



INFRAFRONTIER

mouse disease models



INFRAFRONTIER / IMPC / UAB industry liaison meeting

Martin Hrabé de Angelis, Helmholtz Zentrum München

INFRAFRONTIER / IMPC / UAB Meeting, Barcelona, November 13th 2014



INFRAFRONTIER / IMPC and industry - context

- **National and EU research policy and funding** support collaboration
 - Knowledge transfer and innovation (**Innovation Union**)
 - Basic research and focus on **'translation'**
- **Vendors / Suppliers / CROs / Biotech**
 - Provide academia with platforms and tools to develop and work with mouse models
 - Support innovation
 - E.g. EU market for scientific instrumentation is worth 4b€/yr





INFRAFRONTIER / IMPC and industry - context

- **Pharma / Biotech** exploit mouse models for drug development
 - Use of animal models in developing new therapeutic strategies for treating human diseases, and in drug discovery research, as well as in preclinical studies of drug safety and efficacy
 - 34 / 100 of top drugs (by sales volume, USA) were enabled by the use of a mouse model

Table 4 | **Best-selling drugs and KO-mouse phenotype: CNS and neurology**

Drug target	Drug name (utility)	2001 Sales*	Mouse phenotype
Serotonin transporter	Paxil (depression)	\$2,673.0	Altered open-field behaviour.
	Zoloft	\$2,366.0	
	Prozac	\$1,990.0	
	Effexor	\$1,542.0	
	Celexa	\$714.0	
Dopamine, serotonin and histamine receptors	Zyprexa (psychosis)	\$3,087.0	Multiple targets; however, related KOs display behavioural phenotypes (movement, activity and anxiety).
	Risperdal	\$1,845.0	
	Seroquel	\$700.0	
Dopamine and noradrenaline transporters	Wellbutrin (depression)	\$931.0	Multiple targets; however, increased activity levels (dopamine transporter); increased struggle in tail suspension (noradrenaline transporter).
GABA receptor	Ambien (insomnia)	\$704.0	Hyperactive, hyper-responsive.
	Stilnox	\$902.0	
μ -opioid receptor	Duragesic (pain)	\$875.0	Increased sensitivity to pain.
	Ultram	\$601.0	

*US \$ in millions.

Knockouts model the 100 best-selling drugs—will they model the next 100?

Brian P. Zambrowicz & Arthur T. Sands

Nature Reviews Drug Discovery 2, 38-51 (January 2003)



INFRAFRONTIER / IMPC and industry - challenge

- Raise awareness among industry stakeholders of INFRAFRONTIER / IMPC activities
- Ensure that the output of the INFRAFRONTIER / IMPC does benefit biopharmaceutical research and development programs (access to resources!)
- Alignment of INFRAFRONTIER services with industry demand
- Take into account the expert views and expectations of industry researchers working with mouse models
- Explore and exploit engagement modes with industry



Industry liaison meeting - meeting goals

- **Communication:** Raise awareness of INFRAFRONTIER services and emerging IMPC data and resources
 - Promote industry access to EUCOMM resources
 - What are best ways to communicate with industry?
- **Value add:** What can IMPC / INFRAFRONTIER provide to industry that they can't or are not willing to do themselves
- **Partnering:** Presentation of successful industry engagement models and exploring new opportunities e.g. provided by H2020 instruments
- **Contribution:** What can industry offer the IMPC and INFRAFRONTIER?



Industry liaison meeting - participants

- Up to 80 participants
- INFRAFRONTIER / IMPC PIs, scientists, advisors
- IMPC Industry Sponsors
- BioPharma
- Research instrumentation developers
- CROs, suppliers and platform companies
- Funders



Industry liaison meeting - agenda

INFRAFRONTIER / IMPC / UAB industry liaison meeting / November 13th, 2014

Agenda

08:30 - 09:00 Registration of participants and coffee

INFRAFRONTIER / IMPC

09:00 - 09:05 Welcome address / Meeting objectives - Martin Hrabé de Angelis

09:05 - 09:25 Martin Hrabé de Angelis / INFRAFRONTIER

09:25 - 09:45 Steve Brown / International Mouse Phenotyping Consortium (IMPC)

Collaboration models of INFRAFRONTIER / IMPC partners and industry

Mouse production, phenotyping and preclinical services:

09:45 - 10:00 Alexandre Fraichard (genOway) / Access to EUComm-based KO mouse models

10:00 - 10:15 Tania Sorg (ICS / PhenoPro) / Mouse phenotyping services

10:15 - 10:30 Maria Denis (Biomedcode) / (Humanised) animal models of chronic inflammatory diseases, preclinical drug evaluation services

10:30 - 11:00 Coffee break

Joint development of research instrumentation:

11:00 - 11:15 Lars Breuer - TSE systems GmbH

11:15 - 11:30 Giorgio Rosati - Tecniplast

11:30 - 11:45 Lucas Noldus - Noldus Information Technology

11:45 - 12:00 David Craig - ActualAnalytics

12:00 - 12:15 Valentina Villa - Ayoxxa Biosystems GmbH

12:15 - 12:30 Amit Vasanji - ImageIQ

12:30 - 13:30 Lunch break



Industry liaison meeting - agenda

12:30 - 13:30 Lunch break

Requirements and use of mouse models by BioPharma

13:30 - 13:45 John Mudgett (Merck)

13:45 - 14:00 Fatima Bosch (UAB) and Eduard Valenti (ESTEVE) / Gene therapy approaches for mucopolysaccharidosis: From preclinical studies in mice to the clinic

