DBM FACTS

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

Imaging deep: Visualizing state and sensory coding in identified brain circuits | Board games are not just for geeks anymore | New Zealand

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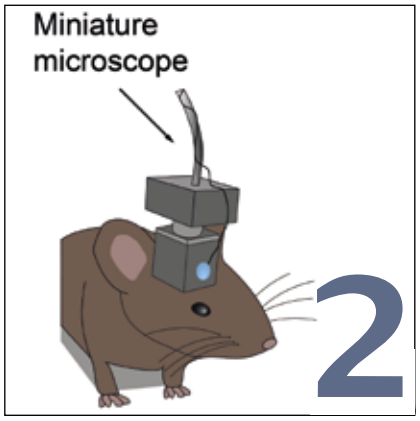

Imaging deep: Visualizing state and sensory coding in identified brain circuits
from Jan Gründemann

Board games are not just for geeks anymore
from Barbara Szczerba

New Zealand
from James Neil Fisher

Das DBM stellt sich vor

IMPRESSUM

Redaktion
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Übersetzungen
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Layout
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IT-Unterstützung
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Administration
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Pixabay

Druck
buysite AG, Basel

Anschrift
Redaktion DBM Facts
Departement Biomedizin
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4031 Basel
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EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Endlich ist der Frühling da – und locker und leicht erscheint mit ihm die neueste Ausgabe der DBM Facts.
Die Planung des Neubau DBM auf dem Schällemätteli geht weiter, die Universität hat die eigene Bau-Organisation gestärkt und ein neuer Generalplaner (Burckhardt+Partner) wurde bestimmt. Jan Gründemann stellt uns seine Forschung im Bereich «Sensory processing and behaviour» vor (ab Seite 2), es folgen die aktuellsten Publikationen aus dem DBM (ab Seite 9).

Dass Gesellschaftsspiele nicht nur etwas für Stubenhocker sind, zeigt uns Barbara Szczerba anschaulich, in dem sie uns mitnimmt auf Entdeckungstour (ab Seite 23). Die Schönheiten Neuseelands lernen wir mit James Neil Fisher kennen, der dort gross geworden ist (ab Seite 27). Den Abschluss bildet Hanane Baidarjad, die sich und ihre Heimat Marrakesch vorstellt (ab Seite 31). Ans Herz legen möchte ich allen auch den 21. August 2019: Am Vormittag findet das DBM-Sommersymposium, am Nachmittag das Summer BBQ statt. Also bitte den Termin vormerken!

Eine spannende Lektüre!

Dear Readers,

Spring is finally here and the latest edition of DBM Facts casually appears with it.
The planning for the new DBM building is progressing; the university have strengthened their own building organisation and a new general planner (Burckhardt+Partner) has been chosen. Jan Gründemann introduces us to his research in the field of "Sensory processing and behaviour" (page 2), and we follow with the latest publications from the DBM (page 9).

Barbara Szczerba shows us how board games are no longer just for geeks as she brings us with her on a tour of the games (page 23). We learn all about the beauty of New Zealand from James Neil Fisher, who grew up there (page 27). Hanane Baidarjad wraps things up by introducing us to her hometown, Marrakesh (page 31). I would also like you all to look forward to the 21st of August 2019: the DBM summer symposium will take place in the morning and the summer BBQ will be in the afternoon. Please make a note of the date!

Happy reading!

Imaging deep: Visualizing state and sensory coding in identified brain circuits

Introduction

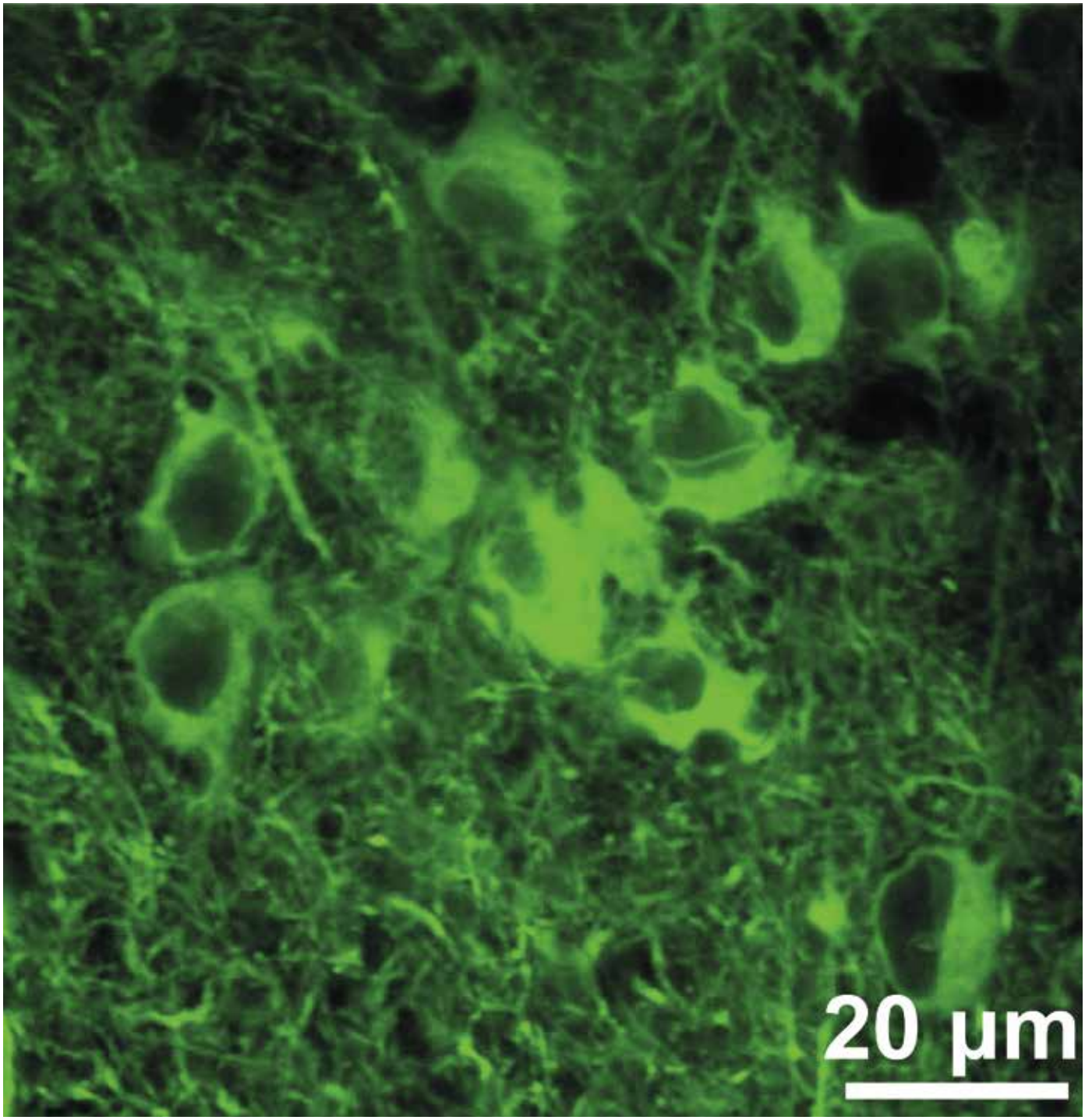
Our brains are complex structures, which encode representations of the environment through dynamic changes in neuronal activity. In the Sensory Processing and Behaviour Lab, we study how large populations of identified neurons encode sensory stimuli from the environment and how they are transformed into behavioural outcomes and adaptations during learning. Our long-term goal is to identify neural circuit computations that are crucial for healthy brain function and their maladaptation in psychiatric disease models, which will potentially provide entry points for neural circuit-directed therapies.

Our brains are constantly bombarded with sensory inputs from the environment, which change on a millisecond timescale. The brain's daunting task is to integrate these sensory inputs and to link them with experiences to ensure appropriate behavioural outputs, which guarantee survival. For example, experiencing a hot stove plate for the first time – and particularly the inconvenient consequences of getting burned – will result in future avoidance behaviour or at least in a certain level of cautiousness around a hot stove. The brain forms an associative memory between the sensory input, the context and the, in this case, negative behavioural outcome. Associative memories are formed by changes on the level of molecules, structural cellular mechanisms as well as changes in neural circuit connectivity. Inherently, these associative learning mechanisms are crucial for our safety and to prevent future harm. In recent years, we have aimed to understand how associative learning is encoded on the level of defined neuronal cell-types and neuronal circuits.

One classical animal model to study associative learning is associative fear learning in rodents. Associative fear learning is based on classical Pavlovian conditioning, but instead of food, which made Pavlov's dog salivate (Pavlov, 2010), the animals receive a pairing of a tone (conditioned stimulus, CS) with a mild electrical stimulus (unconditioned stimulus, US), that results in defensive behaviours. One typical behaviour is called freezing and is characterized by the complete absence of movement of the mouse. In the pre-conditioning phase, mice show no response to the tone. However, after fear conditioning the animals will freeze to the conditioned stimulus, which can be quantified to measure the strength of associative learning. One brain area that has been implicated for decades in associative fear learning is the amygdala, an almond shaped structure in the temporal lobe. Previous research in rodents has shown that the amygdala is involved in fear learning. For example, amygdala inactivation prevents fear conditioning indicating that amygdala function is crucial for the formation of associative memories in aversive learning. Functional cell types like so-called fear cells, that increase their activity when the animal is in a high fear state, and extinction cells, that increase their activity when the animal has extinguished a fear response, where demonstrated (Herry et al., 2008). However, individual cells are most likely not the source of memory formation and behavioural outputs. Just imagine the consequences of losing these individual cells for stimuli that predict harmful outcomes. Thus, we hypothesized that amygdala function has to be encoded on the level of distributed information in large neuronal populations (Gründemann and Lüthi, 2015).

