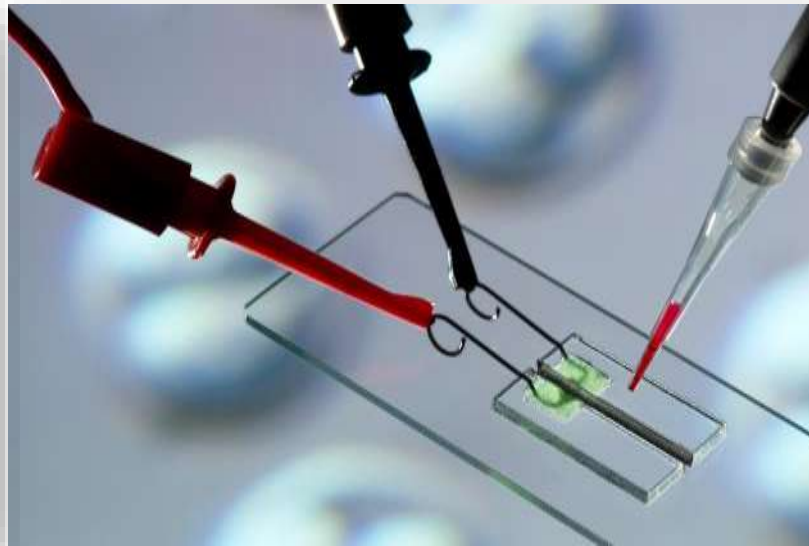


The Infrafrontier RI

Lluís Montoliu (CNB-CSIC & CIBERER-ISCIH)



The INFRAFRONTIER Research Infrastructure

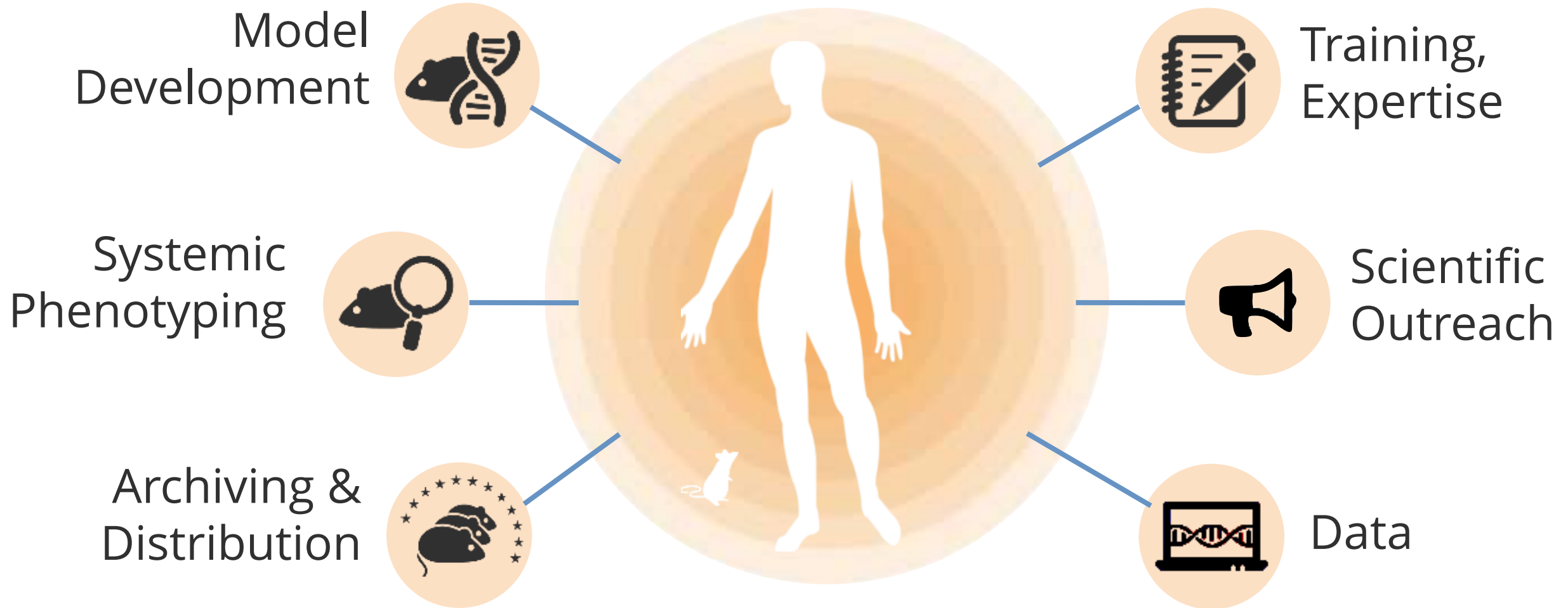
2007



Providing
unique scientific resources, services, and expertise
to advance the understanding and treatment of **human diseases using**
rodent models



