



INFRAFRONTIER
mouse disease models



IMPC

International Mouse Phenotyping Consortium

INFRAFRONTIER / IMPC Stakeholder Meeting

Advancing Rare Disease Research and Gene Therapy Applications with Animal Models

Dec 3 to 4, 2018 | Munich



Dear colleagues,

Welcome to the second joint stakeholder meeting of the European research infrastructure INFRAFRONTIER and the International Mouse Phenotyping Consortium (IMPC) in Munich!

We want to discuss new ways to move towards the precision medicine of the future. How can we discover the genetic cause of rare diseases that affect millions of patients around the world? What can we do to advance the development of new, powerful gene-therapies that can help patients whose diseases have so far been untreatable? Moreover, how can the use of precision modelling, as well as systemic and specialised phenotyping, remove the many uncertainties that are obstacles to better, more efficient, treatment of genetically caused diseases?

We are proud to see 191 outstanding experts from 22 countries and all five continents, as well as from very different areas of expertise – clinical researchers, genomics specialists, biomedical scientists and science policy experts – gathered here with a common goal: to find innovative ways to advance scientific research and cooperation.

I wish you all exciting presentations and inspiring discussions that cross the borders of different research areas! If you leave this conference feeling that you have gained some new scientific insights and met interesting colleagues with whom you will stay in touch, INFRAFRONTIER and IMPC will both be happy to have taken this initiative.

Great to have you here! Enjoy the experience!



Martin Hrabě de Angelis
INFRAFRONTIER
Scientific Director

Martin Hrabě de Angelis



INFRAFRONTIER / IMPC Stakeholder Meeting

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The aims of our meeting are ...

- ... to raise awareness of INFRAFRONTIER / IMPC platforms among the Rare Diseases and Gene Therapy community
- ... to present collaborative mechanisms advancing rare disease research with model organisms
- ... to present use cases for the utility of model organisms to advance rare disease and gene therapy research
- ... to present advances in the preclinical testing of gene therapy approaches to cure human diseases
- ... to strengthen interactions with rare disease and clinical research consortia

Scope and Context

Despite recent successes in identifying causative mutations for human heritable diseases using sequencing technologies, an associated gene has not been identified for approximately half of the reported diseases. Discovery of the genotype-phenotype relationships is a critical step towards understanding of the mechanism of these diseases and the development of new treatments. To address this challenge and to advance the functional analysis of human genetic variation, the International Mouse Phenotyping Consortium (IMPC) is creating a genome- and phenome-wide catalogue of gene function by characterizing new knockout-mouse strains across diverse biological systems through a broad set of standardized phenotyping tests.

Rare disease, clinical genetics and personalised medicine initiatives will benefit greatly from this emerging data and biological resources, which can be used to detect novel genotype-to-phenotype associations in diseases. The continued development of data analyses and integration approaches will be required to translate mouse functional genomics studies to a better understanding of human biology and disease. Furthermore, new genome-editing technologies such as CRISPR/Cas9 now enable the efficient derivation of precision disease models incorporating patient-specific genetic variants as a means of recapitulating essential aspects of human disease in mouse and other model organisms.

INFRAFRONTIER and IMPC offer unique platforms for the functional validation of genetic variants identified in exome/whole-genome sequencing approaches and the development of mouse models with predictive utility for efficient translation. Generation of precision animal models is key for understanding the pathogenesis of human genetic diseases, and the development of new therapies for rare diseases. INFRAFRONTIER partners supported numerous custom model development projects to investigate gene function and pathophysiology

of rare diseases. The IMPC phenotyping discovery resource provides an unprecedented volume of high quality data, supporting clinicians to find relevant mouse models of human disease by orthologous gene and by shared phenotypic features.

Animal models also play an essential role for the development and preclinical testing of gene therapy approaches to cure human diseases. Animal models mimicking human disease conditions are essential at the preclinical stage before embarking on a clinical trial in the assessment of variables related to the use of viral vectors such as safety, efficacy, dosage and localization of transgene expression. Choosing a suitable disease-specific model is of paramount importance for successful clinical translation.

Gene editing is the next frontier in gene therapy and promises to correct genetic mutations that may cause disease, and to create and control genetic information within patient cells. Thousands of incurable genetic diseases are now theoretically treatable by gene editing approaches. In this context, animal models are essential tools for testing gene editing reagents and delivery systems.

The Stakeholder Meeting provides an excellent opportunity to explore a better alignment of INFRAFRONTIER / IMPC platforms with current rare disease and personalised medicine initiatives, and supports interactions with human genetics centers, clinical consortia and biobanks. Effective collaborative mechanisms connecting gene discovery projects with model organism communities such as the Canadian Rare Diseases Models and Mechanisms Network will be presented at the Stakeholder Meeting. New emerging partnerships will support the rapid impact of mouse functional genomics analyses on the understanding of human genetic variation and disease, and the translation into diagnostic and therapeutic approaches.

ORGANIZERS

The very heart of Munich: Town Hall at Marienplatz

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.



Funding Acknowledgements

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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.

AGENDA

DECEMBER 3 TO 4, 2018

Traditional amusement: Chain carousel at the Oktoberfest

MONDAY
DEC
3

Hilton Munich Park, Ballroom & foyer

08:00 – 08:45

Registration

08:45 – 09:00

Welcome & setting the stage
Martin Hrabě de Angelis,
Helmholtz Zentrum München & INFRAFRONTIER GmbH
INFRAFRONTIER Research Infrastructure

SESSION 1

09:00 – 13:00

Model organisms facilitate rare disease diagnosis and therapeutic research
Chairs: **Martin Hrabě de Angelis** and **Colin McKerlie**

KEYNOTE

09:00 – 09:40

Shinya Yamamoto, *Baylor College of Medicine, Undiagnosed Disease Network / Model Organism Screening Center (MOSC)*
Model organisms facilitate rare disease diagnosis and therapeutic research.

09:40 – 10:00

Juliane Winkelmann, *Helmholtz Zentrum München*
Genetic factors of Dystonia

10:00 – 10:20

Holger Prokisch, *Helmholtz Zentrum München*
Mitochondrial diseases: an exemplar for understanding genetic variation in rare disorders

10:20 – 10:40

Yann Herault, *PHENOMIN-ICS*
PHENOMIN and the connection with the rare disease community

10:40 – 11:20

COFFEE BREAK (foyer)

11:20 – 11:40

Lluís Montoliu, *CSIC-CNB*
New CRISPR derived animal models of albinism

MONDAY
DEC
3

11:40 – 12:00

Fabio Mammano, *CNR-IBCN*

In vivo genetic manipulation of inner ear connexin expression by bovine adeno-associated viral vectors

12:00 – 12:20

Monica Justice, *University of Toronto, SickKids Research Institute*

A forward genetic suppressor screen in Mecp2 mice reveals therapies for Rett Syndrome

12:20 – 12:40

Steve Brown, *MRC Harwell, IMPC Scientific Chair*

International Mouse Phenotyping Consortium (IMPC) and Rare Diseases: Comprehensive phenotyping of the mouse genome

12:40 – 13:00

Melissa Haendel, *Oregon Health & Science University (OHSU)*

The Monarch initiative: cross-species phenotype comparison for disease diagnosis and discovery

13:00 – 14:00

LUNCH BREAK (foyer)

SESSION 2

14:00 – 15:20

EU collaborative and national initiatives targeting rare diseases,

Chair: **Yann Herault**

14:00 – 14:20

Olaf Riess, *University of Tübingen, Institute of Medical Genetics*

Solve-RD – solving the unsolved rare diseases

14:20 – 14:40

Daria Julkowska, *French National Research Agency (ANR)*

New opportunities for rare diseases research at European and international scale

14:40 – 15:00

Anna Need, *Genomics England*

Genomics England rare disease programme and GEMM initiative

15:00 – 15:20

Philippe Campeau, *University of Montreal*

The Canadian Rare Diseases Models and Mechanisms (RDMM) Network

MONDAY
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3

15:20 – 16:05

Panel Discussion

Chair: **Paul Lasko**

Advancing rare disease diagnosis and therapeutic research with model organisms – Building bridges between basic and clinical research

Panelists:

Shinya Yamamoto, *Baylor College of Medicine, UDN*

Steve Brown, *MRC Harwell, IMPC*

Olaf Riess, *University of Tübingen, Solve-RD*

Philippe Campeau, *University of Montreal, RDMM*

16:05 – 16:50

COFFEE BREAK (foyer)

SESSION 3

16:50 – 17:40

Stakeholder presentations

Chair: **Radislav Sedlacek**

Speakers selected from submitted abstracts:

Vasanta Subramanian, *University of Bath*

Mice with a targeted deletion in the basal body protein Talpid3 (KIAA0586) exhibit cerebellar defects and ataxia reminiscent of Joubert syndrome.

Genay Pilarowski, *John Hopkins University, School of Medicine*

Haploinsufficiency of a histone modifier, Kmt2d, in a mouse model of Kabuki syndrome leads to defects in the B cell lineage and gut mucosal immunology.

Douglas Strathdee, *Cancer Research UK, Beatson Institute*

Altered cardiac cardiolipin levels in Barth Syndrome induce a stress response resulting in systemic metabolic changes.

Salla Kangas, *University of Oulu*

Creation of a knock-in mouse model for FINCA disease using the CRISPR/Cas9 technique.

MONDAY
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17:40 – 18:00

Policy perspective on sustainability of Research Infrastructures
Jan Hrušák, *European Strategy Forum on Research Infrastructures (ESFRI)*
Long-term sustainability of Research Infrastructures

18:00 – 19:00

DRINKS RECEPTION (foyer)

TUESDAY
DEC
4

Hilton Munich Park, Ballroom & foyer

SESSION 4 08:30 – 10:10

Animal models for human gene therapy applications
Chair: **Fatima Bosch**

KEYNOTE 08:30 – 09:10

Federico Mingozzi, *GENETHON*
Translating proof of concept studies of gene therapy for rare liver disease to humans, the example of Crigler-Najjar syndrome

09:10 – 09:30

Helène Puccio, *Institute of Genetics and Molecular and Cellular Biology (IGBMC)*
Gene therapy for Friedreich ataxia-associated cardiomyopathy

09:30 – 09:50

Martin Biel, *Ludwig-Maximilians-Universität München (LMU)*
Genetic mouse models to develop gene therapies for retinal diseases

09:50 – 10:10

Fatima Bosch, *Autonomous University of Barcelona (UAB)*
Disease correction by AAV-mediated gene therapy in mouse models of mucopolysaccharidosis

10:10 – 10:40

COFFEE BREAK (foyer)

SESSION 5 10:40 – 12:00

Gene editing in gene therapy of human (Rare) Diseases
Chair: **Johanna Myllyharju**

10:40 – 11:00

Pietro Genovese, *San Raffaele Telethon Institute for Gene Therapy (SR-TIGET)*
Preclinical modelling highlights the therapeutic potential of targeted gene correction in T cells and hematopoietic stem/progenitor cells for the treatment of primary immunodeficiencies

11:00 – 11:20

Paula Rio, *CIEMAT/CIBERER-ISCIII*
Therapeutic gene editing in Fanconi anemia hematopoietic stem and progenitor cells

TUESDAY
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11:20 – 11:40

Michal Minczuk, *University of Cambridge*

Genome editing in mitochondria corrects a pathogenic mtDNA mutation in vivo

11:40 – 12:00

Xue Gao, *Rice University*

Treatment of autosomal dominant hearing loss by in vivo delivery of genome editing agents

12:00 – 13:00

LUNCH BREAK (foyer)

SESSION 6

13:00 – 14:00

Optimising gene editing for therapeutics

Chair: **Wolfgang Wurst**

13:00 – 13:20

Wolfgang Wurst, *Helmholtz Zentrum München*

Split-Cas9 in gene therapy approaches

13:20 – 13:40

Jacob Corn, *ETH Zürich*

CRISPR/Cas9 genome editing in human cells occurs via the Fanconi anemia pathway

13:40 – 14:00

Colin Fletcher, *NIH-NHGRI*

The NIH Somatic Cell Genome Editing Program (SCGE)

14:00 – 14:20

Gene editing for advanced therapies – Ethics, governance, and society

Chair: **Wolfgang Wurst**

Lluís Montoliu, *CSIC-CNB*

ARRIGE – Association for Responsible Research and Innovation in Genome Editing

TUESDAY
DEC
4

SESSION 7

14:20 – 15:20

Stakeholder presentations

Chair: **Lluís Montoliu**

Speakers selected from submitted abstracts:

Beatriz Dorado, *Centro Nacional de Investigaciones Cardiovasculares Carlos III*

Generation and characterization of a knockin LMNA c.1824C>T pig model of Hutchinson-Gilford progeria syndrome.

Davide Seruggia, *Boston Children's Hospital, Harvard Medical School*

Uncoupling cellular fitness and fetal hemoglobin repression by targeting CHD4 CHDCT2 domain.

