



INFRAFRONTIER
mouse disease models



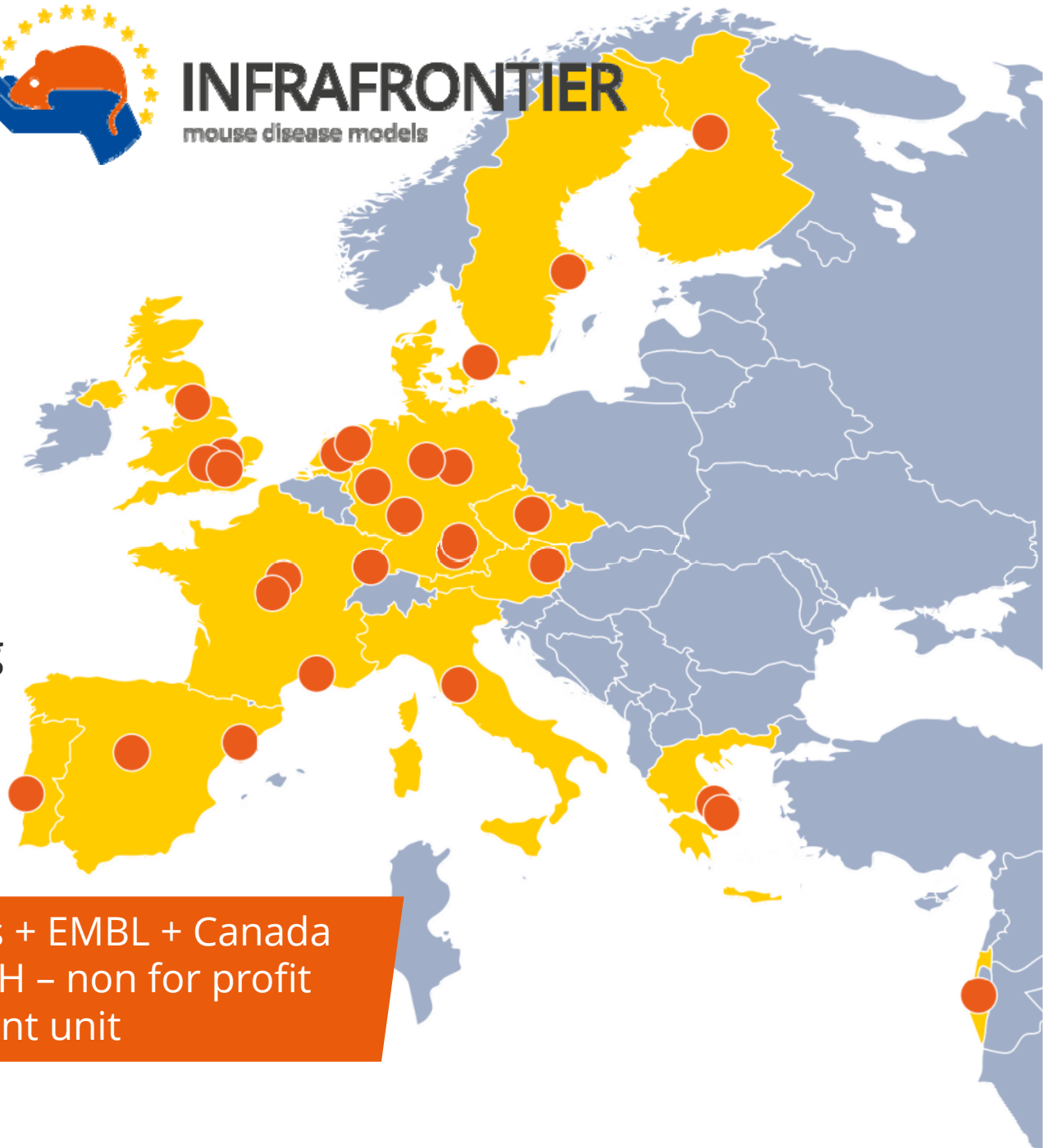
**INFRAFRONTIER – resources and services to
advance the understanding of human health
and disease using mammalian models**