Access to physical resources, analytical platforms, knowledge and data



www.infrafrontier.eu

Promoting responsible and reproducible research

Promoting the 3Rs

Replacement

Reduction

Refinement

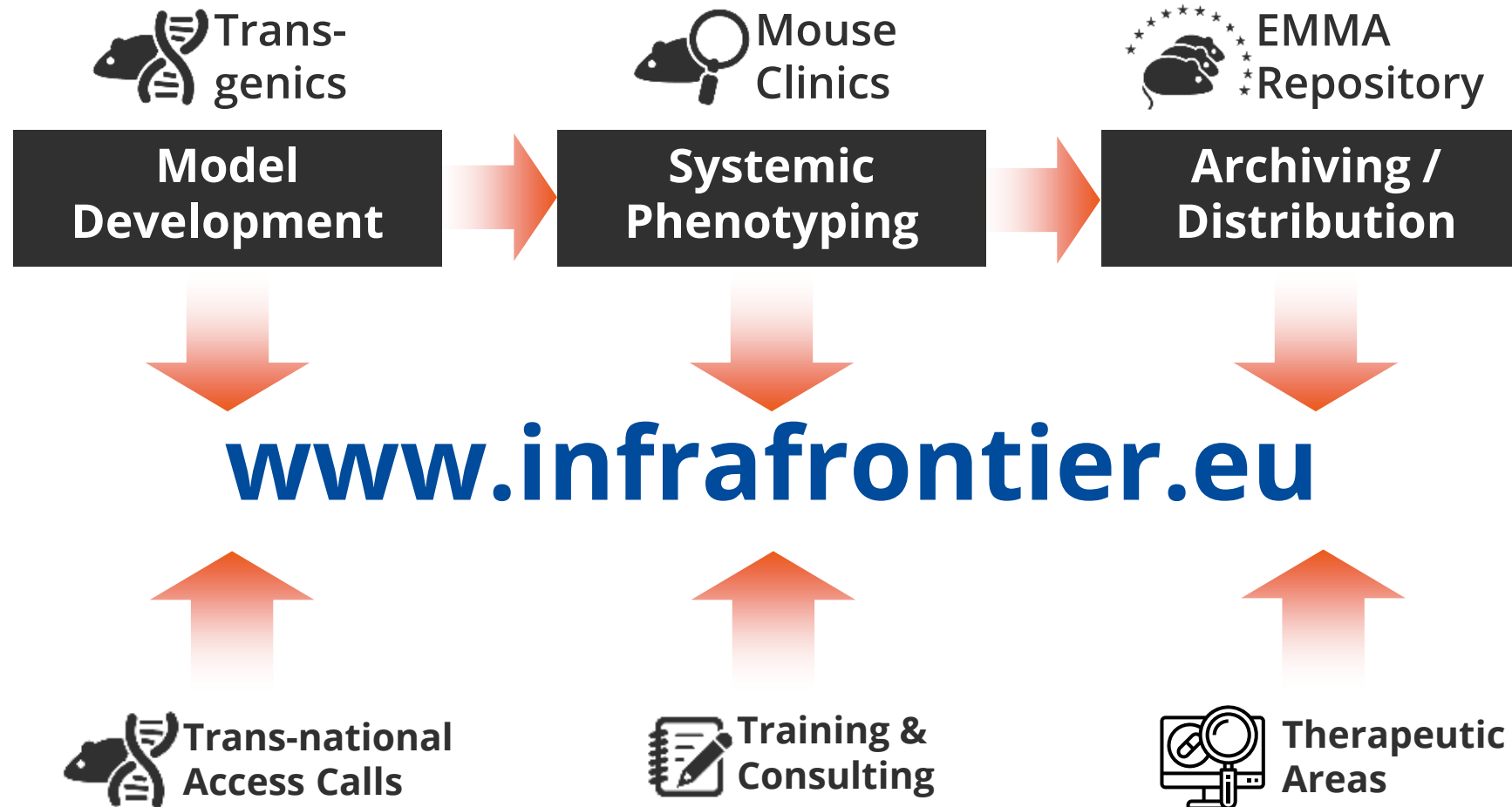


Minimising
duplication by
providing centralised
high-quality resources



INFRAFRONTIER
mouse disease models

INFRAFRONTIER Resources and Services



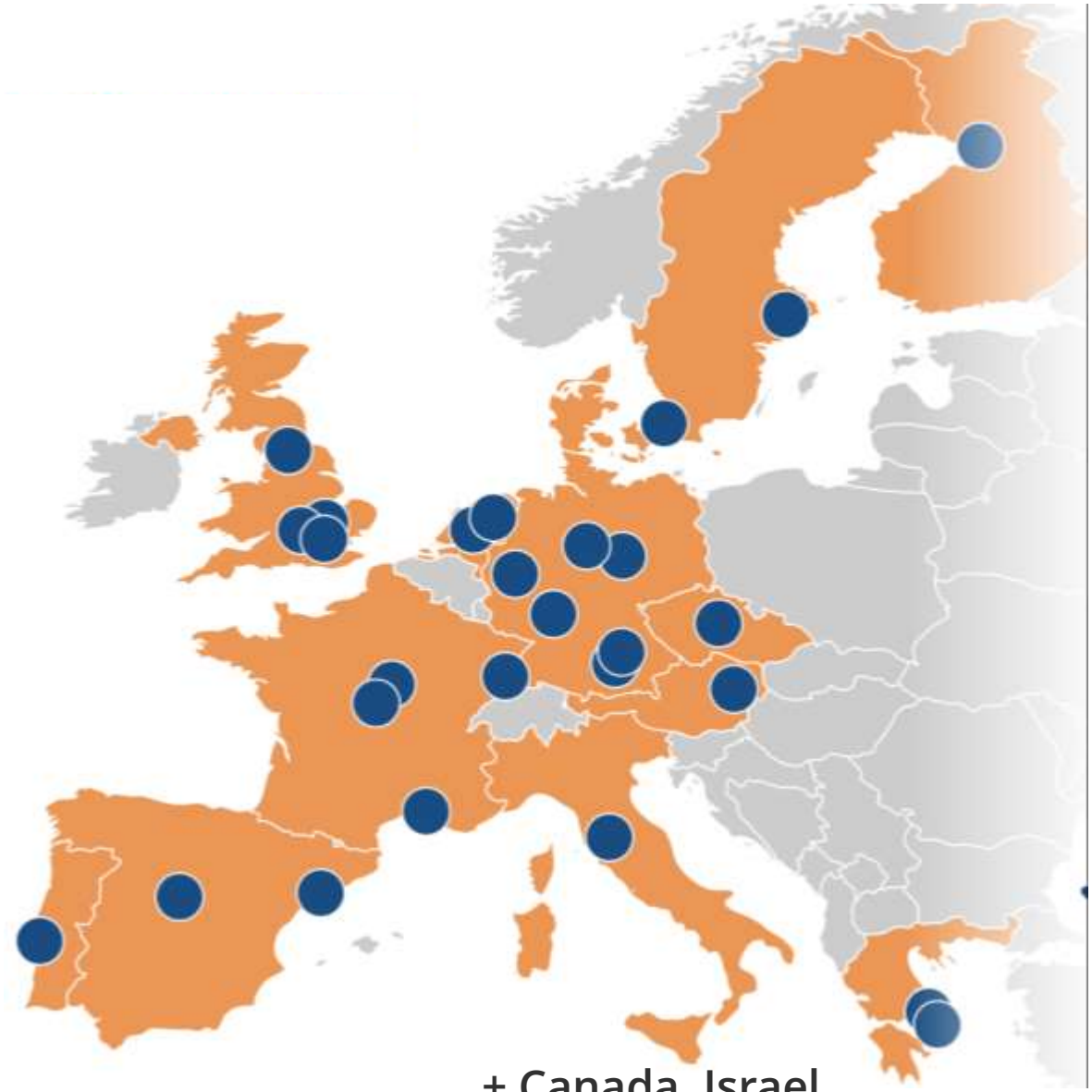
Distributed research infrastructure – one face to the customer



INFRAFRONTIER
mouse disease models

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

A consortium of leading European
research institutions - **29 partners in
15 countries**



Infrafrontier GmbH



2013



UNIVERSITY of OULU
OULUN YLIOPISTO



**Karolinska
Institutet**



Le Centre nationale de la
recherche scientifique



IMG

Institute of Molecular Genetics of the ASCR, v.v.i.

