# DBM FACTS

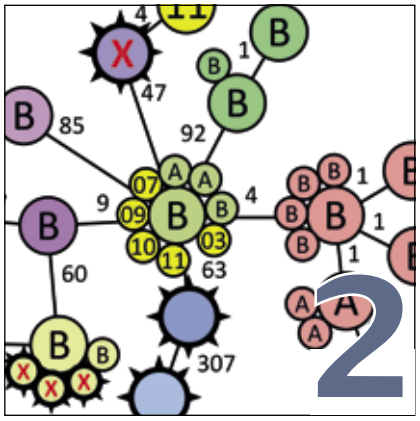
Periodisches Informationsblatt des Departementes Biomedizin
Universität Basel, Universitätsspital Basel und
Universitäts-Kinderspital beider Basel

## Applied Microbiology Research | Christmas in Mexico | Research Day 2021

2 | 20

# INHALT CONTENTS

Departement Biomedizin Basel




**Applied Microbiology Research**
from Adrian Egli and colleagues




**Christmas in Mexico**
from Amanda Ochoa-Espinosa


**DBM-IT**


**Das DBM stellt sich vor**


**IMPRESSUM**

**Redaktion**
Heidi Hoyermann

**Übersetzungen**
Paula Cullen

**Layout**
Chantal Schürch

**IT-Unterstützung**
Niklaus Vogt

**Administration**
Manuela Bernasconi

**Fotos**
Shutterstock, Pixabay

**Druck**
buysite AG, Basel

**Anschrift**
Redaktion DBM Facts
Departement Biomedizin
Hebelstrasse 20
4031 Basel
heidi.hoyermann@usb.ch

# EDITORIAL

***Radek Skoda***
***Leiter DBM***

Liebe Leserinnen und Leser

Ein schwieriges Jahr liegt hinter uns. Die COVID-19 Pandemie ist auch am DBM nicht spurlos vorübergegangen: Nach dem Lockdown im Frühjahr sind die einschränkenden Massnahmen am DBM aktuell weniger einschneidend. Viele Treffen mussten aber abgesagt werden, insbesondere das Sommerfest und die DBM-Weihnachtsfeier, dafür sind wir jetzt Experten in der Durchführung von Online-Meetings geworden. Die Massnahmen haben gewirkt: Am Arbeitsplatz hat sich am DBM bisher niemand mit SARS-CoV-2 infiziert. Dies bleibt unser Ziel auch für die Zukunft. Herzlichen Dank an alle für ihren Beitrag.
Anke Wixmerten hat ad interim die Stelle als «Koordinatorin» DBM übernommen und unterstützt mich bei meiner Tätigkeit als Leiter DBM. Anne-Katrin Pröbstel und Katharina Timper haben je ein Eccellenza Fellowship des SNF erhalten und werden ihre eigenen Forschungsgruppen aufbauen. Andrea Barbero und Arnaud Scherberich wurden von der DBM-Leitung je zu unabhängigen Forschungsgruppenleitern ernannt. Ihnen allen herzliche Gratulation und viel Erfolg beim Aufbau der eigenen Forschung! Das DBM konnte Büroräumlichkeiten im Gebäude des ehemaligen Zahnärztlichen Instituts an der Hebelstrasse 3 gewinnen und so Raum für Forschungsgruppen und unsere Bioinformatik Core-Facility zur Verfügung stellen.
In der nun vorliegenden Ausgabe schildert Adrian Egli die wissenschaftlichen Aktivitäten seiner Forschungsgruppe «Applied Microbiology Research» (Seite 2). Die aktuellsten Publikationen aus dem DBM finden Sie ab Seite 10. Amanda Ochoa-Espinosa lässt uns mit ihr Mexikanische Weihnachten feiern (Seite 24) und Miyoshi Hirotsugu erzählt uns, wie man in seiner Heimat Japan lebt (Seite 30).
Eine interessante Lektüre und frohe Festtage!

Radek Skoda

*Dear Readers,*

*A difficult year is behind us. The COVID-19 pandemic did not pass the DBM without leaving its mark. The current restrictions at the DBM are not as restrictive as those during the lockdown in spring. Many meetings have had to be cancelled, in particular the summer and Christmas celebrations at the DBM, and we have all become experts at carrying out meetings online. The measures have worked: to date, nobody at the DBM has been infected with SARS-CoV-2 at the workplace. This remains our goal for the future as well. Many thanks to everyone for their contribution.*
*Anke Wixmerten has temporarily taken on the position of DBM coordinator and supports me in my work as head of DBM. Anne-Katrin Pröbstel and Katharina Timper have each received an Eccellenza Fellowship from the SNSF and will set up their own research groups. Andrea Barbero and Arnaud Scherberich were both appointed as independent research group leaders by the DBM management. Congratulations to all of you and best of luck with setting up your own research! The DBM was able to gain office space in the building of the former Dental Institute at Hebelstrasse 3 and thus make space available for research groups and for our bioinformatics core facility.*
*In this issue, Adrian Egli describes the scientific activities of its research group "Applied Microbiology Research" (page 2). The latest publications from the DBM can be found on page 10. Amanda Ochoa-Espinosa lets us celebrate a Mexican Christmas with her (page 24) and Miyoshi Hirotsugu tells us how one lives in his native Japan (page 30).*
*Enjoy the read and happy holidays!*

*Radek Skoda*

# Applied Microbiology Research

**Research Summary**

Hosts and pathogens interact in complex ways. The Applied Microbiology Research group aims to contribute to the understanding of the various levels of host-pathogen interactions, from molecules to populations. We use cutting edge molecular techniques, high throughput pathogen genome sequencing, and mass spectrometry. We work closely with the University Hospital Basel, who provide us with access to clinical samples and patient data, allowing us to validate our results. Key findings are translated into clinical applications to improve diagnostics of infections.

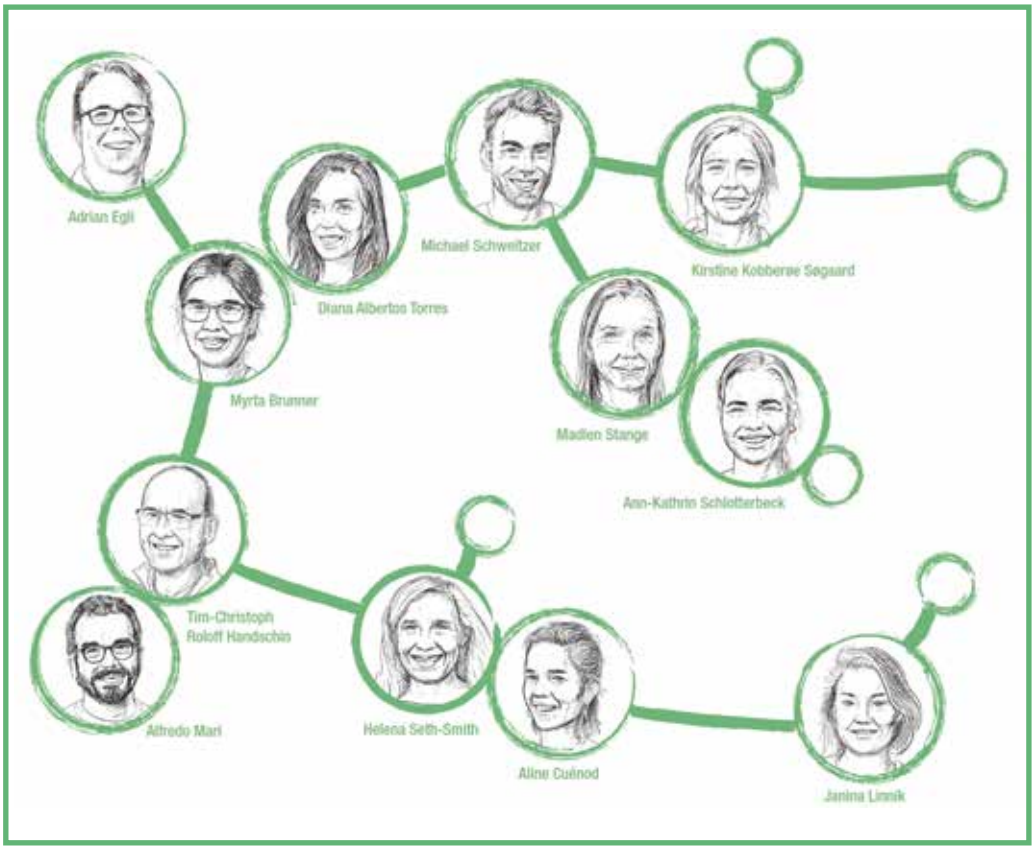



*Figure 1. Members of the Applied Microbiology Research group (November 2020).*

The group has currently twelve international members (Figure 1) with diverse backgrounds in biology, medicine, bioinformatics, and geography. The research group was founded in 2014 with a Swiss National Science Foundation grant and since then many international PhD students and post-doctoral fellows have joined.

**The research topics of our group include:**

› Transmission of clinically relevant pathogens: viruses, bacteria and fungi.
› Bacterial population dynamics within patients colonized or infected.
› Humoral immunity to pathogens.
› Translation into routine diagnostics.

**The goals of our research:**

(i) to **understand pathogen dynamics and transmission** in the context of host/pathogen/animal/environment interactions,
(ii) to **explore the complex changes in bacterial populations** in colonization and infection,
(iii) to develop and translate **new approaches, concepts and technologies for rapid diagnosis** of multidrug resistant and hypervirulent pathogens **and explore changes in bacterial populations** using bacterial genomics, metagenomics, mass-spectrometry, and digital microbiology applications,
(iv) to **form collaborative research networks** to interconnect data and knowledge.

***Selected projects***

**Transmission of clinically relevant pathogens.**

Infectious diseases cause significant morbidity and mortality. Understanding the sources and transmission dynamics of pathogens is key to identifying and preventing outbreaks.

**Viral transmission models.**

We study transmission in the context of local outbreaks and global epidemics using human influenza viruses as a model pathogen and recently applied our know-how to study SARS-CoV-2. We have established virus-specific whole genome sequencing (WGS) and analytical protocols. Together with our collaborating partners, we explore transmission with spatio-temporal models across the Basel region. We investigate viral evolution in clinically relevant contexts, such as the role of superspreading events, the effect of socioeconomics and mobility, and the evolution of anti-viral resistance.

*Influenza*. In a collaboration with the Human Geography research team at the University of Basel (Prof. Rita Schneider-Sliwa) and ETH Zurich (Prof. Tanja Stadler), we have studied influenza transmission in great detail. First, we analyzed PCR-confirmed influenza cases from Basel covering the 2013/2014 to 2017/2018 influenza season (Figure 2A). We conducted a survey focusing on influenza and vaccination and distributed more than 30,000 questionnaires during the 2015/2016 flu season. We collected information on clinical symptoms, vaccination, aspects of urban living, and socioeconomics. Vaccination rates were found to differ greatly between districts (Figure 2B). We showed that net income is positively associated with self-reported vaccination. The self-reported vaccination rate per city district was inversely associated with the likelihood of influenza-like illness (Figure 2C). For the 2016/2017 flu season, we conducted a prospective observational study, sampling several hundred pediatric and adult patients with influenza-like illnesses at different study sites throughout the city. We were able to sequence more than 700 influenza isolates from the Basel area – one of the highest sequence densities of influenza per capita for a single municipal area. Bioinformatic analysis allowed us to (i) determine the number of viral introductions in Basel, (ii) explore transmission rates between age groups and (iii) describe the transmission between city districts (Figure 2D). Of note, within the endemic influenza seasons, dozens of genetically diverse viruses are introduced to Basel. The transmission within the city is complex and almost all districts are connected with each other. Of interest, we can see that there are significant proportions of highly similar viruses transmitted within the districts Gundeldingen and Vorstädte.

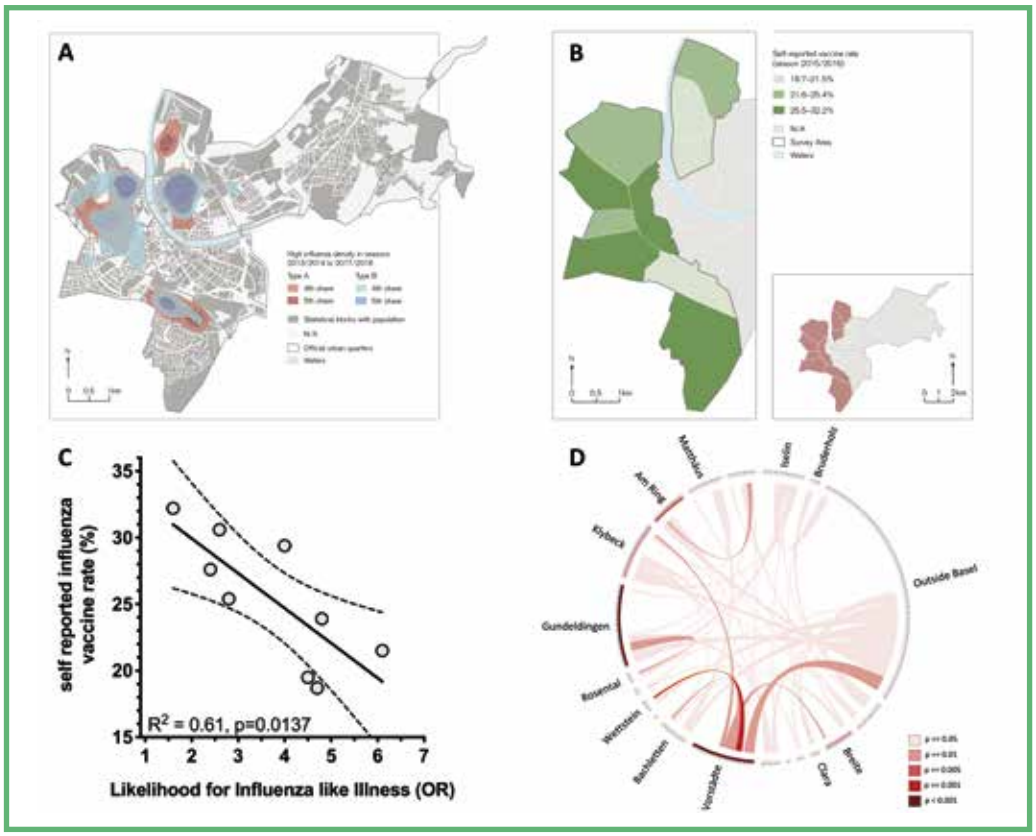



*Figure 2. Transmission of Influenza in Basel.*

*(A) Influenza A (red) and B (blue) cases from seasons 2013/2014 to 2017/2018 shown as a Kernel density plot; (B) Self-reported vaccination rates in ten selected city districts. Dark green areas indicate a region with a high vaccination rate. Red map indicates city overview; (C) Inverse correlation of self-reported vaccination rates and likelihood for Influenza-like illness. Each dot represents a city district; (D) Transmission of highly similar Influenza viruses between city districts, as defined by whole genome sequencing. The red color indicates the level of significance. Whereas Gundeldingen and Vorstädte show high within-quarter transmission, from Vorstädte a significant amount is also exported to other areas of the city.*

*SARS-CoV-2*. Similar to influenza, we have also explored transmission of SARS-CoV-2 within Basel. As SARS-CoV-2 is a new pathogen, new and robust tools were needed to confidently monitor its diversification. We developed our own in-house workflow to draft genomes and track emerging variants: COVGAP, now part of Swiss Pathogen Surveillance Platform (SPSP). Through COVGAP we observed that SARS-CoV-2 has not yet diversified a great deal, and we can see this diversification occurring slowly over time from the first to the second wave. We have also identified geographical hotspots with high case burdens in Basel. These hotspots are similar to those seen for Influenza, explained by high population density in these city districts. During the first wave, a limited diversity of viral lineages was noted (Figure 3A/B). The phylogenetic lineage B.1 (Pangolin nomenclature) dominated the outbreak in Europe. We identified a Basel-specific mutation (C15324T) within the B.1 lineage, which most likely originated in our tri-national region. We postulate that during a superspreading event (an event in Alsace) this particular strain was widely transmitted and subsequently accounted for 70% of the sequenced cases during the first wave in Basel. The C15324T mutation is synonymous and does not impact protein function, but serves as a marker. This specific mutation allowed us to follow transmission chains within the city, but also to study the export of C15324T-marked viruses around the globe. We also identified the "Ischgl mutation" (C1059T) in 21 people from Basel. Epidemiological information indicated that some of these individuals had indeed been skiing in Austria. In collaboration with Prof. Hans H. Hirsch (Clinical Virology), we could achieve an exceptional high sequencing density per capita in the region of Basel (Figure 3C).