Martin Hrabé de Angelis – Helmholtz Zentrum München, Germany



INFRAFRONTIER
mouse disease models

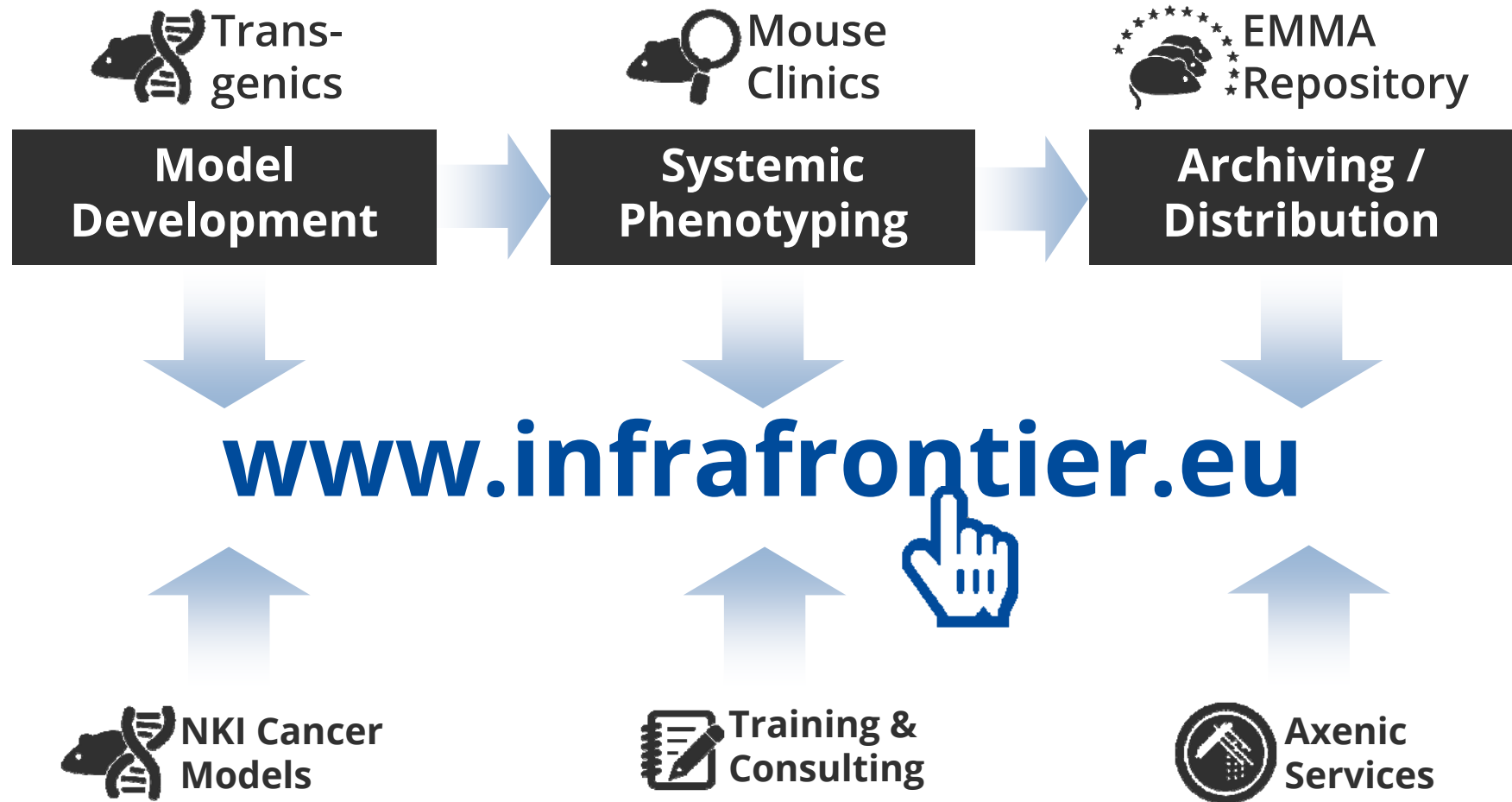
European **Research Infrastructure** for the **generation, systemic phenotyping, archiving** and **distribution** of mammalian models



