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Scientific Meeting 2017

PRINCIPLES OF HOMEOSTASIS

Max Delbrück Centrum for Molecular Medicine, Berlin
May 22nd – 23rd 2017

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Contents

Organization Team

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EU-Life Translational Research Working Group

Sponsors

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EU-LIFE Scientific Meeting

Principles of Homeostasis

MDC, Berlin, 22nd-23rd May 2017

INTRODUCTION

EU-LIFE is an alliance of 13 European top research centers in the life sciences to promote scientific excellence (http://eu-life.eu). Its annual scientific meeting aims at fostering interaction and scientific exchange across the EU-LIFE research community under the umbrella of a common topic.

The upcoming meeting in 2017 will focus on the principles of homeostasis. Biological systems are faced with the challenge to thrive despite continuous internal and external perturbations. They have therefore evolved a multitude of regulatory mechanisms to ensure homeostasis. Importantly, impaired homeostasis is also a hallmark of many diseases. The goal of this meeting is to feature the wealth of exciting research projects and available technologies within EU-LIFE to study the principles of homeostasis. Sessions will cover transcriptional and posttranscriptional gene expression control, proteostasis, metabolic regulation as well as disease mechanisms (e.g. in cancer).

The format of tandem talks was pioneered in previous meetings. Two scientists from different EU-LIFE centers will team up and reflect different aspects of a certain topic. Selected keynote talks, poster sessions, speed talks of young researchers and lunch & learn sessions will round off the program.

Participate in the EU Life scientific meeting, explore and think “out of the box”, learn about hottest technologies, get inspired by other fields, build your own research network and create opportunities for your next career step!

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GENERAL INFORMATION

About the Venue

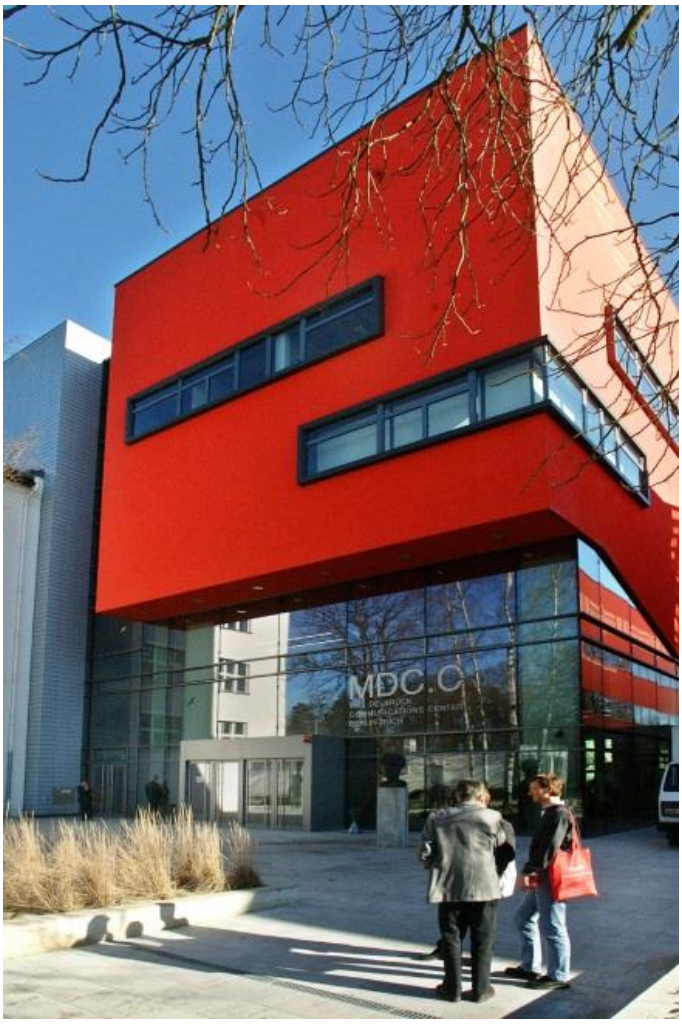
Conference Center - MDC.C

The MDC.C – Max Delbrück Communications Center in the northeast of Berlin is one of the most modern congress centers in Berlin. An international gathering place for scientific dialogue has been established in the center of the campus Berlin-Buch, which focus is on basic molecular research, clinical medicine and modern biotechnology.

Travel Directions

Max-Delbrück-Centrum für Molekulare Medizin (MDC
Robert-Rössle-Str. 10 - 13125 Berlin-Buch

The MDC is located in the North East of Berlin on the Campus Berlin-Buch



See details under: https://www.mdc-berlin.de/directions

DRIVING DIRECTIONS (BY CAR)
From the city center (Berlin-Mitte):

- Follow Prenzlauer Promenade outward (which then becomes the A114) in the direction of Autobahn Prenzlau.
- Take the "Bucher Straße" exit, then turn right at the traffic light onto Hobrechtsfelder Chaussee in the direction of Buch. Continue driving straight for about 4 - 5km
- After passing the HELIOS Klinikum Berlin-Buch, turn right at the next traffic lights onto Wiltbergstraße. Drive straight for about 2km. Pass under the S-Bahn. After a further 500m Wiltbergstraße bends to the right and merges with Karower Chaussee. Continue along this road for another 500m.
- Turn left onto Robert-Rössle-Straße, which will take you to Campus Berlin-Buch and MDC.

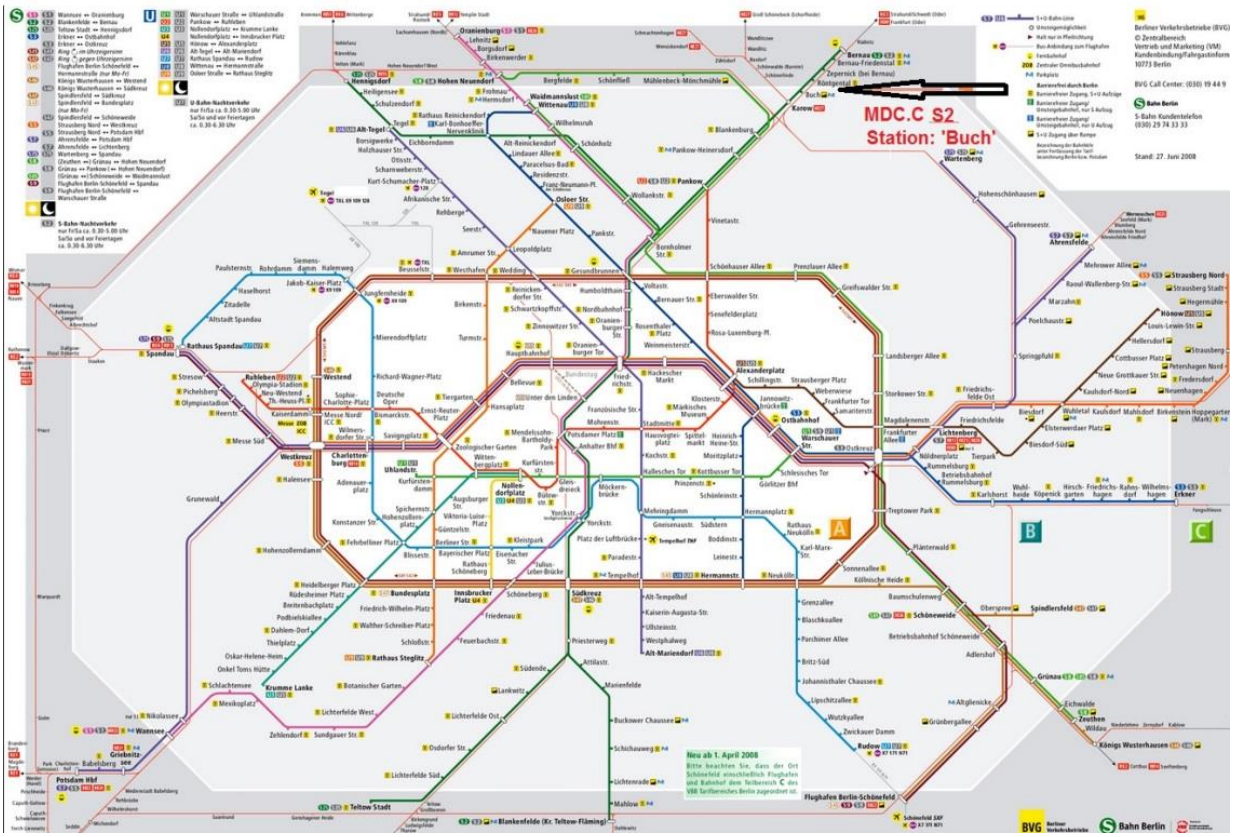
Public Transportation To The MDC

The MDC is very easy to get to by public transport via the S-Bahn to “Berlin-Buch”, then by bus to the campus.

