivo vascularization and host cell infiltration within the bioactivated gels were highly enhanced, the two processes were strongly inhibited in non-functionalized SVF-based hydrogels up to 28 days. ELR-based hydrogels showed a great potential to determine the successful integration of engineered substitutes thanks to their capacity to finely control the angiogenic/ inflammation process at the recipient site, even in presence of SVF cells.

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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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HAND2 Target Gene Regulatory Networks Control Atrioventricular Canal and Cardiac Valve Development

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Summary

The HAND2 transcriptional regulator controls cardiac development, and we uncover additional essential functions in the endothelial to mesenchymal transition (EMT) underlying cardiac cushion development in the atrioventricular canal (AVC). In *Hand2*-deficient mouse embryos, the EMT underlying AVC cardiac cushion formation is disrupted, and we combined ChIP-seq of embryonic hearts with transcriptome analysis of wild-type and mutants AVCs to identify the functionally relevant HAND2 target genes. The HAND2 target gene regulatory network (GRN) includes most genes with known functions in EMT processes and AVC cardiac cushion formation. One of these is *Snai1*, an EMT master regulator whose expression is lost from *Hand2*-deficient AVCs. Reexpression of *Snai1* in mutant AVC explants partially restores this EMT and mesenchymal cell migration. Furthermore, the HAND2-interacting enhancers in the Snai1 genomic landscape are active in embryonic hearts and other *Snai1*-expressing tissues. These results show that HAND2 directly regulates the molecular cascades initiating AVC cardiac valve development.

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Ecotropic viral integration site 1, a novel oncogene in prostate cancer

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Prostate cancer (PCa) is the most commonly diagnosed non-cutaneous cancer in men in the western world. Mutations in tumor suppressor genes and in oncogenes are important for PCa progression, whereas the role of stem cell proteins in prostate carcinogenesis is insufficiently examined. This study investigates the role of the transcriptional regulator *Ecotropic Viral Integration site 1 (EVI1)*, known as an essential modulator of hematopoietic and leukemic stem cell biology, in prostate carcinogenesis. We show that in healthy prostatic tissue, EVI1 expression is confined to the prostate stem cell compartment located at the basal layer, as identified by the stem cell marker CD44. Instead, in a PCa progression cohort comprising 219 samples from patients with primary PCa, lymph node and distant metastases, EVI1 protein was heterogeneously distributed within samples and high expression is associated with tumor progression ($P < 0.001$), suggesting EVI1 induction as a driver event. Functionally, short hairpin RNAmediated knockdown of EVI1 inhibited proliferation, cell cycle progression, migratory capacity and anchorage-independent growth of human PCa cells, while enhancing their apoptosis sensitivity. Interestingly, modulation of EVI1 expression also strongly regulated stem cell properties (including expression of the stem cell marker SOX2) and *in vivo* tumor initiation capacity. Further emphasizing a functional correlation between EVI1 induction and tumor progression, upregulation of EVI1 expression was noted in experimentally derived docetaxel-resistant PCa cells. Importantly, knockdown of *EVI1* in these cells restored sensitivity to docetaxel, in part by downregulating anti-apoptotic BCL2. Together, these data indicate EVI1 as a novel molecular regulator of PCa progression and therapy resistance that may control prostate carcinogenesis at the stem cell level.

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Functionally diverse human T cells recognize non-microbial antigens presented by MR1

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Abstract

MHC class I-related molecule MR1 presents riboflavin- and folate-related metabolites to mucosal-associated invariant T cells, but it is unknown whether MR1 can present alternative antigens to other T cell lineages. In healthy individuals we identified MR1-restricted T cells (named MR1T cells) displaying diverse TCRs and reacting to MR1-expressing cells in the absence of microbial ligands. Analysis of MR1T cell clones revealed specificity for distinct cell-derived antigens and alternative transcriptional strategies for metabolic programming, cell cycle control and functional polarization following antigen stimulation. Phenotypic and functional characterization of MR1T cell clones showed multiple chemokine receptor expression profiles and secretion of diverse effector molecules, suggesting functional heterogeneity. Accordingly, MR1T cells exhibited distinct T helper-like capacities upon MR1-dependent recognition of target cells expressing physiological levels of surface MR1. These data extend the role of MR1 beyond microbial antigen presentation and indicate MR1T cells are a normal part of the human T cell repertoire.

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Long-term observation reveals high-frequency engraftment of human acute myeloid leukemiain immunodeficient mice

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Abstract

Repopulation of immunodeficient mice remains the primary method for functional assessment of human acute myeloid leukemia. Published data report engraftment in ~40-66% of cases, mostly of intermediate- or poor-risk subtypes. Here we report that extending follow-up beyond the standard analysis endpoints of 10 to 16 weeks after transplantation permitted leukemic engraftment from nearly every case of xenotransplanted acute myeloid leukemia (18/19, ~95%). Xenogeneic leukemic cells showed conserved immune pheno-types and genetic signatures when compared to corresponding pre-transplant cells and, furthermore, were able to induce leukemia in re-transplantation assays. Importantly, bone marrow biopsies taken at standardized time points failed to detect leukemic cells in 11/18 of cases that later showed robust engraftment (61%, termed "long-latency engrafters"), indicating that leukemic cells can persist over months at undetectable levels without losing disease-initiating properties. Cells from favorable-risk leukemia subtypes required longer to become detectable in NOD/SCID/IL2Rγ^{null} mice (27.5±9.4 weeks) than did cells from intermediate-risk (21.9±9.4 weeks, P<0.01) or adverse-risk (17±7.6 weeks; P<0.0001) subtypes, explaining why the engraftment of the first was missed with previous protocols. Mechanistically, leukemic cells engrafting after a prolonged latency showed inferior homing to the bone marrow. Finally, we applied our model to favorable-risk acute myeloid leukemia with inv(16); here, we showed that CD34$^+$ (but not CD34$^-$) blasts induced robust, long-latency engraftment and expressed enhanced levels of stem cell genes. In conclusion, we provide a model that allows *in vivo* mouse studies with a wide range of molecular subtypes of acute myeloid leukemia subtypes which were previously considered not able to engraft, thus enabling novel insights into leukemogenesis.

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Serum neurofilament is associated with progression of brain atrophy and disability in early MS

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Abstract

Objective: To investigate a potential effect of riluzole on serum neurofilaments (Nf) compared to placebo and the relationship between longitudinal clinical and MRI outcomes and serum Nf levels.

Methods: Serum samples were obtained from participants enrolled in a randomized double-blind trial of neuroprotection with riluzole vs placebo as an add-on to weekly interferon-β (IFN-β)–1a IM initiated 3 months after randomization. Nf measurements were performed by ELISA and electrochemiluminescence immunoassay.