Belen Molla, *Institute of Biomedicine of Valencia (IBV), CSIC*

Preclinical study of novel pharmacological treatments in a mouse model of Lafora disease (Epm2b-/-).

Francesca Fallarino, *University of Perugia*

Endogenous tryptophan derivatives prevent the development of anti-FVIII antibodies in a hemophilia A mouse model.

Jukka Kallijärvi, *University of Helsinki*

15:20 – 15:30

Meeting wrap up and closing

Martin Hrabě de Angelis

SPEAKERS & PORTRAITS

Martin Biel
Fatima Bosch
Steve Brown
Philippe Campeau
Jacob Corn
Colin Fletcher
Xue Gao
Pietro Genovese
Melissa Haendel
Yann Herault
Martin Hrabě de Angelis

Jan Hrušák
Daria Julkowska
Monica Justice
Paul Lasko
Fabio Mammano
Michal Minczuk
Federico Mingozzi
Lluís Montoliu
Anna Need
Holger Prokisch
Helène Puccio
Olaf Riess
Paula Rio
Juliane Winkelmann
Wolfgang Wurst

Shinya Yamamoto

Ludwig-Maximilians-Universität München (LMU), Germany
Autonomous University of Barcelona (UAB), Spain
MRC Harwell, UK, IMPC Scientific Chair, United Kingdom
University of Montreal, Canada
ETH Zürich, Switzerland
National Institutes of Health (NIH-NHGRI), USA
Rice University, USA
San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), Italy
Oregon Health & Science University (OHSU), USA
PHENOMIN-ICS, France
Helmholtz Zentrum München, Institute of Experimental Genetics & INFRAFRONTIER GmbH, Germany
J. Heyrovsky Institute of Physical Chemistry, Czech Republic
French National Research Agency (ANR), France
University of Toronto, SickKids Research Institute, Canada
McGill University, Canada
CNR – Institute of Cell Biology and Neurobiology, Italy
University of Cambridge, United Kingdom
GENETHON, France
CNB-CSIC, Spain
Genomics England, United Kingdom
Helmholtz Zentrum München, Germany
Institute of Genetics and Molecular and Cellular Biology (IGBMC), France
University of Tübingen, Institute of Medical Genetics, Germany
CIEMAT/CIBERER-ISCIII, Spain
Helmholtz Zentrum München, Institute of Neurogenomics, Germany
Helmholtz Zentrum München, Institute of Developmental Genetics, Germany
Baylor College of Medicine, USA

TUESDAY, DEC 4, 09:30 – 09:50
Genetic mouse models to develop gene therapies for retinal diseases

Martin Biel Professor Dr. rer. nat.
Ludwig-Maximilian-Universität München (LMU)
Department of Pharmacy, Center for Drug Research
Chairman

At Ludwig-Maximilian-University München (LMU), Martin is the chairman of the Department of Pharmacy / Center for Drug Research. Since 2009, he is a member of the Life Science School Munich (LSM) and the Munich Center for Neurosciences (MCN). In research, he focusses on the physiological and pathophysiological role of ion channels, on diseases of the retina, and the development of gene therapies.

TUESDAY, DEC 4, 09:50 – 10:10
Disease correction by AAV-mediated gene therapy in mouse models of mucopolysaccharidosis

Fatima Bosch Ph.D., Professor
Universitat Autònoma Barcelona (UAB)
Professor of Biochemistry and Molecular Biology,
Director of the Center of Animal Biotechnology and Gene Therapy

As full professor of Biochemistry and Molecular Biology at UAB, Fatima is one of the leading scientists for gene therapy research in Europe. She has headed the Spanish Society for Gene and Cell Therapy and is a member of the Gene Doping Expert Group of the World Anti-Doping Agency (WADA) since 2013. Her current research focuses on the pathophysiological causes of diabetes mellitus, using transgenic animal models and developing gene therapy approaches.

MONDAY, DEC 3, 12:20 – 12:40
International Mouse Phenotyping Consortium (IMPC) and Rare Diseases: A comprehensive catalogue of gene function for the mouse genome

Steve Brown Ph.D., Professor
MRC Harwell, Oxfordshire
IMPC, chairman steering committee

As head of the Mammalian Genetics Unit (MGU) at MRC Harwell and chairman of the IMPC steering committee, Steve is one of the leading, most renowned scientists in the international functional mouse genetics field. His top interest in life sciences is researching the genetic background of human deafness in its different forms of appearances.

Philippe Campeau M.D., Professor
University of Montreal
Clinical Assistant Professor, Department of Pediatrics
Principal Investigator at Philippe Campeau Laboratory

In medical research, Philippe's interests have always focused on improving the treatment of inborn errors of metabolism in children through gene and cell therapy. His most recent research interests deal with skeletal dysplasia. Through exome sequencing, he and his colleagues have identified the genetic cause of genitopatellar syndrome (KAT6B), and other similar diseases.

MONDAY, DEC 3, 15:00 – 15:20
The Canadian Rare Diseases Models and Mechanisms network (RDMM)

TUESDAY, DEC 4, 13:20 – 13:40
CRISPR-Cas9 genome editing in human cells occurs via the Fanconi anemia pathway

Jacob Corn Professor Dr.
ETH Zürich
Professor for Genome Biology

Before he became Professor for Genome Biology at ETH Zurich in March 2018, Jacob was the scientific director of the Innovative Genomics Institute, Berkeley and Assistant Professor at UC Berkeley. He researched the mechanisms by which cells repair their DNA, maintain and differentiate hematopoietic stem cells, and use ubiquitin signaling to propagate cellular signals. Jacob's experience covers therapeutic areas like infectious disease, neurobiology and oncology. He computationally designed protein inhibitors and discovered biological mechanisms for therapeutic targets.

TUESDAY, DEC 4, 13:40 – 14:00
The NIH Somatic Cell Genome Editing Program (SCGE)

Colin Fletcher Ph.D.
National Institutes of Health (NIH)
National Human Genome Research Institute (NHGRI),
Director of the Knockout Mouse Program (KOMP)

For more than 12 years, Colin is the driving force behind the KOMP and KOMP2 programmes of the US government, coordinated by the National Human Genome Research Institute (NHGRI). In KOMP's first part, 8,500 knockouts of mouse genes were produced in the form of embryonic stem cells (ES). The goal of KOMP2 is to convert all these ES cell lines into live mice and perform broad phenotyping on these strains – together with international scientific partners like IMPC and INFRAFRONTIER.

TUESDAY, DEC 4, 11:40 – 12:00
Treatment of autosomal dominant hearing loss by in vivo delivery of genome editing agents

Xue (Sherry) Gao Ph.D.
Rice University, Houston, Texas
Assistant Professor of Chemical and Biomolecular Engineering

Sherry's research program covers the interface of chemical biology and biomolecular engineering – with primary focus on small- and macro-molecule discovery and their applications to human health. One focus is to discover and engineer microbiome-based natural products and to develop enzymes involved in the natural product biosynthesis. Another main research interest is to discover and develop advanced genome-editing agents and delivery systems and apply these tools as next-generation therapeutics to clinical treatment of human genetic diseases.

Pietro Genovese Ph.D.
San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), Milan
Project Leader

As a project leader at SR-TIGET in Milan, Pietro dedicates his efforts to developing gene editing tools that improve the safety and efficiency of adoptive immunotherapy or promote safer applications of human stem cell gene therapy.

TUESDAY, DEC 4, 10:40 – 11:00
Preclinical modelling highlights the therapeutic potential of targeted gene correction in T cells and hematopoietic stem / progenitor cells for the treatment of primary Immunodeficiencies

MONDAY, DEC 3, 12:40 – 13:00

The Monarch initiative: cross-species phenotype comparison for disease diagnosis and discovery

Melissa Haendel Ph.D.
Oregon Health & Science University (OHSU)
Associate Professor of Medical Informatics and Clinical Epidemiology

Melissa is assistant professor of clinical epidemiology in the OHSU School of Medicine – and also a high ranking specialist in medical informatics. She is co-director of the university’s library and heads the Ontology Development Group. Melissa represents OSHU in the Monarch Initiative (www.monarchinitiative.org) – an international consortium of universities and research centers that has developed a biomedical database for the Human Phenotype Ontology (HPO). The HPO is a vocabulary to describe human disease features (phenotypes).

MONDAY, DEC 3, 10:20 – 10:40

Phénomin and the connection with the rare disease community

Yann Herault Ph.D.
Phénomin-ICS (Institut Clinique de la Souris), Strasbourg
Research Director at Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC)

As Research Director of the Department of Translational Medicine and Neurogenetics at IGBMC, Yann is a leading figure in French and international genetics, neurological and biological science. He heads the Mouse Clinic Institute (ICS) in Illkirch/Strasbourg, and the PHENOMIN and Celphedia infrastructures in France. At INFRAFRONTIER, Yann is one of the co-founders and member of the directors board. His current scientific focus lies on a better understanding of the genetic background of intellectual disabilities, such as Down syndrome, 16p11.2 and 17q21.31 syndromes.

MONDAY, DEC 3, 08:45 – 09:00

INFRAFRONTIER
Research Infrastructure

Martin Hrabě de Angelis Professor Dr. Dr. h.c. mult.
Helmholtz Zentrum München, Institute of Experimental Genetics (IEG)
Scientific Director of INFRAFRONTIER

Martin, who received his Ph.D. in biology in 1994, is one of the leading genetics scientists worldwide. At Helmholtz Zentrum München, he is director of the IEG and has founded the German Mouse Clinic (GMC) in 2001. Since 2003, he is professor of Experimental Genetics at the Technical University Munich (TUM). In the German Center for Diabetes Research, he is one of the co-founders and spokesperson in the executive board. In 2018, Martin was named a member of the German Academy of Sciences Leopoldina and has gained two honorary doctorates from Ludwigs-Maximilian-Universität Munich (LMU) and Technical University Dresden.

Jan Hrušák Ph.D. (Dr. rer. nat.)
J. Heyrovský Institute of physical chemistry AV ČR, Prague
Vice-Chair in ESFRI (European Strategy Forum on Research Infrastructures)

Jan is holding a leading position in the J. Heyrovský Institute of Physical Chemistry AV ČR in Prague since 1995. He is a senior research fellow and scientific advisor at the Czech Academy of Sciences, where he has served two terms in the executive body (Presidium). Jan is a long-standing member and currently Vice-Chair in ESFRI, the European Strategy Forum on Research Infrastructures. He also is member of the ministerial council for large research infrastructures (RI).

MONDAY, DEC 3, 17:40 – 18:00

Long-term sustainability of research infrastructures

MONDAY, DEC 3, 14:20 – 14:40

New opportunities for rare diseases research at European and international scale

Daria Julkowska Ph.D., MSc
Agence Nationale de la Recherche (ANR), Paris
Coordinator of European funding programmes on rare diseases

Daria is a Scientific Coordinator at the French National Research Agency (ANR). She is responsible for the management of several European and international funding programmes – e.g. E-Rare, the ERA-Net for Research programmes on rare diseases. She has put into action a set of collaborations facilitating rare diseases research, including partnerships with European Research Infrastructures and Patients' Organizations.

Since 2017 Daria serves as the chair of the Funders Constituent Committee of IRDiRC. Starting in 2019, she will be the coordinator of the European Joint Programme on Rare Diseases that will bring together research and funding stakeholders from Europe and beyond.

Monica Justice Ph.D., Professor
University of Toronto, Hospital for Sick Children (SickKids)
Professor for Molecular Genetics

MONDAY, DEC 3, 12:00 – 12:20

A forward genetic suppressor screen in Mecp2 mice reveals therapies for Rett syndrome

At the Toronto University Hospital for Sick Children (SickKids), Monica heads the research institute as senior scientist of Genetics & Genome Biology. Before, she was a professor at Baylor College of Medicine, Houston, in the department of Molecular and Human Genetics and director of the Mouse Embryonic Stem Cell Core. Monica is a pioneer in the field of mouse mutagenesis. Her teams have produced hundreds of new mouse models of human disease, discovering gene functions in areas such as cancer, reproduction, neurobiology, obesity and blood, heart and bone development. Her current work focuses on a genetic suppressor screen in a mouse model for Rett Syndrome (RTT).

MONDAY, DEC 3, 15:20 – 16:05

Advancing rare disease diagnosis and therapeutic research with model organisms – Building bridges between basic and clinical research

Paul Lasko Ph.D., Professor
McGill University, Montreal
Head of the Biology Department

Before joining the Biology Department of McGill University in Montreal in 1990, Paul has done biological and genetic research at the Massachusetts Institute of Technology (MIT) and at Cambridge University. At McGill, he is Full Professor since 1999 and serves as chair of the Biology Department since 2000.

In his research he focuses on oogenesis and on pole plasm assembly using the model organism *Drosophila melanogaster*. In the international scientific community, Paul is widely known as the former Chairman of IRDiRC, the International Rare Disease Research Consortium.

