DBM FACTS

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Universitäts-Kinderspital beider Basel

Pathology of the Human Liver | A change of model organism for me – A new building for the DBM | Why to fall in love with Greece?

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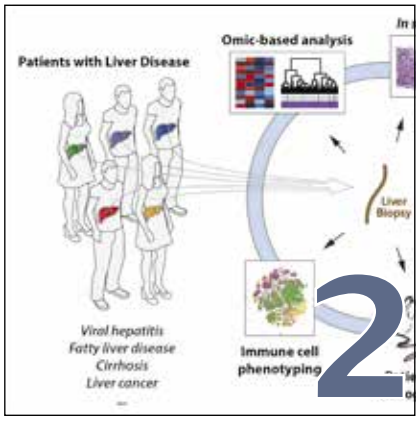

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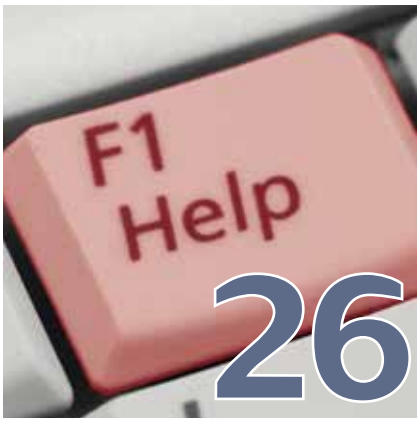

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Das DBM stellt sich vor

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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Die Sommerpause liegt hinter uns. Das Jahr mit seinen immer neuen Herausforderungen schreitet mit grossen Schritten voran. Das Projekt «Spitalgruppe» und «Universitätsspital Nordwest» macht Fortschritte: Im Juli haben das Universitätsspital Basel und das Kantonsspital Baselland ihren Willen, ein gemeinsames Spital zu gründen, mit einem Kooperationsvertrag bekräftigt.
Wichtige Berufungen am USB konnten erfolgreich abgeschlossen werden: Alexander Navarini (Dermatologie) und Karin Hartmann (Allergologie) werden ihre klinische Tätigkeit aufnehmen und neue Forschungsgruppen am DBM gründen. Wir wünschen beiden viel Erfolg und gutes Gelingen!
Stefan Wieland stellt in dieser Ausgabe die wissenschaftliche Expertise der Forschungsgruppe «Hepatology» vor (ab Seite 2). Weitere exzellente Publikationen aus dem DBM erwarten Sie dann ab Seite 12. Über den aktuellen Stand des Neubaus DBM wird Christophe Kunz in seinem Artikel (ab Seite 8) berichten. Mit auf die Reise von Griechenland nach Liechtenstein nehmen uns Daria Belik Monogiou (ab Seite 28) und Philipp Wuggenig (ab Seite 31).

Ich freue mich, Sie möglichst zahlreich an unserem Sommersymposium und anschliessendem Barbecue zu sehen und wünsche Ihnen eine unterhaltsame Lektüre!
Radek Skoda

Dear Readers,

The Summer holidays are behind us, and the year with its endless new challenges is moving on apace. The "Spitalgruppe und Universitätsspital Nordwest" Project is progressing: in July the University Hospital Basel, and the Cantonal Hospital of Basel-Landschaft formally declared their intention to found a joint hospital with the signature of an Agreement of Cooperation.
Some important positions at the University Hospital have been successfully filled: Alexander Navarini (Dermatology), and Karin Hartmann (Allergology) will be taking on clinical responsibilites and starting new research groups at the DBM. We wish both of them every success!
In this edition, Stefan Wieland is presenting the scientific accomplishments of the Hepatology research group (from page 2); and more excellent publications from the DBM await you on page 12 onwards. The current status of the construction of the new DBM is described in Christophe Kunz' article on page 8; and Daria Belik Monogiou and Philipp Wuggenig invite us to accompany them on their voyage from Greece to Liechtenstein (from page 28).

I am looking forward to seeing as many of you as possible at the Summer Symposium and the following barbecue, and happy reading!
Radek Skoda

Pathology of the Human Liver

Introduction

The research in our Hepatology group, as the name suggests, is focused around the human liver and its associated pathologies. Thanks to the generosity of patients that donate a piece of liver tissue for science during routine liver biopsy sampling or in the context of a clinical study, we have the opportunity to get a glimpse into the human liver and the phenomenological and molecular aspects of different liver pathologies *(Figure 1)*. Furthermore, liver biopsy tissue provides an opportunity to establish in vitro and in vivo patient- and disease-specific model systems *(Figure 1)*. Together, these studies are driven by the desire to further our understanding of the underlying causes that can lead to hepatocellular carcinoma (HCC) development in the liver and the difficulties to achieve successful HCC therapy. Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the second cause of cancer-related mortality worldwide [1]. HCC mainly arises in livers with pre-existing underlying diseases such as viral hepatitis, alcoholic liver disease and nonalcoholic steatohepatitis. Among these, chronic infection with hepatitis B (HBV) and/or hepatitis C virus (HCV) represent a major risk factor for HCC [2, 1, 3]. The histopathological progression of a diseased liver towards HCC development is a result of persistent liver inflammation caused by the various underlying risk factors [4]. The development of HCC is thus a yearlong process involving several rounds of hepatocyte death and regeneration and the cumulative deposition of collagen scar tissue. This process ultimately leads to cirrhosis, representing the major risk factor for HCC development, being present in ~90% of HCC patients [1]. Importantly, the wide range of phenotypical composition of HCC at the histological and molecular level makes it very difficult to classify different HCCs and design HCC-specific therapy approaches [5, 6].

The current research in our group is divided in two major topics related to (i) delineating innate immune responses of hepatotropic viral infections as the underlying disease leading to HCC and (ii) characterization of HCC and treatment resistance with the goal to advance HCC therapy development.

Innate Response in Hepatotropic Virus Infection.

There are five known viruses that share a strict tropism for the human liver. They include Hepatitis A, B, C, D and E virus and are collectively known as Hepatitis viruses. These viruses are grouped together because they target the liver and cause liver disease (i.e. hepatitis), even though they are phylogenetically unrelated. Hepatitis A and E viruses are predominantly transmitted by the fecal-oral route and mostly cause acute self-limited inflammatory liver disease and therefore do not present an epidemiological threat [7]. In contrast, HBV and HCV are transmitted via blood and often cause chronic infection leading to gradually progressing liver disease [8, 3]. Together these two viruses infect >5% of total human population and cause >1 million deaths every year due to complications of the virus-related chronic liver disease leading to cirrhosis and hepatocellular carcinoma [9]. Despite the availability of a protective vaccine for HBV and very efficient antiviral therapies against HCV, these viruses are still a major global health problem, especially in the developing world [9, 3]. Hepatitis D virus is a satellite virus that completely depends on HBV for its life cycle. HDV co- or superinfection occurs only in 5 – 10% of HBV infected individuals, but results in an accelerated liver disease progression and is associated with poor prognosis [10]. Chronic HBV and HCV infection is associated with weak adaptive immune responses characterized by a T cell exhaustion phenotype [8, 3]. However, little is known about the mechanisms leading to the impairment and ultimate failure of the innate and adaptive immune systems to clear these infections [11, 3].

It is well established that innate immune responses constitute the first line defense against viral infections and that interferons (IFNs) are the central cytokines responsible for the induction of an antiviral state in cells and for the activation and regulation of the cellular components of innate immunity [3, 12]. Infected cells recognize pathogen-derived molecules via pathogen recognition receptors (PRR) and respond with production of IFNs and proinflammatory cytokines [13] that in turn induce interferon-stimulated genes (ISG) and thereby put cells in an antiviral state [12]. In addition, innate immune recognition

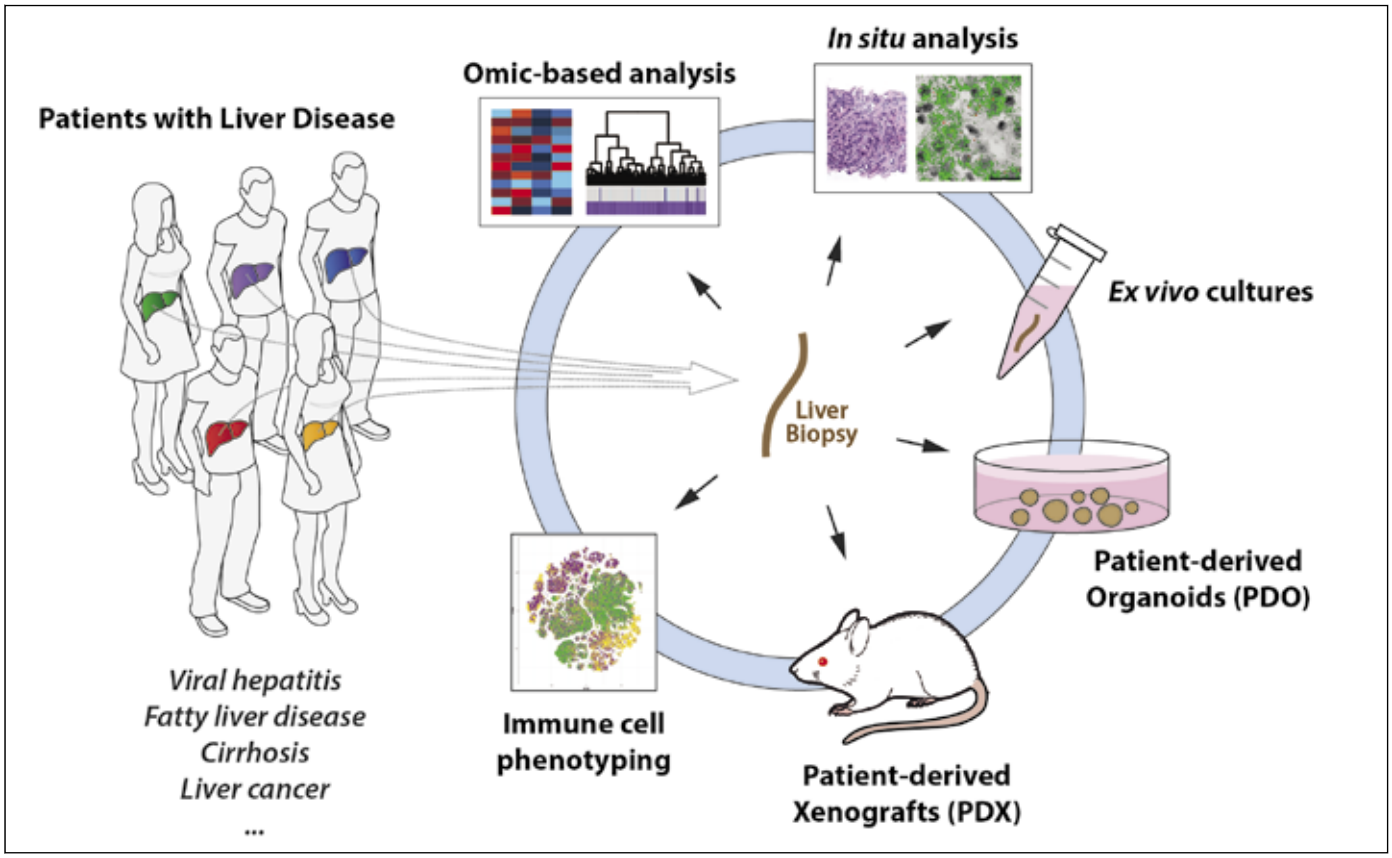

Figure 1. Liver biopsy tissue as the starting point for the study of liver diseases at the whole tissue and cellular level and the establishment of disease model systems. *(by Sandro Nuciforo)*

of viral infection is crucial for mounting an efficient adaptive antiviral response [12]. Therefore, we are interested in delineating the virus host interactions at the whole tissue as well as at the cellular level in the liver of chronically HBV and HCV infected patients.

Chronic HCV Infection (CHC).