In a collaboration with the ETH Zurich (Dr. Sarah Brüningk, Dr. Juliane Klatt, and Prof. Karsten Borgwardt), we currently model SARS-CoV-2 transmission in Basel using an SIR model (susceptible, infected and resistant). Into the model, we have integrated the previously described Basel mutation (C15324T) as the main circulating clone. We have also generated a proximity index considering population density and living space. Not surprisingly, areas with a high proximity index show a higher reproduction number than areas with a lower proximity index. The reproduction number indicates the average number of transmissions from a single infected individual. As an example, a $R_{eff}$ of 2, indicates that one patient infects in average two additional people. We have also investigated

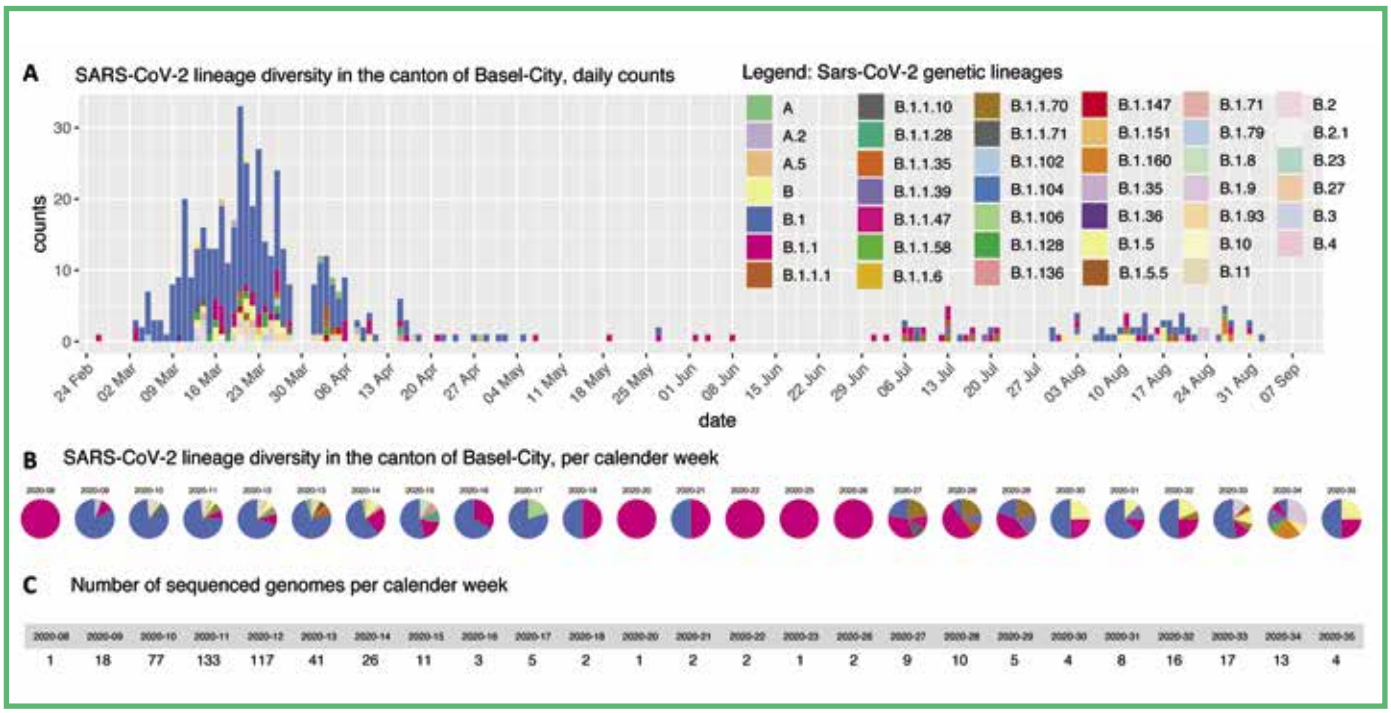



*Figure 3. Analysis of SARS-CoV-2 in Basel.*

*(A) Diversity of viral lineages over time in Basel from whole genome sequencing. (B) Lineage composition and (C) number of sequenced SARS-CoV-2 genomes per calendar week*

the effects of mobility between city districts and areas with different proximity indices on SARS-CoV-2 transmission rates. We received a highly detailed mobility dataset including all public transportation, bike, car, and pedestrian data in Basel from the canton. This has allowed us to simulate the effects of changes in mobility during the first wave on the transmission. Most importantly, we can now simulate, which city district is most highly connected and contributes most to the spread of SARS-CoV-2 within Basel. We are using this new knowledge to run potential vaccine models and can suggest, which districts and populations should be vaccinated first, to maximize the effect for the whole community.

**Transmission of clinically relevant bacteria.**

We also use whole genome sequencing (Illumina and Oxford Nanopore Technologies ONT) and metagenomic approaches to describe genetic relatedness and evolution of bacteria.

In 2017/2018, we observed multiple cases of *Corynebacterium diphtheriae* in people who fled from North-Africa. We conducted an outbreak investigation including all toxigenic and non-toxigenic *Corynebacterium diphtheriae* isolates from Switzerland and Southern Germany (these are shown in a species context in Figure 4). Importantly, we were able to exclude direct transmission events in suspected clusters, and have since identified a single direct transmission cluster within a family. Using mutation rates and a molecular clock model, we could calculate that the transmission events occurred prior to arrival in Basel. In addition to phylogenetic analyses, we also risk assessed single pathogens by determining the presence of genes encoding for the diphtheria toxin and pharyngeal adherence factors.

Other genomic studies have investigated a vancomycin resistant *Enterococcus faecium* outbreak with connections to a new sequence type from Australia, Swiss-wide *Burkholderia cepacia* in contaminated hospital washing gloves, carbapenemase-producing Enterobacteriaceae and non-fermenting bacteria, methicillin resistant *Staphylococcus aureus* (MRSA) and multi-drug resistant *Mycobacterium tuberculosis* in people who fled, *Shigella* spp. as an emerging sexually transmitted disease, the context of multidrug-resistant *Salmonella* Typhi from India, and description of *Mycobacterium basiliense* as a new bacterial species.

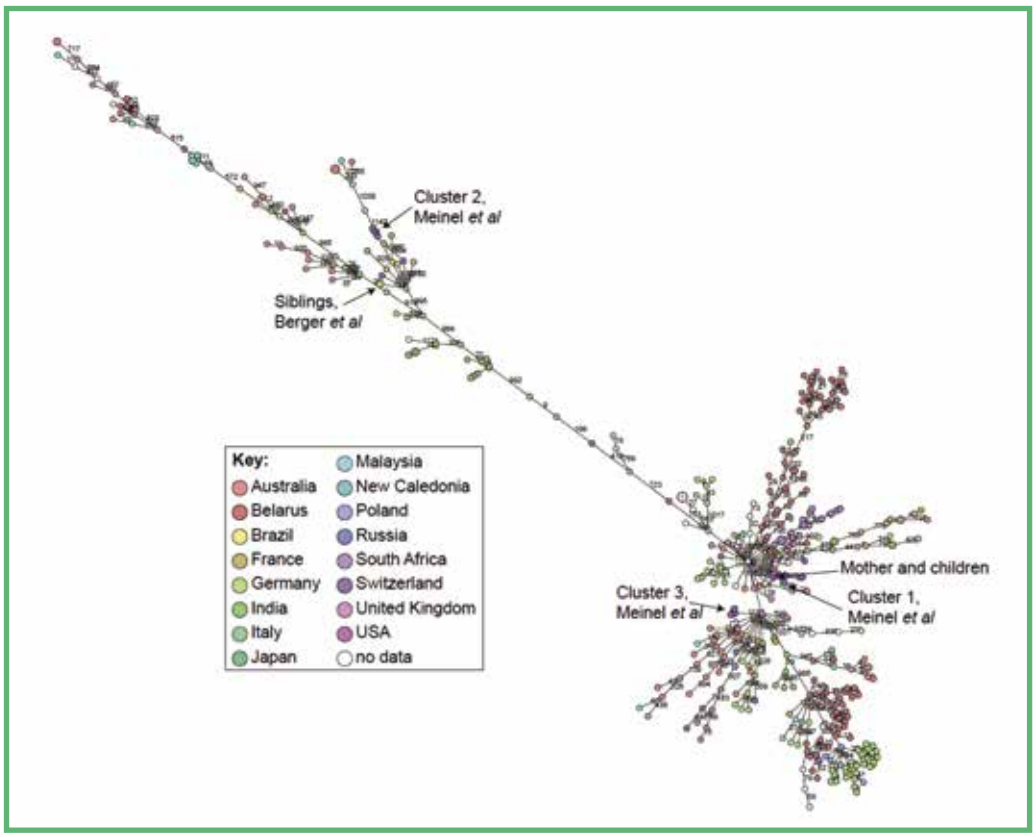



*Figure 4. Diversity of Corynebacterium diphtheriae. Each colored dot represents a case colored by country according to the key. Arrows indicate clusters and transmissions identified by the Division of Clinical Bacteriology of the University Hospital Basel. Only the mother to children cluster was a direct transmission event. Clusters 1-3 were not direct transmissions but based on molecular clock calculations had diversified at least 2 years ago.*

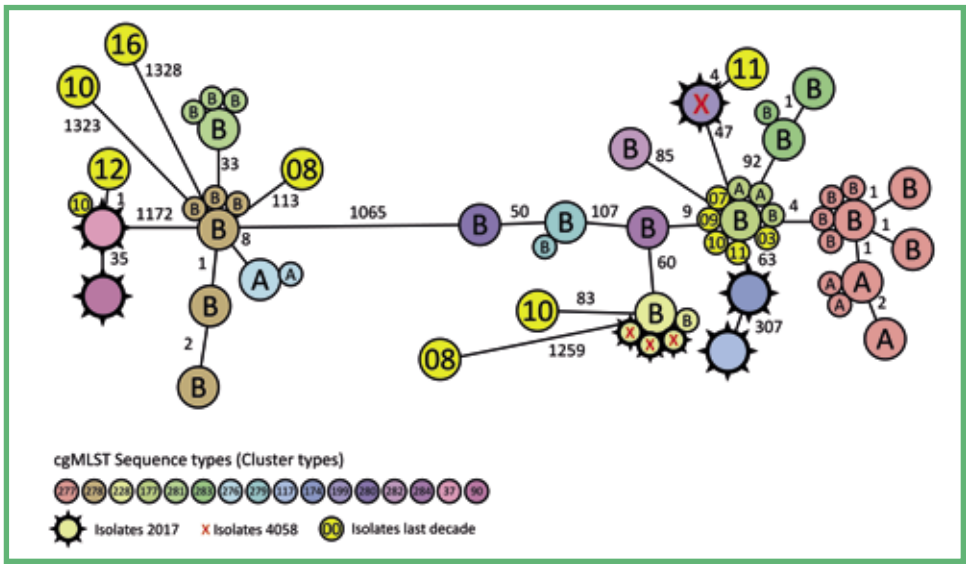



*Figure 5.*
*Identification of infectious sources from Legionella pneumophila in Basel.*
*The graph shows a cgMLST neighbor joining tree. Two air conditioner cooling towers on the roof of large building (labeled with A and B) show an exchange network of bacterial strains and serve as a source for infection. Patients samples from 2017 are marked with black spikes, with those from the outbreak location indicated with red crosses, and isolates from the last decade shown with yellow circles indicated by the year.*

Our technical and analytical expertise is utilized in various collaborations with the Federal Office of Public Health e.g. *Campylobacter* spp. in chicken meat and humans (2017) and a nation-wide *Salmonella* spp. outbreak investigation (2018) or for the national reference laboratory of *Legionella pneumophila* (since 2019).

Together with the cantonal laboratory and health services, we explored an outbreak of *L. pneumophila* in Basel. We rapidly identified two contaminated cooling towers on the rooftops of large buildings, forming a transmission network of *L. pneumophila*, which was driving an outbreak in susceptible people living in the area (Figure 5). We then added strains from our biobank ranging back almost 20 years and could show, that there are persistent clones in Basel having caused infections in patients for almost two decades.

A fundamental tool, which we are currently constructing is the NRP72-funded Swiss Pathogen Surveillance Platform (www.spsp.ch). The platform allows exchange of genomic and epidemiological data with other centers, and offers shared and standardized bioinformatic pipelines, thereby increasing the interoperability of the data. We collaborate with the Universities and University Hospitals of Basel, Geneva and Lausanne, VetSuisse (University of Bern and Zurich) and the Swiss Institute for Bioinformatics (SIB) to form this database for WGS and meta-data sharing. Current work focuses on MRSA and SARS-CoV-2, but will be expanded to multiple clinically relevant pathogens.

**Understanding pathogens and populations.**
Our research group also focuses on pathogen dynamics and prediction of invasiveness. Studying individual isolates at single genome resolution as well as the changes in microbial networks can help to understand pathogenicity.

*New sequencing approaches to screen for resistance.* In an SNSF-funded project, we will develop new metagenomic tools to rapidly determine intestinal colonization with multi-drug resistant pathogens. In this project, we will use ONT long-read sequencing and real-time data analysis to explore patient and environmental samples. We will use "adaptive Nanopore sequencing" to increase the sensitivity in metagenomic samples to find low abundant bacterial pathogens and determine their resistance profile. These tools will allow us to monitor the exchange of bacteria between patients and the environment in a hospital setting, and also allow us to explore the colonization of different compartments over time. The project will start in Winter 2020 with a new PhD student joining our group.

*Displacing ESBL.* In a Gebert-Rüf funded project, we look into the dynamics of extended spectrum beta-lactamase (ESBL) *E. coli* colonization and carriage in healthy individuals. We follow single individuals, who travelled to high endemic regions. Our goal is to identify (i) microbiological factors influencing whether a subject remains colonized or spontaneously clears the pathogen and (ii) whether and which pan-sensitive natural microbiota can displace resistant bacteria such as ESBL *E. coli*. We collaborate with

the Swiss Tropical and Public Health Institute (Dr. Esther Künzli) and groups from ETH Zurich (Prof. Wolf-Dietrich Hardt and Prof. Sebastian Bonhoeffer) for mouse work and mathematical modelling. We have currently finished sampling all enrolled patients over one year. We have collected stool samples and have started to sequence single bacterial isolates of both ESBL-producing and non-ESBL producing *E. coli* bacteria. We will study the evolution of single isolates over time and the role of plasmid transmission between *E. coli* of different sequence types. In addition, we have begun 16S rRNA gene sequencing in order to evaluate the microbiome composition over time in each patient and compare the microbiota in colonized versus non-colonized patients.