Results: Longitudinal serum samples were available from 22 riluzole and 20 placebo participants over 24 months. There was no observed treatment effect with riluzole. Nf light chain (NfL) levels decreased over time ($p = 0.007$ at 24 months), whereas the Nf heavy chain was unchanged ($p = 0.997$). Changes in NfL were correlated with EDSS change ($p = 0.009$) and neuropsychological outcomes. Brain volume decreased more rapidly in patients with high baseline NfL ($p = 0.05$ at 12 months and $p = 0.008$ at 24 months) and this relationship became stronger at 24 months ($p = 0.024$ for interaction). Higher and increasing NfL predicted higher number of gadoliniumenhancing lesions ($p < 0.001$ for both).

Conclusions: Our findings support the potential value of serum NfL as a marker of neuroaxonal injury in early multiple sclerosis. Its reduction over time could represent regression to the mean, or a possible treatment effect of IFN-β-1a. The association with whole brain atrophy and the formation of acute white matter lesions has relevant implications to use serum NfL as a noninvasive biomarker of the overall consequences of brain damage and ongoing disease activity.

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Archives of Toxicology Archives of Toxicology (2017) 91:2223–2234 IF 6,637

IGF-1 prevents simvastatin-induced myotoxicity in C2C12 myotubes

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Abstract

Statins are generally well tolerated, but treatment with these drugs may be associated with myopathy. The mechanisms of statin-associated myopathy are not completely understood. Statins inhibit AKT phosphorylation by an unclear mechanism, whereas insulin-like growth factor (IGF-1) activates the IGF-1/AKT signaling pathway and promotes muscle growth. The aims of the study were to investigate mechanisms of impaired AKT phosphorylation by simvastatin and to assess effects of IGF-1 on simvastatin-induced myotoxicity in C2C12 myotubes. C2C12 mouse myotubes were exposed to 10 μM simvastatin and/or 10 ng/mL IGF-1 for 18 h. Simvastatin inhibited the IGF-1/ AKT signaling pathway, resulting in increased breakdown of myofibrillar proteins, impaired protein synthesis and increased apoptosis. Simvastatin inhibited AKT S473 phosphorylation, indicating reduced activity of mTORC2. In addition, simvastatin impaired stimulation of AKT T308 phosphorylation by IGF-1, indicating reduced activation of the IGF-1R/PI3K pathway by IGF-1. Nevertheless, simvastatin-induced myotoxicity could be at least partially prevented by IGF-1. The protective effects of IGF-1 were mediated by activation of the IGF-1R/AKT signaling cascade. Treatment with IGF-1 also suppressed muscle atrophy markers, restored protein synthesis and inhibited apoptosis. These results were confirmed by normalization of myotube morphology and protein content of C2C12 cells exposed to simvastatin and treated with IGF-1. In conclusion, impaired activity of AKT can be explained by reduced function of mTORC2 and of the IGF-1R/PI3K pathway. IGF-1 can prevent simvastatin-associated cytotoxicity and metabolic effects on C2C12 cells. The study gives insight into mechanisms of simvastatin-associated myotoxicity and provides potential targets for therapeutic intervention.

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Gestational Diabetes Mellitus Is Associated with Altered Neutrophil Activity

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Gestational diabetes mellitus (GDM) is a unique form of glucose intolerance, in that it is transient and solely occurs in pregnancy. Pregnancies with GDM are at high risk of developing preeclampsia (PE), a leading cause of fetal and maternal morbidity or mortality. Since PE is associated with excessive activation of circulatory neutrophils and occurrence of neutrophil extracellular traps (NETs) in affected placentae, we examined these features in cases with GDM, as this could be a feature linking the two conditions. Our data indicate that neutrophil activity is indeed altered in GDM, exhibiting pronounced activation and spontaneous generation of NETs by isolated neutrophils in *in vitro* culture. In this manner, GDM may similarly affect neutrophil behavior and NET formation as witnessed in other forms of diabetes, with the addition of the physiological changes mediated by pregnancy. Since circulatory TNF-α levels are elevated in cases with GDM, a feature also observed in this study, we examined whether this pro-inflammatory cytokine contributed to neutrophil activation. By using infliximab, a clinically utilized TNF-α antagonist, we observed that the pro-NETotic effect of GDM sera was significantly reduced. We also detected pronounced neutrophil infiltrates in placentae from GDM cases. The occurrence of NETs in these tissues is suggested by the extracellular co-localization of citrullinated histones and myeloperoxidase. In addition, elevated neutrophil elastase (NE) mRNA and active enzymatic protein were also detected in such placentae. This latter finding could be important in the context of previous studies in cancer or diabetes model systems, which indicated that NE liberated from infiltrating neutrophils enters surrounding cells, altering cell signaling by the degradation of IRS1. These findings could potentiate the underlying inflammatory response process in GDM and possibly open an avenue for the therapeutic interventions in gestational hyperglycemia.

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Cellular, biochemical and molecular changes in muscles from patients with X-linked myotubular myopathy due to MTM1 mutations

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Abstract

Centronuclear myopathies are early-onset muscle diseases caused by mutations in several genes including *MTM1, DNM2, BIN1, RYR1* and *TTN*. The most severe and often fatal X-linked form of myotubular myopathy (XLMTM) is caused by mutations in the gene encoding the ubiquitous lipid phosphatase myotubularin, an enzyme specifically dephosphorylating phosphatidylinositol-3-phosphate and phosphatidylinositol-3,5-bisphosphate. Because XLMTM patients have a predominantly muscle-specific phenotype a number of pathogenic mechanisms have been proposed, including a direct effect of the accumulated lipid on the skeletal muscle calcium channel ryanodine receptor 1, a negative effect on the structure of intracellular organelles and defective autophagy. Animal models knocked out for *MTM1* show severe reduction of ryanodine receptor 1 mediated calcium release but, since knocking out genes in animal models does not necessarily replicate the human phenotype, we considered it important to study directly the effect of *MTM1* mutations on patient muscle cells. The results of the present study show that at the level of myotubes *MTM1* mutations do not dramatically affect calcium homeostasis and calcium release mediated through the ryanodine receptor 1, though they do affect myotube size and nuclear content. On the other hand, mature muscles such as those obtained from patient muscle biopsies exhibit a significant decrease in expression of the ryanodine receptor 1, a decrease in muscle-specific microRNAs and a considerable up-regulation of histone deacetylase-4. We hypothesize that the latter events consequent to the primary genetic mutation, are the cause of the severe decrease in muscle strength that characterizes these patients.

