INFRAFRONTIER
mouse disease models

IMPC
International Mouse Phenotyping Consortium

**INFRAFRONTIER / IMPC Conference 2019**

# Genetic Variation, Big Data and Ageing

**June 3 to 5, 2019** | Helsinki

#InfrafrontierConf
#InfraConfHelsinki

## Dear colleagues,

**Martin Hrabě de Angelis**
*INFRAFRONTIER, Scientific Director*

**Steve Brown**
*IMPC, Scientific Chair*

After two productive meetings in Athens (2017) and Munich (2018), the joint conference of the INFRAFRONTIER research infrastructure and the International Mouse Phenotyping Consortium (IMPC) has successfully established itself as the global platform for scientific exchange between experts from basic research to clinical research in the biomedical field – with a focus on functional phenogenomics.

This summer, we welcome you to Helsinki, the beautiful capital of Finland. The aim of the INFRAFRONTIER/IMPC Conference 2019 is to discuss three hot topics in modern biomedical research:

**Genetic Variation:** Understanding the functional consequences of human genetic variation and its impact on genetic diseases is critically important. This task involves systematic mutagenesis in appropriate models emulating human genetic variation, together with comprehensive genotypic and phenotypic analysis.

**Big Data:** The availability of vast amounts of genomic and phenotypic data in the IMPC and INFRAFRONTIER databases offers the potential to transform the biomedical research landscape. To carefully collect, analyse and interpret these huge datasets will be essential for the progress of genomic medicine.

**Ageing:** In a setting of rapidly ageing societies across Europe, America, and Asia, new findings into the genetics of ageing processes and age-related disorders uncovered using animal models are pivotal to not only extending life but also improving its quality.

We are grateful to our colleagues at the University of Oulu, together with the Finnish Ministry of Education and Culture and the Academy of Finland, for their kind support in organizing this conference.

Enjoy the INFRAFRONTIER/IMPC Conference 2019 in Helsinki!

**Martin Hrabě de Angelis, Steve Brown**

Carl Ludvig Engel's masterpiece: Helsinki Cathedral – with City Hall in front

## INFRAFRONTIER / IMPC Conference 2019

SCOPE & CONTEXT ..... 06

ORGANIZERS ..... 08

AGENDA ..... 10

SPEAKERS AND ABSTRACTS ..... 20

ABSTRACTS IMPC SESSIONS ..... 48

ABSTRACTS POSTER PRESENTATIONS ..... 62

PARTICIPANTS LIST ..... 82

PERSONAL NOTES ..... 90

### The aims of our meeting are ...

... to raise awareness for INFRAFRONTIER/IMPC platforms among the population genetics research community

... to develop cooperative opportunities in advancing functional genetic variation and ageing research with model organisms

... to present use cases for the utility of model organisms to study genetic variation in population isolates and decipher ageing mechanisms

... to strengthen interactions with ageing and population genetics research consortia

... to showcase emerging insights from IMPC towards understanding functional genetic variation and developing precision medicine

## Scope and Context

This **INFRAFRONTIER / IMPC Conference 2019** is focussed on three main topics: genetic variation, big data and ageing.

Understanding the role of **human genetic variation and its functional consequences** is the next big step in precision medicine. Information on human disease-associated coding variants is available from single case studies, robust genome wide association studies and population genetic screens. Genetic studies on isolated founder populations are a rich source of novel pathogenic variants and new genotype-phenotype associations. However, these association studies do not always confirm causation. An effective way to acquire information about the mechanisms leading to diseases is to replicate genetic changes in appropriate model systems and functionally analysing any resulting phenotypic changes. There is a concerted effort among INFRAFRONTIER partners and IMPC members to accomplish this by designing and producing a genome-wide mouse strain resource of human disease-associated coding variants that can be used for validation of putative pathological variants and provide valuable insight into the disease mechanism.

Recent advances in biomedical technologies like whole exome and genome sequencing, genome-editing and state of the art multi-faceted phenotyping has led to generation of large amounts of valuable data ushering in the era of **'big data genomics'.** These data sets contain a wealth of valuable information that can be combined and complemented to other larger data sets. The genomic and phenotypic data from IMPC and INFRAFRONTIER databases represent a treasure trove of biological information that can be exploited to push the boundaries of fundamental and translational biomedical research. Thus, it is high time to carefully present, collect, analyse and interpret these enormous data sets, as the first steps utilising these recent advances.

The last century has witnessed an ever-increasing ageing population worldwide owing to the improvement in general public health. This has, however, also increased the incidences of late-onset diseases and ageing related co-morbidities resulting in longer but unhealthy lives. This warrants the better understanding of the **ageing processes and ageing-related diseases** to not only improve longevity but also to improve the quality of long life. Ageing research employing animal models offers promising way to understand the genetics behind ageing and age-related disorders as well as to uncover evolutionary conserved ageing mechanisms amenable to therapeutic intervention.

To contribute to these pressing issues, INFRAFRONTIER together with IMPC and Biocenter Oulu has organised this **INFRAFRONTIER / IMPC conference 2019.** The conference involves world-leading experts in functional genetic variation, population genetics and ageing, offers an excellent opportunity for aligning INFRAFRONTIER / IMPC platforms with current frontline research of these selected topics and provides a platform for fruitful interactions between mouse geneticists, population geneticists and ageing experts.

# ORGANISERS

Hanasaari, the Swedish-Finnish Cultural Center – venue for the INFRAFRONTIER/IMPC Conference 2019

## INFRAFRONTIER

*www.infrafrontier.eu*

INFRAFRONTIER is the European Research Infrastructure for phenotyping and archiving of model mammalian genomes. The INFRAFRONTIER Research Infrastructure provides access to first-class tools and data for biomedical research, and thereby contributes to improving the understanding of gene function in human health and disease using the mouse model. The core services of INFRAFRONTIER comprise the systemic phenotyping of mouse mutants in the participating mouse clinics, and the archiving and distribution of mouse mutant lines by the European Mouse Mutant Archive (EMMA). In addition, INFRAFRONTIER provides specialised services such as the generation of germ-free mice, and training in state of the art cryopreservation and phenotyping technologies.

## International Mouse Phenotyping Consortium (IMPC)

*www.mousephenotype.org*

The IMPC addresses one of the grand challenges for biology and biomedical science in the 21st century – to determine the function of all the genes in the human genome and their role in disease. The goal of the IMPC is to develop a comprehensive catalogue of mammalian gene function. The IMPC aims to generate a null mutation for every protein-coding gene in the mouse genome, to acquire broad-based phenotype data for each mutation, and to disseminate the mutant resource and phenotype data to the scientific community. Ultimately, the IMPC program will provide information on the function of all genes and genetic networks and a powerful dataset that will underpin fundamental new insights into the genetic bases for disease.

**Funding Acknowledgements**

Financial support is provided by the INFRAFRONTIER2020 and IPAD-MD projects.

**INFRAFRONTIER2020** receives funding from European Union's Horizon 2020 research and innovation program under Grant Agreement number 730879

**IPAD-MD** receives funding from European Union's Horizon 2020 research and innovation program under Grant Agreement number 653961

# AGENDA

## JUNE 3 TO 5, 2019


Wacky windows for an underground art museum: Amos Rex on Lasipalatsin Square

## MONDAY JUNE 3 — Hanaholmen – *Swedish-Finnish Cultural Centre*

**09:00 – 10:10** — **Introduction and Keynote**

09:00 – 09:30 — **Welcome and Introduction**
**Martin Hrabě de Angelis,** *INFRAFRONTIER, Helmholtz Center Munich*
**Riina Vuorento,** *Ministry of Education and Culture, Finland*
**Riitta Maijala,** *Academy of Finland*
**Marja Makarow,** *Biocenter Finland*

KEYNOTE 09:30 – 10:10 — **Taina Pihlajaniemi,** *University of Oulu*
The Great Power and Versatility of Mouse Models in Understanding MACIT and Multiplexin Collagens in Cell-Extracellular Matrix Interplay

**10:10 – 10:30** — **COFFEE BREAK**

SESSION 1 **10:30 – 12:30** — **Genomic Big Data from Population Isolates**
Chair: **Johanna Myllyharju,** *University of Oulu*

INFRAFRONTIER

10:30 – 10:35 — Intro by Session Chair

KEYNOTE 10:35 – 11:15 — **Aarno Palotie,** *Institute of Molecular Medicine Finland (FIMM)*
Finnish Disease Heritage and FinnGen

11:15 – 11:40 — **Guðrið Andorsdóttir Ellefsen,** *The Genetic Biobank of the Faroe Islands*
FarGen: Genetics, longevity and public health within the Faroese population

11:40 – 12:05 — **Hardip Patel,** *National Centre for Indigenous Genomics*
Australia's National Centre for Indigenous Genomics ensuring the inclusion of Indigenous Australians in Precision Medicine

12:05 – 12:30 — **Terry-Lynn Young,** *Memorial University of Newfoundland*
The Newfoundland Curse

## MONDAY JUNE 3

**12:30 – 13:30** **LUNCH**

**SESSION 2A** **13:30 – 15:00**

IMPC

**Emerging Insights into Genomic and Precision Medicine**

Chair: **Steve Brown,** *IMPC, MRC Harwell*

**13:30 – 14:00** **Introduction to IMPC**

- IMPC: brief summary update **Steve Brown,** *IMPC*
- International Mouse Phenotyping Consortium – Preparing for Horizon Europe and Beyond **Kalliopoi Kostelidou,** *IMPC*

**14:00 – 15:00** **Age-related Phenotyping in IMPC**

- Progress (update on numbers), logistics, SOPs **Sara Wells,** *MRC Harwell*
- DCC and data loading (what is displayed on the portal etc. Remaining tasks) **Piia Keskivali-Bond,** *MRC Harwell*
- Data analysis tools and initial data analysis **MPI2**
- Additional tests and frailty index **Antonio Aguilar-Pimentel,** *Helmholtz Center Munich*
- Pilot tests in the intervening periods **Silvia Mandillo,** *CNR,* **Jan Prochazka,** *IMG,* **Sara Wells,** *MRC Harwell*

**15:00 – 15:15** **COFFEE BREAK**

**SESSION 2B** **15:15 – 17:40**

IMPC

**Emerging Insights into Genomic and Precision Medicine**

Chair: **Mary Dickinson,** *Baylor College of Medicine*

**15:15 – 15:40** **Immunophenotyping**

- Implementation of immunophenotyping data analysis workflow and resulting biological insights **John Seavitt,** *Baylor College,* **Lauryl Nutter,** *TCP*
- EmbedSOM, a self-organizing map-based software tool for multi-dimensional cytometry data analysis **Vendula Novosadova,** *IMG*

## MONDAY JUNE 3

**15:40 – 16:05** **Behaviour and Sensory**

- Emerging insights from neurobehavioural pipeline: paper conclusions
  **Michelle Stewart,** *MRC Harwell,* **Ann Flenniken,** *TCP,*
  **Elissa Chesler,** *Jackson Laboratory*
- New phenotyping developments: Gait analysis, Adhesive removal test, Home cage analysis and ultrasonic vocalisations
  **Michelle Stewart,** *MRC Harwell,* **Silvia Mandillo,** *CNR*

**16:05 – 16:35** **Cardiovascular and Metabolism**

- Update on the IMPC Cardio Paper: New Biological Insights from Cardio Screen **Nadine Spielmann,** *Helmholtz Center Munich*
- Interplay between embryonic and adult phenotypes
  **Mary Dickinson,** *Baylor College,* **Lydia Teboul,** *MRC Harwell,*
  **Henrik Westerberg,** *MRC Harwell*

**16:35 – 17:05** **Embryo Phenotyping**

- MicroCT imaging of early embryos in embryonic lethal pipeline
  **Michaela Prochazkova,** *IMG*
- Embryo Analysis Update **Henrik Westerberg,** *MRC Harwell*
- Subviable Analysis Update **Hugh Morgan,** *MRC Harwell*

## MONDAY JUNE 3

**17:05 – 17:40** **Morphology**

- X-ray test annotation – Reference atlas update **Jesús Ruberte,** *UAB*
- Eye Morphology test annotation – Zegami online image library for baseline and mutant annotation training and jamborees **Colin McKerlie,** *TCP*
- High-throughput in-vivo microCT in skeleton morphology phenotyping **Jan Prochazka,** *IMG*
- Gross Pathology test and Tissue Embedding test Enquiry function at IMPC portal – Implementation **Alba Gómez,** *EMBL-EMI*
- Histopathology test – Completing required annotation gaps in uploaded data, Displaying hits at the Portal, Preliminary LAP histopathology update **Colin McKerlie,** *TCP*

**18:15** **BUS DEPARTURE TO RESTAURANT**

**19:00** **SOCIAL DINNER FOR ALL PARTICIPANTS**

**TUESDAY** JUNE 4 — *Hanaholmen – Swedish-Finnish Cultural Centre*

SESSION 2C **08:15 – 09:45**

IMPC

**Emerging Insights into Genomic and Precision Medicine**

Chair: **Colin McKerlie,** *TCP*

**08:15 – 08:45** **Molecular Phenotyping**

- General Summary **Kent Lloyd,** *UC Davis*
- Metabolomics **Kent Lloyd,** *UC Davis*
- Developments in the analysis of the microbiome **Kent Lloyd,** *UC Davis*
- Proteomics **David Schibli,** *UVic*
- Epigenomics **Archana Tomar,** *Helmholtz Center Munich*
- PCDDP progress update **Anne Grobler,** *PCDDP*

**08:45 – 09:45** **Nociception**

- Overview and outline of the hour session **Jacqui White,** *Jackson Laboratory*
- Formalin **Jacqui White,** *Jackson Laboratory*
- CFA – von Frey, Hargreaves', Edema **Ann Flenniken,** *TCP*
- Adaptations for HTP compatibility: CFA - Cage Lid Interaction, and Dynamic Weight Bearing **Rob Bonin,** *University of Toronto*
- Unchallenged strategies **Michelle Stewart,** *MRC Harwell*
- Landing page **Daniel Delbarre,** *MRC Harwell*
- Summary recommendations, Publication Plans, Acknowledgements & Questions **Jacqui White,** *Jackson Laboratory*

**09:45 – 10:05** **COFFEE BREAK**

## TUESDAY JUNE 4

**SESSION 3** **10:05 – 11:50**

IMPC

**Understanding Genetic Variation using IMPC Big Data**

Chair: **Ann-Marie Mallon**, *MRC Harwell*

**10:10 – 11:50**

**MPI2: Informatics and Big Data**

- New website and comms **Terry Meehan**, *EMBL-EBI*, **Kieran Gibson**, *IMPC*
- Tracking precision medicine models **Alba Gómez**, *EMBL-EBI*
- Data capture, standardisation and QC of phenotyping data **Luis Santos**, *MRC Harwell*
- MPI2 Manuscript updates **Violeta Munoz Fuentes**, *EMBL-EBI*
- Phenopackets and Statpackets **Jeremy Mason**, *EMBL-EBI*
- Novel Disease Gene Discovery in the 100K Genomes using mouse data **Valentina Cipriani**, *QMUL*
- Improvements to integration and comparative analysis of mouse and human large-scale datasets **Tomasz Konopka**, *QMUL*
- RRIDS **Anita Bandrowski**, *UC San Diego*

**KEYNOTE** 11:50 – 12:30

Translational insights to vascular growth factors

**Kari Alitalo**, *University of Helsinki*

**12:30 – 13:30** **LUNCH**

**SESSION 4** **13:30 – 17:30**

INFRAFRONTIER

**Model Organisms in Ageing Research**

Chair: **Valérie Gailus-Durner**, *Helmholtz Center Munich*

13:30 – 13:35 Intro by Session Chair

13:35 – 14:00 **Brun Ulfhake**, *Karolinska Institutet*

Behavioural assessment of ageing and its dependence on the integrity of sensory mechanisms

## TUESDAY JUNE 4

14:00 – 14:25 **Mart Saarma,** *University of Helsinki*
Development of growth factor therapies for Parkinson's disease

14:25 – 14:50 **Peppi Karppinen,** *University of Oulu*
Systemic long-term inactivation of hypoxia-inducible factor prolyl 4-hydroxylase 2 ameliorates aging-induced changes in mice without affecting the life span

14:50 – 15:50 **POSTER SESSION AND COFFEE BREAK**

15:50 – 16:15 **Bruno Reversade,** *A*Star Institute, Singapore*
Solved and unsolved premature ageing syndromes and our use of animal and patient-derived organoids for disease modeling