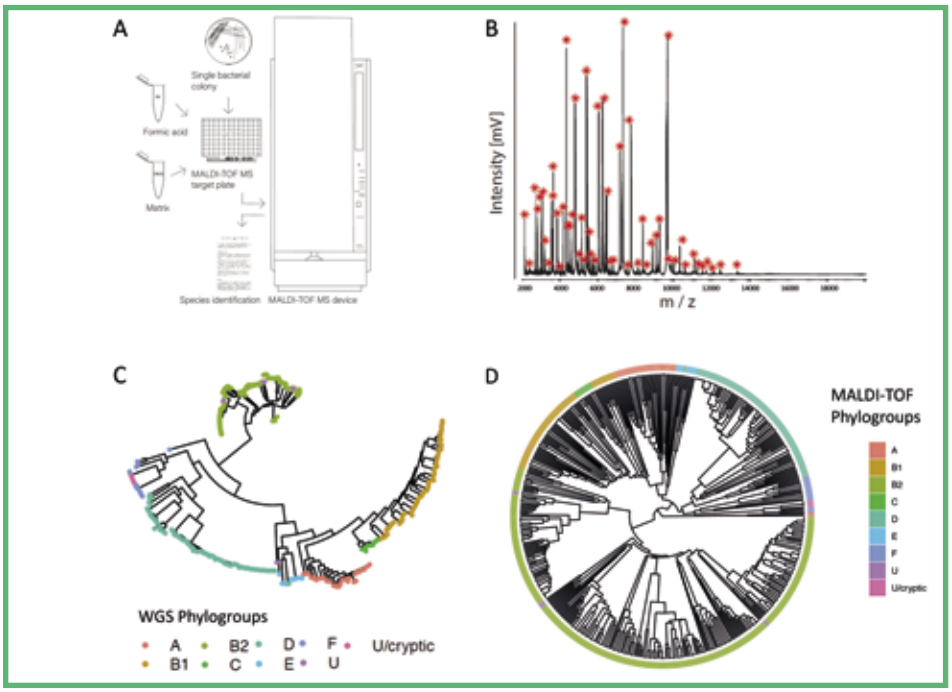



*Figure 6. Using MALDI-TOF MS for species identification and beyond. (A) MALDI-TOF MS workflow; (B) A typical MALDI-TOF MS spectral profile of E. coli. The y-axis describes a peak intensity and the x-axis described the mass to charge ratio. Each peak is marked with a specific position within the spectra. Some peaks are highly reproducible and allow the identification of a bacterial species and also subtyping. (C) A core genome phylogeny of E. coli strains isolated at the USB, colored by phylogroup; (D) Hierarchical clustering of core genome protein markers, predicted from E. coli genomes and potentially detectable in MALDI-TOF MS*

**Development of novel diagnostic tools.**

An important aim of the group is to translate our findings into clinically relevant applications. One commonly used technology, we aim to further improve, is MALDI-TOF mass-spectrometry (MS). This is currently the most used technology for bacterial species identification (Figure 6). In one project, we are studying the factors driving invasiveness of *E. coli* isolates causing first a urinary tract infection, then pyelonephritis, and potential uro-sepsis. We use WGS data to predict specific marker masses based on the bacterial core genome. This allows us, for example in *E. coli* to determine the different phylogroups in MALDI-TOF MS spectra. Some of these phylogroups are linked to clinical phenotypes e.g. uro-pathogenic *E. coli* (UPEC) are more common in B2 phylogroups (Figure 6).

We will continue to explore host-pathogen interaction and currently also focus more on rapid metagenomic developments for research and diagnostics.

Adrian Egli and colleagues

**5 selected Publications 2016-2020** *most recent first*


- Stange M, Mari A, Roloff T, Seth-Smith HMB, Schweitzer M, Brunner M et al. SARS-CoV-2 outbreak in a tri-national urban area is dominated by a B.1 lineage variant linked to mass gathering events. medRxiv 2020.09.01.20186155; doi: https://doi.org/10.1101/2020.09.01.20186155
- Syedbasha M, Bonfiglio F, Linnik J, et al. Interferon-λ Enhances the Differentiation of Naive B Cells into Plasmablasts via the mTORC1 Pathway. *Cell Rep.* 2020 Oct 6;33(1):108211. doi: 10.1016/j.celrep.2020.108211.
- Egli A, Schrenzel J, Greub G. Digital microbiology. *Clin Microbiol Infect.* 2020 Oct;26(10):1324-1331. doi: 10.1016/j.cmi.2020.06.023. Epub 2020 Jun 27.
- Seth-Smith HMB, Imkamp F, Tagini F, et al. Discovery and Characterization of *Mycobacterium basiliense* sp. nov., a Nontuberculous Mycobacterium Isolated From Human Lungs. *Front Microbiol.* 2019 Jan 8;9:3184. doi: 10.3389/fmicb.2018.03184. eCollection 2018.
- Wüthrich D, Gautsch S, Spieler-Denz R, et al. Air-conditioner cooling towers as complex reservoirs and continuous source of *Legionella pneumophila* infection evidenced by a genomic analysis study in 2017, Switzerland. Euro *Surveill.* 2019;24(4):1800192. doi:10.2807/1560-7917.ES.2019.24.4.1800192

# Auszeichnungen

**Cloëtta-Preis an Mohamed Bentires-Alj**

In diesem Jahr wurde der renommierte Cloëtta-Preis, der mit 50'000 CHF dotiert ist und die medizinische Forschung sowie verwandte naturwissenschaftliche Disziplinen in der Schweiz fördert, am 19. November 2020 in einer feierlichen Zeremonie in Zürich an **Mohamed Bentires-Alj** von der FG "Tumor Heterogeneity, Metastasis und Resistance" (DBM Hebelstrasse) für seine wegweisende Brustkrebsforschung verliehen. Zweite Preisträgerin ist Nadia Mercader Huber vom Institut für Anatomie der Universität Bern.

**Krebspreis der Dora Seif Stiftung an Alfred Zippelius**

**Alfred Zippelius** von der FG «Cancer Immunology» (DBM Hebelstrasse) erhält den Preis der Dr. med. Dora-Seif-Stiftung Basel für seine Forschung zur immunologischen Antwort gegen Tumorerkrankungen. Die Stiftung vergibt den Preis, der mit 5'000 Franken dotiert ist, alle zwei Jahre für «die beste Arbeit, die zur Verbesserung der Frühdiagnostik und Therapie des Krebses beiträgt».

**Forschungspreis der Schweizerischen Hirnliga an Jan Gründemann und Andreas Lüthi**

Für ihre Studie, die in der Zeitschrift Science erschienen ist, wurden **Jan Gründemann** von der FG «Sensory processing and behaviour» (DBM Klingelbergstrasse) und Andreas Lüthi im Januar 2020 mit dem Forschungspreis der Schweizerischen Hirnliga ausgezeichnet. Sie erhalten den Preis für ihre Arbeit zur neuronalen Aktivität der sogenannten Amygdala. Das Preisgeld von 20'000 Franken soll der weiteren Forschung dienen und wird zwischen Jan Gründemann und Prof. Andreas Lüthi (FMI) geteilt.

**BBC Preise an Federica Zilli und Milica Vulin**

Am diesjährigen Meeting des Basel Breast Consortium (BBC) im November 2020 haben **Federica Zilli** und **Milica Vulin** von der Forschungsgruppe Tumor Heterogeneity, Metastasis and Resistance (DBM Hebelstrasse) je einen Preis für das beste Poster in der Kategorie «Basic reseach» erhalten. Federica erhielt den Felix Harder Award, Milica Vulin den Nancy Hynes Award. Beide Preise sind mit 500.- CHF dotiert.

**Fakultätspreis an Christian Epple**

**Christian Epple** von der Forschungsgruppe «Tissue Engineering» (DBM Hebelstrasse) hat für seine Dissertation im oben genannten Labor den diesjährigen Fakultätspreis der Medizinischen Fakultät erhalten.

**Stern-Gattiker Preis an Sara Meyer**

**Sara Meyer** von der Forschungsgruppe «Myeloid Malignancies» (DBM Hebelstrasse) hat den Stern-Gattiker Preis 2020 der Schweizerischen Akademie der Medizinischen Wissenschaften (SAMW) erhalten. Mit dem Stern-Gattiker-Preis würdigt die SAMW Frauen in der akademischen Medizin. Der Name geht auf zwei Medizinerinnen zurück: Lina Stern, eine russische Emigrantin, die 1918 die erste Professorin an der Medizinischen Fakultät Genf war, und Ruth Gattiker, eine der ersten Professorinnen an der Medizinischen Fakultät Zürich in den 1970er Jahren. Der Preis ist mit CHF 15'000.– dotiert.

**SSH/SSMO Award an Jan Stetka**

**Jan Stetka** von der Forschungsgruppe «Experimental Hematology» (DBM Hebelstrasse) hat im November 2020 am Swiss Oncology & Hematology Congress (SOHC) den diesjährigen "Award for Experimental Hematology/Oncology" der Swiss Society of Hematology (SSH) / Swiss Society of Medical Oncology (SSMO) für den besten Abstract erhalten.

**Best Abstract Prize und National Scholarship Award an Hassan Melhem**

An der UEG Week 2020, einem der weltweit wichtigsten viszeralmedizinischen Kongresse, hat **Hassan Melhem** von der Forschungsgruppe «Gastroenterology» (DBM Hebelstrasse) den best Abstract Prize und den National Scholarship Award erhalten. Mit dem Best Abstract Prize werden die besten drei Beiträge jedes Fachgebietes ausgezeichnet, mit dem National Scholarship Award wird die beste Arbeit eines jeweiligen Landes geehrt.

**Venia docendi verliehen**

Die Regenz der Universität Basel hat im Oktober 2020 **Marcus Mumme** von der Forschungsgruppe «Tissue Engineering» (DBM Hebelstrasse) die Venia docendi für Orthopädie und Traumatologie des Bewegungsapparates verliehen. Er ist damit befugt, den Titel eines Privatdozenten zu führen.

**Aimee Zuniga RSB Fellow**

**Aimee Zuniga** von der Forschungsgruppe «Developmental Genetics» (DBM Mattenstrasse) ist von der Royal Society of Biology (FRSB) im Oktober 2020 zum «Fellow of the Royal Society of Biology» ernannt worden.

# Dissertationen

Am 29. April 2020 stellte sich **Laurene Ramos Martins** von der Forschungsgruppe «Developmental Genetics» (Departement Biomedizin Mattenstrasse) den Fragen des Dissertationskomitees. Der Titel ihrer Dissertation hiess: «The Gremlin1 cis-Regulatory Landscape: A Paradigm to Study Enhancer Cooperation in Regulation of Transcription Dynamics».

Am 6. Juli 2020 konnte **Ausra Girdziusaite** von der Forschungsgruppe «Developmental Genetics» (Departement Biomedizin Mattenstrasse) ihre Dissertation mit Erfolg beenden. Sie befasste sich in ihrer Dissertation mit dem Thema: «TBX3 and HAND2 controlled gene regulatory networks in the establishment of axis polarity in mouse limb buds».

Am 20. August 2020 stellte sich **Berna Kaya** von der Forschungsgruppe «Gastroenterology» (Departement Biomedizin Hebelstrasse) den Fragen des Dissertationskomitees. Der Titel ihrer Dissertation lautete: «Lysophosphatidic acid-mediated GPR35 signaling in CX3CR1+ macrophages regulates the intestinal cytokine milieu».

Mit der Doktorprüfung am 21. August 2020 schloss **Martin Lett** von der Forschungsgruppe «Liver Immunology» (Departement Biomedizin Hebelstrasse) erfolgreich seine Dissertationszeit ab. Das Thema seiner Doktorarbeit lautete: «Role of liver cells in bacterial antigen metabolism and MAIT cell activation».

Am 24. September 2020 konnte **Corina Frick** von der Forschungsgruppe «Translational Neuroimmunology» (Departement Biomedizin Hebelstrasse) ihre Dissertation mit Erfolg beenden. Sie befasste sich in ihrer Dissertation mit dem Thema: «Microfluidics for understanding basic aspects of directed immune cell migration and translational research».

Am 13. Oktober 2020 stellte sich **Fabian Otte** von der Forschungsgruppe «Molecular Virology» (Departement Biomedizin Petersplatz) den Fragen des Dissertationskomitees. Der Titel seiner Dissertation lautete: «HIV-1 reservoir formation, stability and dynamics during early therapy».

Am 23. Oktober 2020 stellte sich **Jordan Löliger** von der Forschungsgruppe «Immunobiology» (Departement Biomedizin Hebelstrasse) den Fragen des Dissertationskomitees. Der Titel seiner Dissertation hiess: «Metabolic and non-metabolic functions of PHGDH and their impact on T cell immunity».

Am 24. November 2020 konnte **Federica Zilli** von der Forschungsgruppe «Tumor Heterogeneity, Metastasis and Resistance» (Departement Biomedizin Hebelstrasse) ihre Dissertation mit Erfolg beenden. Sie befasste sich in ihrer Dissertation mit dem Thema: «UNBIASED PIGGYBAC MUTAGENESIS SCREENS IDENTIFY TUMORIGENIC AND METASTATIC PATHWAYS IN BREAST CANCER».

## Herzliche Gratulation!

*Wenn Sie möchten, dass die Dissertationen und Auszeichnungen erscheinen, bitten wir um vollständige Angaben. Unvollständige Informationen können nicht berücksichtigt werden.*

Cell Metabolism 32, 457–467, September 1, 2020 IF 21.567

# Memory CD8⁺ T Cells Balance Pro- and Anti-inflammatory Activity by Reprogramming Cellular Acetate Handling at Sites of Infection

**Maria L. Balmer,[1,13,14,*] Eric H. Ma,[2,3,4] Andrew J. Thompson,[5] Raja Epple,[1] Gunhild Unterstab,[1] Jonas Lötscher,[1] Philippe Dehio,[1] Christian M. Schürch,[6] Jan D. Warncke,[1] Gaëlle Perrin,[1] Anne-Kathrin Woischnig,[7] Jasmin Grählert,[1] Jordan Löliger,[1] Nadine Assmann,[1] Glenn R. Bantug,[1] Olivier P. Schären,[8] Nina Khanna,[7] Adrian Egli,[9,10] Lukas Bubendorf,[11] Katharina Rentsch,[12] Siegfried Hapfelmeier,[8] Russell G. Jones,[2,3,4] and Christoph Hess[1,5,15,*]**

**Summary**

Serum acetate increases upon systemic infection. Acutely, assimilation of acetate expands the capacity of memory CD8⁺ T cells to produce IFN-γ. Whether acetate modulates memory CD8⁺ T cell metabolism and function during pathogen re-encounter remains unexplored. Here we show that at sites of infection, high acetate concentrations are being reached, yet memory CD8⁺ T cells shut down the acetate assimilating enzymes ACSS1 and ACSS2. Acetate, being thus largely excluded from incorporation into cellular metabolic pathways, now had different effects, namely (1) directly activating glutaminase, thereby augmenting glutaminolysis, cellular respiration, and survival, and (2) suppressing TCR-triggered calcium flux, and consequently cell activation and effector cell function. *In vivo*, high acetate abundance at sites of infection improved pathogen clearance while reducing immunopathology. This indicates that, during different stages of the immune response, the same metabolite—acetate—induces distinct immunometabolic programs within the same cell type.

1 Department of Biomedicine, Immunobiology, University of Basel, 4031 Basel, Switzerland
2 Center for Cancer and Cell Biology, Van Andel Institute, Grand Rapids, MI, USA
3 Goodman Cancer Research Centre, McGill University, Montreal, QC, Canada
4 Department of Physiology, McGill University, Montreal, QC, Canada
5 Department of Medicine, CITIID, Jeffrey Cheah Biomedical Centre, University of Cambridge, Cambridge CB2 0AW, UK
6 Baxter Laboratory for Stem Cell Biology, Department of Microbiology and Immunology, Stanford University School of Medicine, 269 Campus Drive, Stanford, CA 94305, USA
7 Department of Biomedicine, Laboratory of Infection Biology, University of Basel and University Hospital Basel, 4031 Basel, Switzerland
8 Institute for Infectious Diseases, University of Bern, 3010 Bern, Switzerland
9 Clinical Microbiology, University Hospital Basel, 4031 Basel, Switzerland
10 Applied Microbiology Research, Department of Biomedicine, University of Basel, 4031 Basel, Switzerland
11 Institute for Pathology, University Hospital Basel, University of Basel, 4031 Basel, Switzerland
12 Department of Laboratory Medicine, University Hospital Basel, University of Basel, 4031 Basel, Switzerland
13 Present address: Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Bern University Hospital, University of Bern, 3010 Bern, Switzerland
14 Present address: Diabetes Center Berne, 3010 Bern, Switzerland
15 Lead Contact
* Correspondence: maria.balmer@unibas.ch (M.L.B.), chess@uhbs.ch (C.H.)
https://doi.org/10.1016/j.cmet.2020.07.004

Blood (2020) 136 (22): 2591–2595 IF 17.794

# MPN patients with low mutant *JAK2* allele burden show late expansion restricted to erythroid and megakaryocytic lineages

**Ronny Nienhold,[1] Peter Ashcroft,[2] Jakub Zmajkovic,[1] Shivam Rai,[1] Tata Nageswara Rao,[1] Beatrice Drexler,[3] Sara C. Meyer,[1,3] Pontus Lundberg,[1,3] Jakob R. Passweg,[3] Danijela Leković,[4] Vladan Čokić,[5] Sebastian Bonhoeffer,[2] and Radek C. Skoda[1]**

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic stem cell (HSC) diseases characterized by increased proliferation of erythroid, megakaryocytic, and/or myeloid lineages. The JAK2-V617F mutation can be found in .95% of polycythemia vera (PV) patients, and also in approximately one-half of patients with essential thrombocythemia (ET) or primary myelofibrosis (PMF). Somatic mutations in exon 12 of JAK2 are found in 3% to 5% of PV patients. Quantification of the JAK2-mutant allele burden, also called variant allele frequency (VAF), in DNA from peripheral blood granulocytes is used to monitor the size of the mutant clone. ET patients have lower JAK2 VAF than PMF or PV patients.7 Interestingly, some MPN patients display very low VAF, which calls into question why they develop MPNs if the clone is apparently unable to expand. We therefore studied MPN patients with JAK2 VAF ≤20%.