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Rheumatology RHEUMATOLOGY 2017;56:829–834 IF 4,524

Characteristics of autoantibodies targeting 14-3-3 proteins and their association with clinical features in newly diagnosed giant cell arteritis

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Abstract

Objectives. Autoantibodies are useful biomarkers for diagnosing and monitoring treatment in some autoimmune diseases. Antibodies against isoforms of 14-3-3 protein have been proposed as biomarkers for the presence of aortic aneurysm in large-vessel vasculitis (LVV). Here, we aimed to evaluate the diagnostic role and potential immunopathological involvement of anti-14-3-3 antibodies in newly diagnosed LVV patients.

Methods. Antibodies against three isoforms of 14-3-3 (γ, ε and ζ) were measured in 90 subjects: 48 GCA and 3 Takayasu's arteritis (TA) patients, and 39 controls (non-inflammatory and inflammatory diseases), using a multiplexed bead-based immunoassay and immunoprecipitation studies. The positive cut-off value was defined based on young healthy controls. Anti-14-3-3 IgG antibodies in LVV patients were compared with those in controls in order to assess their diagnostic performance, and the relationship of anti-14-3-3 IgG antibodies to the immunohistopathology of artery explants was assessed.

Results. Antibodies against all three 14-3-3 isoforms were detected in LVV patients as well as in agematched inflammatory and non-inflammatory controls. Among LVV patients, detection of antibodies targeting 14-3-3 ε and ζ was associated with more severe disease. Detection of antibodies against 14-3-3 γ was linked to latent *Toxoplasma gondii* infection, a parasite that secrets a 14-3-3 homologue, suggesting potential cross-reactivity.

Conclusion. Detection of antibodies against 14-3-3 proteins at the time of LVV diagnosis is not disease-specific. Their presence at high levels in LVV patients with stroke, aortitis and—in a previous study—aneurysm formation may indicate an association with extensive tissue destruction. The relevance of 14-3-3 antibodies in non-LVV patients needs to be investigated in larger cohorts.

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Pharmacogenetics of ecstasy: CYP1A2, CYP2C19, and CYP2B6 polymorphisms moderate pharmacokinetics of MDMA in healthy subjects

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Abstract

In vitro studies showed that CYP2C19, CYP2B6, and CYP1A2 contribute to the metabolism of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) to 3,4-methylenedioxyamphetamine (MDA). However, the role of genetic polymorphisms in CYP2C19, CYP2B6, and CYP1A2 in the metabolism of MDMA in humans is unknown. The effects of genetic variants in these CYP enzymes on the pharmacokinetics and pharmacodynamics of MDMA were characterized in 139 healthy subjects (69 male, 70 female) in a pooled analysis of eight double-blind, placebo-controlled studies. MDMA-MDA conversion was positively associated with genotypes known to convey higher CYP2C19 or CYP2B6 activities. Additionally, CYP2C19 poor metabolizers showed greater cardiovascular responses to MDMA compared with other CYP2C19 genotypes. Furthermore, the maximum concentration of MDA was higher in tobacco smokers that harbored the inducible CYP1A2 rs762551 A/A genotype compared with the non-inducible C-allele carriers. The findings indicate that CYP2C19, CYP2B6, and CYP1A2 contribute to the metabolism of MDMA to MDA in humans. Additionally, genetic polymorphisms in CYP2C19 may moderate the cardiovascular toxicity of MDMA.

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Extracellular matrix and $\alpha_5\beta_1$ integrin signaling control the maintenance of bone formation capacity by human adipose-derived stromal cells

Nunzia Di Maggio[1,*], Elisa Martella[2,3,*], Agne Frismantiene[4], Therese J. Resink[4], Simone Schreiner[1], Enrico Lucarelli[2,3], Claude Jaquiery[5], Dirk J. Schaefer[6], Ivan Martin[1] & Arnaud Scherberich[1]

Stromal vascular fraction (SVF) cells of human adipose tissue have the capacity to generate osteogenic grafts with intrinsic vasculogenic properties. However, adipose-derived stromal/stem cells (ASC), even after minimal monolayer expansion, display poor osteogenic capacity *in vivo*. We investigated whether ASC bone-forming capacity may be maintained by culture within a self-produced extracellular matrix (ECM) that recapitulates the native environment. SVF cells expanded without passaging up to 28 days (Unpass-ASC) deposited a fibronectin-rich extracellular matrix and displayed greater clonogenicity and differentiation potential *in vitro* compared to ASC expanded only for 6 days (P0-ASC) or for 28 days with regular passaging (Pass-ASC). When implanted subcutaneously, Unpass-ASC produced bone tissue similarly to SVF cells, in contrast to P0- and Pass-ASC, which mainly formed fibrous tissue. Interestingly, clonogenic progenitors from native SVF and Unpass-ASC expressed low levels of the fibronectin receptor α5 integrin (CD49e), which was instead upregulated in P0- and Pass-ASC. Mechanistically, induced activation of $\alpha_5\beta_1$ integrin in Unpass-ASC led to a significant loss of bone formation in vivo. This study shows that ECM and regulation of $\alpha_5\beta_1$-integrin signaling preserve ASC progenitor properties, including bone tissue-forming capacity, during *in vitro* expansion.

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Journal of Psychopharmacology | Journal of Psychopharmacology | 2017, Vol. 31(5) 589–598 IF 4,179

Multifaceted empathy of healthy volunteers after single doses of MDMA: A pooled sample of placebo-controlled studies

Kim PC Kuypers[1], Patrick C Dolder[2], Johannes G Ramaekers[1] and Matthias E Liechti[2]

Abstract

Previous placebo-controlled experimental studies have shown that a single dose of MDMA can increase emotional empathy in the multifaceted empathy test (MET) without affecting cognitive empathy. Although sufficiently powered to detect main effects of MDMA, these studies were generally underpowered to also validly assess contributions of additional parameters, such as sex, drug use history, trait empathy and MDMA or oxytocin plasma concentrations. The present study examined the robustness of the MDMA effect on empathy and investigated the moderating role of these additional parameters. Participants (n = 118) from six placebo-controlled within-subject studies and two laboratories were included in the present pooled analysis. Empathy (MET), MDMA and oxytocin plasma concentrations were assessed after oral administration of MDMA (single dose, 75 or 125 mg). Trait empathy was assessed using the interpersonal reactivity index. We confirmed that MDMA increased emotional empathy at both doses without affecting cognitive empathy. This MDMA-related increase in empathy was most pronounced during presentation of positive emotions as compared with negative emotions. MDMA-induced empathy enhancement was positively related to MDMA blood concentrations measured before the test, but independent of sex, drug use history and trait empathy. Oxytocin concentrations increased after MDMA administration but were not associated with behavioral effects. The MDMA effects on emotional empathy were stable across laboratories and doses. Sex did not play a moderating role in this effect, and oxytocin levels, trait empathy and drug use history were also unrelated. Acute drug exposure was of significant relevance in the MDMA-induced emotional empathy elevation.