HCV infection is rarely self-limited with the virus persisting in 70 – 80% of infected individuals leading to CHC despite an initial innate response associated with strong ISG induction in the liver [3]. During chronic HCV infection, using liver biopsy of CHC patients, we could establish that some patients maintain a strong intrahepatic ISG response while it is lacking in other patients [14]. Interestingly, and contrary to the expectation, a strong intrahepatic ISG response is very tightly associated with a poor response to IFNα therapy [14]. Moreover, using a highly sensitive duplex in situ hybridization (ISH) system, we were able for the first time to visualize HCV infected cells in the liver of CHC patients and could demonstrate that the intrahepatic ISG induction is strongest in and around the HCV infected cells *(Figure 2;* [15]*)* suggesting that intrahepatic ISG expression is not driven by systemic interferon, but rather by the HCV infected cell [15]. These results underscore the capacity of HCV to persist in the presence of an IFN-induced ISG response and in part explain the poor response to IFN based therapies. These data also raise the question what (transcriptional) changes HCV might induce in the infected cells. Many *in vitro* studies identified and characterized cellular responses other than the innate response to HCV infection [16]. Determining the relevance of those findings for HCV infected cells in the human liver however, is hampered by the strong endogenous ISG expression in the liver of many patients that can mask the changes and responses caused directly by the virus itself [3]. Again, using liver biopsy tissue of CHC patients, we could address this question by comparing the transcriptome of CHC patients lacking an activated endogenous IFN system with uninfected controls [17]. These studies revealed that transcriptomic changes in the HCV infected liver predominantly reflect immune cell associated pathways, but not cell-intrinsic pathways suggesting

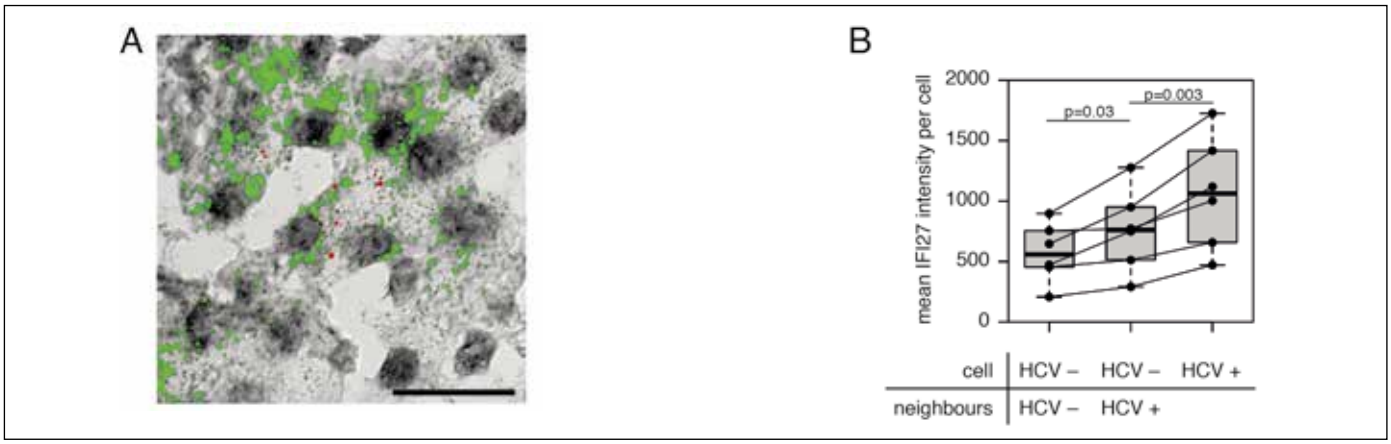

Figure 2. HCV-infected cells and their neighbors have increased probability of high ISG expression compared to noninfected cells. ***(A)*** *Two-color ISH staining for HCV RNA (red) and the ISG IFI27 (green) mRNA in the liver biopsy from a chronically HCV infected patient. Scale bar 25 µm.* ***(B)*** *Integrated intensity of IFI27 mRNA ISH staining per cell in the liver of six different chronically HCV infected patients. Every cell from each patient was grouped into one of the three categories: 1) uninfected cells without any infected adjacent neighbors; 2) uninfected cells with at least one infected adjacent neighbor; 3) infected cells; and the average integrated intensity of IFI27 mRNA staining per cell in each category was calculated. Lines connect measurements from the same patient. P values were calculated using paired two-tailed Student t test.*

that HCV does not significantly alter gene expression in the infected cell [17]. In the same study, we had the opportunity to compare endogenous and IFNα induced transcriptional changes in the liver of CHC patients. Most ISGs were induced both, after recombinant IFN administration and in the liver of CHC patients albeit at a lower level. These results suggested that the innate immune response in CHC is too weak to effectively clear the virus [17]. Surprisingly however, it has recently been recognized that single-nucleotide polymorphisms (SNPs) that lead to the impairment or loss of a functional interferon gene (interferon lambda 4 (IFNλ4)) are tightly associated with a lower endogenous IFN system activation but a higher probability of spontaneous and IFNα therapy mediated clearance of HCV infection [18–21]. Having access to organoid cultures derived from liver biopsies *(Figure 4)* obtained from patients carrying either the functional or disrupted IFNλ4 locus, we are currently investigating the molecular basis for this paradoxical situation.

Chronic HBV Infection (CHB).

Infection with HBV, in contrast to HCV (and most other viruses), does not trigger an innate IFN response in the liver [22] which likely contributes to the development of CHB [23, 22]. Whether the absence of a cellular innate response during HBV infection is due to HBV being invisible (i.e. acting as a stealth virus) to the cell intrinsic innate sensing machinery or HBV actively suppressing innate immune responses remained controversial [23] mostly because of the lack of optimal HBV infection model systems. Again, human liver biopsies obtained from HBV infected and uninfected patients provided an opportunity to address this question directly in the human liver. We developed a short term (i.e. 24 hour) ex vivo culture system for biopsy pieces that enabled investigating pathogen induced cellular innate responses in intact human liver tissue [24]. Using this system, we could demonstrate that innate immunity induction by TLR agonists or Sendai Virus infection are not blocked in the HBV infected liver [24]. And more importantly, we could also demonstrate the absence of HBV interference with pathogen induced IFNβ induction *(Figure 3A)* and IFN-signaling *(Figure 3B)* at the cellular level in the HBV infected cell in the liver of CHB patients [24]. Thus, using liver biopsy tissue, we were able to confirm the hypothesis that HBV is invisible to the innate sensing machinery and behaves like a "stealth" virus in this regard [24]. These findings also suggest that evaluation of compounds capable of activating an intrahepatic, anti-HBV specific innate response as novel therapeutic interventions for CHB is warranted [23]. We are continuing to exploit the availability of liver biopsies from patients with different viral infections for delineating host-virus interactions of other hepatotropic viruses such as for example hepatitis D virus.

Hepatocellular Carcinoma (HCC).

As described in the introduction, HCC is the most common primary liver cancer and the second cause of cancer-related mortality worldwide [1]. Patients with early stage disease can benefit from potentially curative treatment options such as liver transplantation, surgical resection or thermal ablation of the tumor [25]. However, most of the patients are diagnosed at later stages and the current treatment options for patients with intermediate to advanced stage disease are unsatisfactory. Conventional chemotherapies have been extensively tested but none of them has improved survival [26]. For the past ten years, the multikinase inhibitor sorafenib has been the only drug available for the first-line treatment of advanced HCC [27]. However, due to the different backgrounds and the resulting heterogeneity of tumors, its efficacy greatly varies between patients and is further limited due to adverse effects and the development of drug resistance. More than ten additional targeted drugs were tested in the past years, but all failed in phase III trials [27]. More recently, the sorafenib-derivative regorafenib [28] and the immune-checkpoint inhibitor nivolumab [29] showed efficacy in second-line treatments for advanced HCC. Nevertheless, given the limited number and efficacy of current HCC treatment options, there is clearly the need for development of novel therapies targeting HCC. Such efforts will greatly benefit from the characterization of similarities and differences between HCCs in different patients that might identify common drug targets. Similarly, a mechanistic understanding of HCC resistance to the current drugs will provide guidance in developing novel therapies.

HCC Classification.

Currently, there are several transcriptome-based molecular classifications of HCC with different subclass numbers, ranging from two to six ([5] and references therein). They were, however, established using resected tumors that introduce a selection bias towards patients without liver cirrhosis and with early stage HCCs. In a recent study, we were able to include all stages of HCC with and without cirrhosis by using tumor biopsies rather than resected tumors for HCC classification and also included normal liver biopsies as a baseline control group for comparison [5]. Compared to the normal controls, we observed that the subclass-defining 'signature' genes were mostly differentially regulated in the same direction across all tumors, regardless of their subclass membership in our patient cohort. Importantly, the same was also true for the subclasses of previously published molecular classification systems [5]. These results suggested that there might be multiple oncogenic driver pathways that ultimately lead to a similar gene expression pattern. Thus, including pro-

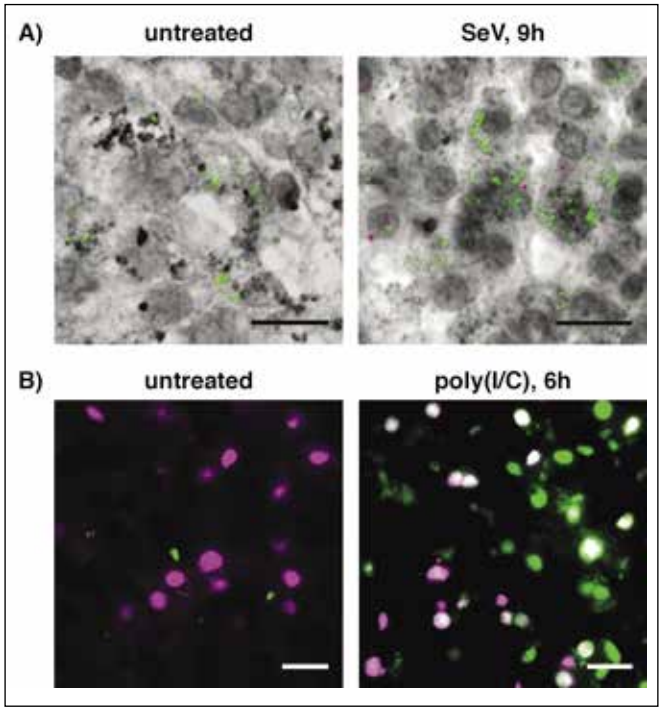

Figure 3.

*Innate immune induction **(A)** and IFN signaling **(B)** are not blocked in HBV infected cells in the human liver.*

***(A)** Liver biopsy pieces obtained from an HBV infected patient were incubated with Sendai Virus (SeV) for 9 hours or immediately processed as a baseline control (untreated) and subjected to multiplex ISH analysis of IFNβ mRNA (purple) and total HBV RNA (green). Scale bar, 20µm.*

***(B)** Liver biopsy pieces obtained from an HBV infected patient were incubated with polyinosinic-polycytidylic acid (poly(I/C)) for 6 hours or immediately processed as a baseline control (untreated) and subjected to immunofluorescence analysis for HBV core protein (HBcAg, purple) and activated (i.e. phosphorylated) Signal Transducer and Activator (pSTAT1, green). The white color indicates HBcAg/pSTAT1 double positive cells.*

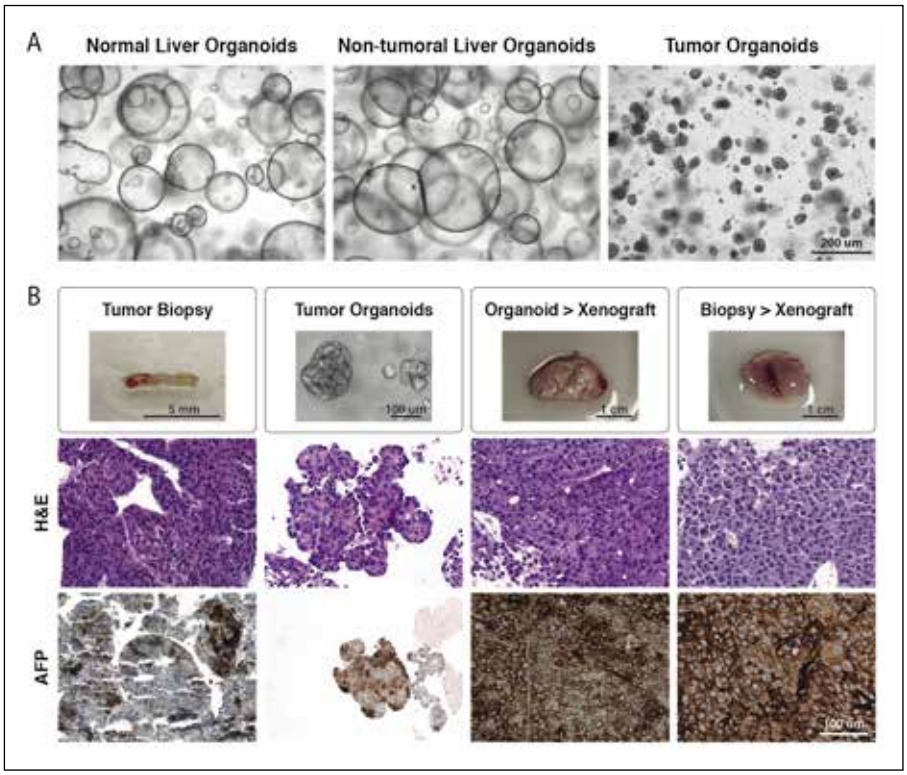

Figure 4. *(by Sandro Nuciforo)*
Establishment and characterization of organoid cultures and xenograft models from needle biopsies.
(A) Bright field images of normal liver, non-tumor liver and paired tumor tissue organoids Tumor organoids form compact spheroids, whereas liver organoids grow as cystic structures.
(B) Histopathological characteristics (from left to right) of primary tumor, its corresponding HCC organoid and xenografts either derived from the HCC organoid or the biopsy tissue of the primary tumor. Top panels, photographs of needle biopsy, single organoid and whole xenograft tumors. Middle panels, histological sections stained with Hematoxylin and Eosin. Bottom panels, AFP expression detected by immunohistochemistry.

teomic and phosphoproteomic assays in HCC classification might be beneficial. Accordingly, we are currently applying different omics approaches for HCC classification of a large and diverse biopsy collection of HCC patients. Similarly, we have demonstrated in a proof of concept study that the same approaches can be used for investigating HCC drug resistance using tumor biopsies taken before and during HCC therapy [30] and are currently applying this approach to a larger patient cohort.