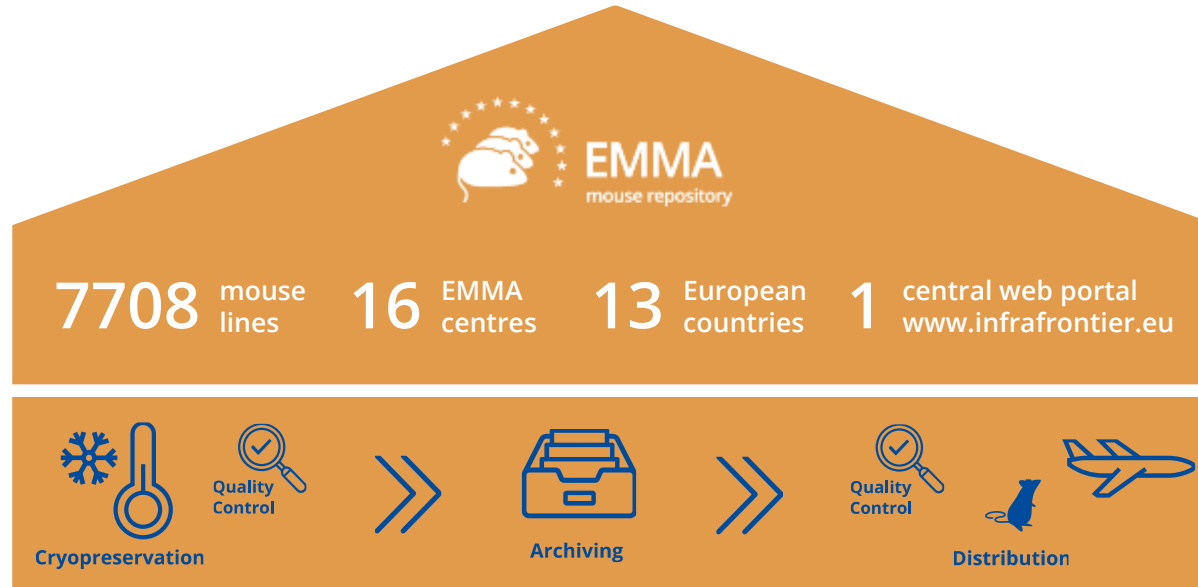
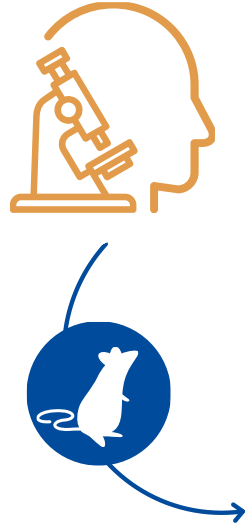
HelmholtzZentrum münchen

German Research Center for Environmental Health

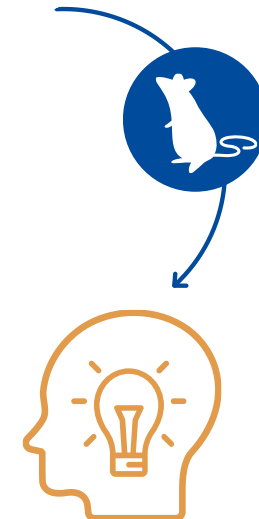


"ALEXANDER FLEMING"
Biomedical Sciences Research Center

The European Mouse Mutant Archive (EMMA)



- **Open access to more than 7708 mouse lines**
- High-quality health controlled mice with defined and verified genotype
- EMMA ships globally