Imaging large neuronal populations in deep brain areas

Classically, amygdala neuronal activity has been studied in rodents using single or multiunit electrophysiological recordings, which allowed the study of small to medium sized neuronal populations. I.e., these types of recordings are typically limited to individual cells or small neuronal ensembles. During the last two decades, this problem could be overcome by optical imaging techniques of neuronal activity. The invention of multiphoton microscopy (Denk et al., 1990; Helmchen and Waters, 2002) allowed neuroscientists to record the activity of large neuronal populations (>100 cells) simultaneously with the help of sophisticated imaging instruments and genetically-en-



coded activity sensors (e.g. GCaMP6, see Figure 1, Chen et al., 2013). These sensors allow targeted labelling of genetically – or projection pathway-defined cell classes. However, due to optical limitations, the activity of identified neurons could only be measured and visualized in superficial brain areas, i.e. neocortex, which lead to a wide range of studies on cortical function and has substantially improved our understanding of neural circuit computations in neocortex.

Figure 1: Ca^{2+} sensor expressing neurons

CamKII-expressing neurons were virally transduced with the genetically-encoded Ca^{2+}-indicator (GECI) GCaMP6f in the mouse brain using an adeno-associated virus. GECIs report the neuronal activity by changes in fluorescence. In combination with advanced microscopy techniques, e.g. two-photon or miniature microscopy, this technique allows a specific activity mapping of genetically-defined neuronal classes in behaving rodents in vivo.
Image: James Alexander Taylor.

Despite their crucial function for the regulation of emotional, homeostatic, navigational and social behaviours, so far, deep brain areas like amygdala, hypothalamus, hippocampus, or medial prefrontal cortex, respectively, were mostly inaccessible to large scale population imaging techniques due to optical limitations. However, these limitations could be overcome in recent years by the development of gradient-refractive index (GRIN) lenses, which allow brain scientists to relay light into deep brain areas, with a sufficient numerical aperture to visualize individual cell bodies and record neuronal activity. In a collaboration with Prof Mark Schnitzer at Stanford University, Prof Andreas Lüthi at the Friedrich Miescher Institute and Prof Benjamin Grewe at ETH Zürich we established a GRIN lens-based imaging technique specifically for the amygdala of rodents (see Figure 2, see also Grewe et al., 2017). Furthermore, to visualize neuronal activity in freely moving animals, we employed a single photon miniaturized microscope approach originally developed in Mark Schnitzer's laboratory (Ghosh et al., 2011, Figure 3, see also www.inscopix.com) to image amygdala activity in freely moving animals (see Figure 2). We have used this technique now across different neuronal brain areas, behaviours and cell types (Douglass et al., 2017; Gründemann et al., 2019; Krabbe et al., 2018; Xu et al., 2017).

Amygdala population coding of behavioural states and fear learning

Besides fear learning, the amygdala has been discovered to be involved in a wide variety of self-driven, state-de-

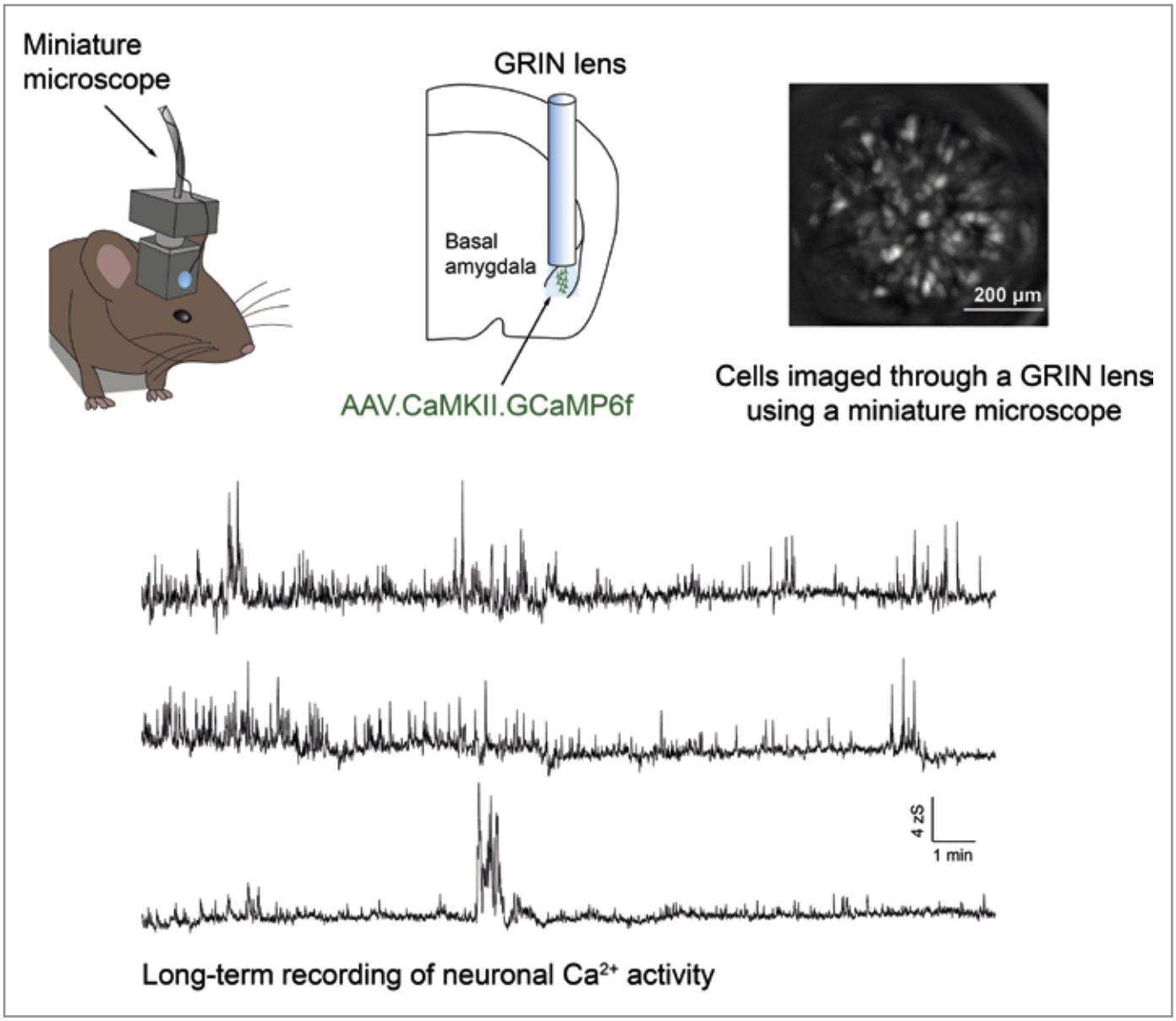


Figure 3: Miniaturized microscope

Miniaturized, head-mountable microscope for deep brain imaging in rodents (nVista3-System).

pendent behaviours including foraging (Amir et al., 2015), eating (Douglass et al., 2017) as well as social (Felix-Ortiz and Tye, 2014) behaviours. To test if we can identify a general amygdala coding scheme across different behaviours, we employed a longitudinal measurement of neuronal activity across days and paradigms using miniaturized microscopy in freely moving mice. We paired classical anxiety tests (open field test, elevated plus maze test) with a fear conditioning and fear extinction paradigm. Strikingly, we found two large, non-overlapping neuronal populations in the basal amygdala that where predictive of relative changes in behavioural state.

Figure 2: Miniature microscope imaging of deep brain areas in freely moving animals

Top left: *Schematic of a mouse with a miniaturized microscope. These microscopes weigh ca. 2 g and can be carried by a mouse during diverse, freely moving behavioural paradigms.*

Top center: *Schematic of a GRIN lens implantation in a deep brain area, e.g. the basal amygdala. GCaMP6 Ca^{2+} activity sensor was expressed using an adeno-associated virus approach.*

Top right: *Deep brain GCaMP6 expression visualized with a GRIN lens and miniature microscope.*

Bottom: *Activity traces of three example neurons recorded for > 10 min in a freely moving mouse.*

Image and traces: James Alexander Taylor

For example, we found ensembles of cells that were more active when the animal explored the corners of an open field compared to the center. The activity patterns in these opposing amygdala state ensembles were predictive of exploratory or non-exploratory behaviours in other spatial anxiety or exploratory tests, suggesting that these two ensembles track exploratory, low anxiety states of the animals.

Amygdala neuronal ensembles strongly encode associative learning not only on the single cell but also on the population level. In a previous collaborative study, we could show that amygdala ensembles representations for the conditioned stimulus (tone) become more similar to the unconditioned stimulus (electrical stimulus) upon fear conditioning. This transformation in the population representation was predictive of the learning levels of the animals (Grewe et al., 2017). However, when comparing sensory coding upon fear learning to state-coding of exploratory behaviours we found that the ensembles representations of sensory stimuli and behaviours are not correlated and orthogonal to each other. This indicates that sensory representations predictive of potential environmental harm are independently processed from internal state representations (Gründemann et al., 2019). All in all, using longitudinal miniature microscope imaging across

different behaviours we identified that amygdala ensembles represent behavioural states which are distributed across a wider brain network and which can act in addition to classical cortical brain states as an affective state signal. As a next step, it will be interesting to study how these state representations are changed in animal models of psychiatric disorders, for example anxiety models or animal models of malfunctioning sensory representations, e.g. schizophrenia models.

Outlook

For our future research, we are now interested in how distributed brain networks outside of the amygdala encode behavioural states and uni – as well as multisensory encoding of learning – related environmental stimuli. We are particularly interested how state changes and multisensory integration affect and guide sensory input-based decision-making.

Jan Gründemann

Figure 4: Sensory Processing and Behaviour Lab

Back left to right: Jan Gründemann, Joana Amorim Freire, James Alexander Taylor, Marine Theodore.

Front left to right: Chloé Benoit, Masashi Hasegawa (Missing: Dan Ganea).

Foto: Bernd Schwendele

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Dissertationen

Am 23. Mai 2018 konnte **Anna Paczulla** von der Forschungsgruppe "Stem Cells and Hematopoiesis" (Departement Biomedizin Hebelstrasse) ihre Dissertation mit Erfolg beenden. Sie befasste sich in ihrer Dissertation mit dem Thema: "Investigation of Mechanisms regulating Leukemogenesis using Mouse Xenograft Models of Human Acute Myeloid Leukemia".