The local tumor microenvironment (TME) in large part consists of immune cells with diverse phenotypes and functions that contribute to intra-tumor and inter-patient HCC heterogeneity and modulate the response to treatment [31]. Accordingly, we also use needle biopsies of tumor and non-tumor tissue from HCC patients for a comprehensive characterization of the tumor infiltrating lymphocyte subpopulations and comparison with the immune cell populations in the blood.

HCC Model Systems.

Current *in vitro* models to study HCC are based on conventional cancer cell lines that fail to recapitulate key features such as tumor architecture, cellular heterogeneity and cell-cell interactions. These limitations can be overcome with three-dimensional organoid cultures [32]. Accordingly, we generated organoid lines from tumor, non-tumor and normal liver biopsies *(Figure 4A)*. We specifically generated a collection of tumor organoids derived from HCCs of different tumor stages and various etiologies. Importantly, morphology, histopathology and tumor marker expression of the primary tumors were retained in the corresponding organoids *(Figure 4B)*. HCC organoids also preserved the mutational landscape of the primary tumors [33]. Finally, in a proof-of-concept study, we demonstrated that HCC organoids are amenable to drug screening studies [33]. Thus, we are currently using HCC organoids not only as an *in vitro* HCC model to study tumor cell biology, but also to investigate drug sensitivity and drug resistance.

While tumor organoid lines provide an excellent *in vitro* model of HCC tumor cells, they only partially reproduce the complete architecture (e.g. vascularization, tumor-nontumor cell interactions) of the corresponding HCC in the liver. These limitations might be overcome with patient derived xenograft (PDX) mouse models produced by xenografting HCC derived tumor cells into immunodeficient mice [34]. We successfully generated HCC xenograft mouse models using subcutaneous transplan-

From left to right: First row: Isabel Fofana, Diego Calabrese, Qian Cheng, Mairene Coto, Tujana Boldanova, Xueya Wang.
Second row: Daniela Di Blasi, Stefan Wieland, Charlotte Ng, Alexandra Gnann, Sylvia Ketterer.
Third row: Marie-Anne Meier, Sandro Nuciforo, Aleksei Suslov, Markus Heim.

tation of patient-derived HCC biopsy tissue into immunodeficient mice. The HCC PDX models not only reflected the histological and tumor marker expression pattern *(Figure 4)* and the mutational landscape of the parental HCC but retained them after serial retransplantation. In addition, we could also establish xenograft models from HCC organoid lines *(Figure 4)*. Importantly, the histological and molecular characteristics of a given HCC is retained in the corresponding HCC organoids, HCC organoid derived xenografts and xenografts established from the original HCC biopsy tissue *(Figure 4)*. Thus, these model systems provide an excellent platform to study basic HCC biology as well as drug resistance and testing of novel HCC therapies. **Stefan Wieland**

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A change of model organism for me – A new building for the DBM

One day, back in 1991, I had to prepare for an exam in business administration. But bored with the dry matter, I began to walk around and stumbled across the cover of a six-year-old issue of the Scientific American. I had no idea what I was holding in my hands, but I was fascinated by the beauty and elegance of this galaxy – like thing *(Figure 1A)*. Nowadays the figure may look a bit rudimentary to some readers, but don't forget that it dates from the time of the first "smartphone" *(Figure 1B)*. So, instead of learning for the exam I read all the corresponding articles and thereby obtained my first lesson in molecular biology. I have to admit that I didn't understand most of what I read at the time, yet I was immediately infected by the magic of molecular biology, especially of DNA. I immediately decided that this would be the topic I would deal with in the future. A rather spontaneous decision which, however, I have never regretted, since it enriched my life with the most fascinating insights into the diverse facets of DNA as well as of cellular and molecular biology. During all the years dealing with DNA repair, genetics, epigenetics, cell differentiation and much more, I began to realize that from the point of view of my family and my "normal" friends I had developed into a "nerd of molecular biology" (NMB) since they had a hard time to understand with what I spent my time at work. So the NMB had the

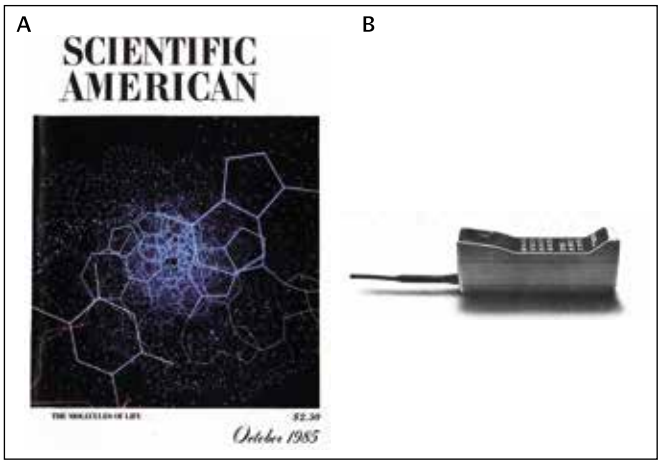

Figure 1 (A) Coverpage of the Scientific American (issue October 1985) showing an end-on view of the DNA double helix. (B) One of the first hand-held mobile phone (found in the same issue)

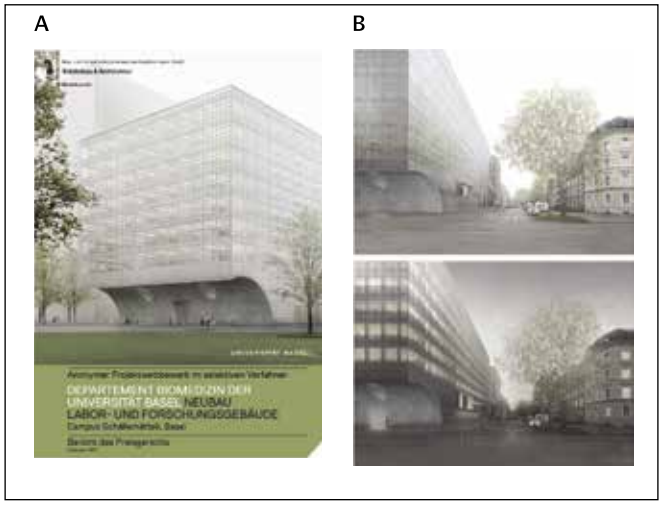

Figure 2 (A) Coverpage of the Jury report about the anonymous architecture competition for the new DBM building. (B) Latest visuals of the outside view of the new DBM building. Subject to modifications.

choice either not to talk about his work in a private setting or to think about adequate strategies and translations to make the topics understandable for "ordinary mortals" – I chose the latter option. At that time I would never have expected that this would be a great help for my future work…

One day, back in early 2016, I was analyzing LFQ ratios of a SILAC experiment. Tired of dealing with endless Excel sheets I went to get a coffee and stumbled over the cover page of an architecture competition *(Figure 2A)*. I had vaguely heard about a new building for the Department of Biomedicine on the Campus Schällemätteli before but hadn't paid much attention to it so far. And while I was leafing through the jury's report, I got infected by a strong enthusiasm for the second time in my life. During the following days, I remembered all the laboratories I had worked in with all the nice aspects but also all the downsides they had. I especially recalled the move into the newly renovated laboratories at Mattenstrasse in 2005. Having performed research in an old, badly insulated and ventilated building with suboptimal logistics, the whole research group was very happy about the opportunity to move into a very nice and brand-new laboratory. At a first glance, everything was just perfect. At second glance we began to realize that not every detail had received the

necessary attention during the planning. Unfortunately, some of them were essential to us - three examples out of several: (1) All benches had cupboards underneath so that one could only sit and work sideways. (2) Space for all our large instruments – wrong! Instead, there was a huge meeting room on our floor (in addition to five others in the building!) but full of useless chairs and tables. That's when we started a second "rebuilding" on our own, removing cupboards, tables, and chairs. Since each group had the same problem, everything escalated into a big race for storage space which was virtually inexistent (3).

This was the first time, I started to suspect that architects are very good at designing and constructing beautiful buildings, but tend to underestimate the needs of users. An assumption which was painfully confirmed when I built my own house a few years later… During the years working at Mattenstrasse, I started to recognize that many of the shortcomings were not due to a "malevolent" ignorance of the architects or planners but simply by their unawareness of how we work and what our specific needs are. During all the years I regularly wondered why nobody had had the idea to include a scientist or even the users themselves in the planning of the reconstruction. So I was all the more pleased when I discovered the job description of my current position on my desk in autumn 2016: This need had indeed been identified for the DBM new building. Like 25 years ago, I didn't hesitate for long and decided that I wanted to participate in this wonderful project.

One application, several interviews and months later, I was finally able to immerse myself in all the fantastic new details of our future building, which at that time was in the pre-project phase. Again I have to admit that I did not understand every detail of the construction documents - but I am working hard on this matter. It is all the more reassuring that there are architects and experts who know more about these construction details than an NMB. This allows me to concentrate entirely on my actual task: the implementation of our user-specific needs. It turned out that a translator function is not only advantageous but even essential for this task. In each meeting, questions come up as to why and for what one needs one or the other scientific device, how certain work processes in the laboratory take place, what a specific scientific slang means, what a special room is needed for and much more. Through the many conversations, it became clear to me that the planners are very curious and mainly pursue one goal: to make our future home as optimal as possible within the bounds of what is feasible. They just need to know and understand what we do and on our side, we have to help them understand our scientific world. Herefore I can give you a very simple example: the catalog of

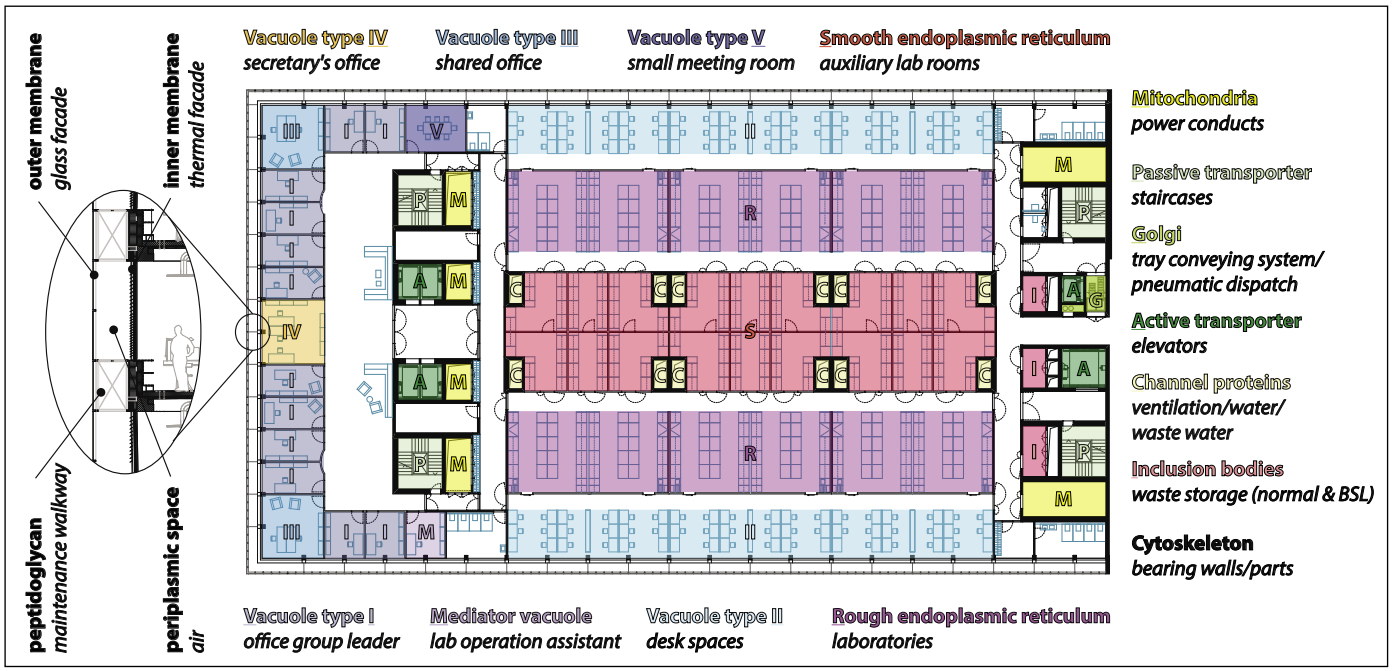

Figure 3

Shown are a standard research floor with organelles, functional/structural components and proteins specific to the new DBM research building

requirements mentions the need for film development rooms. For lack of better knowledge, the architects planned this as a large photo laboratory in the basement. I can reassure you, nobody will have to grab Western blot and films and take them onto a long journey to the basement. After I explained the actual purpose, the catalog of requirements has been adapted and small dark rooms will be planned on the floors.