EMMA: current members

16 nodes / 13 countries



CNR/IBC

Istituto di Biologia Cellulare, Monterotondo, Italy

CNRS/CDTA

Centre de Distribution, de Typage et d'Archivage animal, Orléans, France

MRC/MGU

Mammalian Genetics Unit, Harwell, UK

Karolinska Institutet

Karolinska Institutet, Stockholm, Sweden

FCG/IGC

Instituto Gulbenkian de Ciência, Oeiras, Portugal

HMGU/IEG

Institute of Experimental Genetics, Munich, Germany

EMBL/EBI

European Bioinformatics Institute, Hinxton, UK

GIE-CERBM/ICS

Institut Clinique de la Souris, Illkirch/Strasbourg, France

Sanger Institute

Wellcome Trust Sanger Institute, Hinxton, UK

CNB/CSIC

Centro Nacional de Biotecnología, Madrid, Spain

Fleming

Biomedical Sciences Research Center Al. Fleming, Athens, Greece

OULU

University of Oulu, Oulu, Finland

BIAT

Vetmeduni Vienna, Biomodels Austria, Vienna, Austria

IMG

Institute of Molecular Genetics, Prague, Czech Republic

TAU

Tel Aviv University, Tel Aviv, Israel

NKI

Netherlands Cancer Institute, Netherlands, Amsterdam



www.infrafrontier.eu

EMMA Shipping Destinations

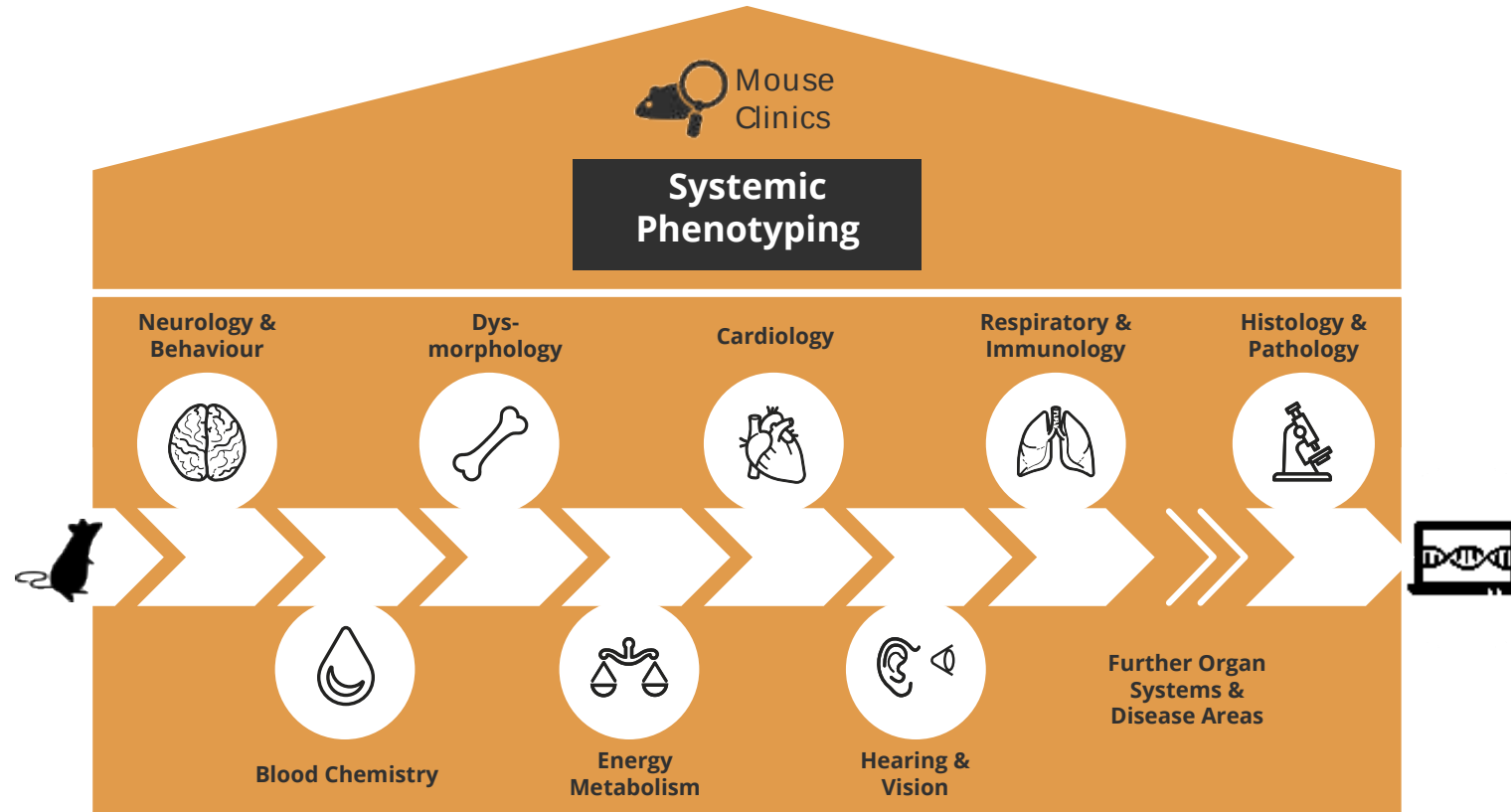


© 2020 Mapbox © OpenStreetMap



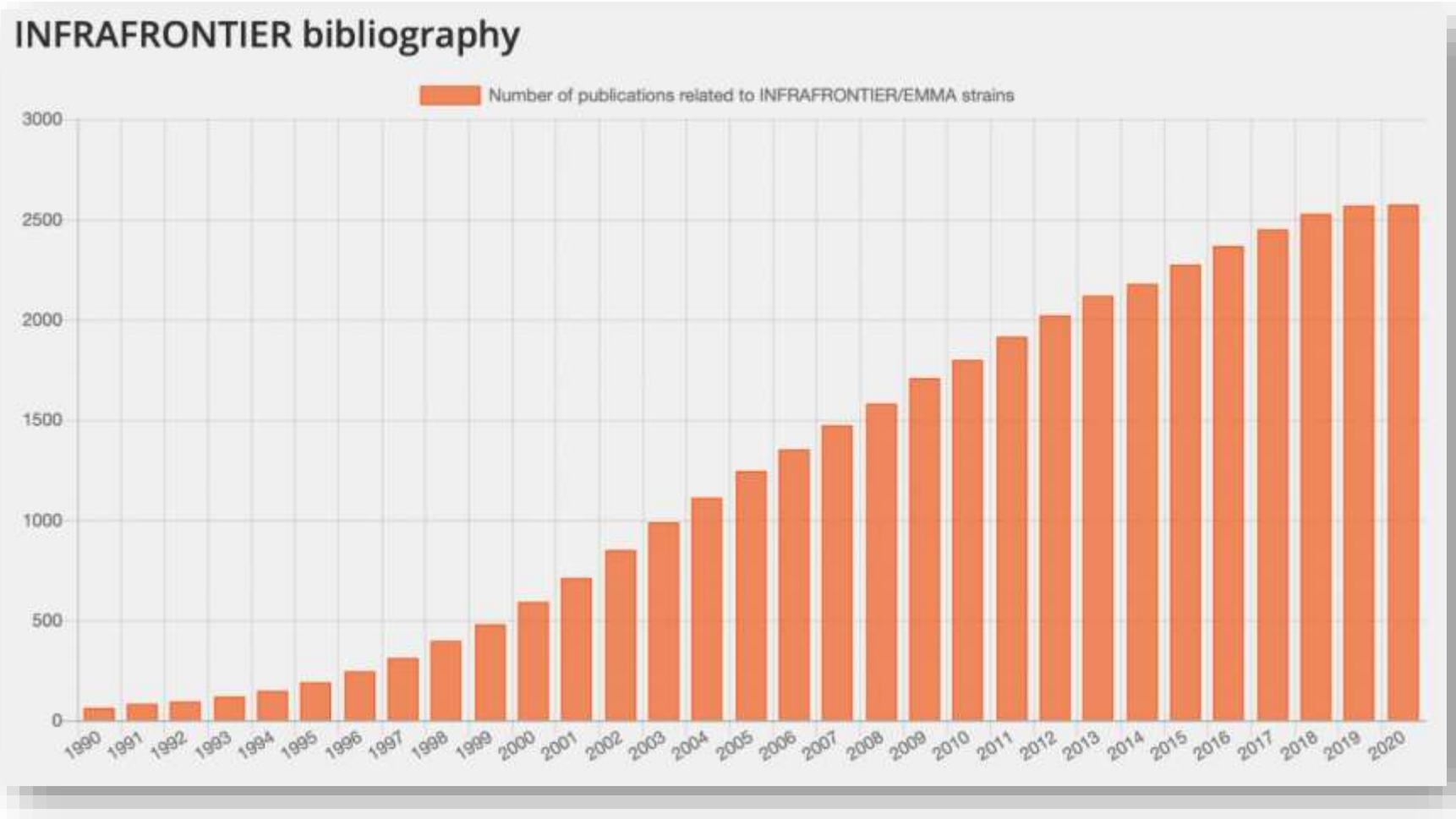
>700 unique
destinations
(cities)
worldwide

Systemic phenotyping and mouse clinics



- Mouse clinics offer a **whole-system screen** covering more than 500 parameters in different disease areas and organ systems
- Added benefit of obtaining **maximum information** using a **minimum amount of animals**

Publications related to INFRAFRONTIER / EMMA



- **2574** publications; both from strain submissions and strain requests
- **49** Cell publications
- **43** Nature Genetics publications
- **82** Nature publications

INFRAFRONTIER and IMPC

- International **M**ouse **P**henotyping Consortium
- Systemic phenotyping of knock-out mice for all ~20.000 protein coding genes → **comprehensive catalogue of gene function**
- Phenotyping data and mice are made **openly available** to the biomedical community
- **INFRAFRONTIER is the largest distributor of IMPC lines worldwide - 350 shipments per year**





We're Celebrating Our 10 Year Anniversary!