Getting to Berlin-Buch

S-Bahn: line S2, direction “Bernau” or “Buch”

Map of Berlin’s S-Bahn and U-Bahn network for connections to the S2



From Berlin-Buch to the MDC

Bus: number 353 until the last station (MDC Campus, in front of the conference center)
On foot: a 15-20 min walk

MDC Campus Map

Common Facilities

A 8	Gate House with Café Max and apartments
A 9	Reception gate
A 13	Life Science Learning Lab; CampusInfo
A 14	Cafeteria

Guesthouses of the MDC

B 54	Hans-Gummel-House
B 61	Salvadore-Luria-House with Kindergarten

Research

Max Delbrück Center for Molecular Medicine (MDC)

A 10	Library
C 27	Walter-Friedrich-House
C 31.1 -2	Max-Delbrück-House,
C 31.3 -5	Energy and Infrastructure Center South (EZS)
B 63 / 64	Research services
C 83	Max-Delbrück-Communications Center (MDC.C)
C 84	Hermann-von-Helmholtz-House
B 88	Ultrahigh Field Facility
B 89	Max-Rubner-House
B 93	Biobank

Leibniz-Institut für Molekulare Pharmakologie (FMP)

C 81	Marthe-Louise-Vogt-House

Shared Facilities by MDC and FMP

C 84.1	Research services
C 87	Timoféeff-Ressovsky-House

Clinical Research

B 42 -53	Experimental and Clinical Research Center (ECRC)

Companies

A 7	Eckert & Ziegler, Eckert Wagniskapital und Frühphasenfinanzierung (EWK)
A 15	car workshop , EZAG, Gardener,
D 16/23	Eckert & Ziegler (Customer Support, shipping & packing quality management, production)
B 55	**Oskar-u.-Cécile-Vogt-House:** BBB-Postoffice, 8sens.biognostic, FILT, MRI.TOOLS, CONGEN, E.R.D.E., ART-CHEM, Lipidomix, Roboklon, I.M.S.M., Fresenius, patent attorney Dr.Baumbach, NIKON, OctreoPharm, Institut e & g, Steinbeis-Transfer-Institut, AJ Innuscreen, Hermes-Analytik, WISE
D 72	BioTeZ
D 79	**Erwin-Negelein-House:** Akademie der Gesundheit, Avitop, Life Science Learning Lab, FGEI, ICP Healthcare, CampusVital, Berlin Cures, LAMSYSTEMS, OMEICOS Therapeutics, Wohlfühler, Source BioScience, Engine
D 80	**Otto-Warburg-House:** ALRISE, Silence Therapeutics, Celares
D 82	**Karl-Lohmann-House:** EPO GmbH
D 85	**Arnold-Graffi-House:** BBB, stratec, aokin, BIOSYNTAN, emp, ascenion, Prof.Wanker, AMAL, π-Pharmalmage, MerLion, GLYCOTOPE, accountant S.Langmacker

Campus Berlin-Buch
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Social Events

Welcome Reception (Scientific Meeting)

Monday, May 22nd, 7.00 p.m. – 10.00 p.m.

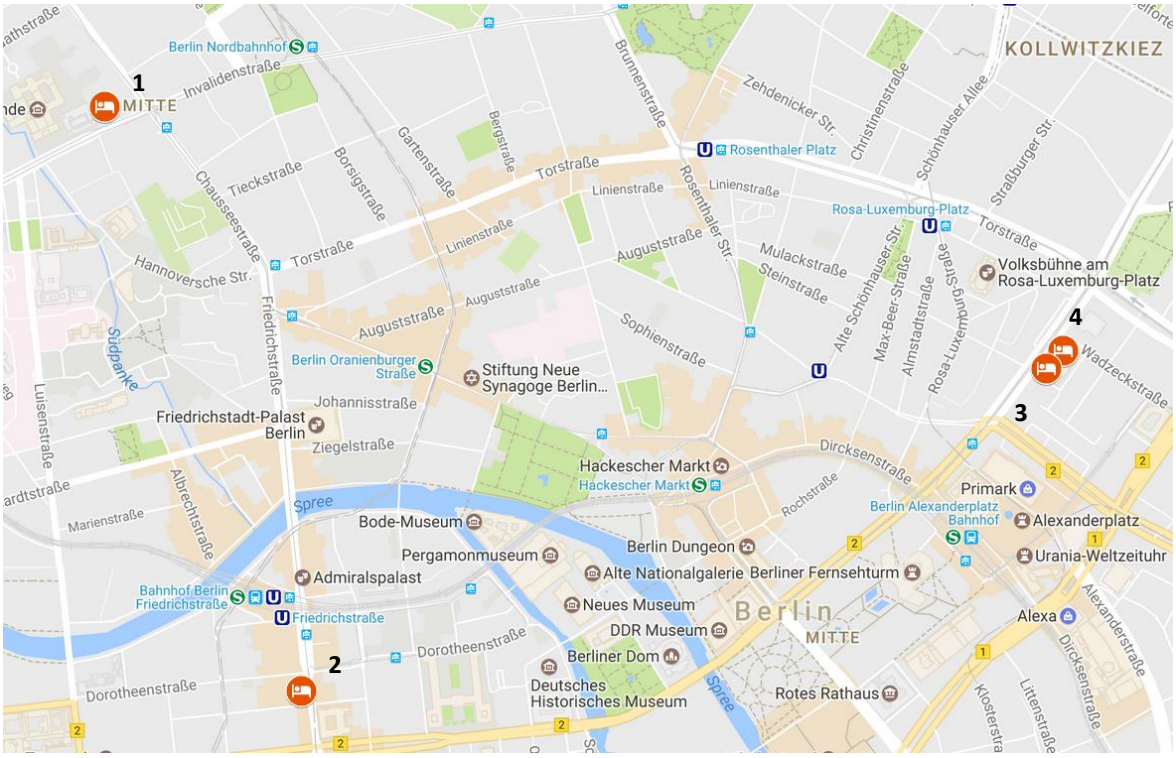
Venue: Spiegelsaal in Clärchens Ballhaus

Auguststrasse 24 ● 10119 Berlin

Participants of the scientific meeting will be shuttled by bus to the venue after the end of the meeting around 6:30 p.m.
Pick up in front of the conference venue (MDC.C) at 7.00 p.m.

HOTELS

We have reserved several rooms including breakfast at the following hotels in Berlin.
By mentioning “EU-LIFE”, the meeting participants will get a better price.
All Hotels are conveniently located in close proximity to one of the stations of the City-Railway line 2 (S-Bahn 2) heading to the station Berlin-Buch.



[1] Maritim Hotel ProArte: www.maritim.de
Single Room: € 169 / Double Room (can also be booked for single use): € 207
4 star hotel located near the railway station: Friedrichstrasse with connection to Buch

[2] Mercure Hotel Berlin City: www.mercure.com
Single Room: € 93.50 / Double Room (can also be booked for single use): € 103
4 star hotel located near the railway station Nordbahnhof or The Central Railway Station with connection to Buch

[3] H2 Hotel Alexanderplatz: www.h-hotels.com
Single Room: € 104 / Double Room (can also be booked for single use): € 114
4 star hotel located near the railway station Alexanderplatz with connection via Pankow to Buch

[4] Ramada Hotel Berlin Alexanderplatz/ H4 Hotel: www.h-hotels.com
Single Room: € 109 / Double Room (can also be booked for single use): € 119
4 star hotel located near the railway station Alexanderplatz with connection via Pankow to Buch

Agenda

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PROGRAM Scientific Meeting

Monday, May 22	
09:00-09:30	Registration
09:30-09:40	Thomas Sommer, Deputy Scientific Director, MDC, Berlin *Welcome*
09:40-10:45	Gabriele Bergers, VIB, Leuwen *Keynote "Dysregulation of Vascular and Immune Homeostasis in Cancer"* Holger Gerhardt, MDC Berlin /VIB Leuwen *"Mechanisms in Vascular Patterning – a Tale of Fate and Forces"*
10:45-11:15	Flash poster presentation (14 x 1 min each)
11:15-11:45	Coffee break
11:45-12:30	Allison Bardin, Institute Curie, Paris *"Adult Stem Cell Genome Stability"* Claus Sørensen, BRIC, Copenhagen *"New Mechanisms Guarding Genome Integrity"*
12:30-12:50	Luis Teixeira, IGC, Oeiras *"Maintenance of Mutualism in Host-Symbiont Interactions"*
12:50-13:00	Marianne S. Andersen, BRIC, Copenhagen *"Defining the Mode of Growth and Replenishment During Epidermal Appendage Formation" (5 min short presentation)*
13:00-14:50	Lunch break & poster session
14:50-15:10	Pia Kvistborg, NKI, Amsterdam *"Properties of T Cell Recognised Neo-Antigens"*
15:10-15:55	Janine Terra Erler, BRIC, Copenhagen *"Disruption of Bone Homeostasis During Cancer Progression"* Leila Akkari, NKI, Amsterdam "*Modulating the Myeloid Cell Response in Radiation-Treated Gliomas to Circumvent Tumor Recurrence"*
15:55-16:25	Stefanie Widder, CeMM, Vienna *"A Switch in the Organization of the Airway Microbiome Links Homoeostasis and Lung Exacerbation in Cystic Fibrosis3 selected short presentations" (5 min short talk)* Karthik Arumugam, CRG, Barcelona *"A Novel Molecular Mechanism of Cell-Fusion Mediated Reprogramming" (5 min short talk)* Marina Petkovic, MDC, Berlin *"Reconstructing the Evolutionary History of Cancer from Allele-Specific Somatic Copy-Number Profiles" (5 min short talk)*

16:25-16:55	Coffee break
16:55-17:40	Ana Domingos, IGC, Oeiras *"A Sympathetic View on Fat Homeostasis"* Rafal Ciosk, FMI, Basel *" Ribonuclease-Mediated Control of Organismal Homeostasis"*
17:40-18:00	Diego Pasinin, IEO, Milano *"The Complex Network of Polycomb-Mediated Transcriptional Control in Regulating Cell Identity and Tissue Homeostasis"*
18:00-18:15	Marta Agostinho, EU-LIFE Coordinator *"New Initiatives of EU-LIFE"*
18:30	Transport to joint dinner in town