At first, I thought I had left science, but I am realizing that I am more involved than ever. Just in a different way and with a few, but subtle differences, of course. The research proposal has already been applied for, been approved and amounts to ~240 million. Instead of using embryonic mouse stem cells, I'm now working with a cell that is "slightly" larger (73 m × 39 m × 41 m; L × W × H), has a rather special and rigid morphology *(Figures 2 and 3)* and will, unfortunately, lack the ability to replicate. But in essence, this new model organism contains functional components which are very similar to the ones found in cells growing in the incubators of the DBM as exemplified by the standard research floor *(Figure 3)*. Another very nice thing about the unusual cell size: for the first time I don't have to rely on indirect methods (e.g. PCR, Western blot, labeling etc.) to make things visible. Later, during the construction process, it will be enough to walk through the site with alert eyes. And currently, as long as the building exists only as a virtual construct, all people involved access the information by the attentive examination of the building plans and precise reading of the construction documentations. The two most central documents being the building (ger.: bauliches) and operating (ger.: betriebliches) specifications (ger.: Pflichtenheft). The former representing the genetic, the latter the epigenetic code of the new DBM building. Similar to the eukaryotic genome, both documents are of a highly dynamic nature. Yet, this will only last until all essential structural aspects have been clarified and incorporated into the "genetic building code". Since the building specification is the basis for all future planning and construction, this document will have its final form at the beginning of the next planning phase, the construction project (expected beginning 2019). In contrast, the operational specifications will continue to be processed and remain dynamic. This document will determine the way we will work in the future and how we will use our new home as a unified department. Up to now, the DBM lives under five different roofs, whereby each location has its own culture and rules for daily operation. With a view to our future research in one common building, our main task now is to erase the imprinting of the five different sites and to develop a common epigenetic code that fits the new building, the unified DBM, and satisfies the needs of all of us. I am aware that this is a great challenge, but I am firmly convinced that together we will master this great mission. To be continued…

Christophe Kunz

Congratulations

Moriz Konantz Schwendele
Geboren am 25. 06. 2018

Louise Romy Aïssata Fofana-Goett
Geboren am 21. 04. 2018

Herzlich willkommen, allerseits!

Dissertationen

Am 1. März 2018 konnte **Sébastien Pigeot** von der Forschungsgruppe "Tissue Engineering" (Departement Biomedizin Hebelstrasse) seine Dissertation mit Erfolg beenden. Er befasste sich in seiner Dissertation mit dem Thema: "Hypertrophic cartilage engineering from human bone and bone marrow regeneration".

Am 10. April 2018 stellte sich **Alexander Haumer** von der Forschungsgruppe "Tissue Engineering" (Departement Biomedizin Hebelstrasse) den Fragen des Dissertationskomitees. Der Titel seine Dissertation hiess: "Prefabrication of vascularized large bone grafts".

Am 17. April 2018 stellte sich **Ana Bento** von der Forschungsgruppe "Ocular Pharmacology and Physiology» (Departement Biomedizin Hebelstrasse) den Fragen des Dissertationskomitees. Der Titel ihrer Dissertation hiess: "UBXD1 and YOD1: p97 cofactors involved in autophagic mitochondrial quality control".

Seit dem 28. Juni 2018 dürfen sich gleich zwei Mitarbeitende des DBM Herr Dr. nennen: **Fabian Baldin** und **Florian Marquardsen**, beide von der Forschungsgruppe «Immunodeficiency» (Departement Biomedizin Hebelstrasse). Fabian befasste sich in seiner Dissertation mit "The role of Sp110 in immunodeficiency and immunopathology", Florian beschäftigte sich mit "Modulation of restimulation induced apoptosis by small molecule compounds targeting Nur77".

Mit der Doktorprüfung am 6. Juli 2018 schloss **David Grünig** von der Forschungsgruppe «Clinical Pharmacology» (Departement Biomedizin Hebelstrasse) erfolgreich seine Dissertationszeit ab. Das Thema seiner Doktorarbeit lautete: "Molecular mechanisms of drug-induced hepatic steatosis".

Am 9. Juli 2018 konnte **Madeleine Vollmer** von der Forschungsgruppe «Molecular Immune Regulation» (Departement Biomedizin Hebelstrasse) ihre Dissertation mit Erfolg beenden. Sie befasste sich in ihrer Dissertation mit dem Thema: „The role of the S1P-pathway in GVHD and T-cell regeneration in murine allo-HSCT".

Auszeichnungen

Claudia Lengerke erhält hochdotierten Förderpreis
Claudia Lengerke von der Forschungsgruppe „Stem Cells and Hematopoiesis" (Departement Biomedizin Hebelstrasse) hat den mit 100'000 Franken dotierten Förderpreis erhalten, den die «Fondation Peter Anton & Anna Katharina Miescher pour la recherche en hématologie» und die Schweizerische Gesellschaft für Hämatologie alle zwei Jahre vergeben.

Experimental Hematology and Oncology Award an Rao Nageswara Tata
Rao Nageswara Tata von der Forschungsgruppe Experimental Hematology (Departement Biomedizin Hebelstrasse) hat am 27. Juni 2018 im Rahmen des SSH/SSMO Meetings in Zürich den ''Swiss Society for Experimental Hematology and Oncology Award'' 2018 erhalten.

Dino Lüthi und Patrick Vizeli am EAPCCT in Bukarest ausgezeichnet
Dino Lüthi von der Forschungsgruppe «Psychopharmacology Research» (Departement Biomedizin Hebelstrasse) hat den The Taylor & Francis Award für die beste wissenschaftliche Präsentation am Kongress der European Association of Poisen Centers and Clinical Toxicologists (EAPCCT) vom 22.05.2018 bis 26.05.2018 in Bukarest erhalten. Patrick Vizeli, ebenfalls von der Forschungsgruppe «Psychopharmacology Research» (Departement Biomedizin Hebelstrasse), erhielt am gleichen Kongress für seine Präsentation mit dem Titel: «Role of norepinephrine transporter gene variations in the cardiostimulant effects of 3,4-methylenedioxymethamphetamine (MDMA)» den Young Investigator Award.

Herzliche Gratulation!

Gastroenterology | Gastroenterology | 2018;154:1778–1790 IF 20.773

Hepatitis B Virus Does Not Interfere With Innate Immune Responses in the Human Liver

Aleksei Suslov,[1] Tujana Boldanova,[1,2] Xueya Wang,[1] Stefan Wieland,[1,§] and Markus H. Heim[1,2,§]

BACKGROUND & AIMS: Most viruses are detected at early stages of cell infection and induce an innate immune response mediated by production of interferons (IFNs). IFNs induce expression of hundreds of IFN-stimulated genes (ISGs). Infection of chimpanzees with hepatitis C virus, but not hepatitis B virus (HBV), induces ISG expression in the liver. HBV might not induce an innate immune response because it is not detected by pattern recognition receptors (the stealth properties of HBV) or because HBV suppresses IFN production or signaling despite detection by pattern recognition receptors. We studied innate immune signaling in liver biopsies from patients with different stages of chronic HBV infection and uninfected individuals (controls).

METHODS: We obtained liver within 10 minutes after collection from 30 patients with chronic HBV infection (hepatitis B e antigen-positive or -negative, with or without hepatitis) and 42 controls (most with fatty liver disease). The liver tissues were analyzed by histology, immunohistochemistry, quantitative reverse-transcription polymerase chain reaction, in situ hybridization, HBV RNA quantification, and HBV genotyping; some specimens were incubated with toll-like receptor (TLR) ligands (polyinosinic-polycytidylic acid) or infected with Sendai virus and then analyzed.

RESULTS: Liver specimens from patients with HBV infection were not expressing more IFN or ISGs than those from control patients, indicating that chronic HBV infection did not activate an innate immune response. However, liver specimens from patients with HBV infection did produce IFN and induce expression of ISGs following activation of TLR3 with poly(I:C) or Sendai virus infections, so the innate immune response is not suppressed in these tissues.

CONCLUSION: Liver tissues from patients with chronic HBV infection do not have induction of an innate immune response, but this response can be activated by other factors (TLR3 binding, Sendai virus infection) in HBV-infected liver tissue. These findings support the hypothesis that HBV is invisible to pattern recognition receptors.

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GI cancer | BMJ Journals | doi.org/10.1136/gutjnl- 2016-313498 IF 17.016

Gut microbiota modulate T cell trafficking into human colorectal cancer

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ABSTRACT

Objective Tumour-infiltrating lymphocytes (TILs) favour survival in human colorectal cancer (CRC). Chemotactic factors underlying their recruitment remain undefined. We investigated chemokines attracting T cells into human CRCs, their cellular sources and microenvironmental triggers. **Design** Expression of genes encoding immune cell markers, chemokines and bacterial 16S ribosomal RNA (16SrRNA) was assessed by quantitative reverse transcription-PCR in fresh CRC samples and corresponding tumour-free tissues. Chemokine receptor expression on TILs was evaluated by flow cytometry on cell suspensions from digested tissues. Chemokine production by CRC cells was evaluated in vitro and in vivo, on generation of intraperitoneal or intracecal tumour xenografts in immune-deficient mice. T cell trafficking was assessed on adoptive transfer of human TILs into tumour-bearing mice. Gut flora composition was analysed by 16SrRNA sequencing. **Results** CRC infiltration by distinct T cell subsets was associated with defined chemokine gene signatures, including CCL5, CXCL9 and CXCL10 for cytotoxic T lymphocytes and T-helper (Th)1 cells; CCL17, CCL22 and CXCL12 for Th1 and regulatory T cells; CXCL13 for follicular Th cells; and CCL20 and CCL17 for interleukin (IL)-17-producing Th cells. These chemokines were expressed by tumour cells on exposure to gut bacteria in vitro and in vivo. Their expression was significantly higher in intracecal than in intraperitoneal xenografts and was dramatically reduced by antibiotic treatment of tumourbearing mice. In clinical samples, abundance of defined bacteria correlated with high chemokine expression, enhanced T cell infiltration and improved survival. **Conclusions** Gut microbiota stimulate chemokine production by CRC cells, thus favouring recruitment of beneficial T cells into tumour tissues.

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American Journal of Respiratory and Critical Care Medicine ATSJournals Vol. 197 Nr. 9, May 1 2018 IF 15.239

Intensified Therapy with Inhaled Corticosteroids and Long-Acting β_2-Agonists at the Onset of Upper Respiratory Tract Infection to Prevent Chronic Obstructive Pulmonary Disease Exacerbations

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Abstract

Rationale: The efficacy of intensified combination therapy with inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABA) at the onset of upper respiratory tract infection (URTI) symptoms in chronic obstructive pulmonary disease (COPD) is unknown.