Fabio Mammano Ph.D., Professor
University of Padova, Professor of Applied Physics
Director of the Institute of Cell Biology and Neurobiology (IBCN) in the National Research Council (CNR) of Italy

Being a full Professor of Applied Physics at the University of Padova (UNIPD) since 2002, Fabio is also Honorary Professor in the Department of Biomedical Science (BMS) at the University of Sheffield (UK) and Visiting Professor at ShanghaiTech University.

In his major scientific role, Fabio is Director of the Institute of Cell Biology and Neurobiology (IBCN) in Monterotondo near Rome. There his research interests focuses on sensory and signal transduction in the inner ear and, more recently, encompassed signaling mechanisms in diabetes and cancer.

MONDAY, DEC 3, 11:40 – 12:00

In vivo genetic manipulation of inner ear connexin expression by bovine adeno-associated viral vectors

TUESDAY, DEC 4, 11:20 – 11:40
Genome editing in mitochondria corrects a pathogenic mtDNA mutation in vivo

Michal Minczuk Ph.D., Professor
University of Cambridge
Head of MRC Mitochondrial Biology Unit

Michal is a Programme Leader at the MRC Mitochondrial Biology Unit, University of Cambridge, heading the Mitochondrial Genetics programme. His work is focused on discovering the genetic links between mitochondrial dysfunction and human disease. His group develops methods for editing of the mammalian mitochondrial genome (mtDNA) using programmable nucleases. Michal's laboratory has been making important contributions to establishing genetic basis and molecular mechanisms of mitochondrial disorders resulting from defects of mitochondrial gene expression.

Federico Mingozzi Ph.D.
Spark Therapeutics Inc., Chief Scientific Officer
Former Coordinator GENETHON

TUESDAY, DEC 4, 08:30 – 09:10
Translating proof of concept studies of gene therapy for rare liver disease to humans, the example of Crigler-Najjar syndrome

Federico is well known as one of the leading international specialists for the development of gene therapy treatments. Since September 2017, he serves as Chief Scientific Officer at Spark Therapeutics, a US-based pharma company specialised on the development of gene therapies for inherited retinal diseases (IRD). Before that, Federico had been the head of the Immunology and Liver Gene Therapy team at GENETHON, a French on-profit R&D organisation focused on rare diseases. There he had coordinated CureCN, a European research project targeted to develop a curative gene therapy for the ultra-rare liver disease Crigler-Najjar syndrome (CN).

MONDAY, DEC 3, 11:20 – 11:40
New CRISPR derived animal models of albinism

Lluís Montoliu Ph.D.
Centro Nacional de Biotecnología (CNB-CSIC)
Research Scientist, former president of the International Society for Transgenic Technologies (ISTT)

Lluís is a Research Scientist of the Spanish National Research Council (CSIC) and heads his laboratory at the National Centre for Biotechnology (CNB) in Madrid. Since 2017, he is also a member of the steering committee of the Spanish Research Initiative on Rare Diseases (CIBERER-ISCIII). At CNB Lluís is working on a better understanding of the mechanisms controlling gene expression and organization in mammalian genomes. His team is generating animal models for the study of human rare diseases, such as albinism. As a specialist in bioethics, he is a member of the CSIC Ethics Committee and the Ethics Panel of ERC in Brussels.

Anna Need Ph.D.
Imperial College London, Lecturer in the Division of Brain Sciences, Leader of the GeCIP team at Genomics England

Anna is a medical researcher and honorary lecturer in the Centre for Psychiatry of Imperial College London (ICL). She works on the genetics of mental illness and leads big projects to identify genetic variants that have highly penetrant effects on psychiatric and cognitive phenotypes. Within the 100,000 Genomes Project of Genomics England, Anna is coordinating the GeCIP team. The aim of the Genomics England Clinical Interpretation Partnership (GeCIP) is to advance the interpretation of genomic data which will lead to better clinical understanding and better patient outcomes.

MONDAY, DEC 3, 14:40 – 15:00
Genomics England rare disease programme and GEMM initiative

MONDAY, DEC 3, 10:00 – 10:20

Mitochondrial diseases:
an exemplar for understanding
genetic variation in rare disorders

Holger Prokisch Dr.
Helmholtz Zentrum München,
Institute of Human Genetics (IHG)

Holger is heading the Genetics of Mitochondrial Disorders group at the Technical University Munich (TUM) as well as at Helmholtz Zentrum München. His team seeks to understand genetic variations in both rare and common disorders leading to mitochondria-related disease. In researching the basic pathomechanism of these diseases, they want to contribute to new treatment options for affected patients.

TUESDAY, DEC 4, 09:10 – 09:30

Gene therapy for Friedreich
ataxia-associated cardiomyopathy

Helène Puccio Dr.
Institute of Genetics and Molecular and Cellular Biology (IGBMC),
Strasbourg
Team leader Translational Medicine and Neurogenetics

In the IGBMC, Helène leads the research team of Translational Medicine and Neurogenetics. Her special interest are hereditary ataxias – a heterogeneous set of severely disabling neurological disorders caused by the degeneration of the cerebellum and/or the spinal cord. The team focuses on understanding the pathophysiology of ataxia, discovering disease biomarkers and developing therapeutic approaches. They collaborate with clinicians to develop new diagnostics tools for cerebellar ataxia and identify novel genes causing ataxia.

MONDAY, DEC 3, 14:00 – 14:20

Solve-RD – solving the
unsolved rare diseases

Olaf Riess Prof. Dr. med.
University of Tübingen
Head of Institute of Medical Genetics and Applied Genomics

Olaf is Medical Director of the Institute of Medical Genetics and Applied Genomics in the University of Tübingen. He has more than 20 years of experience in treating and researching genetically caused disorders. His main focus is on neurodegenerative diseases, both from the clinical as well as from the basic research perspective, with special focus on Parkinson, Dystonia and Spinocerebellar Ataxias. Olaf has been coordinator of numerous international, European and national funded consortia. He also has taken this part recently in ‘Solve-RD - solving the unsolved rare diseases’, a research project funded by the European Commission for five years (2018–2022).

Paula Rio Dr.
Centro Investigaciones Energéticas,
Medioambientales y Tecnológicas (CIEMAT), Madrid
Principal Investigator

At CIEMAT Paula is Senior Researcher and Principal Investigator of the Hematopoietic Innovative Therapies group. She has more than 15 years experience in the field of gene therapy for Fanconi anemia, a rare autosomal recessive disease, characterized by bone marrow failure and cancer predisposition.

TUESDAY, DEC 4, 11:00 – 11:20

Therapeutic gene editing in
Fanconi anemia hematopoietic
stem and progenitor cells

MONDAY, DEC 3, 09:40 – 10:00
Genetic factors of Dystonia

Juliane Winkelmann Prof. Dr.
Helmholtz Zentrum München
Director of the Institute of Neurogenomics,
Technical University Munich (TUM), Professor of Neurogenetics

After several years as Professor of Neurology and Neuroscience at Stanford University, Juliane returned to Munich in 2015, taking over as Chair of Neurogenetics at TUM and head of the Institute of Neurogenomics at Helmholtz Zentrum München. Juliane’s research focuses on the genetic architecture and underlying molecular mechanisms of complex neurological diseases – especially movement and sleep disorders. She has made primary discoveries of genetic variants for common neurological disorders including Restless Legs Syndrome and Dystonia.

TUESDAY, DEC 4, 13:00 – 13:20
Split-Cas9 in gene therapy approaches

Wolfgang Wurst Prof. Dr.
Helmholtz Zentrum München, Scientific Director IDG
Technical University Munich, Professor of Developmental Genetics

Since 2002, Wolfgang is Professor of Developmental Genetics at the Technical University Munich (TUM) and Scientific Director of the Institute of Developmental Genetics (IDG) at Helmholtz Center Munich. With his team he develops tools and methods for large scale gene function annotation in mouse which provides preclinical resources to determine the underlying molecular causes of human diseases – with a focus on Parkinson’s disease, dementia, ALS and others. Mouse und cellular human models are used to identify the molecular disease signatures that determine the interplay of genetic predispositions, environmental and life style factors in combination with aging.

Shinya Yamamoto Ph.D.
Baylor College of Medicine, Houston
Assistant Professor, Department of Molecular and Human Genetics
Department of Neuroscience

At the Baylor College of Medicine in Houston, Texas, Shinya is Assistant Professor at the Department of Molecular and Human Genetics. His scientific focus lies on discovering new disease causing genes, using model organisms like fruit flies (drosophila) and others.

MONDAY, DEC 4, 09:40 – 09:40
Model organisms facilitate rare disease diagnosis and therapeutic research

ABSTRACTS

INVITED SPEAKERS

MONDAY, DEC 3, 09:00 – 09:40

Model organisms facilitate rare disease diagnosis and therapeutic research

The Undiagnosed Diseases Network (UDN) is a multi-center effort of the top clinical centers in the USA aimed at solving the most challenging medical mysteries with advanced medical technology. As part of this effort we established the Model Organisms Screening Center (MOSC) that focuses on functional studies of genes and variants identified in patients enrolled in the UDN by whole-exome sequencing (WES) or whole-genome sequencing (WGS) using *Drosophila* and Zebrafish. In Phase I (2015–2018), we analyzed 236 variants in 179 genes for 118 UDN cases and prioritized 72 genes for functional studies in model organisms based on the MARRVEL (<http://marrvel.org>) informatics tool. In the *Drosophila* core, we have been studying variants in 58 genes using a number of genetic technologies to assess the impact of specific missense variants from UDN cases. Our work led to a number of novel disease gene discoveries including EBF3, ATP5F1D, TBX2 and IRF2BPL, while we characterized new human disease phenotypes for CACNA1A, ACOX1 and NR5A1 amongst others. These discoveries required in depth studies in flies as well as identification of additional cases in human databases and contributed to over 11% of the successful diagnoses in the UDN. Importantly, some biological findings suggested specific therapeutic interventions that are being applied in the clinics. Model organism studies of human genomic variation are effective tools in undiagnosed disease research, and a continuous dialog between clinicians and model organism biologists is a key element for success.

Shinya Yamamoto
Baylor College of Medicine,
Department of Molecular and
Human Genetics

KEYNOTE

MONDAY, DEC 3, 09:40 – 10:00

Genetic factors of Dystonia

Juliane Winkelmann
Helmholtz Zentrum München,
Institute of Neurogenomics

Dystonic disorders are debilitating neurological syndromes characterized by unwanted or excess movements. These diseases are a significant cause of physical impairment in child- and adulthood and result in major long-term morbidity and socioeconomic burden. The etiological bases of dystonias are heterogeneous and poorly understood. Though genetic determinants do exist molecular testing is usually not pursued in dystonia routine care, hampering the elucidation of specific diagnostic entities and their underlying pathomechanisms.

The overall aim of our work is to couple the creation of a systematic biobank for dystonia-affected individuals and their families with a comprehensive delineation of phenotypic and molecular-genetic aspects and to translate these results into patient care and personalized therapeutic interventions. We employ high-throughput sequencing of whole-exome- and whole-genome-captured genomic DNA from dystonia-affected individuals and their parents, followed by meticulous bioinformatics studies in order to identify actionable mutations in known and novel disease-causing genes as well as to identify new genetic variants for the disease. Whenever possible, mechanism-informed therapies will be administered.

Our research is expected to have far-reaching implications for diagnostic algorithms, clinical decision-making, molecular pathway definition, and drug-target discovery in dystonia. Here, we present newly identified genetic factors with functional follow up as well as the establishment of an animal model for dystonia. We anticipate that our findings will represent an important step towards the introduction of genomically-guided pharmacotherapies and precision medicine in dystonia and also other hyperkinetic disorders.

MONDAY, DEC 3, 10:00 – 10:20

Mitochondrial diseases: an exemplar for understanding genetic variation in rare disorders

Holger Prokisch
Helmholtz Zentrum München,
Institute of Human Genetics (IHG)

Mitochondrial diseases pose a diagnostic challenge due to clinical and genetic heterogeneity, propelling unbiased whole exome sequencing (WES) into the early diagnostic setting. To date, over 300 disease-associated genes implicated in mitochondrial energy metabolism are known, and this number continues to grow. Within the extended European Network for Mitochondrial Diseases, GENOMIT, we systematically analysed WES data from 1630 patients with a suspected mitochondrial disease. A genetic diagnosis was established in 752 cases (46%) within 323 different genes. Of these genes, 194 were seen in single cases only. Furthermore, through this endeavour and subsequent follow-up studies over 40 novel disease genes have been discovered. GENOMIT is hence establishing a valuable global registry for both clinical and genomic data.

However, despite the revolutionizing impact of genome wide sequencing on the molecular genetics of Mendelian disease, about half of patients do not receive a genetic diagnosis. To further improve the diagnostic yield we developed an integrated omics pipeline and demonstrated the power of RNA sequencing and proteomics to discover intronic pathogenic variants and to validate coding variants of uncertain significance.

To date almost 40 mitochondrial diseases, potentially amendable to a specific disease-modifying treatment, have been described, such as the cofactor metabolism defects where supplementation can be efficacious. Of our molecularly confirmed mitochondrial disease cases,

99 fall into this category. However, effective defect-targeted treatments for the majority of mitochondrial diseases remain elusive, thus genotyping is fast becoming the prerequisite for clinical trial inclusion and the development of treatment.