16:15 – 16:40 **Dan Ehninger,** *German Center for Neurodegenerative Diseases*
Lifespan and healthspan in mice: mechanisms and interventions

16:40 – 17:05 **Celia Martinez-Jimenez,** *Helmholtz Center Munich*
Effect of ageing on cellular variability and transcriptional dynamics

17:05 – 17:30 **Fabio Mammano,** *CNR*
An INFRAFRONTIER mouse model of partial connexin 26 deficiency provides critical insight into the etiopathogenesis of age-related hearing loss

17:30 – 20:00 **SOCIAL EVENT:**
**BOAT TRIP ACROSS THE HELSINKI ARCHIPELAGO**

**WEDNESDAY** JUNE 5 — *Hanaholmen – Swedish-Finnish Cultural Centre*

| | | |
|---|---|---|
| SESSION 5 | **09:00 – 10:20** | **Animal Models for Studying Genetic Variation**<br>Chair: **Jukka Kallijärvi,** *University of Helsinki* |
| INFRAFRONTIER | 09:00 – 09:05 | Intro by Session Chair |
| | 09:05 – 09:30 | **Hannes Lohi,** *University of Helsinki*<br>Canine models of human disease |
| | 09:30 – 09:55 | **Anu Suomalainen-Wartiovaara,** *University of Helsinki*<br>Mechanisms for mitochondrial disorders using genetically tailored disease models |
| | 09:55 – 10:20 | **Fuad Iraqi,** *University of Tel Aviv*<br>Collaborative Cross mice offer the greatest genetic diversity resource population for studying complex diseases and modifiers for IMPC project |
| | **10:20 – 10:40** | **COFFEE BREAK** |
| SESSION 6 | **10:40 – 12:20** | **Stakeholder Presentations**<br>Chair: **Michael Raess,** *INFRAFRONTIER* |
| INFRAFRONTIER | 10:40 – 11:00 | **Daniel Rhodes,** *Queen Mary University of London (QMUL)*<br>Constraint and phenotypic similarity characterization of drug targets and their paralogs to inform on drug side effects |
| | 11:00 – 11:20 | **Eleonora Leucci,** *KU Leuven, LifeTime*<br>PDX as relevant preclinical models: Trace experience |

## **WEDNESDAY** JUNE 5

| | |
|---|---|
| 11:20 – 11:40 | **Satu Kuure,** *University of Helsinki*<br>Omics profiling as a tool to identify metabolic profiles of kidney progenitors |
| 11:40 – 12:00 | **Jukka Kallijärvi,** *University of Helsinki*<br>A spontaneous mitonuclear epistasis converging on Rieske Fe-S protein exacerbates complex III deficiency in mice |
| 12:00 – 12:20 | **Pasi Kankaanpää,** *Euro-BioImaging*<br>Euro-BioImaging can complement INFRAFRONTIER/IMPC services in life sciences |
| **12:20 – 12:30** | **Wrap Up and Closing Remarks**<br>**Michael Raess,** *INFRAFRONTIER* |
| **12:30 – 13:30** | **LUNCH** |

# SPEAKERS & ABSTRACTS

Helsinki University: Think Corner

## MONDAY, 3 JUNE 2019 — Speakers in order of appearance

| | |
|---|---|
| **Taina Pihlajaniemi** | *University of Oulu,* Finland |
| SESSION 1 | |
| **Aarno Palotie** | *FIMM,* Finland |
| **Guðrið Andorsdóttir Ellefsen** | *FarGen,* Faroe Isles |
| **Hardip Patel** | *Australian Phenotyping Network,* Australia |
| SESSION 2A | |
| **Steve Brown** | *IMPC, MRC Harwell,* UK |
| **Terry-Lynn Young** | *University Newfoundland,* Canada |
| **Kalliopoi Kostelidou** | *IMPC,* UK |
| **Sara Wells** | *MRC Harwell,* UK |
| **Antonio Aguilar-Pimentel** | *Helmholtz Center Munich,* Germany |
| **Silvia Mandillo** | *CNR Monterotondo,* Italy |
| **Jan Prochazka** | *IMG Prague,* Czech Republic |
| SESSION 2B | |
| **John Seavitt** | *Baylor College,* USA |
| **Lauryl Nutter** | *TCP Toronto,* Canada |
| **Vendula Novosadova** | *IMG Prague,* Czech Republic |
| **Michelle Stewart** | *MRC Harwell,* UK |
| **Ann Flenniken** | *TCP Toronto,* Canada |
| **Elissa Chesler** | *Jackson Laboratory,* USA |
| **Nadine Spielmann** | *Helmholtz Center Munich,* Germany |
| **Mary Dickinson** | *Baylor College,* USA |
| **Lydia Teboul** | *MRC Harwell,* UK |
| **Henrik Westerberg** | *MRC Harwell,* UK |
| **Michaela Prochazkova** | *IMG Prague,* Czech Republic |
| **Hugh Morgan** | *MRC Harwell,* UK |
| **Jesús Ruberte** | *UAB Barcelona,* Spain |
| **Piia Keskivali-Bond** | *MRC Harwell,* UK |
| **Colin McKerlie** | *TCP Toronto,* Canada |

## TUESDAY, 4 JUNE 2019

## Speakers in order of appearance

| SESSION 2C | |
|---|---|
| **Kent Lloyd** | *UC Davis,* USA |
| **Christoph Borchers** | *University of Victoria,* Canada |
| **Archana Tomar** | *Helmholtz Center Munich,* Germany |
| **Jacqui White** | *Jackson Laboratory,* USA |
| **Robert Bonin** | *University of Toronto,* Canada |
| **Daniel Delbarre** | *MRC Harwell,* UK |

| SESSION 3 | |
|---|---|
| **Terry Meehan** | *EMBL-EBI,* UK |
| **Kieran Gibson** | *IMPC,* UK |
| **Alba Gomez Segura** | *EMBL-EBI,* UK |
| **Luis Santos** | *MRC Harwell,* UK |
| **Violeta Munoz Fuentes** | *EMBL-EBI,* UK |
| **Jeremy Mason** | *EMBL-EBI,* UK |
| **Valentina Cipriani** | *QMUL London,* UK |
| **Tomasz Konopka** | *QMUL London,* UK |

| SESSION 4 | |
|---|---|
| **Anita Bandrowski** | *UC San Diego,* USA |
| **Kari Alitalo** | *University Helsinki,* Finland |
| **Brun Ulfhake** | *University Helsinki,* Finland |
| **Mart Saarma** | *University Helsinki,* Finland |
| **Peppi Karppinen** | *University of Oulu,* Finland |
| **Bruno Reversade** | *A-STAR Institute,* Singapore |
| **Dan Ehninger** | *German Center of Neurodegenerative Diseases,* Germany |
| **Celia Martinez-Jiminez** | *Helmholtz,* Germany |
| **Fabio Mammano** | *CNR Monterotondo,* Italy |

## WEDNESDAY, 5 JUNE 2019 **Speakers in order of appearance**

| SESSION 5 | |
|---|---|
| **Hannes Lohi** | *University Helsinki,* Finland |
| **Anu Wartiovara** | *University Helsinki,* Finland |
| **Fuad Iraqui** | *University Tel Aviv,* Israel |

| SESSION 6 | |
|---|---|
| **Daniel Rhodes** | *QMUL,* United Kingdom |
| **Eleonora Leucci** | *Catholic University of Leuven, LifeTime,* Netherlands |
| **Satu Kuure** | *University Helsinki,* Finland |
| **Jukka Kallijärvi** | *University Helsinki,* Finland |
| **Pasi Kankaanpää** | *Euro-BioImaging,* Germany |

**Prof. Taina Pihlajaniemi, M.D., Ph.D.**
*University of Oulu*
Professor of Medical Biochemistry
Vice Rector for Research

*Since 1990, Taina is Professor of Medical Biochemistry at the University of Oulu. From 1996 to 2009, she was Scientific Director of BCO and founding Director of Biocenter Finland. She also was Director of the Academy of Finland Centre of Excellence for Cell-Extracellular Matrix Research, and director of the Finnish node of INFRAFRONTIER in 2006-2014. Additionally, she is a scientific co-founder of FibroGen Inc.*
*Taina is a leading scientist in extracellular matrix (ECM) and collagen research, including discovery of collagen XIII, collagen XV and collagen XVIII. Understanding their properties and physiological functions have become the central theme of her research, and now the focus has shifted to their roles in pathological processes and stem cell biology.*

MONDAY, JUNE 3, **09:30 – 10:10**

## The Great Power and Versatility of Mouse Models in Understanding MACIT and Multiplexin Collagens in Cell-Extracellular Matrix Interplay

A complex interplay between cells and the extracellular matrix (ECM) regulates developmental processes and tissue homeostasis, and changes in the ECM composition and amount markedly affect cellular function in health and disease. The 28 different collagens (Col) form a major ECM protein family marked by extraordinary functional diversity, ranging from structural support to tissues to critical regulatory binding activities and biologically active cryptic domains releasable through ECM proteolysis. Two subfamilies of collagens, identified by us, have proven highly interesting players at the complex milieu of cell-ECM interphase, including stem cells (SC) and tumour microenvironments, namely the MACITs (membrane-associated collagens with interrupted triple-helices), especially ColXIII and ColXXIII, and the multiplexins (multiple triple-helix domains with interruptions), ColXV and ColXVIII. With respect to the MACITs, we have shown that ColXIII affects cell adhesion and signalling and is required for the development and function of neuromuscular junctions (NMJ) and bone. Moreover, intrinsic alterations at the NMJ in Col13a1-/- mice contribute to impaired and incomplete NMJ regeneration and functional recovery after peripheral nerve injury. We have shown that the multiplexins have distinct biological functions, e.g., whereas ColXV functions in microvessels and in skeletal and cardiac muscles, ColXVIII has specific roles in the eye, the brain, the skin, the adipose tissue and the developing kidney. ColXVIII is upregulated in several types of SCs, including hair follicle and hematopoietic SCs, and breast cancer SCs, hence suggesting roles in regulating SC properties and function. The significance and mechanisms of these collagens in development and tumourigenesis will be discussed.

MONDAY, JUNE 3, **10:35 – 11:15**

## FinnGen: a unique resource of 500,000 Finns

**Aarno Palotie, M.D., Ph.D., Professor**
*University of Helsinki*
Institute for Molecular Medicine Finland (FIMM), HiLIFE

*Aarno is the research director of the Human Genomics program at FIMM. He is also a faculty member at the Center for Human Genome Research at the Massachusetts General Hospital in Boston and associate member of the Broad Institute of MIT and Harvard. He has a long track record in human disease genetics, holding professorships and group leader positions at the University of Helsinki, UCLA, anf the Wellcome Trust Sanger Institute. He has also been the director of the Finnish Genome Center and Laboratory of Molecular Genetics in the Helsinki University Hospital.*

FinnGen is a large public-private partnership aiming to collect and analyse genome and health data from 500,000 Finns. FinnGen aims on one hand to provide novel medically and therapeutically relevant insights but also construct a world-class resource that can be applied for future studies.

The FinnGen study collection will consist of 200,000 already existing legacy biobank samples and 300,000 prospective biobank samples. The study aims to produce comprehensive genome variant data from all the participants using genome-wide genotyping and imputation that is based on a population specific sequencing imputation backbone. Using this strategy, variants can be reliably imputed down to very low frequency due to the strong bottleneck effect which the Finnish population has experienced.

The study will utilize the extensive longitudinal health register data available on all Finns that record hospital and outpatient visits, prescription drug purchases, causes of death and many others. These registers cover the entire lifespan and have been digitalized for decades. This data provides unique opportunities to study disease associations (GWAS and PheWAS), disease trajectories and comorbidities.

The FinnGen analysis delivers every sixth month data freezes with approximately 40 – 50,000 sample increments. During the first 1.5 years, FinnGen has already delivered genotype and health data from 142,000 Finns. FinnGen offers an exciting collaborative opportunity to study genetic impacts on human conditions over time. The study currently involves Finnish biobanks, University Hospitals and their respective Universities, the Institute of Health and Welfare (THL), the Finnish Red Cross Blood Service and nine large pharmaceutical companies.

MONDAY, JUNE 3, **11:15 – 11:40**

## FarGen: Genetics, longevity and public health within the Faroese population

**Guðrið Andorsdóttir Ellefsen, M.SC**
*University of Oslo*
Director of the Genetic Biobank of the Faroe Islands

The goal of the next phase of the FarGen project is to extend the FarGen-infrastructure with additional samples, as well as additional information regarding general health status, longevity and socio-demographics. The multidimensional data will enable combined analyses in order to increase our understanding of familial longevity, disease biology and pathogenesis.

The Multi-Generation register of the Genetic Biobank comprises hereditary records of all individuals registered in the Faroe Islands since 1800; the majority of the individuals (85%) have records dating back to 1650. The FarGen project is using the genealogy records to show familial longevity, consanguinity and inbreeding within the Faroese population.

Pedigrees are used in combination with genotype data to gain information on population stratification and the demographical history of the Faroe Islands.

The project will involve collecting blood samples from additionally 3500 individuals for genetic and biochemical analysis, stool samples for microbiome analysis, as well as collecting health status information through body measurements and questionnaires. The data will be use in future genetic studies e.g. genome-wide association studies, candidate-region studies or candidate-gene studies.

The project will improve the knowledge of the genetic variation within the Faroese population i.e. knowledge of known, unknown and de novo mutations. Further, the multidimensional data will be available for combined analysis in order to describe and predict polygenic risk scores for various diseases in the Faroese population.

MONDAY, JUNE 3, **11:40 – 12:05**

## Australia's National Centre for Indigenous Genomics ensuring the inclusion of Indigenous Australians in Precision Medicine

Large-scale projects that develop perpetual community resources, such as UK Biobank, IGSR, TCGA, IMPC, and APN play an increasingly important role in biomedical research, and precision medicine. The National Centre for Indigenous Genomics (NCIG) is similarly establishing a resource of whole genome sequence data, and related biospecimens and records from Indigenous Australians. It is an example of a community resource build to enable broad-scale representation of ancestrally diverse populations that will ensure the benefits of genomics are extended to all humans, irrespective of their ancestry; an example of equitable innovation for precision public health. In the current era of „genomical" scale data and the availability of advanced machine learning techniques, resources such as NCIG need to be appropriately managed to extract maximum value for all. Towards that end, we are creating a managed data repository in partnership with National Computational Infrastructure. This dynamic repository integrated with biospecimen information linked to participating individuals across generations will provide the essential connection between Indigenous and research communities; this is vital for sustainable benefit and capability development. Our mission is strengthened by Indigenous Governance backed by federal statutory powers, with an Indigenous-majority Board that has custodianship of the samples and data. We have established a world-leading model for persistent community engagement and partnership ensuring trust and involvement of communities at all levels of our operations. We are discovering novel variants for clinical interpretation and discovery and showing that isolated populations can have distinct genetic characteristics that requires modification of standard approaches to data analysis.

**Hardip Patel, Ph.D.**
*The Australian National University, Canberra, John Curtin School of Medical Research*
Research Fellow

*Trained in Pharmacy, Biotechnology, and Genomics, Hardip received his Ph.D. degree in Biomedical Science and Biochemistry. Today, he is a Research Fellow at the National Centre for Indigenous Genomics at the John Curtis School of Medical Research, focusing on understanding the genome biology of humans utilizing high-throughput sequencing technologies. His specific interest is in identifying genetic aberrations that cause human diseases, molecular epidemiology for mechanistic understanding of systems biology and comparative genomics to understand evolution of genomes and gene families.*

**Steve Brown, Professor**
**Ph.D., FRS MedSci**
*IMPC, MRC Harwell*
Director of the MRC Harwell Institute
Chairman of the IMPC Steering Committee

*Steve is one of the most renowned scientists in the international functional mouse genetics. His research interests cover mouse functional genomics, including the use of large-scale mouse mutagenesis and comparative genomic analysis to study the genetic basis of disease and to develop pre-clinical disease models. A particular focus has been the use of mouse models to study the molecular basis of genetic deafness. Over the last ten years Steve has led a substantial research effort in the genetics of otitis media or glue ear, a common cause of hearing loss in children, employing mouse models to elaborate the key genetic pathways involved and develop novel therapeutic strategies.*

MONDAY, JUNE 3, **13:30 – 14:00**

## The International Mouse Phenotyping Consortium (IMPC) – a comprehensive catalogue of gene function for the mammalian genome.