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PROGRAM Scientific Meeting

Tuesday, May 23	
09:00-09:30	Registration
09:30-10:10	Genevieve Almouzni, Institute Curie, Paris *Keynote "Shaping Chromatin in the Nucleus, the Bricks and the Architects"*
10:10-10:30	Tiziana Bonaldi, IEO, Milano *"Homeostasis of Cancer Cells Maintained by the Multi-layer Interplay of Gene Expression Modulators: a Proteomic View"*
10:30-11:00	Coffee break
11:00-11:20	Susan Gasser, FMI, Basel *"Homeostasis of Repressive Chromatin"*
11:20-11:40	Jing Tang, FiMM, Helsinki *"Network Pharmacology Modeling to Facilitate the Discovery of Personalized Drug Combinations in Cancer"*
11:40-12:00	Jörg Menche, CeMM, Vienna *"Understanding Drug-Drug Interactions through High-Content Imaging"*
12:00-13:45 12:45-13:30	Lunch break Choice of parallel lunch & learn sessions during lunch break: • *Consideration of the Sex/Gender Dimension of Research* Chair: Sabine Oertelt-Prigione, Institute of Gender in Medicine, Charité • *A Short Guide to Writing a Marie Skłodowska-Curie Fellowship and other European Grant Applications* Chair: Ioannis Legouras, Grant Department, MDC • *How Postdocs Can Engage in Peer Reviewing* Chair: Andy Collings, Executive Editor, eLife
13:45-14:30	Martin Turner, Babraham Institute, Cambridge *"The RNA binding Protein Ptbp1 Mediates B Cell Selection in Germinal Centres"* Fatima Gebauer, CRG, Barcelona *"Role of RNA Binding Proteins in Metastasis"*
14:30-14:50	Roland Schwarz, MDC, Berlin *"The Role of Chromosomal Instability in Cancer Fitness and Progression"*
14:50-15:10	Matthias Selbach, MDC, Berlin *"A Peptide-based Interaction Screen on Disease Related Mutations"*
15:10-15:15	Wrap-up/ end of scientific meeting

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Locations of Meeting & Seminar Rooms

Date	Time	Activities	Location	Room
22.5.2017	9:30 a.m.- 6:15 p.m.	Scientific Meeting	MDC.C – House 83	Axon 2 1st Floor
22.5.2017	9:30 a.m.-5:30 p.m.	Communication WG	HvH – House 84	1007 ground-floor
22.5.2017	9:30 a.m.-5:30 p.m.	Grants WG	MDC.C – House 83	Dendrit 2/3 3rd floor
23.5.2017	9:30 a.m.-3:15 p.m.	Scientific Meeting	MDC.C – House 83	Axon 2 1st Floor
23.5.2017	entire day	IT WG	IT – House 23	IT Building
23.5.2017	3:30 – 6:45 p.m.	Strategy Meeting	MDC.C – House 83	Dendrit 2/3 3rd floor
23.5.2017	9:30 - 12:00 a.m.	Communication WG	HvH – House 84	1007 ground-floor
23.5.2017	12:45 -1:30 p.m.	Lunch & learn *Peer Reviewing*	HvH – House 84	1207 2nd floor
23.5.2017	12:20 -1:30 p.m.	Translational Research WG	HvH – House 84	1107 1st floor
23.5.2017	12:45 -1:30 p.m.	Lunch & learn *Gender Dimension*	MDC.C – House 83	Dendrit 1 3rd floor
23.5.2017	12:45 -1:30 p.m.	Lunch & learn *Grant Writing*	MDC.C – House 83	Dendrit 2/3 3rd floor
24.5.2017	10:30 a.m. - 5:00 p.m.	Training WG	HvH – House 84	1107 1st floor
24.5.2017	9:00 a.m. - 4:00 p.m.	Strategy Meeting	MDC.C – House 83	Dendrit 2/3 3rd floor

Location of the conference & seminar rooms: see the MDC Campus Map, page 6

Speaker’s Abstracts

Dysregulation of Vascular and Immune Homeostasis in Cancer

Gabriele Bergers

VIB-CCB, KU Leuven Center for Cancer Biology, Leuven

Sustained angiogenesis and immune suppression are hallmarks of cancer. There is increasing evidence that these two phenotypes are interconnected and facilitated by shared regulators not only during normal physiological processes, but also in cancer. Tumors modify the homeostatic tissue repair program to their advantage by converting immune cells from an immunestimulating to an immunosuppressive and angiogenic phenotype and keeping blood vessels immunosuppressive. In line with the dual function of VEGF as a potent angiogenic and immune-suppressive factor, we had found that the efficacy of angiogenic inhibitors targeting the VEGF/VEGFR pathway hinged on their ability to induce an immune-stimulatory milieu in tumors by repolarizing innate immune cells to a Th1 phenotype, and that this capability dictated the degree of therapeutic response. Tumors in turn reacted to angiogenic blockade by producing factors that activated PI3K (g/d) signaling in intratumoral innate immune cells which converted them back into an immune suppressive and angiogenic state, and importantly disabled repolarization thereby rendering tumors resistant to anti-angiogenic therapy. More recently we discovered that the immunosuppressive relapse is also caused by upregulation of PD-L1, the ligand of the negative checkpoint regulator PD-1 found on T-cells, providing an adaptive immune-suppressive mechanism that limited the efficacy of anti-angiogenic agents. Using a combination of vascular and immune-modulating inhibitors, we were able to induce high endothelial venules (HEV) in tumors that are normally specialized to facilitate lymphocyte trafficking in lymphoid organs. HEV induction lead to the formation of tertiary lymphoid structures (TLS), centers of mixed immune infiltrates that attacked tumor cells and elicited enhanced survival benefits.

Mechanisms in Vascular Patterning - A tale of fate and forces

Holger Gerhardt

Max Delbrück Center for Molecular Medicine (MDC), Berlin
VIB-KU Leuven Center for Cancer Biology, Leuven

How developing vascular networks acquire the right number and balance of arteries, veins and lymphatic vessels to efficiently supply and drain tissues, and to maintain tissue homeostasis, is poorly understood. In zebrafish embryos, the robust and regular 50:50 balance of intersegmental veins and arteries that form along the trunk, with lymphatics forming along each artery, prompts the intriguing question how the organism keeps “count”. Recent studies suggest that veins and lymphatics originating from bipotential endothelial precursors experience deterministic signals, which through transcriptional master regulators restrict their fates even before they form the appropriate vascular connections. Similarly Notch signaling is important for artery formation, together suggesting that local molecular signals instruct when and where to form vessels of appropriate identity and connectivity. Contrary to this idea, we discovered that the seemingly stereotyped process is inherently plastic and that vessel identity and connectivity arise as emergent property as endothelial cells respond to changing blood flow. Hemodynamics and endothelial mechanobiology are modified by tissue derived signals to orchestrate the formation, maintenance and adaptation of vascular networks in tissue homeostasis.

Adult Stem Cell Genome Stability

Allison Bardin

Institute Curie, Paris

During aging, adult stem cells may acquire somatic mutations capable of modifying cellular behavior leading to a functional decline or to a competitive advantage resulting in a premalignant state. However the mechanisms, phenotypic impact, and frequency of spontaneous mutation in adult stem cells in vivo are currently unclear. Our recent data reported two mechanisms of genome instability in adult Drosophila intestinal stem cells leading to phenotypic alteration in the intestine. First, mitotic recombination-based mechanisms promote frequent loss of heterozygosity. Secondly, somatic deletion and genomic rearrangement of DNA sequences leads to gene inactivation. The latter contributes to somatic inactivation of a tumor suppressor gene in intestinal stem cells leading to spontaneously arising neoplasias in 10% of wild-type males. I will present our ongoing unpublished work exploring genome alteration in somatic stem cells during aging including roles of large structural variation and transposable element associated modification.

New Mechanisms Guarding Genome Integrity

Claus Sørensen

Biotech Research & Innovation Centre (BRIC), University of Copenhagen

Cells are constantly exposed to genotoxic challenges from endogenous and exogenous sources. The cellular responses to such challenges include pathways that control cell cycle progression allowing time for repair or permanent cell cycle exit. The initial response to genotoxic stresses has to be flexible, which allows resumption of cell proliferation once genomic lesions are cleared. I will present our recent findings based on targeted genetic screening. Here, we uncovered a new pathway governing cell fate decisions following genotoxic challenges. Intriguingly, we find that this pathway has an inbuilt homeostatic component allowing cells to fine-tune the response to genotoxic stresses.

Maintenance of Mutualism in Host-Symbiont Interactions

Luis Teixeira

Institute Gulbenkian, Orias

Bacteria from the genus Wolbachia are probably the most common endosymbionts in animals, infecting nematodes and many arthropods. They can cause strong phenotypes in their hosts, ranging from manipulation of reproduction to protection to viruses. Regulation of Wolbachia levels is a crucial aspect of their biology given that they are maternally transmitted. Higher titres increase transmission fidelity and strength of phenotypes. However, Wolbachia fitness is dependent on female host reproduction success and, therefore, titres have to be controlled so that the endosymbiont is not too costly. We are analysing Wolbachia growth regulation in Drosophila melanogaster. By phenotyping different sequenced Wolbachia variants we are identifying genetic variation associated with growth control. Analysis of the over-replicating and life-shortening Wolbachia variant wMelPop led us to discover the cause of its virulence at the genome level. We showed that virulence of the symbiont and antiviral protection can change rapidly with changes in gene copy number and that regulation of its titers can be broken with a single genetic change in Wolbachia. Therefore, our results provide a link between genotype and phenotype in this unculturable endosymbiont.