1 Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland;
2 Institute of Integrative Biology, Eidgenössische Technische Hochschule (ETH) Zürich, Zürich, Switzerland;
3 Division of Hematology, University Hospital Basel, Basel, Switzerland;
4 Clinic of Hematology, Clinical Center of Serbia, Belgrade, Serbia; and
5 Institute for Medical Research, University of Belgrade, Belgrade, Serbia
https://doi.org/10.1182/blood.2019002943

Nienhold, R., Ashcroft, P., Zmajkovic, J., Rai, S., Rao, N.R., Drexler, B., Meyer, S.C., Lundberg, P., Passweg, J.R., Leković, D., Čokić, V.P., Bonhoeffer, S., Skoda, R.C.
MPN patients with low mutant JAK2 allele burden show late expansion restricted to erythroid and megakaryocytic lineages. (2020) Blood, 136: 2591-95 [letter]

**Biosensors and Bioelectronics** 166 (2020) 112467 IF 10.257

# Sensing tissue engineered cartilage quality with Raman spectroscopy and statistical learning for the development of advanced characterization assays

**Laura J. Power[a,b], Claudia Fasolato[c,d], Andrea Barbero[b], David J. Wendt[a,b], Anke Wixmerten[b], Ivan Martin[a,b,*], M. Adelaide Asnaghi[b]**

**Abstract**

Nasal chondrocyte-derived engineered cartilage has been demonstrated to be safe and feasible for the treatment of focal cartilage lesions with promising preliminary evidences of efficacy. To ensure the quality of the products and processes, and to meet regulatory requirements, quality controls for identity, purity, and potency need to be developed. We investigated the use of Raman spectroscopy, a nondestructive analytical method that measures the chemical composition of samples, and statistical learning methods for the development of quality controls to quantitatively characterize the starting biopsy and final grafts. We provide a proof-of-concept to show how Raman spectroscopy can be used to identify the types of tissues found in a nasal *septal* biopsy, i.e., hyaline cartilage and perichondrium, for a novel tissue identity assay. The tissues could be classified with a sensitivity of 89% and specificity of 77%. We also show how clinically relevant and mature nasal chondrocyte-derived engineered cartilage can be assessed with Raman spectroscopy for the development of potency assays. The maturity of engineered grafts, based on the quantified ratio of glycosaminoglycans to DNA and histological score, could be accurately assessed ($R^2$ = 0.78 and 0.89, respectively, between predicted and measured values). Our results demonstrate the potential of Raman spectroscopy for the development of characterization assays for regenerative therapies that could be integrated into a good manufacturing practice-compliant process.

a Department of Biomedical Engineering, University of Basel, Gewerbestrasse 14-16, 4123, Allschwil, Switzerland
b Department of Biomedicine, University Hospital Basel, University of Basel, Hebelstrasse 20, 4031, Basel, Switzerland
c Department of Physics and Geology, Perugia University, Via Alessandro Pascoli, 06123, Perugia, Italy
d Department of Physics, University of Basel, Klingelbergstrasse 82, 4056, Basel, Switzerland
* Corresponding author. Department of Biomedicine, University Hospital Basel, University of Basel, Hebelstrasse 20, 4031, Basel, Switzerland. E-mail addresses: laura.power@uniabs.ch (L. J. Power), claudia.fasolato@unipg.it (C. Fasolato), andrea.barbero@usb.ch (A. Barbero), david.wendt@usb.ch (D. J. Wendt), anke.wixmerten@usb.ch (A. Wixmerten), ivan.martin@usb.ch (I. Martin), adelaide.asnaghi@usb.ch (M.A. Asnaghi).
https://doi.org/10.1016/j.bios.2020.112467

**Journal for ImmunoTherapy of Cancer** 2020;8:e000238 IF 10.252

# Fibroblast activation protein-targeted-4-1BB ligand agonist amplifies effector functions of intratumoral T cells in human cancer

**Marta Trüb,[1] Franziska Uhlenbrock,[1] Christina Claus,[2] Petra Herzig,[1] Martin Thelen,[3] Vaios Karanikas,[2] Marina Bacac,[2] Maria Amann,[2] Rosemarie Albrecht,[2] Claudia Ferrara-Koller,[2] Daniela Thommen,[4] Sacha Rothschield,[5] Spasenija Savic Prince,[6] Kirsten D Mertz,[7] Gieri Cathomas,[7] Robert Rosenberg,[8] Viola Heinzelmann-Schwarz,[9] Mark Wiese,[10] Didier Lardinois,[10] Pablo Umana,[2] Christian Klein,[2] Heinz Laubli,[5] Abhishek S Kashyap,[1] Alfred Zippelius[5]**

**Background** The costimulatory receptor 4-1BB (CD137, TNFRSF9) plays an important role in sustaining effective T cell immune responses and is investigated as target for cancer therapy. Systemic 4-1BB directed therapies elicit toxicity or low efficacy, which significantly hampered advancement of 4-1BB-based immunotherapy. Therefore, targeted delivery of 4-1BB agonist to the tumor side is needed for eliciting antitumor efficacy while avoiding systemic toxicity.

**Methods** We analyzed the immunostimulatory properties of a fibroblast activation protein (FAP)-targeted 4-1BB agonist (FAP-4-1BBL) by assessing tumor-infiltrating lymphocytes' (TIL) activity from patients with non-small cell lung cancer and epithelial ovarian cancer.

**Results** Combination treatment with FAP-4-1BBL and T cell receptor stimulation by either anti-CD3 or T cell bispecific antibodies significantly enhanced TIL activation and effector functions, including T cell proliferation, secretion of proinflammatory cytokines and cytotoxicity. Notably, costimulation with FAP-4-1BBL led to de novo secretion of interleukin (IL)−13. This was associated with cytokine-mediated tumor cell apoptosis, which was partially dependent on IL-13 alpha 1/2 receptors and STAT6 phosphorylation.

**Conclusions** Our study provides mechanistic insights into T cell stimulation induced by FAP-4-1BBL in primary human tumors and supports the investigation of FAP-4-1BBL compound in early clinical trials.

1 Laboratory of Cancer Immunology, Department of Biomedicine, University of Basel, Basel, Switzerland
2 Roche Innovation Center Zurich, Schlieren, Switzerland
3 Center for Molecular Medicine Cologne, University of Cologne, Cologne, Germany
4 Division of Molecular Oncology and Immunology, Oncode Institute, The Netherlands Cancer Institute, Amsterdam, The Netherlands
5 Medical Oncology, University Hospital Basel, Basel, Switzerland
6 Institute of Pathology, University Hospital Basel, Basel, Switzerland
7 Institute of Pathology, Cantonal Hospital Basel-Landschaft, Liestal, Switzerland
8 Department of Surgery, Cantonal Hospital Basel-Landschaft, Liestal, Switzerland
9 Department of Gynecology and Obstetrics, University Hospital Basel, Basel, Switzerland
10 Division of Thoracic Surgery, University Hospital Basel, Basel, Switzerland
MT, FU and CC contributed equally.
HL, ASK and AZ are joint senior authors.
doi:10.1136/jitc-2019-000238

Cancer Research 2020;80:3631–48 IF 9.727

# A Pygopus 2-Histone Interaction Is Critical for Cancer Cell Dedifferentiation and Progression in Malignant Breast Cancer

**Meera Saxena[1], Ravi K.R. Kalathur[1], Natalia Rubinstein[1], Andrea Vettiger[1], Nami Sugiyama[1], Melanie Neutzner[1], Mairene Coto-Llerena[2], Venkatesh Kancherla[2], Caner Ercan[2], Salvatore Piscuoglio[2], Jonas Fischer[1], Ernesta Fagiani[1], Claudio Cantù[3,4], Konrad Basler[3], and Gerhard Christofori[1]**

**Abstract**

Pygopus 2 (Pygo2) is a coactivator of Wnt/β-catenin signaling that can bind bi- or trimethylated lysine 4 of histone-3 (H3K4me$^{2/3}$) and participate in chromatin reading and writing. It remains unknown whether the Pygo2–H3K4me$^{2/3}$ association has a functional relevance in breast cancer progression *in vivo*. To investigate the functional relevance of histone-binding activity of Pygo2 in malignant progression of breast cancer, we generated a knock-in mouse model where binding of Pygo2 to H3K4me$^{2/3}$ was rendered ineffective. Loss of Pygo2–histone interaction resulted in smaller, differentiated, and less metastatic tumors, due, in part, to decreased canonical Wnt/β-catenin signaling. RNA- and ATAC-sequencing analyses of tumor-derived cell lines revealed downregulation of TGFβ signaling and upregulation of differentiation pathways such as PDGFR signaling. Increased differentiation correlated with a luminal cell fate that could be reversed by inhibition of PDGFR activity. Mechanistically, the Pygo2–histone interaction potentiated Wnt/β-catenin signaling, in part, by repressing the expression of Wnt signaling antagonists. Furthermore, Pygo2 and β-catenin regulated the expression of miR-29 family members, which, in turn, repressed PDGFR expression to promote dedifferentiation of wild-type Pygo2 mammary epithelial tumor cells. Collectively, these results demonstrate that the histone binding function of Pygo2 is important for driving dedifferentiation and malignancy of breast tumors, and loss of this binding activates various differentiation pathways that attenuate primary tumor growth and metastasis formation. Interfering with the Pygo2–H3K4me$^{2/3}$ interaction may therefore serve as an attractive therapeutic target for metastatic breast cancer.

**Significance:** Pygo2 represents a potential therapeutic target in metastatic breast cancer, as its histone-binding capability promotes β-catenin–mediated Wnt signaling and transcriptional control in breast cancer cell dedifferentiation, EMT, and metastasis.

1 Department of Biomedicine, University of Basel, Basel, Switzerland.
2 Institute of Pathology, University Hospital Basel, Basel, Switzerland.
3 Institute of Molecular Life Sciences, University of Zurich, Zurich, Switzerland.
4 Wallenberg Centre for Molecular Medicine Linköping; Department of Biomedical and Clinical Sciences, Faculty of Health Science, Linköping University, Linköping, Sweden.
R.K.R. Kalathur and N. Rubinstein contributed equally to this article.
Corresponding Authors: Gerhard Christofori, University of Basel, Mattenstrasse 28, Basel CH-4058, Switzerland. Phone: 41-61-207-3562; Fax: 41-61-207-3566; E-mail: gerhard.christofori@unibas.ch; and Meera Saxena, meera.saxena@unibas.ch
doi: 10.1158/0008-5472.CAN-19-2910

Genetics in Medicine volume 22(9), pages1524–1532(2020) IF 8.683

# Disease expression in juvenile polyposis syndrome: a retrospective survey on a cohort of 221 European patients and comparison with a literature-derived cohort of 473 *SMAD4/BMPR1A* pathogenic variant carriers

**Robert Blatter, PhD[1], Benjamin Tschupp, MMed[1], Stefan Aretz, MD[2,3], Inge Bernstein, MD[4] Chrystelle Colas, MD[5,16], D. Gareth Evans, MD[6], Maurizio Genuardi, MD[7,8], Frederik J. Hes, MD, PhD[9], Robert Hüneburg, MD[3,10], Heikki Järvinen, MD[11], Fiona Lalloo, MD[6], Gabriela Moeslein, MD[12], Laura Renkonen-Sinisalo, MD[11], Nicoletta Resta, PhD[13], Isabel Spier, MD[2,3], Dora Varvara, MD[13], Hans Vasen, MD[14], Andrew R. Latchford, MD[15] and Karl Heinimann, MD, PhD[1]**

**Purpose** Juvenile polyposis syndrome (JPS) is a rare, autosomal-dominantly inherited cancer predisposition caused in approximately 50% of cases by pathogenic germline variants in *SMAD4* and *BMPR1A*. We aimed to gather detailed clinical and molecular genetic information on JPS disease expression to provide a basis for management guidelines and establish open access variant databases.

**Methods** We performed a retrospective, questionnaire-based European multicenter survey on and established a cohort of *SMAD4/BMPR1A* pathogenic variant carriers from the medical literature.

**Results** We analyzed questionnaire-based data on 221 JPS patients (126 kindreds) from ten European centers and retrieved literature-based information on 473 patients. Compared with *BMPR1A* carriers, *SMAD4* carriers displayed anemia twice as often (58% vs. 26%), and exclusively showed overlap symptoms with hemorrhagic telangiectasia (32%) and an increased prevalence (39% vs. 13%) of gastric juvenile polyps. Cancer, reported in 15% of JPS patients (median age 41 years), mainly occurred in the colorectum (overall: 62%, *SMAD4*: 58%, *BMPR1A*: 88%) and the stomach (overall: 21%; *SMAD4*: 27%, *BMPR1A*: 0%).

**Conclusion** This comprehensive retrospective study on genotype–phenotype correlations in 694 JPS patients corroborates previous observations on JPS in general and *SMAD4* carriers in particular, facilitates recommendations for clinical management, and provides the basis for open access variant *SMAD4* and *BMPR1A* databases.

1 Institute for Medical Genetics and Pathology, University Hospital Basel, and Research Group Human Genomics, Department of Research, University of Basel, Basel, Switzerland;
2 Institute of Human Genetics, University Hospital Bonn, Bonn, Germany;
3 National Center for Hereditary Tumour Syndromes, University Hospital, Bonn, Germany;
4 Department of Surgical Gastroenterology, Aalborg University Hospital, Aalborg, and Danish HNPCC Registry, Department of Surgical Gastroenterology, Hvidovre University Hospital, Hvidovre, Denmark;
5 Department of Oncogenetics and Angiogenetics, Pitie-Salpetriere Hospital, Sorbonne Université, Paris, France;
6 Department of Genomic Medicine, Manchester Universities NHS Foundation Trust and Division of Evolution and Genomic Sciences, University of Manchester, Manchester, United Kingdom;
7 Fondazione Policlinico Universitario A. Gemelli IRCCS, UOC Genetica Medica, Rome, Italy;
8 Università Cattolica del Sacro Cuore, Istituto di Medicina Genomica, Rome, Italy;
9 Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands;
10 Department of Internal Medicine I, University Hospital Bonn, Bonn, Germany;
11 Department of Surgery, Helsinki University Central Hospital, Helsinki University, Helsinki, Finland;
12 Center for Hereditary Tumors, HELIOS Klinikum Wuppertal, University Witten-Herdecke, Wuppertal, Germany;
13 Division of Medical Genetics, Department of Biomedical Sciences and Human Oncology (DIMO), University of Bari "Aldo Moro", Bari, Italy;
14 Department of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, The Netherlands;
15 Polyposis Registry, St. Mark's Hospital, Harrow, United Kingdom;
16 Present address: Department of Genetics, Institut Curie, Université de Recherche Paris Sciences et Lettres, Paris, France.
Correspondence:
Andrew R. Latchford (andrew.latchford@nhs.net) or Karl Heinimann (karl.heinimann@usb.ch)
These authors contributed equally: Robert Blatter, Benjamin Tschupp.
doi.org/10.1038/s41436-020-0826-1

Leukemia Volume 34, pages 1487–1494(2020) IF 8.665

# Frequently asked questions regarding SARS-CoV-2 in cancer patients—recommendations for clinicians caring for patients with malignant diseases

**Marie von Lilienfeld-Toal[1,2], Jörg Janne Vehreschild[3,4,5], Oliver Cornely[4,5,6,7,8], Livio Pagano[9], Francesca Compagno[10], EHA Infectious Disease Scientific Working Group · Hans H. Hirsch[11,12,13]**

**Abstract**

Since early 2020, the SARS-CoV-2 pandemic has a massive impact on health care systems worldwide. Patients with malignant diseases are assumed to be at increased risk for a worse outcome of SARS-CoV-2 infection, and therefore, guidance regarding prevention and management of the infection as well as safe administration of cancer-therapy is required. Here, we provide recommendations for the management of patients with malignant disease in the times of COVID-19. These recommendations were prepared by an international panel of experts and then consented by the EHA Scientific Working Group on Infection in Hematology. The primary aim is to enable clinicians to provide optimal cancer care as safely as possible, since the most important protection for patients with malignant disease is the best-possible control of the underlying disease.