Am 14. Dezember 2018 stellte sich **Sandro Nuciforo** von der Forschungsgruppe "Hepatology" (Departement Biomedizin Hebelstrasse) den Fragen des Dissertationskomitees. Der Titel seine Dissertation hiess: "Liver cancer in a dish: modelling hepatocellular carcinoma using patient-derived tumor organoids".

Am 27. Februar 2019 stellte sich **David Büchel** von der Forschungsgruppe "Tumor Biology" (Departement Biomedizin Mattenstrasse) den Fragen des Dissertationskomitees. Der Titel seiner Dissertation lautete: "Wnt/β-catenin signaling in malignant mammary tumor progression and metastasis formation & Mechanisms of evasive resistance to sorafenib in hepatocellular carcinoma".

Mit der Doktorprüfung am 5. April 2019 schloss **Aleksei Suslov** von der Forschungsgruppe "Hepatology" (Departement Biomedizin Hebelstrasse) erfolgreich seine Dissertationszeit ab. Das Thema seiner Doktorarbeit lautete: "Host-Virus Interactions in Chronic Hepatitis B".

Am 9. April 2019 konnte **Romain Amante** von der Forschungsgruppe "Tumor Heterogeneity Metastasis and Resistance" (Departement Biomedizin Hebelstrasse) seine Dissertation mit Erfolg beenden. Er befasste sich in seiner Dissertation mit dem Thema: "SHP2 Blockade Sensitizes Triple Negative Breast Cancers To PI3K Inhibition Leading To Metastatic Shrinkage".

Auszeichnungen

Venia docendi verliehen

In ihrer Sitzung am 13. Dezember 2018 hat die Regenz der Universität Basel **Thorsten Schäfer** von der Forschungsgruppe "Stem Cells and Hematopoiesis" (Departement Biomedizin Hebelstrasse) die Venia docendi für Stammzellforschung verliehen.

Jamal Bouitbir von der Forschungsgruppe "Clinical Pharmacology" erhielt am 6. März 2019 die Lehrbefugnis für Pharmakologie. Beide sind damit befugt, den Titel eines Privatdozenten zu führen.

Barbara Szczerba ausgezeichnet

Gleich drei Auszeichnungen erhielt **Barbara Szczerba** von der Forschungsgruppe "Cancer Metastasis" (Departement Biomedizin Mattenstrasse). Am 16. November 2018 hat Barbara den Nancy Hynes Award für das beste Poster in "Basic Research" am dritten Meeting des Basel Breast Consortium entgegennehmen dürfen. Am 1. Februar 2019 folgte die Verleihung des Charles Rodolphe Brupbacher Young Investor Award in Zürich für ihren Beitrag zum 14. Symposium der Stiftung. Last but not least erhielt Barbara am 11. April 2019 bei der jährlichen Konferenz des Basel Stem Cell Network den Bruno Speck Award für klinisch-orientierte Forschung, insbesondere für die Veröffentlichung ihrer Forschungsergebnisse in einem "high-ranking journal".

Herzliche Gratulation!

Nature Volume 566, pages 553–557 (2019) IF 41.577

Neutrophils escort circulating tumour cells to enable cell cycle progression

Barbara Maria Szczerba[1], Francesc Castro-Giner[1,2], Marcus Vetter[3,4], Ilona Krol[1], Sofia Gkountela[1], Julia Landin[4], Manuel C. Scheidmann[1], Cinzia Donato[1], Ramona Scherrer[1], Jochen Singer[2,5], Christian Beisel[5], Christian Kurzeder[3,6], Viola Heinzelmann-Schwarz[3], Christoph Rochlitz[4], Walter Paul Weber[6], Niko Beerenwinkel[2,5] & Nicola Aceto[1*]

A better understanding of the features that define the interaction between cancer cells and immune cells is important for the development of new cancer therapies[1]. However, focus is often given to interactions that occur within the primary tumour and its microenvironment, whereas the role of immune cells during cancer dissemination in patients remains largely uncharacterized[2,3]. Circulating tumour cells (CTCs) are precursors of metastasis in several types of cancer[4,5,6], and are occasionally found within the bloodstream in association with non-malignant cells such as white blood cells (WBCs)[7,8]. The identity and function of these CTC-associated WBCs, as well as the molecular features that define the interaction between WBCs and CTCs, are unknown. Here we isolate and characterize individual CTC-associated WBCs, as well as corresponding cancer cells within each CTC–WBC cluster, from patients with breast cancer and from mouse models. We use single-cell RNA sequencing to show that in the majority of these cases, CTCs were associated with neutrophils. When comparing the transcriptome profiles of CTCs associated with neutrophils against those of CTCs alone, we detect a number of differentially expressed genes that outline cell cycle progression, leading to more efficient metastasis formation. Further, we identify cell–cell junction and cytokine–receptor pairs that define CTC–neutrophil clusters, representing key vulnerabilities of the metastatic process. Thus, the association between neutrophils and CTCs drives cell cycle progression within the bloodstream and expands the metastatic potential of CTCs, providing a rationale for targeting this interaction in treatment of breast cancer.

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https://doi.org/10.1038/s41586-019-0915-y

Cell 176, 98–112, January 10, 2019 IF 31.398

Circulating Tumor Cell Clustering Shapes DNA Methylation to Enable Metastasis Seeding

Sofia Gkountela,[1] Francesc Castro-Giner,[1,2] Barbara Maria Szczerba,[1] Marcus Vetter,[3,4] Julia Landin,[4,5] Ramona Scherrer,[1] Ilona Krol,[1] Manuel C. Scheidmann,[1] Christian Beisel,[6] Christian U. Stirnimann,[7] Christian Kurzeder,[3,5] Viola Heinzelmann-Schwarz,[3] Christoph Rochlitz,[4] Walter Paul Weber,[5] and Nicola Aceto[1,8,*]

Summary

The ability of circulating tumor cells (CTCs) to form clusters has been linked to increased metastatic potential. Yet biological features and vulnerabilities of CTC clusters remain largely unknown. Here, we profile the DNA methylation landscape of single CTCs and CTC clusters from breast cancer patients and mouse models on a genome-wide scale. We find that binding sites for stemness- and proliferation-associated transcription factors are specifically hypomethylated in CTC clusters, including binding sites for OCT4, NANOG, SOX2, and SIN3A, paralleling embryonic stem cell biology. Among 2,486 FDA-approved compounds, we identify Na^+/K^+ ATPase inhibitors that enable the dissociation of CTC clusters into single cells, leading to DNA methylation remodeling at critical sites and metastasis suppression. Thus, our results link CTC clustering to specific changes in DNA methylation that promote stemness and metastasis and point to cluster-targeting compounds to suppress the spread of cancer.

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https://doi.org/10.1016/j.cell.2018.11.046

Cancer Cell 35, 17–32, January 14, 2019 IF 22.844

Gain Fat—Lose Metastasis: Converting Invasive Breast Cancer Cells into Adipocytes Inhibits Cancer Metastasis

Dana Ishay-Ronen,[1,*] Maren Diepenbruck,[1] Ravi Kiran Reddy Kalathur,[1] Nami Sugiyama,[1] Stefanie Tiede,[1] Robert Ivanek,[1] Glenn Bantug,[2] Marco Francesco Morini,[1] Junrong Wang,[1] Christoph Hess,[2] and Gerhard Christofori[1,3,*]

Summary

Cancer cell plasticity facilitates the development of therapy resistance and malignant progression. De-differentiation processes, such as an epithelial-mesenchymal transition (EMT), are known to enhance cellular plasticity. Here, we demonstrate that cancer cell plasticity can be exploited therapeutically by forcing the trans-differentiation of EMT-derived breast cancer cells into post-mitotic and functional adipocytes. Delineation of the molecular pathways underlying such trans-differentiation has motivated a combination therapy with MEK inhibitors and the anti-diabetic drug Rosiglitazone in various mouse models of murine and human breast cancer *in vivo*. This combination therapy provokes the conversion of invasive and disseminating cancer cells into post-mitotic adipocytes leading to the repression of primary tumor invasion and metastasis formation.

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NATURE IMMUNOLOGY VOL 19 | JULY 2018 | 711–722 IF 21.809

Distinct progenitor lineages contribute to the heterogeneity of plasmacytoid dendritic cells

Patrick Fernandes Rodrigues[1], Llucia Alberti-Servera[1,2], Anna Eremin[1], Gary E. Grajales-Reyes[3], Robert Ivanek[1,4] and Roxane Tussiwand[1*]

Plasmacytoid dendritic cells (pDCs) are an immune subset devoted to the production of high amounts of type 1 interferons in response to viral infections. Whereas conventional dendritic cells (cDCs) originate mostly from a common dendritic cell progenitor (CDP), pDCs have been shown to develop from both CDPs and common lymphoid progenitors. Here, we found that pDCs developed predominantly from IL-7R^{+} lymphoid progenitor cells. Expression of SiglecH and Ly6D defined pDC lineage commitment along the lymphoid branch. Transcriptional characterization of SiglecH^{+}Ly6D^{+} precursors indicated that pDC development requires high expression of the transcription factor IRF8, whereas pDC identity relies on TCF4. RNA sequencing of IL-7R^{+} lymphoid and CDP-derived pDCs mirrored the heterogeneity of mature pDCs observed in single-cell analysis. Both mature pDC subsets are able to secrete type 1 interferons, but only myeloid-derived pDCs share with cDCs their ability to process and present antigen.

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https://doi.org/10.1038/s41590-018-0136-9

The Journal of Clinical Investigation 2019, 10.1172/JCI98785 IF 13.251

Targeting compensatory MEK/ERK activation increases JAK inhibitor efficacy in myeloproliferative neoplasms

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Constitutive JAK2 signaling is central to myeloproliferative neoplasm (MPN) pathogenesis and results in activation of STAT, PI3K/AKT, and MEK/ERK signaling. However, the therapeutic efficacy of current JAK2 inhibitors is limited. We investigated the role of MEK/ERK signaling in MPN cell survival in the setting of JAK inhibition. Type I and II JAK2 inhibition suppressed MEK/ERK activation in MPN cell lines in vitro, but not in *Jak2*V617F and MPLW515L mouse models in vivo. JAK2 inhibition ex vivo inhibited MEK/ERK signaling, suggesting that cell-extrinsic factors maintain ERK activation in vivo. We identified PDGFRα as an activated kinase that remains activated upon JAK2 inhibition in vivo, and PDGF-AA/PDGF-BB production persisted in the setting of JAK inhibition. PDGF-BB maintained ERK activation in the presence of ruxolitinib, consistent with its function as a ligand-induced bypass for ERK activation. Combined JAK/MEK inhibition suppressed MEK/ERK activation in Jak2V617F and MPLW515L mice with increased efficacy and reversal of fibrosis to an extent not seen with JAK inhibitors. This demonstrates that compensatory ERK activation limits the efficacy of JAK2 inhibition and dual JAK/MEK inhibition provides an opportunity for improved therapeutic efficacy in MPNs and in other malignancies driven by aberrant JAK-STAT signaling.