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Properties of T cell Recognized Neo-Antigens

Pia Kvistborg, NKI

Pia Kvistborg, Marit van Buuren, Daisy Philips, Nienke van Rooij, Arno Velds, Sam Behjati, Marlous van der Braber, Mireille Toebes, Lorenzo Fanchi, Maarten Slagter, Joost van den Berg, Michael Stratton, Christian Blank, John Haanen, Can Kasmir, Ton Schumacher

Netherland Cancer Institute (NKI), Amsterdam

At this point in time it is broadly appreciated that T cell immunity towards tumor-specific mutated antigens (neo-antigens) is an important component in control of human cancer. A challenge to unravel the T cell response towards neo-antigens lies in identifying which neo-antigens are more likely to be true T cell epitopes.
Here we present our cumulative data in which we have analyzed neo-antigen specific T cell reactivity in a cohort of 12 melanoma patients. To predict neo-antigens more likely to be recognized by T cells we factor in the following parameters; RNA expression of the gene in which the mutation is located, predicted binding affinity of the epitopes to the patient specific HLA alleles, likelihood of proteasomal processing, and degree of self-similarity. Using our pMHC multimer technology, we have screened for T cell recognition of approximately 7000 epitopes. A total of 19 neo-antigen specific T cell responses were detected.
Based on this current data set we have discovered that RNA expression and predicted binding affinity to HLA are the most informative parameters for selecting T cell recognized epitopes. By increasing the cut offs for these parameter we can increase the precision of our predictions significantly without compromising sensitivity. A striking observation is that predicted binding affinity not only correlates with likelihood of observing a T cell response but also the magnitude of this T cell response suggesting a qualitative hierarchy within neo-antigens.

Disruption of Normal Bone Homeostasis Generates Pre-Metastatic Osteolytic Lesions

Janine Terra Erler

Biotech Research & Innovation Centre (BRIC), University of Copenhagen

Tumour metastasis is a complex process involving reciprocal interplay between cancer cells and host stroma at both primary and secondary sites, and is strongly influenced by microenvironmental factors such as hypoxia. Tumour-secreted proteins play a crucial role in these interactions and present strategic therapeutic potential. Metastasis of breast cancer to the bone affects approximately 85% of patients with advanced disease and renders them largely untreatable. Specifically, osteolytic bone lesions, where bone is destroyed, lead to debilitating skeletal complications and increased patient morbidity and mortality. The molecular interactions governing the early events of osteolytic lesion formation are currently unclear. Here we show hypoxia to be specifically associated with bone relapse in ER-negative breast cancer patients. Global quantitative analysis of the hypoxic secretome identified Lysyl Oxidase (LOX) as significantly associated with bone-tropism and relapse. High expression of LOX in primary breast tumours or systemic delivery of LOX leads to osteolytic lesion formation, whereas silencing or inhibition of LOX activity abrogates tumour-driven osteolytic lesion formation. We identify LOX as a novel regulator of NFATc1-driven osteoclastogenesis independent of RANK ligand, disrupting normal bone homeostasis and leading to the formation of focal pre-metastatic lesions. We show that these lesions subsequently provide a platform for circulating tumour cells to colonise and form bone metastases. Our study identifies a novel mechanism of regulation of bone homeostasis and metastasis, opening up opportunities for novel therapeutic intervention with important clinical implications.

Modulating the Myeloid Cell Response in Radiation-Treated Gliomas to Circumvent Tumor Recurrence

Leila Akkari

Netherlands Cancer Institut (NKI), Amsterdam

Eighty percent of tumors that develop in the central nervous system are malignant gliomas, with over half being glioblastoma multiforme (GBM), the most aggressive form of this disease. Even following treatment with standard of care therapy, the overall 5-year survival rate of patients diagnosed with GBM is less than 5%.

In GBM patients and mouse models of the disease, the major non-cancerous cell type in the glioma microenvironment is tumor-associated macrophages/microglia (TAMMs). We previously used an inhibitor of colony stimulating factor 1 receptor (CSF-1R), BLZ945, to target macrophages in the PDG mouse model of gliomagenesis. CSF-1R inhibition dramatically improves survival in a long-term intervention trial and markedly regresses established high-grade lesions.

To determine the translational clinical potential for CSF-1R inhibition, we designed preclinical trials in combination with radiation. In recurrent irradiated tumors, the ratio and transcriptional program of macrophages infiltrating from the periphery and tissue-resident microglia are significantly altered, suggesting that changes in TAMM sub-populations may support glioma recurrence. We treated established GBMs with fractionated radiation concomitant with acute, short-term BLZ945 treatment and observed that the overall survival of animals was significantly extended compared to single treatment modalities by affecting the DNA damage response to radiation. Incorporating long-term treatment with BLZ945 in tumors treated with fractionated radiation led to a block in tumor recurrence, indicating that reversing cancer-induced macrophage ‘education’ has the potential to inhibit disease relapse.Together these results identify critical roles for CSF1R-dependent TAMMs in blunting the response to standard of care treatment, and promoting glioma recurrence.

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A Sympathetic View on Fat Homeostasis

Ana Domingos

Institute Gulbenkian, Orias

Obesity is a major public health concern, yet no safe medications exist owing to the prohibitive side effects, as well as difficult delivery to the brain. The brain controls weigh homeostasis via central and peripheral neural circuits and the era of molecular genetics has enabled the mechanistic dissection of brain circuits in spectacular ways. However, the molecular and cellular organization of the sympathetic nervous system (SNS), a part of the peripheral nervous system that innervates all organs, is essentially unexplored. To push this frontier, we have recently used molecular genetic tools such as optogenetics to uncover a direct and functional connection between the SNS and adipocytes. Further, we found this neuro-adipose junction to drive lipolysis and fat mass reduction. As obesity is a chronic inflammatory state, we have recently started to define the molecular mechanisms that link inflammation to SNS neurons in fat, which will be discussed in this presentation. The identification of the fundamental biological mechanisms that govern the neuro-adipose junction could set up the stage for a new anti-obesity therapy with less side effects while circumventing the challenge of drug delivery to the brain.

Ribonuclease-Mediated Control of Organismal Homeostasis

Rafal Ciosk

*Friedrich Miescher Institute for Biomedical Research (*FMI*), Basel*

Obesity and obesity-related diseases are global health issues, sparking interest in molecular mechanisms controlling body fat. Because hibernators preferentially use fat to fuel survival, we used C. elegans cold sensitivity to identify genes regulating fat. This approach uncovered a conserved RNase (related to MCPIP1/Regnase-1, a key player in mammalian innate immunity), and its mRNA target encoding a fat loss-promoting transcription factor, as a novel functional module regulating body fat. We hypothesize that this module may be critical for rapid but reversible remodeling of metabolism for survival in the face of environmental change.

The Complex Network of Polycomb-mediated Transcriptional Control in Regulating Cell Identity and Tissue Homeostasis

Diego Pasini

Istituto Europeo di Oncologia (IEO)/ European Institute of Oncology, Milano

Establishing and then maintaining cellular identity during differentiation requires signaling events to be transmitted to the chromatin level; transcription factors (TFs) and chromatin-remodelling activities work together to orchestrate the transcription programs underlying this transmission. It is now clear that chromatin remodelers play a major role in regulating cellular identity, resulting one of the most mutated pathways among all type of human cancers. In this context, Polycomb proteins (PcG) play a crucial role as regulators in development and differentiation and are frequently mutated or altered in their activity in numerous types of human cancers, via molecular mechanisms that are still poorly understood. At the meeting will be presented the recent advances of our laboratory aimed to dissect the molecular mechanisms underlying the activity of distinct PcG activities in establishing and maintaining cell type specific transcriptional identity during both normal homeostasis and pathological conditions.

Shaping Chromatin in the Nucleus, the Bricks and the Architects

Geneviève Almouzni

Institut Curie, Paris

Chromatin organization in the nucleus provides a large repertoire of information in addition to that encoded genetically. A major goal for my group involves understanding how histones, the major protein components of chromatin, the bricks, can mark functional regions of the genome through their variants or post-translational modifications, along with non-coding RNA and other chromatin regulators. Errors in the establishment and propagation of these chromatin components, possibly involving imbalance in their deposition pathways, can lead to mis-regulation of genome functions and pathological outcomes, such as cancer. The propagation of centromeric identity represents a model of choice for the study of epigenetic mechanisms. Our work has focused on histone chaperones, as architects of chromatin organisation. We will present our latest findings.