1 Klinik für Innere Medizin II, Abteilung für Hämatologie und Internistische Onkologie, Universitätsklinikum Jena, Jena, Germany
2 Leibniz-Institut für Infektionsbiologie und Naturstoff Forschung, Hans-Knöll Institut, Jena, Germany
3 Department of Internal Medicine, Hematology/Oncology, Goethe University Frankfurt, Frankfurt am Main, Germany
4 Department I of Internal Medicine, Excellence Center for Medical Mycology (ECMM), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany
5 German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany
6 Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany
7 Clinical Trials Centre Cologne (ZKS Köln), University of Cologne, Cologne, Germany
8 EHA Infectious Diseases Scientific Working Group, Cologne, Germany
9 Department of Hematology, Fondazione Policlinico Universitario A. Gemelli—IRCCS, Universita Cattolica del Sacro Cuore, Rome, Italy
10 Pediatric Hematology Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
11 Clinical Virology, Laboratory Medicine, University Hospital Basel, Basel, Switzerland
12 Transplantation & Clinical Virology, Department Biomedicine, University of Basel, Basel, Switzerland
13 Infectious Diseases & Hospital Epidemiology, University Hospital Basel, Basel, Switzerland
Correspondence: Marie von Lilienfeld-Toal Mail: Marie.von_Lilienfeld-Toal@med.uni-jena.de
doi.org/10.1038/s41375-020-0832-y

Cell Reports 32, 108105, September 8, 2020 IF 8.109

# Hypoxia Triggers the Intravasation of Clustered Circulating Tumor Cells

**Cinzia Donato,[1] Leo Kunz,[2] Francesc Castro-Giner,[1,3] Aino Paasinen-Sohns,[1] Karin Strittmatter,[1] Barbara Maria Szczerba,[1] Ramona Scherrer,[1] Nunzia Di Maggio,[4] Wolf Heusermann,[5] Oliver Biehlmaier,[5] Christian Beisel,[2] Marcus Vetter,[6,7,8] Christoph Rochlitz,[7,8] Walter Paul Weber,[8,9] Andrea Banfi,[4] Timm Schroeder,[2] and Nicola Aceto[1,10,*]**

**Summary**

Circulating tumor cells (CTCs) are shed from solid cancers in the form of single or clustered cells, and the latter display an extraordinary ability to initiate metastasis. Yet, the biological phenomena that trigger the shedding of CTC clusters from a primary cancerous lesion are poorly understood. Here, when dynamically labeling breast cancer cells along cancer progression, we observe that the majority of CTC clusters are undergoing hypoxia, while single CTCs are largely normoxic. Strikingly, we find that vascular endothelial growth factor (VEGF) targeting leads to primary tumor shrinkage, but it increases intra-tumor hypoxia, resulting in a higher CTC cluster shedding rate and metastasis formation. Conversely, pro-angiogenic treatment increases primary tumor size, yet it dramatically suppresses the formation of CTC clusters and metastasis. Thus, intra-tumor hypoxia leads to the formation of clustered CTCs with high metastatic ability, and a pro-angiogenic therapy suppresses metastasis formation through prevention of CTC cluster generation.

1 Department of Biomedicine, Cancer Metastasis Laboratory, University of Basel and University Hospital Basel, 4058 Basel, Switzerland
2 Department of Biosystems Science and Engineering, ETH Z€urich, 4058 Basel, Switzerland
3 SIB Swiss Institute of Bioinformatics, 1015 Lausanne, Switzerland
4 Department of Biomedicine, Cell and Gene Therapy Laboratory, University of Basel and University Hospital Basel, 4056 Basel, Switzerland
5 IMCF Imaging Core Facility Biozentrum, University of Basel, 4056 Basel, Switzerland
6 Gynecologic Cancer Center, University Hospital Basel, 4056 Basel, Switzerland
7 Department of Medical Oncology, University Hospital Basel, 4056 Basel, Switzerland
8 Breast Cancer Center, University Hospital Basel, 4056 Basel, Switzerland
9 Department of Surgery, University of Basel and University Hospital Basel, 4056 Basel, Switzerland
10 Lead Contact
*Correspondence: nicola.aceto@unibas.ch
https://doi.org/10.1016/j.celrep.2020.108105

Cell Reports 32, 108070, August 25, 2020 IF 8.109

# Sequential Organization of Critical Periods in the Mouse Auditory System

**Mari Nakamura,[1] Patricia Valerio,[1] Stitipragyan Bhumika,[1] and Tania Rinaldi Barkat[1,2,*]**

**Summary**

Critical periods—time windows of heightened plasticity in postnatal development—are specific to sensory features and are asynchronous. Whether they are timed by a temporally precise developmental program or are sequentially organized is not known. We use electrophysiology and molecular or sensory manipulations to elucidate the biological constraints on critical period timing. Passive sound exposure shows that the cortical representations of two sound features, pure tone and frequency-modulated sweep (FMS), are not influencing each other. Enhancing inhibition before the critical period for pure tone accelerates it without changing the critical period for FMS. Similarly, delaying the critical period for pure tone with white noise exposure has no effect on the critical period for FMS. However, the critical period for FMS starts only if the one for pure tone has occurred. Together, these results indicate that distinct critical periods, although sequentially organized, can be temporally shifted independently of each other.

1 Department of Biomedicine, Basel University, 4056 Basel, Switzerland
2 Lead Contact
* Correspondence: tania.barkat@unibas.ch
https://doi.org/10.1016/j.celrep.2020.108070

Cell Reports 32, 107979, August 4, 2020 IF 8.109

# Lysophosphatidic Acid-Mediated GPR35 Signaling in CX3CR1$^{+}$ Macrophages Regulates Intestinal Homeostasis

**Berna Kaya,[1] Cristian Doñas,[2,3] Philipp Wuggenig,[1] Oscar E. Diaz,[2,3] Rodrigo A. Morales,[2,3] Hassan Melhem,[1] Swiss IBD. Cohort Investigators, Pedro P. Hernández,[4] Tanay Kaymak,[1] Srustidhar Das[2,3] Petr Hruz,[5] Yannick Franc,[6] Florian Geier,[1,7] C. Korcan Ayata,[1] Eduardo J. Villablanca,[2,3,8,9,*] and Jan Hendrik Niess[1,5,8,*]**

**Summary**

Single-nucleotide polymorphisms in the gene encoding G protein-coupled receptor 35 (GPR35) are associated with increased risk of inflammatory bowel disease. However, the mechanisms by which GPR35 modulates intestinal immune homeostasis remain undefined. Here, integrating zebrafish and mouse experimental models, we demonstrate that intestinal *Gpr35* expression is microbiota dependent and enhanced upon inflammation. Moreover, murine GPR35$^{+}$ colonic macrophages are characterized by enhanced production of pro-inflammatory cytokines. We identify lysophosphatidic acid (LPA) as a potential endogenous ligand produced during intestinal inflammation, acting through GPR35 to induce tumor necrosis factor (*Tnf*) expression in macrophages. Mice lacking *Gpr35* in CX3CR1$^{+}$ macrophages aggravate colitis when exposed to dextran sodium sulfate, which is associated with decreased transcript levels of the corticosterone-generating gene *Cyp11b1* and macrophage-derived *Tnf*. Administration of TNF in these mice restores *Cyp11b1* expression and intestinal corticosterone production and ameliorates DSS-induced colitis. Our findings indicate that LPA signals through GPR35 in CX3CR1$^{+}$ macrophages to maintain TNF-mediated intestinal homeostasis.

1 Department of Biomedicine, University of Basel, 4031 Basel, Switzerland
2 Division of Immunology and Allergy, Department of Medicine, Solna, Karolinska Institutet and University Hospital, 17176 Stockholm, Sweden
3 Center for Molecular Medicine (CMM), 17176 Stockholm, Sweden
4 Institut Curie, PSL Research University, INSERM U934/CNRS UMR3215, Development and Homeostasis of Mucosal Tissues Group, 75005 Paris, France
5 University Center for Gastrointestinal and Liver Diseases, St. Clara Hospital and University Hospital of Basel, 4031 Basel, Switzerland
6 Center for Primary Care and Public Health (Unisante´ ), University of Lausanne, 1011 Lausanne, Switzerland
7 Swiss Institute of Bioinformatics, 4031 Basel, Switzerland
8 These authors contributed equally
9 Lead Contact
* Correspondence: eduardo.villablanca@ki.se (E.J.V.), janhendrik.niess@unibas.ch (J.H.N.)
https://doi.org/10.1016/j.celrep.2020.107979

Oncogene Volume 39, pages 4728–4740(2020) IF 7.971

# A dual role of Irf1 in maintaining epithelial identity but also enabling EMT and metastasis formation of breast cancer cells

**Nathalie Meyer-Schaller[1], Stefanie Tiede[1], Robert Ivanek[1,2], Maren Diepenbruck[1], Gerhard Christofori[1]**

**Abstract**

An epithelial to mesenchymal transition (EMT) is an embryonic dedifferentiation program which is aberrantly activated in cancer cells to acquire cellular plasticity. This plasticity increases the ability of breast cancer cells to invade into surrounding tissue, to seed metastasis at distant sites and to resist to chemotherapy. In this study, we have observed a higher expression of interferon-related factors in basal-like and claudin-low subtypes of breast cancer in patients, known to be associated with EMT. Notably, Irf1 exerts essential functions during the EMT process, yet it is also required for the maintenance of an epithelial differentiation status of mammary gland epithelial cells: RNAi-mediated ablation of Irf1 in mammary epithelial cells results in the expression of mesenchymal factors and Smad transcriptional activity. Conversely, ablation of Irf1 during TGFβ-induced EMT prevents a mesenchymal transition and stabilizes the expression of E-cadherin. In the basal-like murine breast cancer cell line 4T1, RNAi-mediated ablation of Irf1 reduces colony formation and cell migration in vitro and shedding of circulating tumor cells and metastasis formation in vivo. This context-dependent dual role of Irf1 in the regulation of epithelial-mesenchymal plasticity provides important new insights into the functional contribution and therapeutic potential of interferon-regulated factors in breast cancer.

1 Department of Biomedicine, University of Basel, 4058 Basel, Switzerland
2 Swiss Institute of Bioinformatics, 4058 Basel, Switzerland
Correspondence:
Nathalie Meyer-Schaller Mail: nathalie.meyer-schaller@unibas.ch,
Gerhard Christofori Mail: gerhard.christofori@unibas.ch
https://doi.org/10.1038/s41388-020-1326-0

Neuropsychopharmacology (2020) 45:462–471 IF 6.751

# Distinct acute effects of LSD, MDMA, and D-amphetamine in healthy subjects

**Friederike Holze[1], Patrick Vizeli[1], Felix Müller[2], Laura Ley[1], Raoul Duerig[1], Nimmy Varghese[2,3], Anne Eckert[2,3], Stefan Borgwardt[2] and Matthias E. Liechti[1]**

**Abstract**

Lysergic acid diethylamide (LSD) is a classic psychedelic, 3,4-methylenedioxymethamphetamine (MDMA) is an empathogen, and D-amphetamine is a classic stimulant. All three substances are used recreationally. LSD and MDMA are being investigated as medications to assist psychotherapy, and D-amphetamine is used for the treatment of attention-deficit/hyperactivity disorder. All three substances induce distinct acute subjective effects. However, differences in acute responses to these prototypical psychoactive substances have not been characterized in a controlled study. We investigated the acute autonomic, subjective, and endocrine effects of single doses of LSD (0.1 mg), MDMA (125 mg), D-amphetamine (40 mg), and placebo in a randomized, double-blind, cross-over study in 28 healthy subjects. All of the substances produced comparable increases in hemodynamic effects, body temperature, and pupil size, indicating equivalent autonomic responses at the doses used. LSD and MDMA increased heart rate more than D-amphetamine, and D-amphetamine increased blood pressure more than LSD and MDMA. LSD induced significantly higher ratings on the 5 Dimensions of Altered States of Consciousness scale and Mystical Experience Questionnaire than MDMA and D-amphetamine. LSD also produced greater subjective drug effects, ego dissolution, introversion, emotional excitation, anxiety, and inactivity than MDMA and D-amphetamine. LSD also induced greater impairments in subjective ratings of concentration, sense of time, and speed of thinking compared with MDMA and D-amphetamine. MDMA produced greater ratings of good drug effects, liking, high, and ego dissolution compared with D-amphetamine. D-amphetamine increased ratings of activity and concentration compared with LSD. MDMA but not LSD or D-amphetamine increased plasma concentrations of oxytocin. None of the substances altered plasma concentrations of brain-derived neurotrophic factor. These results indicate clearly distinct acute effects of LSD, MDMA, and D-amphetamine and may assist the dose-finding in substance-assisted psychotherapy research.

1 Department of Biomedicine and Department of Clinical Research, Division of Clinical Pharmacology and Toxicology, University Hospital Basel, University of Basel, Basel 4056, Switzerland;
2 Psychiatric University Hospital (UPK), University of Basel, Basel 4012, Switzerland and
3 Transfaculty Research Platform Molecular and Cognitive Neuroscience, University of Basel, Basel, Switzerland
Correspondence: Matthias E. Liechti (matthias.liechti@usb.ch)
https://doi.org/10.1038/s41386-019-0569-3

Cell Proliferation 2019;00:e12653 IF 5.753

# Bioreactor-manufactured cartilage grafts repair acute and chronic osteochondral defects in large animal studies

**Andreja Vukasovic[1], Maria Adelaide Asnaghi[2], Petar Kostesic[3], Helen Quasnichka[4], Carmine Cozzolino[5], Maja Pusic[1], Lauren Hails[6], Nuala Trainor[6], Christian Krause[7], Elisa Figallo[8], Giuseppe Filardo[9], Elizaveta Kon[9], Anke Wixmerten[2], Drazen Maticic[3], Graziella Pellegrini[5], Wael Kafienah[4], Damir Hudetz[10], Tim Smith[6], Ivan Martin[2,11,12], Alan Ivkovic[10], David Wendt[2,11,12,13]**

**Objectives** Bioreactor-based production systems have the potential to overcome limitations associated with conventional tissue engineering manufacturing methods, facilitating regulatory compliant and cost-effective production of engineered grafts for widespread clinical use. In this work, we established a bioreactor-based manufacturing system for the production of cartilage grafts.

**Materials & Methods** All bioprocesses, from cartilage biopsy digestion through the generation of engineered grafts, were performed in our bioreactor-based manufacturing system. All bioreactor technologies and cartilage tissue engineering bioprocesses were transferred to an independent GMP facility, where engineered grafts were manufactured for two large animal studies.

**Results** The results of these studies demonstrate the safety and feasibility of the bioreactor-based manufacturing approach. Moreover, grafts produced in the manufacturing system were first shown to accelerate the repair of acute osteochondral defects, compared to cell-free scaffold implants. We then demonstrated that grafts produced in the system also facilitated faster repair in a more clinically relevant chronic defect model. Our data also suggested that bioreactor-manufactured grafts may result in a more robust repair in the longer term.

**Conclusion** By demonstrating the safety and efficacy of bioreactor-generated grafts in two large animal models, this work represents a pivotal step towards implementing the bioreactor-based manufacturing system for the production of human cartilage grafts for clinical applications.