15 European Countries + EMBL + Canada
INFRAFRONTIER GmbH – non for profit
management unit

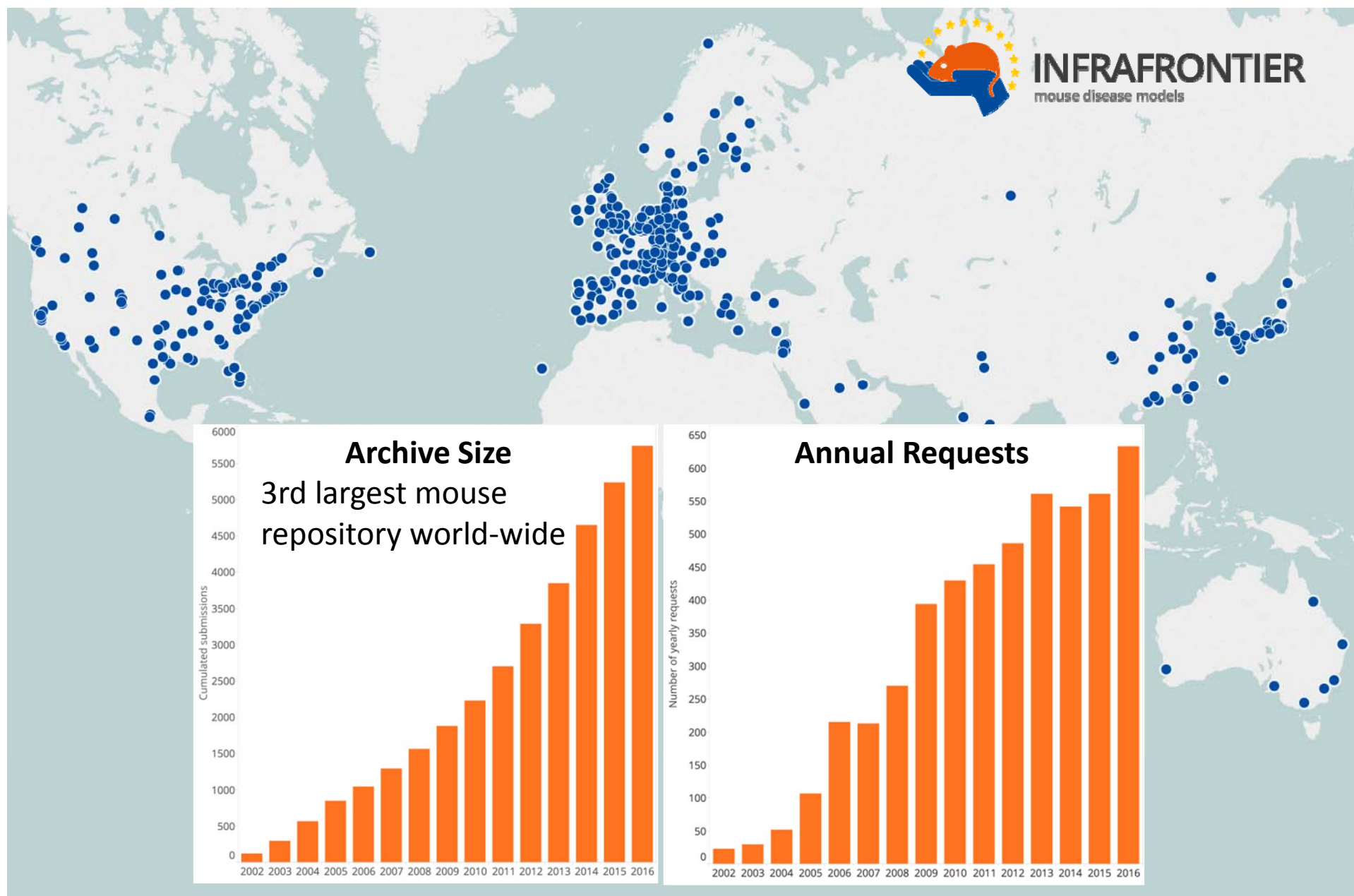


INFRAFRONTIER resources and services



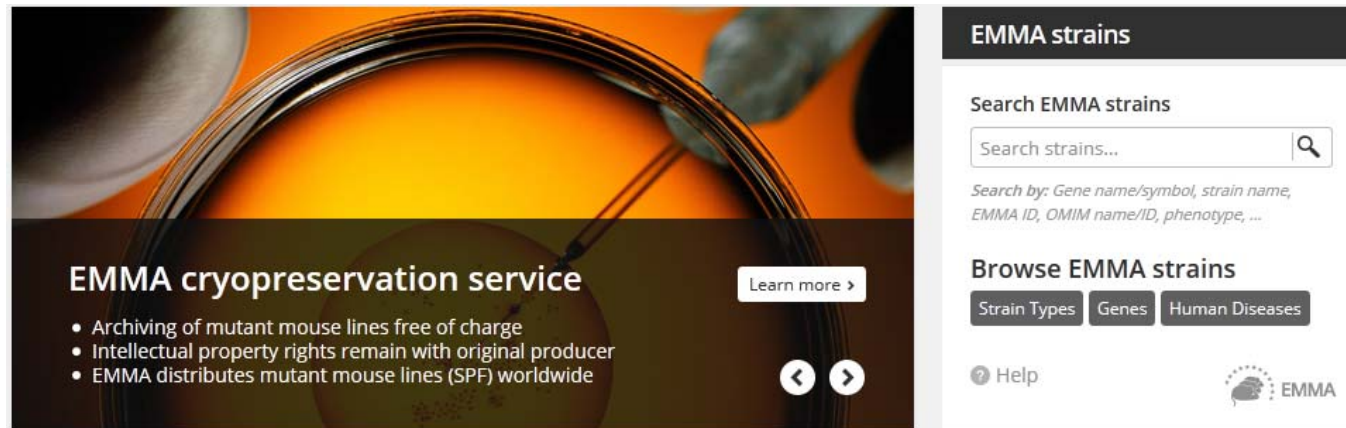
Distributed research infrastructure – one face to the customer

World-wide user community of INFRAFRONTIER / EMMA





European Mouse Mutant Archive (EMMA)



- 6000 mouse mutant lines archived
- 50% of strains deposited by individual scientists
- 5000 mouse mutant lines shipped
- Operating on partial cost-recovery model
Archiving free of charge for depositor



INFRAFRONTIER's contribution to IKMC/IMPC

- Preserve investment made in mouse production
 - 2713** strains on EMMA strain list
 - 163** Cre drivers from EUCOMMTools (C57BL/6N)
 - 1696** EUCOMM KO strains available to industry via genOway
- Facilitate availability and accessibility of IMPC mouse lines and connect IMPC effort to the global research community
 - 2528** shipments
 - 1139** alleles
 - 1091** genes
 - 1852** unique users
- Allele conversion and tissue service