The IMPC is celebrating 10 years of research and mouse knockout production. We are launching a series of thematic workshops starting on October 25th, 2021 and recently hosted the Celebratory Conference on Mouse Genetics and Genomic Medicine

[Read more on our upcoming workshops](#)

[GENES](#)

[PHENOTYPES](#)

[HELP, NEWS, BLOG](#)

Search All 7824 Knockout Data...



[! What you need to know about IMPC data](#)

www.mousephenotype.org



7824 total knockout genes
phenotyped

IMPC Data Release 15.1 Notes

IMPC

- Release: 15.1
- Published: 11 October 2021

Statistical Package

- OpenStats
- Version: 1.4.0

Genome Assembly

- Mus musculus
- Version: GRCm38

Summary

- Number of phenotyped genes: 7.824
- Number of phenotyped mutant lines: 8.457
- Number of phenotype calls: 90.010

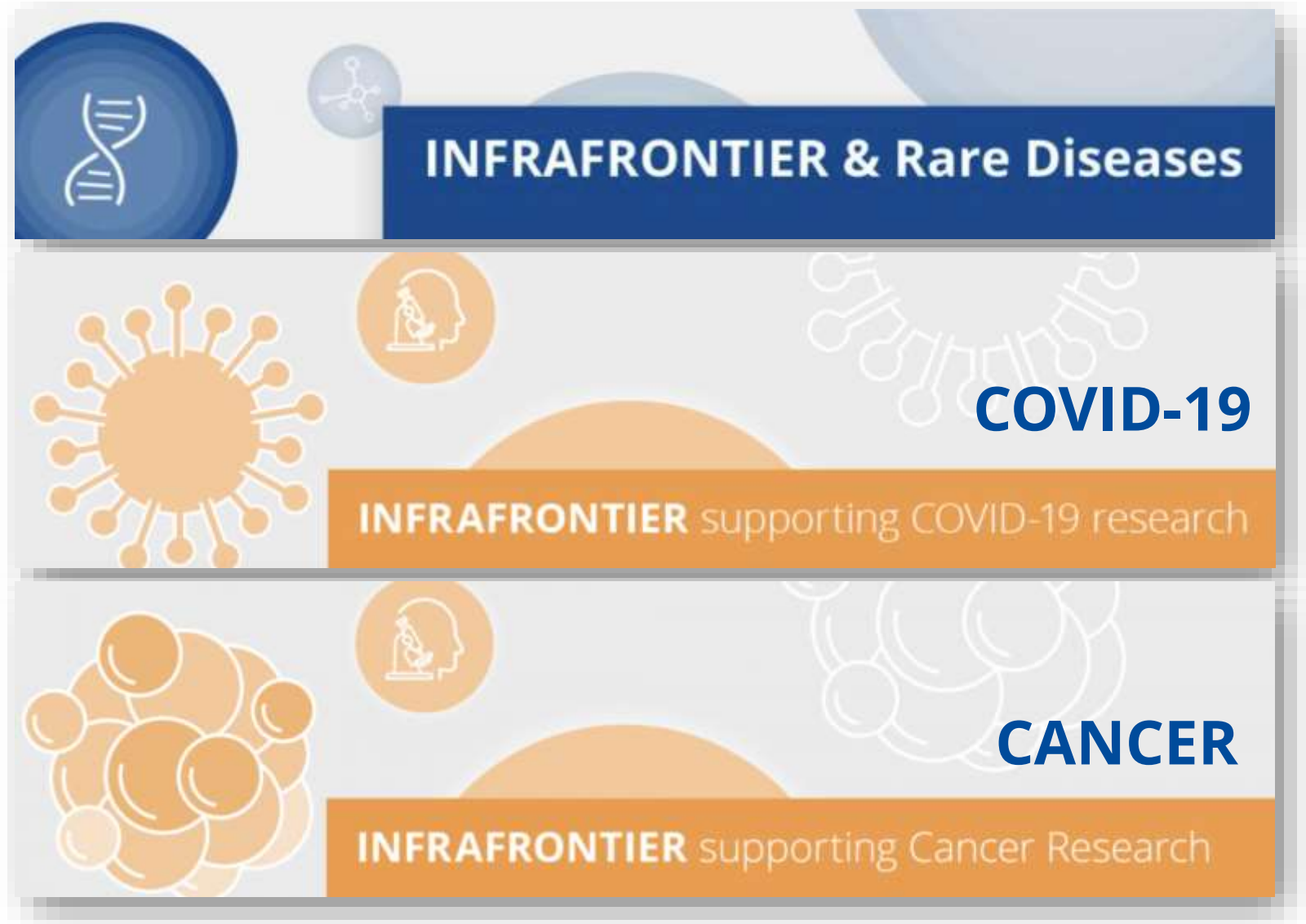
Data access

- Ftp interface: ftp
- RESTful interfaces: APIs

www.mousephenotype.org

INFRAFRONTIER Therapeutic Areas

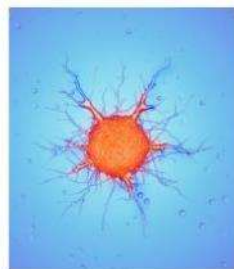
Collection of
INFRAFRONTIER
resources and services
related to a therapeutic
area in one page



INFRAFRONTIER resources for



Covid-19
research



Cancer
research



Rare Diseases
research

Resources and Services

Deposit mice



EMMA archives your
mouse mutant free of
charge >

Order mice



Access to 8000 mouse
mutants and research
tools >

Axenic service



INFRAFRONTIER produces
germ-free mice free of
charge >

NKI GEMM-ESC archive



Rapid target gene
validation in complex
cancer mouse models >

Mouse production and phenotyping



INFRAFRONTIER open
calls >

Training and consulting



Hands-on courses in
cryopreservation and
phenotyping >

Procedures & Knowledgebase

Information on service fees, legal issues,
health monitoring and animal welfare >

Validated laboratory protocols and a
comprehensive list of relevant
publications >

News & Events

Uqcrrh – a new player in mitochondrial
complex III disorders

[More news and events >](#)

EMMA strains

Search EMMA strains



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

Browse EMMA strains

Collections

Human Diseases

[Help](#)



EMMA strains

Search EMMA strains



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

Browse EMMA strains

Collections

Human Diseases

[Help](#)



www.infrafrontier.eu

[Home](#)

EMMA strain search

[Help](#)**Status:**

- Line available to order
- Only small colony available
- Under development - register interest



Due to the current coronavirus (COVID-19) situation, there may be delays in providing the EMMA services. While traffic restrictions and other measures taken to slow down spreading of the virus are in force, work at EMMA nodes is impaired considerably. Therefore, delivery times will be longer than usual.