1 Department of Histology and Embriology, School of Medicine, University of Zagreb, Zagreb, Croatia
2 Department of Biomedicine, University Hospital Basel, University of Basel, Basel, Switzerland
3 Clinic for Surgery, Ophthalmology & Orthopaedics, Veterinary Faculty, University of Zagreb, Zagreb, Croatia
4 School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK
5 Holostem Terapie Avanzate SRL, Modena, Italy
6 Octane Biotech, Kingston, Ontario, Canada
7 PreSens Precision Sensing GmbH, Regensburg, Germany
8 Fin-Ceramica Faenza SPA, Bologna, Italy
9 IRCCS, Istituto Ortopedico Rizzoli, Bologna, Italy
10 Department of Orthopaedic Surgery, University Hospital "Sveti Duh," Zagreb, Croatia
11 Department of Surgery, University Hospital Basel, University of Basel, Basel, Switzerland
12 Department of Biomedical Engineering, University Hospital Basel, University of Basel, Basel, Switzerland
13 Cellec Biotek AG, Basel, Switzerland
Correspondence:
Ivan Martin, University Hospital Basel, Hebelstrasse 20, ZLF, Room 405, 4031 Basel, Switzerland.
Email: ivan.martin@usb.ch
Andreja Vukasovic and Maria Adelaide Asnaghi are Equally contributing authors.
https://doi.org/10.1111/cpr.12653

Cancer Immunology, Immunotherapy Volume 69, pages1505–1517(2020) IF 5.442

# PD-1$^+$ natural killer cells in human non-small cell lung cancer can be activated by PD-1/PD-L1 blockade

**Marcel P. Trefny[1], Monika Kaiser[1], Michal A. Stanczak[1], Petra Herzig[1], Spasenija Savic[3], Mark Wiese[4], Didier Lardinois[4], Heinz Läubli[1,2], Franziska Uhlenbrock[1], Alfred Zippelius[1,2]**

**Abstract**

Natural killer (NK) cells are critically involved in anti-tumor immunity by targeting tumor cells. In this study, we show that intratumoral NK cells from NSCLC patients expressed elevated levels of the immune checkpoint receptor PD-1 on their cell surface. In contrast to the expression of activating receptors, PD-1$^+$ NK cells co-expressed more inhibitory receptors compared to PD-1$^-$ NK cells. Intratumoral NK cells were less functional compared to peripheral NK cells, and this dysfunction correlated with PD-1 expression. Tumor cells expressing PD-L1 inhibited the functionality of PD-1$^+$ NK cells in ex vivo models and induced PD-1 clustering at the immunological synapse between NK cells and tumor cells. Notably, treatment with PD-1 blockade was able to reverse PD-L1-mediated inhibition of PD-1$^+$ NK cells. Our findings highlight the therapeutic potential of PD-1$^+$ NK cells in immune checkpoint blockade and could guide the development of NK cell-stimulating agents in combination with PD-1 blockade.

1 Laboratory of Cancer Immunology, Department of Biomedicine, University of Basel and University Hospital of Basel, Hebelstrasse 20, 4031 Basel, Switzerland
2 Department of Internal Medicine, Division of Oncology, University Hospital Basel, Basel, Switzerland
3 Institute of Pathology, University Hospital Basel, Basel, Switzerland
4 Department of Surgery, University Hospital Basel, Basel, Switzerland
Franziska Uhlenbrock and Alfred Zippelius these authors jointly directed this work.
Correspondence:
Marcel P. Trefny Mail: marcel.trefny@unibas.ch
Alfred Zippelius Mail: alfred.zippelius@usb.ch
https://doi.org/10.1007/s00262-020-02558-z

Human Molecular Genetics 2020, Vol. 29, No. 8 1330–1339 IF 5.101

# Molecular basis of impaired extraocular muscle function in a mouse model of congenital myopathy due to compound heterozygous *Ryr1* mutations

**Jan Eckhardt[1], Christoph Bachmann[1], Sofia Benucci[1], Moran Elbaz[1], Alexis Ruiz[1], Francesco Zorzato[1,2] and Susan Treves[1,2,*]**

**Abstract**

Mutations in the *RYR1* gene are the most common cause of human congenital myopathies, and patients with recessive mutations are severely affected and often display ptosis and/or ophthalmoplegia. In order to gain insight into the mechanism leading to extraocular muscle (EOM) involvement, we investigated the biochemical, structural and physiological properties of eye muscles from mouse models we created knocked-in for *Ryr1* mutations. *Ex vivo* force production in EOMs from compound heterozygous RyR1p.Q1970fsX16+p.A4329D mutant mice was significantly reduced compared with that observed in wild-type, single heterozygous mutant carriers or homozygous RyR1p.A4329D mice. The decrease in muscle force was also accompanied by approximately a 40% reduction in RyR1 protein content, a decrease in electrically evoked calcium transients, disorganization of the muscle ultrastructure and a decrease in the number of calcium release units. Unexpectedly, the superfast and ocular-muscle-specific myosin heavy chain-EO isoform was almost undetectable in RyR1p.Q1970fsX16+p.A4329D mutant mice.

The results of this study show for the first time that the EOM phenotype caused by the RyR1p.Q1970fsX16+p.A4329D compound heterozygous Ryr1 mutations is complex and due to a combination of modifications including a direct effect on the macromolecular complex involved in calcium release and indirect effects on the expression of myosin heavy chain isoforms.

1 Departments of Biomedicine, Basel University Hospital, 4031 Basel, Switzerland and
2 Department of Life Science and Biotechnology, University of Ferrara, 44100 Ferrara, Italy
* To whom correspondence should be addressed at:
Department of Biomedicine, Hebelstrasse 20, 4031 Basel, Switzerland. Tel: +41 612652373;
Fax: +41 612653704; Email: susan.treves@unibas.ch

Frontiers in Immunology July 2020 | Volume 11 | Article 1522 IF 5.085

# Complement C1q Enhances Primary Hemostasis

**Claudia Donat[1*], Robert Kölm[1], Kinga Csorba[1], Eylul Tuncer[1], Dimitrios A. Tsakiris[2] and Marten Trendelenburg[1,3]**

The cross-talk between the inflammatory complement system and hemostasis is becoming increasingly recognized. The interaction between complement C1q, initiation molecule of the classical pathway, and von Willebrand factor (vWF), initiator molecule of primary hemostasis, has been shown to induce platelet rolling and adhesion *in vitro*. As vWF disorders result in prolonged bleeding, a lack of C1q as binding partner for vWF might also lead to an impaired hemostasis. Therefore, this study aimed to investigate the *in vivo* relevance of C1q-dependent binding of vWF in hemostasis. For this purpose, we analyzed parameters of primary and secondary hemostasis and performed bleeding experiments in wild type (WT) and C1q-deficient (*C1qa*$^{-/-}$) mice, with reconstitution experiments of C1q in the latter. Bleeding tendency was examined by quantification of bleeding time and blood loss. First, we found that complete blood counts and plasma vWF levels do not differ between *C1qa*$^{-/-}$ mice and WT mice. Moreover, platelet aggregation tests indicated that the platelets of both strains of mice are functional. Second, while the prothrombin time was comparable between both groups, the activated partial thromboplastin time was shorter in *C1qa*$^{-/-}$ mice. In contrast, tail bleeding times of *C1qa*$^{-/-}$ mice were prolonged accompanied by an increased blood loss. Upon reconstitution of *C1qa*$^{-/-}$ mice with C1q, parameters of increased bleeding could be reversed. In conclusion, our data indicate that C1q, a molecule of the first-line of immune defense, actively participates in primary hemostasis by promoting arrest of bleeding. This observation might be of relevance for the understanding of thromboembolic complications in inflammatory disorders, where excess of C1q deposition is observed.

1 Laboratory of Clinical Immunology, Department of Biomedicine, University of Basel, Basel, Switzerland,
2 Department of Diagnostic Hematology, University Hospital Basel, Basel, Switzerland,
3 Division of Internal Medicine, University Hospital Basel, Basel, Switzerland
* Correspondence: Claudia Donat Mail: claudia.donat@unibas.ch
doi: 10.3389/fimmu.2020.01522

Clinical Epigenetics Volume 11, Article number: 196 (2019) IF 5.028

# DNA methylation instability by BRAF-mediated TET silencing and lifestyle-exposure divides colon cancer pathways

**Faiza Noreen[1,2], Taya Küng[1], Luigi Tornillo[3], Hannah Parker[4], Miguel Silva[5], Stefan Weis[1], Giancarlo Marra[4], Roland Rad[5], Kaspar Truninger[1,6*] and Primo Schär[1*]**

**Background** Aberrations in DNA methylation are widespread in colon cancer (CC). Understanding origin and progression of DNA methylation aberrations is essential to develop effective preventive and therapeutic strategies. Here, we aimed to dissect CC subtype-specific methylation instability to understand underlying mechanisms and functions.

**Methods** We have assessed genome-wide DNA methylation in the healthy normal colon mucosa (HNM), precursor lesions and CCs in a first comprehensive study to delineate epigenetic change along the process of colon carcinogenesis. Mechanistically, we used stable cell lines, genetically engineered mouse model of mutant $BRAF^{V600E}$ and molecular biology analysis to establish the role of $BRAF^{V600E}$-mediated-TET inhibition in CpG-island methylator phenotype (CIMP) initiation.

**Results** We identified two distinct patterns of CpG methylation instability, determined either by age–lifestyle (CC-neutral CpGs) or genetically (CIMP-CpGs). CC-neutral-CpGs showed age-dependent hypermethylation in HNM, all precursors, and CCs, while CIMP-CpGs showed hypermethylation specifically in sessile serrated adenomas/polyps (SSA/Ps) and CIMP-CCs. *$BRAF^{V600E}$*-mutated CCs and precursors showed a significant downregulation of *TET1* and *TET2* DNA demethylases. Stable expression of *$BRAF^{V600E}$* in nonCIMP CC cells and in a genetic mouse model was sufficient to repress TET1/TET2 and initiate hypermethylation at CIMP-CpGs, reversible by *$BRAF^{V600E}$* inhibition. *$BRAF^{V600E}$*-driven CIMP-CpG hypermethylation occurred at genes associated with established CC pathways, effecting functional changes otherwise achieved by genetic mutation in carcinogenesis.

**Conclusions** Hence, while age–lifestyle-driven hypermethylation occurs generally in colon carcinogenesis, *$BRAF^{V600E}$*-driven hypermethylation is specific for the "serrated" pathway. This knowledge will advance the use of epigenetic biomarkers to assess subgroup-specific CC risk and disease progression.

1 Department of Biomedicine, University of Basel, Mattenstrasse 28, CH-4058 Basel, Switzerland
2 Swiss Institute of Bioinformatics, 4053, Basel, Switzerland
3 Institute of Pathology, University Hospital Basel, 4056, Basel, Switzerland
4 Institute of Molecular Cancer Research, University of Zurich, 8057, Zurich, Switzerland
5 Department of Medicine II, Klinikum Rechts der Isar, Technische Universität München, 81675, Munich, Germany
6 Gastroenterologie Oberaargau, CH-4900, Langenthal, Switzerland
* Correspondence: k.truninger@gastroenterologie-oberaargau.ch; primo.schaer@unibas.ch
https://doi.org/10.1186/s13148-019-0791-1

The Journal of Infectious Diseases Vol. 222, Issue 8, 15.10.2020, Pages 1270–1279 IF 5.022

# Epidemiology of Severe Acute Respiratory Syndrome Coronavirus 2 Emergence Amidst Community-Acquired Respiratory Viruses

**Karoline Leuzinger,[1,2] Tim Roloff,[3,4] Rainer Gosert,[1] Kirstin Sogaard,[3,4] Klaudia Naegele,[1] Katharina Rentsch,[5] Roland Bingisser,[6] Christian H. Nickel,[6] Hans Pargger,[7] Stefano Bassetti,[8] Julia Bielicki,[9] Nina Khanna,[10], Sarah Tschudin Sutter,[10] Andreas Widmer,[10] Vladimira Hinic,[4] Manuel Battegay,[10] Adrian Egli,[3,4,a] and Hans H. Hirsch[1,2,10,a]**

**Background** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China as the cause of coronavirus disease 2019 in December 2019 and reached Europe by late January 2020, when community-acquired respiratory viruses (CARVs) are at their annual peak. We validated the World Health Organization (WHO)–recommended SARS-CoV-2 assay and analyzed the epidemiology of SARS-CoV-2 and CARVs.

**Methods** Nasopharyngeal/oropharyngeal swabs (NOPS) from 7663 patients were prospectively tested by the Basel S-gene and WHO-based E-gene (Roche) assays in parallel using the Basel N-gene assay for confirmation. CARVs were prospectively tested in 2394 NOPS by multiplex nucleic acid testing, including 1816 (75%) simultaneously for SARS-CoV-2.

**Results** The Basel S-gene and Roche E-gene assays were concordant in 7475 cases (97.5%) including 825 (11%) SARS-CoV-2 positives. In 188 (2.5%) discordant cases, SARS-CoV-2 loads were significantly lower than in concordant positive ones and confirmed in 105 (1.4%). Adults were more frequently SARS-CoV-2 positive, whereas children tested more frequently CARV positive. CARV coinfections with SARS-CoV-2 occurred in 1.8%. SARS-CoV-2 replaced CARVs within 3 weeks, reaching 48% of all detected respiratory viruses followed by rhinovirus/enterovirus (13%), influenza virus (12%), coronavirus (9%), respiratory syncytial virus (6%), and metapneumovirus (6%).

**Conclusions** Winter CARVs were dominant during the early SARS-CoV-2 pandemic, impacting infection control and treatment decisions, but were rapidly replaced, suggesting competitive infection. We hypothesize that preexisting immune memory and innate immune interference contribute to the different SARS-CoV-2 epidemiology among adults and children.

1 Clinical Virology, Laboratory Medicine, University Hospital Basel, Basel, Switzerland,
2 Transplantation and Clinical Virology, Department of Biomedicine, University of Basel, Basel, Switzerland,
3 Applied Microbiology Research, Laboratory Medicine, Department of Biomedicine, University of Basel, Basel, Switzerland,
4 Clinical Bacteriology and Mycology, Laboratory Medicine, University Hospital Basel, Basel, Switzerland,
5 Clinical Chemistry, Laboratory Medicine, University Hospital Basel, Basel, Switzerland,
6 Emergency Medicine, University Hospital Basel, Basel, Switzerland,
7 Intensive Care Unit, University Hospital Basel, Basel, Switzerland,
8 Internal Medicine, University Hospital Basel, Basel, Switzerland,
9 Pediatric Infectious Diseases and Hospital Epidemiology, University Children's Hospital Basel, Basel, Switzerland, and
10 Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland
a A. E. and H. H. H. contributed equally to this work.
Correspondence: Hans H. Hirsch, MD, MSc, Transplantation and Clinical Virology, Department of Biomedicine, University of Basel, Petersplatz 10, 4009 Basel, Switzerland (hans.hirsch@unibas.ch).
DOI: 10.1093/infdis/jiaa464

The FASEB Journal 2020;00:1–18 IF 4.966

# DNA aptamers against the DUX4 protein reveal novel therapeutic implications for FSHD

**Christian Klingler[1,2], Jon Ashley[1,2,3], Ke Shi[4], Adeline Stiefvater[1,2], Michael Kyba[5,6], Michael Sinnreich[1,2], Hideki Aihara[4], Jochen Kinter[1,2]**

**Abstract**

Aberrant expression of the transcription factor double homeobox protein 4 (DUX4) can lead to a number of diseases including facio-scapulohumeral muscular dystrophy (FSHD), acute lymphoblastic leukemia, and sarcomas. Inhibition of DUX4 may represent a therapeutic strategy for these diseases. By applying Systematic Evolution of Ligands by EXponential Enrichment (SELEX), we identified aptamers against DUX4 with specific secondary structural elements conveying high affinity to DUX4 as assessed by fluorescence resonance energy transfer and fluorescence polarization techniques. Sequences analysis of these aptamers revealed the presence of two consensus DUX4 motifs in a reverse complementary fashion forming hairpins interspersed with bulge loops at distinct positions that enlarged the binding surface with the DUX4 protein, as determined by crystal structure analysis. We demonstrate that insertion of specific structural elements into transcription factor binding oligonucleotides can enhance specificity and affinity.