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Nature Communications (2019) 10: 1331 IF 12.353

Complex formation of APP with $GABA_B$ receptors links axonal trafficking to amyloidogenic processing

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$GABA_B$ receptors (GBRs) are key regulators of synaptic release but little is known about trafficking mechanisms that control their presynaptic abundance. We now show that sequence-related epitopes in APP, AJAP-1 and PIANP bind with nanomolar affinities to the N-terminal sushi-domain of presynaptic GBRs. Of the three interacting proteins, selectively the genetic loss of APP impaired GBR-mediated presynaptic inhibition and axonal GBR expression. Proteomic and functional analyses revealed that APP associates with JIP and calsyntenin proteins that link the APP/GBR complex in cargo vesicles to the axonal trafficking motor. Complex formation with GBRs stabilizes APP at the cell surface and reduces proteolysis of APP to Aβ, a component of senile plaques in Alzheimer's disease patients. Thus, APP/GBR complex formation links presynaptic GBR trafficking to Aβ formation. Our findings support that dysfunctional axonal trafficking and reduced GBR expression in Alzheimer's disease increases Aβ formation.

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https://doi.org/10.1038/s41467-019-09164-3

J. Exp. Med. 216 (3): 638 IF 10.790

The transcription factor Duxbl mediates elimination of pre-T cells that fail β-selection

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T cell development is critically dependent on successful rearrangement of antigen-receptor chains. At the β-selection checkpoint, only cells with a functional rearrangement continue in development. However, how non-selected T cells proceed in their dead-end fate is not clear. We identified low CD27 expression to mark pre-T cells that have failed to rearrange their β-chain. Expression profiling and single-cell transcriptome clustering identified a developmental trajectory through β-selection and revealed specific expression of the transcription factor Duxbl at a stage of high recombination activity before β-selection. Conditional transgenic expression of Duxbl resulted in a developmental block at the DN3-to-DN4 transition due to reduced proliferation and enhanced apoptosis, whereas RNA silencing of Duxbl led to a decrease in apoptosis. Transcriptome analysis linked Duxbl to elevated expression of the apoptosis-inducing Oas/RNaseL pathway. RNaseL deficiency or sustained Bcl2 expression led to a partial rescue of cells in Duxbl transgenic mice. These findings identify Duxbl as a regulator of β-selection by inducing apoptosis in cells with a nonfunctional rearrangement.

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https://doi.org/10.1084/jem.20181444

The EMBO Journal e99242 | 2018 IF 10.557

SUMOylation coordinates BERosome assembly in active DNA demethylation during cell differentiation

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Abstract

During active DNA demethylation, 5-methylcytosine (5mC) is oxidized by TET proteins to 5-formyl-/5-carboxylcytosine (5fC/5caC) for replacement by unmethylated C by TDG-initiated DNA base excision repair (BER). Base excision generates fragile abasic sites (AP-sites) in DNA and has to be coordinated with subsequent repair steps to limit accumulation of genome destabilizing secondary DNA lesions. Here, we show that 5fC/5caC is generated at a high rate in genomes of differentiating mouse embryonic stem cells and that SUMOylation and the BER protein XRCC1 play critical roles in orchestrating TDG-initiated BER of these lesions. SUMOylation of XRCC1 facilitates physical interaction with TDG and promotes the assembly of a TDG-BER core complex. Within this TDG-BERosome, SUMO is transferred from XRCC1 and coupled to the SUMO acceptor lysine in TDG, promoting its dissociation while assuring the engagement of the BER machinery to complete demethylation. Although well-studied, the biological importance of TDG SUMOylation has remained obscure. Here, we demonstrate that SUMOylation of TDG suppresses DNA strand-break accumulation and toxicity to PARP inhibition in differentiating mESCs and is essential for neural lineage commitment.

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DOI 10.15252/embj.201899242

Developmental Cell 48, 539–553, February 25, 2019 IF 9.616

A Hierarchical Regulatory Landscape during the Multiple Stages of EMT

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Summary

Epithelial-mesenchymal transition (EMT) enables cells to gain migratory and invasive features underlined by major transcriptional and epigenetic reprogramming. However, most studies have focused on the endpoints of the EMT process, and the epistatic hierarchy of the transcriptional networks underlying EMT has remained elusive. We have used a siRNA-based, functional high-content microscopy screen to identify 46 (co)transcription factors ((co)TFs) and 13 miRNAs critically required for EMT in normal murine mammary gland (NMuMG) cells. We compared dynamic gene expression during EMT kinetics and used functional perturbation of critical (co)TFs and miRNAs to identify groups and networks of EMT genes. Computational analysis as well as functional validation experiments revealed interaction networks between TFs and miRNAs and delineated the hierarchical and functional interactions of multiple EMT regulatory networks in NMuMG cells.

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https://doi.org/10.1016/j.devcel.2018.12.023

Biomaterials 192 (2019) 118–127 IF 8.806

Prefabrication of a large pedicled bone graft by engineering the germ for de novo vascularization and osteoinduction

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Abstract

Large and complex bone defects represent challenging clinical scenarios, typically requiring autologous vascularized bone transplants. In order to bypass the numerous associated limitations, here we aimed at ectopically prefabricating a bone graft surrogate with vascular pedicle.

A hollow cylinder of devitalized cancellous bone was used to define the space of a large bone substitute. This space was filled with devitalized pellets of engineered hypertrophic cartilage as bone-inducing material, in combination or not with stromal vascular fraction (SVF) of adipose tissue as source of osteoprogenitors and endothelial cells. Vascularization of the space was targeted through axial insertion of an arterio-venous (AV) bundle. Constructs were subcutaneously implanted in nude rats for 12 weeks and analyzed for bone formation and vascularization by histology and microtomography.

Retrieved constructs were extensively vascularized in all conditions, with vessels sprouting from the AV bundle and reaching a higher density in the axially central volume. Bone tissue was formed through remodeling of hypertrophic cartilage, and quantitatively correlated with de novo vascularization.

Our study demonstrates feasibility to prefabricate large, pedicled bone grafts in predefined shapes. The combination of an AV bundle with engineered hypertrophic cartilage provided a germ for the coupled processes of vascularization and bone formation. The demonstrated osteoinductivity of devitalized hypertrophic cartilage offers the opportunity of implementing the proposed regenerative surgery strategy through off-the-shelf materials.

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Journal for ImmunoTherapy of Cancer (2019) 7:16 IF 8.374

A novel anti-HER2 anthracycline-based antibody-drug conjugate induces adaptive anti-tumor immunity and potentiates PD-1 blockade in breast cancer

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Abstract

Increasing evidence suggests that antibody-drug conjugates (ADCs) can enhance anti-tumor immunity and improve clinical outcome. Here, we elucidate the therapeutic efficacy and immune-mediated mechanisms of a novel HER2-targeting ADC bearing a potent anthracycline derivate as payload (T-PNU) in a human HER2-expressing syngeneic breast cancer model resistant to trastuzumab and ado-trastuzumab emtansine. Mechanistically, the anthracycline component of the novel ADC induced immunogenic cell death leading to exposure and secretion of danger-associated molecular signals. RNA sequencing derived immunogenomic signatures and TCRβ clonotype analysis of tumor-infiltrating lymphocytes revealed a prominent role of the adaptive immune system in the regulation of T-PNU mediated anti-cancer activity. Depletion of CD8 T cells severely reduced T-PNU efficacy, thus confirming the role of cytotoxic T cells as drivers of the T-PNU mediated anti-tumor immune response. Furthermore, T-PNU therapy promoted immunological memory formation in tumor-bearing animals protecting those from tumor rechallenge. Finally, the combination of T-PNU and checkpoint inhibition, such as α-PD1, significantly enhanced tumor eradication following the treatment. In summary, a novel PNU-armed, HER2-targeting ADC elicited long-lasting immune protection in a murine orthotopic breast cancer model resistant to other HER2-directed therapies. Our findings delineate the therapeutic potential of this novel ADC payload and support its clinical development for breast cancer patients and potentially other HER2 expressing malignancies.

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https://doi.org/10.1186/s40425-018-0464-1

Cell Reports 26, 1627–1640, February 5, 2019 IF 8.032

RNA-Seq Signatures Normalized by mRNA Abundance Allow Absolute Deconvolution of Human Immune Cell Types

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Summary

The molecular characterization of immune subsets is important for designing effective strategies to understand and treat diseases. We characterized 29 immune cell types within the peripheral blood mononuclear cell (PBMC) fraction of healthy donors using RNA-seq (RNA sequencing) and flow cytometry. Our dataset was used, first, to identify sets of genes that are specific, are co-expressed, and have housekeeping roles across the 29 cell types. Then, we examined differences in mRNA heterogeneity and mRNA abundance revealing cell type specificity. Last, we performed absolute deconvolution on a suitable set of immune cell types using transcriptomics signatures normalized by mRNA abundance. Absolute deconvolution is ready to use for PBMC transcriptomic data using our Shiny app (https://github.com/giannimonaco/ABIS). We benchmarked different deconvolution and normalization methods and validated the resources in independent cohorts. Our work has research, clinical, and diagnostic value by making it possible to effectively associate observations in bulk transcriptomics data to specific immune subsets.

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https://doi.org/10.1016/j.celrep.2019.01.041

Breast Cancer Research (2018) 20:141 IF 6.142

Denosumab treatment is associated with the absence of circulating tumor cells in patients with breast cancer

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Abstract

Background The presence of circulating tumor cells (CTCs) in patients with breast cancer correlates to a bad prognosis. Yet, CTCs are detectable in only a minority of patients with progressive breast cancer, and factors that influence the abundance of CTCs remain elusive.