Objectives: To evaluate whether intensified combination therapy with ICS/LABA, at the onset of URTI symptoms, decreases the incidence of COPD exacerbation occurring within 21 days of the URTI.

Methods: A total of 450 patients with stable, moderate to very severe COPD, were included in this investigator-initiated and -driven, double-blind, randomized, placebo-controlled study. At inclusion, patients were assigned to open-labeled low-maintenance dose ICS/LABA. Each patient was randomized either to intensified-dose ICS/LABA or placebo and instructed to start using this medication only in case of a URTI, at the onset of symptoms, twice daily, for 10 days.

Measurements and Main Results: The incidence of any exacerbation following a URTI was not significantly decreased in the ICS/LABA group, as compared with placebo (14.6% vs. 16.2%; hazard ratio, 0.77; 95% confidence interval, 0.46–1.33; $P=0.321$) but the risk of severe exacerbation was decreased by 72% (hazard ratio, 0.28; 95% confidence interval, 0.11–0.74%; P = 0.010). In the stratified analysis, effect size was modified by disease severity, fractional exhaled nitric oxide, and the body mass index–airflow obstruction–dyspnea, and exercise score. Compared with the stable period, evidence of at least one virus was significantly more common at URTI, 10 days after URTI, and at exacerbation.

Conclusions: Intensified combination therapy with ICS/LABA for 10 days at URTI onset did not decrease the incidence of any COPD exacerbation but prevented severe exacerbation. Patients with more severe disease had a significant risk reduction for any exacerbation.

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Biological Psychiatry Biological Psychiatry A Journal of Psychiatric Neuroscience and Therapeutics July 1, 2018; 84:55–64 IF 11.982

Antidepressants Rescue Stress-Induced Disruption of Synaptic Plasticity via Serotonin Transporter–Independent Inhibition of L-Type Calcium Channels

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Abstract

BACKGROUND: Long-term synaptic plasticity is a basic ability of the brain to dynamically adapt to external stimuli and regulate synaptic strength and ultimately network function. It is dysregulated by behavioral stress in animal models of depression and in humans with major depressive disorder. Antidepressants have been shown to restore disrupted synaptic plasticity in both animal models and humans; however, the underlying mechanism is unclear.

METHODS: We examined modulation of synaptic plasticity by selective serotonin reuptake inhibitors (SSRIs) in hippocampal brain slices from wild-type rats and serotonin transporter (SERT) knockout mice. Recombinant voltagegated calcium (Ca^{2+}) channels in heterologous expression systems were used to determine the modulation of Ca^{2+} channels by SSRIs. We tested the behavioral effects of SSRIs in the chronic behavioral despair model of depression both in the presence and in the absence of SERT.

RESULTS: SSRIs selectively inhibited hippocampal long-term depression. The inhibition of long-term depression by SSRIs was mediated by a direct block of voltage-activated L-type Ca^{2+} channels and was independent of SERT. Furthermore, SSRIs protected both wild-type and SERT knockout mice from behavioral despair induced by chronic stress. Finally, long-term depression was facilitated in animals subjected to the behavioral despair model, which was prevented by SSRI treatment.

CONCLUSIONS: These results showed that antidepressants protected synaptic plasticity and neuronal circuitry from the effects of stress via a modulation of Ca^{2+} channels and synaptic plasticity independent of SERT. Thus, L-type Ca^{2+} channels might constitute an important signaling hub for stress response and for pathophysiology and treatment of depression.

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PNAS PNAS vol. 115, no. 25, E5688–E5695 IF 9.504

In vitro biomimetic engineering of a human hematopoietic niche with functional properties

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In adults, human hematopoietic stem and progenitor cells (HSPCs) reside in the bone marrow (BM) microenvironment. Our understanding of human hematopoiesis and the associated niche biology remains limited, due to human material accessibility and limits of existing in vitro culture models. The establishment of an in vitro BM system would offer an experimentally accessible and tunable platform to study human hematopoiesis. Here, we develop a 3D engineered human BM analog by recapitulating some of the hematopoietic niche elements. This includes a bone-like scaffold, functionalized by human stromal and osteoblastic cells and by the extracellular matrix they deposited during perfusion culture in bioreactors. The resulting tissue exhibited compositional and structural features of human BM while supporting the maintenance of HSPCs. This was associated with a compartmentalization of phenotypes in the bioreactor system, where committed blood cells are released into the liquid phase and HSPCs preferentially reside within the engineered BM tissue, establishing physical interactions with the stromal compartment. Finally, we demonstrate the possibility to perturb HSPCs' behavior within our 3D niches by molecular customization or injury simulation. The developed system enables the design of advanced, tunable in vitro BM proxies for the study of human hematopoiesis.

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Developmentally inspired programming of adult human mesenchymal stromal cells toward stable chondrogenesis

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It is generally accepted that adult human bone marrow-derived mesenchymal stromal cells (hMSCs) are default committed toward osteogenesis. Even when induced to chondrogenesis, hMSCs typically form hypertrophic cartilage that undergoes endochondral ossification. Because embryonic mesenchyme is obviously competent to generate phenotypically stable cartilage, it is questioned whether there is a correspondence between mesenchymal progenitor compartments during development and in adulthood. Here we tested whether forcing specific early events of articular cartilage development can program hMSC fate toward stable chondrogenesis. Inspired by recent findings that spatial restriction of bone morphogenetic protein (BMP) signaling guides embryonic progenitors toward articular cartilage formation, we hypothesized that selective inhibition of BMP drives the phenotypic stability of hMSC-derived chondrocytes. Two BMP type I receptor-biased kinase inhibitors were screened in a microfluidic platform for their time- and dose-dependent effect on hMSC chondrogenesis. The different receptor selectivity profile of tested compounds allowed demonstration that transient blockade of both ALK2 and ALK3 receptors, while permissive to hMSC cartilage formation, is necessary and sufficient to maintain a stable chondrocyte phenotype. Remarkably, even upon compound removal, hMSCs were no longer competent to undergo hypertrophy in vitro and endochondral ossification in vivo, indicating the onset of a constitutive change. Our findings demonstrate that adult hMSCs effectively share properties of embryonic mesenchyme in the formation of transient but also of stable cartilage. This opens potential pharmacological strategies to articular cartilage regeneration and more broadly indicates the relevance of developmentally inspired protocols to control the fate of adult progenitor cell systems.

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Tumor Biology and Immunology | Cancer Research | Cancer Res. 78(11); June 1, 2018 IF 9.130

Transition of Mesenchymal and Epithelial Cancer Cells Depends on α1-4 Galactosyltransferase-Mediated Glycosphingolipids

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Abstract

The reversible transitions of cancer cells between epithelial and mesenchymal states comprise cellular and molecular processes essential for local tumor growth and respective dissemination. We report here that globoside glycosphingolipid (GSL) glycosyltransferase- encoding genes are elevated in epithelial cells and correlate with characteristic EMT signatures predictive of disease outcome. Depletion of globosides through CRISPR-*Cas9*–mediated deletion of the key enzyme A4GALT induces EMT, enhances chemoresistance, and increased $CD24^{low}/CD44^{high}$ cells. The cholera toxin–induced mesenchymal-to-epithelial transition occurred only in cells with functional A4GALT. Cells undergoing EMT lost E-cadherin expression through epigenetic silencing at the promoter region of *CDH1*. However, in ΔA4GALT cells, demethylation was able to rescue E-cadherin–mediated cell–cell adhesion only in the presence of exogenous A4GALT. Overall, our data suggest another class of biomolecules vital for epithelial cancer cells and for maintaining cell integrity and function.

Significance: This study highlights the essential role of glycosphingolipids in the maintenance of epithelial cancer cell properties.

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Biomaterials | Biomaterials | 171 (2018) 219–229 IF 8.806

Spatially confined induction of endochondral ossification by functionalized hydrogels for ectopic engineering of osteochondral tissues

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Abstract

Despite the various reported approaches to generate osteochondral composites by combination of different cell types and materials, engineering of templates with the capacity to autonomously and orderly develop into cartilage-bone bi-layered structures remains an open challenge. Here, we hypothesized that the embedding of cells inducible to endochondral ossification (i.e. bone marrow derived mesenchymal stromal cells, BMSCs) and of cells capable of robust and stable chondrogenesis (i.e. nasal chondrocytes, NCs) adjacent to each other in bi-layered hydrogels would develop directly in vivo into osteochondral tissues. Poly(ethylene glycol) (PEG) hydrogels were functionalized with TGFβ3 or BMP-2, enzymatically polymerized encapsulating human BMSCs, combined with a hydrogel layer containing human NCs and ectopically implanted in nude mice without pre-culture. The BMSC-loaded layers reproducibly underwent endochondral ossification and generated ossicles containing bone and marrow. The NC-loaded layers formed cartilage tissues, which (under the influence of BMP-2 but not of TGFβ3 from the neighbouring layer) remained phenotypically stable. The proposed strategy, resulting in orderly connected osteochondral composites, should be further assessed for the repair of osteoarticular defects and will be useful to model developmental processes leading to cartilage-bone interfaces.

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EMBO reports | EMBO reports | e45054, 2018 IF 8.749

EphrinB2/EphB4 signaling regulates non-sprouting angiogenesis by VEGF

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Abstract

Vascular endothelial growth factor (VEGF) is the master regulator of angiogenesis, whose best-understood mechanism is sprouting. However, therapeutic VEGF delivery to ischemic muscle induces angiogenesis by the alternative process of intussusception, or vascular splitting, whose molecular regulation is essentially unknown. Here, we identify ephrinB2/EphB4 signaling as a key regulator of intussusceptive angiogenesis and its outcome under therapeutically relevant conditions. EphB4 signaling fine-tunes the degree of endothelial proliferation induced by specific VEGF doses during the initial stage of circumferential enlargement of vessels, thereby limiting their size and subsequently enabling successful splitting into normal capillary networks. Mechanistically, EphB4 neither inhibits VEGF-R2 activation by VEGF nor its internalization, but it modulates VEGF-R2 downstream signaling through phospho- ERK1/2. *In vivo* inhibitor experiments show that ERK1/2 activity is required for EphB4 regulation of VEGF-induced intussusceptive angiogenesis. Lastly, after clinically relevant VEGF gene delivery with adenoviral vectors, pharmacological stimulation of EphB4 normalizes dysfunctional vascular growth in both normoxic and ischemic muscle. These results identify EphB4 as a druggable target to modulate the outcome of VEGF gene delivery and support further investigation of its therapeutic potential.

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Influenza vaccination of cancer patients during PD-1 blockade induces serological protection but may raise the risk for immune-related adverse events

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Abstract

Background

Immune checkpoint inhibiting antibodies were introduced into routine clinical practice for cancer patients. Checkpoint blockade has led to durable remissions in some patients, but may also induce immune-related adverse events (irAEs). Lung cancer patients show an increased risk for complications, when infected with influenza viruses. Therefore, vaccination is recommended. However, the efficacy and safety of influenza vaccination during checkpoint blockade and its influence on irAEs is unclear. Similarly, the influence of vaccinations on T cell-mediated immune reactions in patients during PD-1 blockade remains poorly defined.

Methods

We vaccinated 23 lung cancer patients and 11 age-matched healthy controls using a trivalent inactivated influenza vaccine to investigate vaccine-induced immunity and safety during checkpoint blockade.

Results

We did not observe significant differences between patients and healthy controls in vaccine-induced antibody titers against all three viral antigens. Influenza vaccination resulted in protective titers in more than 60% of patients/participants. In cancer patients, the post-vaccine frequency of irAEs was 52.2% with a median time to occurrence of 3.2 months after vaccination. Six of 23 patients (26.1%) showed severe grade 3/4 irAEs. This frequency of irAEs might be higher than the rate previously published in the literature and the rate observed in a non-study population at our institution (all grades 25.5%, grade 3/4 9.8%).

Conclusions

Although this is a non-randomized trial with a limited number of patients, the increased rate of immunological toxicity is concerning. This finding should be studied in a larger patient population.

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

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Summary

Interleukin-1 receptor antagonist (IL-1Ra) is elevated in the circulation during obesity and type 2 diabetes (T2D) but is decreased in islets from patients with T2D. The protective role of local IL-1Ra was investigated in pancreatic islet β cell (βIL-1Ra)-specific versus myeloid-cell (myeloIL-1Ra)-specific IL-1Ra knockout (KO) mice. Deletion of IL-1Ra in β cells, but not in myeloid cells, resulted in diminished islet IL-1Ra expression. Myeloid cells were not the main source of circulating IL-1Ra in obesity. βIL-1Ra KO mice had impaired insulin secretion, reduced β cell proliferation, and decreased expression of islet proliferation genes, along with impaired glucose tolerance. The key cell-cycle regulator E2F1 partly reversed IL-1β-mediated inhibition of potassium channel *Kir6.2* expression and rescued impaired insulin secretion in IL-1Ra knockout islets. Our findings provide evidence for the importance of β cell-derived IL-1Ra for the local defense of β cells to maintain normal function and proliferation.