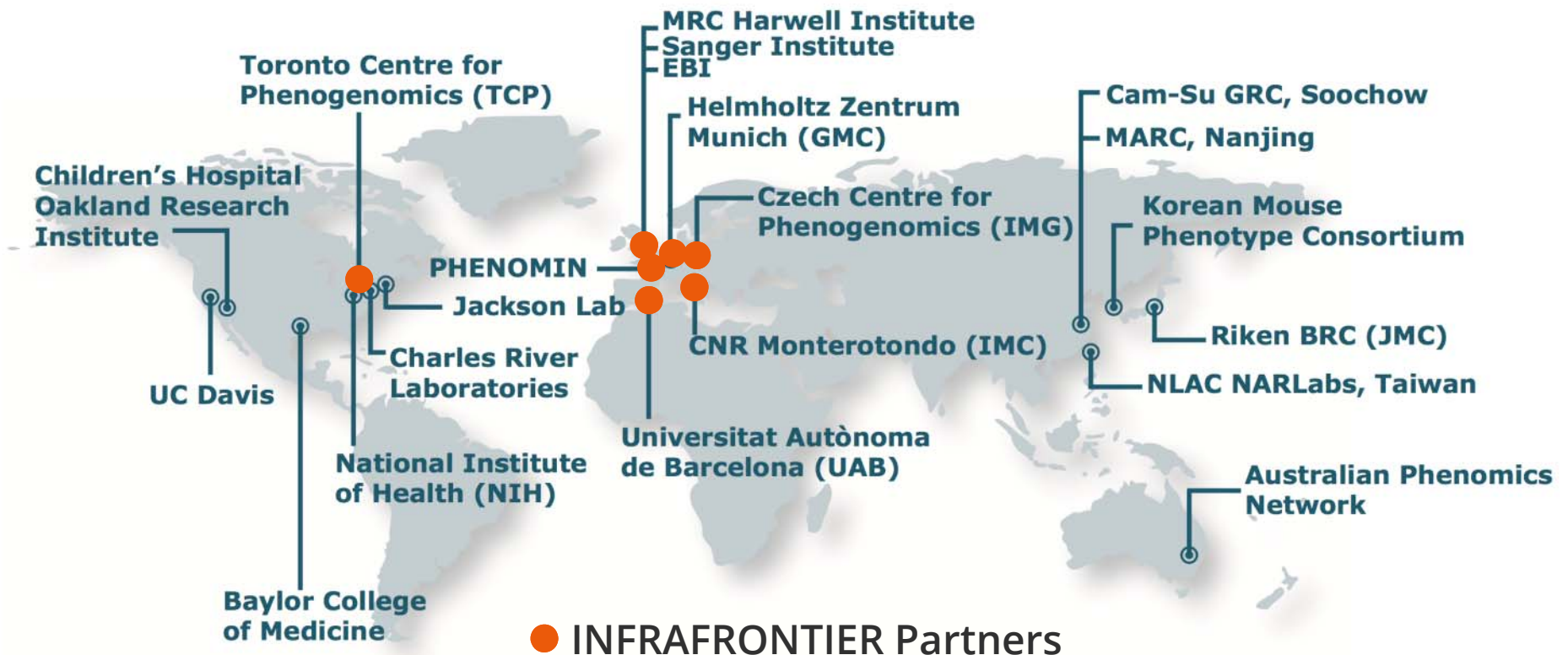




International Cooperation International Mouse Phenotyping Consortium



- First comprehensive catalogue of mammalian gene function
- An engine for discovering the genetic basis for disease
- Open access to data and resources





INFRAFRONTIER RI – model development & phenotyping

INFRAFRONTIER phenotyping capacities and expertise

- Systemic phenotyping
- Specialised phenotyping
- Excellence based access (collaboration / TA calls)
- Market based access



Czech Centre for Phenogenomics





INFRAFRONTIER open calls

INFRAFRONTIER-I3 project (EC - FP7)
INFRAFRONTIER2020 project (H2020)
INFRAFRONTIER open call

- 8 Open calls
- 260 Proposals
- 77 User projects





INFRAFRONTIER2020 open calls (Trans-national Access)

EU Horizon 2020 funded, coordinated by INFRAFRONTIER GmbH

Service	Description	Publication dates
Precision mammalian model development	CRISPR/Cas9 genome-editing 6 rat models 22 mouse models	➤ Nov 2017 2018
Specialised phenotyping/ data analysis	Metabolic-, behavioral-, immune-, inflammatory conditions 15 access units	Dec 2017 2018
Ageing pipeline	Systemic late-onset phenotyping of 4 aged mouse mutant lines	✓ June 2017
Axenic service	Derivation of germ-free mice 10 access units	✓ Aug 2017 2018

Calls published on webpage and announced via mailing



INFRAFRONTIER2020 public calls

Ageing pipeline - 4 projects started @ MRC Harwell

- Down Syndrome
- Cockayne Syndrome (CS) is a rare disorder characterized by hypersensitivity to UV, growth failure, cachexia, accelerated ageing and progressive neurological defects
- Impact of mitochondrial DNA mutations on inflammaging
(chronic, low-grade inflammation that occurs with advanced age without overt infection)
- Inhibit histone methyltransferase proteins as a therapeutic tool to counteract obesity



INFRAFRONTIER2020 public calls

Derivation of germ-free mice - 5 projects started

@ Karolinska Institute, PHENOMIN-TAAM, Gulbenkian

- Analyze the effect of eliminating **gut bacteria** in FVB-d16HER2 transgenic mice on **tumor onset/multiplicity** and **tumor response to trastuzumab**
- Investigate the role of the **microbiome on bile acid pool composition**, improved **glucose metabolism, insulin resistance and insulin secretion** observed in mice with a targeted deletion in the bile acid gene, *Cyp8b1*
- Understand how the **gut microbiome can drive immune cell activation** and lead to **PD** pathology



Technology development in INFRAFRONTIER

- Use of fewer animals
- Cost reduction
- Increased throughput
- User friendly services
- Robust SOPs

[Transgenic Res.](#) 2015 Oct;24(5):921-7. doi: 10.1007/s11248-015-9897-1. Epub 2015 Jul 16.

Blastocyst genotyping for quality control of mouse mutant archives: an ethical and economical approach.

[Scavizzi F¹](#), [Ryder E²](#), [Newman S²](#), [Raspa M¹](#), [Gleeson D²](#), [Wardle-Jones H²](#), [Montoliu L^{3,4}](#), [Fernandez A^{3,4}](#), [Dessain ML⁵](#), [Larrigaldie V⁵](#), [Khorshidi Z⁶](#), [Vuolteenaho R⁷](#), [Soininen R⁷](#), [André P⁸](#), [Jacquot S⁸](#), [Hong Y⁹](#), [de Angelis MH⁹](#), [Ramirez-Solis R²](#), [Doe B¹⁰](#).

[Theriogenology](#). 2017 Jul 1;96:49-57. doi: 10.1016/j.theriogenology.2017.04.003. Epub 2017 Apr 3.

Dry ice is a reliable substrate for the distribution of frozen mouse spermatozoa: A multi-centric study.