Nevertheless, please go ahead and place your orders, so that we can already organize the paperwork with you. Even this could take longer, as people at EMMA nodes or at the involved authorities and carriers might not be able to always go to work, while social distancing is advised. The situation is beyond our control and we will resume all activities whenever our institutions/governments will authorize us to do so.

Thank you for your understanding.

[Browse by Strains](#)**Browse curated disease models**
(by Disease Ontology categories)[Cardiovascular system](#)
[Musculoskeletal system](#)[Endocrine system](#)
[Nervous system](#)[Gastrointestinal system](#)
[Respiratory system](#)[Immune system](#)
[Urinary system](#)[Hematopoietic system](#)[Integumentary system](#)[Cellular proliferation](#)[Mental health](#)[Metabolism](#)[Genetic disease](#)[Syndrome](#)[Show all disease models](#)

Please hover over the submenu to start

Nervous System

Cardiovascular
system

Endocrine system

Gastrointestinal
system

Immune system

Hematopoietic
systemIntegumentary
systemMusculoskeletal
system

Nervous system

Respiratory
system

Urinary system

Cellular
proliferation

Mental health

Metabolism

Genetic disease

Syndrome

Show all disease
models

Found 3 entries

Show

10



entries

Filter:

EMMA ID	Disease name / DOID	gene symbol	common strain name(s)	(International) Strain Designation	Status	
EM:08444	multiple sclerosis / DOID:2377	Tg(Gfap-TNF*)K21Gkl	TgK21 [CBA;B6-Tnfrsf1a ^{tm1Bl} Tg(Gfap-TNF*)K21Gkl/Flmg]	STOCK Tnfrsf1a ^{tm1Bl} Tg(Gfap-TNF*)K21Gkl/Flmg		
EM:00143	multiple sclerosis / DOID:2377 [... view all DOIDs]	Prf1	Pfp-KO	NOD.B6-Prf1 ^{tm1Sdz} /Cnrm		
EM:07765	multiple sclerosis / DOID:2377 [... view all DOIDs]	Prf1	AJ.PKO-/- or AJ.PKO-/+	A.B6-Prf1 ^{tm1Sdz} /Biat		

Showing 1 to 3 of 3 entries

First

Previous

1

Next

Last



**Multiple sclerosis
mouse models
in Infrafrontier**

INFRAFRONTIER Trans-national Access Calls

- One of our main avenues to support biomedical research
- INFRAFRONTIER has published **25 trans-national access calls**
- Selection of projects based on **scientific excellence**
- **More than 400 projects** have been supported
- Recent calls:
 - **Precision model development** (mice, rats)
 - Derivation of **germ-free mice**
 - Late-onset phenotyping for **ageing research**
 - Specialised phenotyping (**metabolic, behavioural, inflammatory**)
 - **COVID-19 Therapeutics Pipeline**

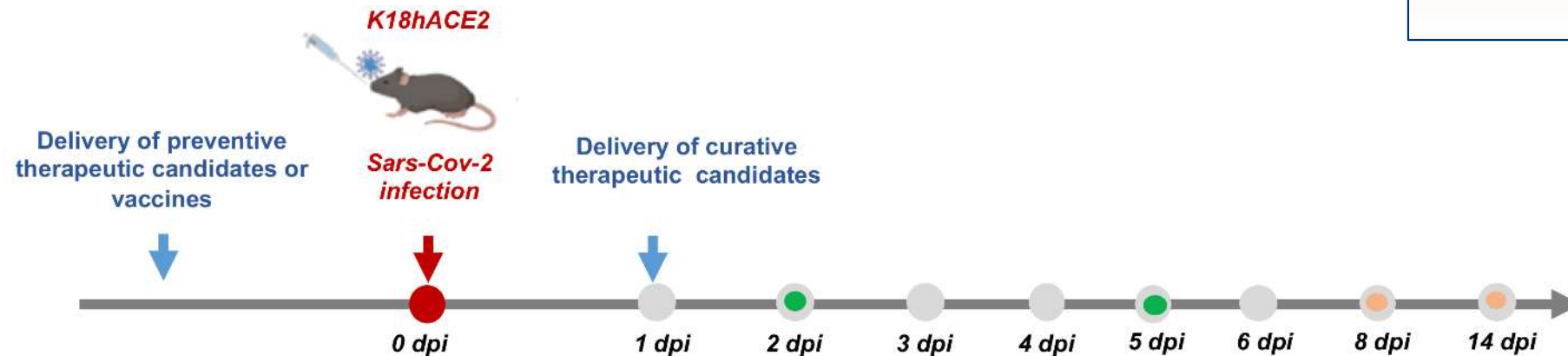
NEW!!!



New TA – COVID-19 Therapeutics Pipeline

- BSL3 pipeline and COVID-19 models
- Test therapeutic candidates
- Further analysis on collaboration

**Application
Deadline: 28
Feb**

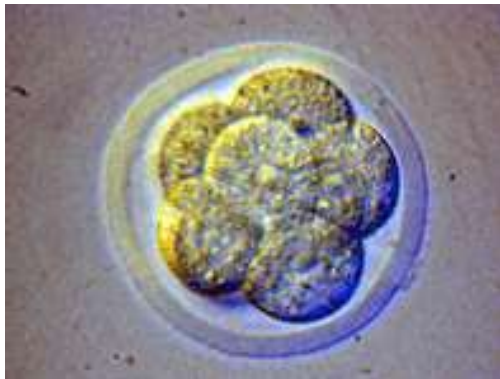


STANDARD Access Unit: Clinical monitoring, scoring and viral load

- ☐ Mice monitored daily for morbidity (body weight), mortality (survival) and scored for clinical symptoms (weight loss, eye closure, appearance of fur, posture, and respiration). ●
- ☐ Viral titers in the lung and brain of infected mice (PFU, TCID50, qRT-PCR) at day 2 and 5 post infection ●



The EMMA-Infrafrontier Spanish node at CNB



EMMA-Infrafrontier Services provided from CNB



- **Depositing mouse lines **into** EMMA**
 - Depositing requests evaluated by external committee
 - Approved requests are cryopreserved for **free**
 - Depositor covers shipping costs
 - Cryopreserved mouse lines freely available to everyone
 - Grace period possible (up to 2 years), MTAs accepted
- **Requesting mouse lines **from** EMMA**
 - Access to EMMA archive requires payment of **repository fee**
 - Frozen sperm/embryos: 1,600 Euros + shipping costs
 - Live mice: 3,200 Euros + shipping costs