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Modulation of bacterial metabolism by the microenvironment controls MAIT cell stimulation

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Abstract

Mucosal-associated invariant T (MAIT) cells are abundant innate-like T lymphocytes in mucosal tissues and recognize a variety of riboflavin-related metabolites produced by the microbial flora. Relevant issues are whether MAIT cells are heterogeneous in the colon, and whether the local environment influences microbial metabolism thereby shaping MAIT cell phenotypes and responses. We found discrete MAIT cell populations in human colon, characterized by the diverse expression of transcription factors, cytokines and surface markers, indicative of activated and precisely controlled lymphocyte populations. Similar phenotypes were rare among circulating MAIT cells and appeared when circulating MAIT cells were stimulated with the synthetic antigens 5-(2-oxoethylideneamino)-6-D-ribitylaminouracil, and 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil. Furthermore, bacteria grown in colon-resembling conditions with low oxygen tension and harvested at stationary growth phase, potently activated human MAIT cells. The increased activation correlated with accumulation of the above antigenic metabolites as indicated by mass spectrometry. Thus, the colon environment contributes to mucosal immunity by directly affecting bacterial metabolism, and indirectly controlling the stimulation and differentiation of MAIT cells.

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BK Polyomavirus-Specific 9mer CD8 T Cell Responses Correlate With Clearance of BK Viremia in Kidney Transplant Recipients: First Report From the Swiss Transplant Cohort Study

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BK polyomavirus (BKPyV) causes premature kidney transplant (KT) failure in 1–15% of patients. Because antivirals are lacking, most programs screen for BKPyV-viremia and, if positive, reduce immunosuppression. To evaluate the relationship of viremia and BKPyV-specific immunity, we examined prospectively cryopreserved plasma and peripheral blood mononuclear cells at the time of transplantation (T0) and at 6 mo (T6) and 12 mo (T12) after transplant from 28 viremic KT patients and 68 nonviremic controls matched for the transplantation period. BKPyV IgG seroprevalence was comparable between cases (89.3%) and controls (91.2%; p = 0.8635), but cases had lower antibody levels (p = 0.022) at T0. Antibody levels increased at T6 and T12 but were not correlated with viremia clearance. BKPyV-specific T cell responses to pools of overlapping 15mers (15mer peptide pool [15mP]) or immunodominant CD8 9mers (9mer peptide pool [9mP]) from the early viral gene region were not different between cases and controls at T0; however, clearance of viremia was associated with stronger 9mP responses at T6 (p = 0.042) and T12 (p = 0.048), whereas 15mP responses were not informative (T6 p = 0.359; T12 p = 0.856). BKPyV-specific T cells could be expanded *in vitro* from all patients after transplant, permitting identification of 78 immunodominant 9mer epitopes including 50 new ones across different HLA class I. Thus, 9mP-responses may be a novel marker of reconstituting CD8 T cell function that warrants further study as a complement of plasma BKPyV loads for guiding immunosuppression reduction.

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Two Distinct Pathways in Mice Generate Antinuclear Antigen-Reactive B Cell Repertoires

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The escape of anti-self B cells from tolerance mechanisms like clonal deletion, receptor editing, and anergy results in the production of autoantibodies, which is a hallmark of many autoimmune disorders. In this study, we demonstrate that both germline sequences and somatic mutations contribute to autospecificity of B cell clones. For this issue, we investigated the development of antinuclear autoantibodies (ANAs) and their repertoire in two different mouse models. First, in aging mice that were shown to gain several autoimmune features over time including ANAs. Second, in mice undergoing a chronic graft-versus-host disease (GVHD), thereby developing systemic lupus erythematosus- like symptoms. Detailed repertoire analysis revealed that somatic hypermutations (SHM) were present in all Vh and practically all Vl regions of ANAs generated in these two models. The ANA B cell repertoire in aging mice was restricted, dominated by clonally related Vh1-26/Vk4-74 antibodies. In the collection of GVHD-derived ANAs, the repertoire was less restricted, but the usage of the Vh1-26/Vk4-74 combination was still apparent. Germline conversion showed that the SHM in the 4-74 light chain are deterministic for autoreactivity. Detailed analysis revealed that antinuclear reactivity of these antibodies could be induced by a single amino acid substitution in the CDR1 of the Vk4-74. In both aging B6 and young GVHD mice, conversion of the somatic mutations in the Vh and Vl regions of non Vh1-26/Vk4-74 using antibodies showed that B cells with a germline-encoded V gene could also contribute to the ANA-reactive B cell repertoire. These findings indicate that two distinct pathways generate ANA-producing B cells in both model systems. In one pathway, they are generated by Vh1-26/Vk4-74 expressing B cells in the course of immune responses to an antigen that is neither a nuclear antigen nor any other self-antigen. In the other pathway, ANA-producing B cells are derived from progenitors in the bone marrow that express B cell receptors (BCRs), which bind to nuclear antigens and that escape tolerance induction, possibly as a result of crosslinking of their BCRs by multivalent determinants of nuclear antigens.

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Decoration of RGD-mimetic porous scaffolds with engineered and devitalized extracellular matrix for adipose tissue regeneration

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Abstract

Fat grafting is emerging as a promising alternative to silicon implants in breast reconstruction surgery. Unfortunately, this approach does not provide a proper mechanical support and is affected by drawbacks such as tissue resorption and donor site morbidity. Synthetic scaffolds can offer a valuable alternative to address these challenges, but poorly recapitulate the biochemical stimuli needed for tissue regeneration. Here, we aim at combining the positive features of a structural, synthetic polymer to an engineered, devitalized extracellular matrix (ECM) to generate a hybrid construct that can provide a mix of structural and biological stimuli needed for adipose tissue regeneration. A RGD-mimetic synthetic scaffold OPAAF, designed for soft tissue engineering, was decorated with ECM deposited by human adipose stromal cells (hASCs). The adipoinductive potential of the hybrid ECM-OPAAF construct was validated *in vitro*, by culture with hASC in a perfusion bioreactor system, and *in vivo*, by subcutaneous implantation in nude mouse. Our findings demonstrate that the hybrid ECM-OPAAF provides proper mechanical support and adipoinductive stimuli, with potential applicability as *off-the-shelf* material for adipose tissue reconstruction.

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The role of IL-1 in postprandial fatigue

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ABSTRACT

Objectives: Cytokines such as IL-1 seems to play a role in the pathogenesis of fatigue associated with some chronic diseases and antiinflammatory treatment has been shown to reduce these symptoms. Ingestion of a calorie rich meal leads to postprandial fatigue, and is associated with increased systemic concentrations of cytokines, which is more pronounced in obese than lean subjects. We investigated whether postprandial fatigue is regulated by IL-1, and therefore reduced by IL-1 antagonism, in lean and obese subjects.

Methods: In a double-blind, crossover study in 8 lean and 8 obese male subjects, randomized to receive either saline (placebo) or the IL-1 receptor antagonist anakinra, we investigated whether postprandial fatigue was regulated by IL-1. To promote postprandial fatigue, subjects ran 30 min prior to a high-fat, high-carbohydrate meal. Fatigue was determined using the Stanford Sleepiness Scale and blood samples were drawn at baseline and after the intervention.

Results: IL-1 antagonism led to a reduction in postprandial fatigue and this effect was more pronounced in obese than lean individuals.

Conclusions: We conclude that IL-1 is involved in the regulation of postprandial fatigue under physiologic conditions in lean and obese individuals. It remains to be shown whether this effect translates into clinical relevant effects.

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Donor-derived, metastatic urothelial cancer after kidney transplantation associated with a potentially oncogenic BK polyomavirus

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Abstract

BK polyomavirus has been linked to urothelial carcinoma in immunosuppressed patients. Here, we performed comprehensive genomic analysis of a BK polyomavirus-associated, metachronous, multifocal and metastatic micropapillary urothelial cancer in a kidney transplant recipient. Dissecting cancer heterogeneity by sorting technologies prior to array-comparative genomic hybridization followed by short tandem repeat analysis revealed that the metastatic urothelial cancer was of donor origin (4-year-old male). The top 50 cancer-associated genes showed no key driver mutations as assessed by next-generation sequencing. Whole genome sequencing and BK polyomavirus-specific amplification provided evidence for episomal and subgenomic chromosomally integrated BK polyomavirus genomes, which carried the same unique 17-bp deletion signature in the viral non-coding control region (NCCR). Whereas no role in oncogenesis could be attributed to the host gene integration in chromosome 1, the 17-bp deletion in the NCCR increased early viral gene expression, but decreased viral replication capacity. Consequently, urothelial cells were exposed to high levels of the transforming BK polyomavirus early proteins large tumour antigen and small tumour antigen from episomal and integrated gene expression. Surgery combined with discontinuation of immunosuppression resulted in complete remission, but sacrificed the renal transplant. Thus, this report links, for the first time, BK polyomavirus NCCR rearrangements with oncogenic transformation in urothelial cancer in immunosuppressed patients.

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Prophylactic and Therapeutic Effects of Interleukin-2 (IL-2)/Anti-IL-2 Complexes in Systemic Lupus Erythematosus-Like Chronic Graft-Versus-Host Disease

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Murine chronic graft-versus-host-disease (cGvHD) induced by injection of parental lymphocytes into F1 hybrids results in a disease similar to systemic lupus erythematosus. Here, we have used DBA/2 T cell injection into (C57BL/6 × DBA/2)F1 (BDF1) mice as a model system to test the prophylactic and therapeutic effects of interleukin-2 (IL-2)/ anti-IL-2 immune complexes on the course of cGvHD. Our findings demonstrate that pretreatment with Treg inducing JES6/IL-2 complexes render BDF1 mice largely resistant to induction of cGvHD, whereas pretreatment with $CD8^+$ T cell/NK cell inducing S4B6/IL-2 complexes results in a more severe cGvHD. In contrast, treatment with JES6/ IL-2 complexes 4 weeks after induction had no beneficial effect on disease symptoms. However, similar treatment with S4B6/IL-2 complexes led to a significant amelioration of the disease. This therapeutic effect seems to be mediated by donor $CD8^+$ T cells. The fact that a much stronger cGvHD is induced in BDF1 mice depleted of donor $CD8^+$ T cells strongly supports this conclusion. The contrasting effects of the two different IL-2 complexes are likely due to different mechanisms.

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PGE2 mediates EGFR internalization and nuclear translocation *via* caveolin endocytosis promoting its transcriptional activity and proliferation in human NSCLC cells

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ABSTRACT

Prostaglandin E_2 (PGE_2) contributes to tumor progression by promoting cancer cell growth, invasion and by creating a favorable pro-tumor microenvironment. PGE_2 has been reported to transactivate and internalize into the nucleus receptor tyrosine kinases such as Epidermal growth factor receptor (EGFR), thereby supporting tumor progression. Here we demonstrate that in non-small cell lung carcinoma (NSCLC) cells, PGE_2 induces EGFR nuclear translocation via different dynamin-dependent endocytic pathways, promotes the formation of an EGFR-STAT3 complex, affects nuclear EGFR target gene expression and mediates tumor cell proliferation. Indeed, we find that PGE_2 induces EGFR internalization and consequent nuclear import through Clathrin- and Caveolin-mediated endocytosis and through the interaction of EGFR with Importin β1. Within the nucleus, EGFR forms a complex with STAT3, an event blocked by ablation of Clathrin Heavy Chain or Caveolin-1. The combination of EGF and PGE_2 prolongs nuclear EGFR transcriptional activity manifested by the upregulation of *CCND1, PTGS2, MYC* and *NOS2* mRNA levels and potentiates nuclear EGFR-induced NSCLC cell proliferation. Additionally, NSCLC patients with high expression of a nuclear EGFR gene signature display shorter survival times than those with low expression, thus showing a putative correlation between nuclear EGFR and poor prognosis in NSCLC. Together, our findings indicate a complex mechanism underlying PGE_2-induced EGF/EGFR signaling and transcriptional control, which plays a key role in cancer progression.