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Journal of Psychopharmacology | Journal of Psychopharmacology | 2017, Vol. 31(5) 576–588 IF 4,179

Safety pharmacology of acute MDMA administration in healthy subjects

Patrick Vizeli and Matthias E Liechti

Abstract

3,4-Methylenedioxymethamphetamine (MDMA; ecstasy) is being investigated in MDMA-assisted psychotherapy. The present study characterized the safety pharmacology of single-dose administrations of MDMA (75 or 125 mg) using data from nine double-blind, placebo-controlled, cross-over studies performed in the same laboratory in a total of 166 healthy subjects. The duration of the subjective effects was 4.2 ± 1.3 h (range: 1.4–8.2 h). The 125 mg dose of MDMA produced greater 'good drug effect' ratings than 75 mg. MDMA produced moderate and transient 'bad drug effect' ratings, which were greater in women than in men. MDMA increased systolic blood pressure to >160 mmHg, heart rate >100 beats/min, and body temperature >38°C in 33%, 29% and 19% of the subjects, respectively. These proportions of subjects with hypertension (>160 mmHg), tachycardia, and body temperature >38°C were all significantly greater after 125 mg MDMA compared with the 75 mg dose. Acute and subacute adverse effects of MDMA as assessed by the List of Complaints were dose-dependent and more frequent in females. MDMA did not affect liver or kidney function at EOS 29 ± 22 days after use. No serious adverse events occurred. In conclusion, MDMA produced predominantly acute positive subjective drug effects. Bad subjective drug effects and other adverse effects were significantly more common in women. MDMA administration was overall safe in physically and psychiatrically healthy subjects and in a medical setting. However, the risks of MDMA are likely higher in patients with cardiovascular disease and remain to be investigated in patients with psychiatric disorders.

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Journal of Leukocyte Biology | JLB | 101: 481–491; 2017 IF 4,165

Anti-C1q autoantibodies from patients with systemic lupus erythematosus induce C1q production by macrophages

Sophia Thanei[1], and Marten Trendelenburg[1,2]

Abstract

Antibodies against C1q (anti-C1q) are frequently found in patients with systemic lupus erythematosus (SLE). The anti-C1q antibodies strongly correlate with the occurrence of lupus nephritis and low-circulating C1q levels. Previous studies have demonstrated that myeloid cells, i.e., dendritic cells and macrophages, are a major source of C1q. However, a direct effect of anti-C1q on C1q secretion by macrophages has not yet been established. In the present study, we investigated the C1q secretion profile of in vitro human monocyte-derived macrophages (HMDMs) obtained from healthy donors and from patients with SLE. The effect of SLE patient-derived anti-C1q bound to immobilized C1q (imC1q) and imC1q alone on HMDMs was investigated by C1q secretion levels, the expression of membrane-bound and intracellular C1q using flow cytometry and ImageStreamX technology, and testing the ability of secreted C1q to activate the classical pathway (CP) of the complement. Bound anti-C1q induced significantly greater C1q secretion levels as compared with imC1q alone or healthy donor IgG. The extent of C1q secretion by HMDMs correlated with IgG anti-C1q levels of patients with SLE but not of healthy controls. Furthermore, bound autoantibodies and imC1q induced continuous and de novo C1q synthesis as evident by the intracellular C1q content, which correlated with C1q secretion levels. Finally, secreted C1q was able to activate the CP, as reflected by C4b deposition. Interestingly, anti-C1q–dependent C1q secretion could also be observed in SLE patient-derived cells. In conclusion, our data indicate that imC1q-bound anti-C1q strongly stimulate the C1q production by HMDMs. Anti-C1q–induced C1q secretion might be an important immune-modulatory factor in SLE.

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Materials Science and Engineering | MATERIALS SCIENCE & ENGINEERING | C 76 (2017) 543–550 IF 4,164

Bimodal morphological analyses of native and engineered tissues

Sasan Jalili-Firoozinezhad, IvanMartin, Arnaud Scherberich

Abstract

Assessing the morphological features of native and engineered tissues is pivotal to evaluate their degree of development and to identify possible structure-function relationships. Conventional histological or immunohistochemical imaging of stained sections provides limited information about their architecture. Scanning electron microscopy (SEM) yields submicrometric resolution images of tissues, but typically cannot be associated with the morphological structures identified by histology. The aim of this study was to establish a technique based on SEM analysis of sections of paraffin-embedded tissues prepared for histological processing (Histo-SEM) for the assessment of morpho-architectural properties of native and engineered tissues. Histo-SEM was performed on sections of cartilaginous, bone and fibrous tissues, native or engineered, in parallel with histological/immunohistochemical staining. Histo-SEM technique allowed evaluating morpho-architectural features typically unreachable by conventional histological staining, like (i) the extent of cartilage maturation based on collagen fibers' diameter and orientation, (ii) the formation of bone tissue/osteoid based on the presence of nanoscaledense matrix structures, and (iii) tissue integration and vascularization based on collagen fibers' density and average vessel walls thickness of fibrous tissue growing within ectopically implanted porous materials. In conclusion, Histo-SEM allows integrating bimodal morphological assessments of native or engineered tissues and deriving complementary qualitative and quantitative parameters related to their structural organization and level of maturation.