References

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Homeostasis of Cancer Cells Maintained By the Multi-Layer Interplay Of Gene Expression Modulators: A Proteomic View

Tiziana Bonaldi

Istituto Europeo di Oncologia (IEO)/ European Institute of Oncology, Milano

Cellular homeostasis, the intrinsic property of the cell to maintain the stability of the internal environment in spite of changing external conditions, relies on a complex network of intertwining regulatory circuits. When the internal equilibrium is broken, cells undergo uncontrolled proliferation or programmed cell death.
The oncogene c-MYC is a major gatekeeper of the equilibrium between cell death and proliferation and its deregulation is observed in about 70% human cancers. The tight control of MYC is therefore crucial for cell homeostasis and survival.
MicroRNA have also emerged as important regulators of cellular homeostasis, by modulating the regulatory circuits that maintain complex gene expression programs. The miR-17-92 cluster is paradigmatic, having emerged as a regulatory hub at the crossroad between cellular proliferation and death, with both oncogenic and tumor-suppressor roles, depending on the context. Interestingly, its oncogenic role has been linked to distinct functional interplays with MYC. We have expanded the comprehension on this relationship by integrating SILAC- proteomics, transcriptomics and 3' UTR analysis in MYC-driven lymphoma. We demonstrated that the interplay between the cluster and MYC is highly dynamic during lymphoma progression. By keeping MYC level under control, miR-17-92 maintains the correct equilibrium between apoptosis and proliferation that guarantees cancer cell homeostasis
Recently, through an unbiased MS-based protein-methylation analysis, we have unraveled an additional level of miRNA modulation, discovering that the Large Drosha Complex (LDC)- that catalyzes miRNA processing and thus maintains their correct levels- is highly methylated, suggesting that this modification may regulate miRNA biogenesis. I will present recent data collected on this novel regulatory mechanism, with emphasis on the description of the first LDC methyl-proteome and of its profiling upon modulation of the PRMT1 enzyme, which directly impinge on miRNA biogenesis.

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Homeostasis in Silencing Genes and Repeats

Susan Gasser

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Histone H3K9 methylation is a conserved modification that correlates broadly with gene repression in organisms ranging from fission yeast to man. In *C. elegans*, di- and tri-K9 methylation is abundant on repetitive elements (RE), including both transposons and simple repeats, and coats both pseudogenes and silent tissue-specific genes. Using a double mutant that eliminates the two *C. elegans* H3K9 histone methyltransferases, SET-25 and MET-2, we find that H3K9me is dispensable for development1,2, although worms become ts sterile. This correlates with extensive DNA damage-driven apoptosis in the germline, but there is no elevation in either mitotic or meiotic chromosome missegregation. Instead, we find that the loss of H3K9methylation leads to the promiscuous and widespread expression of all classes of repetitive elements (DNA and RNA transposons, and simple repeats) in both germline and somatic tissues. The loss of transcriptional silencing correlates with an accumulation of insertions and deletions at repetitive sequences, and renders worms sensitive to replication fork stalling, but not ionizing radiation. RNA-DNA hybrids accumulate in the absence of H3K9me even without exogenous stress, which is exacerbated by the loss of the *C. elegans* BRCA1 complex, specifically at tandem repeats and not at RNA or DNA transposons. We conclude that a key function of H3K9me is to ensure the stability of a repeat-rich genome, most specifically by suppressing the transcription of simple repeats. This is distinct from the role of H3K9me in sequestering chromatin at the nuclear envelope, which contributes to the stability of cell fate decisions2. 1. Zeller, P., Padeken, J., van Schendel, R., Kalck, V., Tijsterman, M. and Gasser, S.M. (2016) Histone H3K9 methylation is dispensable for *C. elegans* development, but suppresses RNA-DNA hybrid-associated repeat instability. Nature Genetics, 48, 1385 - 1395. doi: 10.1038/ng.3672 2. Gonzalez-Sandoval, A., Towbin, B.D., Kalck, V., Cabianca

Network Pharmacology Modeling to Facilitate the Discovery of Personalized Drug Combinations in Cancer

Jing Tang

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Cancer cells with heterogeneous mutation landscape and functional redundancy can easily develop drug resistance by emerging activation of compensating or bypassing pathways. To reach effective and sustained clinical responses, synergistic interactions of druggable targets that may inhibit redundant cancer survival pathways are highly sought. However, the exponentially increasing number of possible target interactions is making a pure experimental approach quickly unfeasible even with automated screening instruments. Furthermore, a valid target interaction that works for one cancer cell often does not apply for the other cancer cells, which exemplifies the need of a personalized medicine paradigm in the understanding of cellular processes in cancer. We provided a novel strategy to use multi-targeted kinase inhibitors to interrogate the cellular responses for a given cancer cell line. Through the network modeling of drug sensitivity and target selectivity, the phenotypic responses of target interactions can be accurately inferred. We applied the approach on the MDA-MB-231 triple negative breast cancer cell, and identified a novel synergistic interaction of Aurora B kinase and ZAK kinase, the mechanism of which was further illustrated using a dynamic simulation of MDA-MB-231-specific signaling networks. The proposed computational and experimental approach offers improved efficiency for predicting and understanding target interactions for individual cancer cell lines. We believe that the results on Aurora B and ZAK interaction may provide potential clinically-actionable drug combinations for treating triple-negative breast cancer,

Understanding Drug-Drug Interactions through High-Content Imaging

Jörg Menche

The CeMM Research Center for Molecular Medicine of the Austrian *Academy of Sciences, Vienna*

Drug-Drug interactions (DDIs), i.e. changes in the effect of one drug, when used in combination with another, are of great importance in medicine, both as contraindication and as combination or multicomponent treatments. Drugs and their interactions are also of great interest from a more fundamental perspective, as they provide an opportunity to systematically probe the combinatorial complexity of the underlying biological system. In my talk, I will give an overview of our recent efforts to characterize and ultimately understand the response of cellular networks to multiple perturbations. The key components of the project are (i) high-throughput high-content imaging screens of a representative library of FDA-approved drugs, (ii) a novel methodology to extract interaction patterns from cell morphology signatures and (iii) integrative network analyses of the resulting DDI network in the context of molecular and phenotypic networks.

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The RNA Binding Protein Ptbp1 Mediates B cell Selection In Germinal Centres

Martin Turner, Babraham Institute

Elisa Monzón -Casanova[1,6], Michael Screen[1], Manuel D. Díaz-Muñoz[1], Sarah E. Bell[1], Greta Lamers[1], Tomaz Curk[2], Jernej Ule[3], Michele Solimena[4], Douglas L. Black[5], Christopher W.J. Smith[6] and Martin Turner[1]

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Polypyrimidine tract binding protein (PTBP1) is a RNA binding protein that regulates multiple aspects of RNA biology including alternative splicing, IRES-driven translation, mRNA stability, localization and polyadenylation. PTBP1 is increased in germinal centre (GC) B cells compared to naïve B cells. Moreover, PTBP1 is most highly expressed in positively selected C-myc+ GC B cells. The use of conditional PTBP1 knock out (cKO) mouse models revealed that *Ptbp1* function in B cells is necessary for the germinal centre (GC) response. In particular, *Ptbp1* cKO GC B cells have a reduction in the highly proliferative cells of the dark zone and a defect in the generation of high affinity antibodies.

In order to elucidate the targets regulated by PTBP1 in GC B cells we identified PTBP1 binding sites in B cells by individual nucleotide-resolution cross-linking and immuno-precipitation (iCLIP) and we assessed the changes due to the absence of PTBP1 on the transcriptome of light zone and dark zone GC B cells by RNAseq. The lack of PTBP1 affects genes necessary for nucleotide biosynthesis and proliferation, which are induced by T cell help and C-myc re-expression. Notably, alternative splicing patterns of PKM and thymidylate synthase were altered due in the absence of PTBP1. *Ptbp1* cKO GC B cells have an impaired progression through the cell cycle with a reduced proportion of cells in late S-phase. Therefore *Ptbp1*, acting downstream of c-myc, is necessary for the selection of B cell in germinal centres.

Role of RNA Binding Proteins in Metastasis

Fátima Gebauer

Center for Genomic Regulation (CRG), Barcelona

RNA binding proteins (RBPs) are essential players in RNA metabolism, and are gaining great attention in the oncology field for their potential to regulate essentially every hallmark of tumor development. The molecular mechanisms by which RBPs modulate cancer progression are very poorly understood. My talk will focus on the RNA binding protein UNR/ CSDE1, for which we found a role in selectively promoting metastasis. (1). I will show our approach to identify cancer-relevant targets of UNR, and our current efforts to identify additional RBPs with potential roles in metastasis. (1) Wurth et al. 2016. UNR/CSDE1 drives a post-transcriptional program to promote melanoma invasion and metastasis.
Cancer Cell 30:1-14.

The Role of Chromosomal Instability in Cancer Fitness and Progression

Roland Schwarz

Max Delbrück Center for Molecular Medicine (MDC), Berlin

Cancer is characterised by ubiquitous somatic alterations such as somatic copy-number alterations (SCNAs), chromosomal rearrangements and point mutations that contribute to intra-tumour heterogeneity (ITH) and genome plasticity. Tumour sequencing projects frequently target one sample per patient, limiting our ability to reconstruct tumour evolution and to understand the aetiology and consequences of ITH.
I will demonstrate how SCNAs and genomic rearrangements contribute to tumour fitness and progression in the clinic and to what extent somatic variation interacts with the germline genetic background to shape the regulatory landscape of cancer. Using pan-cancer evolutionary reconstructions I will demonstrate the power of multi-sample cohorts, where each patient was sequenced multiple times at different regions of the tumour. I will show how this data allows us to phase somatic copy-number events and allows us to detect convergent copy-number evolution, with wide-reaching implications for our understanding of tumour evolution and progression.