Methods We conducted CTC isolation and enumeration in a selected group of 73 consecutive patients characterized by progressive invasive breast cancer, high tumor load and treatment discontinuation at the time of CTC isolation. CTCs were quantified with the Parsortix microfluidic device. Clinicopathological variables, blood counts at the time of CTC isolation and detailed treatment history prior to blood sampling were evaluated for each patient.

Results Among 73 patients, we detected at least one CTC per 7.5 ml of blood in 34 (46%). Of these, 22 (65%) had single CTCs only, whereas 12 (35%) featured both single CTCs and CTC clusters. Treatment with the monoclonal antibody denosumab correlated with the absence of CTCs, both when considering all patients and when considering only those with bone metastasis. We also found that low red blood cell count was associated with the presence of CTCs, whereas high CA 15-3 tumor marker, high mean corpuscular volume, high white blood cell count and high mean platelet volume associated specifically with CTC clusters.

Conclusions In addition to blood count correlatives to single and clustered CTCs, we found that denosumab treatment associates with most patients lacking CTCs from their peripheral circulation. Prospective studies will be needed to validate the involvement of denosumab in the prevention of CTC generation.

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https://doi.org/10.1186/s13058-018-1067-y

Cell Death & Disease (2019) 10:110 IF 5.638

Pasireotide protects mammalian cochlear hair cells from gentamicin ototoxicity by activating the PI3K–Akt pathway

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Abstract

Gentamicin is a widely used antibiotic for the treatment of gram-negative bacterial infections; however, its use often results in significant and permanent hearing loss. Hearing loss resulting from hair cell (HC) degeneration affects millions of people worldwide, and one major cause is the loss of sensory HCs in the inner ear due to aminoglycoside exposure. Strategies to overcome the apparently irreversible loss of HCs in mammals are crucial for hearing protection. Here, we report that the somatostatin analog pasireotide protects mouse cochlear HCs from gentamicin damage using a well-established in vitro gentamicin-induced HC loss model and that the otoprotective effects of pasireotide are due to Akt up-regulation via the PI3K–Akt signal pathway activation. We demonstrate active caspase signal in organ of Corti (OC) explants exposed to gentamicin and show that pasireotide treatment activates survival genes, reduces caspase signal, and increases HC survival. The neuropeptide somatostatin and its selective analogs have provided neuroprotection by activating five somatostatin receptor (SSTR1–SSTR5) subtypes. Pasireotide has a high affinity for SSTR2 and SSTR5, and the addition of SSTR2- and SSTR5-specific antagonists leads to a loss of protection. The otoprotective effects of pasireotide were also observed in a gentamicin-injured animal model. In vivo studies have shown that 13 days of subcutaneous pasireotide application prevents gentamicin-induced HC death and permanent hearing loss in mice. Auditory brainstem response analysis confirmed the protective effect of pasireotide, and we found a significant threshold shift at all measured frequencies (4, 8, 16, 24, and 32 kHz). Together, these findings indicate that pasireotide is a novel otoprotective peptide acting via the PI3K–Akt pathway and may be of therapeutic value for HC protection from ototoxic insults.

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https://doi.org/10.1038/s41419-019-1386-7

Frontiers in Immunology October 2018 | Volume 9 | Article 2258 IF 5.511

Accumulation of Multipotent Hematopoietic Progenitors in Peripheral Lymphoid Organs of Mice Over-expressing Interleukin-7 and Flt3-Ligand

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Interleukin-7 (IL-7) and Flt3-ligand (FL) are two cytokines important for the generation of B cells, as manifested by the impaired B cell development in mice deficient for either cytokine or their respective receptors and by the complete block in B cell differentiation in the absence of both cytokines. IL-7 is an important survival and proliferation factor for B cell progenitors, whereas FL acts on several early developmental stages, prior to B cell commitment. We have generated mice constitutively over-expressing both IL-7 and FL. These double transgenic mice develop splenomegaly and lymphadenopathy characterized by tremendously enlarged lymph nodes even in young animals. Lymphoid, myeloid and dendritic cell numbers are increased compared to mice over-expressing either of the two cytokines alone and the effect on their expansion is synergistic, rather than additive. B cell progenitors, early progenitors with myeloid and lymphoid potential (EPLM), common lymphoid progenitors (CLP) and lineage$^-$, Sca1$^+$, kit$^+$ (LSK) cells are all increased not only in the bone marrow but also in peripheral blood, spleen and even lymph nodes. When transplanted into irradiated wild-type mice, lymph node cells show long-term multilineage reconstitution, further confirming the presence of functional hematopoietic progenitors therein. Our double transgenic mouse model shows that sustained and combined over-expression of IL-7 and FL leads to a massive expansion of most bone marrow hematopoietic progenitors and to their associated presence in peripheral lymphoid organs where they reside and potentially differentiate further, thus leading to the synergistic increase in mature lymphoid and myeloid cell numbers. The present study provides further *in vivo* evidence for the concerted action of IL-7 and FL on lymphopoiesis and suggests that extramedullary niches, including those in lymph nodes, can support the survival and maintenance of hematopoietic progenitors that under physiological conditions develop exclusively in the bone marrow.

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doi: 10.3389/fimmu.2018.02258

STEM CELLS TRANSLATIONAL MEDICINE 2019;8:194–204 IF 4.929

Challenges Toward the Identification of Predictive Markers for Human Mesenchymal Stromal Cells Chondrogenic Potential

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Abstract

Human bone marrow derived mesenchymal stromal cells (BMSCs) represent a putative cell source candidate for tissue engineering-based strategies to repair cartilage and bone. However, traditional isolation of BMSCs by adhesion to plastic leads to very heterogeneous cell populations, accounting for high variability of chondrogenic differentiation outcome, both across donors and across clonally derived strains. Identification of putative surface markers able to select BMSC subpopulations with higher chondrogenic capacity (CC) and reduced variance in chondrogenic differentiation could aid the development of BMSC-based cartilage and bone regeneration approaches. With the goal to identify predictive markers for chondrogenic BMSC populations, we assessed the gene expression profile of single cell-derived clones with high and low CC. While a clustering between high and low CC clones was observed for one donor, donor-todonor variability hampered the possibility to achieve conclusive results when different donors were considered. Nevertheless, increased NCAM1/CD56 expression correlated in clones derived from one donor with higher CC, the same trend was observed for three additional donors (even if no significance was achieved). Enriching multiclonal BMSCs for CD56$^+$ expression led to an increase in CC, though still highly affected by donor-to-donor variability. Our study finally suggests that definition of predictive marker(s) for BMSCs chondrogenesis is challenged by the large donor heterogeneity of these cells, and by the high complexity and plasticity of the BMSCs system. Multiple pathways and external parameters may be indeed involved in determining the chondrogenic potential of BMSCs, making the identification of putative markers still an open issue.

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The Journal of Immunology 2019, 202: 37–47 IF 4.539

TGF-β Upregulated Mitochondria Mass through the SMAD2/3→C/EBPβ→PRMT1 Signal Pathway in Primary Human Lung Fibroblasts

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Tissue remodeling of subepithelial mesenchymal cells is a major pathologic condition of chronic obstructive pulmonary disease and asthma. Fibroblasts contribute to fibrotic events and inflammation in both airway diseases. Recent mechanistic studies established a link between mitochondrial dysfunction or aberrant biogenesis leading to tissue remodeling of the airway wall in asthma. Protein arginine methyltransferase-1 (PRMT1) participated in airway wall remodeling in pulmonary inflammation. This study investigated the mechanism by which PRMT1 regulates mitochondrial mass in primary human airway wall fibroblasts. Fibroblasts from control or asthma patients were stimulated with TGF-β for up to 48 h, and the signaling pathways controlling PRMT1 expression and mitochondrial mass were analyzed. PRMT1 activity was suppressed by the pan-PRMT inhibitor AMI-1. The SMAD2/3 pathway was blocked by SB203580 and C/EBPβ by small interference RNA treatment. The data obtained from unstimulated cells showed a significantly higher basal expression of PRMT1 and mitochondrial markers in asthmatic compared with control fibroblasts. In all cells, TGF-β significantly increased the expression of PRMT1 through SMAD2/3 and C/EBPβ. Subsequently, PRMT1 upregulated the expression of the mitochondria regulators PGC-1α and heat shock protein 60. Both the inhibition of the SAMD2/3 pathway or PRMT1 attenuated TGF-β-induced mitochondrial mass and C/EBPβ and α-SMA expression. These findings suggest that the signaling sequence controlling mitochondria in primary human lung fibroblasts is as follows: TGF-β→SMAD2/3→C/EBPβ→PRMT1→PGC-1α. Therefore, PRMT1 and C/EBPβ present a novel therapeutic and diagnostic target for airway wall remodeling in chronic lung diseases.