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Journal of Tissue Engineering and Regenerative Medicine | Journal of Tissue Engineering and Regenerative Medicine | 2017; 11: 1542–1552 IF 3,989

Pooled thrombin-activated platelet-rich plasma: a substitute for fetal bovine serum in the engineering of osteogenic/vasculogenic grafts

Laurent A. Tchang[1,2], Benjamin E. Pippenger[2], Atanas Todorov Jr[2], Francine Wolf[2], Maximilian G. Burger[1], Claude Jaquiery[2], Karen Bieback[3], Ivan Martin[2], Dirk J. Schaefer[1] and Arnaud Scherberich[2]

Abstract

The use of fetal bovine serum (FBS) as a culture medium supplement in cell therapy and clinical tissue engineering is challenged by immunological concerns and the risk of disease transmission. Here we tested whether human, thrombin-activated, pooled, platelet-rich plasma (tPRP) can be substituted for FBS in the engineering of osteogenic and vasculogenic grafts, using cells from the stromal vascular fraction (SVF) of human adipose tissue. SVF cells were cultured under perfusion flow into porous hydroxyapatite scaffolds for 5 days, with the medium supplemented with either 10% tPRP or 10% FBS and implanted in an ectopic mouse model. Following in vitro culture, as compared to FBS, the use of tPRP did not modify the fraction of clonogenic cells or the different cell phenotypes, but increased by 1.9-fold the total number of cells. After 8 weeks in vivo, bone tissue was formed more reproducibly and in higher amounts (3.7-fold increase) in constructs cultured with tPRP. Staining for human-specific ALU sequences and for the human isoforms of CD31/CD34 revealed the human origin of the bone, the formation of blood vessels by human vascular progenitors and a higher density of human cells in implants cultured with tPRP. In summary, tPRP supports higher efficiency of bone formation by SVF cells than FBS, likely by enhancing cell expansion in vitro while maintaining vasculogenic properties. The use of tPRP may facilitate the clinical translation of osteogenic grafts with intrinsic capacity for vascularization, based on the use of adipose-derived cells.

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Psychopharmacology Psychopharmacology (2017) 234:1499–1510 IF 3,540

Alterations of consciousness and mystical-type experiences after acute LSD in humans

Matthias E. Liechti[1] & Patrick C. Dolder[1] & Yasmin Schmid[1]

Abstract

Rationale Lysergic acid diethylamide (LSD) is used recreationally and in clinical research. Acute mystical-type experiences that are acutely induced by hallucinogens are thought to contribute to their potential therapeutic effects. However, no data have been reported on LSD-induced mystical experiences and their relationship to alterations of consciousness. Additionally, LSD dose-and concentration-response functions with regard to alterations of consciousness are lacking.

Methods We conducted two placebo-controlled, double-blind, cross-over studies using oral administration of 100 and 200 μg LSD in 24 and 16 subjects, respectively. Acute effects of LSD were assessed using the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale after both doses and the Mystical Experience Questionnaire (MEQ) after 200 μg.

Results On the MEQ, 200 μg LSD induced mystical experiences that were comparable to those in patients who underwent LSD-assisted psychotherapy but were fewer than those reported for psilocybin in healthy subjects or patients. On the 5D-ASC scale, LSD produced higher ratings of blissful state, insightfulness, and changed meaning of percepts after 200 μg compared with 100 μg. Plasma levels of LSD were not positively correlated with its effects, with the exception of ego dissolution at 100 μg.

Conclusions Mystical-type experiences were infrequent after LSD, possibly because of the set and setting used in the present study. LSD may produce greater or different alterations of consciousness at 200 μg (i.e., a dose that is currently used in psychotherapy in Switzerland) compared with 100 μg(i.e., a dose used in imaging studies). Ego dissolution may reflect plasma levels of LSD, whereas more robustly induced effects of LSD may not result in such associations.

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Current Topics in Behavioral Neurosciences (2017) 32: 49–72

Interactions of Cathinone NPS with Human Transporters and Receptors in Transfected Cells

Linda D. Simmler and Matthias E. Liechti

Abstract

Pharmacological assays carried out in transfected cells have been very useful for describing the mechanism of action of cathinone new psychoactive substances (NPS). These in vitro characterizations provide fast and reliable information on psychoactive substances soon after they emerge for recreational use. Well-investigated comparator compounds, such as methamphetamine, 3,4-methylenedioxymethamphetamine, cocaine, and lysergic acid diethylamide, should always be included in the characterization to enhance the translation of the in vitro data into clinically useful information. We classified cathinone NPS according to their pharmacology at monoamine transporters and receptors. Cathinone NPS are monoamine uptake inhibitors and most induce transportermediated monoamine efflux with weak to no activity at pre-or postsynaptic receptors. Cathinones with a nitrogen-containing pyrrolidine ring emerged as NPS that are extremely potent transporter inhibitors but not monoamine releasers. Cathinones exhibit clinically relevant differences in relative potencies at serotonin vs. dopamine transporters. Additionally, cathinone NPS have more dopaminergic vs. serotonergic properties compared with their non-β-keto amphetamine analogs, suggesting more stimulant and reinforcing properties. In conclusion, in vitro pharmacological assays in heterologous expression systems help to predict the psychoactive and toxicological effects of NPS.

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REVIEWS

Cancer Cell | Cancer Cell | 31, May 8, 2017 IF 27,407

Tackling Resistance to PI3K Inhibition by Targeting the Epigenome

Shany Koren[1] and Mohamed Bentires-Alj[1]

Phosphoinositide-3-kinase (PI3K) pathway inhibitors have emerged as promising therapeutic agents for estrogen receptor (ERα)-positive breast cancers. However, incipient resistance limits the clinical benefit. Toska and colleagues identified that the epigenetic regulator KMT2D enhances ERα activity in BYL719-treated *PIK3CA* mutant breast cancer, leading to a rationale for targeting the epigenome and PI3K signaling.

Over 1.6 million women worldwide are diagnosed annually with breast cancer, and ~600,000 lives are lost to the disease, in most cases due to persisting drug-resistant metastases. The key challenges for successful cancer therapy are the identification of reliable predictive biomarkers, an efficacious and well-tolerated drug or combination of drugs, and the means to overcome resistance. Tumor heterogeneity and numerous processes leading to resistance limit the efficacy of targeted therapy, and their delineation is fundamental to the development of combination therapies.

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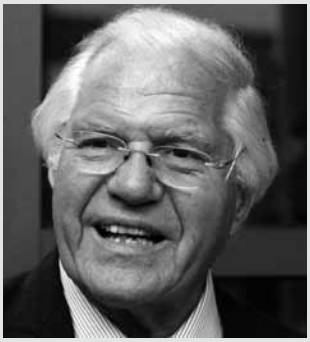
Zwetschgenkonfitüre

Zutaten: 1 kg Früchte, 1 kg Zucker.

Zubereitung: Nicht überreife, noch feste Früchte werden gewaschen und in gleichmässige, kleinere Stücke geschnitten. Der Zucker wird mit 2 dl Wasser 2-3 Minuten gekocht, die Früchte beigefügt und vom Siedepunkt an 10 – 15 Minuten gekocht.

Alternativ:: Die klein geschnittenen Früchte mit dem Zucker vermischen, über Nacht stehen lassen und unter Rühren 20 Minuten kochen.