The function of the majority of the genes in the human and mouse genomes remains dark. A major challenge for biomedical sciences is to build a comprehensive understanding of gene function that will support studies of rare and common disease and underpin advances in precision medicine. The International Mouse Phenotyping Consortium (IMPC) is building a catalogue of mammalian gene function by the generation and broad-based phenotyping of a knockout mouse line for every protein-coding gene. To date, over 8,000 knockout mouse lines, many for poorly understood genes, have been generated and over 6,000 phenotyped in a coordinated effort involving more than a dozen global research centers and dedicated publicly-available online resources. The data enables an unprecedented view of the mammalian genome landscape including the enrichment of human Mendelian disease genes among the embryonic lethal strains, the pervasive and wide-ranging sexual dimorphism of phenotypic traits in both wild-type and mutant mice, and the identification of novel disease genes and mechanisms in areas as diverse as metabolism, hearing and vision. The plethora of new genetic disease models as well as the basic and translational knowledge that has arisen from our analysis is being applied in collaboration with rare disease, biobank and other consortia to provide a more profound understanding of the function of human genetic variation.

TUESDAY, JUNE 4, **11:50 – 12:30**

## Translational insights to vascular growth factors

Antiangiogenic therapy has been a success in the treatment of age-related macular degeneration, whereas cancer patients are often either refractory or acquire resistance to anti-angiogenic therapeutics. Better knowledge of the interacting angiogenesis signaling pathways should advance the efficacy of current combination therapies of cancer.

Impaired angiogenesis has been implicated in adipose tissue dysfunction and the development of obesity-associated metabolic disorders. New findings indicate that vascular endothelial growth factors can activate the thermogenic program in adipose tissue, thus preventing diet-induced obesity and related metabolic complications. Attempts have been made to stimulate angiogenesis and arteriogenesis in tissue ischemia, with limited success. One of the obstacles has been the VEGF-induced vascular leakage, leading to tissue edema and subsequent inflammation, which can be counteracted by angiopoietins. So far, angiogenic growth factors have not yet provided significant help for patients with cardiovascular disease, but a better understanding of the biology of the vascular growth factors should facilitate therapeutics development.

The growth of lymphatic vessels, lymphangiogenesis, is involved in a number of pathological processes including tissue inflammation and tumor dissemination, but is insufficient in patients suffering from lymphedema, characterized by chronic tissue edema and impaired immunity. A lymphangiogenic growth factor is currently moving to phase 2 clinical trial in human lymphedema. Furthermore, the recent discovery of meningeal lymphatic vessels may extend the therapeutic potential of lymphangiogenic growth factors and their inhibitors to neurodegenerative and neuroinflammatory diseases.

**Kari Alitalo, M.D., Dr. Med.Sci., Professor**
*University of Helsinki, Wihuri Research Institute*
Academy of Finland Centre of Excellence in Translational Cancer Biology, Director

*As Director of the Translational Cancer Medicine Research Program at the University of Helsinki and of the Academy of Finland´s Digital Precision Cancer Medicine Platform, Kari is a leading specialist for cancer research in Scandinavia and in Europe. He is a board member in the EMBO Molecular Medicine Journal, the Journal of Experimental Medicine, and a lot of other oncology-related publications.*
*In his laboratory Kari is interested in pathophysiology of cancer, tumor angiogenesis and metastasis. His team has unraveled the molecular basis of lymphangiogenesis, the formation of lymphatic vessels and their involvement in tumor metastasis. So three of the currently known five vascular endothelial growth factors (VEGF-B, -C and -D) were identified in its studies.*

**Brun Ulfhake, Ph.D., Professor**
*Karolinska Institutet, Department of Neuroscience*
Professor of Anatomy

*Since 2001, Brun is Professor of Anatomy at Karolinska Institutet, Stockholm´s big medical university. As the Director of Anatomy Education and of Comparative Medicine, he was heavily engaged in laboratory animal ethical matters for a long time.*
*Brun is specialised on ageing research – trying to find out more about its deciding factor: the integration of our genetic material and our behavior in combination with different epigenetic and environmental factors. The research aims at creating understanding for which genes and the regulation thereof that lie behind those deficiencies in function that arise with increasing age.*

TUESDAY, JUNE 4, **13:35 – 14:00**

## Behavioral assessment of ageing and its dependence on the integrity of sensory mechanisms

For half a century phenotyping of small rodents used in research and development of disease interventions have been recognized as a key tool and subject to protocol standardization (e.g. SHIRPA). Behavioural assays represent a high-end read-out of a phenotype effect at the level of the whole organism. With the Infrafrontier and IMPC initiatives, basic phenotyping of genetically modified mice became standardized providing data repositories to the research community as Phenoview, complementing services like Mouse Phenome database at JAX.

Ageing research is attracting increased attention due to demographic changes and the increased prevalence of conditions where aging contributes, such as late-onset diseases. The need for comprehensive, reliable and validated behavioural assay screens to capture phenotype deviations that come with advancing age is obvious and an example of such an effort is the recent COST action Standardization of protocols – assessing cognition in aging mice models by the MouseAge consortium. It is of fundamental importance for the reliability of such screens that they also comprise a coherent assessment of sensory and motor functions since dissipation with age of such capacities show variances not only between species and strains but also within strains that will impact the outcome of tests aiming to uncover for example changes to exploration, anxiety, learning and cognition.

I will address some of the problems with adopting established behavioural test to assay age and also present new possibilities to use non-intrusive home-cage monitoring to assess behaviours and its potential use in the context of assessing ageing.

TUESDAY, JUNE 3, **14:00 – 14:25**

## Development of growth factor therapies for Parkinson's disease

In Parkinson's disease (PD) dopamine (DA) neurons located in the substantia nigra (SN) and projecting to caudate putamen degenerate and die. Since all available therapies provide symptomatic treatment, there is an urgent need to develop novel disease modifying therapies for PD. These therapies should slow down or even stop disease progression.

We have discovered an endoplasmic reticulum (ER) located protein with neurotrophic factor (NTF) properties called cerebral dopamine neurotrophic factors (CDNF). The structure and mode of action of this unconventional trophic factor completely differs from other known NTFs. We have demonstrated that CDNF can protect and repair midbrain DA neurons in rodent and primate neurotoxin models of PD more efficiently than other NTFs. CDNF is mainly located in the ER, where it regulates ER stress and unfolded protein response (UPR) pathways. Moreover, it can also regulate the levels of pro-inflammatory cytokines. To understand the role of CDNF in mammals we created CDNF knockout mice that surprisingly develop an age-dependent loss of enteric neurons and constipation, similar to PD patients. Although the number of midbrain dopamine neurons in CDNF knockout mice is normal there is also an age-dependent amphetamine-induced hyperactivity in Cdnf-/- mice that most probably is the result of aberrant dopamine transporter function. Finnish company Herantis Pharma PLc. is currently testing CDNF in phase I-II clinical study on Parkinson's disease patients in three Scandinavian medical centres.

**Mart Saarma, Ph.D., Professor**
*University of Helsinki, Institute of Biotechnology*
HiLIFE, Laboratory of Molecular Neuroscience

*Mart is Professor of Biotechnology and head of the Laboratory of Molecular Neuroscience at HiLIFE, the Institute of Biotechnology. His research group is investigating the signalling and biological functions of GDNF family ligands and endoplasmic reticulum located CDNF/MANF neurotrophic factor families, both within and outside of the nervous system*
*Mart´s team is researching the therapeutic potential of these proteins in various diseases, testing their efficacy in animal models of Parkinson's disease, ALS, stroke and diabetes mellitus.*
*A highlight has been, in 2017, the initiation of phase I-II clinical trials of CDNF protein in Parkinson's disease patients by the Finnish company Herantis Pharma Plc.*
*Mart has been the Vice President of the European Research Council (ERC) in 2015 and 2016, and a member of the EMBO Council from 2011 to 2016.*

**Peppi Leena Karppinen, MD, Ph.D., Professor**
*University of Oulu, Faculty of Biochemistry and Molecular Medicine*
Professor of Medical Biochemistry

*Peppi´s main research interests focus on areas like hypoxia, metabolism, and cancer. She has 25 years of experience studying the enzymology of 2-oxoglutarate-dependent dioxygenases, such as the collagen P4Hs and the hypoxia-inducible factor (HIF) P4Hs. Her work laid the basis for the development of HIF-P4H inhibitors aimed for therapeutic applications, such as for the treatment of anemia.*
*During recent years Peppi has extended her research to study the role and regulation of the hypoxia response pathway in vivo. Her team has generated a unique mouse line which has continuos activation of the hypoxia response and has allowed them to study the effects of long-term activation of this pathway.*

TUESDAY, JUNE 4, **14:25 – 14:50**

## Systemic long-term inactivation of hypoxia-inducible factor prolyl 4-hydroxylase 2 ameliorates aging-induced changes in mice without affecting the life span

Hypoxia inactivates hypoxia-inducible factor (HIF) prolyl 4-hydroxylases (HIF-P4Hs), which stabilize HIF and upregulate numerous genes to restore tissue oxygenation. HIF-P4Hs can also be inhibited with small molecules, which are studied in clinical trials for renal anemia.

Understanding of the effects of systemic long-term inactivation of HIF-P4Hs, and the concomitant HIF stabilization, is limited but crucial since HIF overexpression is associated with cancers. We set out to determine the effects of systemic genetic inhibition of the most abundant isoenzyme HIF-P4H-2/PHD2/EglN1 on life span and tissue homeostasis in aged mice.

Our data showed no difference between wild-type (WT) and HIF-P4H-2-deficient mice in average age reached. However, there were several differences in the primary causes of death and comorbidities, the HIF-P4H-2-deficient mice having less infections, liver diseases, myocardial infarctions and not developing anemia. These data suggest that chronic inactivation of HIF-P4H-2 is not harmful but likely improves the quality of life in senescence.

TUESDAY, JUNE 4, **15:50 – 16:15**

## Discovery & Modeling of Premature Ageing syndromes

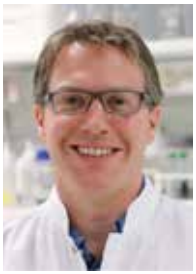
Over the last ten years, a revolution in the speed and accessibility of high volume sequencing has introduced a paradigm shift in human genetics and medicine. Rare diseases – the human experiment – are now the primary tool for annotating function to the human genome.

By identifying the genes responsible for rare diseases, we are best positioned to pinpoint the subverted biological pathways which not only underlie the pathology of a specific condition but which will, in many cases, reveal biological nodes whose perturbation contributes to more common pathologies – i.e. rare begets common.

I will illustrate this paradigm by highlighting how we have gone from discovering mutations in several genes causing premature ageing syndromes to the development of therapeutic drugs for oncology indications.

**Bruno Reversade, Ph.D., Professor**
*A*Star Institute, Singapore*

*Bruno is a Research Director at A*STAR´s Institute of Medical Biology in Singapore, and a distinguished Professor of Genetics at KOÇ University (Turkey) and Amsterdam UMC (Netherlands). Trained as a developmental biologist at UCLA, he went to Singapore and switched to human genetics, placing emphasis on monogenic, fully penetrant and unique genetic traits as a means to understand complex and common diseases.*
*Combining the power of Mendelian genetics, patient-derived organoids and animal modeling in zebrafish, Xenopus and mice, his team has resolved various human disorders affecting embryogenesis, metabolism, ageing, cognition and familial cancers.*



**Dan Ehninger, Ph.D., MD**
*German Center for Neurodegenerative Diseases (DZNE)*
Research Group Leader

*Dan Ehninger is a Senior Research Group Leader at the German Center for Neurodegenerative Diseases (DZNE) in Bonn. He studied medicine at Charité University Medicine/Berlin, Harvard Medical School/Boston and University College London (1997-2003). Dan Ehninger carried out his dissertation at the Max-Delbrück-Center for Molecular Medicine in Berlin (2001-2004) before moving to a postdoctoral position at UCLA Medical Center in Los Angeles (2004-2009). He joined the DZNE faculty in 2010. His research focuses on the biology of ageing and the development of therapeutics for age-related disorders.*

TUESDAY, JUNE 4, **16:15 – 16:40**

## Lifespan and healthspan in mice: mechanisms and interventions

Ageing is a major risk factor for a large number of adult-onset disorders, including neurodegenerative disorders, cardiovascular diseases and cancers, and is associated with a broad range of functional impairments. Targeting ageing processes with suitable pharmacological or dietary interventions could potentially represent a powerful inroad for the development of preventatives or treatments for aging-associated disorders.

A large number of genes and pathways have been identified that extend lifespan in invertebrates as well as in mice but more needs to be learned about possible healthspan effects that corresponding interventions may have. This presentation will cover data detailing how ageing phenotypes, in a range of physiological systems, unfold across the lifespan of mice and humans.

Moreover, I will share data examining how key biological processes implicated in ageing change over the murine lifespan. Finally, I will discuss the question to what extent lifespan-extending manipulations slow mammalian ageing rates and promote overall healthy ageing in mammals on the level of organs and tissues.

TUESDAY, JUNE 4, **16:40 – 17:05**

## Effect of ageing on cellular variability and transcriptional dynamics

The precise molecular mechanisms affecting cellular dynamics during ageing is not well characterized. Ageing induces a progressive decline of physiological and cellular functions and can have a complex and tissue-specific impact on gene expression levels. Approaches that analyse the expression of sets of genes on a single-cell basis have suggested that aging may have further effects altering cell-to-cell variability of gene expression, in contrast, additional evidences also suggest that transcriptional instability may not be a universal attribute of aging.

Whether cell-to-cell gene expression variability increases during ageing on a genome-wide basis, particularly for dynamic activation programs, remains largely unexplored.

**Celia Martinez-Jimenez**
*Helmholtz Center Munich*
Helmholtz Pioneer Campus (HPC), Group Leader

*Celia has focused her studies consequently on mechanisms of gene regulation. She has obtained a European Ph.D. acknowledged by a National Ph.D. award, at the University of Valencia in 2007 and spent her post-doctoral fellowships in Greece and Spain. After finishing an additional MBA study in 2012, she had been working as Business Development Manager at a private spinoff company, followed by a 3 years post-doctoral fellowship in the UK at the University of Cambridge and the Sanger Institute.*
*At present, she is a principal investigator in the Helmholtz Pioneer Campus (HPC) of the Helmholtz Center Munich.*

**Fabio Mammano, M.Phil, Ph.D., Professor**
*University of Padova*
Full Professor of Physics and Astronomy

*Fabio is Italy's MIUR/CNR National Delegate for INFRAFRONTIER/IMPC; Full Professor at the University of Padova (Padua) – Department of Physics and Astronomy „G. Galilei"; Visiting Professor at ShanghaiTech University – Shanghai Institute for Advanced Immunochemical Studies – China; Principal Investigator at, and former Director of, the CNR Institute of Cell Biology and Neurobiology in Monterotondo, Italy. His research interests include biophysical mechanisms and signal transduction in hearing and connexin-related syndromic hearing loss.*

TUESDAY, JUNE 4, **17:05 – 17:30**

## An INFRAFRONTIER mouse model of partial connexin 26 deficiency provides critical insight into the etiopathogenesis of age-related hearing loss

Mutations in GJB2, the gene that encodes connexin 26 (Cx26), are the most common cause of sensorineural hearing impairment. The truncating variant 35delG, which determines a complete loss of Cx26 protein function, is the prevalent GJB2 mutation in several populations[1].

We generated and analyzed Gjb2$^{+/-}$ mice (EM: 11478) as a model of heterozygous human carriers of 35delG[2]. Compared to control mice, auditory brainstem responses (ABRs) and distortion product otoacoustic emissions (DPOAEs) worsened over time more rapidly in Gjb2$^{+/-}$ mice, indicating they were affected by accelerated age-related hearing loss (ARHL), or presbycusis. We linked causally the auditory phenotype of Gjb2$^{+/-}$ mice to apoptosis and oxidative damage in the cochlear duct, reduced release of glutathione from connexin hemichannels, decreased nutrient delivery to the sensory epithelium via cochlear gap junctions and deregulated expression of genes that are under transcriptional control of the nuclear factor erythroid 2-related factor 2 (Nrf2), a pivotal regulator of tolerance to redox stress.