A Peptide-Based Interaction Screen on Disease Related Mutations

Matthias Selbach

Max Delbrück Center for Molecular Medicine (MDC), Berlin

Mutations in intrinsically disordered regions (IDRs) of proteins can cause a wide spectrum of diseases. However, since IDRs lack a fixed three-dimensional structure, the mechanism how such mutations cause disease remains unknown. Here, we employ a proteomic screen to investigate how mutations in IDRs affect protein-protein interactions. We find that mutations in the cytosolic tails of the transmembrane proteins GLUT1, ITPR1 and CACNAH1 lead to increased binding of clathrins. In all three cases, the mutation creates a di-leucine motif which is known to mediate clathrin-dependent endocytosis. Follow-up experiments on GLUT1, a glucose transporter involved in GLUT1 deficiency syndrome, showed that mutated GLUT1 mislocalizes to endolysosomal compartments. Analyzing all known disease-causing mutations in transmembrane proteins revealed a significant overrepresentation of di-leucine motifs. In summary, our proteomic screen identifies “di-leucineopathies” as novel and potentially druggable class of disease-causing mutations.

Poster Abstracts

Poster Presenters: Alphabetical Order

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P2	**Arumugam**, Karthik	**A Novel Molecular Mechanism of Cell-Fusion Mediated Reprogramming**
P3	**de Biase**, Maria Stella	**Assessing the Potential of Nasal Swaps as an Alternative to Bronchoscopy for Early Diagnosis of Lung Cancer**
P4	**Erickson,** Andrew	**Identification and Validation of Biomarkers in Human Prostate Cancer**
P5	**Estruch Alrich,** Montserrat	**Targeted Combination Therapy against Oncogenic PI3K/AKT/MTOR and NFKB Signalling Pathways In Cancer Patients**
P6	**Gupta,** A.; **Gautam,** P., **Wennerberg**, K. & **Aittokallio,** T.	**Improved drug Response Quantification Based on the Elimination of Experimental Variabilities in High-Throughput Cell-Based Screenings**
P7	**Hultsch,** Susanne	**Vulnerabilities of Tamoxifen Resistant Breast Cancer Cell Lines Revealed by RNA-Sequencing and Systematic Drug Testing**
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P13	**Petkovic,** Marina	**Reconstructing the Evolutionary History of Cancer from Allele-Specific Somatic Copy-Number Profiles**
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P15	**Praktiknjo,** Samantha	**Single-Cell Transcriptional Profiling by Droplet-Based Microfluidics and its Application in Cancer Research**
P16	**Prieto Barja,** Pablo	**Genome Instability and Genetic Diversity - How the Pathogen L. Donovani Adapt in the Absence of Sex**
P17	**Widder,** Stefanie	**A Switch in the Organization of the Airway Microbiome Links Homoeostasis and Lung Exacerbation in Cystic Fibrosis**
P18	**Xia,** Tian	**Nidogen-1 Regulation of Breast Cancer Metastasis**

P1

Defining the Mode of Growth And Replenishment During Epidermal Appendage Formation

Marianne S. Andersen

*Biotech Research & Innovation Centre, Kopenhagen (*BRIC*), University of Copenhagen*

Marianne S. Andersen1, Sviatlana Ulyanchanka1, Edouard Hannezo2,3, Kim Boonekamp1, Sara Sendrup1, Ditte Clement1, Benjamin D. Simons2,3, Kim B. Jensen1 1Biotech Research and Innovation Centre, University of Copenhagen, Denmark 2Cavendish Laboratory, Department of Physics, University of Cambridge, UK 3Gurdon Institute, University of Cambridge

The epidermis is the outer layer of the skin, which protects us against the hostile environment and keeps bodily fluid inside. Along with interfollicular epidermis, which makes up the protecting barrier, various adnexal structures such as pilosebaceous units provide auxiliary functions. Previous work from our group has shown that the epidermis is compartmentalized into distinct functional units, which are maintained autonomously. It remains unknown when, during tissue morphogenesis, these self-maintained epidermal tissue compartments are first established and subsequently reach homeostasis. To address these questions, we have performed clonal lineage tracing in multicolour reporter mice followed by mathematical modeling of the dynamical changes in clone size, three-dimensional composition and distribution in upper pilosebaceous units. We find that tissue compartmentalisation into distinct functional units occur prior to the formation of actual physical tissue compartments with mature functions. During homeostasis the individual compartments are subsequently maintained at compartment specific paces and balanced growth factor signaling appears to control compartment size. Our results feed directly into a more broad understanding of the underlying machinery that dictates tissue integrity and more specifically, how this is set up during morphogenesis and maintained. Such knowledge is essential to the future development of therapeutic tools that can reset tissue homeostasis in devastating diseases such as cancer.

P2

A Novel Molecular Mechanism of Cell-Fusion Mediated Reprogramming

Karthik Arumugam

Center for Genomic Regulation (CRG), Barcelona

Cell fusion-mediated reprogramming is a physiological process where a somatic cell fuses with a stem cell to form a hybrid and the dominant stem cell genome can reprogram the somatic genome to pluripotency. This process is known to play a role in regenerative mechanisms after injury to maintain tissue homeostasis. Tcf3 is an effector of Wnt canonical pathway and deletion of Tcf3 in mouse embryonic stem cells (mESCs) strongly enhances reprogramming efficiency after fusion. We fused murine Tcf3-/- mESCs with human B-lymphocytes and isolated heterokaryons for RNA-sequencing at different time points after fusion. We used computational reverse-engineering algorithms to identify transcription factor regulatory networks that drive the early events during reprogramming of the somatic human B cell. This approach led us to a surprising discovery that the human B cell genome within the heterokaryon was reprogrammed to a hematopoietic stem cell (HSC) like state within 5 days after fusion. Importantly, we identified a sequential activation of two novel transcription factor regulatory networks in the human B-lymphocytes, namely “early”• and “late” that are associated with this reprogramming process. A correlation analysis with a human HSC dataset showed that these early and late transcription networks were highly similar to the lineage-committed hematopoietic progenitors and the hematopoietic stem progenitors respectively. In conclusion, we have obtained novel insights into regulatory mechanisms that could reprogram human B-lymphocytes into human hematopoietic stem progenitors. Simultaneously, we have also discovered novel regulatory mechanisms that could control human hematopoietic stem cell maintenance and renewal.

P3

Assessing the Potential of Nasal Swaps as an Alternative to Bronchoscopy for Early Diagnosis of Lung Cancer

Maria Stella de Biase

Max Delbrück Center for Molecular Medicine (MDC), Berlin

Diagnosis of lung cancer requires a tissue sample that is usually obtained through invasive procedures such as needle biopsy, bronchoscopy and mediastinoscopy. Moreover, lung cancer is often diagnosed when patients show symptoms, and the disease is already in an advanced stage, which significantly lowers the probability of survival. An effective, non-invasive test for early detection of lung cancer in high risk individuals (history of smoking), would thus be of great value in clinical practice. Previous studies have shown that alterations are present in the nasal and bronchial transcriptome of patients diagnosed with lung cancer, however so far reliable classification remains elusive due to noisy data and the small number of samples available. To overcome this, we here present a model for the identification of lung cancer-positive patients based on a large cohort of allele-specific expression (ASE) profiles. ASE allows for a locally-normalised expression readout independent of sequence depth and total expression level of a gene, that is highly sensitive to somatic regulatory alterations. As part of the TCGA/ICGC PanCancer Analysis of Whole Genomes (PCAWG) project, we have developed generalized linear models to predict ASE from germline variants, somatic point mutations and somatic copy-number alterations in 1200 tumour and matched normal cancer samples. Using this model as a baseline, we quantify ASE in a novel cohort of 490 current or former smokers, for which RNA-sequencing has been performed on nasal and/or bronchial tissue samples. After correcting for the germline genetic background, we compare the remaining ASE variabililty with the PCAWG training cohort, and investigate to what extent this prior knowledge improves classification accuracy over traditional small sample classifiers. We then test the potential of nasal swaps as a tool for early diagnosis of lung cancer by comparing classification performance to bronchoscopy samples obtained from the same patient.

P4

Identification and Validation of Biomarkers in Human Prostate Cancer

Andrew Erickson

Institute for Molecular Medicine, Finland (FiMM), Helsinki

Prostate cancer (PCa) is the most common solid malignancy among men in the western world. One out of every 8 men will be affected at some point in their lives by PCa. Measuring serum PSA has allowed clinicians to detect PCa at earlier stages of disease progression. However, less than 10% of men diagnosed with PCa will die due to disease. Many men with PCa harbor indolent disease which will not significantly harm them. A large proportion of these patients, however, will receive active treatments and suffer from harmful side effects of those treatments. On the other hand, a considerable proportion of PCa progresses to an aggressive phenotype after initial response to therapy. The discovery and validation of biomarkers for PCa progression is an active field of medical research and there is an urgent clinical need for biomarkers to distinguish indolent and aggressive disease. Additionally, such biomarker findings may indicate novel avenues for drug development and individualized therapies.

P5

Targeted combination Therapy against Oncogenic PI3K/AKT/MTOR and NFKB Signalling Pathways in Cancer Patients

Montserrat Estruch Alrich

Biotech Research & Innovation Centre, Copenhagen (*BRIC*)

Cancer entities are addicted to aberrant activity of an oncogenic signaling pathway in order to maintain their malignant phenotype. Patients treated with therapeutics targeting such a pathway often demonstrate robust initial clinical responses. However, chronic treatment usually gives way to relapse, due to various escape mechanisms including loss of negative feedback regulation promoting activation of a bypass signaling pathway, rendering cancer cells independent of their primary oncogenic signaling pathway. We aim to unravel the molecular mechanisms of an undescribed crosstalk of the PI3K/AKT/MTOR and NFKB signaling pathways and define how combinatorial as compared to individual targeting will affect growth and survival of primary cancer cells in preclinical therapeutic programs. To identify small molecule inhibitors targeting these signaling pathways, we use acute myeloid leukemia (AML) as a cancer model and apply mouse models harbouring prognostic relevant driver aberrations that mimic the genetics of AML patients as initial drug screening experiments that can be applied in preclinical trials using AML patient cells in xenograft assays. We have identified a) a dual PI3K/MTOR inhibitor abrogating phosphorylation of downstream substrates and b) two proteasome inhibitors abrogating NFKB translocation to the nucleus, both leading to inhibition of these constitutively active pathways and impairing clonogenic growth of AML cells. Significantly, coinhibition of both signaling pathways demonstrated strong synergistic inhibitory effect on growth and survival of clonogenic murine AML cells vs their normal counterparts, suggesting potential crosstalk and need of coinhibition of oncogenic signaling rather than inhibition of a single pathway to effectively kill AML cells. Noteworthy, we are currently conducting in vivo preclinical trials in our mouse model to decipher the adequate combinatorial treatment to impair leukaemic progression and increase survival.