1 Neuromuscular Research Group, Department of Neurology, University Hospital Basel, Basel, Switzerland
2 Neuromuscular Research Group, Department of Biomedicine, University Hospital Basel, Basel, Switzerland
3 Department of Health Technology, Technical University of Denmark, Kgs Lyngby, Denmark
4 Department of Biochemistry, Molecular Biology, and Biophysics, University of Minnesota, Minneapolis, MN, USA
5 Lillehei Heart Institute, University of Minnesota, Minneapolis, MN, USA
6 Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA
Correspondence: Michael Sinnreich, Neuromuscular Research Group, Department of Neurology, University Hospital Basel, Basel CH 4031, Switzerland. Email: michael.sinnreich@unibas.ch
DOI: 10.1096/fj.201902696

Int. J. Molecular Sciences 2020, 21, 7233 IF 4.556

# Orthotopic Bone Formation by Streamlined Engineering and Devitalization of Human Hypertrophic Cartilage

**Sébastien Pigeot[1], Paul Emile Bourgine[1,†], Jaquiery Claude[2], Celeste Scotti[3,4], Adam Papadimitropoulos[1], Atanas Todorov[1], Christian Epple[2], Giuseppe M. Peretti[4,5] and Ivan Martin[1,2,*]**

**Abstract**

Most bones of the human body form and heal through endochondral ossification, whereby hypertrophic cartilage (HyC) is formed and subsequently remodeled into bone. We previously demonstrated that HyC can be engineered from human mesenchymal stromal cells (hMSC), and subsequently devitalized by apoptosis induction. The resulting extracellular matrix (ECM) tissue retained osteoinductive properties, leading to ectopic bone formation. In this study, we aimed at engineering and devitalizing upscaled quantities of HyC ECM within a perfusion bioreactor, followed by in vivo assessment in an orthotopic bone repair model. We hypothesized that the devitalized HyC ECM would outperform a clinical product currently used for bone reconstructive surgery. Human MSC were genetically engineered with a gene cassette enabling apoptosis induction upon addition of an adjuvant. Engineered hMSC were seeded, differentiated, and devitalized within a perfusion bioreactor. The resulting HyC ECM was subsequently implanted in a 10-mm rabbit calvarial defect model, with processed human bone (Maxgraft®) as control. Human MSC cultured in the perfusion bioreactor generated a homogenous HyC ECM and were efficiently induced towards apoptosis. Following six weeks of in vivo implantation, microcomputed tomography and histological analyses of the defects revealed an increased bone formation in the defects filled with HyC ECM as compared to Maxgraft®. This work demonstrates the suitability of engineered devitalized HyC ECM as a bone substitute material, with a performance superior to a state-of-the-art commercial graft. Streamlined generation of the devitalized tissue transplant within a perfusion bioreactor is relevant towards standardized and automated manufacturing of a clinical product.

1 Department of Biomedicine, University Hospital Basel, University of Basel, 4031 Basel, Switzerland
2 Department of Surgery, University Hospital Basel, University of Basel, 4031 Basel, Switzerland
3 Novartis Institutes for Biomedical Research, 4056 Basel, Switzerland
4 IRCCS Istituto Ortopedico Galeazzi, 20161 Milan, Italy
5 Department of Biomedical Sciences for Health, University of Milan, 20133 Milan, Italy
* Author to whom correspondence should be addressed.
† Current affiliation: Wallenberg Center for Molecular Medicine, Lund University, 221 84 Lund, Sweden.
doi:10.3390/ijms21197233

iScience 19, 504–513, September 27, 2019 IF 4.447

# Fate Distribution and Regulatory Role of Human Mesenchymal Stromal Cells in Engineered Hematopoietic Bone Organs

**Paul E. Bourgine,[1,2,5,6] Kristin Fritsch,[3] Sebastien Pigeot,[2] Hitoshi Takizawa,[4] Leo Kunz,[1] Konstantinos D. Kokkaliaris,[1] Daniel L. Coutu,[1] Markus G. Manz,[2,*] Ivan Martin,[2,*] and Timm Schroeder[1,7,*]**

**Summary**

The generation of humanized ectopic ossicles (hOss) in mice has been proposed as an advanced translational and fundamental model to study the human hematopoietic system. The approach relies on the presence of human bone marrow-derived mesenchymal stromal cells (hMSCs) supporting the engraftment of transplanted human hematopoietic stem and progenitor cells (HSPCs). However, the functional distribution of hMSCs within the humanized microenvironment remains to be investigated. Here, we combined genetic tools and quantitative confocal microscopy to engineer and subsequently analyze hMSCs' fate and distribution in hOss. Implanted hMSCs reconstituted a humanized environment including osteocytes, osteoblasts, adipocytes, and stromal cells associated with vessels. By imaging full hOss, we identified rare physical interactions between hMSCs and human CD45+/CD34+/CD90+ cells, supporting a functional contact-triggered regulatory role of hMSCs. Our study highlights the importance of compiling quantitative information from humanized organs, to decode the interactions between the hematopoietic and the stromal compartments.

1 Department of Biosystems Science and Engineering (D-BSSE), ETH Zurich, Mattenstrasse 26, 4058 Basel, Switzerland
2 Tissue Engineering, Department of Biomedicine, University of Basel and University Hospital Basel, 4056 Basel, Switzerland
3 Department of Hematology, University Hospital Zurich and University of Zurich, 8091 Zurich, Switzerland
4 International Research Center for Medical Sciences, Kumamoto University, Kumamoto 860-0811, Japan
5 Department of Clinical Sciences, Lund Stem Cell Center, Lund University, BMC B11, 221 84 Lund, Sweden
6 Wallenberg Centre for Molecular Medicine, Lund University, Lund, Sweden
7 Lead Contact
* Correspondence:
markus.manz@usz.ch (M.G.M.), ivan.martin@usb.ch (I.M.), timm.schroeder@bsse.ethz. ch (T.S.)
https://doi.org/10.1016/j.isci.2019.08.006

Communications Biology Volume 3, Article number: 130 (2020) IF 4.165

# Loss of the branched-chain amino acid transporter CD98hc alters the development of colonic macrophages in mice

**Philipp Wuggenig[1], Berna Kaya[1], Hassan Melhem[1], C. Korcan Ayata[1], Swiss IBD Cohort Investigators[*], Petr Hruz[2], A. Emre Sayan[3], Hideki Tsumura[4], Morihiro Ito[5], Julien Roux[1,6] & Jan Hendrik Niess[1,2]**

**Abstract**

Comprehensive development is critical for gut macrophages being essential for the intestinal immune system. However, the underlying mechanisms of macrophage development in the colon remain elusive. To investigate the function of branched-chain amino acids in the development of gut macrophages, an inducible knock-out mouse model for the branched-chain amino acid transporter CD98hc in CX3CR1$^{+}$ macrophages was generated. The relatively selective deletion of CD98hc in macrophage populations leads to attenuated severity of chemically-induced colitis that we assessed by clinical, endoscopic, and histological scoring. Single-cell RNA sequencing of colonic lamina propria macrophages revealed that conditional deletion of CD98hc alters the "monocyte waterfall"-development to MHC II$^{+}$ macrophages. The change in the macrophage development after deletion of CD98hc is associated with increased apoptotic gene expression. Our results show that CD98hc deletion changes the development of colonic macrophages.

1 Department of Biomedicine, University of Basel, Basel, Switzerland.
2 University Center for Gastrointestinal and Liver Diseases, St. Clara Hospital and University Hospital, Basel, Switzerland.
3 Cancer Sciences Division, Somers Cancer Research Building, Southampton University, Southampton, UK.
4 Division of Laboratory Animal Resources, Nation Research Institute for Child Health and Development, Tokyo, Japan.
5 Department of Microbiology, College of Life and Health Science, Chubu University, Aichi, Japan.
6 Swiss Institute of Bioinformatics, Basel, Switzerland.
* A list of authors and their affiliations appears at the end of the paper.
email: janhendrik.niess@unibas.ch
https://doi.org/10.1038/s42003-020-0842-3

## REVIEWS

Journal of Hepatology 2020 vol. 73, 186–201 IF 20.582

# Innate immune cells in cirrhosis

**Christine Bernsmeier[1,2,*], Schalk van der Merwe[3,4,*], Axel Périanin[5,6,7,*]**

**Summary**

Cirrhosis is a multisystemic disease wherein inflammatory responses originating from advanced liver disease and its sequelae affect distant compartments. Patients with cirrhosis are susceptible to bacterial infections, which may precipitate acute decompensation and acute-on-chronic liver failure, both of which are associated with high short-term mortality. Innate immune cells are an essential first line of defence against pathogens. Activation of liver macrophages (Kupffer cells) and resident mastocytes generate proinflammatory and vaso-permeating mediators that induce accumulation of neutrophils, lymphocytes, eosinophils and monocytes in the liver, and promote tissue damage. During cirrhosis progression, damage- and pathogen-associated molecular patterns activate immune cells and promote development of systemic inflammatory responses which may involve different tissues and compartments. The antibacterial function of circulating neutrophils and monocytes is gradually and severely impaired as cirrhosis worsens, contributing to disease progression. The mechanisms underlying impaired antimicrobial responses are complex and incompletely understood. This review focuses on the continuous and distinct perturbations arising in innate immune cells during cirrhosis, including their impact on disease progression, as well as reviewing potential therapeutic targets.

1 Department of Biomedicine, University of Basel, Switzerland;
2 University Centre for Gastrointestinal and Liver Diseases, Basel, Switzerland;
3 Laboratory of Hepatology, Department of Chronic Diseases, Metabolism and aging (CHROMETA), University of Leuven, Leuven, Belgium;
4 Department of Gastroenterology and Hepatology, University Hospital Gasthuisberg, Leuven, Belgium;
5 INSERM U1149, Centre de Recherche sur l'Inflammation, Paris, France;
6 UMRS1149, Université Paris Diderot-Paris 7, Paris, France;
7 Centre National de la Recherche Scientifique (CNRS), Paris, France
* Corresponding authors.
Addresses: INSERM1149, Centre de Recherche sur l'Inflammation, Faculté Xavier Bichat, 16, rue Henri Huchard, 75018 Paris, France. Tel.: +33 157277473 (A. Périanin), or Department of Gastroenterology and Hepatology, University Hospital Gasthuisberg, 49 Here street, 3000 Leuven, Belgium (S. van der Merwe), or University Centre for Gastrointestinal and Liver Diseases, Petersgraben 4, 4031 Basel, Switzerland (C. Bernsmeier).
E-mail addresses: axel.perianin@inserm.fr (A. Périanin), schalk.vandermerwe@uzleuven.be (S. van der Merwe), c.bernsmeier@unibas.ch (C. Bernsmeier).
https://doi.org/10.1016/j.jhep.2020.03.027

# «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 March 31, 2021.

Departement Biomedizin
Hebelstrasse

**Jennifer Gröli**
Animal Facility Hebelstrasse

**Myrta Brunner**
Applied Microbiology Research

**Srinithi Purushothaman**
Applied Microbiology Research

**Dragos Inta**
Brain Ischemia and Regeneration

**Ilia Smolenskii**
Brain Ischemia and Regeneration

**Valentina Bicvic**
Brain Tumor Immunotherapy

**Alexandra Gerber**
Brain Tumor Immunotherapy

**Maryam Akramisomeabozorg**
Cancer Immunology

**Adrian Filip**
Cancer Immunology

**Nora Liewen**
Cancer Immunology

**Emanuele Carlini**
Cancer Immunotherapy

**Mirza Sarcevic**
Cancer Immunotherapy

**Dominique Schlienger**
Cancer Immunotherapy

**Lukas Schönenberger**
Cancer Immunotherapy

**Florian Gregor Meissner**
Cardiac Surgery and Engineering

**Antonio Sileo**
Cardiac Surgery and Engineering

**Bendikt Stöckli**
CardioBiology

**Samira Wyttenbach**
Cardiovascular Molecular Imaging

**Pauline Bicker**
Cell and Gene Therapy

**Daniele Reggio**
Cell and Gene Therapy

**Sarah Dräger**
Clinical Immunology

**Loredana Messina**
Clinical Immunology

**Jessica Weiss**
Clinical Immunology

**Ana Beatriz Ayrosa Galvao Ribeiro Gomes**
Clinical Neuroimmunology

**Julia Flammer**
Clinical Neuroimmunology

**Sebastian Holdermann**
Clinical Neuroimmunology

**Laura Rieder**
Clinical Neuroimmunology

**Jana Möller**
Diabetes Research

**Riikka Kivioja**
Experimental Hematology

**Damien Luque Paz**
Experimental Hematology

**Daniel Constantin**
Experimental Immunology

**George Rosenberger**
Hepatology

**Tagore Sanketh Bandaru**
Immune Cell Biology

**Sara Ostertag**
Immune Cell Biology

**Adria-Arnau Marti Lindez**
Immunobiology

**Yannick Schlup**
Immunobiology

**Dominique Tschopp**
Immunodeficiency

**Fanny Linder-Hengy**
Infection Biology

**Simon Garaude**
Molecular Immune Regulation

**Subashree Srinivasan**
Ocular Pharmacology and Physiology

**Nadia Gina Maggi**
Ovarian Cancer Research

**Ronya Nieminen**
Ovarian Cancer Research

**Jan Thomann**
Psychopharmacology Research

**Andreas Wüst**
Pulmonary Cell Research

**Miyoshi Hirotsugu**
Skeletal Muscle Disorders

**Sophie Lalevee**
Skin Biology

**Janhavi Apte**
Tissue Engineering

**Wilson Idemudia**
Tissue Engineering

**Evrim Ceren Kabak**
Tissue Engineering

**Andrea Mainardi**
Tissue Engineering

**Federico Mariuzzo**
Tissue Engineering

**Adrien Moya**
Tissue Engineering

**Cecilia Palma**
Tissue Engineering

**Esma Tankus**
Tissue Engineering

**Sylvia Pecenko**
Translational Hepatology

**Gina Boot**
Visceral Surgery and Precision Medicine

**Mattia Marinucci**
Visceral Surgery and Precision Medicine

**Ziyuan Xia**
Visceral Surgery and Precision Medicine

Departement Biomedizin
Klingelbergstrasse

**Sebastian Reinartz**
Brain and Sound

**Bartosz Frycz**
Molecular Neurobiology Synaptic Plasticity

Departement Biomedizin
Petersplatz

**Corinne Salvisberg**
Zentrale Dienste Petersplatz

**Stanka Matic**
Molecular Virology

Departement Biomedizin
Pestalozzistrasse

**Sina Hohler**
Cell Adhesion

**Alicia Lorena Kasper**
Cell Adhesion

**Jakob Mitgau**
Cell Adhesion

**Mylène Toranelli**
Musculoskeletal Research

Departement Biomedizin
Mattenstrasse

**Karin Burger**
Embryology and Stem
Cell Biology

# Congratulations

**Eleni Methot Litzler**
Geboren am 22. Oktober 2020

**Yi-Cheng Liang Huang**
Geboren am 30. Oktober 2020

**Herzlich willkommen, allerseits!**

# Christmas in Mexico

I left Mexico 17 years ago, but since then I have returned every year in December, to meet my family and some old friends. I can escape the cold European winters for the temperate Mexico city I come from and, moreover, can visit one of our beautiful beaches on the pacific coast or the Caribbean.

As Mexico is a huge country in America, with 126.2 million inhabitants and a vast area of 1,972,550 km$^2$, describing Navidad (Christmas season) for my country will lead to some generalizations but I will give it a try.

If I just think about Christmas, the following words/themes come to mind: las posadas, el nacimiento, las pastorelas, la flor de nochebuena, la piñata, los reyes magos la familia and oh yes la comida… I will come to a few of them in a minute, but first a bit of history/theory.

Several of our traditions have a counterpart in western catholic traditions. When the Spanish arrived in America more than 500 years ago, they tried to teach (and sometimes violently impose) their catholic traditions onto the native Americans. They did this by, for example, burning original indigenous temples and building churches on top of them or, more nicely, by making theatrical representations of the nativity (Jesus birth story), imbued with indigenous themes to evangelize the locals. This history of colonization and mestizaje (mixing of ethnic groups) lives on today in our traditions. Religious or not, nowadays most Mexicans take part in Christmas celebrations, which for many are more about our culture than our beliefs.