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Pharmacological profile of methylphenidate-based designer drugs

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ABSTRACT

Background: Methylphenidate-based designer drugs are new psychoactive substances (NPS) that are used outside medical settings and their pharmacology is largely unexplored. The aim of the present study was to characterize the pharmacology of methylphenidate-based substances *in vitro*.

Methods: We determined the potencies of the methylphenidate-based NPS *N*-benzylethylphenidate, 3,4-dichloroethylphenidate, 3,4-dichloromethylphenidate, ethylnaphthidate, ethylphenidate, 4-fluoromethylphenidate, isopropylphenidate, 4-methylmethylphenidate, methylmorphenate, and propylphenidate and the potencies of the related compounds cocaine and modafinil with respect to norepinephrine, dopamine, and serotonin transporter inhibition in transporter-transfected human embryonic kidney 293 cells. We also investigated monoamine efflux and monoamine receptor and transporter binding affinities. Furthermore, we assessed the cell integrity under assay conditions.

Results: All methylphenidate-based substances inhibited the norepinephrine and dopamine transporters 4 to >1000-fold more potently than the serotonin transporter. Similar to methylphenidate and cocaine, methylphenidate-based NPS did not elicit transporter-mediated efflux of monoamines. Besides binding to monoamine transporters, several test drugs had affinity for adrenergic, serotonergic, and rat trace amine-associated receptors but not for dopaminergic or mouse trace amine-associated receptors. No cytotoxicity was observed after drug treatment at assay concentrations.

Conclusion: Methylphenidate-based substances had pharmacological profiles similar to methylphenidate and cocaine. The predominant actions on dopamine transporters *vs.* serotonin transporters may be relevant when considering abuse liability.

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Pharmacological profile of mephedrone analogs and related new psychoactive substances

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ABSTRACT

Background: Mephedrone is a synthetic cathinone and one of the most popular recreationally used new psychoactive substances. The aim of the present study was to characterize the *in vitro* pharmacology of novel analogs of mephedrone and related newly emerged designer stimulants.

Methods: We determined norepinephrine, dopamine, and serotonin transporter inhibition potencies and monoamine release in transporter-transfected human embryonic kidney 293 cells. We also assessed monoamine receptor and transporter binding affinities.

Results: Mephedrone analogs potently inhibited the norepinephrine transporter and, with the exception of 3-methylmethcathinone (3-MMC), inhibited the serotonin transporter more potently than the dopamine transporter. Similar to classic amphetamines, mephedrone analogs were substrate-type monoamine releasers. 5-(2-Aminopropyl)indole (5-IT) was a highly potent monoamine transporter inhibitor and a releaser of dopamine and serotonin. 4-Methylamphetamine (4-MA) mediated efflux of all three monoamines and inhibited the serotonin transporter more potently than the dopamine transporter, unlike amphetamine. *N*-methyl-2-aminoindane (*N*-methyl-2-AI) was a selective norepinephrine transporter inhibitor and norepinephrine releaser, whereas 5-methoxy-6-methyl-2-aminoindane (MMAI) was a selective serotonin transporter inhibitor and serotonin releaser. All of the drugs interacted with monoamine receptors.

Conclusion: The predominant actions on serotonin vs. dopamine transporters suggest that dimethylmethcathinones, 4-MA, and MMAI cause entactogenic effects similar to 3,4-methylenedioxymethamphetamine, whereas 3-MMC, 5-IT, and *N*-methyl-2-AI have more stimulanttype properties like amphetamine. Because of pharmacological and structural similarity to mephedrone, similar health risks can be expected for these analogs.

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Monoamine receptor interaction profiles of 4-thio-substituted phenethylamines (2C-T drugs)

Dino Luethi [a], Daniel Trachsel [b], Marius C. Hoener [c], Matthias E. Liechti [a, *]

ABSTRACT

Background: 4-Thio-substituted phenethylamines (2C-T drugs) are potent psychedelics with poorly defined pharmacological properties. Because of their psychedelic effects, 2C-T drugs are sometimes sold as new psychoactive substances (NPSs). The aim of the present study was to characterize the monoamine receptor and transporter interaction profiles of a series of 2C-T drugs.

Methods: We determined the binding affinities of 2C-T drugs at monoamine receptors and transporters in human cells that were transfected with the respective receptors or transporters. We also investigated the functional activation of serotonergic 5-hydroxytryptamine 2A (5-HT_{2A}) and 5-HT_{2B} receptors, activation of human trace amine-associated receptor 1 ($TAAR_1$), and inhibition of monoamine uptake transporters.

Results: 2C-T drugs had high affinity for 5-HT_{2A} and 5-HT_{2C} receptors (1–54 nM and 40–350 nM, respectively). With activation potencies of 1–53 nM and 44–370 nM, the drugs were potent 5-HT_{2A} receptor and 5-HT_{2B} receptor, respectively, partial agonists. An exception to this were the benzylthiophenethylamines, which did not potently activate the 5-HT_{2B} receptor ($EC_{50} > 3000$ nM). Furthermore, the compounds bound to serotonergic 5-HT_{1A} and adrenergic receptors. The compounds had high affinity for the rat $TAAR_1$ (5–68 nM) and interacted with the mouse but not human $TAAR_1$. The 2C-T drugs did not potently interact with monoamine transporters ($K_i > 4000$ nM).

Conclusion: The receptor binding profile of 2C-T drugs predicts psychedelic effects that are mediated by potent 5-HT_2 receptor interactions.

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Experimental Neurology | Experimental Neurology | 305 (2018) 76–88 IF 4.706

Molecular pathology of Multiple Sclerosis lesions reveals a heterogeneous expression pattern of genes involved in oligodendrogliogenesis

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ABSTRACT

Little is known about the decisive molecular factors that regulate lesion remyelination in Multiple Sclerosis. To identify such factors, we performed a differential gene expression analysis of normal appearing white matter (NAWM), active, remyelinating, and inactive demyelinated lesions. As expected, many genes involved in inflammatory processes were detected to be differentially regulated between these tissue types. Among them, we found an increased expression of members of the STAT6 pathway such as STAT6, IL4 and IL4R in active, remyelinated and inactive demyelinated lesions. This suggests that a protective, anti-inflammatory reaction, as already reported to be present in MS NAWM, is further enhanced in lesion tissues. Focusing on genes influencing oligodendrogliogenesis, we found a decreased expression of NKX2-2 in active, remyelinated and inactive demyelinated lesions, whereas SOX10 was downregulated in inactive demyelinated lesions, when compared to NAWM. Simultaneously, CXCL12 (SDF1) expression was strongly increased in active, remyelinated and inactive demyelinated lesions, but increased expression of the IGF1 and IGF2 genes was found in inactive demyelinated lesions. This demonstrates that, in principle, expression of genes promoting oligodendrogliogenesis occurs in MS lesion tissue - even in inactive demyelinated lesions. In contrast, oligodendrogenesis inhibiting genes such as JAG1 were also expressed at higher levels in inactive demyelinated lesions. Both, oligodendrogliogenesis promoting as well as inhibiting genes are expressed in all lesion tissues. However, no clear promoting or inhibiting expression pattern could be detected in any of the different types of lesioned tissues. This might reflect the heterogeneity of lesion development in MS patients, both in terms of mechanisms and temporal differences.

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Novel Human Polyomavirus Noncoding Control Regions Differ in Bidirectional Gene Expression according to Host Cell, Large T-Antigen Expression, and Clinically Occurring Rearrangements

Elvis T. Ajuh,[a] Zongsong Wu,[a] Emma Kraus,[b,c] Fabian H. Weissbach,[a] Tobias Bethge,[a*] Rainer Gosert,[a,d] Nicole Fischer,[b] Hans H. Hirsch[a,d,e]

ABSTRACT

Human polyomavirus (HPyV) DNA genomes contain three regions denoted the early viral gene region (EVGR), encoding the regulatory T-antigens and one microRNA, the late viral gene region (LVGR), encoding the structural Vp capsid proteins, and the noncoding control region (NCCR). The NCCR harbors the origin of viral genome replication and bidirectional promoter/enhancer functions governing EVGR and LVGR expression on opposite DNA strands. Despite principal similarities, HPyV NCCRs differ in length, sequence, and architecture. To functionally compare HPyV NCCRs, sequences from human isolates were inserted into a bidirectional reporter vector using dsRed2 for EVGR expression and green fluorescent protein (GFP) for LVGR expression. Transfecting HPyV NCCR reporter vectors into human embryonic kidney 293 (HEK293) cells and flow cytometry normalized to archetype BKPyV NCCR revealed a hierarchy of EVGR expression levels with MCPyV, HPyV12, and STLPyV NCCRs conferring stronger levels and HPyV6, HPyV9, and HPyV10 NCCRs weaker levels, while LVGR expression was less variable and showed comparable activity levels. Transfection of HEK293T cells expressing simian virus 40 (SV40) large T antigen (LTag) increased EVGR expression for most HPyV NCCRs, which correlated with the number of LTag-binding sites (Spearman's *r*, 0.625; $P < 0.05$) and decreased following SV40 LTag small interfering RNA (siRNA) knockdown. LTagdependent activation was specifically confirmed for two different MCPyV NCCRs in 293MCT cells expressing the cognate MCPyV LTag. HPyV NCCR expression in different cell lines derived from skin (A375), cervix (HeLaNT), lung (A549), brain (Hs683), and colon (SW480) demonstrated that host cell properties significantly modulate the baseline HPyV NCCR activity, which partly synergized with SV40 LTag expression. Clinically occurring NCCR sequence rearrangements of HPyV7 PITT-1 and -2 and HPyV9 UF1 were found to increase EVGR expression compared to the respective HPyV archetype, but this was partly host cell type specific.

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REVIEWS

Cell Stem Cell | Cell Stem Cell | Vol. 22, ISSUE 3, P298-301, March 01, 2018 IF 23.290

Engineering Human Bone Marrow Proxies

Paul E. Bourgine,[1,2] Ivan Martin,[2] and Timm Schroeder[1,*]

Recent advances in engineering complex organs *in vitro* inspire the development of human bone marrow equivalents to foster scientific discovery and innovative therapeutics. Here, we discuss challenges in generating relevant human bone marrow proxies, potential design principles, and future directions.

Growing increasingly complex tissue and organ structures in the laboratory is no longer science fiction. Advances in culture systems, together with progress in understanding of tissue formation processes by stem/progenitor populations, is steering the development of micro-organ systems recapitulating features and functions of kidney, intestine, gut, liver, or brain (Shamir and Ewald, 2014). Use of human cells in particular allows both the development of highly relevant therapeutic and/or regenerative strategies, as well as contributes new fundamental knowledge. Along the same lines, generation of a human bone marrow (BM) *in vitro* model would provide a powerful platform for basic science and clinical translation. However, despite broad interest and promising research efforts, the engineering of a functional human BM proxy remains a challenge.

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«Selected publications by DBM members»

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

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

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

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

Deadline for the next issue is October 31, 2018.

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Brain and Sound

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Petersplatz

Schuler Dominik
Experimental Virology

Characters which should **not** be used in file names

What Characters are not allowed in file names?

Mac OS X uses HFS+ file system, Windows uses NTFS. Both operating systems encode file names using UTF-16, although the exact encoding scheme is a bit different. Both also allow a max of 254 Unicode characters in one single file name, including all the characters, of the folders which contain the document.

The example below uses exactly 251 Characters. Red characters are part of the fileserver share. Blue characters describe the path, and the green characters are, the so called "file name" itself. But this is actually wrong. The file name used by operating systems is all of the red and all the blue and all the green characters together; together these form the whole file name.

\\dbm.pot.unibas.ch\ITSE$\Group Folder\Computers\Research Groups\Resources\A very very secret Folder\containing all the important Files, my Boss will never need again\so i can name it as i like to\maybe like\this is Sparta\or maybe not\Spreadsheet.xlsx

Black characters are also counted even when they are only separating different nesting folders

Chars not allowed on Windows

NTFS does not allow the following chars: / \ : * ? " < > |

Chars not allowed on MacOS

In MacOS, you can not use the colon : and the dot .
That's it.

File name characters issues

In practice, this means, when you have files names with these chars you'll have problems transferring them from MacOS to Windows. Depending on what tool you use to transfer the file (on a Mac it is the "Finder", or "Desktop Explorer" on a Windows-PC), the tool may stop working, or change the file name in different ways.