P6

Improved Drug Response Quantification Based on the Elimination of Experimental Variabilities in High-Throughput Cell-Based Screenings

Abhishekh Gupta, Prson Gautam*, Krister Wennerberg & Tero Aittokallio (* equal contribution)*

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Accurate and robust quantification of drug effects is crucial for identifying pharmaceutically actionable cancer vulnerabilities. The current end-point cell viability measurements, however, lead to biased response estimates due to varying cell behaviors and experimental artifacts in large-scale screening setups that often represent with heterogeneous response phenotypes. To address these limitations, we developed an improved drug scoring model, percent response (PR), which controls for differences in seeding densities and growth rates of cells in both control and drug-treated conditions to characterize the drug-induced biological effects. Using systematic simulations and drug-screens in various cell models, we demonstrate superior performance of the PR metric compared to the existing metrics in assessing drug responses of cancer cells, irrespective of their tissue types or growth rates. In particular, the PR metric accurately characterizes the drugsâ€™ behavior based on a single viability readout, hence substantially reducing the time and resources required in large-scale screening-based drug discovery applications.

P7

Vulnerabilities of Tamoxifen Resistant Breast Cancer Cell Lines Revealed By RNA-Sequencing and Systematic Drug Testing

Susanne HultschM

Hultsch, Susanne, Kangaspeska, M. Kankainen, L. Paavolainen, E. Ikonen, V. Pietiäinen & O. Kallioniemi

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Tamoxifen, as a standard treatment of estrogen receptor (ER)-positive breast cancer, reduces breast cancer mortality by 31%. However, de novo resistance exists in 50% of advanced ER-positive cancers and acquired resistance evolves in 40% of patients initially responding to tamoxifen. In order to explore mechanisms underlying endocrine therapy resistance in breast cancer and to identify new opportunities to treat patients, we created tamoxifen-resistant breast cancer cell lines that represent the luminal A subtype and express ER and the luminal B subtype that express ER and HER2 oncoprotein [1]. We have now explored the molecular profiles of 7 drug-resistant variants by RNA-seq in comparison to their 4 isogenic parental cells. We did not detect any common genes with significantly altered gene expression across all the resistant cell lines. However, with further pathway analysis we identified that resistant cell lines share altered gene patterns, which are associated with cell, protein modification and metabolism, especially with the cholesterol pathway. To further investigate the altered lipid metabolism in tamoxifen resistance, we focused on T47D cell line. By immunofluorescence staining for free cholesterol and neutral lipids, we observed a striking increase of free cholesterol in the lysosomes as well as accumulation of lipid droplets. Accordingly, the biochemical lipid determination revealed an increased amount of neutral lipids in tamoxifen resistant cells. Currently, we are studying potential compounds that can reverse the intracellular lipid phenotypes with imaging to reveal new drug vulnerabilities for tamoxifen resistance. In summary, by combining drug testing data with the RNA-sequencing results, we hope to provide a number of potential (approved) drugs or drug combinations as well as matching biomarkers.

[1] DOI: 10.1186/s12885-016-2452-5

P8

Dynamic Chromatin Responses in CLL and non-Neoplastic Peripheral Blood Cell Types to the BTK Inhibitor Ibrutinib

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Chronic lymphocytic leukemia (CLL), characterized by the progressive and uncontrolled accumulation of CD5+ B cells, remains an incurable malignancy despite recent treatment success using Brutonâ€™s tyrosine kinase (BTK) inhibitors. BTK is a critical component of the B cell receptor pathway, but BTK and BTK-related enzymes such as ITK, Tec, BMX and RLK are also expressed in T cells, NK cells and myeloid cells, all of which are important sources of CLL-associated immune dysfunction. It is therefore important to consider the effects of novel BTK inhibitor drugs, such as Ibrutinib, on non-neoplastic immune cells. Here, we followed 8 patients longitudinally (9 time-matched samples per patient) and established the phenotypic (flow cytometry), epigenetic (ATAC-seq), and transcriptional (single-cell RNA-seq) response to Ibrutinib for CLL cells and selected peripheral blood mononuclear cell types. Our analysis identified patient-specific variation on top of a shared core regulatory program, providing a basis for the molecular mechanism of Ibrutinib action in CLL cells and the contextual effect on effector immune cells. In summary, we reveal the dynamic changes in the CLL cells during Ibrutinib treatment and highlight the critical role of the microenvironment for disease progression.

P9

Breaking Nuclear Symmetry - Control of Cell Cycle Entry By Modulating Nuclear Pore Complexes During Asymmetric Cell Division

Arun Kumar

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The acquisition of cellular identity is coupled to changes in the nuclear periphery and nuclear pore complexes (NPCs), but how these are established is unclear. We describe a mechanism driving changes in the nuclear periphery that directs cell fate after asymmetric division. The lysine deacetylase Hos3 associates with daughter cell NPCs during late mitosis, where it delays cell cycle entry (Start) through two independent mechanisms. Hos3 deacetylates NPCs in order to establishes asymmetric nuclear distribution of the Whi5 transcriptional repressor, which becomes higher in daughter cells than in mother during G1. Furthermore, Hos3 targets the G1/S cyclin gene CLN2 to the nuclear periphery specifically in daughter cell, where it is silenced to delay Start. Both Whi5 nuclear levels and CLN2 gene tethering require Hos3-dependent deacetylation of NPC components Nup60 and Nup49. Thus, asymmetric partitioning of Hos3 during mitosis establishes asymmetries in NPC function between mother and daughter cells, leading to differentially regulated cell cycle programs. Similar mechanisms might establish nuclear identity in multicellular organisms.

P10

Molecular Basis of mRNA Regulation by the TRIM-NHL Protein LIN-41

Pooja Kumari,

Florian Aeschimann, Jeremy J. Keusch, Cristina Tocchini, Dimosthenis Gaidatzis, Helge Grosshans, Heinz Gut, Rafal Ciosk

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The TRIM-NHL family of proteins is conserved among metazoans and several members have well established roles in development and disease. A common feature of some members is a positively charged NHL domain, which has been shown to mediate the binding to RNA but the mechanisms, underlying the binding specificity of different members, remain unknown. LIN-41, a founding member of the TRIM-NHL family, functions as a post-transcriptional regulator in the *C.elegans* heterochronic pathway. Recent findings show that LIN-41 silences somatic mRNA by distinct position dependent mechanisms1. Additionally, we identified LIN-41 as a regulator of pluripotency in the germline2. Current experiments show that LIN-41 mRNA targets are different in the *C. elegans* germline and soma with distinct mechanisms of binding. In order to understand the molecular basis of mRNA regulation by LIN-41, we have solved the crystal structure of the NHL domain and are working towards identifying the RNA motif recognized by LIN-41. So far, among the TRIM-NHL proteins, RNA binding and motif recognition has been systematically studied only for the NHL domain of Drosophila Brat3. The amino-acid residues that make contact with RNA in the Brat NHL domain are not conserved in LIN-41 or human TRIM71. Consistently, we found that the RNA motif recognized by LIN-41 NHL domain is different from that of Brat. Hence, this study provides an interesting paradigm to study tissue specific mechanisms of mRNA regulation by LIN-41 and how minor changes in the RNA binding surface of a domain can lead to recognition of different RNA motifs.

1. F. Aeschimann et al., LIN41 Post-transcriptionally silences mRNAs by two distinct and position-dependent mechanisms. Mol. Cell 65:1–14 (2017).
2. C. Tocchini et al., The TRIM-NHL protein LIN-41 controls the onset of developmental plasticity in Caenorhabditis elegans. PLoS Genet. 10(8):e1004533 (2014).
3. I. Loedige et al., The Crystal Structure of the NHL Domain in Complex with RNA Reveals the Molecular Basis of Drosophila Brain-Tumor-Mediated Gene Regulation. Cell Rep. 13(6):1206-20 (2015).

P11

A Peptide-Based Interaction Screen on Disease Related Mutations

Katrina Meyer

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Many disease-associated mutations prevent proteins from folding correctly and lead to a complete loss-of-function. Those mutations are often found in the hydrophobic core or in ordered regions of proteins. Other disease related mutations, however, can be found in disordered regions and are thought to impair only specific parts of the proteins functions. Those mutations could, for example, modify short linear motifs that mediate protein-protein interactions. Here, we designed a novel peptide-based screen to identify interactions that are affected by disease-associated mutations in disordered regions. We used synthetic peptides corresponding to the wild-type and mutated regions spotted on cellulose membrane to pull-down interaction partners. This setup allows for the screening of more than hundred disease-associated mutations at a time. We focused on neurological diseases and hence pulled down interaction partners from lysate of the neuroblastoma cell line SH-SY5Y. SILAC-based quantification allowed us to compare the interaction partners of the wild-type and the mutated variant. We identified several interactions that are affected by disease-associated mutations, including binding partners of FUS and TDP-43, two RNA-binding proteins involved in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). These data highlight the power of differential interactome mapping as a generic approach to unravel disease mechanisms caused by faulty protein-protein interactions.