A major limitation in rare disorders is the number of patients with the same pathological genotype. Hence, we have started to complement human studies with mouse genetics to facilitate validation of novel disease genes, to study disease mechanism and to develop and verify new treatment options.

MONDAY, DEC 3, 10:20 – 10:40

PHENOMIN and the connection with the rare disease community

Rodent models are essential and a key element for fundamental and preclinical researches. They are used to better understand variation in the human genome, fundamental mechanism and to test therapeutics in vivo with the aim to answer the society needs to improve human health. In the field of rare diseases, rodent models represent integrative approaches to understand the physiopathology in the complexity of a whole organism, place for exchanges and communication between cells, organs and environment and to approach the syndromic condition often visible in rare disease as a whole.

In this context, PHENOMIN, the French national Infrastructure for mouse phenogenomics has been developing links with the rare disease scientific community to develop models for those conditions, to improve the impact of preclinical studies regarding therapies development and now to decode the pathological variation and the function of the mammalian genome. Several examples will be presented here, that have been supported by various initiatives and a long partnership with the French Foundation for rare disease to support research in this domain.

Yann Herault
PhénomIn Consortium

MONDAY, DEC 3, 11:20 – 11:40

New CRISPR derived animal models of albinism

Lluís Montoliu
CSIC-CNB

Albinism is a human rare genetic condition associated with mutations in at least 20 loci identified to date¹. This genetic heterogeneity explains the high variability of phenotypes observed in people with albinism. Nonetheless, they have, all of them, severe visual deficits, whose impact is also variable, according to the genes and mutations involved. The hypopigmentation phenotype is also variable and without a correlating with visual deficits. After years of observing and genetically diagnosing hundreds of people with albinism, it has become obvious that universal therapeutic solutions will not work. Instead, individual approaches will have to be assessed, for each gene and for each mutation type. This laborious strategy has been greatly eased by the advent of CRISPR genome-editing techniques. These innovative methods can be used to recreate patient-specific mutations at the corresponding homologous genes in the murine genome. In this talk, we will summarize our current research efforts aiming to a better understanding of the pathophysiology of albinism. Using CRISPR-based genome editing techniques we have generated a variety of new mouse models of several types of albinism. These animal models will be instrumental not only for our comprehension of this complex genetic condition but also as unique recipients for testing novel and innovative therapeutic approaches that are being currently explored.

MONDAY, DEC 3, 11:40 – 12:00

In vivo genetic manipulation of inner ear connexin expression by bovine adeno-associated viral vectors

Fabio Mammano
CNR-IBCN

Mutations in the genes that encode inner connexin 26 (Cx26) and connexin 30 (Cx30) are the most common cause of sensorineural hearing impairment. We have previously shown that in vitro transduction with bovine adeno-associated viral (BAAV) vectors restores connexin expression and rescues gap junction coupling in cochlear organotypic cultures from connexin-deficient mice that are models of DFNB1 nonsyndromic hearing loss and deafness. The aims of this study were to manipulate inner ear connexin expression in vivo using BAAV vectors, and to identify the optimal route of vector delivery. Injection of a BAAV vector encoding a bacterial Cre recombinase via canalostomy in adult mice with floxed connexin 26 (Cx26) alleles promoted Cre/LoxP recombination, resulting in decreased Cx26 expression, decreased endocochlear potential, increased hearing thresholds, and extensive loss of outer hair cells. Injection of a BAAV vector encoding GFP-tagged Cx30 via canalostomy in P4 mice lacking connexin 30 (Cx30) promoted formation of Cx30 gap junctions at points of contacts between adjacent non-sensory cells of the cochlear sensory epithelium. Levels of exogenous Cx30 decayed over time, but were still detectable four weeks after canalostomy. Our results suggest that persistence of BAAV-mediated gene replacement in the cochlea is limited by the extensive remodeling of the organ of Corti throughout postnatal development and associated loss of non-sensory cells.

MONDAY, DEC 3, 12:00 – 12:20

A forward genetic suppressor screen in Mecp2 mice reveals therapies for Rett syndrome

Monica Justice
University of Toronto, The Hospital for Sick Children

The onset and expression of clinical features can vary widely in genetic diseases with a common molecular root, often due to second site gene modifiers. Identifying the modifiers represents a transformative discovery for the disease they alter, shifting understanding of pathogenesis and providing avenues for diagnosis, prognosis, and therapy development.

We carried out a forward genetic ENU suppressor screen in a mouse model for Rett syndrome (RTT), a neurological condition caused by mutations in methyl CpG binding protein 2 (MECP2). MECP2 regulates key activities in the brain and body, with mutations impacting both adult and childhood neuropsychiatric and immune disorders. Whole exome sequencing of 72 mouse lines carrying modifiers that improve health traits and prolong life has identified genes that fall into a limited number of biological pathways.

One modifier pointed to lipid metabolism as being perturbed in RTT, suggesting that metabolic modulation is a treatment avenue. MeCP2 provides a bridge for the repressor complex NCoR1/SMRT/HDAC3 to regulate its targets on DNA, and the modifiers suggest that this complex is key to Rett syndrome pathology. Surprisingly, mutations in multiple genes involved in the DNA damage response, which repairs double-stranded breaks, can improve RTT-like symptoms in mice. Because neurons are non-dividing cells, an ongoing question is why mutations in this pathway improve symptoms.

Many of the lines carry more than one modifier locus, and combining modifiers from two different pathways greatly improves symptoms, suggesting that combination therapies will be effective in treating RTT.

MONDAY, DEC 3, 12:20 – 12:40

International Mouse Phenotyping Consortium (IMPC) and Rare Diseases: A comprehensive catalogue of gene function for the mouse genome

Steve Brown
Chairman of IMPC

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 generating and phenotyping a knockout mouse line for every protein-coding gene. To date, over 7,500 knockout mouse lines, many for poorly understood genes, have been generated and 6,000 phenotyped in a coordinated effort involving more than a dozen global research centers and dedicated publicly-available online resources. Using a standardized adult phenotyping pipeline, centers test each mouse for more than 250 phenotypic parameters covering all major organ and disease systems. In addition, over 1,000 embryonic lethal mouse lines have been analyzed in a specialized embryonic development pipeline that uses high-resolution 3D imaging. All data is quality controlled and analyzed by a dedicated informatics consortium and all abnormal phenotypes automatically compared to clinical features of human disease populations to identify robust mouse models of disease. We present our discoveries into 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 over 300 new mouse models of human disease now available for further studies. The latest findings in relation to metabolism, hearing and aging will also be presented. 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.

MONDAY, DEC 3, 12:40 – 13:00

The Monarch initiative: cross-species phenotype comparison for disease diagnosis and discovery

Melissa Haendel
Oregon Health & Science University
(OHSU), Medical Informatics and
Clinical Epidemiology

Our understanding of human disease mechanisms and therapies is crucially illuminated by information discovered in model systems. Although numerous resources exist that collect information about model organisms, their very multiplicity makes it difficult for researchers and clinicians to effectively utilize such resources, since each one focuses on a different species, disease, or data type. Furthermore, models do not faithfully recapitulate all aspects of disease pathology, and we need better methods for identifying and designing disease models that focus on elucidating aspects of phenotype and pathophysiology that are most relevant to human disease. To maximize the computational utility of our knowledge of model organisms, we need systematic ways to represent knowledge across organisms such that it can be reasoned over--in other words, we need ontologies. Ontologies go beyond standard clinical taxonomies by defining relationships between concepts to enable computational logical reasoning. The Monarch Initiative is a global, translational consortium that provides sophisticated ontology-based algorithms for phenotype comparison within and across species that leverage a large corpus of deeply integrated human and model data. We have developed the Human Phenotype Ontology (HPO), which encodes phenotypic abnormalities encountered in human disease and is logically interoperable with phenotypes of model organisms. Monarch's Exomiser tool supports the clinical community by prioritizing whole exome and whole genome variants according to variant pathogenicity, phenotypic relevance, and protein-protein interactions to support disease-gene discovery.

The HPO has also been translated into layperson-ese (as well as many other languages) to enable patients to record their own phenotypic data (using tools such as Phenotypr.org) to facilitate discussions with their physicians and help improve diagnosis and treatment. The discovery of disease mechanisms can be greatly enhanced by precision phenotyping across patients, clinical settings, and model and non-model organisms. The creation and application of computational models of disease, phenotypes, and the environment using interoperable ontologies will be a game changer, with profound impact on patients, diagnostic practices, and healthcare.

MONDAY, DEC 3, 14:00 – 14:20

Solve-RD – solving the unsolved rare diseases

Olaf Riess
*University of Tübingen, Institute of
Medical Genetics*

Solve-RD is a H2020 funded flagship EU project that brings together 22 partners from 10 countries and which will be running from 2018 to 2022. The main ambitions are (i) to solve large numbers of RD, for which a molecular cause is not known yet, by sophisticated combined Omics approaches, and (ii) to improve diagnostics of RD patients through a “genetic knowledge web”. Solve-RD will pursue a clear visionary and integrated “beyond the exome” approach. The entire Solve-RD project has been motivated, designed and put together by a core group of four European Reference Networks.

Solve-RD will deliver 7 main implementation steps: (i) Collect Phenotypes, (ii) New phenotype patterns, (iii) Re-analyse exomes / genomes, (iv) Novel molecular strategies, (v) Functional analysis, (iv) Clinical utility and (vii) Towards therapy. For analysis Solve-RD will apply data driven and expert driven approaches. We anticipate to increase diagnostic yield from 19.000 unsolved exomes/genomes by about 3-5%. Cohort specific innovative -omics strategies will be pursued, also addressing cost-effective issues.

Analysis of more than 800 patients with highly peculiar phenotypes will highly increase the chance to find novel disease genes and novel disease mechanisms. We anticipate to solve more than 2.000 cases. Finding further matching patients will be secured by newly developed matchmaking approaches and by screening using MIPs technology in the more than 20.000 unclassified patients. For the first time in Europe we will also implement a novel brokerage structure connecting clinicians, gene discoverer and basic researcher to quickly verify novel genes and disease mechanisms.

MONDAY, DEC 3, 14:20 – 14:40

**New opportunities for rare diseases research
at European and international scale**

Daria Julkowska
*French National research Agency
(ANR) / INSERM*

RD research in Europe can be improved to overcome fragmentation, leading to efficacious use of data and resources, faster scientific progress and increase of competitiveness, and most importantly to decrease unnecessary hardship and prolonged suffering of RD patients.

In the specific context of the massive generation, need for reuse and efficient interpretation of data, introduction of omics into care practice and the structuration of RD care centers in European Reference Networks, it appears crucial and timely to maximize the potential of already funded tools and programmes by supporting them further, scaling up, linking, and most importantly, adapting them to the needs of end-users through implementation tests in real settings. Such a concerted effort is necessary to develop a sustainable ecosystem allowing a virtuous circle between RD care, research and medical innovation.

The European Joint Programme Cofund is a European instrument allowing high-level strategic organization and performance of research activities in an organized and transversal manner. Participation of research funders and research performing organisations accompanied by other relevant stakeholders allows the necessary level of integration and unique strategy to efficiently tackle societal challenges. Rare diseases community takes the advantage of already existing networks, programmes, tools and resources like E-Rare, RD-Connect, Orphanet, EU infrastructures, European Reference Networks, patients’ organizations, regulatory bodies and private sector that can be used to further improve the integration, the efficacy, the production and the social impact of research on RD. Thus, the ambition of the future European Joint Programme for RD is to establish an urgently needed comprehensive strategy covering research, tools and clinics leading to optimization and exploitation of results, faster drug discovery at reduced costs, improved patients’ care as well as giving Europe a leading role in the field of RD in the coming years.

MONDAY, DEC 3, 14:40 – 15:00

Genomics England rare disease programme and GEMM initiative

Anna Need
Genomics England

As recognized by the Council Recommendation 2009/C 151/02, rare diseases (RD) are a prime example of a research area that can strongly profit from coordination on a European and international scale. RD research should be improved to overcome fragmentation, leading to efficacious use of data and resources, faster scientific progress and competitiveness, and most importantly to decrease unnecessary hardship and prolonged suffering of RD patients. In the specific context of the massive generation, need for reuse and efficient interpretation of data, introduction of omics into care practice and the structuration of RD care centers in European Reference Networks, it appears crucial and timely to maximize the potential of already funded tools and programmes by supporting them further, scaling up, linking, and most importantly, adapting them to the needs of end users through implementation tests in real settings. Such a concerted effort is necessary to develop a sustainable ecosystem allowing a virtuous circle between RD care, research and medical innovation. To achieve this goal, the European Joint Programme on RD (EJP RD) has two major objectives: (i) To improve the integration, the efficacy, the production and the social impact of research on RD through the development, demonstration and promotion of Europe/world-wide sharing of research and clinical data, materials, processes, knowledge and know-how; (ii) To implement and further develop an efficient model of financial support for all types of research on RD (fundamental, clinical, epidemiological, social, economic, health service) coupled with accelerated exploitation of research results for benefit of patients. To this end, the EJP RD actions will be organized within four major Pillars assisted by the central coordination: (P1): Funding of research; (P2): Coordinated access to data and services; (P3) Capacity building; (P4): Accelerated translation of research projects and improvement outcomes of clinical studies.