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www.jimmunol.org/cgi/doi/10.4049/jimmunol.1800782

The Journal of Steroid Biochemistry and Molecular Biology 186 (2019) 212–225 IF 4.095

Effects of lisdexamfetamine on plasma steroid concentrations compared with D-amphetamine in healthy subjects: A randomized, double-blind, placebo-controlled study

Petra Strajhar[a,1], Patrick Vizeli[b,1], Melanie Patt[a], Patrick C. Dolder[b], Denise V. Kratschmar[a], Matthias E. Liechti[b,], Alex Odermatt[a,*]**

Abstract
The novel D-amphetamine prodrug lisdexamfetamine is applied to treat attention-deficit/hyperactivity disorder (ADHD). D-Amphetamine releases dopamine and norepinephrine and stimulates the hypothalamic-pituitaryadrenal (HPA) axis, which may contribute to its reinforcing effects and risk of abuse. However, no data is currently available on the effects of lisdexamfetamine on circulating steroids. This randomized, double-blind, placebo-controlled, cross-over study evaluated the effects of equimolar doses of D-amphetamine (40 mg) and lisdexamfetamine (100 mg) and placebo on circulating steroids in 24 healthy subjects. Plasma steroid and Damphetamine levels were determined up to 24 h. Delayed increase and peak levels of plasma D-amphetamine concentrations were observed following lisdexamfetamine treatment compared with D-amphetamine administration, however the maximal concentrations and total exposure (area under the curve [AUC]) were similar. Lisdexamfetamine and D-amphetamine significantly enhanced plasma levels of adrenocorticotropic hormone, glucocorticoids (cortisol, cortisone, corticosterone, 11-dehydrocorticosterone, and 11-deoxycortisol), androgens (dehydroepiandrosterone, dehydroepiandrosterone sulfate, and Δ4-androstene-3,17-dione [androstenedione]), and progesterone (only in men) compared with placebo. Steroid concentration-time curves were shifted to later time points due to a non-significantly later onset following lisdexamfetamine administration than after D-amphetamine, however maximal plasma steroid concentrations and AUCs did not differ between the active treatments. None of the active treatments altered plasma levels of the mineralocorticoids aldosterone and 11- deoxycorticosterone or the androgen testosterone compared with placebo. The effects of the amphetamines on glucocorticoid production were similar to those that were previously reported for methylphenidate (60 mg) but weaker than those for the serotonin releaser 3,4-methylenedioxymethamphetamine (MDMA; 125 mg) or direct serotonin receptor agonist lysergic acid diethylamide (LSD; 0.2 mg). Lisdexamfetamine produced comparable HPA axis activation and had similar pharmacokinetics than D-amphetamine, except for a delayed time of onset. Thus, serotonin (MDMA, LSD) may more effectively stimulate the HPA axis than dopamine and norepinephrine (D-amphetamine).

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https://doi.org/10.1016/j.jsbmb.2018.10.016

Biotechnology and Bioengineering 2019;116:132–142 IF 3.952

Paracrine potential of adipose stromal vascular fraction cells to recover hypoxia-induced loss of cardiomyocyte function

Myroslava Mytsyk[1,2*], Giuseppe Isu[1,2 *], Giulia Cerino[1,2], Martin T. R. Grapow[1], Friedrich S. Eckstein[1], Anna Marsano[1,2]

Abstract

Cell-based therapies show promising results in cardiac function recovery mostly through paracrine-mediated processes (as angiogenesis) in chronic ischemia. In this study, we aim to develop a 2D (two-dimensional) in vitro cardiac hypoxia model mimicking severe cardiac ischemia to specifically investigate the prosurvival paracrine effects of adipose tissue-derived stromal vascular fraction (SVF) cell secretome released upon three-dimensional (3D) culture. For the 2D-cardiac hypoxia model, neonatal rat cardiomyocytes (CM) were cultured for 5 days at < 1% (approaching anoxia) oxygen (O_2) tension. Typical cardiac differentiation hallmarks and contractile ability were used to assess both the cardiomyocyte loss of functionality upon anoxia exposure and its possible recovery following the 5-day-treatment with SVF-conditioned media (collected following 6-day-perfusion-based culture on collagen scaffolds in either normoxia or approaching anoxia). The culture at < 1% O_2 for 5 days mimicked the reversible condition of hibernating myocardium with still living and poorly contractile CM (reversible state). Only SVF-medium conditioned in normoxia expressing a high level of the prosurvival hepatocyte-growth factor (HGF) and insulin-like growth factor (IGF) allowed the partial recovery of the functionality of damaged CM. The secretome generated by SVF-engineered tissues showed a high paracrine potential to rescue the non-functional CM, therefore resulting in a promising patch-based treatment of specific low-perfused areas after myocardial infarction.

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DOI: 10.1002/bit.26824

Cancer Management and Research 2018:10 4709–4718 IF 3.702

Impact of the new FIGO 2013 classification on prognosis of stage I epithelial ovarian cancers

Céline Montavon Sartorius[1], Uzma Mirza[1], Andreas Schötzau[2], Gillian Mackay[1], Daniel Fink[3], Neville F Hacker[4], Viola Heinzelmann-Schwarz[1,2]

Purpose: The stage of disease is one of the strongest prognostic factors in epithelial ovarian cancer. The International Federation of Gynecology and Obstetrics (FIGO) classification was revised in 2013; stage IC was subdivided into IC1 (intraoperative surgical spill), IC2 (capsule rupture before surgery or tumor on surface), and IC3 (positive peritoneal washing or ascites). Our aim was to compare the outcome of patients in the new FIGO stage I subgroups, as this might influence adjuvant therapy decisions.

Patients and methods: Patient databases of three gynecological oncology centers were retrospectively analyzed. Patients with FIGO stage I ovarian cancers were restaged according to the revised classification, based on operative and pathological reports, and determined patient outcomes.

Results: We analyzed 128 patients with ovarian cancers. In FIGO IA, we found 11.3% recurrences and 4.2% deaths. In FIGO IC, 21.8% of the patients recurred and 7.3% died. There was a trend toward a shorter time to recurrence when comparing IA to IC (P=0.076). Within all new subgroups of FIGO IC, there was no difference in time to recurrence (P=0.59). There was also no significant difference in survival when FIGO IA was compared to FIGO IC in comparison with the new individual classifications (IA to IC, IA to IC1, 2, or 3; P=0.60, P=0.15, P=0.61, P=0.66, respectively) or within the different subgroups (P=0.56). Platinum-based chemotherapy was given to the majority (82.6%, n=38/46) of the FIGO IC patients compared to 30.9% in FIGO IA (n=17/55). There was no significant difference within the new subgroups of FIGO IC (P=0.88).

Conclusion: In our retrospective analysis, the new FIGO staging of IC ovarian cancers did not predict prognosis, but the use of adjuvant chemotherapy in 82.6% of the stage IC patients may have biased the outcome.

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REVIEWS

SCIENCE TRANSLATIONAL MEDICINE 11, eaat2189 (2019) IF 16.710

Challenges for mesenchymal stromal cell–based therapies

Ivan Martin[1*], Jacques Galipeau[2], Charles Kessler[3], Katarina Le Blanc[4], Francesco Dazzi[5]

Clinical trials of mesenchymal stromal cell therapies reveal a challenging heterogeneous landscape, including diverse therapeutic targets, patient categories, cell sources, and potential mechanisms of action.

Early results in the therapeutic use of cell populations typically referred to as mesenchymal stromal (stem) cells (MSCs) have prompted great interest in harnessing their potential for promoting tissue regeneration and modulating inflammation. There is a substantial portfolio of MSC clinical trial studies in Europe, many of them supported by the European Union's (EU) health research program (Table 1). Multinational collaborations, a requirement for most EU funding, have resulted in a productive combination of groups active in clinical research and sustained by others investigating MSC biology and mechanisms of action. The multicenter nature of the clinical trials also enables access to larger patient populations and exposes health regulators in different domains to the new treatments. The advantages of multicenter clinical studies are offset by the challenges for approval of harmonized protocols by the different national authorities. The latter may implement the same directives in specific ways and within various time frames, often leading to delays in patient recruitment. These clinical studies have revealed marked heterogeneity in MSC treatments, with diverse therapeutic targets, various sources of tissue-specific MSCs, multiple manufacturing protocols, and different routes of delivery (Table 1). Here, we identify biological, manufacturing, and clinical challenges of MSC therapies and propose design criteria for clinical trials with high impact.

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«Selected publications by DBM members»

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

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

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

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

Deadline for the next issue is June 30, 2019.

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Immune Regulation

Athansios Kouklas
Immune Regulation

James Canales Murillo
Tumor Biology

Marjorie Delahaye
Tumor Biology

Vincenzo Prestigiacomo
Tumor Biology

Congratulations

Leilana Schnitter
Geboren am 28.11.2018

Laura Meier
Geboren am 10.01.2019

Eric Xu Ding
Geboren am 10.12.2018

Louise Maria Golfieri Ferreira
Geboren am 26.12.2018

Herzlich willkommen, allerseits!

Board games are not just for geeks anymore

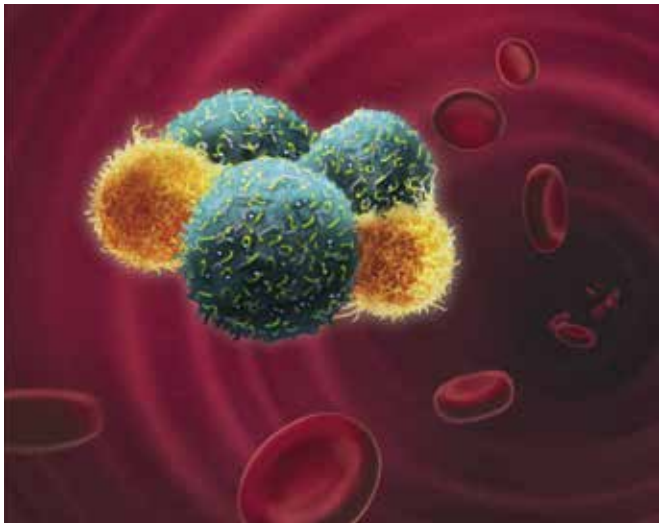
I can only blame Lucia

Lucia Kubovcakova, a former postdoc in Skoda's Lab, had her desk right next to mine. For about two years I did not foresee her mischievous plan to turn my life upside down. It was rather inconspicuous and elegantly done. The very first time she told me about board games, I ignored it. Yet, a few months later this topic reappeared and I asked her for more details. I was stunned. Lucia immediately brought Ignacy Trzewiczek a Polish designer from Portal Games (finally, a name that is more difficult than mine!) to my attention, along with his game about Robinson Crusoe exploring a cursed island, building a shelter to survive harsh weather and trying to get back home. The catch for me was the fact that this game is co-operative, meaning that everyone plays together against the game. What's more, there are different scenarios, the goal changes, events will sometimes bring you food, but another time this food might poison you… This was enough for me to try this out. And so, the adventure began.

One thousand games

Lucia did not forget to mention that every October around 200'000 visitors go to Essen (Germany) to explore the new releases from the booming board game industry. Game designers and publishers release around one thousand new games every year, ranging from five-minute party games about exploding kittens to an eight-hour game of galactic conquest and strategic diplomacy. There is something for everyone and I had to see it for myself. I walked among the crowds for four days, found seven new games for my home collection and made new friends from around the world (mostly from Poland though…). This was four years ago. Now, I no longer passively participate in this madness, I actively create it by demoing new releases to hundreds of people. These are by far the best four days in the year. And who knew that a graphic designer, Aga Jakimiec from Portal Games, could draw amazing tumor cells?!