[Raspa M¹](#), [Guan M²](#), [Paoletti R³](#), [Montoliu L⁴](#), [Ayadi A⁵](#), [Marshall S⁶](#), [EMMA/Infrafrontier Technical Working Group](#), [Fray M²](#), [Scavizzi F⁷](#).

[Curr Protoc Mouse Biol.](#) 2014 Jun 16;4(2):47-65. doi: 10.1002/9780470942390.mo140064.

Transporting mouse embryos and germplasm as frozen or unfrozen materials.

[Kenyon J¹](#), [Guan M](#), [Bogani D](#), [Marshall S](#), [Raspa M](#), [Pickard A](#), [Takeo T](#), [Nakagata N](#), [Fray M](#).

TSE Metabolic PhenoCage, 8997 Infrafrontier: features and innovations





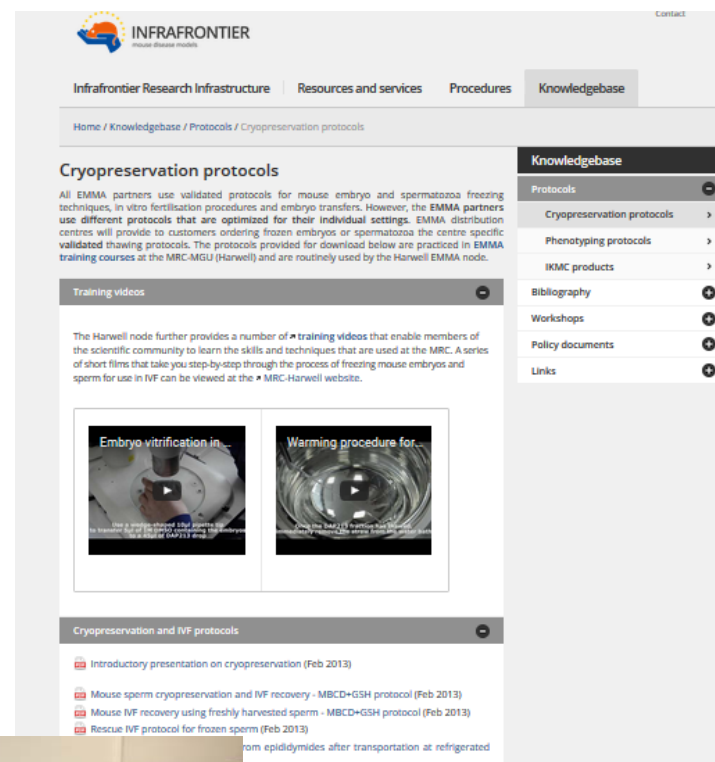
INFRAFRONTIER RI and IMPC deliver quality and reproducibility

- EMMA repository guards health and genetic quality of deposited mice
 - EMMA distributes identical reference resources
 - IMPReSS (International Mouse Phenotyping Resource of Standardised Screens), contains standardized phenotyping protocols
 - IMPC Validation of test robustness through reference lines
- Continuous evolvement of rigor and standardisation applied to operational procedures and data QC

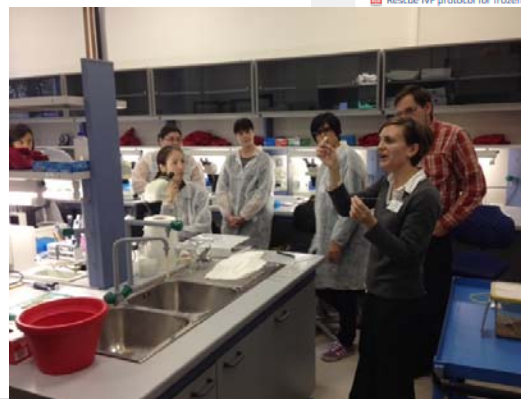




INFRAFRONTIER outreach / training



- 40 training courses in cryopreservation and mouse phenogenomics
- 400 participants





INFRAFRONTIER outreach / stakeholder meetings

INFRAFRONTIER Stakeholder Meeting

Advancing Personalised Medicine with Animal Models



INFRAFRONTIER / IMPC Stakeholder Meeting

14-16 November 2017, Athens, Royal Olympic Hotel

- INFRAFRONTIER2020 project supports 4 Stakeholder Meetings
- Focus on human disease modelling / (ageing / microbiome)
- Continued engagement of IMPC
- Next meetings in Munich, Helsinki
- Establish a sustainable meeting format

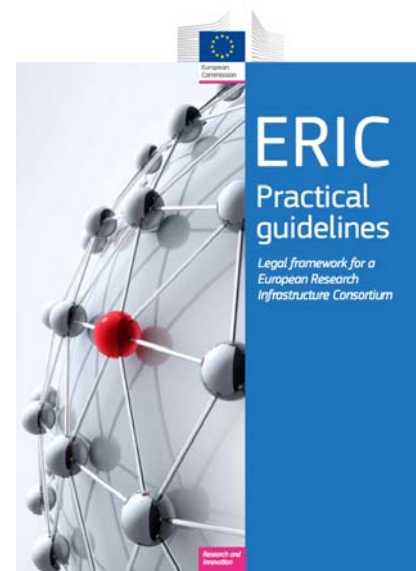


Policy background and sustainability

ESFRI – The European Strategy Forum on Research Infrastructures

Biomedical projects selected from 150 proposals:

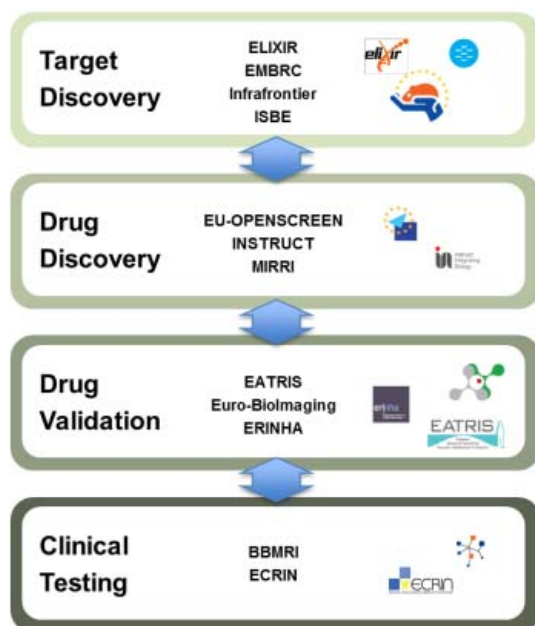
- BBMRI - biobanking
- EATRIS - translational research
- ECRIN - clinical trials
- ELIXIR - bioinformatics
- **INFRAFRONTIER - animal disease models**
- INSTRUCT - structural biology





INFRAFRONTIER international cooperation / CORBEL

- Horizon 2020-funded Research Infrastructure (RI) cluster project
- Create a platform for harmonised user access to biological and medical technologies, biological samples and data services



INFRAFRONTIER/Helmholtz use case: Restless Legs Syndrome (RLS)

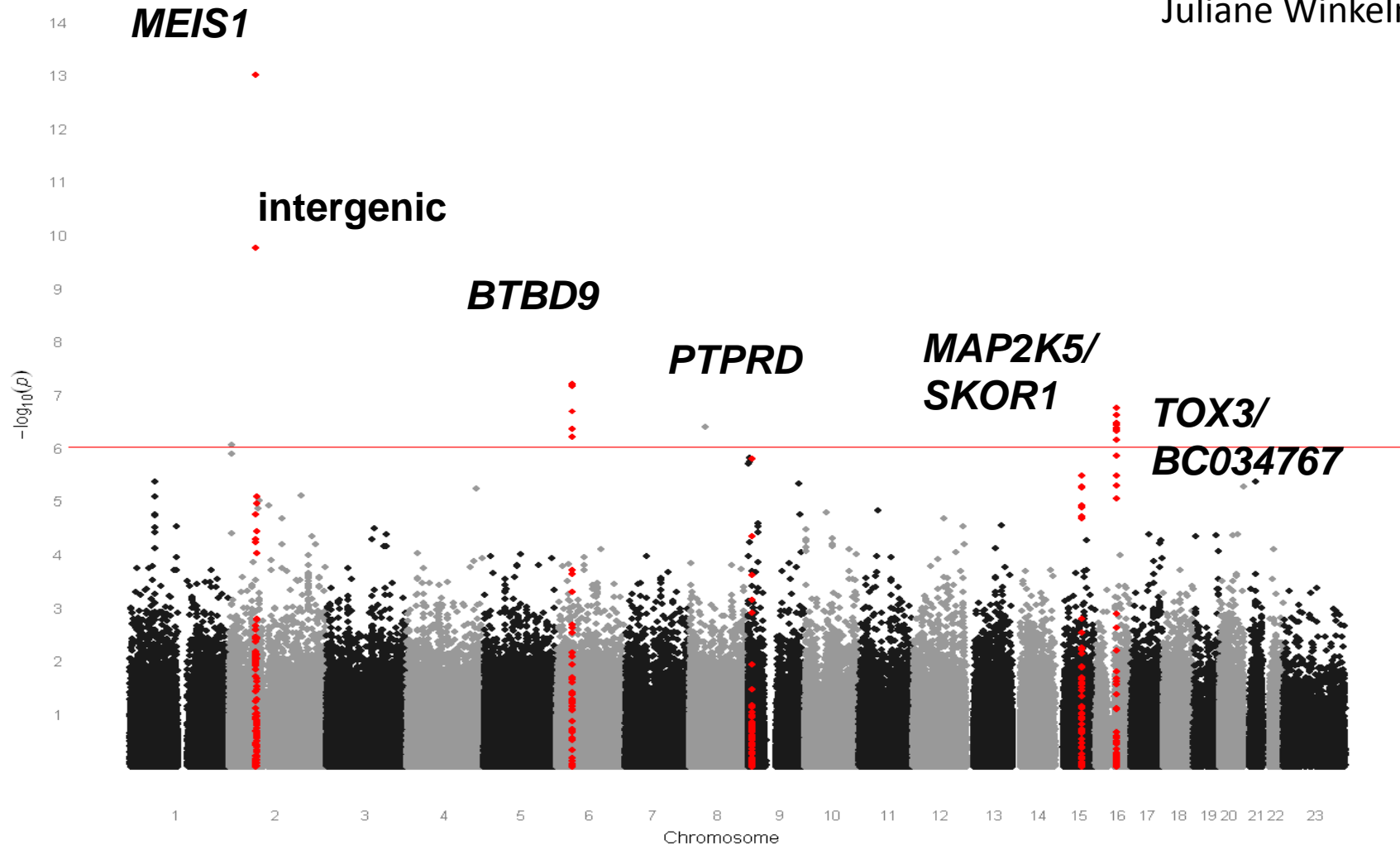
- Prevalence 3 – 10%
- Phenotype:

An urge to move the legs,
uncomfortable and unpleasant sensations in the legs



RLS - Genome-wide association studies

Juliane Winkelmann



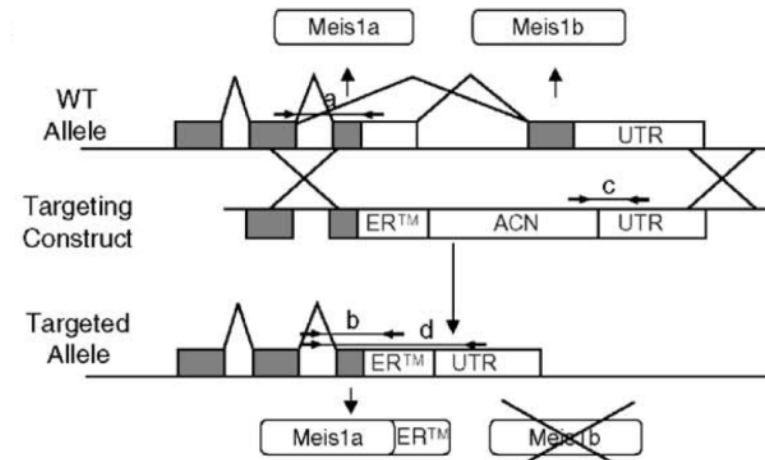
Meis1 – mouse models

- ERT2 domain knocked in in-frame
- MEIS1 p.Arg272His

		Age [weeks]																
		7	8	9	10	11	12	13	14	15	16	17	18					
Screens	Methods																	
Behaviour	Open Field																	
	Acoustic startle response & PPI																	
Neurology	Modified SHIRPA, Grip Strength																	
	Rotarod																	
Nociception	Hot Plate																	
Dysmorphology	Anatomical observation																	
Clinical Chemistry	Clinical chemistry after fasting (available soon)																	
Energy Metabolism	Indirect calorimetry, NMR																	
Clinical Chemistry	IpGTT																	
Cardiovascular	Awake ECG / Echo																	
Eye	Scheimpflug, OCT, LIB, Drum																	
Clinical Chemistry	Clinical-chemical analysis, Hematology																	
Immunology	FACS analysis of PBCs																	
Allergy	BIOPLEX ELISA (Ig concentration)																	
Steroid Metabolism	Corticost., androst., testosterone																	
Neurology	ABR (Auditory Brain Stem Response)																	
Dysmorphology	X-ray, DEXA																	
Clinical Chemistry	Clinical-chemical analysis, Hematology (optional)																	
Lung Function	Lung function measurement																	
Molecular Phenotyping	Expression Profiling																	
Pathology	Macro & microscopic analysis																	