MONDAY, DEC 3, 15:00 – 15:20

The Canadian Rare Diseases Models and Mechanisms network (RDMM)

Philippe Campeau
University of Montreal (UdeM),
Department of Pediatrics

In Canada, a series of rare disease gene discovery projects led to the identification of >300 disease genes over the past five years. A complementary national project was established to facilitate and support the collaboration between basic scientists and clinicians for model organism-based functional studies of rare disease genes, and for the development of new therapeutic strategies using these models.

The RDMM connects Canada's disease gene discovery scientists with the model organism communities of yeast, *C. elegans*, *Drosophila*, zebrafish, and mouse researchers. Once the candidate variants are vetted by a committee of geneticists, the gene discovery scientists are matched using our database (in which over 300 model organism researchers entered over 5500 genes of interest). Once the model organism studies proposed are approved by another committee, a seed grant of CAD\$25,000 is awarded to support immediate functional experiments, and reports requested after 6 and 12 months.

Over 75 such projects have been supported to date, and this helps not only to confirm the pathogenicity of variants and better understand the diseases, but also leads to high impact papers, long term collaborations, larger subsequent grants, and models to test novel therapies. The RDMM was recently renewed for another 4 years, and now aims for international collaborations, for example to match gene discovery scientists from Canada to model organisms from abroad, and vice-versa. The network will be presented with its successes and limitations, along with its outlook for the years to come.

MONDAY, DEC 3, 17:40 – 18:00

Long-term sustainability of research infrastructures (RI)

Jan Hrušák
J. Heyrovský Institute of physical chemistry AV ČR, Prague

Long term sustainability (LTS) of research infrastructures as a prerequisite for their effective operations and for the capability of providing high quality services to the broader scientific community is a longstanding issue and has been broad to the top levels of political agendas. The Competitiveness Council (COMPET) of ministers responsible for research (June 2011) – „... recognizes the importance of the LTS of RIs.“ and the COMPET held in May 2016 in connection with discussion about the ESFRI Roadmap 2016 “... underlines the importance of ensuring long-term sustainability of Research Infrastructures and invites the Commission to prepare together with ESFRI and relevant stakeholders a targeted action plan“. In response to those Council conclusions ESFRI has set up a Working group on LTS with the aim „... to analyse the current LTS challenges and will formulate recommendations on potential policy measures which could be implemented at different levels – national, regional, European and International – to respond to these challenges.“ The report of this group was approved by ESFRI in June 2017 and published as ESFRI Scripta series Vol 2. It contains 7 Main recommendations:

- Establish and maintain excellence through the entire life cycle of RIs by all appropriate means, by securing adequate framework conditions, and by opening the RIs up to the world.
- Ensure that RIs have the right people in the right place at the right time by strengthening and harmonizing national research and educational systems to make sure that all essential skills are available.
- Harmonise and integrate a vision for convergent operation of RIs and e-infrastructures in Europe to ensure cost-effective service provision to the user communities.
- Fully exploit the potential of RIs as innovation hubs by incorporating strategies for their development into national and European innovation policies.

- Set up effective means of determining the economic and wider social value of RIs, and incorporate these benefits into science-policy-society dialogues.
- Establish adequate framework conditions for effective governance and sustainable long-term funding for RIs at every stage in their life-cycle, together with effective management.
- Foster broader coordination at national and European levels when designing processes for planning and supporting national and pan European RIs and so enhance their strategic value.

and 35 sub- recommendations. These recommendations entered into a EC- Staff working document and are building the basis for a European action plan, which is now being implemented. The main elements are:

- Ensuring RI at the forefront of scientific excellence,
- Configuring European RI as skills development and mobility actors,
- Unlocking RI Innovation potential and stimulating industry engagement,
- Boosting RI impact, value and benefits of RI,
- Enhancing RI as the pillar for data production and sharing,
- Ensuring effective governance and sustainable life-cycle management,
- Promoting European RI in the international arena.

Policy discussion with the Member States and stakeholders on LTS has started and the Implementation of the action plan is foreseen under the MFF 2020+

TUESDAY, DEC 4, 08:30 – 09:10

Translating proof of concept studies of gene therapy for rare liver disease to humans, the example of Crigler-Najjar syndrome

Federico Mingozzi
Spark Therapeutics

KEYNOTE

The liver is an attractive target organ for the development of AAV vector-based therapies for enzyme deficiencies and metabolic disorders. Among the monogenic diseases affecting the liver, Crigler Najjar syndrome (CN) represents an ideal model for the development of gene therapy approaches based on the adeno-associated virus (AAV) vector platform. CN is a rare, autosomic recessive disorder caused by mutations in the uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) enzyme. The resulting enzyme deficiency is associated with the accumulation of unconjugated bilirubin, which leads to acute, severe neurotoxicity and, consequently, disability and early death. Current therapy for severe CN is based on intensive phototherapy, while liver transplantation is the only curative option for the disease. For the translation of early proof of concept studies of AAV-mediated in vivo gene transfer for UGT1A1 to severely affected patients, several studies were conducted in different animal models of CN as well as in wild-type animals. This presentation will address the key challenge of the choice of the models for translational gene therapy studies, for the assessment of safety and efficacy profile of AAV vectors. Critical issues like the choice of the best model for dose-finding studies (thus the relative efficiency of liver-directed gene transfer in a given model), the assessment of immunogenicity of AAV vectors in preclinical models, and the design of informative toxicology and biodistribution studies will also be discussed. Other examples of use of animal models in AAV-mediated liver gene transfer will also be discussed, particularly focusing on the development of animal models with a disease phenotype as representative as possible to the target patient population.

TUESDAY, DEC 4, 09:30 – 09:50

Genetic mouse models to develop gene therapies for retinal diseases

Martin Biel
Ludwigs-Maximilian-Universität
München, Pharmacology Department

Vision is a multistep process that is initiated by transduction of light into electrical signals in the light-sensitive neurons (the photoreceptors) of the retina. Mutations in genes encoding proteins involved in phototransduction and/or intraretinal image processing are often linked to severe visual impairment or even blindness in man. Our laboratory has generated a variety of genetic mouse models that recapitulate basic clinical features of human retinal diseases. Mouse models have been also widely used as preclinical model systems to develop gene therapy approaches for retinal diseases. In my talk, I will exemplarily discuss for achromatopsia, a genetic retinal disease that has been extensively studied in our laboratory, the steps that are necessary to translate basic studies in cell and preclinical mouse models into a clinical setting. Achromatopsia is a clinically well-defined inherited retinal disorder characterized by day blindness, poor visual acuity, photophobia, nystagmus, and lack the ability to discriminate colours. About 95 % of the patients carry loss-of-function mutations in either the CNGA3 or the CNGB3 subunit of the cone photoreceptor cyclic nucleotide-gated cation (CNG) channel. Previously, we have established a murine model for CNGA3-linked achromatopsia. Importantly, in this preclinical model we were able to restore impaired cone-mediated vision using AAV (adeno-associated virus) -mediated gene supplementation. Based on this work we have designed AAV8.CNGA3, a recombinant AAV vector for gene supplementation therapy of human CNGA3-linked achromatopsia (ACHM2). The vector expresses human CNGA3 under control of a short human arrestin 3 promoter and was packaged with AAV8 capsid. A first-in-man dose escalation clinical trial with nine ACHM2 patients (NCT02610582) was conducted. Safety profile was excellent and there was also evidence for an improvement of clinical features of achromatopsia. Altogether, the ACHM2 project shows that genetic mouse models not only are an extremely valuable tool to study the pathomechanism of retinal diseases but are also well-suited to validate viral vectors for gene therapy in man.

TUESDAY, DEC 4, 09:50 – 10:10

Disease correction by AAV-mediated gene therapy in mouse models of mucopolysaccharidosis

Fatima Bosch
Universitat Autònoma de Barcelona
and CIBERDEM

Mucopolysaccharidosis Type II (MPSII), Hunter Syndrome, and Type III (MPSIII), Sanfilippo Syndrome, comprises 5 autosomic recessive disorders caused by mutations in genes that encode for enzymes involved in the stepwise degradation of glycosaminoglycans (GAGs). Accumulation of GAGs in lysosomes leads to lysosomal pathology, and affected patients undergo severe neurodegeneration with mild somatic disease, and usually die during adolescence. There is no cure and MPS diseases constitute an unmet medical need. This presentation will discuss the potentiality of intracerebrospinal fluid adeno-associated viral (AAV) vector-mediated gene therapy to counteract neurologic and somatic MPS. Using this approach to treat for MPSII and MPSIII (IIIA, IIIB and IIID), expression of the different therapeutic genes was detected in widespread brain regions and in the liver, leading to increased enzyme activity in CNS and serum and simultaneous correction of both central and somatic disease. The results of this study provide strong evidence supporting the clinical translation of the approach not only for MPS but also for other genetic diseases that course with neurodegeneration.

TUESDAY, DEC 4, 10:40 – 11:00

Preclinical Modelling Highlights the Therapeutic Potential of Targeted Gene Correction in T cells and Hematopoietic Stem/Progenitor Cells for the Treatment of Primary Immunodeficiencies

Pietro Genovese
SR-TIGET, Milan

The scope of genetic engineering of hematopoietic stem/progenitor cells (HSPC) has broadened from gene replacement to targeted genome editing using a range of artificial nucleases, which enable precise and targeted modification of endogenous genes. We were the first to exploit this strategy on HSPC to insert a functional cDNA into an inherited defective gene, downstream its own promoter, thus allowing restoration of both its function and physiologic expression control while avoiding the risk of random insertional mutagenesis (Genovese, Nature 2014). The former feature is particularly relevant when the affected gene must be tightly regulated because of its direct impact on cell proliferation, as in the case of Severe Combined Immunodeficiency (SCID)-X1 and the X-linked hyper-IgM Syndrome (HIGM1). Here, we developed new ZFNs or CRISPR/Cas9 reagents targeting an upstream intron of both IL2RG and CD40LG genes to correct the majority of disease causing mutations with the same nuclease/donor set. By using improved gene editing protocols we validated this strategy on human T cells and HSPC, reaching similarly high levels of editing (up to 40%) using ZFNs or CRISPR/Cas9. To support the scientific rationale and explore the safety of the proposed treatment we are taking advantage of suitable preclinical models of disease. For SCID-X1, we developed a mouse model carrying the human IL2RG gene including a common disease-causing mutation in place of the mouse Il2rg. To evaluate efficacy and safety of the hematopoietic reconstitution from a limited number of corrected HSPC we performed competitive transplantation with wild-type and IL2RG-/- HSPC and found that 1% of wild-type cells are sufficient to partially reconstitute the lymphoid compartments and that the administration of a conditioning regimen before HSPC infusion is required to avoid the risk of thymic lymphoma development from the transplanted progenitors. Similar experiments are now ongoing with the HIGM1 murine model to identify the

conditioning regimen and the degree of donor chimerism required to correct this disease. In order to obtain proof-of-correction of the disease phenotype by gene editing, we developed a protocol based on CRISPR/Cas9 that enables substantial levels of targeted DNA repair by NHEJ (70%) and HDR (~25%) on murine IL2RG^{-/-} HSPC. Upon transplant, only the gene corrected cells were able to generate functional B and T lymphoid lineages, showing a clear selective advantage over uncorrected cells. The corrected lymphoid cells persisted long-term in the mice and generated a functional T cell response upon challenging the mice with a murine pathogen, thus indicating that successful IL2RG edited progenitor cells are able to sustain lymphopoiesis and partially correct the disease phenotype. Overall, these studies will allow establishing the safety and robustness of our gene editing strategy in HSPC and will be instrumental for the design of the protocol for its first clinical testing.

TUESDAY, DEC 4, 11:00 – 11:20

Therapeutic gene editing in Fanconi Anemia hematopoietic stem and progenitor cells

Fanconi anemia is a DNA repair disorder characterized by a marked defect in hematopoietic stem cells that finally leads to bone marrow failure. Recent results from our lab have shown that gene therapy mediated by lentiviral vectors may constitute a true alternative for Fanconi Anemia (FA) patients, suggesting that gene editing could be explored as an even safer alternative for the treatment of FA hematopoietic stem and progenitor cells (HSPCs). With this aim we initially showed the possibility to correct HSPCs from FA patients by Homologous directed repair (HDR) by targeting the FANCA gene in the safe harbor AAVS1 locus. However, since non-homologous end-joining (NHEJ) is the preferential DNA-repair mechanism in HSCs – particularly in the case of Fanconi anemia (FA) cells – we aimed at exploiting this pathway to correct FANCA gene mutations, mimicking spontaneous reversions observed in FA mosaic patients. To demonstrate the feasibility to target FANCA in repopulating HSCs, healthy donor (HD) hCD34⁺ cells were electroporated with designed CRISPR/Cas9 nucleases and transplanted into immunodeficient mice. Edited cells demonstrated unaltered long-term engraftment and differentiation capacities, both in primary and secondary recipients. Interestingly, Next-generation sequencing (NGS) evidenced that the percentage of insertions/deletions (indels) in the pool of hCD34⁺ cells was similar to the one obtained in primary and secondary recipients, demonstrating the possibility to target true HSCs. Using the CRISPR/Cas9 system we targeted two common mutations described in Spanish FA-A patients and show for the first time the possibility to correct HSPCs from FA patients not only by HDR but also by a NHEJ-based gene editing strategy. This study paves the way to apply this safe and simple gene editing approach for the future treatment of the disease.