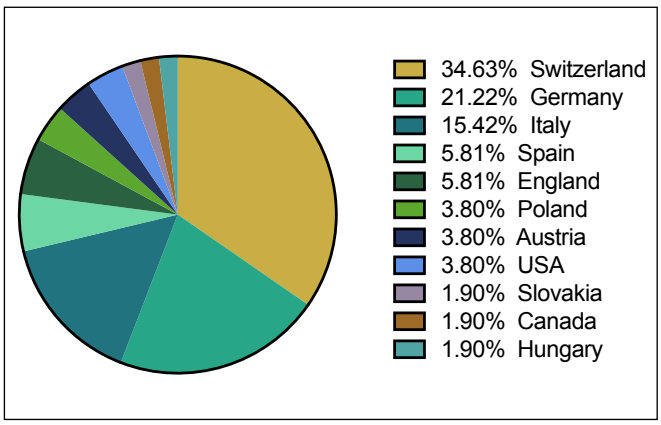
Portal Games booth at Essen Spiel 2018



CTC-neutrophil cluster by Aga Jakimiec

Why is Basel so different?

Normally, when you look for a gaming experience you would search for a Board Game Café in the area. But Basel is not an average city and you will not find such a place here. Instead, there is an entire association for gamers called Board Game Basel (BGB). BGB is run by Rubén Martin (astrophysicist) and Hirginia Vallejo (pianist) who dedicate their free time to promoting card and board games in our area. They have managed to bring together people from different backgrounds and supply the collection with hundreds of games. Over the past five years, members of BGB have been gaming, exchanging their interests and making new friends.



The nationalities of BGB members

BasGame

Once a year, BGB shares their massive game library with the public. Hundreds of people join this event, ranging from passionate geeks to entire families that only seek casual games. It is an opportunity for the community to experience alternatives to TV- and computer-based leisure time. The next BasGame will take place on the 28th of September, 2019 (book your calendars!).

BASGAME DER BASLER BRETTSPIELTAG

More details at www.basgame.ch

7th Continent

Games, finally

Forget Monopoly, Scrabble and Uno. Modern games compete for our attention by introducing innovative concepts. Firstly, the looks. Playing a game has become a truly esthetically-pleasing activity (e.g. Scythe).

Secondly, the concepts. Novel and brain-twisting ideas have been implemented to enhance the experience (e.g. co-operative gameplay, time travel, escape room in the box).

Thirdly, storytelling. When opening a box, you might find descriptive text on the cards or even a whole book next to the game. It will contain paragraphs which you will read while playing the game to uncover the story behind it. An extreme example is the *legacy* approach, where stickers are used to mark changes on the board that will be carried to the next game and so your choices have consequences that impact on the future gameplay (e.g. actual destruction of components so that you cannot use them in the future).

Lastly, technology. App integration is the marriage between analog and digital. For example, the game "Detective" uses an entire online database containing data on suspects or interrogation recordings, and real-life information can be searched online to help with the game progression. Apps can also replace big card decks or simply provide a matching soundtrack to help with immersion in the theme of the game. Soon, the Dized app will allow us to learn how to play a game without reading long rulebooks, and Alexa (from Amazon) will answer any questions about rules in the middle of gameplay. (Note: games without rulebooks exist as well – just open the box and learn while playing, e.g. This War of Mine and the Fast Forward series.)

Terraforming Mars

Below I provide some of my favorite titles
(yes, this section is for you, Emmanuel! :-)).
Happy gaming! Basia

Gateway Games (where to start):
Ticket to Ride, Forbidden Island, Bang!, 7 Wonders, Carcassonne, Hero Realms, Istanbul, Super Motherload

Bio/medical Games:
Pandemic, Holding On, Bios Megafauna, Viral, Lobotomy, Evolution, Cytosis

Escape Room/Puzzle Games:
Escape Tales: The Awakening, Exit, Werewolf Experiment, Deckscape, Unlock!

Party Games:
The Mind, Codenames, Dixit, Cards Against Humanity, Exploding Kittens, Captain Sonar

Co-operative Games:
7th Continent, Arkham Horror LCG, Robinson Crusoe, Gloomhaven, Mansions of Madness, Dead of Winter, Time Stories

Deduction Games:
Detective (a must try!), Chronicles of Crime, Mythos Tales, Sherlock Holmes CD

Legacy Games:
Pandemic Legacy, Betrayal at the House on the Hill Legacy, Risk Legacy

Strategic Games:
Terraforming Mars, Scythe, Terra Mystica, A Feast for Odin, Caverna, Castles of Burgundy, Viticulture

Solitary Games
(when all your friends are laughing at you, but you still want to try something new):
7th Continent (life-changer), Hostage Negotiator, Friday, Onirim


Rezepte: www.spargelseiten.de

New Zealand

Fast Facts

Population: 4.78 million humans, 30 million sheep.

Land mass: 268 000 km^2 spread over two main Islands (creatively named "the North Island" and "the South Island") as well as many smaller surrounding islands.

Population density: 18 people per km^2
(for perspective, Switzerland has a population density of 206 people/km^2). Although for much of the South Island there is fewer than 1 person/km^2.

Official languages: English and *Te Reo Maori* (the Maori language)

Cultural makeup: 75% European, 15% Maori, 10% Asian

Famous for:
› The All Blacks and the Haka
› First self-governing country to give women the vote (1893)
› Sir Edmund Hillary (first to summit Mt. Everest in 1953 with Sherpa Tenzing Norgay)
› Ernest Rutherford
› Natural parks
› Hobbits

New Zealand (NZ), or Aotearoa in Maori, is a country in the south Pacific Ocean which is home to about 5 million people who refer to themselves as "Kiwis" (not to be confused with the flightless bird or the fruit of the same name).

History

New Zealand has been inhabited since about the 13th century. Initially by a group of Polynesian seafaring people, the Maori, then later by Europeans. In 1642 a Dutchman, Abel Tasman, first "discovered" New Zealand, the British explorer James Cook mapped the coastline in 1769 and by the 1800s waves of settlers from England and France were arriving. In 1840 a group of about 40 Maori chiefs representing many of the various tribes, signed a treaty with the British government, the Treaty of Waitangi. This gave the British sole rights to purchase land, and in return granted Maori the same rights and protections as British


30 million sheep

subjects. Owing to a mis-translation of a few key words in the Maori copy (which was completed the night before the talks began) the two sides agreed to significantly different things. The British thought they were gaining *sovereignty* over the country (supreme power or authority), whereas the Maori version of the treaty used a term that is much closer to *governance*, indicating a more custodial role. Essentially, the Maori thought they were letting the Brits take responsibility for the land – to look after it, while the British thought they were getting control of it. This soon led to disagreements, and eventually a series of wars between the British government and the Maori, lasting almost 30 years. Claims against the government are ongoing up to the present day and the treaty continues to be an important document for the rights of indigenous people in NZ. The signing of the Treaty is marked each year in February on Waitangi Day. Celebrations are usually peaceful, but previous Prime Ministers have declined to attend for fear of protesters. In 2016 the PM did not attend; instead a Minister who was there in his stead shot to notoriety when he was hit in the head with a pink rubber sex toy, earning him the moniker "Dildo Baggins" by the Press.

Geography

New Zealand is located on what is known as the Pacific Rim of Fire, which sounds like a Michael Bay film but is actually a massive chain of increased volcanic and seismic activity that follows the border of the Pacific tectonic plate. The same plate boundary is responsible for the seismic activity in Japan, California, Mexico and Chile. Because of this, earthquakes are fairly common in NZ with about 200 per year that are noticeable and 1 or 2 per year


Mt. Ruapehu

that are felt throughout the entire country. The most recent "big one" hit the southern Island in 2011, killing 185 people and destroying much of the city of Christchurch. Volcanic and geothermal activity is very noticeable in the North Island, New Zealanders choosing not only to go skiing on an active volcano (Mt. Ruapehu) but also to build the country's largest city (Auckland) around and amongst a field of over 50 dormant volcanoes. Geothermal activity has become a tourist attraction in the North Island town of Rotorua, which is famous for both its hot mud pools and the egg-like smell that accompanies them, which can usually be smelt about 30 minutes before actually arriving in Rotorua. At Hot Water Beach to the north of Rotorua, it is possible to dig a hole in the sand at high tide; the water that fills the hole from below is about 40°C and makes for a great do-it-yourself hot pool to warm up in between swims. The subduction of the Pacific plate under NZ is also responsible for pushing up mountain ranges down the length of the South Island, creating the highest peak (Aoraki/Mt. Cook, 3724m) and the spectacular fjords of Fiordland at the very southern end of the South Island.

Because NZ was geographically isolated and human-free for thousands of years, it is home to a number of unique native animals and birds. The most well-known is the national bird, the Kiwi. There are five species of Kiwi, all are small, nocturnal, flightless birds that forage for insects and live in burrows under the ground. The introduction of stoats, ferrets, and cats by human settlers nearly wiped them out. Nowadays there are several sanctuaries on the main two islands and more on nearby smaller islands where predators have been systematically eradiated, however the species remains on the endangered list with only about 70000 in existence. Other unique creatures include the Tuatara (an ancient type of lizard), the Kea (a playful mountain parrot with a taste for destruction of skier's rental cars) and the Giant Weta (a 10cm-long insect that looks like a big cricket and weighs about the same as an adult BL/6 mouse!). Many more impressive species, like the 4m tall Moa (imagine a huge Emu) and the Haast's eagle were sadly hunted out of existence by Maori and Europeans or perished as a result of introduced species such as ferrets and rodents.


Kea


Tuatara

Culture

It is an understatement to say that New Zealanders are keen on sport. The national sport is rugby, and the national team, the All Blacks, are practically superstars. Rugby is everywhere and pervades almost every aspect of life. The closest thing I have ever seen to NZs obsession with rugby is the Italian obsession with football. The All Blacks are also one of the best-known kiwi representatives internationally. This is probably because they are one of the best teams in the world, but also partially due to the *Haka*, the iconic Maori-derived war dance that is performed before kick-off.