14:00 - 14:15 European Federation of Pharmaceutical Industries and Associations (EFPIA)

14:15 - 14:30 Discussion

Partnering session

14:30 - 16:00 INFRAFRONTIER / IMPC PIs and meeting attendees

Wrap up

16:00 - 16:15 Martin Hrabé de Angelis



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The INFRAFRONTIER Research Infrastructure

Martin Hrabé de Angelis, Helmholtz Zentrum München

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Selected from 150 proposals:

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

(up-dated in 2008 and 2010 for additional projects)



BMS Research Infrastructures

- Implementation and operation of cross-cutting services and solutions for the BMS cluster of ESFRI research infrastructure
- **Proposal:** COordinated Research Infrastructures Building Enduring Life-science Services (CORBEL)





Building the INFRAFRONTIER Research Infrastructure

Preparatory Phase (2008-2012)

Infrafrontier Project

- **Capacity building** to meet the increasing demands
- Developing the **European Research Area**
- Developing a **business plan** based on a sustainable funding concept
- Providing a **strategic plan** for the implementation phase
- Reaching a **legal agreement** between all partners

Implementation and Operation (from 2013)

Infrafrontier Research Infrastructure

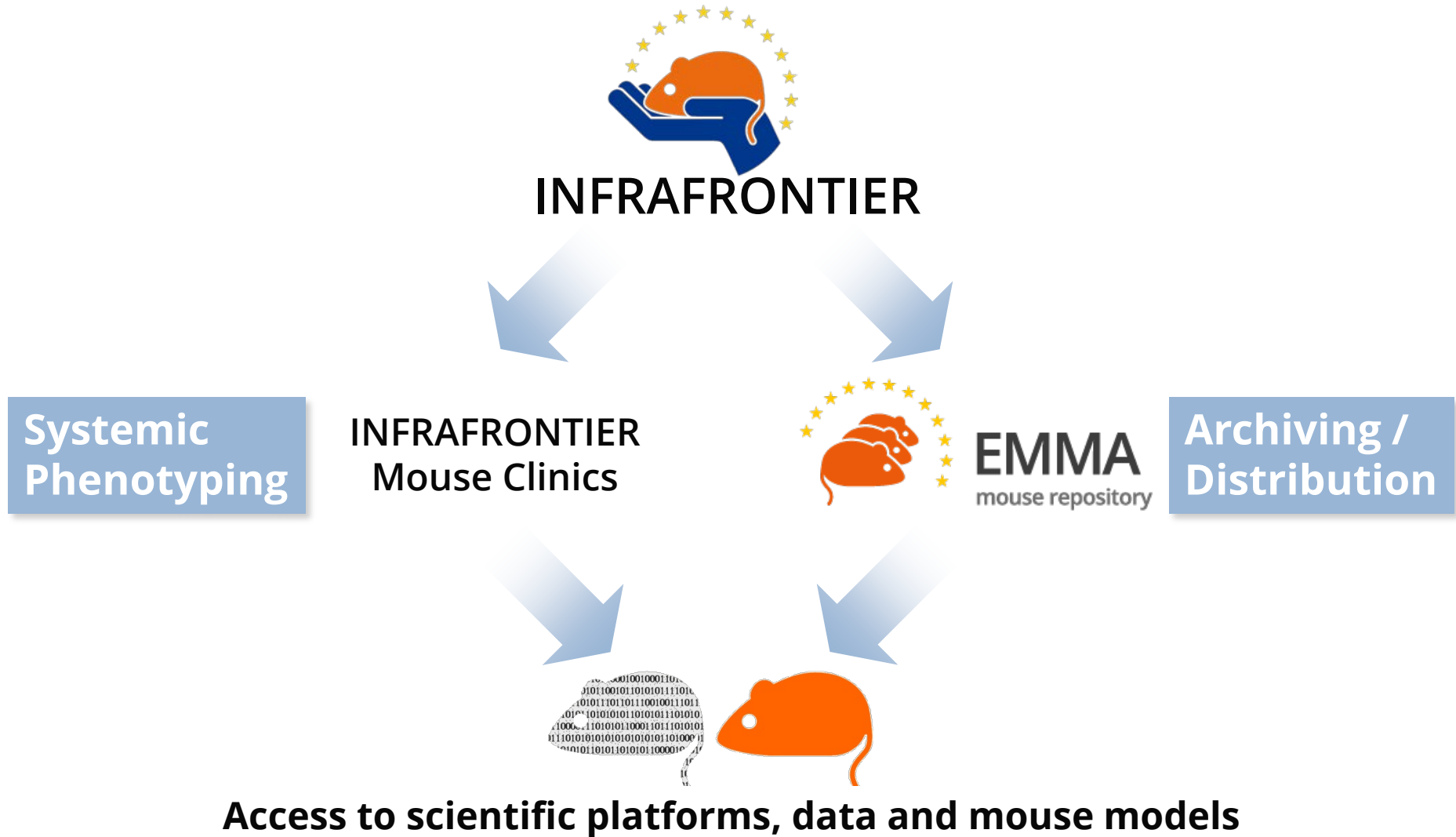
Infrafrontier Legal
Entity

National Infrafrontier
Partners

Infrafrontier-I3 Project

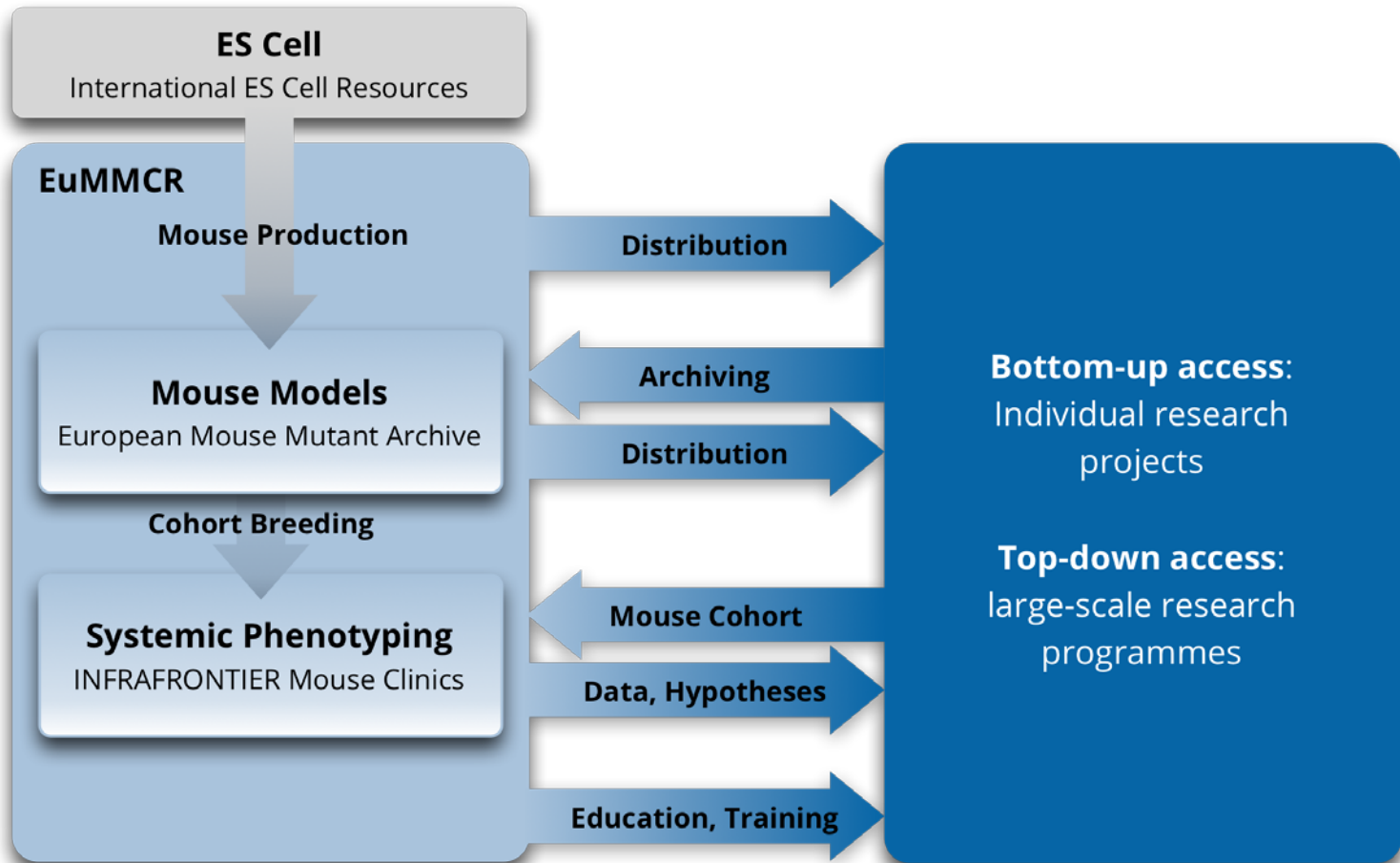


The INFRAFRONTIER Research Infrastructure





Serving the biomedical research community

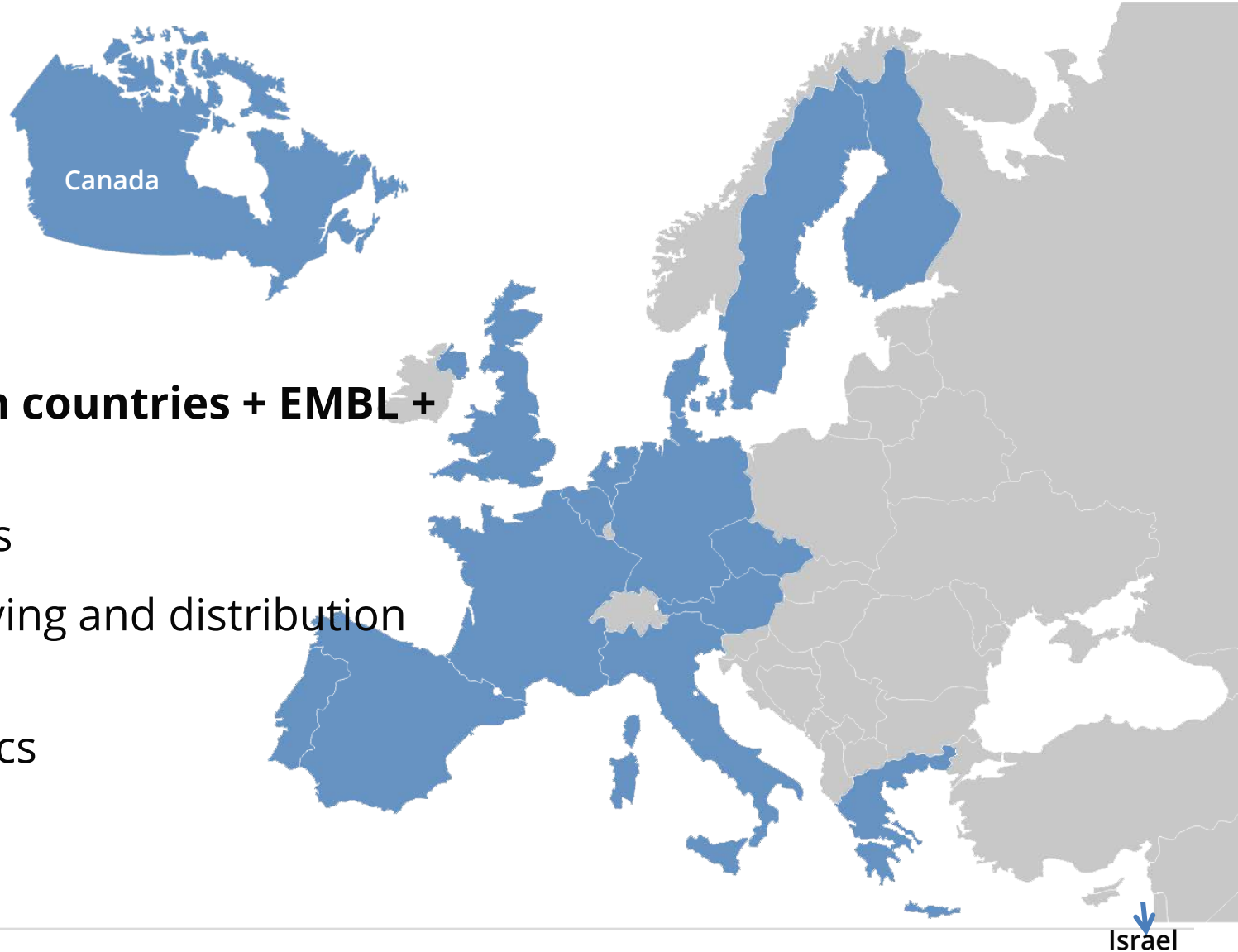


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**Biomedical Research
Community**