Paula Rio
CIEMAT, Madrid

TUESDAY, DEC 4, 11:20 – 11:40

Genome editing in mitochondria corrects a pathogenic mtDNA mutation in vivo

Michal Minczuk
University of Cambridge,
MRC Mitochondrial Biology Unit

Mutations of the mitochondrial genome (mtDNA) underlie a substantial portion of mitochondrial disease burden. These disorders are currently incurable and effectively untreatable, with heterogeneous penetrance, presentation and prognosis. To address the lack of effective treatment for these disorders, we exploited a recently developed mouse model that recapitulates common molecular features of heteroplasmic mtDNA disease in cardiac tissue: the m.5024C>T tRNAAla mouse. Through application of a programmable nuclease therapy approach, using systemically administered, mitochondrially targeted zinc-finger nucleases (mtZFN) delivered by adeno-associated virus, we induced specific elimination of mutant mtDNA across the heart, coupled to a reversion of molecular and biochemical phenotypes. These findings constitute proof of principle that mtDNA heteroplasmy correction using programmable nucleases could provide a therapeutic route for heteroplasmic mitochondrial diseases of diverse genetic origin.

TUESDAY, DEC 4, 11:40 – 12:00

Treatment of autosomal dominant hearing loss by in vivo delivery of genome editing agents

Xue Gao
Rice University, Department of
Biochemistry and Cell Biology

Although genetic factors contribute to almost half of all cases of deafness, treatment options for genetic deafness are limited. We developed a genome-editing approach to target a dominantly inherited form of genetic deafness. In this talk, I will show that cationic lipid-mediated in vivo delivery of Cas9–guide RNA complexes can ameliorate hearing loss in a mouse model of human genetic deafness. We designed and validated, both in vitro and in primary fibroblasts, genome editing agents that preferentially disrupt the dominant deafness-associated allele in the Tmc1 (transmembrane channel-like gene family 1) Beethoven (Bth) mouse model, even though the mutant Tmc1Bth allele differs from the wild-type allele at only a single base pair. Injection of Cas9–guide RNA–lipid complexes targeting the Tmc1Bth allele into the cochlea of neonatal Tmc1Bth/+ mice substantially reduced progressive hearing loss, which suggests that protein–RNA complex delivery of target gene-disrupting agents in vivo is a potential strategy for the treatment of some types of autosomal-dominant hearing loss.

TUESDAY, DEC 4, 13:00 – 13:20

Split-Cas9 in gene therapy approaches

Wolfgang Wurst
Helmholtz Zentrum München,
Institute of Developmental Genetics
(IDG)

The CRISPR/Cas9 technology revolutionizes gene editing and its application in gene therapy. Nevertheless, the efficient delivery of the tools is still a challenge. Since the most prevalent strategies are based on delivery via recombinant adeno-associated virus (rAAV), we developed a split-Cas9 system, bypassing the packaging limit using split-inteins. Each Cas9 half was fused to the corresponding split-intein moiety and, only upon co-expression, the intein-mediated transsplicing occurs and the full Cas9 protein is reconstituted. We are currently applying this system in a gene therapy approach in a porcine model. AAV-mediated delivery of split-Cas9 together with specific gRNA targeting endogenous loci and restoring protein function.

Moreover, we developed a variant of the split-Cas9 system; we are taking advantage of a CRISPR/Cas9 gene-induction system with which we can induce the transcription of endogenous genes. For this, a nuclease-dead version of Split-Cas9 fused to transcriptional activators is translocated to promoter regions, where these activators are inducing robust overexpression of endogenous genes of interest. This system offers a valuable tool for regenerative approaches for common diseases like neurodegenerative diseases or diabetes, where somatic cells are utilized, by converting them directly into the cell type of interest. In respect to gene therapy approaches, the CRISPR/Cas9 gene-induction technology resembles a valuable tool to induce cell fate changes in vitro as well as in vivo and concerning future therapeutic application advantageous in comparison to overexpression-based approaches with its limitations and safety issues. We are currently applying this approach to mouse models in vivo to reprogram endogenous astrocytes into neurons. The progress of these applications will be reported.

TUESDAY, DEC 4, 13:20 – 13:40

CRISPR-Cas9 genome editing in human cells occurs via the Fanconi anemia pathway

CRISPR-Cas genome editing creates targeted DNA double-strand breaks (DSBs) that are processed by cellular repair pathways, including the incorporation of exogenous DNA via single-strand template repair (SSTR). To determine the genetic basis of SSTR in human cells, we developed a coupled inhibition-cutting system capable of interrogating multiple editing outcomes in the context of thousands of individual gene knockdowns. We found that human Cas9-induced SSTR requires the Fanconi anemia (FA) pathway, which is normally implicated in interstrand cross-link repair. The FA pathway does not directly impact error-prone, non-homologous end joining, but instead diverts repair toward SSTR. Furthermore, FANCD2 protein localizes to Cas9-induced DSBs, indicating a direct role in regulating genome editing. Since FA is itself a genetic disease, these data imply that patient genotype and/or transcriptome may impact the effectiveness of gene editing treatments and that treatments biased toward FA repair pathways could have therapeutic value.

Jacob Corn
ETH Zurich,
Professor of Genome Biology

TUESDAY, DEC 4, 13:40 – 14:40

The NIH Somatic Cell Genome Editing Program (SCGE)

Colin Fletcher
NIH-NHGRI

Recent scientific advances in genome editing have made the possibility of treating, and even curing, genetic diseases much closer to reality. Research in this technology has increased at a tremendous pace and the first clinical trials are already underway. To fully realize the vision of treating many genetic diseases, the National Institutes of Health has launch an effort aimed at removing barriers that slow the adoption of genome editing. This program, Somatic Cell Genome Editing, will award researchers approximately \$190 million over five years. These researchers will collaborate to improve the delivery mechanisms for targeting gene editing tools in patients, develop new and improved genome editors, develop assays for testing the safety and efficacy of the genome editing tools in animal and human cells, and assemble a genome editing toolkit containing the resulting knowledge, methods, and tools to be shared with the scientific community.

TUESDAY, DEC 4, 14:00 – 14:20

ARRIGE – Association for Responsible Research and Innovation in Genome Editing.

Lluís Montoliu
CSIC-CNB, Madrid

In 2015, a group of researchers and ethicists from France and neighboring countries, initiated by the INSERM Ethics Committee, began organizing a series of meetings in Europe, India, Africa and South America, addressing the diverse ethical aspects associated with the responsible use of genome editing. In November 2017, at INSERM in Paris, numerous existing reports on the ethical and societal aspects of genome editing, and the responsible uses of these technologies were assessed.

Those discussions crystalized on March 23, 2018, in Paris, at a conference featuring about 160 participants from 35 countries, where we decided to launch the ARRIGE (Association for Responsible Research and Innovation in Genome Editing) initiative. The goal of this new non-profit association is to promote a global governance of genome editing through a comprehensive setting for all stakeholders – including academics, researchers, clinicians, public institutions, private companies, patient organizations and other NGOs, regulators, citizens, media, governmental agencies and decision makers, from all continents.

The aims of ARRIGE association are: (1) fostering an inclusive debate with a risk-management approach, considering human, environmental, animal and economic issues; (2) getting involved in the governance of genome editing technology with governmental and intergovernmental stakeholders; (3) creating an ethical tool box and informal guidance for genome editing technology users, regulators, governance and the civil society at large, including those living in low- and middle-income countries; and (4) developing a robust and specific reflection on the role of the lay public in this debate and the necessity for improved public engagement.

Anyone interested in the ARRIGE initiative is welcome to contact through (join@arrige.org) and/or visit the ARRIGE web site where information, documents, publications, pictures, talks and videos can be retrieved (<https://arrige.org>).

ABSTRACTS

SELECTED SPEAKERS

Mice with a targeted deletion in the basal body protein Talpid3 (KIAA0586) exhibit cerebellar defects and ataxia reminiscent of Joubert syndrome

Joubert syndrome (JS) is a ciliopathy, a group of rare genetic diseases. Talpid3 (KIAA0586) is a recently identified Joubert syndrome (JS) causative gene which is essential for cilia assembly. Herein, we describe a novel mouse JS model with a conditional deletion of Talpid3 in the nervous system which recapitulates the JS cerebellar phenotype. Talpid3 mutant mice are ataxic, have severely hypoplastic cerebellar hemispheres and vermis together with abnormal decussation of the superior cerebellar peduncles. The Purkinje cell layer is disorganized with abnormal dendritic arborization and parallel fibre derived synapses. The external granule layer lacks primary cilia, is thinner due to reduced proliferation caused by aberrant hedgehog signalling. In addition, the glial scaffold is defective resulting in abnormal granule cell migration. We also identified one JS case without a known molecular diagnosis which was a compound heterozygote for mutations in TALPID3. These findings reveal a role for Talpid3 in cell migration which together with defective hedgehog signalling underlies the JS phenotype. Our findings also illustrate the utility of creating conditional mouse models to assist in unravelling the molecular and cellular mechanisms underlying this group of disorders.

Vasanta Subramanian
*University of Bath, Department
of Biology and Biochemistry*

Genay Pilarowski
Johns Hopkins University,
School of Medicine

Haploinsufficiency of a histone modifier, Kmt2d, in a mouse model of Kabuki syndrome leads to defects in the B cell lineage and gut mucosal immunology

Kabuki syndrome (KS) Type 1 affects approximately 1 in 30,000 live births and is caused by single allele loss of function mutations in the histone modifying protein KMT2D. KMT2D adds histone 3, lysine 4 (H3K4) mono- and trimethylation, epigenetic marks found at active enhancers and promoters, respectively. Characteristics of Kabuki syndrome include developmental delay, facial dysmorphism, short stature, and immune dysfunction. Hypogammaglobulinemia (especially low serum IgA), splenomegaly, and diminished response to immunizations are frequently observed in individuals with Kabuki syndrome, however the underlying causes are not well understood. To clarify the mechanism(s) driving Kabuki syndrome associated immune deficiency, we evaluated humoral immunity in the Kmt2d+/geo mouse model, which our lab has previously established as a reliable model of Kabuki syndrome. These mice have splenomegaly ($p<0.03$), slightly elevated serum IgM ($p<0.02$) levels, and a 4-fold decrease of serum IgA levels ($p<0.0002$) compared to WT littermates. IgA is a major component of mucosal immunity that is primarily produced in the gut. Therefore, to investigate the mechanism of observed IgA defects, we examined the secondary lymphoid tissues of the gut, the Peyer's patches and mesenteric lymph nodes (MLN). We detected significantly decreased levels (50%; $p<0.02$) of a post-IgA-class-switch-recombination transcript in the mesenteric lymph nodes in Kmt2d+/geo mice compared to WT littermates. Consistently, we also observe a decrease in mature IgA-producing plasma cells, but an increase in immature IgA+ B220+ plasma cells, indicating a possible stall in B cell differentiation in

Kmt2d+/geo mice. Additionally, Peyer's patches in Kmt2d+/geo mice are strikingly smaller and there are significantly fewer Peyer's patches compared to WT littermates (Kmt2d+/geo mean=2.4; WT mean=7.2; $p<0.0001$). To interrogate the underlying mechanism, we completed RNA-sequencing of immature B220+ CD19+ and mature IgA+ B220- cells from the small intestine, which revealed a significant decrease (\log_2 fold change = -0.54) of Itgb7, the gene encoding beta 7 integrin. Beta 7 integrin is required for lymphocyte (B and T cell) homing to the gut. We hypothesize that Kmt2d regulates Itgb7, resulting in a diminished ability for immature B cells to home to the gut. We are actively confirming protein levels of the observed Itgb7 RNA expression differences by flow cytometry and additional functional assays. To follow up, we seek to answer whether lymphocytes in Kabuki syndrome mice have a diminished ability to home to the gut and if this contributes to the observed IgA deficiency. Our data suggest novel defects in mucosal immunity and widespread defects of the B cell lineage in Kmt2d+/geo mice. These findings will inform patient care regarding immune and GI issues and stimulate further studies of the B cell lineage in individuals with Kabuki syndrome.