Equipment: **ISOLATOR UNITS**

for **EMMA** procedures

(allow **safe importation of mice** from different research centres, irrespective of their health status, without interfering with mice kept at the CNB animal house)





CNB-CSIC Madrid EMMA node

European
Mouse
Mutant
Archive

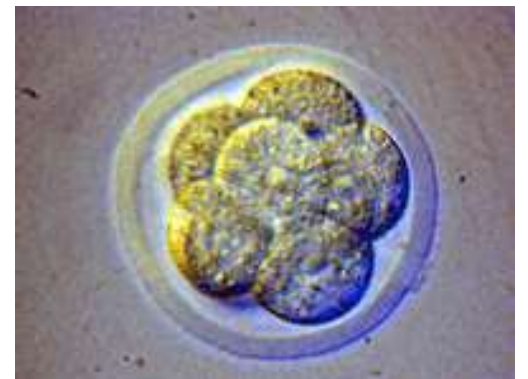


BELL B60
Isolator
(three units)



EMMA procedures at CNB - I

- **Cryopreservation of mouse strains**
 - Cryopreservation of mouse embryos, sperm, oocytes
 - Genotyping (single embryos) and quality control
- **Rescue of mouse strains from frozen material**
 - Thawing of mouse embryos, sperm, oocytes
 - In vitro fertilization and embryo transfer
 - Genotyping and quality control



EMMA procedures at CNB - II

- **Importing mouse lines**
 - Receiving frozen mouse embryos (LN₂)
 - Receiving frozen mouse sperm (LN₂ and dry ice)
 - Receiving refrigerated mouse embryos (+4/+8°C)
 - Receiving refrigerated mouse epididymes (+4/+8°C)
 - Receiving live mice
- **Exporting mouse lines**
 - Shipping frozen mouse embryos (LN₂)
 - Shipping frozen mouse sperm (LN₂ and dry ice)
 - Shipping refrigerated mouse embryos (+4/+8°C)
 - Shipping refrigerated mouse epididymes (+4/+8°C)
 - Shipping live mice



The CARD cold transportation kit



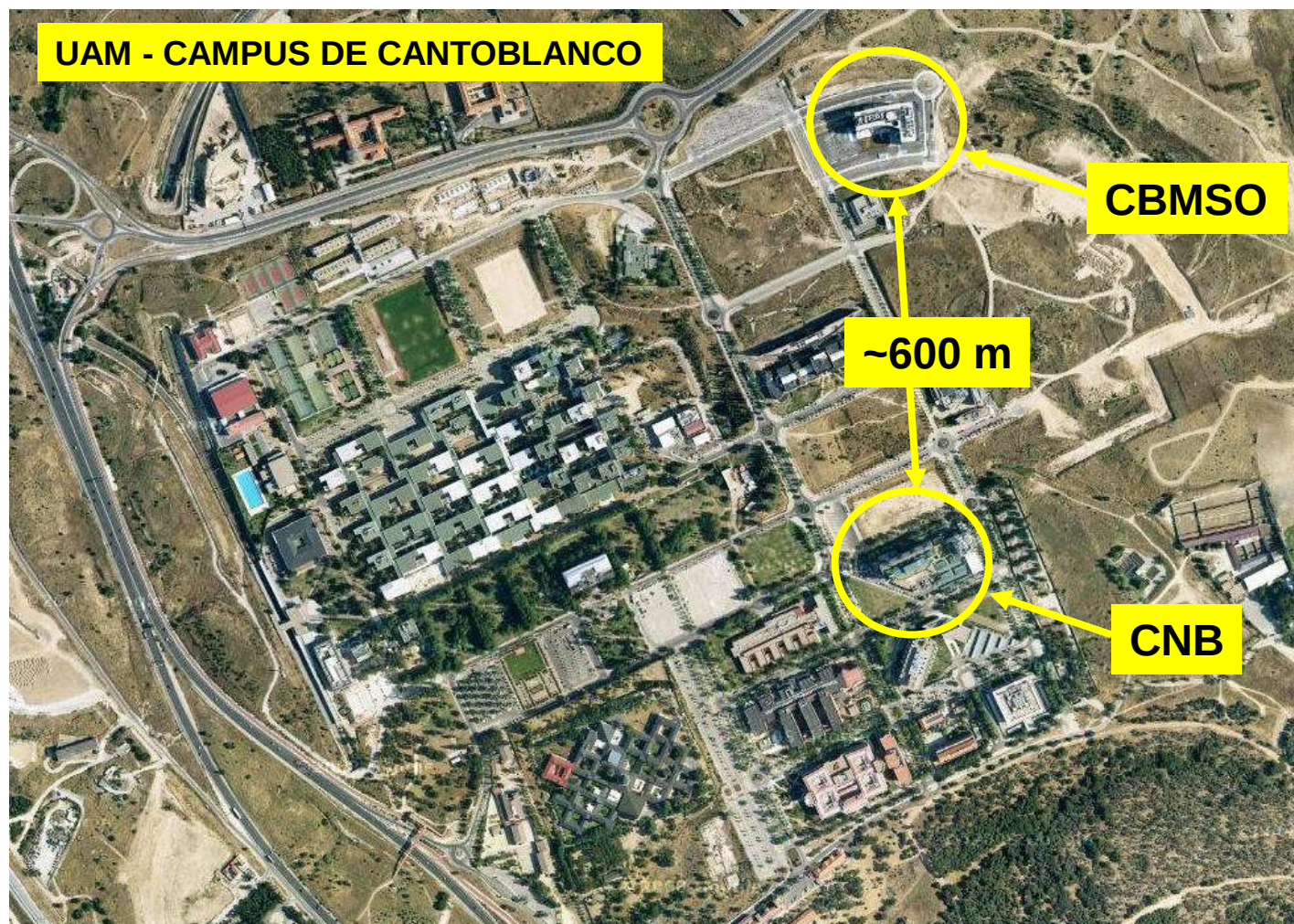


- Cryopreserved mouse sperm and embryo simples kept in LN2 tanks totally immersed
- Backup samples stored at a second independent location in Campus