Traurig haben wir Kenntnis genommen, dass Prof. Fritz R. Bühler, ehemaliger Leiter des Departements Forschung (DF), in diesem Frühjahr nach längerer Krankheit verstorben ist. Fritz Bühler kam als Leitender Arzt 1977 an das Universitätsspital Basel, wo er die Verantwortung für die Hypertonie Sprechstunde übernahm und am DF über die Pathophysiologie der Hypertonie forschte. Fritz Bühler verschaffte sich als ausgewiesener Experte auf diesem Gebiet eine international sehr hohe Reputation, gleichzeitig engagierte er sich als Ordinarius für Pathophysiologie stark für die universitäre Lehre. Er wurde 1988 Vorsteher des DF und leitete die Professionalisierung der Forschung am DF ein, indem er Stellen für vollzeitliche Forschungsgruppenleiter schuf und Kooperationen mit anderen Universitäten und der Industrie förderte. Die Qualität der Forschung am DF nahm unter seiner Führung stark zu und bildete die Voraussetzung für die erfolgreiche weitere Entwicklung zum heutigen DBM. Dafür sind wir Fritz Bühler sehr dankbar.

Radek Skoda

Our dear colleague Antonius G. Rolink, Professor of Immunology at the DBM, has passed away on August 6, 2017.

Antonius Rolink was the Roche-Professor of Immunology and Head of the Laboratory of Molecular and Developmental Immunology at the Department of Biomedicine (DBM). Born in The Netherlands in 1953, he started his academic career at the University of Amsterdam, The Netherlands, where he studied lymphocyte biology and the development of autoimmunity. In 1983, he moved to Switzerland as a member of the world-renowned Basel Institute for Immunology, where he served as a permanent member from 1995 to 2001. He authored more than 150 scientific publications, including many in top-ranking journals, and organized several EMBO workshops and the Basel Immunology Focus Symposium (BIFS), an international meeting that has become a regular and successful event. His research focused on understanding the molecular mechanisms guiding T and B lymphocyte diversity and B cell development, starting from earliest B cell progenitors all the way to antibody producing plasma cells. His work significantly contributed to a better understanding of how the immune system develops self-tolerance and how autoimmune diseases arise.

His vision and engagement had a major influence on the scientific community and contributed significantly Basel's reputation as a centre for research in immunology with international reach. Ton Rolink was not only a brilliant scientist, but also a passionate teacher and mentor. He was responsible for teaching Basic Immunology at both the Phil.-Nat. Faculty and at the Faculty of Medicine. He had a clear, structured and interesting lecture style that was both inspiring and motivating.

With Ton Rolink we lose an outstanding scientist, academic teacher and friend, whose passion, character and knowledge will be dearly missed.

Radek Skoda

DEPARTEMENT BIOMEDIZIN HEBELSTRASSE

Lucas Degrugiller
Brain Ischemia and Regeneration
Katharina Prautsch
Brain Ischemia and Regeneration
Nicole Kirchhammer
Cancer Immunology
Natalia Rodrigues Mantuano
Cancer Immunology
Jinyu Wang
Cancer Immunology
Alexandra Kosareva
Cardiovascular Molecular Imaging
Francesca Mai
Cell and Gene Therapy
Hugues-Etienne Chatel-Soulet
Childhood Leukemia
Matheus Filgueira Bezerra
Childhood Leukemia
Qinmei Yang
Experimental Immunology
Christian Baumann
Hepatology
Daniel Kirchmeier
Immune Cell Biology
Jonas Lötscher
Immunobiology
Veronika Gajdos
Inner Ear Research
Ali Coskun Tülek
Inner Ear Research
Anne Bärenwaldt
Myeloid Malignancies
Leandra Ramin-Wright
Myocardial Research
Claus Hultschig
Perioperative Patient Safety
Thomas Geiger
Stab
Jan Demner
Tissue Engineering
Claudia Gutierrez
Tissue Engineering
Bogdan-Tiberius Preca
Tumor Heterogeneity Metastasis and Resistance

DEPARTEMENT BIOMEDIZIN KLINGELBERG-STRASSE

Myeongjeong Choo
Molecular Neurobiology Synaptic Plasticity
Antonio José P. Yarzagaray
Molecular Neurobiology Synaptic Plasticity
Christian Klingler
Neuromuscular Research

DEPARTEMENT BIOMEDIZIN MATTENSTRASSE

Martina Gonella
Cancer Metastasis
Chiara Borsari
Cancer- and Immunobiology
Tom Masson
Cancer- and Immunobiology
Aymeric Ontani
Cancer- and Immunobiology
Shalu Jhanwar
Developmental Genetics
Benedict David Gutbrod
Developmental Immunology
Beena Patricia Jeevan Raj
Tumor Biology

DEPARTEMENT BIOMEDIZIN PESTALOZZI-STRASSE

Swetha Kalagara
Inner Ear Research
Alejandro Giesenow
Musculoskeletal Research
Efthalia Natalia Tousiaki
Neuronal Development and Degeneration

DEPARTEMENT BIOMEDIZIN PETERSPLATZ

André Tiaden
Experimental Rheumatology
Ulrike Seeburg
Molecular Virology
Ahmet Cagkan Inkaya
Transplantation and Clinical Virology

Congratulations

Andreas Phaedon Petrovas
Geboren am 30.03.2017

Syuan-Cheng Huang
Geboren am 12.04.2017

Joris Leonards
Geboren am 25.05.2017

Das DBM gratuliert ganz herzlich!

Gabriel Contador Bustos
Geboren am 29.03.2017

Marie Bippes
Geboren am 22.04.2017

Clara Seth-Smith
Geboren am 10.04.2017

Afonso Correia
Geboren am 22.04.2017

Herzlich willkommen, allerseits!

Into the deep

"What is a scientist after all? It is a curious man looking through a keyhole, the keyhole of nature, trying to know what's going on."
Jacques Cousteau (Diving Pioneer)

The world beneath the oceanic surface has always held a deep fascination for mankind, accounting for the fact that diving dates back to as early as 4500 B.C. Of course at that time diving was not a recreational activity, but rather a form of commerce in cultures like Mesopotamia, Greece and China, securing the trade of seafood and pearls and later on of natural sponges. The use of diving equipment allowing divers to stay under water for extended amounts of time has been mentioned in various early historical reports. Greek divers Scyllias and his daughter Cyana used hollow reeds as a snorkeling device during the Greco-Persian Wars to escape the Persian army, and in Aristoteles writings described he for the first time the use of an air-supplied diving bell used by Alexander the Great during the siege of Tyre in 360 B.C. However, it took until the 17th century until the diving bell was routinely used in salvage missions. Concurrent with these advances in diving with surface supplied air, scientists explored the possibility of self-contained diving systems. Modern recreational diving as we know it is based on the invention of two Frenchmen, navy officer and undersea explorer Jacques-Yves Cousteau and engineer Emile Gagnan who,

in the 1940s, invented the so called "Aqua-Lung", an open circuit, self-contained underwater breathing apparatus (SCUBA). This technology enabled them to conduct various underwater expeditions and to produce some of the first underwater movies such as the famous 1956 documentary "The Silent World". Since then the popularity of diving increased tremendously and has as well become accessible to the general population.