Douglas Strathdee
Cancer research UK Beatson Institute

Altered cardiac cardiolipin levels In Barth Syndrome induce a stress response resulting in systemic metabolic changes

Tafazzin (Taz) is a mitochondrial transacylase required for the production of the mature form of the mitochondrial phospholipid, cardiolipin. Mutations of Taz underlie Barth syndrome, a serious X-linked inherited genetic disease that, in affected individuals, results in a broad range of clinical features. Cardinal signs include cardiomyopathy, lipid abnormalities and growth delay. The molecular mechanisms underlying the development and progression of the disease are still poorly understood. Here we show that Taz is required for postnatal appropriate mitochondrial maturation in mouse hearts. We demonstrate that there is pronounced reduction in cardiolipin levels in mice carrying a mutation in the Taz gene, and the knockout mice develop severely compromised cardiac function following the failure of proper mitochondrial maturation. This is accompanied by an alteration of metabolism, mitochondrial morphology and consequently the induction of the mitochondrial unfolded protein stress response. Reversing the induction of this stress response may represent an effective route for the development of a therapy for the Barth Syndrome.

Although the development of a mouse model represents a valuable resource for the understanding of Barth syndrome, there are some differences between the mouse (mTaz) and human Taz (hTaz) genes. For example, there is an entire exon present in hTaz, not present in mTaz. To test if this results in any functional differences, we have generated a mouse line where the entire wild-type mTaz locus has been replaced by the corresponding hTaz genomic locus. The human pattern of splicing, including the incorporation of the additional exon, appears to be maintained in hTaz mice. Early indications are that the hTaz gene rescues the phenotype of the mTaz mutation. We will present our analysis of the expression and function of the hTaz gene in mice, as well as the introduction of disease relevant mutations in the hTaz gene.

CREATION OF KNOCK IN MOUSE MODEL FOR FINCA DISEASE USING THE CRISPR/CAS9 TECHNIQUE

The aim of our research is to clarify the functional mechanisms caused by novel genetic factors in human disease pathogenesis that could be potentially treatable by drugs in future. We have recently found compound heterozygous variants in NHLRC2 gene as a cause of novel FINCA disease in three patients from the region of Northern Finland. FINCA disease is named based on the unique histopathological findings of the patients, such as fibrosis, neurodegeneration, and cerebral angiomatosis. The children were born in two unrelated families appearing healthy, but at the age of 2 months, they started to manifest progressive multi-organ symptoms resembling no previously known disease. All three patients died before the age of two years.

A whole-exome sequencing of the families with the affected children revealed the transmission of two heterozygous variants in the gene coding NHL repeat-containing protein 2 (NHLRC2); an amino acid substitution p.Asp148Tyr and a frameshift 2-bp deletion p.Arg-201GlyfsTer6. We had the access to patient-derived fibroblasts and we found out, that NHLRC2 protein levels were notably lower compared to healthy control, and only variant p.Asp148Tyr was expressed in protein level. Therefore we conclude, that the allele with the frameshift deletion is likely non-functional and only point mutant variant is expressed at protein level.

Function of NHLRC2 is currently unknown, but it is expressed ubiquitously in human and mouse tissues. NHLRC2 is highly conserved across the species, and mouse has NHLRC2 protein ortholog, being 84 % similar to human NHLRC2. We decided to use mouse as a model to study the role of NHLRC2 during development and in different tissues. We obtained heterozygous C57BL/6N-Atm1Brd Nhlrc2tm1a(KOMP)Wtsi/Wtsi mice from Infrafrontier-EMMA repository (strain number EM:10219). These mice carry the knock out (KO) first allele with a LacZ reporter tagged insertion.

Salla Kangas
University of Oulu
Pediatric neurology/CRC, Aapistie 5A

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Homozygous Nhlrc2 KO turned out to be lethal early in development. We analyzed E10.5 embryos and subsequently E2.5 morulae, but no Nhlrc2 KO homozygotes were detected. However, heterozygous Nhlrc2 KO mice were healthy and showed β -galactosidase signal throughout the body at embryonic day (E) 14.5.

Because the homozygous Nhlrc2 KO was lethal in mouse, we decided to generate knock in (KI) mouse model carrying the same point mutation, c.G442T; p.Asp148Tyr, as the patients to study the pathomechanisms of FINCA disease in vivo. We used CRISPR/Cas9 gene editing and homology directed repair (HDR) template to introduce the desired point mutation and a novel, silent Tatl restriction site to make screening of the mutant mice easier.

We obtained three founders with a mutation in the intended Cas9 cut site and two of them had the new Tatl restriction site. One of the founders produced pups with the desired G442T point mutation, the "FINCA allele". However, this male founder did not succeed to reproduce after the first litter. At the age of 5 months, we sacrificed the mouse to collect its sperm for IVF. This strategy turned out to be successful, and we could establish a mouse line carrying the FINCA allele.

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Next, we crossed the heterozygous FINCA allele carrying KI mice with heterozygous KO mice to produce compound heterozygous Nhlrc2FINCA/- genotype to mimic the patient genotype. Currently, we are phenotyping these FINCA mice. First results indicate, that mutant Nhlrc2 protein levels are strongly decreased in FINCA mice compared to wild type littermates in the tissues we have analyzed using Western blotting, which was also observed in the patients. We also crossed FINCA mice to produce homozygous Nhlrc2FINCA/FINCA genotype, and we noticed that in this double mutant, Nhlrc2 protein levels are higher than in FINCA (Nhlrc2FINCA/-) mice. Now, we are doing histopathological analyses and testing neuromuscular function of these mice to see, if we can capture the pathological aspects of the human disease with this mouse model.

Beatriz Dorado
Centro Nacional de Investigaciones
Cardiovasculares Carlos III (CNIC)

Generation and characterization of a knockin LMNA c.1824C>T pig model of Hutchinson-Gilford progeria syndrome

Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare genetic disorder (prevalence of 1 in 20 million) for which no cure exists. The disease is characterized by premature aging and invariably leads to death in adolescence due to cardiovascular complications. Most HGPS patients carry a heterozygous de novo LMNA c.1824C>T mutation which provokes the expression of a dominant-negative mutant protein called progerin. Our laboratory investigates the molecular and cellular mechanisms underlying cardiovascular disease (CVD) and premature aging in HGPS, with the ultimate goal of developing effective therapies. Using progeroid HGPS-like mouse models, we have identified molecular and cellular mechanisms that contribute to CVD in progeria, including excessive vascular calcification, vessel stiffening, atherosclerotic disease, and cardiac repolarization defects. We recently demonstrated that restricting progerin expression to vascular smooth muscle cells (VSMC) aggravates atherosclerosis, promotes myocardial infarction and reduces lifespan, thus identifying progerin-induced VSMC death as a major contributor to HGPS.

Clinical trials based on preclinical results in mouse models have yielded only modest benefit to HGPS patients. To overcome this translational gap, we have generated the first knockin heterozygous LMNA c.1824C>T (HGPS) pig model by CRISPR-Cas9-mediated gene editing

of Yucatan minipig primary skin fibroblasts, followed by somatic cell nuclear transfer of the engineered cell clone to enucleated Large White oocytes and transfer of reconstructed embryos to surrogate Large White sows. Like HGPS patients, HGPS minipigs endogenously co-express progerin and lamin A/C and exhibit growth retardation, lipodystrophy, skin and bone alterations, CVD, and premature death. HGPS minipigs also show previously undescribed myocardial fibrosis and microvascular dysfunction, which may become useful readouts for monitoring disease progression in patients. Moreover, the HGPS minipig model will permit testing of interventional devices and candidate therapies in a large animal model before advancing to clinical trials, thus expediting the development of effective applications for HGPS patients.

Davide Seruggia
Boston Children’s Hospital –
Harvard Medical School

Uncoupling cellular fitness and fetal hemoglobin repression by targeting CHD4 CHDCT2 domain

Hereditary persistence of fetal hemoglobin (HPFH) mitigates disease severity of sickle cell disease and -thalassemia. However, the molecular mechanisms underlying the developmental repression of HbF remain incompletely understood. The nucleosome remodeling and deacetylase (NuRD) complex is a major negative regulator of HbF level, through interaction with two known globin switch regulators, BCL11A and LRF. In this study, we sought to test therapeutic strategies targeting critical NuRD determinants.

We employed saturation mutagenesis of coding sequences using pooled CRISPR screening in HUDEP-2 human erythroid precursors to disrupt protein coding sequences of all 13 genes of the NuRD complex, including CHD, MTA, GATAD2, HDAC, MBD, and RBBP family members. The custom sgRNA library included 5,038 sgRNAs. We found that only 5 genes, CHD4, MTA2, GATAD2A, HDAC2, and MBD2, were required for HbF repression, suggesting that a non-redundant NuRD sub-complex contributes to HbF silencing. Disruption of CHD4 resulted in the highest HbF induction of any of the NuRD subunits. However, unlike the other NuRD genes, CHD4 disruption also led to cellular toxicity. We observed a small group of sgRNAs within the CHDCT2 domain of CHD4 associated with high HbF induction, yet relatively modest negative fitness.

To uncouple the roles of this chromatin remodeler in globin gene regulation from overall cellular fitness in the mouse, we targeted homologous amino acid residues within mouse Chd4 CHDCT2 domain by Cas9 mutagenesis in mouse oocytes. We generated 2 targeted in-frame deletions at the Chd4 C-terminal domain by zygote electroporation of nucleases along with ssDNA templates. NGS analyses indicated that targeted mutations were introduced at high rate (17.14

to 49% of mapped reads) without additional indels. Only a small percentage of reads represented NHEJ-derived alleles (0.1 to 9.6%), suggesting that the HDR and NHEJ DNA repair pathways are mutually exclusive in mouse one-cell embryos.

We focused on two edited Chd4 mouse lines carrying alleles mimicking CHD4 mutations associated with high γ -globin expression and modest negative fitness in HUDEP-2 cells. While loss of Chd4 is lethal at the blastocyst stage, homozygous in-frame deletions within the Chd4 CHDCT2 domain are tolerated in mouse embryos and result in increased β -globin expression up to 3-fold in mid-gestation embryos bearing transgenic human γ -globin gene clusters.

In summary, we have used dense CRISPR mutagenesis in vitro and in vivo to interrogate the relevance of distinct protein domains within members of the NuRD complex, uncouple functions of the CHD4 gene, and test novel options of potential therapeutic up-regulation of HbF. This strategy is general and applicable to other biological contexts for generation of protein functional maps and nomination of domains for rational design of therapeutic interventions.

Belén Mollá
institute of Biomedicine of Valencia (IBV) - Spanish National Research Council (CSIC)

Preclinical study of novel pharmacological treatments in a mouse model of Lafora disease (Epm2b-/-)

Progressive myoclonus epilepsy of the Lafora type or Lafora Disease (LD; OMIM# 274780) is a rare neurodegenerative disease characterized by generalized epileptic seizures and polyglucosan inclusions, called Lafora bodies (LBs), typically in brain but also in other peripheral tissues such as heart, liver or muscle. LD is a recessive autosomic pathology caused by mutations in two genes EPM2A and EPM2B, which respectively encode laforin, a dual specificity phosphatase, and malin, a E3-ubiquitin ligase. Both proteins assemble to work as a functional complex which is involved in the regulation of glycogen synthesis. Loss of function of laforin or malin are clinically indistinguishable and have been related with oxidative stress, endoplasmic reticulum stress, autophagic impairment and malfunction of cellular proteostasis. However, much still remains unknown about the molecular bases of LD and unfortunately an appropriate treatment is missing, therefore patients die within 10 years from the onset of the disease.

Using a malin-deficient mouse model (Epm2b-/-) we are testing different pharmacological strategies in order to assess their efficacy ameliorating the pathological phenotype such as polyglucosan inclusions, neuropsychological decline, neurodegeneration and inflammation. With this aim, we have performed a battery of behavioral tests including locomotor tests, memory tests, anxiety-like and depressive like-behaviour tests and hindlimb clasping test to evaluate abnormal postures related with neurodegeneration. Furthermore, we have carried out a histopathological analysis in brain conducting a PAS staining to quantify polyglucosan inclusions and an immunofluorescence labeling to quantify astrogliosis and neuronal mass in hippocampus. On the whole, this work shows a preclinical study in Epm2b-/- mice to evaluate the therapeutic effectiveness of potential novel pharmacological treatments in LD.

Endogenous tryptophan derivatives prevent the development of anti-FVIII antibodies in hemophilia A mouse model

Hemophilia A is a genetic disorder that manifests itself through an inability to form blood clots within the body. Since this is due to the absence of a clotting protein (factor VIII), the gold-standard treatment is to inject the protein that is missing into the patient's circulation to make up for the deficiency. Unfortunately, about 30% of hemophilia A patients develop inhibitors against this infused protein and render the treatment ineffective. The interaction between factor VIII and the body's white blood cells are important for inhibitor generation, as well as the tolerance to factor VIII, which is the absence of inhibitor generation to the protein.