Moreover, a statistically significant genome-wide association with two genes (PRKCE and TGFB1) related to the Nrf2 pathway (p-value < 4 x $10^{-2}$) was detected in a very large cohort of 4091 individuals, originating from Europe, Caucasus and Central Asia, with hearing phenotype (including 1076 presbycusis patients and 1290 healthy matched controls). We conclude that (i) elements of the Nrf2 pathway are essential for hearing maintenance, and (ii) their dysfunction plays an important role in the etiopathogenesis of human presbycusis[3].

WEDNESDAY, JUNE 5, **09:05 – 09:30**

## Canine models of human disease

**Hannes Lohi, Ph.D., Professor**
*University of Helsinki, Faculty of Medicine and Veterinary Medicine*
Group leader at Folkhälsan Research Center, Helsinki

*Hannes is Professor of Molecular Genetics at the Faculties of Medicine and Veterinary Medicine, University of Helsinki. He is also a group leader in Folkhälsan Research Center since 2006 and holds an adjunct professorship at the Ontario Veterinary College in Canada.*
*His laboratory focuses on canine models of human genetic disorders and has built up canine biobanks with >80,000 samples from 330 breeds of dog. This resource provides access to various disease models, with a focus on involving the molecular etiology of common brain disorders, such as epilepsy, neurodegeneration and anxiety. Hannes´ latest efforts involve the genomics and genetics of about one hundred diseases, transcriptomics to improve canine genome annotation, and metabolomics of disease and behavioural traits.*

Our research is focused on the development of canine models of human complex diseases. We take advantage of an experiment initiated by man ~15,000 years ago, taming of the wolf and, more recently, generating 400 strictly inbred pure dog breeds. Canine purebreeding has resulted in highly uniform genomes within each breed, in which the "noise" of background genetic variation is reduced making it easier to detect genetic "signals" that contribute to disease.

That alone would not be very helpful without the fact that several of the essential components of most disease phenotypes can be found and measured in dogs. Dog is a large animal and clinically and physiologically closer to human than typical laboratory rodent models. Dogs develop biologically analogous, if not homologous, conditions to human genetic disorders. Canine disorders usually respond to human medications and also other clinical and phenomenological studies suggest that these traits may share biological mechanisms across species. We aim to utilize this unique genetic system to identify new genes for morphology, behaviour and various disorders.

Although we work with many genetic traits in dogs, our research focuses on neurological, neurodegenerative and neurobehavioral conditions such as common epilepsy, ataxia and anxiety. We have already mapped several new loci and genes in these disorders and believe that the natural canine models provide clinically and physiologically relevant models to corresponding human diseases. Comparison of the identified loci, genes and pathways across species will establish dogs as novel therapeutic models to understand the molecular pathogenesis of these complex traits. Our research has also led to novel successful commercial diagnostic innovations such as the first advanced gene panel test for dogs, and a NMR-based serum metabolomics test.

**Anu Suomalainen (Wartiovaara)**
**M.D., Ph.D., Professor**
*University of Helsinki,*
*Faculty of Medicine*
Research Group Leader at FinMIT Center, Academy of Finland

*Anu completed her M.D. degree in 1991, and in 1993 she obtained her Ph.D. on mitochondrial DNA mutations in diseases. After working at McGill University in Canada for three years, she returned to Finland to build up her own lab at the University of Helsinki. Since 2007 she is the Sigrid Jusélius Professor of Clinical Molecular Medicine.*
*The mission of her lab is to understand the molecular background of mitochondrial disorders, and to develop new ways for diagnosis and therapy.*

WEDNESDAY, JUNE 5, **09:30 – 09:55**

## Mechanisms for mitochondrial disorders using genetically tailored disease models

Mitochondrial diseases manifest with an unprecedented clinical variability, affect children and adults, are always progressive and involve different organ systems. However, the molecular basis of the exceptional clinical variability in these disorders is lacking.

To elucidate the background of tissue-specificity of the manifestations, we have generated mouse models with inactivation of the disease-associated proteins or with knock-in patient mutations, and validated findings in human materials. Using our mitochondrial myopathy model, we characterized tissue-specific metabolic stress responses that are specific for different primary disease signals, and cause major remodeling of metabolism, through transcriptomic, metabolic and cytokine pathways.

Our results indicate that

1) the type of mitochondrial dysfunction determines the local stress responses;
2) acute and chronic responses are different, the latter being induced by secretory components of the acute response;
3) the responses in a single tissue modify metabolism in the whole organism;
4) the responses in mice are fully replicated in human patients;
5) components of the responses are specific and sensitive biomarkers for mitochondrial disease;
6) metabolic "by-pass" therapies, redirecting pathological pathways in a specific tissue are promising therapeutic avenues for mitochondrial diseases.

We have translated the findings in mice to human patients, to develop tools for diagnosis and intervention.

WEDNESDAY, JUNE 5, **09:55 – 10:20**

## Collaborative Cross mice offer the greatest genetic diversity resource population for studying complex diseases and modifiers for IMPC project

Complex traits/diseases are multifactorial, controlled by polygenic host factors. Genetic mapping of these traits in health and disease is essential for the targeted development of personalized therapies. Genetic diversity is a key factor underlying and defining the severity of the disease/trait of interest. The Collaborative Cross (CC) mouse population is a genetically highly diverse recombinant inbred lines created by full reciprocal matings of 8 divergent strains of mice: A/J, C57BL/6J, 129S1/SvImJ, NOD/LtJ, NZO/HiLtJ, CAST/Ei, PWK/PhJ, and WSB/EiJ. Five of the founders including laboratory inbred and three wild derived stains, and representing three mouse species, which carry more than 42 million genetic variants (SNP). Based on recent studies and publications by collaborators and us, we have demonstrated the power of the Collaborative Cross (CC) mouse model for dissecting variety of complex traits, and some, which was not possible without CC mice. Results showing the utilization of the CC lines power for dissecting host susceptibility towards infectious diseases, i.e. Aspergillus fumigatus, Klebsiella pneumonaie/ P. gingivalis and F. nucleatum, Pseudomonas aeruginosa, Sepsis, Chronic diseases (Diabetes/Obesity) and Colorectal cancer, as well body traits (Body composition/ Immune profile/ trabecular bone microarchitecture) will be presented at the conference.

Furthermore, using CC mice, it was possible to map modifiers of number of cancers underlined by mutant genes. Currently, we have extended this approach for mapping modifiers for Smad4 and Kras, which cause head and neck squamous cell carcinoma (HNSCC) and pancreatic cancers, respectively. Based on the success of this approach, it is proposed that we can offer a unique, successful and powerful platform for mapping modifiers for knockout genes developed by the IMPC.

**Fuad A. Iraqi, Ph.D., Professor**
*Tel Aviv University, Sackler Faculty of Medicine*
Department of Clinical Microbiology and Immunology, Chairman

*Fuad is a molecular geneticist and world leader in the area of dissecting complex traits including hosts susceptibility to infection and chronic diseases. His current research is focused on understanding diseases etiology and host susceptibility to infectious and chronic diseases including Klebsiella pneumonia, Aspergillus fumigatus, dental infection (Periodontitis), Type 2 Diabetes and cardiovascular diseases (CVD) associated with obesity, gut microbiota and mapping modifiers for colon cancer development. For studying these diseases, he uses the mouse model, especially the unique mouse resource population known as the Collaborative Cross (CC).*

**Daniel Rhodes**
*Queen Mary University of London (QMUL)*
Centre for Translational Bioinformatics, William Harvey Research Institute

WEDNESDAY, JUNE 5, **10:40 – 11:00**

## Constraint and phenotypic similarity characterization of drug targets and their paralogs to inform on drug side effects

Side effects are a major concern in drug development due to their contribution to clinical trial failures or reducing patient compliance. A possible source of side effects include non-specific binding to paralogs - homologous genes resulting from prior gene duplication events. Here we describe efforts to systematically identify whether an association between the number of paralogs of a target protein and the number of side effects exists. There are multiple challenges associated to this analysis, among them: how to properly define relevant paralog groups, how to differentiate between on target and off target effects and how to identify relevant side effects amongst the redundant or infrequent side effects reported.

First we curated 2,806 high confidence sets of paralogs (components) covering 13,337 unique proteins based on Ensembl 95 annotations and subsequent filtering using pairwise gene ontology semantic similarity, InterPro protein sequence functional characterizations, amino acid sequence similarity, and finally network based community detection algorithms. 530 proteins targeted by approved drugs were labelled across 177 components (Pharos Tclin targets). Of these, 91 were the most constrained of the component as measured by their loss-of-function observed/expected upper bound fraction (LOEUF) score; however within this set, 61 components also contained less constrained drug targets. We also found that components containing drug targets are double the size (mean 8.55 vs 4.5) and showed greater within-component phenotypic similarity (mean score 71.3 vs 64.8) than non-drug target containing components. Phenotypic similarity scores were computed using mouse orthologue phenotype data from the Mouse Genome Informatics resource. We expanded our list of Tclin drug targets to include those indicated via text mining approaches as reported on Pharos.nih.gov for downstream analysis.

WEDNESDAY, JUNE 5, **11:00 – 11:20**

## PDX as relevant preclinical models: Trace experience

**Eleonora Leucci**
*Catholic University of Leuven*
Ph.D., Research Professor
Member in the EU´s LifeTime consortium

*Since Eleonora has done her Ph.D. in Medical Biotechnology at the University of Siena, she has held a number of research positions in Italy, Denmark, and Belgium. The special focus of her research lies on oncology, namely on studying melanoma cells.*
*As a research professor at the KU Leuven since 2017, Eleonora is representing her university in the new LifeTime consortium. This EU project has only been launched on 9 May, 2019. Its mission is to make it possible for physicians to assess the molecular state of patient tissues in real time, leading to early diagnosis and effective interception of diseases.*

Cancer is one of the leading causes of death worldwide and the number of new cases is expected to increase by 70% over the next two decades. Hence, the identification and validation of novel therapeutic strategies to improve survival and quality of life of cancer patients represent a major public health challenge.

Despite the substantial efforts dedicated by the pharmaceutical industry to preclinical drug development, 95% of promising anti-cancer compounds fail at the clinical trial stage, due to poor efficacy or to limited numbers of responding patients. This discouraging failure rate is mainly due to the use of inappropriate preclinical models, unable to recapitulate the heterogeneity of human tumours and to reliably predict the responses to treatment that are often variable in patients.

Patient-derived tumour xenograft (PDX) models, where human tumours are transplanted into immune deficient mice, have been existing for decades. But recently they have gained increasingly recognition as clinically relevant preclinical models. Grafted tumours have been shown to retain close similarities with the originating cancer and preclinical trials in PDXs have demonstrated the ability of these models to mimic (and, in some instances, also anticipate) data obtained in the clinic.

Moreover, in well-characterized PDXs the possibility to correlate therapeutic response with extensive molecular annotation has enabled the identification of several sensitivity and resistance biomarkers in a number of different tumour types, with immediate clinical relevance.

**Satu Kuure, Ph.D.**
*University of Helsinki,*
*Faculty of Medicine*
Director of the Genetically Modified Animal Unit

*At the University of Helsinki's Faculty of Medicine, Satu is the Principal Investigator for the HiLIFE Laboratory animal centre, as well as Director of the Genetically Modified Animal Unit. Her research topics cover areas like the genetic and molecular regulation of development, congenital kidney anomalies, organ- and tissue-specific progenitor cells, and others.*

WEDNESDAY, JUNE 5, **11:20 – 11:40**

## Omics profiling as a tool to identify metabolic profiles of kidney progenitors

We recently demonstrated that kidney development critically depends on MAPK/ERK signaling, which regulates both collecting ductal and nephron progenitor cells. Tissue-specific transcriptomics analysis of control and MAPK-deficient progenitor populations identified a huge number (<5000) of significantly differentially expressed genes (DEG) with massive fold changes in nephron progenitors and slightly less (492) in collecting ductal progenitors.

Analysis of the DEGs with multiple pathway analysis software revealed that several identified genes associate to metabolic control in many cell types. Preliminary validation of the RNAseq results with Seahorse technology measuring mitochondrial metabolism demonstrated significant reduction in oxygen consumption rate and in distinct respiratory processes. This suggests that MAPK-activity regulates progenitors through its important function in metabolic control of these cell populations. As understanding of metabolism in developing kidney and its potential consequences on kidney differentiation are insufficient, we are currently performing an untargeted metabolic profiling in control and MAPK-deficient cells to identify global metabolic profiles in these biological samples.

Utilising systems biology to integrate data from different omics studies is a key advance to ascertain functional linkages within a biomolecular framework. Understanding the basic metabolism and its regulation in renal progenitors is expected to provide insight into underlying mechanisms causing congenital renal defects and may thus help development of new diagnostic and/or therapeutic strategies for kidney diseases.

WEDNESDAY, JUNE 5, **11:40 – 12:00**

## A spontaneous mitonuclear epistasis converging on Rieske Fe-S protein exacerbates complex III deficiency in mice

BCS1L, frequently mutated in respiratory chain complex III (CIII, cytochrome $bc_1$) deficiency, is required for Rieske iron-sulphur protein (RISP, UQCRFS1) assembly into CIII. Knock-in mice carrying a homozygous Bcs1l$^{p.S78G}$ patient mutation display growth restriction, hepatopathy, kidney tubulopathy and premature lethality.

We observed over five times longer survival (35d vs. 200d) of Bcs1l$^{p.S78G}$ mice in C57Bl/6JCrl in Helsinki as compared to a C57BL/6JBomTac background in Lund. Whole genome sequencing revealed a novel homoplasmic mtDNA variant (m.14904G>A, mt-Cyb$^{p.D254N)}$ in the short-lived mice. The variant affects a highly conserved negatively charged amino acid in the RISP-interacting region of the CYTB subunit of CIII. A crossbreeding experiment showed that the short survival was maternally inherited and thus caused by mt-Cybp.D254N. The variant further decreased hepatic CIII activity and respiration in Bcs1l$^{p.S78G}$ mice to below survival threshold.

Remarkably, mt-Cyb$^{p.D254N}$ alone increased electron transfer coupling efficiency and was sufficient to decrease nocturnal energy expenditure and induce hepatic Fgf21 expression in juvenile mice. Molecular dynamics simulations showed restricted conformational flexibility of the mutant ef loop, potentially affecting RISP kinetics. In isolated Rhodobacter capsulatus cytochrome bc1 complex the mutation stiffened the ef loop with consequent longer occupancy of RISP head domain towards the quinol oxidation site.

These findings represent a unique case of spontaneous mitonuclear epistasis and highlight the importance of mtDNA variation as modifier of mitochondrial disease phenotypes.

**Jukka Kallijärvi, Ph.D.**
*University of Helsinki, Faculty of Medicine*
Group Leader at the Folkhälsan Research Center

*Jukka has received his Ph.D. in medical genetics at the University of Helsinki´s Faculty of Medicine in 2006. Since then, he is a staff member there – today as the Principal Investigator for the Stem Cells and Metabolism Research Program. Since 2016, he is also the Administrative Group Leader at the Folkhälsan Research Center.*
*Jukka is a specialist for basic medical research based on working with small animal models like drosophila and (transgenic) mice. His research interests focus on areas like respiratory chain deficiencies and metabolic disorders.*

**Pasi Kankaanpää, Ph.D.**
*Euro-BioImaging*
Åbo Akademi University,
University of Turku

*Pasi is the Project Manager for Euro-BioImaging in Finland and Administrative Director of Turku BioImaging. He is a cell biologist with a background in advanced bioimaging and bioimage informatics. He has previously led a team that developed software for visualizing and analyzing multidimensional bioimages and worked as the coordinator of the Turku Cell Imaging Core. Since 2014, Pasi has worked for the development of Euro-BioImaging and its Hub in Finland, and managed the development of its web portal – the software that works as the access point to all Euro-BioImaging services. He is also a management committee member of the Network of European Bioimage Analysts and the Finnish Euro-BioImaging representative in the H2020-funded EOSC-Life project.*

WEDNESDAY, JUNE 5, **12:00 – 12:20**

## Euro-BioImaging can complement INFRAFRONTIER/IMPC services in life sciences

Euro-BioImaging is a pan-European research infrastructure for biological and biomedical imaging. It will be established as an ERIC during 2019, with 16 founding members. Euro-BioImaging is led by a tripartite Hub, consisting of Finland, Italy and EMBL, and the ERIC will be hosted by Finland. Euro-BioImaging provides imaging-related open access services on three major fronts: imaging instruments, training and data services. Most services are offered by independent units, called Nodes, in the member states. Euro-BioImaging has been providing limited services since 2016, while preparations for the ERIC have been underway, and this “interim operation” will seamlessly transform into “actual operation” once the ERIC has been established. User feedback during interim operation has been very positive and indicates clear need for imaging infrastructure in life sciences.