**Christmas season**

The Christmas season begins on December 12$^{th}$ with the fiesta de la Guadalupana. In this festivity religious believers celebrate the apparition of the Virgin Mary in the form of Guadalupe to a native Mexican, Juan Diego, around 500 years ago in what is now Mexico city. This virgin unites attributes of both pre-Columbian Mexican and Spanish cultures and is truly adored by many Mexicans.

*Flor de Noche Buena*

*Nativity scenes from a family friend*

The Christmas season ends on 6th of January with the arrival of the three kings "Reyes Magos". Colloquially we call this period "el marathon Guadalupe-Reyes" because there are non-stop festivities during the whole time and everybody is exhausted by the end of it.

**Flor de Nochebuena/Poinsettia/Weihnachtsstern**

This flower originates from Mexico where it was first used in religious rituals, for herbal remedies and to make pigments. The Spanish colonizers took it on as an ornamental element for Christmas and it was a US ambassador to Mexico that later made it famous internationally by bringing it back to his country in the 1800's.

**Los nacimientos (Nativity Scene)**

This tradition belongs to many catholic countries. El nacimiento is a craft where the barn where Joseph and Maria arrive in Bethlehem to give birth is created and filled with animals, shepherds, angels as well as the three kings and the Bethlehem star. Mexican craftsman make beautiful artisanal versions of them. We always had one at my place and I loved to play with it and bring the baby Jesus to his crib on December 24th.

**Las posadas (The Inns)**

Las posadas are parties celebrated every night during the 9 days before December 24th, around different houses in the neighbourhood. At these parties, the pilgrimage of Mary and Joseph from Nazareth to Bethlehem is re-enacted. At the beginning of the party two groups are formed one with Joseph and Mary outside and another group inside the house. Joseph and Mary sing asking for refuge to give birth and they are denied entrance a couple of times until they are finally let in. During these parties a piñata in the form of a star, and traditionally filled with fruits, nuts and sugar cane, is hit and broken by the children, there is also a traditional fruit punch, sparklers and partying.

**Las pastorelas (Nativity Play)**

This is truly a very Mexican tradition, it is again about the birth of Jesus and it was originally used by priests to teach Catholicism to Mexicans. Pastorelas are theater plays performed by schools, theater companies, amateurs and other volunteers. This play tells the story of the shepherds that heard that Jesus had been born and who then decide to pilgrim towards him to pay their respects. They

*Colorful Christmas Piñatas from my local market in Mexico city*

use the Bethlehem star as guidance and on their journey the devil tries to convince them not to go to Jesus, while an angel tries to bring them back on track. The play also shows how the three kings are slowly traveling to Bethlehem. Not unlike Fasnacht here in Basel, these pieces highlight important current events and intermingle them with the main story to make fun of them. Sadly there probably won't be many pastorelas this year due to lockdowns but I am sure that topics like covid 19, the migration and the drug dealing crises would be covered in a cynical way with song, theater and dance.

**Christmas Dinner and Food**

We eat special dishes on Christmas Eve and each family has its favourites, for example, romeritos en mole, bacalao a la vizcaina, ham in adobo, stuffed turkey, tamales. I would not dare to try to teach you how to cook these incredible dishes but I will just let you know that Mexican cuisine has attained the status of Intangible Cultural Heritage of Humanity by UNESCO so you should not miss the opportunity to try it. For example, my favourite sauce is mole. Mole comes in different versions and it consists of more than 20, mostly ground ingredients, including different chillies, chocolate, cumin, cloves, anise, tomatoes, tomatillos, garlic, sesame seeds, nuts, dried fruits, corn tortillas cooked into a paste that we later dissolve in bouillon and pour on top of chicken and then serve with a side of rice and tortillas. If you ever have a chance to try original Mexican food don't forget to taste mole - you will be pleasantly surprised!

Many families spend Christmas Eve with grandparents or elder relatives but before dinner all sort of other family visits have to be done and some family members also join the misa de gallo (a Christmas mass) before midnight. Only thereafter dinner is served and the only reason all the kids can stay awake that long is that the opening of the presents is the last event of this long day!!

*My son hitting a piñata*

**Dia de los reyes magos (The Three Kings Day)**

Dia de reyes is especially cool for children and it celebrates the arrival of the three kings Melchor, Gaspar and Baltasar to meet Jesus. Children write letters to the kings asking for presents, place them in an old shoe and wake up at dawn on the 6th of January to receive them. On this day we also eat the Rosca de reyes, a cake similar in flavour to the Italian panettone. Hidden inside is a small plastic baby and whoever finds it has to invite all the guests for tamales, a sort of steamed corn cake, on February 2nd.

I hope I could give you a tiny flavour of our traditions. The ones I described are catholic customs mixed with the original pre-Columbian rituals that have kept evolving to fit our Latin-American character and history.
Feliz Navidad!!

Amanda Ochoa-Espinosa

*Barrio de l Niño Jesus party*

*This is a photo of my neighborhood on December 31st. My quarter is called Barrio del Niño Jesus and from December 31st until January 2nd there is a big fun party where we celebrate… who? Yes, you guessed right, Jesus! During this event a music band playing traditional music parades around the streets behind a colourful star further followed by the people from the area. The main street is blocked by a street fair and there are castles made out of fireworks next to the church. One can barely sleep for those two nights because of the fireworks and the parties that run until the morning.*

# DBM-IT

**Dear colleagues**

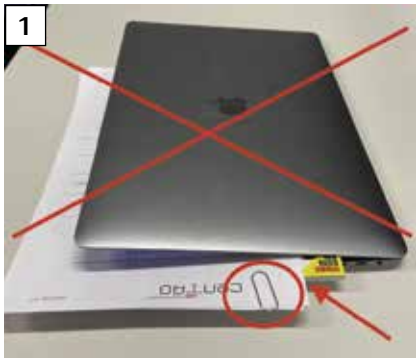
In recent years, we have been experiencing many broken Computers. The costs incurred as a result could have been avoided with simple awareness. We would like to ask you to take the following tips to heart:

**1.** Broken screens: Please do not put something between the screen and keyboard of your MacBook/Laptop. Use a folder and transport your documents independently of your laptop. The repair of a broken screen costs up to CHF 1'000.–.

**2.** The swollen battery: Please do not cover the airflow to the computer, as overheating leads to a swollen battery. Consider the airflow picture to be aware of how it works. This costs up to CHF 300.–.

**3.** Liquids and electricity: They are not friends. Absolutely not! Keep liquids, like your tea or your coffee for instance, away from electrical devices, including keyboards! An Apple keyboards costs over CHF 100.–.

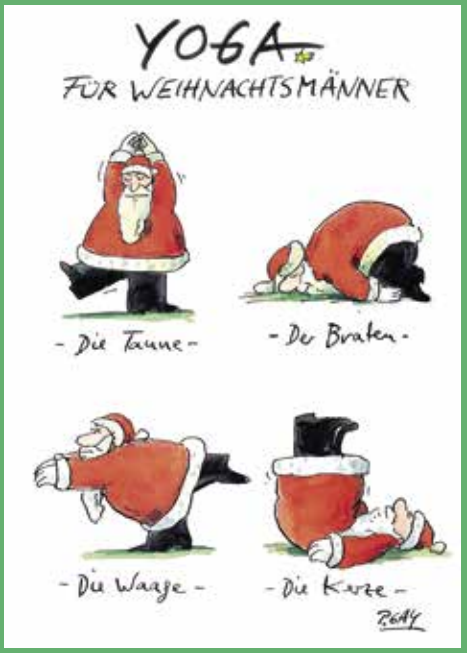
**4.** Stickers: They do not cost us something financially, but we must spend a lot of time to remove them. So please remove stickers before returning your computer or do not put stickers on them at all. The next computer user will be grateful for this.







The Editorial Team of DBM Facts wishes all its readers a Merry Christmas and a Happy New Year!



# Today: Miyoshi Hirotsugu, Skeletal Muscle Disorders


1

Hey everyone! My name is Hirotsugu Miyoshi. I come from Japan and I am an anesthesiologist specialized in cardiovascular anesthesia. I also obtained my PhD from Hiroshima University four years ago and my studies focused on Malignant Hyperthermia. After my PhD, I was completely devoted to clinical work, but last year I felt that I wanted to continue some research work and thought it would be useful to go abroad and so I came to Switzerland. I am honored to study at the University of Basel and I am grateful to Professor Susan Treves, Dr Francesco Zorzato, and the kind staff at Lab 408 for their willingness to accept me. Thanks to everyone who has helped me live in Basel.

Now, I would like to introduce you to life in Japan. Japan does not have a large land area, but it is long from north to south. The northern end of Japan is at the same latitude as Switzerland and the southern end is at the same latitude as Egypt. Including the area of the sea, Japan is actually a fairly large country. We are rich in water and plants, and we enjoy incorporating them into our lives. (Photo 1) I was born and raised in Hiroshima, Japan. Hiroshima prefecture is one of 47 prefectures in Japan and is located in the west middle of Japan. It is known to the world as the city where the atomic bomb was dropped. About 75 years have passed since the atomic bomb was dropped, and Hiroshima is now a city that symbolizes peace. We pray for peace every year at 8:15 am on August 6th. This is the time when the atomic bomb was dropped. Even now, the building directly under the atomic bomb remains. It is called the "Atomic Bomb Dome" and is a tourist attraction along with "Peace Memorial Park". (Photo 2)


2

The year in Japan begins in April. April is the cherry blossom season. Cherry blossoms are loved in Japan, so cherry blossom trees are planted in every space. We bring food and alcohol under the cherry blossoms to eat. (Photo 3) Japanese cherry blossoms will disperse in just about 10 days. Very ephemeral. However,

3

we love the way the petals of the cherry blossom, especially "Somei Yoshino", falls. It matches our aesthetics that every thing should end gracefully, with no regret or struggles. This gracefulness leaves us with a sense of the "samurai" spirit.

Hiroshima is also famous for "Itsukushima Shrine" in Miyajima iland. Itsukushima Shrine is a very unique shrine built from the coast to the sea. The 16-meter-high "torii" that stands on the sea is a symbol of Itsukushima Shrine. (Photo 4) Torii is found in every shrine in Japan and means the path of God. And it is said that we will be purified when we pass through here and enter the shrine. There are more than 90,000 shrines in Japan, each with a god. This means that there are at least 90,000 gods in Japan. This symbolizes the unique view of religion. Japanese religion is basically a mixture of "Shinto" and "Buddhism". By the way, the "shrine" is a Shinto building and the "temple" is a Buddhist building. Shinto is polytheistic, and it is said that God dwells in everything in our world. We think that God dwells especially in old things. That's why we like the new, but sometimes we value the old. So old European buildings feel very mysterious and attractive to Japanese.

4


5

Since we are polytheistic, we only think that the number of gods has increased even if religious culture comes in from overseas. I think this is related to the flexible attitude of the Japanese. And, this is symbolized by the way Japan spends the end of the year, which will be described later.

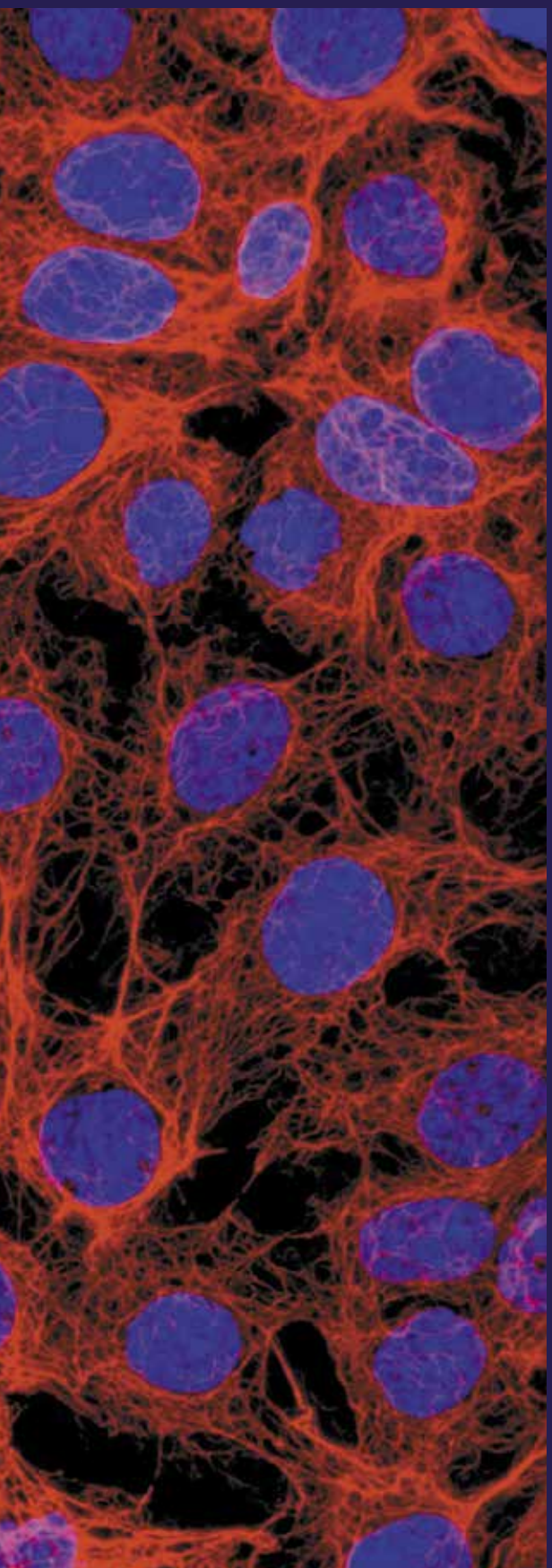
Summer in Japan is extremely humid and hot. At the end of summer, there are festivals and firework displays in each region. (Photo 5) And in the fall, the trees turn red and are very beautiful. (Photo 6)

By the way, this year will be over soon. The end of the year in Japan is generally very busy. First of all, in December, a party called "Bounenkai (year-end party)" is held almost every week. Most of the staff in each department participates, so 50 to 100 people will gather in each party. Last year, I attended the Anesthesiology department, Surgical department, and ICU department end of year parties, so I was exhausted. Next is Christmas. Christmas culture is pervasive in Japan. The whole town is decorated at Christmas time. In Japan, children receive gifts (usually toys) from Santa Claus while sleeping on Christmas night. Perhaps during elementary school, the kids really truly believe that Santa Claus is really bringing presents. As children grow older, they find that their parents give them gifts instead of Santa Claus, but they don't tell them directly. On the other hand, parents naturally find that their children do not believe in Santa Claus, but parents also do not ask their children about it. So we sometimes pretend to believe in Santa Claus with each other. This is a mysterious relationship between Japanese parents and children. After Christmas, we will go to the temple on the night of December 31st to listen to the "Joya no kane (Temple bells ringing out the old year)" and celebrate the New Year. Then, when the new year begins, we go to the shrine and swear our aspirations for the year. Thus, during the year-end and new year we will have all Christian, Buddhist and Shinto events.

Currently, due to the COVID-19, various events are restricted in Japan as well as in other countries around the world. Entry into Japan from overseas is also restricted. I hope these restrictions will be lifted in the near future. Which country would you like to visit if the coronavirus situation has calmed down? Japan of course, right? Japan awaits you!


6

# Department of Biomedicine Research Day 2021



**Thursday, January 21, 13:00 – 18:45 h**
**Zentrum für Lehre und Forschung**
**Hebelstrasse 20, 4031 Basel**

## Speakers

Mohamed Bentires-Alj
Karin Hartmann
Georg Holländer
Lukas Jeker
Nina Khanna
Gabriela Kuster Pfister
Anna Marsano
Eline Pecho-Vrieseling
Salvatore Piscuoglio
Michael Sinnreich

image courtesy of Diego Calabrese, DBM Histology

« Die grössten Ereignisse, das sind nicht unsere lautesten, sondern unsere stillsten Stunden. »

*Friedrich Nietzsche*