To be sure your files will not be renamed, truncated etc. DO NOT use the following characters

# hash tag	? question mark
% percent	! exclamation point
& ampersand	/ forward slash
{ left curly bracket	blank spaces
} right curly bracket	$ dollar sign
\ back slash	' single quotes
< left angle bracket	" double quotes
> right angle bracket	: colon
* asterisk	@ at sign
. dot	; semicolon

Also, keep these rules in mind:

- keep your filenames to a reasonable length and don't use all possible 256 characters
- remember: most operating systems are case sensitive
- don't start or end your filename with a space, period, hyphen, or underline. Start with numbers, if you want to have your files in a sorted manor

Examples of bad filenames:

- F&A Costs .html
- my PDF file#name.pdf
- Starts.with.space.and.uses Dots.DocX

Webbrowsers will see:

- F&A%20Costs.html
- my%20PDF%20file%23name.pdf

Good filenames:

- index.html
- my-pdf-file-name.pdf

So müssen Sommerferien sein!

So müssen Sommerferien sein! Über den Bergen ein enzianblauer Himmel, wochenlang ein strahlend heißer Tag am andern, nur zuweilen ein heftiges, kurzes Gewitter. Der Fluss, obwohl er seinen Weg durch so viel Sandsteinfelsen und Tannenschatten und enge Täler hat, war so erwärmt, dass man noch spät am Abend baden konnte. Rings um das Städtchen her war Heu- und Öhmdgeruch, die schmalen Bänder der paar Kornäcker wurden gelb und goldbraun, an den Bächen geilten mannshoch die weiß blühenden, schierlingartigen Pflanzen, deren Blüten schirmförmig und stets von winzigen Käfern bedeckt sind und aus deren hohlen Stengeln man Flöten und Pfeifen schneiden kann. An den Waldrändern prunkten lange Reihen von wolligen, gelbblühenden, majestätischen Königskerzen, Weiderich und Weidenröschen wiegten sich auf ihren schlanken, zähen Stielen und bedeckten ganze Abhänge mit ihrem violetten Rot. Innen unter den Tannen stand ernst und schön und fremdartig der hohe, steile rote Fingerhut mit den silberwolligen breiten Wurzelblättern, dem starken Stengel und den hochaufgereihten, schönroten Kelchblüten. Daneben die vielerlei Pilze: der rote, leuchtende Fliegenschwamm, der fette, breite Steinpilz, der abenteuerliche Bocksbart, der rote, vielästige Korallenpilz; und der sonderbar farblose, kränklich feiste Fichtenspargel. Auf den vielen heidigen Rainen zwischen Wald und Wiese flammte brandgelb der zähe Ginster, dann kamen lange, lilarote Bänder von Erika, dann die Wiesen selber, zumeist schon vor dem zweiten Schnitte stehend, von Schaumkraut, Lichtnelken, Salbei, Skabiosen farbig überwuchert. Im Laubwald sangen die Buchfinken ohne Aufhören, im Tannenwald rannten fuchsrote Eichhörnchen durch die Wipfel, an Rainen, Mauern und trockenen Gräben atmeten und schimmerten grüne Eidechsen wohlig in der Wärme, und über die Wiesen hin läuteten endlos die hohen, schmetternden, nie ermüdenden Zikadenlieder.

Aus: Hermann Hesse, «Unterm Rad»

Why to fall in love with Greece?

There are so many reasons to fall in love with Greece. Beauty in Greece is exquisite, timeless, unspoiled. From ancient monuments to magnificent landscapes it always manages to catch the attention of the visitors through its magical intricate details.

It has been one of the most famous destinations all around the world attracting millions of travellers. Approximately 16.5 million tourists visit Greece each year, that is more than the country's entire population and it is the only country in the world whose tourists' numbers are double its population (which stands at slightly less than eleven million).

First of all, rugged mountains, exotic, pristine beaches with crystal-clear blue and turquoise waters, green valleys, quiet lakes and lush forests – Greece has it all. Its natural beauty and diversity is bound to astonish. With its extensive coastline, Greece has a plethora of beaches that seduce everyone, thus some of them have been nominated as the most beautiful in the world. From sandy to pebbly beaches, isolated coves and quiet bays, there is always a place somewhere to soak up some vitamin D.

Greece is also, famous for the perfect weather conditions with mild Mediterranean climate. Not tropical and not arctic, it is a fantastic destination all the year round. Did you know that most places in Greece get sunshine 300 days per year? Therefore, it is ideal for exploring nature and the hidden places far away from the main tourist attractions, for water sports including cruising over the numerous islands of the Greek archipelago, parasailing, kayaking and many more, or simply laying on the beach enjoying freshly squeezed orange juice.

Greece has more than 2,000 islands included within the country`s borders, of which only approximately 170 are inhabited by people. The islands are an integral part of the country's history, culture and traditions. Scattered across the Aegean and Ionian Seas, each island has its own unique charm. The Cyclades islands are known for their whitewashed towns with blue shutters and doors, while the Ionian Islands are more known for their greenery and Venetian influence.

One more peculiarity is that Greece combines the beauty of the landscapes, the sea and the sunshine together with the vibrant ancient history and cultural values. There are so many artefacts and edifices that have survived thousands of years of war, turmoil and the sheer test of time. Interestingly, while subways were being constructed before the Olympic Games in 2004 in Athens, workers found a large number of ancient artefacts and they decided to frame them inside the subway walls. You can literally check out ancient pottery and coins while you wait for the subway. Where else do you see that but Greece? Taking into account the country's rich history and culture, Greece has the highest number of archaeological museums in the world. The most famous of all is the new

Acropolis Museum that lies on a hill below the Parthenon and it has already received several awards and thousands of people visit it on daily basis.

Furthermore, maybe it is the weather or it is simply in their blood, but Greeks know how to genuinely enjoy and celebrate their lives and party like there is no tomorrow. Electrifying scenes of Greek nightlife can be witnessed in all parts of the country. Being loud and expressive, they dance the night away in clubs that stay open until the sun rises or enjoy sophisticated cocktails in the beach bars almost every day, especially during the summer time. World widely known for its unique and multidimensional nightlife, Greece is an ideal destination for those who want to have fun, leaving stress and problems behind. Greek nights last longer and enthusiasm is undiminished, offering unique experiences.

The warm hospitality is also one of the main features of the Greek culture. People are always kind, friendly and welcoming. They will help you in getting to that secret beach on the other side of the island, treat you to a glass of tsipouro or feed you like you have never had food in your life.

Greek cuisine is irresistible and holds a special place in the international culture of flavours for its large variety of quality products, cleverly combined, telling age-old secrets handed down from generation to generation. The basic ingredients that make this cuisine so tempting are fresh produce of fruits, vegetables, legumes and sea food, herbs, spices, the renowned Greek olive oil, feta cheese, gyros, moussaka, wine and of course simplicity.

Greece is home to one of the most ancient languages. The Greek language is special and has influenced the world in many ways. The Greek alphabet was the first to use vowels. And guess what? The word "alphabet" comes from the first two letters alpha (α) and beta (β). Greek is considered the oldest written language still in existence with nearly 5000 years of continuous usage and is widely considered the richest and most influential worldwide since Latin, English and Spanish (among other languages) were based, whether directly or indirectly, on the Greek language and alphabet. Thousands of English words come from the Greek language, sometimes via the Roman adaptation into Latin and then to English. Common English words from Greek include "academy," "apology," "marathon," "siren" and the majority of the terms used in the field of biology and science in general. Can you recall the phases (Greek word here as well) of the cell cycle (both Greek too)?

Continuously inhabited for over 7,000 years, Athens, the capital of Greece, is one of the oldest cities in Europe. It is also the birthplace of democracy, Western philosophy, the Olympic Games, political science, Western literature, historiography, major mathematical principles and Western theories of tragedy and comedy.

Last but not least, the Greek flag includes nine blue and white horizontal stripes which stands for the nine syllables of the Greek motto "Ελευθερία ή Θάνατος" ("Eleftheria i Thanatos" / "Freedom or Death"). Blue represents Greece`s sea and sky. White stands for the purity of the struggle for freedom. In the upper-left corner there is the traditional Greek Orthodox cross.

All in all, the feeling of freedom and immense history is profoundly noticeable everywhere in the country. That great "openness" is an indispensable part of the Greek culture, entertainment and tradition. For all the mentioned above and much more, anyone can fall in love with Greece. So just go, explore, admire and savour all the treasures, it generously has to offer!

PS Thank you to my friends in Athens who shared their vacation pictures with me!

Σας ευχαριστώ πολύ, Ράνια, Βάσια, Κων!

Daria Monogiou Belik

Today: Philipp Wuggenig, Gastroenterology

Canoeing on the Aare

Being from the Principality of Liechtenstein, I will tell you some facts about this doubly landlocked German-speaking microstate in Central Europe and how it is to grow up in this country as well as a description of one of my hobbies, which is still not so popular: Floorball. The principality is a constitutional monarchy headed by the Prince of Liechtenstein and one of the five bordering countries of Switzerland. It has an area of 160km² and an estimated population of 37,000 inhabitants.

The capital is Vaduz and the largest municipality is Schaan, where I actually come from. Liechtenstein is a member of the United Nations, European Free Trade Association, and the Council of Europe, and while not being a member of the European Union, the country participates in both the Schengen Area and European Economic Area. It also has a customs union and a monetary union with Switzerland, that's why we have the Swiss franc as the national currency.

During our childhood, my brother and I spent the most time outdoors, whether on fields, in the forest or on the mountains. Everything is really close, be it hiking directly from the village to the mountains or relaxing in the forest or by the Rhine, which is also the border to Switzerland. These all are lovely advantages of growing up in a rural area embedded in the middle of mountains. Additionally, as you are able to travel from Liechtenstein into three different countries within "seconds" it makes it easy for adventure trips. On a summer, friends of mine and I decided to make a canoeing trip with self-made canoes on the river Aare from Münsingen to Solothurn. It took four days and it was a fantastic trip with beautiful sunsets, grill sessions, and uncountable impressions. By the way, if you do not know which three countries I mean: Switzerland (mentioned above), Austria (also a bordering state) and Germany.

Vaduz Castle is the palace and official residence of the Prince of Liechtenstein

I love to spend my free time in the forest. Therefore, I worked in forestry most of the time during study free time and especially during the summer holidays, but I also worked in the alpine economy of Schaan. On nice days you can see Lake Con-







Alpabtrieb: Gritsch, the route passes the Vaduz Castle / Forestry work with the winch / Impressions: Men's World Floorball Qualification 2018

stance from the Alps of Schaan, which sweetened the hard working day. In Liechtenstein, we also have an old tradition, the "Alpabtrieb" (autumnal ceremonial cattle drive from mountain pastures into valleys). It is an honor for me to be a part of the "crew" bringing the cattle safely back to the valley every year.

Another passion of mine is the sport. As a young ice hockey fan, I played inline hockey as well as ice hockey with some other hockey addicted friends, and sometimes also floorball…okay, I also played football, what else in a country like Liechtenstein ;) However, when I was studying in Innsbruck (Austria), I joined a floorball club for the first time. Floorball is played with five players and a goalkeeper in each team, similar to ice hockey. I played four seasons in total for the Hot Shots Innsbruck and the last two seasons in the first league (Bundesliga). During the "Bundesliga" time I got the call of the Liechtenstein National Team. I am proud to play for this small country, although we are not such a strong team. Nonetheless, I was able to make many experiences at the "Men's World Floorball Qualification" in Škofja Loka, Slovenia (2016) and Tallinn, Estonia (2018). One of the unforgettable moments was the game against the reigning world champion Finland in Tallinn. I thought we were playing against "Terminators"… I don't know how to describe it properly; it was amazing! I am just happy to have the chance to play in the national team! Invaluable experiences! I hope now that I can help my new team here in Basel ;) and I am looking forward to the next WFCQ in 2020 if I am still in good enough shape for the national team.

Now I have been in Basel for two years. It is kind of funny that I am finally here because I originally wanted to study in Basel, but as you know, things don't always work out as you plan, especially when friends move you to another place. How life goes, here I am! So, let's see what kind of adventure Basel will offer me, even though there are some language differences and most Basel citizens believe that I am a "Bündner" (from Canton of Grisons). Dialects. The most difficult languages.

Save the date

DBM Summer Symposium

Wednesday, August 22, 2018

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

Presentations by DBM postdocs, PhD students and project leaders

DBM Summer Barbecue

Wednesday, August 22, 2018

16:30 – 21:30
Kraftwerkinsel Birsfelden

For DBM members only

« Der Herbst ist immer unsere beste Zeit. »

Johann Wolfgang von Goethe an
Friedrich Schiller am 27. 06. 1797