Euro-BioImaging is a founding member of the Global BioImaging network, and Euro-BioImaging actively collaborates with other European research infrastructures, such as INFRAFRONTIER, especially through projects like CORBEL and EOSC-Life. Euro-BioImaging sees collaboration and synergy between different networks and infrastructures as being of growing importance.

Considering the realm of this conference, imaging continues to grow in significance in the analysis of genetic functions and variation. There is also increasing need and potential in linking genomic and imaging data, and Euro-BioImaging actively develops services that e.g. provide curated, large image datasets with detailed metadata for public sharing and re-use. Some of these services are already in use. Overall, Euro-BioImaging can complement INFRAFRONTIER and IMPC services and extend research possibilities in life sciences.

# ABSTRACTS

## IMPC SESSIONS

Traditional Finnish recreation in an ultra-modern style: Löyly design sauna

MONDAY, 3 JUNE, SESSION 2A **14:00**

## Age-related Phenotyping

**Sara Wells**
*MRC Harwell*

**Antonio Aguilar-Pimentel**
*Helmholtz Center Munich*

**Silvia Mandillo**
*CNR*

A later adult phenotyping pipeline has been instigated as part of phase II of the IMPC in recognition that some phenotypes may manifest later than 16 weeks (the end-point of the IMPC phenotyping pipeline). The phenotypes of older animals (typically between 12 and 18 months) are being investigated in a subset of IMPC lines with additional tests being piloted by individual IMPC centres during the ageing period. The objectives of this working group include 1) what additional value, in terms of phenotypes, does a later adult phenotyping pipeline deliver 2) what are the logistics and challenges of phenotyping at two time points 3) how can our processes of data collection and data analysis be adapted to later adult phenotyping.

The later adult phenotyping pipelines have been established in 10 IMPC centres with a target of phenotyping over 500 IMPC lines later in life. Concurrently the infrastructure required to capture, export and analyse data has been developed by the individual LIM systems and MPI2. To date, over 300 lines are in progress or have been completed with many others being bred to be aged for later adult phenotyping.

Keeping mice for many weeks offers both opportunities for new tests which the working group will present examples of, as well as challenges in terms of attrition, losses and health issues. A specific SOP has been developed to facilitate the collection of welfare data during the whole life time of an animal. The working group have been exploring how to use this data in combination with the phenotyping data to generate a frailty index of each of the aged lines as an indicator of declining physiological function.

MONDAY, 3 JUNE, SESSION 2B **15:15**

## Immunophenotyping

**John Seavitt**
*Baylor College*

**Lauryl Nutter**
*The Centre for Phenogenomics (TCP)*

The IMPC Immunology Working Group is responsible for coordinating development, data analysis, and resource sharing for the IMPC Immunophenotyping test. This is a steady state flow cytometry assessment of immune cell populations in the spleen in the course of the terminal procedure at the end of the standard IMPC phenotyping pipeline. Our recent focus has been on the development of an enhanced workflow suitable for a cutting-edge data analysis and biostatistics pipeline that has as its hallmark algorithm-based methods of flow cytometry data analysis. We likewise coordinate with IMPC informatics teams to develop accessible and informative visualization at the public portal. We facilitate input from an expert Round Table to provide external guidance to ensure this test remains contemporary to developing understandings of immune system biology.

## EmbedSOM: Self-organizing maps improve efficiency of high-dimensional cytometry data analysis in massive immuno-phenotyping

**Vendula Novosadova**
*Institute of Molecular Genetics (IMG)*

Efficient unbiased data analysis is a major challenge for laboratories handling large flow and mass cytometry data. We present a workflow based on EmbedSOM, a non-linear embedding algorithm that cooperates with FlowSOM to provide a high-performance analysis and visualization method for the flow cytometry (FCM) data. The algorithms are designed for speed suitable for interactive analysis of millions of cells without downsampling. We used this algorithm to analyze large FCM datasets generated each week by immuno-phenotyping of mouse knockout (KO) strains, in order to determine particular gene function, as a part of the International Mouse Phenotyping Consortium (IMPC) effort.

Specifically, we have used hundreds of different datasets for self-organizing maps (SOM) training to create a robust system for detection of cell populations defined by IMPC guidelines. These populations are shown and analyzed as subclusters of all cells. We demonstrate that the use of the new workflow improves precision and data throughput when compared with traditional manual gating. Moreover, this approach vastly simplifies batch effect detection and removal. Trained SOM can be used for analysis and visualization the newly acquired data without necessity of retraining, therefore calculation time is reduced, and analysis is repeatable with only minimal input from human expert.

MONDAY, 3 JUNE, SESSION 2B **15:40**

## Behaviour and Sensory

**Michelle Stewart**
*MRC Harwell*

**Ann Flenniken**
*TCP*

**Elissa Chesler**
*Jackson Lab*

**Silvia Mandillo**
*CNR*

The behaviour and sensory working group discusses and review's SOPs for all behaviour and sensory tests in the IMPC pipeline. Data across centres is regularly reviewed and any unexpected differences in the data is discussed. As behavioural tests in particular are very sensitive to the user and environment, investigation of any changes is an important role for the group. Data analysis of behaviour tests can be complex, therefore members of this working group work closely with the data wranglers and the data working group. This allows us to develop the most appropriate data manipulation and statistical methods to apply to each dataset.

A recent focus of the behaviour working group has been a manuscript reporting behaviour data gathered across the IMPC centres. A subset of behaviour parameters has been selected, data QC'd and further analysis carried out. Additional data analysis is necessary in this case to reduce the incidence of type 1 error and ensure we are reporting robust phenotypes. A list of genes with behavioural phenotypes has been produced and is being interrogated by several members of the working group. This includes cross comparison of pre-pulse inhibition phenotypes with GWAS from human schizophrenia patients, data mining of published papers and the Mouse Genome Database to ascertain novel and recapitulated phenotypes and analysis of brain expression.

Finally, this working group actively investigates new tests which could be implemented into the IMPC pipeline to better characterize behavioural changes in genetically altered lines. Mouse behaviour is complex and only a subset of behaviours is currently assessed as part of the IMPC. Behavioural tests are developing and improving all the time and this working group is keen to stay at the forefront of behavioural research, discussing and trialling new tests that will give us further insight into the complexities of mouse behaviour.

MONDAY, 3 JUNE, SESSION 2B **16:05**

## Cardiovascular and Metabolism

**Nadine Spielmann**
*Helmholtz Center Munich*

**Mary Dickinson**
*Baylor College*

**Lydia Teboul**
*MRC Harwell*

**Henrik Westerberg**
*MRC Harwell*

The aims of the metabolism and cardiovascular workgroup are to review SOP adherence, address quality control issues, exchange ideas and best practice amongst contributing centers and data wranglers, identify parameters for inclusion/exclusion based on our increased data and experience, and seek additional value to the pipeline by evaluating new technologies and equipment. Recent topics under discussion were related to the IMPC clinical chemistry data set, the glucose tolerance test and body composition analysis. However, the main focus of the workgroup concentrates currently on the analysis of the cardiovascular data set and a publication of new genes linked to heart disease. Making use of the recently implemented windowing approach for refined statistical analysis and the latest data release, a list of genes was compiled having effects on morphological, electrophysiological and functional features of the heart. The group is currently investigating if these mouse-relevant genes can also be linked to human pathology.

MONDAY, 3 JUNE, SESSION 2B **16:35**

## Embryo Phenotyping

**Michaela Prochazkova**
*IMG*

**Henrik Westerberg**
*MRC Harwell*

**Hugh Morgan**
*MRC Harwell*

Approximately one-third of all mammalian genes are essential for life as the knockout either causes complete or partial lethality. The IMPC continues to asses the viability of all genes and as such we identify 1308 lethal genes, 533 subviable genes, out of 5546 unique gene knockouts. Most IMPC centres have adopted a standardised embryo phenotyping pipeline for homozygous knockout embryos that incorporates a windowed developmental lethality, a gross morphological assessment and high-resolution 3D imaging. We identify phenotypes at multiple key developmental time points for previously uncharacterized genes and additional phenotypes for genes with previously reported mutant phenotypes. This talk will focus on the continued development of automated annotation software pipelines to identify phenotypes within 3D embryonic data. We will go on to summarise some of the early results of analysing a large proportion of the lethal lines. The data has great value as it has been shown that human disease genes are enriched for essential genes, thus providing a dataset that facilitates the identification of new mouse models for human diseases.

MONDAY, 3 JUNE, SESSION 2B **17:05**

## Morphology

**Jesús Ruberte**
*UAB*

**Piia Keskivali-Bond**
*MRC Harwell*

**Colin McKerlie**
*TCP*

The International Mouse Phenotyping Consortium (IMPC) Morphology Workgroup is a consensus Special Interest Group (SIG) with responsibility to; 1) develop IMPReSS standard operating protocols, 2) advise and consult with the IMPC Data Coordination Centre Harwell and IMPC Central Data Archive and Portal at EBI Hinxton on data gathering, curation, annotation, uploading, quality control, statistical analysis, and visualization, 3) engage external domain experts as needed, 4) initiate or respond to requests for piloting new tests or refinement or standardization of existing tests, and 5) provide input and responses to questions from the IMPC Steering Committee, its Panel of Scientific Consultants, and the research community.

The Workgroup is currently responsible for two mandatory clinical tests (X-ray and Eye Morphology), two mandatory terminal tests (Heart Weight and Gross Pathology & Tissue Collection), and three optional terminal tests (Organ Weight, Tissue Embedding & Block Banking, and Histopathology). Membership includes interested individuals from IMPC phenotyping centres and informatics personnel from the DCC and the CDA/portal. Timely topics, reports on progress, and challenges across all test domains will be presented and discussed.

## High-throughput in-vivo microCT in skeleton morphology phenotyping

Jan Prochazka
*IMG*

The plain x-ray imaging has been used for morphological analysis of skeletons for years, however in vivo microCT technology development opened new dimensions in skeleton morphology phenotyping with unbeatable view on bone anatomical features. Among the most advantages are the three-dimensional anatomical context, higher detail of bone anatomical features, easier identification morphological deviants and availability of 3D datasets to additional analysis (e.g. volumetric, bone density, or body composition) compared with plain 2D X-ray images. The caveat of microCT implementation in routine standardized phenotyping is challenge in data processing and analysis. The bioinformatic solution has to be taken in account and customised data software pipeline implemeneted. At CCP we succeed in all critical steps how to implement in vivo microCT technology for routine phenotyping procedures.

TUESDAY, 4 JUNE, SESSION 2C **08:15**

## Molecular Phenotyping

**Kent Lloyd**
*UC Davis*

**Archana Tomar**
*Helmholtz Center Munich*

**Anne Grobler**
*PCDDP*

In an effort to maximize utilization of live mice and capitalize on sophisticated analytical technologies, there is interest in additional phenotyping platforms to augment the expanding knowledge base of gene function being generated through the IMPC Consortium. Discussions among IMPC participants, results from previous and ongoing pilot studies, and input from the IMPC Panel of Scientific Consultants have posited that data generated by various omic analyses (transcriptome, proteome, metabolome, epigenome, microbiome, etc) could contribute significant and critical new knowledge on gene function and relevance to human biology and disease. Several hurdles need to be addressed and overcome to realize this vision, including costs and funding sources, disruption or interference with the primary phenotyping pipelines, and assurance that approaches to collecting data use established standards to ensure compatibility and linkage with extant databases. To that end, IMPC participants created the Molecular Phenotyping and OMICS working Group (WG) to communicate results from internal studies, offer insights on specific analytical profiles, and offer working protocols and procedures across a spectrum of -omics platforms. At this meeting, the WG will provide a summary of general progress to date, specific results related to projects in proteomics and epigenomics, and an update on an NIH-funded pilot effort to classify and compare the gut microbiota community, or “FecalPrint”, across 3 KOMP2-funded centers.

## Using Highly-Multiplexed Panels of Quantitative MRM Assays for Molecular Phenotyping of Normal and Knockout Mice

David Schibli
(for Christoph Borchers)
*Univ. of Victoria*

While advances in gene editing techniques have enabled rapid generation of novel knockout mouse strains, our ability to phenotype the proteome of these mice is limited. To advance our knowledge of normal protein concentrations in mouse tissues and aid molecular phenotyping, we are developing MRM-mass spectrometry assays to quantify 3000 proteins across 20 mouse tissues. Our assays use stable isotope-labelled standard (SIS) peptides for quantitation via standard curve calibration. To date, assays have been developed and validated for 1734 unique proteins in 12 tissues. Following validation, assays are multiplexed into panels of 125 proteins, which represent a combination of tissue-specific proteins and proteins widely expressed in many tissues.

We are now using these panels to measure normal tissues from n=6 male and n=6 female C57BL/6N, BALB/c, and NOD/SCID mice. All measured protein concentrations will be made publicly available via our Mouse Quantitative Targeted Proteomics Knowledge base, currently being developed in-house. We have also used our plasma panel to analyze samples from 30 knockout mouse strains (n=3 male and n=3 female, provided by The Center for Phenogenomics, Toronto, Canada) and establish a unique plasma phenotype for each knockout. For example, C8a knockout mice had decreased plasma concentrations of all 3 components of the C8 heterotrimer, formed by C8a, C8b, and C8y chains, compared to control mice.

This study demonstrates the usefulness of our targeted MRM-MS assays for molecular phenotyping of both normal and knockout mice, and the normal tissue protein concentrations obtained provide a resource for researchers using mouse models.

TUESDAY, 4 JUNE, SESSION 2C **08:45**

## Nociception

The search for novel mechanisms and targets for pain therapeutics is an urgent priority due to the current opiate use and overdose epidemic affecting the US population. The Knockout Mouse Project (KOMP) is part of an international effort designed to extend the functional annotation of the mammalian genome through the large scale and high throughput generation and phenotypic characterization of single gene mouse knockouts on the C57BL/6N genetic background. By evaluating and enhancing existing pain assessment platforms for use in this population we will establish the feasibility of a high throughput-compatible, biologically and clinically relevant pain assay that can be incorporated into the KOMP Phenotyping Pipeline for the discovery of novel pain related genes.

**Jacqui White**
*Jackson Lab*

**Ann Flenniken**
*TCP*

**Robert Bonin**
*Univ. of Toronto*

**Michelle Stewart**
*MRC Harwell*

**Daniel Delbarre**
*MRC Harwell*

TUESDAY, 4 JUNE, SESSION 3 **10:10**

## MPI2: Informatics and Big Data

**Terry Meehan**
*EMBL-EBI*

**Kieran Gibson**
*IMPC*

**Alba Gomez Segura**
*EMBL-EBI*

**Luis Santos**
*MRC Harwell*

**Violeta Munoz Fuentes**
*EMBL-EBI*

**Jeremy Mason**
*EMBL-EBI*

**Valentina Cipriani**
*QMUL*

**Tomasz Konopka**
*QMUL*

**Anita Bandrowski**
*UC San Diego*

The Mouse Phenotyping Informatics Infrastructure (MPI2) provides the informatic support for the IMPC and consists of members from EMBL-EBI, MRC Harwell and Queen's Mary- London with funding provided by the NIH Common Fund. MPI2 coordinates the development of standardised protocols as well as mechanisms to transfer data from IMPC centres to a centralised data hub. Dedicated 'data wranglers' work with each phenotyping center to ensure proper transfer and quality control of data and an automated statistical analysis pipeline identifies knockout strains with significant changes in phenotype parameters. Annotation with biomedical ontologies allows biologists and clinicians to easily find mouse strains with phenotypic traits relevant to their research. MPI2 provides services to integrate IMPC with other human genetic resources as well as highlight IMPC models that have significant phenotype overlap with human disease populations. Users can freely access all data including new gene-phenotype associations via APIs and an intuitive web portal that MPI2 maintains and develops. The community is invited to explore and provide feedback as we build this rich resource for precision medicine at: www.mousephenotype.org

# ABSTRACTS

## POSTER PRESENTATIONS

Huvilakatu street in Eira, Helsinki's beautiful Art Nouveau district

POSTER 1

## INFRAFRONTIER and Rare Diseases

**Asrar Ali Khan**
*INFRAFRONTIER GmbH*

According to the EU, a rare disease is defined as a disease afflicting fewer than 1 in 2000 individuals. It is estimated that 30 million people in Europe suffer from a rare disease. There are currently about 7000 rare diseases known with more being discovered continually. The field of rare diseases suffers from a deficit of medical and scientific knowledge. These diseases reside in the 'unchartered space' of biomedical research with their treatment marred by a dearth of medical and biochemical knowledge.