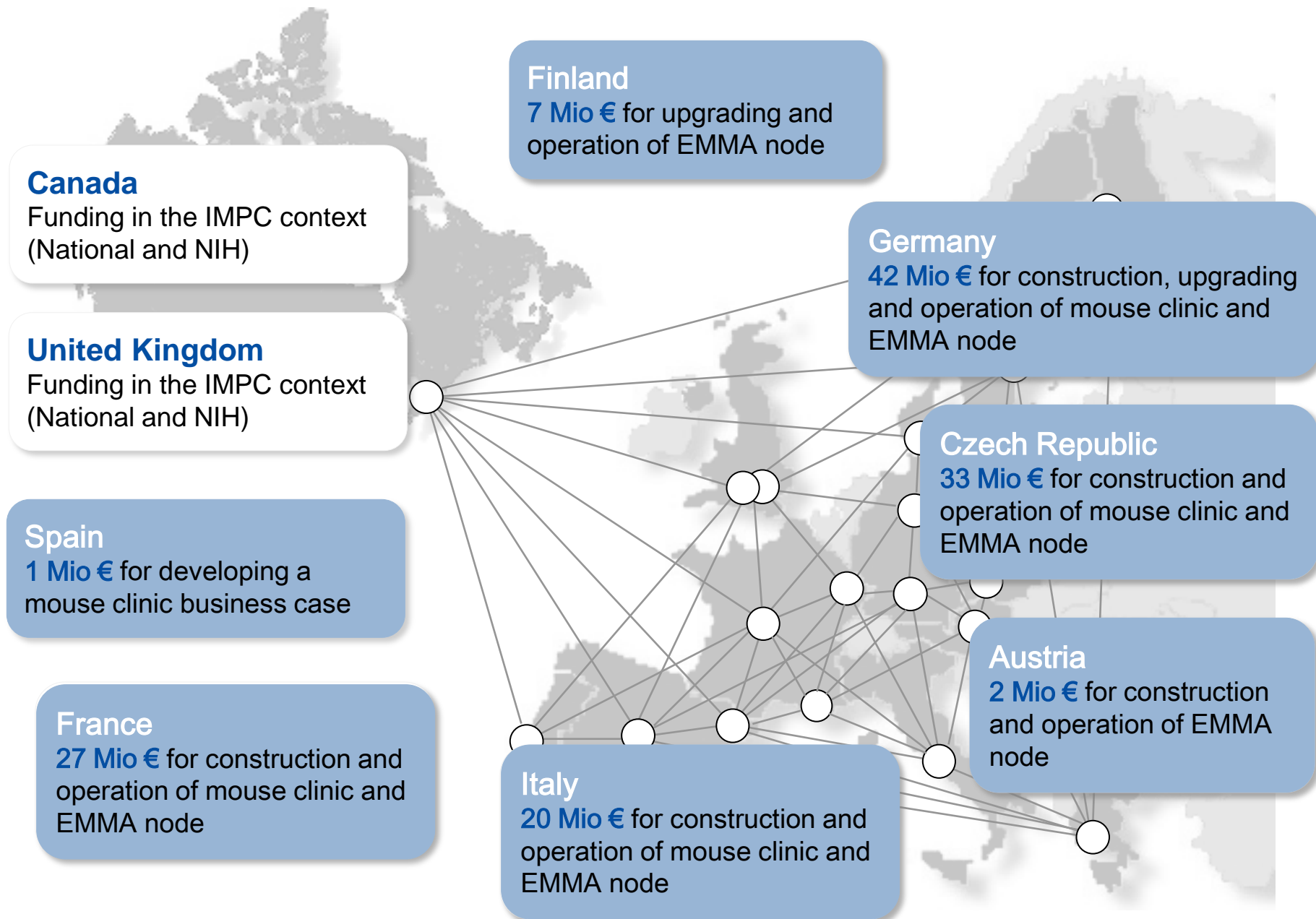


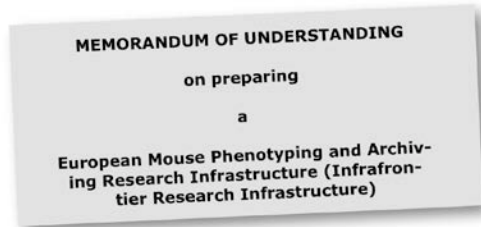
The INFRAFRONTIER partner network



- **23 Partners**
- **14 European countries + EMBL + Canada**
- Mouse clinics
- EMMA archiving and distribution nodes
- Bioinformatics

Capacity building – Funding commitments





INFRAFRONTIER GmbH established in 2013


Partners:

- DE – HMGU 11 Apr 13
- FR - CNRS 05 Dec 13
- CZ – IMG 05 Dec 13
- FI – U OULU 05 Dec 13
- GR - Fleming 05 Dec 13
- more to come ...


Next step: Setting up the INFRAFRONTIER ERIC



User access through www.infrafrontier.eu

**INFRAFRONTIER**
mouse disease models

Infrafrontier Research Infrastructure | Resources and services | Procedures | Knowledgebase





INFRAFRONTIER core services


- European Mouse Mutant Archive (EMMA) Archiving and distribution of mouse models
- First-line phenotyping of mouse mutants


[Learn more >](#)


Resources and Services


Deposit mice
EMMA archives your mouse mutant free of charge >

Order mice
Access to 4000 mouse mutants and research tools >

Axenic service
EMMA produces germ-free mice free of charge >

NKI GEMM-ESC archive
Rapid target gene validation in complex cancer mouse models

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Free of charge services for European researchers >

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Hands-on courses in cryopreservation and phenotyping >

News & Events