We reported that the inhibitor-positive status was associated with reduced activity of the immune-regulatory enzyme indoleamine 2,3-dioxygenase 1 (IDO1) in dendritic cells, that promotes regulatory effects via the production of tryptophan catabolites, known as kynurenines. Some of those tryptophan derivatives are endogenous ligands for the Aryl hydrocarbon receptor (AhR).

In this study, we tested the potential of tryptophan-related AhR ligands for inhibiting the development of anti-FVIII antibodies in hemophilic (F8 KO) mice. To this aim, F8 KO mice hemophilic mice were treated with recombinant human FVIII (rhFVIII) alone or in combination with selected AhR ligands once weekly for four weeks. All mice

Francesca Fallarino
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treated with rhFVIII developed high-titer anti-FVIII antibodies after 4 weeks of treatment. Administration of specific tryptophan metabolites prevented the generation of anti-FVIII antibodies in almost 80% of F8 KO mice. The protective effect of these AhR ligands was negated by co-administration of a AhR antagonist or in AhR KO mice. Similar results were obtained by administration of engineered gold nanoparticles loaded with the same tryptophan metabolite and rhFVIII. In addition, in the same model, we found that treatment with AhR ligands not only suppressed FVIII-specific antibody titers but, resulted in increased protection against specific bacteria and fungi infection.

Thus, these results suggest that the engagement of AhR, by specific tryptophan derivatives, may be a possible new strategy to control the immune response to rhFVIII, while protecting against specific infections.

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Alternative oxidase-mediated respiration prevents lethal mitochondrial cardiomyopathy

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Mitochondrial respiratory chain (RC) deficiencies are among the most prevalent of inborn errors of metabolism, but largely lack treatments. Upon RC complex III (CIII) or IV blockade by toxins or disease-causing mutations, ectopic alternative oxidase (AOX) can restore electron flow, decrease reactive oxygen species (ROS) and rescue lethality in fruit flies and mammalian cells. We crossed viable RC complex III (CIII) deficient Bcs1l mutant mice, displaying multiple visceral manifestations and early death, with transgenic mice broadly expressing Ciona intestinalis AOX. The homozygotes expressing AOX were viable and without overt adverse effects but, surprisingly, their growth restriction and altered whole body metabolism were essentially unaffected. However, their survival was dramatically increased from median P210 to P590 due to permanent prevention of lethal cardiomyopathy. Loss of kidney tubular mass and astrogliosis of the somatosensory cortex were also robustly ameliorated by AOX. Respirometry showed that AOX was active in the symptomatic mutant, but not in wild-type, tissues, indicating that the respiration defect activated AOX. CI and CII-linked respiration was restored to wild-type level in heart mitochondria. ROS production by isolated mitochondria respiring with CI&CII-linked substrates was increased in the mutants and normalized by AOX. However, analysis of ROS defense and indirect damage suggested that ROS were not instrumental in the rescue of tissue pathology. These findings demonstrate the value of AOX, both as a mechanistic tool and a potential therapeutic strategy, for CIII deficiencies.

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OUTLOOK 2019

Science and religion, business and leisure: Munich is one of the economically strongest urban areas in Europe





INTERNATIONAL TRAINING COURSES 2018-2019

MOUSE phenotyping & MOUSE/RAT genetics

Mouse embryology: practical training course



March 13th-15th, 2019 - Strasbourg, France

Theoretical and practical background knowledge destined for researchers and engineers that are willing to acquire primary expertise in mouse development. The topics cover dissection of post implant embryos, histology, whole mount Lac Z staining and confocal imaging of whole embryos.

Objectives

- Acquire primary expertise in mouse development
- Be able to design primary phenotyping experiment on mouse embryos
- Learn about all the primary phenotyping analysis on mouse embryos
- Be able to dissect post-implanted embryos
- Be able to determine the window of lethality in utero
- Be able to evaluate embryos viability at neonatal stage
- Increase awareness of relevant technics to image embryos

In vivo CRISPR-Cas9 genome editing



October 09th-10th, 2019 - Strasbourg, France

General framework to get scientists started using CRISPR-Cas9 for *in vivo* gene editing in rodents: principles, rodent's models, PRO and CONS, achievement, challenge. Technical insight are discussed based on practical cases, in house results and bibliographic analysis. The interactive discussion groups allow attendees to expose and discuss with experts their own scientific issues and give crucial skill to progress in their projects.

Objectives

- Learn more about gene editing and how it works
- Hear about current advances on many technical aspects
- Optimize the RNA guide design to the genotyping analysis (bioinformatics workshop)
- Highlight crucial issue in your own scientific project

More information and registration online
<http://www.phenomin.fr/training-courses/>



www.phenomin.fr



An International Centre for Mouse Genetics

MRC Harwell will be hosting a range of **training courses** in 2019 which are open to all interested parties.

18th to 22nd March
Mouse genetics training week

- Monday – Tuesday*
Mouse genetics for animal technicians
- Wednesday – Thursday*
Mouse genetics for researchers
- Friday*
Genome editing using CRISPR/Cas9

25th to 28th March
Technical training week
(Spring Workshops)

Mouse IVF and embryo/sperm cryopreservation course
(parallel training course)

15th to 17th May
Advanced mouse genetics course

If you would like more information please visit
www.har.mrc.ac.uk or contact MLC-training@har.mrc.ac.uk



phenomin

European advanced school for mouse phenogenomics

3rd edition
May 20th - 24th 2019
Château du Liebfrauenberg,
Alsace, France






INTERACTION WITH EXPERTS METHODS SHARE OF KNOWLEDGE SCIENTIFIC AND EXPERIMENTAL DESIGN INNOVATION - ETHICS AND WELFARE

Methods and the good practices for the use of mouse models for scientific research

Program and application form :
<https://advanced-school.phenomin.eu>





19 – 21 JUNE 2019


10th Workshop on Innovative Mouse Models (IMM2019)

Leiden, The Netherlands

The workshop encourages an in-depth and unvarnished discussion of novel developments in the field of mouse modeling in a 3-day program.

TOPICS


- How to make genetically-engineered mice in the CRISPR/Cas9 era?
- Novel in vivo applications of CRISPR/Cas9 technology
- Advanced imaging and phenotyping
- How to deal with the mouse microbiota?
- Closing debate: the future of mouse models in fundamental and/or translational research



The goal of IMM2019 is to bring together a diverse group of scientists interested in all aspects of advanced mouse experiments within current ethical standards:

- Key developers of emerging technologies
- Researchers who want to apply and assess these new approaches
- Young researchers who want to share their experiences with a specialized audience.

www.immworkshop.nl

The workshop is supported by  **INFRAFRONTIER**



INFRAFRONTIER



EMMA



Vienna Cryo & Embryo Transfer Course

August 26th – 30th, 2019

The Institute of Laboratory Animal Science and Biomodels Austria at the University of Veterinary Medicine Vienna offer a comprehensive course on cryopreservation, embryo transfer and other methods of assisted reproduction in mice. The course is intended to give technicians and scientists state-of-the-art background knowledge and hands-on training in the methods routinely used at the Vetmeduni Vienna. Enrollment is limited to 8 participants. Early application is advised.

Registration will be open as of April 1st 2019, 9:00 am

An online registration form will be available at

<http://www.vetmeduni.ac.at/de/labortierkunde/kurse/cryo-embryo-transfer-course/>

The Course will include:

Theory Lectures:

Mouse Anatomy and Biology of Reproduction, Introduction to Embryo Transfer, Anesthesia & Analgesia, Introduction to Sperm Freezing, In Vitro Fertilisation and Embryo Freezing methods, The European Mouse Mutant Archive, Worldwide shipping of mice and of cooled / frozen material

Hands-on Practical Training:

Preparation of Media and Capillaries, Sperm Collection and Cryopreservation, Superovulation, Oviduct and Uterus Flushing, Handling and Culture of Preimplantation Embryos, In vitro Fertilisation, Controlled Freezing of 2-cell embryos, Vasectomy, Plug Check of Recipients, Surgical Oviduct and Uterus Embryo Transfer

Demonstrations: Percutaneous and Microsurgical Collection of Spermatozoa from Live Mice, Ovary Transplantation

Enrollment:

Course Fees*:

Academic or Non-Profit Institutions: Euro 980,00

Other Institutions: Euro 1.280,00

*Fees do not include participant's travel and lodging.



33rd International Mammalian Genome Conference

Strasbourg - France
September 25th - 29th 2019



Supported by





EXCELLENCE IN MOUSE PHENOGENOMICS

THE EUROPEAN MOUSE MUTANT ARCHIVE (EMMA)

CHALLENGE:
Maintaining mutant mouse lines is **expensive, time-consuming, complex** and **requires additional breeding**

PROVIDER
Researchers submit their mutant mouse lines in EMMA for free-of-charge archiving.

SCIENTIFIC COMMUNITY

RECIPIENT
Researchers request mutant mouse lines from EMMA.

CHALLENGE:
Give researchers **easy access to interesting mutant mouse lines** generated in laboratories worldwide



EMMA is the largest non-profit mouse repository in Europe and part of INFRAFRONTIER.
6000 mouse lines | **16** EMMA centres | **13** European countries | **1** Central web portal www.infrafrontier.eu

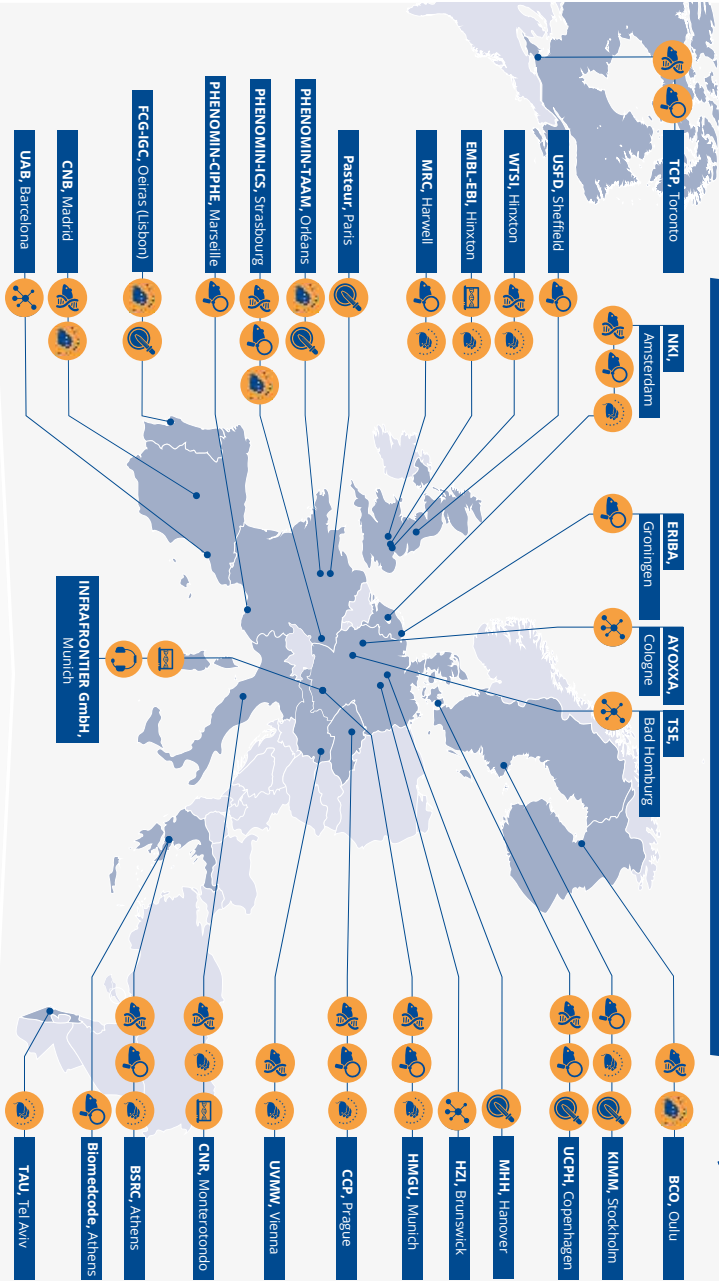


SOLUTION:
EMMA offers **free-of-charge archiving** via cryopreservation

BENEFITS OF EMMA FOR ...
Society: Support of efficient research | High quality standards | Promotion of animal welfare and the 3Rs | Dissemination of knowledge
Providers: Safe back-up of deposited strains | High visibility of mouse strains through EMMA | Ownership stays with provider
Recipients: Open access to 6000 mutant mouse lines | High-quality health-controlled material with defined genotype | global distribution

SOLUTION:
EMMA makes archived **mutant mouse lines** available to the global scientific community

THE INFRAFRONTIER RESEARCH INFRASTRUCTURE



Model Development
Networking Partner

Phenotyping
Bioinformatics

EMMA (Archiving/Distribution)
Management & Coordination

Gnotobiology/Axenic Models

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INFRAFRONTIER / IMPC Stakeholder Meeting

December 3 to 4, 2018 | Munich, *Hotel Hilton Park*