This has led to development and implementation of several strategies to tackle the treatment of rare and debilitating diseases. For example, the EU supports research into rare diseases through Horizon 2020, the EU Framework Programme for Research and Innovation. Via Horizon 2020, about €900 million is available to more than 160 collaborative projects related to rare diseases.

The core services of INFRAFRONTIER comprise the systemic phenotyping of mouse mutants in the participating mouse clinics, and the archiving and distribution of mouse mutant lines by the European Mouse Mutant Archive (EMMA) which also include lines important for rare disease research. To consolidate and present the INFRAFRONTIER / EMMA resources related to rare diseases in an easily accessible location, the INFRAFRONTIER and Rare Diseases web page was created, providing access to a) EMMA strains related to rare diseases b) EMMA publications related to rare diseases and c) information on INFRAFRONTIER activities at rare disease conferences. This webpage can be found at:
https://www.infrafrontier.eu/infrafrontier-and-rare-diseases.

POSTER 2

## Implementation of metabolomics in IMPC pipeline

**Karel Chalupsky**
*Institute of Molecular Genetics (IMG), Prague*

The Czech Centre for Phenogenomics (CCP) is part of the International Mouse Phenotyping Consortium (IMPC). Clinical biochemistry analysis of blood is part of the IMPC primary screening. In this screening, we analyze about 30 biochemical parameters.

Since we know that by measuring only a limited number of biochemical markers, we may miss the onset of disease or an interesting phenotype, we try to use metabolomics to analyze blood. Metabolomics has shown a great potential in several biological applications. Discovery of diagnostic biomarkers, drug metabolization, their effects on whole metabolome and progression of diseases are examples where studying of metabolome is mainly focused.

One of the biggest tasks in metabolomics is to obtain reliable and reproducible data in reasonable time. Over the past year, we have been able to optimize the IMPC method and store the rest of the mouse plasma to -80C and implement metabolomics in our phenotyping pipeline. After complete phenotyping screening, the most significant mouse phenotypes are selected, including WT mice, and plasma samples are subjected to metabolomic analysis. By using statistical methods such as PCA, it allows the processing of large data sets and group comparisons between WT and mutant animals. Subsequently, we try to identify the metabolites and to specify the metabolic pathways in which they appear. In the final step, we try to tie this metabolic pathway with the described primary phenotype and thus specify the exact function of the gene in the particular mouse model.

POSTER 3

## Core binding factor β protects osteoarthritis development through stabilization of Runx1

**Je-Yong Choi**
*Korea Mouse Phenotype Consortium (KMPC)*

Osteoarthritis (OA), a leading age-related disease in society, still lacks a clear molecular mechanism. Here, we explored in vivo role of core binding factor β (Cbfβ) in OA by generating articular cartilage-specific Cbfβ-deleted mice ($Cbf\beta^{+ ac/+ ac}$) using Gdf5 promoter-driven Cre mice.

OA was induced through destabilization of the medial meniscus (DMM) surgery in 12-week-old male mice. At 8 weeks after surgery, OA phenotypes were exacerbated in $Cbf\beta^{+ ac/+ ac}$ mice compared to wild type with increased expression of Mmp13 and decreased expression of Type II collagen. Interestingly the expression of Cbfβ was reduced during ageing as determined by immunohistochemisty.

Furthermore, at 5 months of age, $Cbf\beta^{+ ac/+ ac}$ mice, but not in wild type, exhibited OA naturally without developmental defects in joint and skeletal tissue formation. To explore the molecular mechanism of its protective role in OA, we measured the expression level of Runx transcription factors, a partner protein of Cbfβ in articular cartilage. Among Runx family, Runx1, but not Runx2 and Runx3, was highly expressed in articular chondrocytes. Expression of Runx1 was gradually decreased during OA progression in wild type mice. Importantly, Runx1 expression was further diminished in $Cbf\beta^{+ ac/+ ac}$ OA mice. Cbfβ formed a complex with Runx1 and stabilized Runx1 from proteosomal degradation in primary articular chondrocytes as well as in ATDC5 cells. Consistently, forced expression of Cbfβ in Cbfβ-deficient primary articular chondrocytes restored the chondrocyte markers and Runx1 expression.

Collectively, these results demonstrate that Cbfβ is required for Runx1 stability as a partner protein in articular cartilage and that the formation of the Cbfβ-Runx1 complex plays an essential role for maintenance of articular cartilage integrity.

POSTER 4

## The Japan Mouse Clinic

**Tamio Furuse**
*RIKEN BioResource Research Center (BRC)*
*Japan Mouse Clinic*

The Japan Mouse Clinic (JMC) at RIKEN RioResource Research Center (BRC) provides mouse phenotyping platforms to community of Japanese scientists. In the JMC, we are conducting systematic and comprehensive phenotyping of mutant mice in order to add values to deposited mice strains in the BRC.

The phenotyping platform includes two pipelines named as pipeline 1 and pipeline 2. Pipeline1 contains comprehensive test items that examine morphological, behavioural, sensory, hematological, clinical chemistry, and pathological phenotypes of the mice. In pipeline 2, we carry out multiple behavioural tests in order to evaluate behavioural traits of the mice. In the pipeline 2, behavioural tests were conducted in order of following, light/dark transition test (6w), open-field test (7w), Crawley's social interaction test (3-chamber test) (8, 9w), home-cage activity test (10-11w), Y-maze test (12w), fear-conditioning test (13w), and pre-pulse inhibition test (14w). In order to collect baseline data, we used C57BL/6J. The baseline data which were collected in this pipeline were statistically stable and had less variation among subjects.

In this meeting, we will introduce the pipeline 2, baseline data, and some examples of significant results we have already collected.

POSTER 5

## New Database for production of transgenic mice

**Alba Gomez Segura**
*EMBL-EBI, Cambridge / UK*
Software Developer

Clinicians and human geneticists are accumulating large amounts of sequence data from patients with the rise of interest in precision medicine and the advent of high-throughput genome-wide DNA-sequencing techniques. Recent advances in DNA editing techniques, such as the CRISPR-Cas9 system, have made it much easier to create transgenic animals carrying a specific allele or variant of a gene. The analysis of the phenotypes displayed by a model organism engineered to carry a sequence variant found in a patient can provide evidence that it has an important role in the development of a disease or a biological mechanism. This is especially useful where the cause of a disease or mechanism cannot be inferred easily from DNA sequence alone.

We present work on a new database designed to coordinate the production of transgenic mice between mouse production facilities and consortia of clinicians and human geneticists. This is a secure resource that can house various types of alleles linked to genes, and will provide different data access policies to users. Our intention is that some data will be publicly available immediately, and that eventually all data will become available following a limited embargo period.

The project is currently being piloted with data from the Centers for Mendelian Genomics (CMG) and Genome Editing Mice for Medicine (GEMM) projects, and our aim is to launch the resource in the autumn.

POSTER 6

## Function of Nhlrc2 in neuronal precursor cells of FINCA mice

**Anniina Hiltunen**
*University of Oulu*
*University Hospital,*
*PEDEGO Research Unit*

NHL repeat containing 2 protein (NHLRC2) is highly transcribed early in human brain development. In FINCA disease, connected to variants of NHLRC2, neurological symptoms are among the first to appear (Uusimaa et al., 2018). In mice, Nhlrc2 is highly expressed in the ventricular layer of E14.5 cortex and there it has been detected in transcriptional waves of differentiating neurons. Recent studies on human fibroblasts and macrophages reveal potential roles for NHLRC2 in cytoskeleton organization, phagocytosis and vesicle transport (Haney et al., 2018; Paakkola et al., 2018). However, the function of NHLRC2 in neurons is still unknown. In the present study, we generated a mouse model to study the function of Nhlrc2 in developing neurons.

Since knock out of Nhlrc2 leads to preimplantation lethality, we generated a knock in mouse harbouring the FINCA patient mutation. This led to 10-fold decrease in Nhlrc2 protein level in compound FINCA/KO mice. To study the function of Nhlrc2 in developing neurons, we compared the proteomes of cultured neuronal precursor cells (NPC) obtained from FINCA/KO and wild type (wt) embryos by two-dimensional gel electrophoresis and mass spectrometry. We discovered 19 proteins that were significantly increased (n=18) or decreased (n=1) in FINCA NPCs.

Many of the identified proteins are involved in protein degradation, cytoskeletal organization and intracellular transport pathways. We propose that the disturbance of these processes may contribute to the neuronal loss in FINCA patients, since protein accumulation and axonal transport deficits are implicated in neurodegenerative diseases. In the ongoing study, we aim to understand the role of NHLRC2 in the intracellular protein processing in NPCs.

POSTER 7

## Systemic long-term inactivation of hypoxia-inducible factor prolyl 4-hydroxylase 2 ameliorates aging-induced changes in mice without affecting the life span

**Riikka Huttunen**
*University of Oulu*

Hypoxia inactivates hypoxia-inducible factor (HIF) prolyl 4-hydroxylases (HIF-P4Hs), which stabilize HIF and upregulate numerous genes to restore tissue oxygenation. HIF-P4Hs can also be inhibited with small molecules, which are studied in clinical trials for renal anemia.

Understanding of the effects of systemic long-term inactivation of HIF-P4Hs, and the concomitant HIF stabilization, is limited but crucial since HIF overexpression is associated with cancers. We set out to determine the effects of systemic genetic inhibition of the most abundant isoenzyme HIF-P4H-2/PHD2/EglN1 on life span and tissue homeostasis in aged mice.

Our data showed no difference between wild-type (WT) and HIF-P4H-2-deficient mice in average age reached. However, there were several differences in the primary causes of death and comorbidities, the HIF-P4H-2-deficient mice having less infections, liver diseases, myocardial infarctions and not developing anemia. These data suggest that chronic inactivation of HIF-P4H-2 is not harmful but likely improves the quality of life in senescence.

POSTER 8

## Radiation potentiates the induction of macrophage infiltration into tumors by Ninjurin1 expression in endothelial cells

**Min Woo Kim**
*Seoul National University*
*College of Veterinary Medicine*

Radiation is a widely used treatment for cancer patients, with over half the cancer patients receiving radiation therapy during course of treatment. The Ninj1 gene, encoding a cell surface protein showing homophilic adhesion, was found to be regulated following p53 activation. More recently, Ninjurin1 was also reported to be upregulated in inflammatory lesions, particularly in macrophages/monocytes, neutrophils, and endothelial cells. Considerable evidence from both preclinical and clinical studies show that tumor recurrence gets restored following radiotherapy, due to influx of circulating cells consisting primarily of monocytes. The attachment of macrophage to endothelial cell is the first step of extravasation process. However, the exact molecules that direct the transmigration of macrophage from blood vessels to tumors remain largely unknown.

Endothelial cells were grown to sub-confluence and irradiated. Radiation-mediated up-regulation of Ninjurin1 was observed in endothelial cell lines. Consistent with this, we found over-expressed Ninjurin1 in irradiated xenograft tumors, and increased macrophage infiltration into tumors. Radiation-induced Ninjurin1 was transcriptionally regulated by p53, as confirmed by p53 knock-down. In addition, Ninjurin1 over-expression in endothelial cells accelerated macrophage adhesion. Irradiation-induced endothelial cells and macrophage interaction was inhibited by knock-down of Ninjurin1. Furthermore, over-expressed Ninjurin1 stimulated MMP2 and MMP9 expression in macrophage cell lines, whereas the MMP2 and MMP9 expression were attenuated by Ninjurin1 knock-down.

Taken together, we provide evidence that Ninjurin1 is a key molecule that generates an interaction between endothelial cells and macrophages. This result suggests that radiation-mediated Ninjurin1 expression in endothelial cells could be involved in the post-radiotherapy recurrence mechanism.

POSTER 9

## FAIR-biomed – facilitating investigative research

**Tomasz Konopka**
*Queen Mary University of London (QMUL)*

Online databases contain vast amounts of information about gene function and variation, but often specialise in just a few modalities, e.g. gene expression or protein interactions. Researchers investigating a lead, e.g. a gene from a high-throughput screen, must thus query several sources to assess the relevance of that hit.

To aid investigative work, the browser extension FAIR-biomed interfaces to several open data repositories and allows a researcher to access snippets of data from reliable sources in a few clicks. For example, the browser extension can display - within any web page - a general summary of recent publications on a topic, molecular pathways for a gene, or phenotypes observed in knock-out mouse models.

FAIR-biomed provides a user-centred mechanism to explore existing data repositories. From the perspective of the individual investigator, it delivers a productivity boost by displaying relevant data faster. From the perspective of data curators, the browser extension provides a new means to deliver content to target users, thus making data more findable, accessible, and thus used in practical research in line with the FAIR principles of data stewardship.

The software is freely available: search „chrome extension FAIR-biomed".

POSTER 10

## New phenotyping developments: 3 – chamber sociability

**Agnieszka Kubik-Zahorodna**
*Czech Centre for Phenogenomics (BIOCEV/IMG)*
*Prague, Czech Republic*

To diagnose a plethora of pervasive developmental diseases (PDD) requires the recognition of core symptoms that manifest in impaired social behaviour and restricted interest/repetitive behaviour. The 2013 DSM-V categorised autism and other PDD into a broader category of Autistic Syndrome Disorders (ASD). Identifying the genetic determinants of ASD is of current interest to the scientific community and indicates the need to develop standardized and automated tests that evaluate social preference and recognition in mouse models of autism.

The Czech Centre for Phenogenomics is currently addressing this need by developing three-chamber sociability tests, which utilize a tracking system that analyses video recordings in order to determine the animal's ability to recognize new conspecific animals and to evaluate animal preferences in regards to conspecifics over novel objects. Using a pharmacological model of autism (valproic acid injections during mouse gestation), the three-chamber sociability test is currently subject of validation.

POSTER 11

## Data integration for bioresource in RIKEN BioResource Research Center

**Hiroshi Masuya**
*RIKEN BioResource Research Center*

Development of the data dissemination and sharing infrastructures for meta-information of bioresources is one of the significant issues for research resource centers. In 2018, RIKEN BRC have launched the Integrated Bioresource Information Division committing to offer bioresource-related information worldwide for promotions of research and development that facilitates the use and application of bioresources. The Integrated Bioresource Information Division has three missions: 1) Development of homepage contents which plays crucial roles to promote uses of bioresource, by carrying resource catalog, window of the collection and distribution of resources as well as advertisement of resources to potential users. 2) Promotion of the data integration and standardization. Data integration of bioresource data with meta-information such as use cases and quality of bioresources also is significant issue for facilitation of application of bioresources. Especially, phenotype data is important for researchers to choose appropriate experimental materials for their studies. Data standardization is also important for wider dissemination of bioresource data across databases and linking bioresource data with related data such as genome, human health and environments. 3) Big data analysis to discover novel biological functions or principles of life systems applying large-scale data analysis technologies with mathematical analysis. Data submission to IMPC-DCC is also managed in the Division.

POSTER 12

## Deletion of hypoxia-inducible factor prolyl 4-hydroxylase 2 in FoxD1-lineage mesenchymal cells leads to congenital truncal alopecia

**Mia Monnius**
*University of Oulu*

The main regulator of the hypoxia response in the cells, the hypoxia inducible transcription factor (HIF), induces hundreds of target genes in hypoxic conditions. HIF prolyl 4-hydroxylases (HIF-P4Hs), of which HIF-P4H-2 is the main isoform, regulate HIF in an O2 dependent manner.

Inactivation of HIF-P4H-2 in FoxD1- lineage mesenchymal cells in the skin results in postnatal truncal alopecia and epidermal cyst formation, which shows that HIF-P4H-2 function in FoxD1-lineage cells is essential for the development and homeostasis of hair follicles. The hair follicle cycle response to alterations of its surroundings. Dermal papilla located in the hair follicle bulge area acts as a control centre of the hair follicle, having a vast interaction with keratinocytes.