P12

Essential Role of the Tumour Suppressor Bap1 in Regulating Trophoblast Differentiation and Invasiveness

Vicente Perez-Garcia

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BRCA-associated protein 1 (Bap1) is a tumour suppressor that binds BRCA1 (breast cancer 1). It is involved in the regulation of the cell cycle, cellular differentiation, cell death, gluconeogenesis and DNA damage response. Bap1 mutations and deletion have been associated with several tumours including mesothelioma, uveal melanoma, cutaneous melanoma and myeloid transformation. Trophoblast stem cells (TSCs) share many key similarities with metastatic cancer cells, in particular as far as cell invasiveness and breaching of basement membranes is concerned. In mice, the deletion of the Bap1 gene is lethal during embryogenesis around midgestation (E9.5), a stage commonly linked to placental failure. Preliminary data have revealed that the placentae of Bap1-mutant embryos exhibit severe defects that are likely to contribute to the embryonic lethality phenotype. Here, we analyse the function of Bap1 in the modulation of TSC self-renewal and differentiation by deletion using the CRISPR/Cas9 genome editing system. Bap1 deficient TSCs exhibited higher levels of stem cell marker gene expression such as Cdx2 and Esrrb, a higher proliferation rate and decreased cell adhesiveness compared to wild type (WT) cells, a phenotype linked to transformation. Under differentiation conditions Bap1-/- TSCs failed to downregulate stem cell markers appropriately, whilst at the same time differentiation towards trophoblast giant cells was promoted. These data suggest a new role for Bap1 in regulating trophoblast self-renewal and in modulating the invasive properties of trophoblast.

P13

Reconstructing the Evolutionary History of Cancer from Allele-Specific Somatic Copy-Number Profiles

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Intra-tumour heterogeneity (ITH) is one of the leading causes of resistance development in the clinic. In addition to point mutations, cancer genomes are characterized by extensive chromosomal rearrangements and somatic copy-number alterations (SCNAs). We recently introduced MEDICC (Minimum Event Distance for Intra-tumour Copy-number Comparisons), to infer evolutionary trees in cancer from allele-specific copy-number profiles and for quantification of ITH. MEDICC employs finite-state transducers (FSTs) to compute pairwise evolutionary distances as the minimum number of amplifications and deletions between two genomes. We have successfully demonstrated the power of the method in a clinical study, where we could show how different levels of SCNA-induced ITH are associated with patient survival. However, several challenges remain. While allele-specific CN profiles allow us to assign separate CN states to parental alleles, their phasing, i.e. assignment to the parental haplotypes, remains unknown. Further, due to computational complexity of the algorithm, MEDICC was so far limited to allelic CN states up to 4. We here present a new algorithm for the phasing of CN profiles when multiple samples per patient are available, and a novel formulation of the algorithm which makes computation more lightweight and efficient. Our phasing algorithm allows the detection of independent evolutionary events on opposite parental haplotypes (mirrored subclonal allelic imbalance, MSAI), which together with our new implementation of MEDICC allows for the accurate inference even of focal amplifications with high CN count. We further discuss the inclusion of additional evolutionary events, most prominently whole-genome and whole-chromosome duplications and chromothripsis.

P14

Essential Role for Centromeric Factors Following P53 Loss and Oncogenic Transformation

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In mammals, centromere definition involves the histone variant CENP A deposited by its chaperone HJURP. Alterations in this process impair chromosome segregation and genome stability, which are also compromised by p53 inactivation in cancer. Here we find that CENP A and HJURP are transcriptionally upregulated in p53 null human tumors. Using an established mouse embryonic fibroblast (MEF) model combining p53 inactivation with E1A or HRas-V12 oncogene expression, we reproduce a similar upregulation of HJURP and CENP A.

P15

Single-Cell Transcriptional Profiling by Droplet-Based Microfluidics and its Application in Cancer Research

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A tissue is composed of many different cell types, each of which can have variable biological states. Rather than studying global processes, molecular characterization at the single-cell level would provide a much more complete and accurate picture of its biological function. Such an approach has been very limited though, since conventional methods typically fail to recognize this complexity as they only consider a given input material as a whole. Recent advances in single-cell technologies are currently revolutionizing many fields of biological research by making it possible to profile individual cells in a large-scale manner. I will present our implementation of droplet-based microfluidics for transcriptional profiling of single cells as well as a cell fixation method that we recently established to overcome critical steps in upstream sample processing. Finally, I will show how we can apply these methods to cancer research to study the mechanisms of tumor formation and heterogeneity in established models.

P16

Genome Instability and Genetic Diversity - How The Pathogen l. Donovani Adapt in the Absence of Sex

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Leishmania donovani causes visceral leishmaniasis, a fatal disease when left untreated. The process through which Leishmania adapts to environmental changes is poorly understood. During its life cycle it undergoes major developmental transitions from insect to mammalian hosts. It can also adapt to a variety of fluctuations of the host immune system during infection progression. As a result parasites selected for higher fitness impact severely the disease and can give rise to drug resistance. Aneuploidy has emerged as an important driver in cancer and in evolutionary adaptation of fungal pathogens, but beyond its effect on gene count, it can also impact its response through the selection of beneficial alleles. Yet, the role of aneuploidy on allelic selection has not been covered. Using HT-seq we have analyzed genotype and haplotype variations derived from genome-wide aneuploidies in two datasets. One obtained from a previous large-scale study of 204 clinical isolates, together with new passages of a hybrid species LD1S. In the former longitudinal analysis both DNA and RNA were ultimately obtained and correlated with phenotypic measurements such as infectivity. Aneuploidy events were further inspected and confirmed by FISH. We show that beneficial haplotype combinations in a given parasite population arise independently in a polyclonal fashion. We observed stable co-existence of subpopulations that share common driver aneuploidies but maintain significant differences in karyotypes and haplotypes thus providing the genetic substrate for new populations to be rapidly founded in response to environmental change. Second, we reveal aneuploidy as a mechanism to generate genetic diversity on an evolutionary scale through the accumulation of polymorphisms in super-numerous chromosomes. We found that the parasite evolved a novel strategy to utilize its genomic instability as a substitute for sexual reproduction. This process relies on aneuploidy dynamics to modulate transcriptome, and the ability to change its genetic diversity and to increase its fitness through combinations of karyotypes and haplotypes. This mechanism has important implications in pathogenesis as it may explain the phenotypic variability observed in clinical isolates with respect to drug susceptibility, virulence, and tissue tropism.

P17

A Switch in the Organization of the Airway Microbiome Links Homoeostasis and Lung Exacerbation in Cystic Fibrosis

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Microbes are everywhere and make up most of the biomass on earth. Frequently, they form microbial communities (MCs) and conduct complex, collective functions that are of highest importance for human well-being. Such emergent community behavior is driven by microbial interactions that pervade all levels of organization from individual metabolic interactions up to ecological roles and community dynamics. These need to be taken into account in order to build predictive understanding and manage high-level microbial functions involved in human health. I will present our modeling approach that allows interaction-based detection of keystone species from NGS data. Such keystones are not only relevant for community homoeostasis, but are also prime targets for managing human health. I will show how networks and graph theory are applicable for pinpointing the dynamics of the human microbiome in the showcase of cystic fibrosis (CF) patients. The CF lung microbiome is dynamically characterized by a switch between a pseudo-homoeostatic, nearly symptom-free state and a dysregulated, acute inflammatory state causing dangerous lung exacerbations. We link community organization and disease dynamics and present how our generic keystone framework enables prediction of drug targets in metabolic networks of the CF microbiome. Moreover, the presented concepts are directly transferable to other lung disorders with poly-microbial implication, such as COPD or asthma.

P18

Nidogen-1 Regulation of Breast Cancer Metastasis

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Metastasis is responsible for over 90% of cancer patient deaths. It is a complex process strongly influenced by the extracellular matrix (ECM). A quantitative mass spectrometry analysis of the global ECM proteome in normal and cancerous tissues from mice has previously been performed, and the ECM protein nidogen-1 (NID1) has been identified to be up-regulated in metastatic lymph nodes, as well as down-regulated in primary tumour and metastatic lung. In this project, the role of NID1 in metastasis is being studied using mouse models. NID1 is a basement membrane component. Using both in vitro and in vivo assays, NID1 was shown to be expressed by fibroblasts but not 4T1 breast cancer cells. NID1 was also shown to increase the adhesion ability of 4T1 cells to fibronectin, the migration speed and directionality of 4T1 cells. Using in vivo mice models, NID1 was shown to be secreted into the stromal matrix of tumours, as well as located at the basement membrane regions. In healthy lymph node regions, NID1 was deposited strongly around blood vessels, high endothelial venules and reticular networks, and weakly around lymphatic vessels, while in metastatic tumour regions, it showed a secreted pattern. NID1 was up-regulated in metastatic lymph nodes, while not in metastatic lungs. In our preliminary study, the growth of primary tumour in NID1 knockout mice was slower than in wildtype mice. Our current hypothesis is that, NID1 secreted by fibroblasts increases the adhesion of cancer cells to the stromal matrix to increase the migration and metastatic abilities of cancer cells.

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