14 Aug 2014
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[Read more >](#)

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Knowledgebase

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[Read more >](#)

Projects

INFRAFRONTIER runs the EC-funded project INFRAFRONTIER-13 and is a key partner in the International Mouse Phenotyping Consortium (IMPC).
[Read more >](#)


About INFRAFRONTIER

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 (axenic service) and training in state of the art cryopreservation and phenotyping technologies.

The INFRAFRONTIER GmbH coordinates the transnational activities of the national partners that together form the European INFRAFRONTIER Research Infrastructure.


European Partnership




INFRAFRONTIER is on the ESFRI Roadmap.
[Read more >](#)





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EMMA repository



EMMA cryopreservation service

- Archiving of mutant mouse lines free of charge
- Intellectual property rights remain with original producer
- EMMA distributes mutant mouse lines (SPF) worldwide

[Learn more >](#)

EMMA strains

Search EMMA strains

Search by: Gene name/symbol, strain name, EMMA ID, OMIM name/ID, phenotype, ...

Browse EMMA strains

[Strain Types](#) [Genes](#) [Human Diseases](#)

[? Help](#)

Major collections

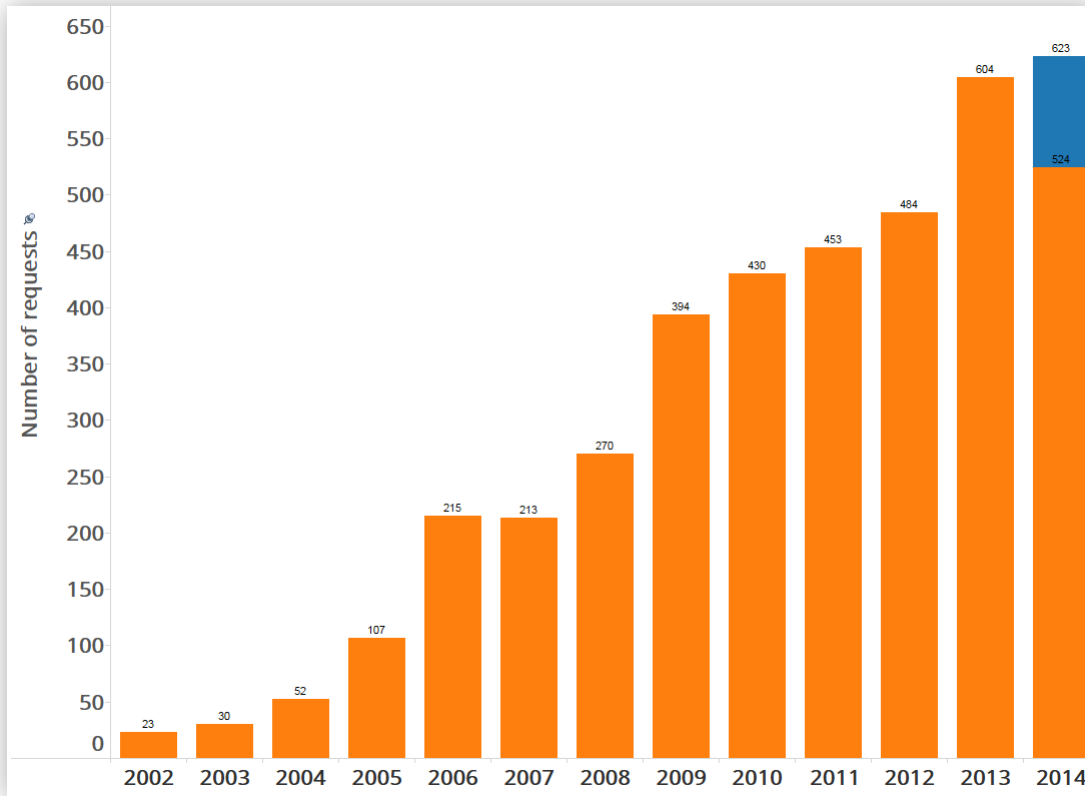
4404 mouse mutant lines are displayed on the public EMMA strain list