According to our results, the dermal papilla composes of FoxD1-lineage cells and thus in HIF-P4H-2/FoxD1-cre (cKO) mice PHD2 is knocked out in the dermal papilla cells. Depletion of HIF-P4H-2 and stabilization of HIF in the skin and hair follicles alters local Notch and TGF-b signalling, leading to disrupted hair follicle cycling and formation of epithelial lined hair follicle cysts filled by keratin and hair fragments. Additionally, cKO mice have significantly increased the thickness of epidermis and dermis when compared to the controls. These alterations manifest as a disruption of hair follicle cycle and a certain phenotype of cKO mice in which the mice suffer from progressive congenital truncal alopecia and smaller bodyweight compared to controls.

POSTER 13

## High-Throughput Pain Phenotyping in The Jackson Laboratory's Knockout Mouse Program

**Emma Peterson**
*The Jackson Laboratory, Bar Harbor / USA*

The search for novel mechanisms and targets for pain therapeutics is an urgent priority due to the current opiate use and overdose epidemic affecting the US population. The Knockout Mouse Project (KOMP) is part of an international effort designed to extend the functional annotation of the mammalian genome through the large scale and high throughput generation and phenotypic characterization of single gene mouse knockouts on the C57BL/6N genetic background. By evaluating and enhancing existing pain assessment platforms for use in this population we will establish the feasibility of a high throughput-compatible, biologically and clinically relevant pain assay that can be incorporated into the KOMP Phenotyping Pipeline for the discovery of novel pain related genes. The intra-plantar injection of formalin into the mouse hind-paw elicits a biphasic response of lifting, licking and shaking the paw, which is typically video recorded and then manually scored by a trained observer. We are evaluating the use of advanced video analysis using neural nets to automate scoring and contrasting this approach to manual scoring. Adjuvant (CFA) induces a delayed thermal and mechanical hyperalgesia response. Thermal hyperalgesia is assessed using the Hargreaves' test, whilst mechanical hyperalgesia and allodynia is assayed using von Frey fibers. We have evaluated the use of various endpoints for Hargreaves and von Frey assessment in the CFA assay to further optimize the observation schedule for the C57BL/6N genetic background. Phenotyping is well advanced on a prioritized set of potential candidate genes and preliminary results will be presented. The development of new drugs that target central or peripheral pain mechanisms with high specificity and efficacy will require identification of novel targets, and mouse populations including the KOMP provide a rapid, statistically powerful means of screening novel genes for a role in chronic pain.

POSTER 14

## Embryonic and neonatal echocardiographic phenotyping

**Silvia Petrezselyova**
*Institute of Molecular Genetics (IMG), Prague / Czech Republic*
*Czech Centre for Phenogenomics*

The systematic IMPC cardiovascular phenotyping approaches include electrocardiography and echocardiography performed on viable adult mice, whereas characterization of structural cardiac or other developmental malformations potentially occurring in embryonic or neonatal lethal mutations is currently not realized. However, these mouse models would be of particular interest to gain insights into congenital diseases. Ultrasound imaging, being noninvasive, can be deployed as a rapid high throughput method for phenotyping in the critical developmental period. Real-time embryonic ultrasound imaging provides the earliest functional tests of heart function and blood flow analysis, even though imaging is limited in regards to the field of view that can be imaged at fine–temporal and –spatial resolution.

Thus, the assessment of cardiovascular function is rather indirect, inferred from the color flow and spectral Doppler imaging. Here we present an example showing how we revealed low heart rate and arrhythmia in E9.5 embryos carrying a lethal mutation using color flow Doppler imaging modality measured one day prior the embryonic death. Similarly, the method was successfully applied to assess blood flow velocities and heart rate of another two mouse knockout models at later embryonic stages or just after birth. In addition, mouse newborns were interrogated with M-mode imaging modality, which allows measurement of chamber wall thickness and lumen dimensions in systole and diastole, which together can be used to quantitatively assess cardiac contractility, and detect hypertrophy/hyperplasia of the ventricular myocardium.

On these examples we demonstrate that the detection of abnormal heart rates is a good indicator of the dysfunction of the heart and thus constitutes a first step in identification of developmental defects that may lead to cardiovascular system failure.

POSTER 15

## Nhlrc2 is required for the first mitosis in zygotes

**Ilkka Pietilä**
*University of Oulu / Finland*
*PEDEGO Research Unit and Medical Research Center Oulu*

Nhlrc2 is conserved, soluble protein with unknown function. Mutations in NHLRC2 cause fatal, early-onset FINCA disease in humans (Uusimaa et al. 2018). Nhlrc2 knock out (KO) mice are embryonically lethal, however, Nhlrc2 KO haploid gametes are vital and capable for fertilization. Thus, in Nhlrc2 KO zygotes, the development is blocked before the first mitosis.

Here we have carried out in vitro fertilization (IVF) with Nhlrc2 KO gametes to study the first steps after the fertilization and before the first mitosis. We have analysed the dynamics of genetic material migration with staining's and characterised how far the normal development proceed in Nhlrc2 knock outs.

Absence of polyspermy indicates that cortical reaction occurs in Nhlrc2 KO zygotes. In addition, presence of single nucleus in the zygote suggests that pronucleus membranes are digested and the genetic material from gametes is capable to fuse. Interestingly, the developmental block caused by the lack of Nhlrc2 is not leading to apoptosis as after 30h of IVF since the Nhlrc2 KO cells appear healthy single cell stage zygotes. We conclude that Nhlrc2 is a novel protein in fertilization, but the mechanism requires further studies.

POSTER 16

## High temporal resolution Indirect Calorimetry & behavioral screening for Energy Expenditure studies in Rodents

**Holger Russig**
*TSE Systems GmbH*

Modern solid-state sensor technology allows for a much higher temporal resolution of gas concentration & behavioral measurements. Metabolic cages are already capable of high temporal resolution (100Hz) measurement of behavior such as Food intake, Water intake, Body weight monitoring, ambulatory activity, running wheel activity, and in some cases, these can be combined with cognitive in-cage testing or optogenetic feedback. The time resolution of the close associated changes in metabolism as measured via indirect calorimetry was, however, lagging far behind.

Several factors contribute to this reduced temporal resolution:
1) the speed of the gas measurement in the gas measurement unit (GMU).
2) the dilution effect of the small breath volume in relationship to the overall cage volume.
3) the flow rate through the cages and
4) the animal position in relation to the sampling position in the cage.

We have designed a new GMU capable of second-by-second measurement of gas concentrations. Combined with a new real-time high-spatial-resolution location capability and newly developed software algorithm, including principal component analysis applied to very large data sets, to deconvolute the volume, flow, and location effects, we can now intimately resolve specific behavior associated metabolic rates such as sleep-, eating-, activity (walking, running)- related metabolic rates. The possibility to apply this algorithm to deconvolve group housed animal metabolic rates will be discussed.

POSTER 17

## The INFRAFRONTIER Research Infrastructure and the European Mouse Mutant Archive (EMMA)

**Fei Song**
*INFRAFRONTIER GmbH*

INFRAFRONTIER is the European Research Infrastructure for the development, phenotyping, archiving and distribution of mammalian models. INFRAFRONTIER provides access to first-class tools and data for biomedical research, therefore contributing to improved understanding of gene functions from mouse to human. The INFRAFRONTIER network of 29 partners is engaged in several EC funded projects, such as INFRAFRONTIER2020, IPAD-MD, CORBEL and EOSC-Life, and contributes to the International Mouse Phenotyping Consortium (IMPC).

The core services of INFRAFRONTIER comprise model generation, systemic phenotyping of mouse mutants in the participating mouse clinics, as well as archiving and distribution of mouse mutant lines by the European Mouse Mutant Archive (EMMA). In addition, INFRAFRONTIER offers specialized services, such as germ-free mouse generation, training in state-of-the-art cryopreservation and phenotyping technologies. The ‘3 R’s’ to improve animal welfare –Replacement, Reduction and Refinement – are among the major goals of INFRAFRONTIER’s technology development activities.

The EMMA branch of INFRAFRONTIER offers the worldwide scientific community a free archiving service for mutant mouse lines and access to a wide range of disease models and other research tools. EMMA currently holds over 7100 mutant mouse strains, half of which have been produced from the International Mouse Knockout Consortium (IKMC) resource. For the latter, an allele conversion service can be provided. The EMMA network is comprised of 16 partners from 13 countries who operate as the primary mouse repository in Europe. EMMA is funded by the partner institutions and national research programmes. Information on mouse strain submission and ordering and all other services offered by INFRAFRONTIER can be accessed online at *www.infrafrontier.eu*.

POSTER 18

## To develop an effective method for the preservation of active sperm

**Zhu Yichen**
*Soochow University, Suzhou / China.*
*CAM-SU Genomic Resource Center*

Resource sharing in mice is desired by almost all researchers who use mice as animal model. But the mice's transport, especially the isolation between facilities, makes it difficult for researchers to share.

Recently, we have successful obtained offspring mice by transport of mouse cauda epididymis instead of live mice, which greatly reduces the cost of transport of mice and reduces the facilities isolation space, benefiting a lot of researchers. But there are still some technical uncertainties such as sperm quality. Some current formulas can effectively improve the fertilization ability of sperm in mice with cauda epididymis after refrigerated transportation or refrozen. However, we found that the method was difficult to recover live mice during long distance transport oversea, especially at low temperatures, after exposure to screening radiation.

Therefore, this project aims to study (1) To optimize the formula of protectant to improve the sperm viability after long-term storage of epididymis and its resistance to radiation dose for security check; (2) The formula should be further improved, especially the strain that has long been difficult to cryopreservation and recovery in the CAM-SU resource bank, so as to study the method suitable for the long-term preservation and transportation of epididymis of these mice.

The ultimate goal is to develop a preservation method that can meet the requirements of long-term preservation, resistance to low dose radiation and enhancement of sperm survival. Meanwhile improve the technique of cryopreservation and resuscitation of mouse sperm, Improve efficiency by establishing methods for large-scale operations. The sperm viability, cryopreservation and recovery ability of the mice were systematically analyzed to try to screen out the key genes affecting sperm function.

POSTER 19

## Update report of IMPC production, phenotyping and informatics at RIKEN BioResource Research Center

**Atsuhi Yoshiki**
*RIKEN BioResource Research Center*

As the core facility of the mouse resource in the National BioResource Project (NBRP) by MEXT/AMED, RIKEN BioResource Research Center (BRC) has collected, preserved, quality-controlled and distributed mouse models for studies to decipher sophisticated biological phenomena and cure human diseases. We have collected 8,800 strains created mainly by Japanese scientists and distributed our mouse resources to 1,400 organizations around the world.

The mice are distributed in high-quality by strict microbial and genetic quality control programs which cover mutated alleles generated by various methods. Our users have so far published over 880 outstanding papers and 37 patents. RIKEN BRC has participated in the International Mouse Phenotyping Consortium (IMPC) and contributed to knockout mice production, phenotyping and data integration.

Recent genome editing technology enables us to collaborate with external clinical scientists and co-produce knock-in mice of variants or mutations found in patients in addition to the null-knockout mice in the same production platform. We have started to collaborate with clinical scientists of Strategic Research Program for Brain Sciences (SRPBS), Initiative on Rare and Undiagnosed Diseases (IRUD), The Japanese Teratology Society.

To disseminate IMPC resources and relevant mouse technologies and facilitate collaborations in Asia/Australia, we will hold the 8th Mouse Workshop entitled “Precision Modelling of Human Diseases in Mice and Cell Resources” on August 26-28, 2019 at RIKEN BRC.

# PARTICIPANTS

Helsinki's new top level attraction: Oodi library

| A | |
|---|---|
| Antonio Aguilar-Pimentel | *Helmholtz Center Munich,* Germany |
| Asrar Ali Khan | *INFRAFRONTIER GmbH,* Germany |
| Kari Alitalo | *University of Helsinki,* Finland |
| Oana Veronica Amarie | *Helmholtz Center Munich,* Germany |
| Margarita Andreadou | *BSRC Alexander Fleming,* Greece |
| Renee Araiza | *University of California Davis (UC Davis),* USA |
| Shinya Ayabe | *RIKEN BioResource Research Center,* Japan |

| B | |
|---|---|
| In-Jeoung Baek | *Asan Institute for Life Sciences, Seoul,* Korea |
| Anita Bandrowski | *University of California San Diego (UCSD),* USA |
| Arthur Beaudet | *Baylor College of Medicine,* USA |
| Lore Becker | *Helmholtz Center Munich,* Germany |
| Auke Boersma | *University of Veterinary Medicine Vienna,* Austria |
| Jinwoong Bok | *Yonsei University Seoul,* Korea |
| Robert Bonin | *University of Toronto,* Canada |
| Fatima Bosch | *Universitat Autonoma de Barcelona UAB,* Spain |
| Lynette Bower | *UC Davis – Mouse Biology Program,* USA |
| Kostas Bozonelos | *BSRC Alexander Fleming,* Greece |
| Cord Brakebusch | *University of Copenhagen,* Denmark |
| Robert Braun | *The Jackson Laboratory,* USA |
| Lars Breuer | *Sable System Europe GmbH,* Germany |
| Steve Brown | *IMPC, MRC Harwell,* United Kingdom |

| C | |
|---|---|
| Pilar Cacheiro | *Queen Mary University of London QMUL,* United Kingdom |
| Karel Chalupsky | *Institute of Molecular Genetics IMG,* Czech Republik |
| Elissa Chesler | *The Jackson Laboratory,* USA |
| Cheol Soo Choi | *Gachon University,* Korea |
| Je-Yong Choi | *Kyungpook National University,* Korea |
| Valentina Cipriani | *Queen Mary University of London QMUL,* United Kingdom |
| David Clary | *University of California Davis (UC Davis),* USA |

| | |
|---|---|
| **D** | |
| Oluwaseun Dada | *Finnish Institute for Molecular Medicine (FIMM),* Finland |
| Daniel Delbarre | *MRC Harwell Institute,* United Kingdom |
| Mary Dickinson | *Baylor College of Medicine,* USA |
| Michael Dobbie | *Australian National University,* Australia |
| **E** | |
| Hilke Ehlich | *INFRAFRONTIER GmbH,* Germany |
| Dan Ehninger | *German Center for Neurodegenerative Diseases (DZNE),* Germany |
| Ivet ELIAS | *Universitat Autonoma de Barcelona UAB,* Spain |
| Guðrið Andorsdóttir Ellefsen | *Ílegusavnið/Genetic Biobank,* Faroe Islands |
| **F** | |
| Sabine Fessele | *INFRAFRONTIER GmbH,* Germany |
| Steve Festin | *Charles River Laboratories,* USA |
| Ann Flenniken | *The Centre for Phenogenomics (TCP),* Canada |
| Colin Fletcher | *National Institutes of Health NIH,* USA |
| Martin Fray | *MRC Harwell Institute,* United Kingdom |
| Anthony Frost | *MRC Harwell Institute,* United Kingdom |
| Helmut Fuchs | *Helmholtz Center Munich,* Germany |
| Tamio Furuse | *RIKEN BioResource Research Center,* Japan |
| **G** | |
| Valerie Gailus-Durner | *Helmholtz Center Munich,* Germany |
| Nicholas Gale | *Regeneron Inc.,* USA |
| Juan Gallegos | *Baylor College of Medicine,* USA |
| Isabella Galter | *Helmholtz Center Munich,* Germany |
| Sofia Gargani | *BSRC Alexander Fleming,* Greece |
| Lillian Garrett | *Helmholtz Center Munich,* Germany |
| Emilie Gesina | *EPFL SV CPG,* Switzerland |
| Kieran Gibson | *MRC Harwell Institute,* United Kingdom |
| Alba Gomez Segura | *EMBL-EBI,* United Kingdom |
| Anne Grobler | *PCDDP, North-West University,* South Africa |

| | |
|---|---|
| **H** | |
| **Hamed Haseli Mashhadi** | *EMBL-EBI,* United Kingdom |
| **Christiane Hauk** | *Leibniz Institute DSMZ / CORBEL,* Germany |
| **Jason Heaney** | *Baylor College of Medicine,* USA |
| **Yann Herault** | *PHENOMIN-iCS,* France |
| **Anniina Hiltunen** | *University of Oulu,* Finland |
| **Reetta Hinttala** | *University of Oulu,* Finland |
| **Young Shin Hong** | *Korea Mouse Phenotyping Center KMPC,* Korea |
| **Neil Horner** | *MRC Harwell Institute,* United Kingdom |
| **Tertius Hough** | *MRC Harwell Institute,* United Kingdom |
| **Martin Hrabě de Angelis** | *Helmholtz Center Munich,* Germany |
| **Ivo Huijbers** | *The Netherlands Cancer Institute NKI,* Netherlands |
| **Riikka Huttunen** | *University of Oulu,* Finland |
| **I** | |
| **Fuad Iraqui** | *Tel Aviv University*, Israel |
| **J** | |
| **Sawan Jha** | *University of Helsinki,* Finland |
| **Wang Jing** | *Soochow University,* Taiwan |
| **Sheethal Jose** | *National Human Genome Research Institute NHGRI,* USA |
| **K** | |
| **Jukka Kallijärvi** | *Folkhälsan Research Center,* Finland |
| **Salla Kangas** | *University of Oulu,* Finland |
| **Pasi Kankaanpää** | *Euro-BioImaging ERIC,* Finland |
| **Peppi Karppinen** | *University of Oulu,* Finland |
| **Sanna Kauppinen** | *Biocenter Oulu/Transgenic Core Facility,* Finland |
| **Tiina Kelkka** | *University of Helsinki,* Finland |
| **Piia Keskivali-Bond** | *MRC Harwell Institute,* United Kingdom |
| **Hongkyung Kim** | *Yonsei University Seoul,* Korea |
| **Minwoo Kim** | *Seoul National University,* Korea |
| **Ruairidh King** | *MRC Harwell Institute,* United Kingdom |
| **Tanja Klein-Rodewald** | *Helmholtz Center Munich,* Germany |
| **Hyuk Wan Ko** | *Yonsei University Seoul,* Korea |

| | |
|---|---|
| Tomasz Konopka | *Queen Mary University of London,* United Kingdom |
| Kalliopi Kostelidou | *IMPC Programme Manager,* United Kingdom |
| Markus Kraiger | *Helmholtz Center Munich,* Germany |
| Agnieszka Kubik-Zahorodna | *Institute of Molecular Genetics IMG,* Czech Republik |
| Satu Kuure | *University of Helsinki,* Finland |