So how did I get into scuba diving? Well, for as long as I can remember, I have been drawn to water. Even at a young age I liked to wear a diving mask and snorkel in the paddling pool. And beach vacations and my earliest memories of marine underwater life in the Mediterranean sea definitely fur-

ther fed my desire to explore the underwater world. Finally, at the age of 20 I decided to do a diving course and contacted a nearby diving center. I registered for an “Open Water Diver” course. Having seen documentaries showing abundant underwater life and colorful images of tropical reefs my first diving experiences in some German lakes were a little different to what I had in mind. One of my first training dives I completed in Lake Constance with a visibility of close to 1 meter and the only underwater “life” I spotted was a dead fish. That, however, did not discourage me.

Since that time I have dived in many places around the world. I have had amazing underwater adventures with a great bunch of interesting people. So you might ask yourself doesn’t it get boring? The answer is definitely: no. And this is because there are moments you will never forget. I remember an early morning dive in the Maldives. Of course, at

first when the alarm clock rings at 4 am in the morning and when you have to get into a wet, cold diving suit, which had not time to dry out from the day before, you ask yourself: Why am I doing this? Yet, you are anticipating what lies ahead of you. That day the experience already started before the actual dive. When we approached the boat we saw from afar the blue sparkling waves crushing onto the beach, lit by bioluminescent phytoplankton. The whole boat ride was like in a dream, the blue shiny waves in the wake of the boat lighting up the night. When we finally jumped into the water, it felt like diving in a star lit sky. We descended fast and then from the deep dark nothing beneath a school of hammerhead sharks appeared and started to circle around us. We watched them for around 15 minutes before they disappeared again into the endless depths of the ocean. We ended this dive exploring an amazing colorful reef. Years later I still remember this early morning dive as it was yesterday. It's for experiences like that that I dive. Because no matter how many times you have been underwater before, you never know what awaits you.

For me diving is the ultimate relaxation. The moment when you leap off the boat and submerge into the serenity of the ocean is like entering into a different world. Yet, to also enable future generations to experience this magnificent world in all its diversity it's necessary to preserve it. Our oceans are facing enormous threats including overfishing, pollution, warming and acidification. It is therefore on us to take steps to preserve this delicate underwater ecosystem so that future divers may also explore this mysterious habitat and experience unforgettable diving adventures. So leave the fish alone, and eat more beef!

Corina Kohler

Tere tulemast Eestisse! / Welcome to Estonia!

Instead of introduction

Before joining the European Union and NATO in 2004, Estonia remained largely unknown to the world. Clearly, awareness of this small country, and its popularity as a touristic destination, has increased significantly in the recent years with the number of visitors each year doubling the country's population. It is for this reason that I am writing this article to introduce my homeland to the readers of DBM Facts.

So, what is Estonia? Officially the Republic of Estonia, it is a small country in the Baltic region of Northern Europe. Located at the same latitude as the north of Scotland, Estonia is the most northern of the three Baltic States (the other two are Latvia and Lithuania). To answer the frequently asked question – yes, Estonia has its own language that is called Estonian! It is most closely related to Finnish (and more distantly to Hungarian). Most of the population still speaks Russian which is a legacy of its Soviet past and for ~25%, including me, it is our mother tongue.

Estonia is similar in size to Switzerland, but is much flatter and has ~7 times less people (the population of Estonia is just 1.3 million!). Low population density and lots of unspoiled nature makes this country a paradise for introverts and for people looking for peace and solitude.

The History

The first traces of human culture on the territory of modern Estonia date back to ~10 000 B.C. and predecessors of modern Estonians have been settled there since ~1800 B.C. However, these people never were a unified nation nor had they their own state. Since the 13th century, Estonians were consecutively under German, Danish, Swedish and Russian rule until 1918, when, driven by the national awakening, Estonian people gained independence from the Russian Empire on 24th of February (nowadays celebrated as the Independence Day). After World War II Estonia was forcedly joined to the USSR, until regaining its independence on 20th of August 1991, following the collapse of the Soviet Union.

Summer landscape in South Estonia

Elk in Elistvere Biopark

Modern Estonia

After restoring the independence, and with its economy devastated by the communist rule, the country had a chance for a clean start. Thanks to the visionary actions of the young Estonian government that made an active effort to integrate Internet technology into the structure of civic life, Estonia became what it is now – a truly digital society (sometimes referred to as E-stonia or e-Estonia). Estonia is the world leader in start-ups and most famously, Estonians invented Skype (yes, we are really proud of it). Estonia was the first country to implement online voting in 2005, the tax returns are filed electronically within minutes, citizens can sign legal documents remotely with their ID cards and register their business online in less then 20 minutes. And this is just a small part of the com-

View over Tallinn rooftops from the Oleviste church.

plete list. Anyone in the world can apply to be an e-resident and get access to hundreds of public e-services. Moreover, 100% of the country is covered by high-speed 4G Internet, meaning that you can stay online even in the middle of the woods. Essentially, everything can be done online without leaving your house or apartment, which fits very well to the Estonian mentality.

The People

As you can guess from the geographical location, the weather in Estonia is really cold in winter and unpredictable in summer. Low population density and, as a result, a lot of free space have shaped Estonian mentality in a certain way. We need our personal space and much prefer to be alone with nature than in company. We do not like talking to people until it is absolutely necessary and that is also a reason why alcohol is a must at many social events (the other reason is that it is cold most of the year). At the same time, we value friendship and choose friends carefully. Because Estonians were under foreign rule for so long, they learned to hide their emotions really well and might appear "cold" during conversation. So, if you meet an Estonian and feel like they are rude – don't jump to conclusions, it is most likely that they are just being Estonian.

A huge part of the Estonian national identity is the love to sing. Sometimes called a "singing nation", Estonians have one of the biggest collections of folk songs in the world, with written records of about 133 000 folk songs. As Estonians also like a good party, song and music festivals are popular all over the country, but mostly in summer time.

Among other things, we really like sauna and beer (which is very good in Estonia), and we often combine them together. Funnily enough, because of the sauna culture, nudity is totally cool, while talking to a stranger on the street is not.