Commercial access to IKMC resource via genOway as intermediary

- **2198** mouse strains from IKMC resource
- **588** ENU strains
- **187** Cre expressing strains
- **86** mouse strains from Lexicon / Deltagen collection (Wellcome Trust KO mouse resource)
- **46** strains with Tet expression system



EMMA repository – orders / status 03 Nov 2014



Demanded lines

Cre resource

- 187 Cre driver lines account for 537 shipments

IKMC / IMPC resource

- 1429 shipments for IKMC mice
- 664 different IKMC strains were shipped

Turnaround times 2013 (order – shipment (including all paperwork, MTA etc.))

Mice on shelf: 6.1 weeks; frozen stock: 9.9 weeks; rederivation: 23.3 weeks

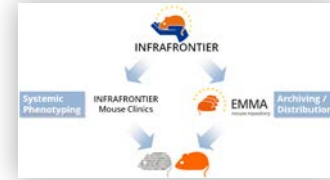


World-wide distribution of EMMA users





Phenotyping: The challenge



- The function of the majority of genes is still unknown
- We are remarkably poor at predicting the functions of genes – pleiotropy will be key to understanding diseases
- Functional data on genes are patchy – and are dependent on the experience and interests of the investigator
- Impact of environmental factors on health and disease is poorly understood

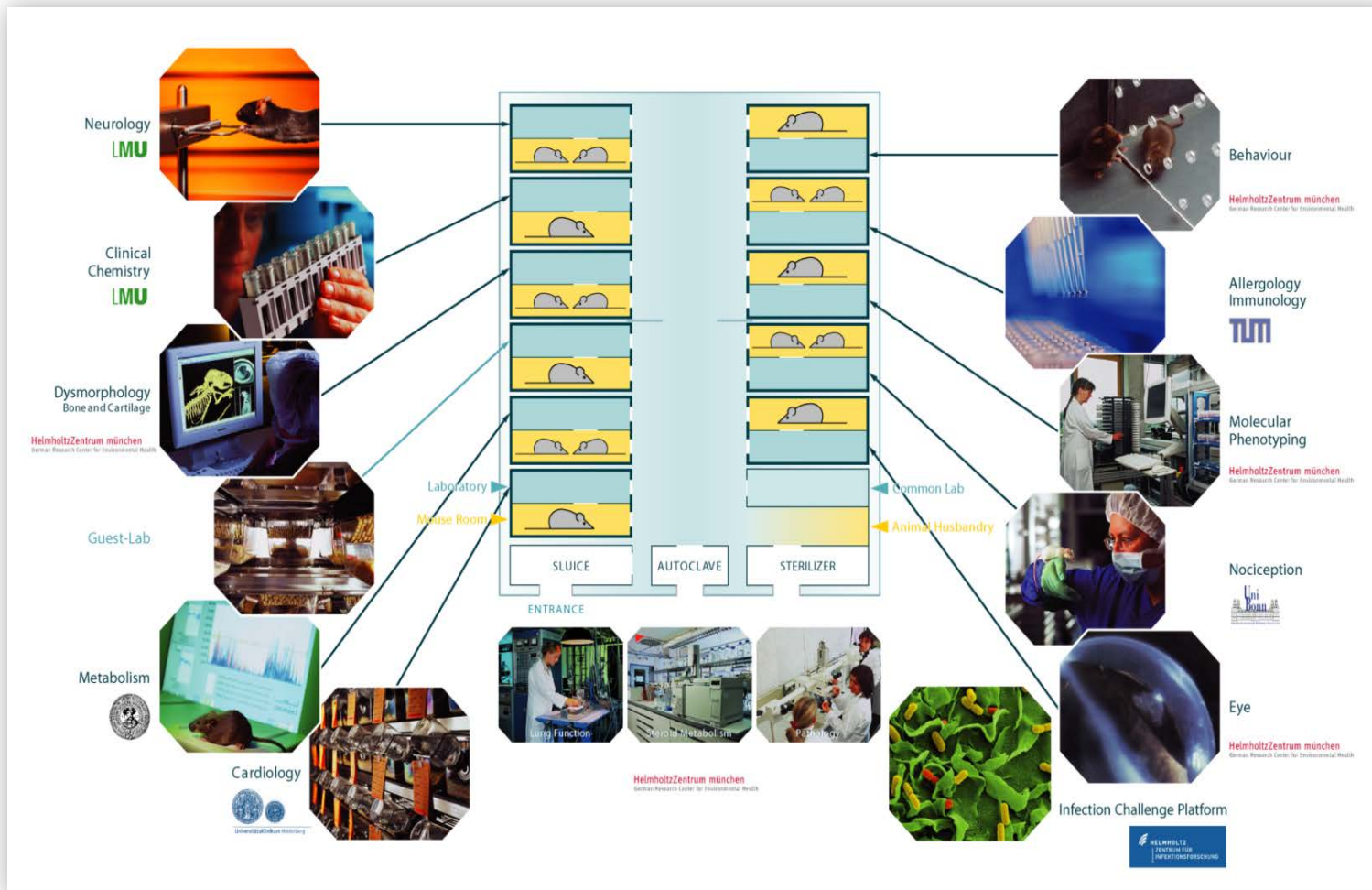


Phenotyping: The mouse clinic concept

- Open access phenotyping platform for the scientific community
- Offer a systemic primary phenotypic screen
(more than 550 parameters)
- Provide interpretation of results
- „Hypothesis Generation Machine“
- Provide the possibility of follow-up studies in secondary and tertiary screens