Vilariño-Güell et al. Neurology 2010

Schulte et al. Neurology 2011, Schulte et al. Am J Hum Genet. 2014



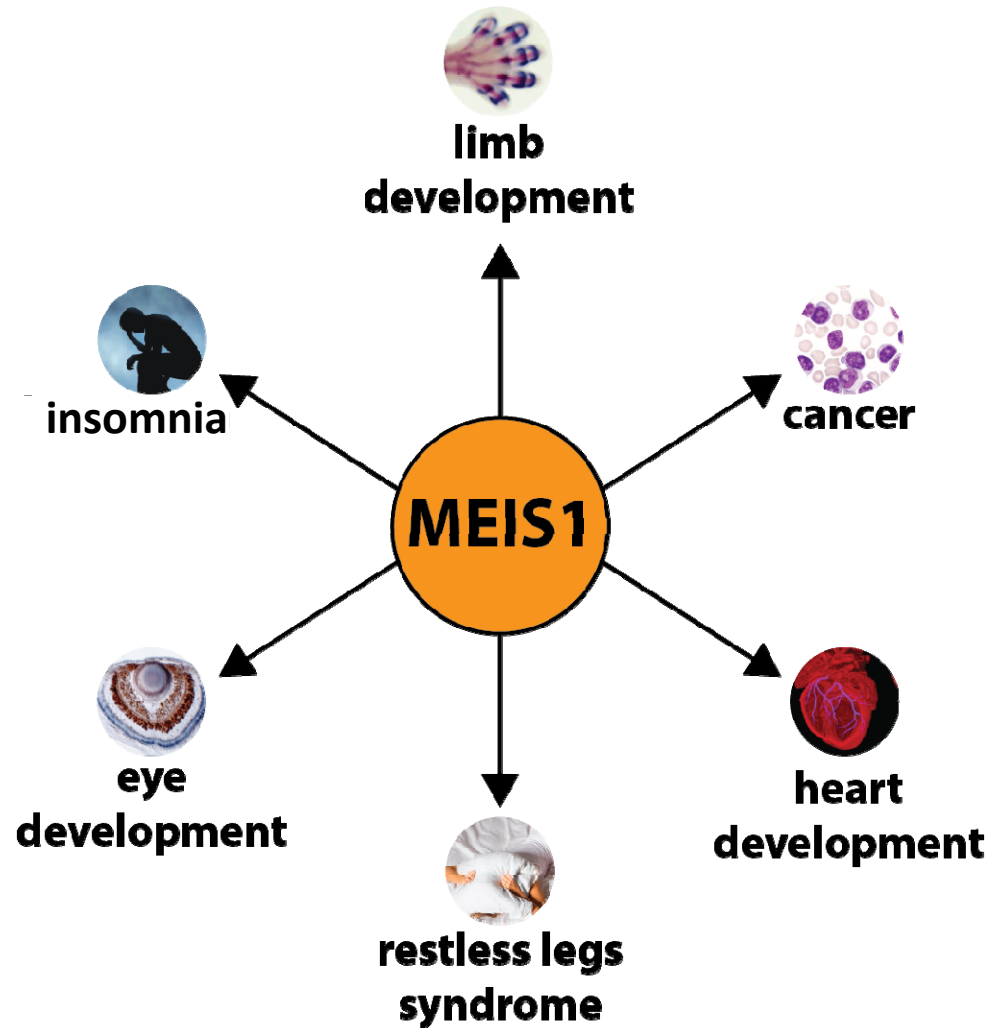
IDG Institute of Developmental Genetics

cnic

M. Torres



MEIS1 – pleiotropic function

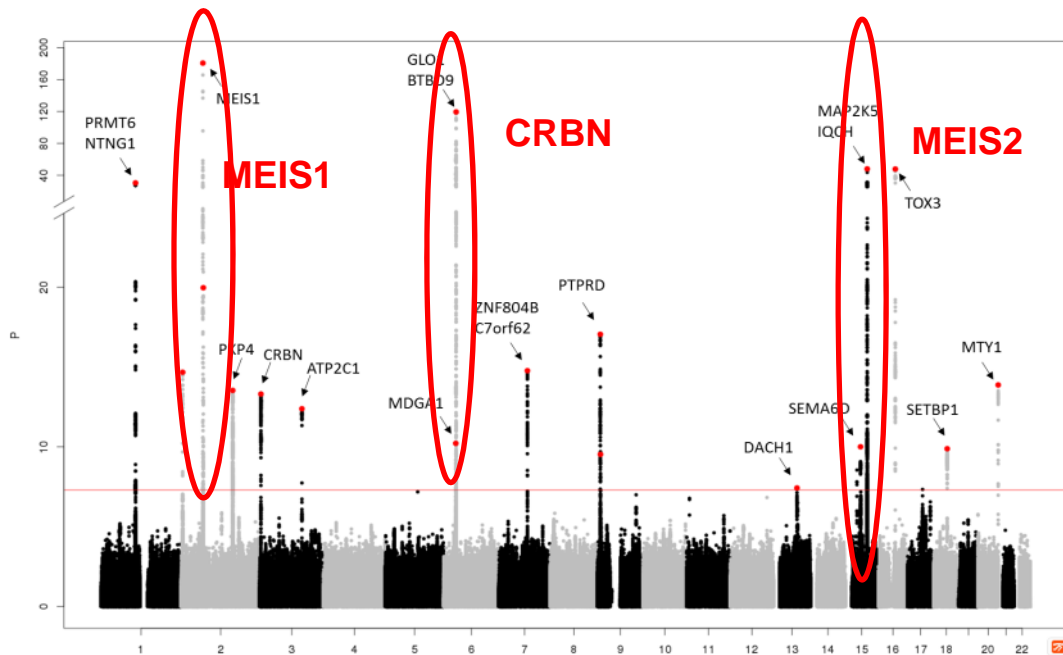


ING: New RLS-GWAS - Novel drug targets

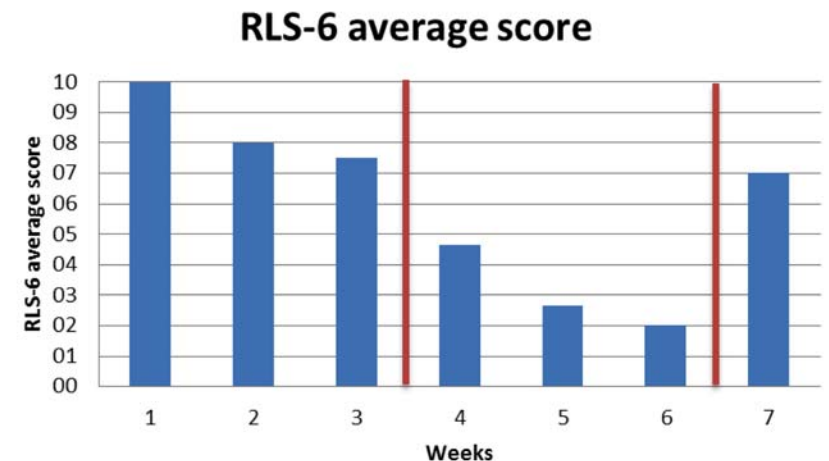
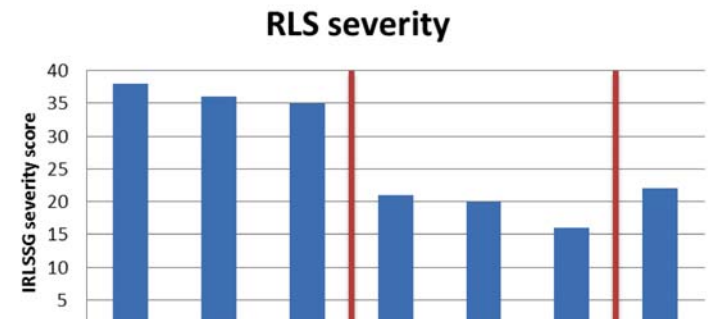
GWAS 2017:
45,577 patients
318,000 controls

19 loci/13 novel +
Repurposing of a small molecule

First patient:



Schormair, Zhao, et al., in revision





INFRAFRONTIER / Summary

- Unique resources and expertise to advance the understanding of human health and disease, and precision medicine
- Customized services: Precision model development, late-onset systemic phenotyping, systemic and specialised secondary phenotyping, axenic (germ-free) service
- 6000 EMMA mouse strains / global user community
- Technology development and training programmes
- Dedicated partner of the International Mouse Phenotyping Consortium (IMPC) / phenotyping, archiving, distribution
- Single point of entry to all services: www.infrafrontier.eu