Because of all that free space and long summer days, time seems to go slowly in Estonia and people do not hurry – Estonian tardiness is almost anecdotal in neighbouring countries (or, perhaps, it is just a way to save energy during colder periods).

Flowering rapeseed field right before the storm.

Hiking trail through the pine forest in South Estonia

Baltic Sea coast in Toila (Gulf of Finland)

Visiting Estonia

Estonia is perfect for those who love nature. That is where this country has to offer the most. With 50% of land covered by forests, with >2000 islands, >1000 lakes, numerous rivers, fens and bogs it offers enough places and activities to suit every taste. Despite the widespread joke about typical Estonian summer, when people warn you not to miss the sunny day, you might enjoy all the seasons in Estonia. Yes, winter seems to be the longest one here, but it is captivating, beautiful and cozy. If you like winter sports, it's a perfect time and place to experience cross-country skiing, kick sledging or even driving across the ice road from the mainland to the islands, enjoying the beautiful snow-covered landscapes with fairytale Estonian forests, national parks, lakes and seaside. Do not miss the most romantic walk around Tallinn Old Town (the best preserved medieval city in Northern Europe) with all its charming cafeterias and restaurants, souvenir shops and Christmas market! When it is not snowing or raining - it is time for hiking and camping, birdwatching and fishing, swimming and canoeing, exploring the beauty of well-preserved nature and wildlife (which is really abundant here, compared to many other European countries). By the way, the longest summer days last for over 19 hours, followed by so called "white nights" (when it does not get completely dark at night) – an ideal time for an overnight party!

I find Estonia a perfect place for reflection, solitude if needed, oneness with nature and in the end the fresh breath of air for those, who want to relax.

A walk around the Old Town in Tallinn.

Tiny but shiny

Estonia is the smallest from Baltic States, but it is surprisingly versatile and contains a lot of surprises. Here old and new live side by side, technologies coexist with pristine nature. Imagine, it has 2355 islands; some of them are quite big, like Saaremaa, where the biggest meteorite crater Kaali is located (speaking of which, Estonia has the highest number of craters per land in the world!). At the same time, here, on Saaremaa, you will find the best spa centers and recreation zones, and, surprisingly, the best-preserved medieval castle in Europe! In fact, there are dozens of them all over the country. One of them, the 9th century Toompea Castle in Tallinn, build by inhabitants of ancient Estonia is nowadays housing the Parliament of Estonia.

There is so much more to say about my homeland, but the best way is to go there and explore it yourself. And of course, don't hesitate to ask me for any information or advice.

Aleksei Suslov (and Viktoriya Shyp)

Today: Duvini De Silva, THMR

It is my great pleasure to introduce myself to you/DBM. I am Duvini De Silva, a technician in the THMR group. I come from Sri Lanka, which is an island nation located in the Indian Ocean. I was born and brought up in Colombo, which is the largest city and the commercial capital of Sri Lanka, and is situated on the western coast of the island. The island lies just above the equator, which allows us to have warm weather through the year.

As children, my sisters and I spent most of the weekends on the beach playing cricket or touch rugby (no tackling allowed!) with the neighbourhood kids.

Sunday lunch is a feast – everyone including extended family gather to enjoy a meal together.

I spent most of my school holidays either in the national parks, archaeological sites or in the hill stations enjoying the cooler climate. The national parks are protected areas, which are abundant in wildlife including elephants, sloth bears, crocodiles, buffalos, deer, monkeys and various species of birds such as peacocks. I spent many days on safari counting elephants, 103 was the highest number I spotted on one day. The marine parks in the south and east of the island are home to sea turtles, reef sharks, dolphins and whales on their migration path.

During the very warm months, we went up to the hill stations to escape the heat.
The cooler climate in the hills favour the cultivation of tea, which the British brought to Sri Lanka from China. Tamil women in colourful saris picking tea leaves by hand – is one of the island's most famous sights.

My father thought that visiting the archaeological sites would be a fun way for my sisters and me to learn our history modules for school. These sites take you on a fascinating journey through the history and heritage of the island. The archaeological sites include ancient cities with their many temples, lakes, palaces with vast water and green gardens built by the ancient kings.

At the age of 18, I moved to another island, Singapore. This city-state is a global financial center with a tropical climate and a multicultural population. With the exception of the weather, this was a completely new experience for me. The feature of Singapore that most amazed me, made me curious and sometimes intimidated me was the diversity.

The food culture, a favourite past time of many Singaporeans, has

been greatly influenced by its geographical location and its diverse population. Needless to say, with everything from hawker centres to the gourmet restaurants open around the clock serving diverse cuisines, I was few kilos heavier during my time in Singapore. The hawker centres are a unique aspect of Singapore. These are mostly open-air complexes with many stalls, some of which have existed for generations, selling a wide variety of food.

Vivocity hawker centre

Singapore has been working hard at establishing connections between developed urban environments and nature. With city parks, reservoirs, forest preserves, undeveloped scrublands and the manicured street trees in developed areas, there are plenty of green areas for outdoor activities

It was during my time in Singapore that I started meeting people from different nationalities and started traveling around Asia. Taking advantage of the geographical location of Singapore I hiked my first peak-mount Kinabalu in Malaysia, got my diving license in the Mal-

Bedok Resevoir, Singapore

dives, ate some of the spiciest food I have ever had in Thailand and drank some of the cheapest beers, Bia hoi, in Vietnam.

Now I've been in Switzerland for 3 years and I've been traveling in Europe, hiking some of the whitest peaks I have seen, swimming in some of the coldest waters I have ever experienced, eating some of the finest food and drinking some of the best beers and still, I am looking forward to more...

Save the date

DBM Summer Symposium

Thursday August 31, 2017

8:00 – 13:15
Kleiner Hörsaal, ZLF, Hebelstrasse 20

Presentations by DBM postdocs, PhD students and project leaders

DBM Summer Barbecue

Thursday, August 31, 2017

16:30 – 21:30
Kraftwerkinsel Birsfelden

For DBM members only

Das ist nicht Sommer mehr

Das ist nicht Sommer mehr, das ist September … Herbst:
diese großen weichen Wolken am Himmel,
diese feinen weißen Spinnwebschleier in der Ferne
und hinter den Gärten mit den Sonnenblumen
der ringelnde Rauch aufglimmender Krautfeuer …
und diese süsse weiche Müdigkeit und diese
frohe ruhige Stille überall und trotzdem wieder
diese frische, satte, erntefreudige, herbe Kraft …
das ist nicht Sommer … das ist Herbst.

Cäsar Otto Hugo Flaischlen
(1864 - 1920)