German Mouse Clinic:

The first systemic mouse phenotyping research infrastructure with open access



Selection:

Nat Med (2012)
 Science (2010)
 Hum Mol Genet (2012)
 EMBO J (2014, 2010)
 BBRC (2013)
 Eur J Immunol (2014)
 Development (2013)
 Acta Neuropathol (2012)
 Nucleic Acids Res (2010)
 PLoS Genet (2012)
 PLoS One (2014, 2013, 2012, 2010)
 PLoS Biol (2010)
 Blood (2011)
 Histo Histopath (2013)
 J Cell Science (2011)
 J Biol Chem (2014, 2013, 2011)
 Genome Res (2014)
 Faseb J (2012)
 Eur J Endocrinol (2012)
 J Comp Neurol (2012)
 BMC Neurosci (2012)

German Mouse Clinic: Quality management system, ISO9001:2008 certification

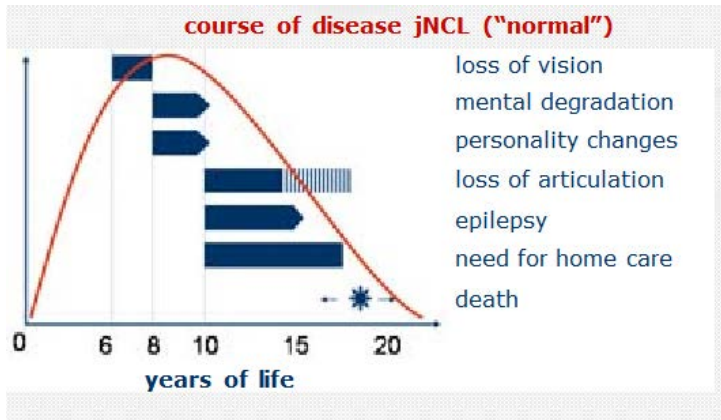
- GMC
- ICS
- MRC MLC



Systemic phenotyping in the GMC

jNCL / Batten disease

- jNCL or **Batten disease**, lysosomal storage disease
- **most common inherited neurodegenerative** condition of childhood
- progressive loss of vision, seizures, and loss of cognitive and motor functions
- GMC approached by **German NCL foundation** to study mouse model of **Cln3**



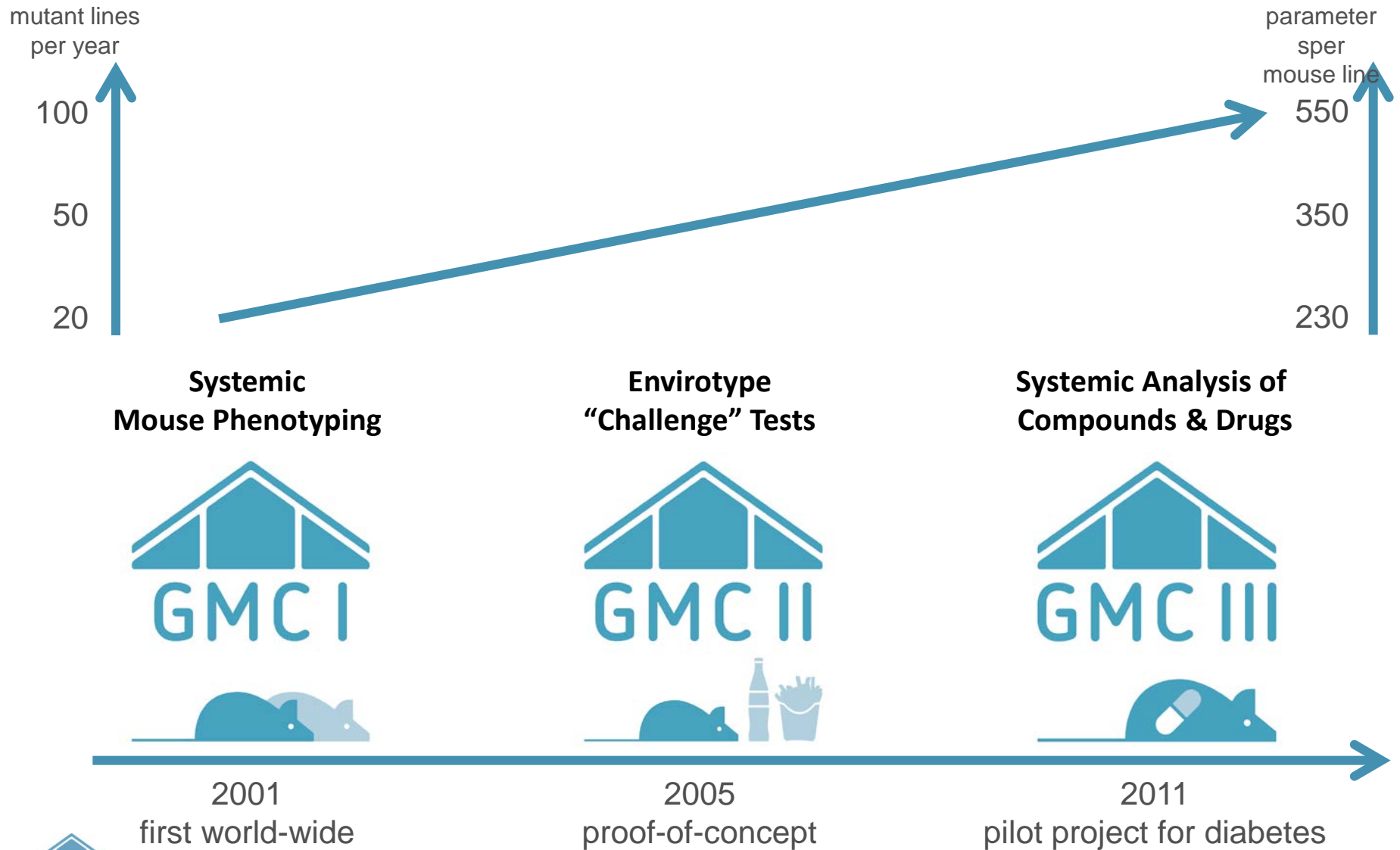
- **Precise genetic mouse model** of jNCL existent (recapitulates human disease progression)
- **Systemic phenotypic analysis in the German Mouse Clinic** to reveal pleiotropic effects