While the major cities are fairly cosmopolitan and as modern and cultured as Basel, not everywhere has the same cultural sophistication. Visiting smaller towns can feel like a trip back in time, which lends them a certain charm if that's your kind of thing. However, this isn't to everyone's taste; after touring the country in 2005, the British actor John Cleese wrote "if you wish to kill yourself but lack the courage, I think a visit to Palmerston North will do the trick…"

New Zealand also has a small film industry in the capital city Wellington, where Peter Jackson's company produced the film trilogy *The Lord of the Rings* which was filmed largely in NZ. To capitalise on the influx of tourists the films brought, a "Minister of the Rings" (seriously) was appointed, tours sprang up offering everything from bus tours around the country to see the locations used to helicopter flights "over Rivendell", and an enormous Gollum was erected at Wellington airport.

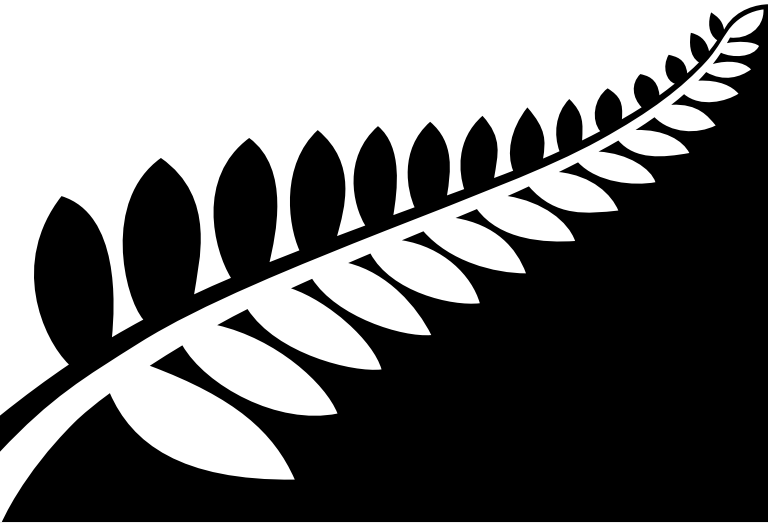
Haka

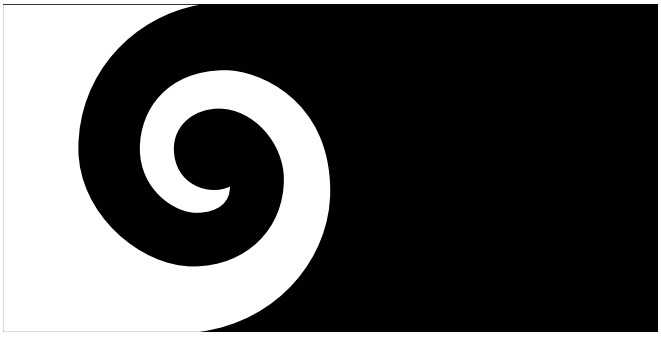
New Zealand also has a lively music scene, you may have even heard of some of the bigger musical acts such as Lorde, Crowded House, Fat Freddy's Drop, and Flight of the Conchords.

The Flag

New Zealand made international news a few years ago when it was decided that there would be a referendum to change the flag. The flag was and *(spoiler alert)* still is a blue rectangle with the Union Jack (the British flag) in the top left corner and 4 red stars on the right side. The motives for change were simple:

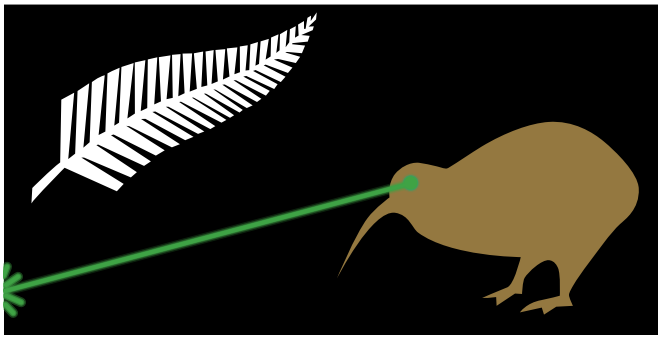
3 of 4 Finalists





A) NZ is no longer a British outpost, and the flag should reflect that, and
B) it's far too similar to Australia's (which it is).

So, the public was asked to send in their suggestions for what the new flag ought to look like. Many entries were serious attempts to define the national identity, but these were vastly outnumbered by more "creative" suggestions. Eventually, 4 finalists were chosen and a final referendum was held with the 5th option to just keep the current flag. So now, $26 000 000 later, we have the same flag as before but at least the late-night comedy shows got something to talk about!



Outdoors

Like the Swiss, Kiwis love getting into nature, and tramping (hiking) is popular. The low population density over much of the country and the abundance of natural parks means you usually don't have to go far to find yourself in "the wops" (see Talk like a Kiwi, below). Because NZ is long and thin, with mountain ranges down the middle there are vast differences in the climate as you go from north (warmer) to south (colder) and from the east coast (drier and calmer) to the west (wet and stormy).

In summer months, Kiwis flock to the beach. But if you go there, don't expect to find deckchairs, or a tapestry of towels laid one next to the other like you might find in Europe. Unless it's near a major city, the beach will be nearly deserted by European standards. Most people will walk for 5 or 10 minutes down the beach to find a patch (or even several hundred meters of beach) to themselves.

A word of caution to anyone visiting NZ in the summer: thanks to high levels of UV radiation, NZ and Australia have the highest incidences of melanoma in the world. Fair-skinned Europeans will typically burn after about 15-20 minutes in the midday summer sun. Sunscreen is advised and freely available at most popular public beaches.

Relationship with Neighbours – Aussie rivalry

The relationship between New Zealanders and their nearest neighbours, the Australians ("Aussies") is best thought of as being akin to the relationship between siblings; a relationship that superficially is defined by rivalry and competition (especially surrounding sports) but with a strong underlying bond between the two. New Zealanders and Australians fought together in both world wars and from a European perspective their cultures are very similar. It should be pointed out that New Zealand is not part of Australia. Despite 2000km of ocean between the two countries, some people manage to confuse the two (perhaps it's that damn flag – we should really change it…. Oh wait, no…).

James Neil Fisher

Talk like a local – a cheat sheet for communicating with Kiwis

Gidday	Hello
Mate	Friend (e.g. gidday mate)
Choice	Good
Chur	Thanks
No worries	You're welcome
She'll be right	Don't worry about it/the situation will resolve itself
Dairy	Small convenience store
Bloke	Man
Bogan	Unrefined or unsophisticated person
Pakeha	Maori term for a white/European person
Eh	Added to the end of a phrase, makes the phrase a question.
Yeah nah	Literally means "Yes, No". Used to indicate indecision
The wops	A remote location
Heaps	Lots

Today: Hanane Baidarjad, Brain Tumor Immunotherapy

You can call it the ochre city or the capital of tourism. It is one of the most visited cities in the world, this has been proved by it being ranked at the top of many international charts for several years in a row. It is also known for its special architecture, the fact that the number of floors in its buildings is exclusively restricted to five and all buildings must be painted in ochre. The one and only tall building that exists in that city is 77 metres (253 ft) high, and it is a part of the very famous Koutoubia mosque that was founded under the reign of Almohad Caliph Yaqub al-Mansur (1184 to 1199).

Koutoubia mosque

Jemaa El Fna square

The mosque is in the heart of the ochre city just in front of Jemaa El Fna square, nobody visits my home town without passing by that square, known for its permanent crowd. It is famous for music, comedy and game and dancing shows. If you want to taste the local food, it is the perfect spot to find the gastronomy specific to the city or even the country.

It is known internationally that the gastronomy of my city, and more generally my country, is highly diversified. Nowadays it is becoming more of a mixture of the classical meals and modern ones, making it even more tasty and nicely presented. The basics are the same: Meat, fish, chicken, vegetables and fruits. However, creative hands always manage to make the most delicious meals and when mixed with the

New town, Marrakesh

Old Royal palace, Marrakesh, centre of Morocco

local spices, it makes it even better. I highly recommend that you try: TANJIA, PASTIA, COUSCOUS with 7 vegetables and all the different TAJINES.

If you decide to go for a walk along the narrow streets of the old town, you will be fascinated by the local culture. You will also understand the history that our ancestors went through. You can find all kind of souvenirs to remind you of your visit to my home town. You will defintiely not be lost. You don't even need to ask, local people are always offering to guide you and are willing to do that from their hearts and with pleasure.

Due to the globalisation, the city is becoming more and more of a mixture of the old and modern cultures. This undoubtedly influences the mentality of local people and their beliefs. This makes it an open space for welcoming people from different cultures and beliefs. When you visit all the corners of the city, you can already see the mixture between old and modern architectures, the difference between local peoples' clothing. Music taste is also changing.

In short, my home town is Marrakesh, localized in the centre of Morocco. It is a north African country which is influenced by Berber, French, Spanish, Portuguese but mainly Arab cultures. All of this makes it a mixture of oriental and occidental cultures, you can already notice that from the language. It is true that the official language of the country is Arabic, but it is also mixed with Berber, French, Spanish and Portuguese words.
It is common, that when you hear someone mention Morocco, that you automatically think about desert and camels. It is true that we have a very large desert in the south where you can find camels. However, the country is not limited to these stereotypes. If you come visit Morocco, you will find all kinds of diversity. You will find nice spots for surfing, hiking, skiing, and swimming. You will find all sorts of natural landscapes that will take your breath away.

Agadir city, Paradise valley, N of Morocco

Dakhla city, South of Morocco

Marrakesh city, old town, centre of Morocco

Ifrane city, called Switzerland of Morocco

Save the date

DBM Summer Symposium

Wednesday, August 21, 2019

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

Presentations by DBM postdocs, PhD students and project leaders

DBM Summer Barbecue

Wednesday, August 21, 2019

16:30 – 21:30
Kraftwerkinsel Birsfelden

For DBM members only

« Das Leben ist ein einziger Frühling!
Man weiss nicht, was einem alles so blüht. »

Siegfried Wache