**L**

| | |
|---|---|
| Gina La Sala | *CNR Monterotondo,* Italy |
| Paul Lasko | *McGill University,* Canada |
| Daekee Lee | *Ewha Women's University,* Korea |
| Ho Lee | *National Cancer Center,* Korea |
| Young Jae Lee | *Gachon University,* Korea |
| Huini Li | *University of Helsinki,* Finland |
| Kent Lloyd | *UC Davis,* USA |
| Hannes Lohi | *University of Helsinki,* Finland |
| Federico Lopez Gomez | *EMBL-EBI / IMPC,* United Kingdom |
| Teija Luoto | *University of Oulu,* Finland |

**M**

| | |
|---|---|
| Holger Maier | *Helmholtz Center Munich,* Germany |
| Riitta Maijala | *Academy of Finland,* Finland |
| Marja Makarow | *BioCenter Finland,* Finland |
| Ann-Marie Mallon | *MRC Harwell Institute,* United Kingdom |
| Carlos Malpica | *MLP Vision Biotech SL,* Spain |
| Astha Malviya | *MRC Harwell Institute,* United Kingdom |
| Fabio Mammano | *CNR Monterotondo,* Italy |
| Silvia Mandillo | *CNR Monterotondo,* Italy |
| Susan Marschall | *Helmholtz Center Munich,* Germany |
| Jeremy Mason | *EMBL-EBI,* United Kingdom |
| Hiroshi Masuya | *RIKEN BioResource Center,* Japan |
| Jimenez Mauricio Martinez | *EMBL-EBI,* United Kingdom |
| Aaron McCoy | *MRC Harwell Institute,* United Kingdom |
| Colin McKerlie | *The Centre for Phenogenomics,* Canada |
| Terrence Meehan | *EMBL-EBI,* United Kingdom |
| Gregor Miller | *Helmholtz Center Munich,* Germany |
| Oleg Mirochnitchenko | *National Institute of Health NIH,* USA |
| Mia Monnius | *University of Oulu,* Finland |

| | |
|---|---|
| Lluis Montoliu | *CNB-CSIC,* Spain |
| Hugh Morgan | *MRC Harwell Institute,* United Kingdom |
| Violeta Munoz-Fuentes | *EMBL-EBI,* United Kingdom |
| Steve Murray | *The Jackson Laboratory,* USA |
| Johanna Myllyharju | *University of Oulu,* Finland |

**N**

| | |
|---|---|
| Ki Taek Nam | *Yonsei University,* Korea |
| Ki-Hoan Nam | *Korea Research Institute of Bioscience and Biotechnology,* Korea |
| Aikaterini Nanou | *BSRC Alexander Fleming,* Greece |
| Hyuna Noh | *Korea Mouse Phenotyping Center (KMPC),* Korea |
| Vendula Novosadova | *Czech Centre for Phenogenomics,* Czech Republik |
| Vasileios Ntafis | *BSRC Alexander Fleming,* Greece |
| Lauryl Nutter | *The Centre for Phenogenomics,* Canada |

**O**

| | |
|---|---|
| Manuela Oestereicher | *Helmholtz Center Munich,* Germany |
| Seung Hyun Oh | *Gachon University,* Korea |

**P**

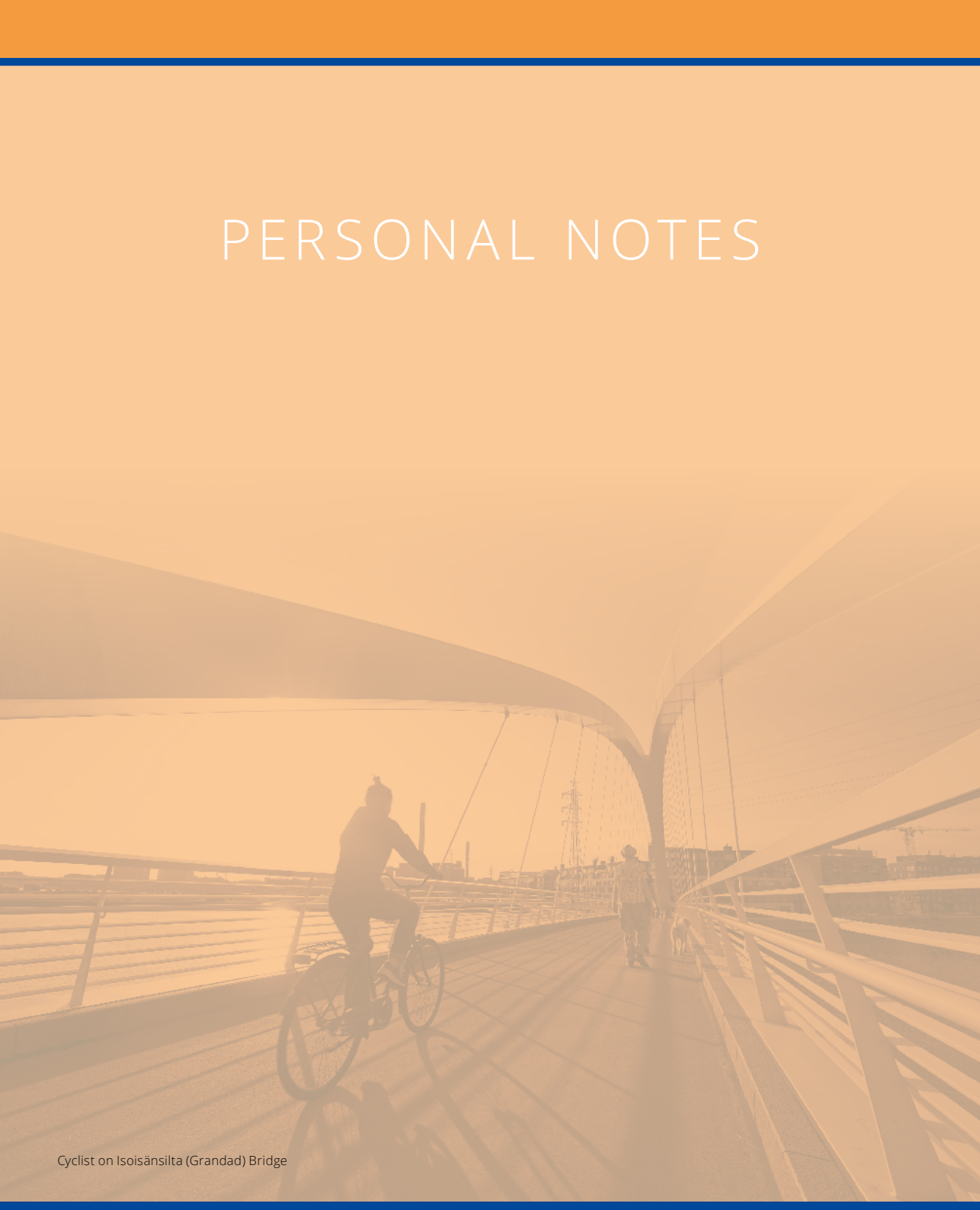
| | |
|---|---|
| Aarno Palotie | *Institute for Molecular Medicine FIMM,* Finland |
| Dejing Pan | *CAM-SU Genomic Resource Center, Soochow University,* China |
| Panagiotis Pandis | *MRC Harwell Institute,* United Kingdom |
| Piyi Papadaki | *BSRC Alexander Fleming,* Greece |
| Helen Parkinson | *EMBL-EBI,* United Kingdom |
| Hardip Patel | *The Australian National University,* Australia |
| Guillaume Pavlovic | *PHENOMIN-iCS,* France |
| Emma Peterson | *The Jackson Laboratory,* USA |
| Kevin Peterson | *The Jackson Laboratory,* USA |
| Silvia Petrezsélyová | *Institute of Molecular Genetics IMG,* Czech Republik |
| Benoit Piavaux | *Institute of Molecular Genetics IMG,* Czech Republik |
| Ilkka Pietilä | *University of Oulu,* Finland |
| Taina Pihlajaniemi | *University of Oulu,* Finland |
| Jan Prochazka | *Institute of Molecular Genetics IMG,* Czech Republik |
| Michaela Prochazkova | *Institute of Molecular Genetics IMG,* Czech Republik |
| Ilari Pulli | *Euro-BioImaging ERIC,* Finland |

| R | |
|---|---|
| Michael Raess | *INFRAFRONTIER GmbH,* Germany |
| Marcello Raspa | *CNR Monterotondo,* Italy |
| Birgit Rathkolb | *Helmholtz Center Munich,* Germany |
| Winfried Rauscheder | *INFRAFRONTIER GmbH,* Germany |
| Mike Relac | *EMBL-EBI,* United Kingdom |
| Bruno Reversade | *A*STAR Institute,* Singapore |
| Daniel Rhodes | *Queen Mary University London QMUL,* United Kingdom |
| Im Joo Rhyu | *Korea University College of Medicine,* Korea |
| Jan Rozman | *Czech Centre for Phenogenomics,* Czech Republik |
| Jesus Ruberte | *Universitat Autonoma de Barcelona UAB,* Spain |
| Thomas Rülicke | *University of Veterinary Medicine Vienna,* Austria |
| Holger Russig | *TSE-Systems,* Germany |

| S | |
|---|---|
| Mart Saarma | *University of Helsinki,* Finland |
| Kirsi Säkkinen | *Biocenter Oulu,* Finland |
| Rodney Samaco | *Baylor College of Medicine,* USA |
| Luis Santos | *MRC Harwell Institute,* United Kingdom |
| Ferdinando Scavizzi | *CNR Monterotondo,* Italy |
| David Schibli | *UVic-Genome BC Proteomics Centre,* Canada |
| Bartosz Schramm | *Sable System Europe GmbH,* Germany |
| John Seavitt | *Baylor College of Medicine,* USA |
| Radislav Sedlacek | *Institute of Molecular Genetics IMG,* Czech Republik |
| Claudia Seisenberger | *Helmholtz Center Munich,* Germany |
| Kyoung Yul Seo | *Yonsei University,* Korea |
| Je Kyung Seong | *Korea Mouse Phenotyping Center KMPC,* Korea |
| Hanna Seppälä | *Biocenter Oulu,* Finland |
| Raisa Serpi | *University of Oulu,* Finland |
| Subodh Sharma | *University of Oulu,* Finland |
| Damian Smedley | *Queen Mary University of London QMUL,* United Kingdom |
| Fei Song | *INFRAFRONTIER GmbH,* Germany |
| Tania Sorg | *PHENOMIN-iCS,* France |
| Nadine Spielmann | *Helmholtz Center Munich,* Germany |
| Michelle Stewart | *MRC Harwell Institute,* United Kingdom |

| | |
|---|---|
| Ewan Straiton | *MRC Harwell Institute,* United Kingdom |
| Jun Gyo Suh | *Hallym University,* Korea |
| Anu Suomalainen-Wartiovaara | *University of Helsinki,* Finland |
| **T** | |
| Amano Takanori | *RIKEN BioResource Research Center,* Japan |
| Masaru Tamura | *RIKEN BioResource Research Center,* Japan |
| Lydia Teboul | *MRC Harwell Institute,* United Kingdom |
| Archana Tomar | *Helmholtz Center Munich,* Germany |
| **U** | |
| Brun Ulfhake | *Karolinska Institutet Department of Neuroscience,* Sweden |
| **V** | |
| Vootele Voikar | *University of Helsinki,* Finland |
| Reetta Vuolteenaho | *University of Oulu,* Finland |
| **W** | |
| Jonathan Warren | *EMBL-EBI,* United Kingdom |
| Gonghong Wei | *University of Oulu,* Finland |
| Sara Wells | *MRC Harwell Institute,* United Kingdom |
| Henrik Westerberg | *MRC Harwell Institute,* United Kingdom |
| Jacqui White | *The Jackson Laboratory,* USA |
| Brandon Willis | *UC Davis Mouse Biology Program,* USA |
| Robert Wilson | *EMBL-EBI,* United Kingdom |
| Joshua Wood | *UC Davis Mouse Biology Program,* USA |
| **Y** | |
| Zhu Yichen | *Soochow University, CAM-SU Genomic Research Center,* China |
| Atsushi Yoshiki | *RIKEN BioResource Research Center,* Japan |
| Qian Yu | *Soochow University, CAM-SU Genomic Research Center,* China |
| **Z** | |
| Ana Zarubica | *PHENOMIN-CIPHE,* France |
| Dagmar Zudova | *Institute of Molecular Genetics IMG,* Czech Republik |

# PERSONAL NOTES



Cyclist on Isoisänsilta (Grandad) Bridge

**ORGANISATIONAL TEAM**
**Asrar Ali Khan, *INFRAFRONTIER***
**Reetta Hinttala, *BioCenter Oulu***
**Sheetal José, *IMPC***
**Teija Luoto, *BioCenter Oulu***
**Michael Raess, *INFRAFRONTIER***
**Winfried Rauscheder, *INFRAFRONTIER***
**Reetta Vuolteenaho, *BioCenter Oulu***

**DESIGN**
**Frank Gehrke, *frank&frei, Munich***
frank_gehrke@t-online.de

**PRINT**
**Alpha-Teamdruck GmbH, *Munich***

**PHOTOS**
**http://materialbank.myhelsinki.fi**
Page 1 **gettyimages**
Page 4 **Omar El Mrabt**
Page 10 **Tuomas Uusheimo**
Page 20 **Jussi Hellsten**
Page 48 **Pekka Keränen**
Page 62 **Jenna Pietikäinen**
Page 82 **Tuomas Uusheimo**
Page 90 **Riku Pihlanto**

## Contact

**INFRAFRONTIER GmbH**
Ingolstaedter Landstrasse 1
85764 Neuherberg (München)
*Germany*

**Directors:**
Martin Hrabě de Angelis, Daniel Lahne

*www.infrafrontier.eu*
*info@infrafrontier.eu*

**INFRAFRONTIER / IMPC Conference 2019**
**3 to 5 June, 2019** | Helsinki,
*Hanaholmen Swedish-Finnish Cultural Center*

#InfrafrontierConf
#InfraConfHelsinki