Major results:

- **New hypothesis:** jNCL caused by impaired cellular transport
- **New early biomarkers discovered** such as impaired PPI and altered blood count **prior** to neurodegeneration



Dynamic advancement of the GMC





INFRAFRONTIER and the IMPC




- INFRAFRONTIER partners are major contributors to IMPC mouse production and phenotyping efforts
- EMMA is one of the main repositories for the IMPC resources
- Coordination and common strategies required








More information on <https://www.infrafrontier.eu>

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



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 **CSIC**

 **EMBL-EBI**

 **HELMHOLTZ ZENTRUM FÜR INFECTIÖNENFORSCHUNG**

Helmholtz Zentrum münchen
German Research Center for Environmental Health

 **ANNOBERG INSTITUT FÜR KLINISCHE GENOMIK UND GENOMIK**



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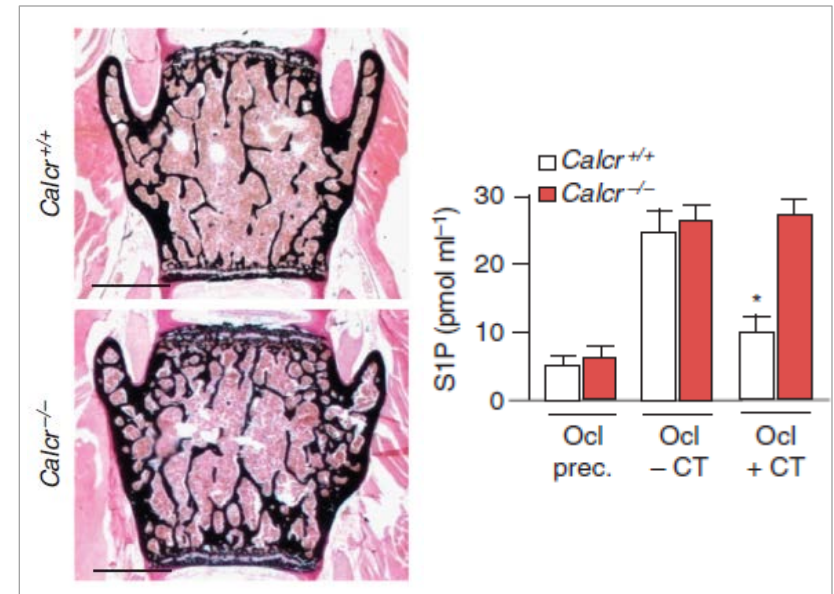
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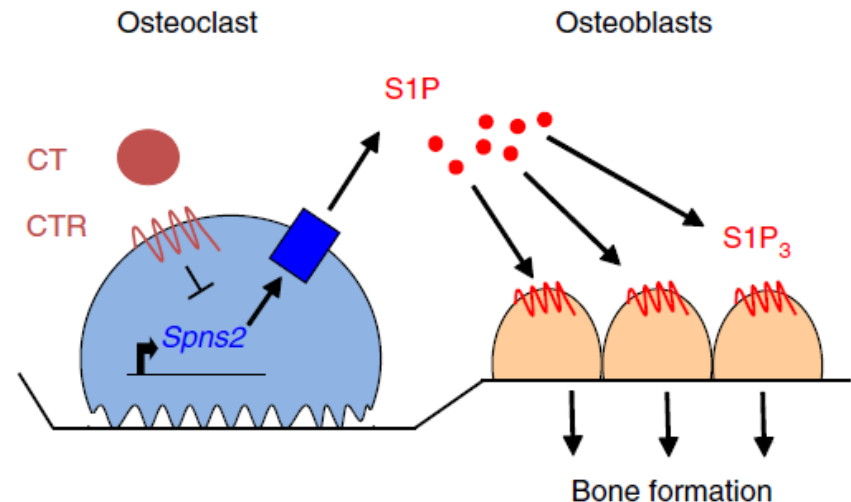


- Reduction of calcitonin action by inactivation of the murine calcitonin receptor causes **increased bone formation**
- Leads to **increase of sphingosine-1-phosphate (S1P)**
- S1P acts as an **osteoanabolic molecule *in vivo*** -- starting point to develop new approaches for the treatment of osteoporosis



➤ Systemic phenotyping of calcitonin receptor Knock-out :

- Only minor side effects
- Increased ALP
- Hypoactivity (OF, IC)



Keller, J. et al.(2014), **Nature Communications**