CNB-CSIC Madrid EMMA node

European
Mouse
Mutant
Archive



SPLIT ARCHIVE AT THE SPANISH EMMA NODE at CNB-CSIC

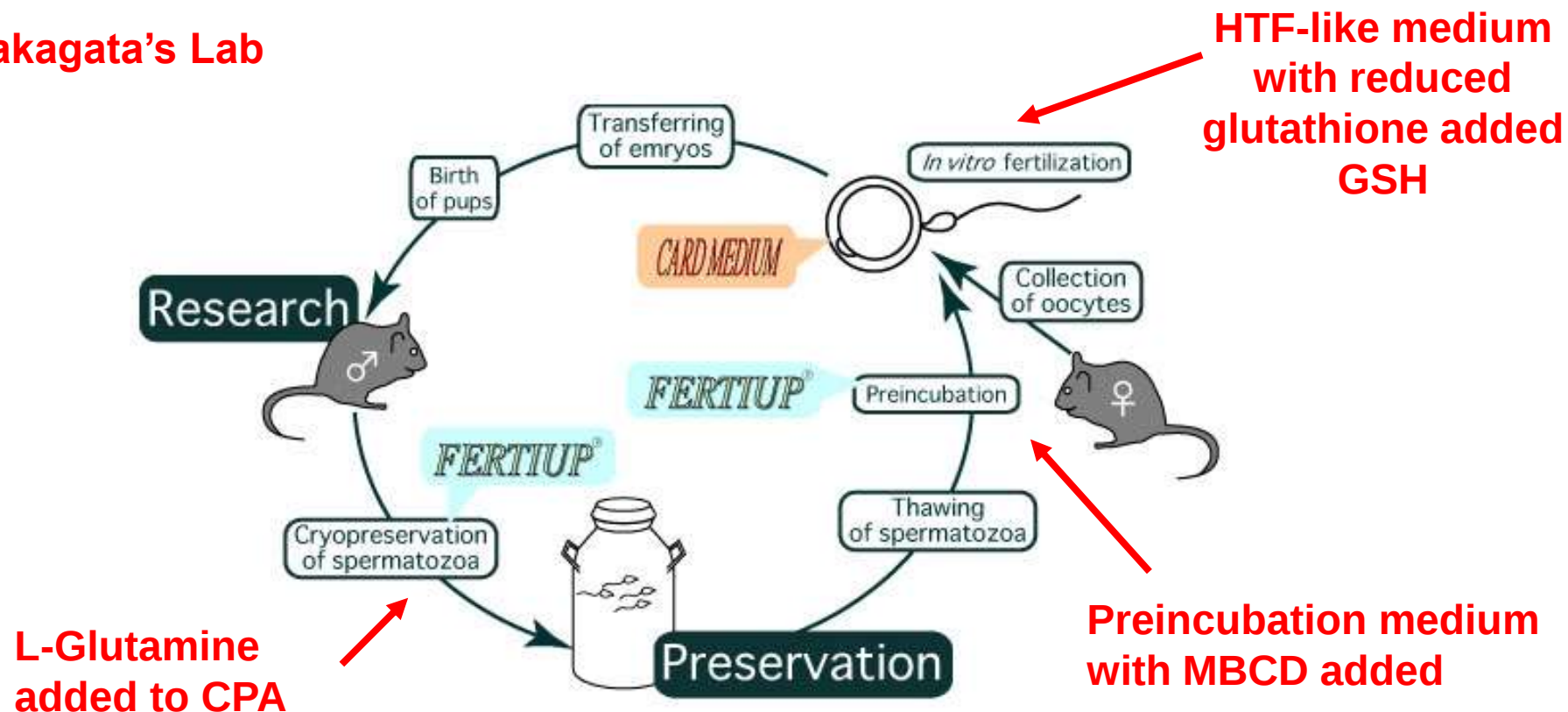






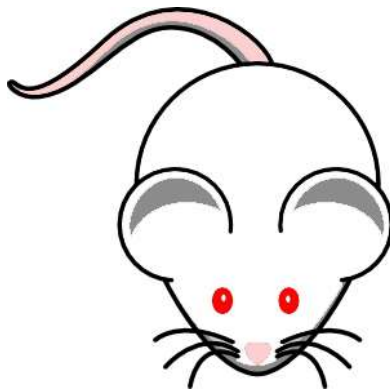
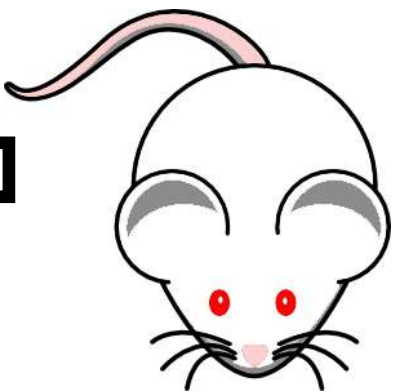
The *CARD* revolution

Nakagata's Lab



KYUDO and Cosmo Bio Co., Ltd. Japan (www.cosmobio.co.jp)

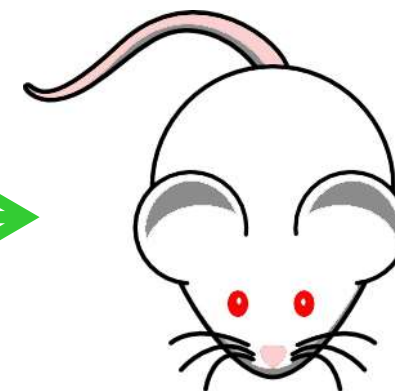




IVF



QC OK



FREEZE



THAW

SPERM CRYOPRESERVED

FREEZE



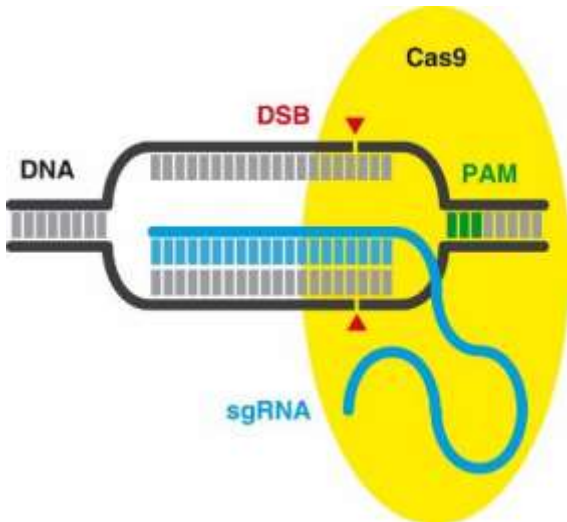
THAW

EMBRYOS CRYOPRESERVED

RESCUE

EMMA procedures at CNB - III

- Rederivation of mouse strains (into SPF zone)
- Generation of knockout mice from ES cell clones (TNAs)
- Generation of genome edited (CRISPR) mice (TNAs)
 - Advice / experimental design / guide RNA selection
 - Gene disruptions
 - Gene deletions/inversions
 - Gene substitutions/mutations (ssDNA oligos)
 - Electroporation of mouse embryos
 - Embryo transfer into pseudopregnant females



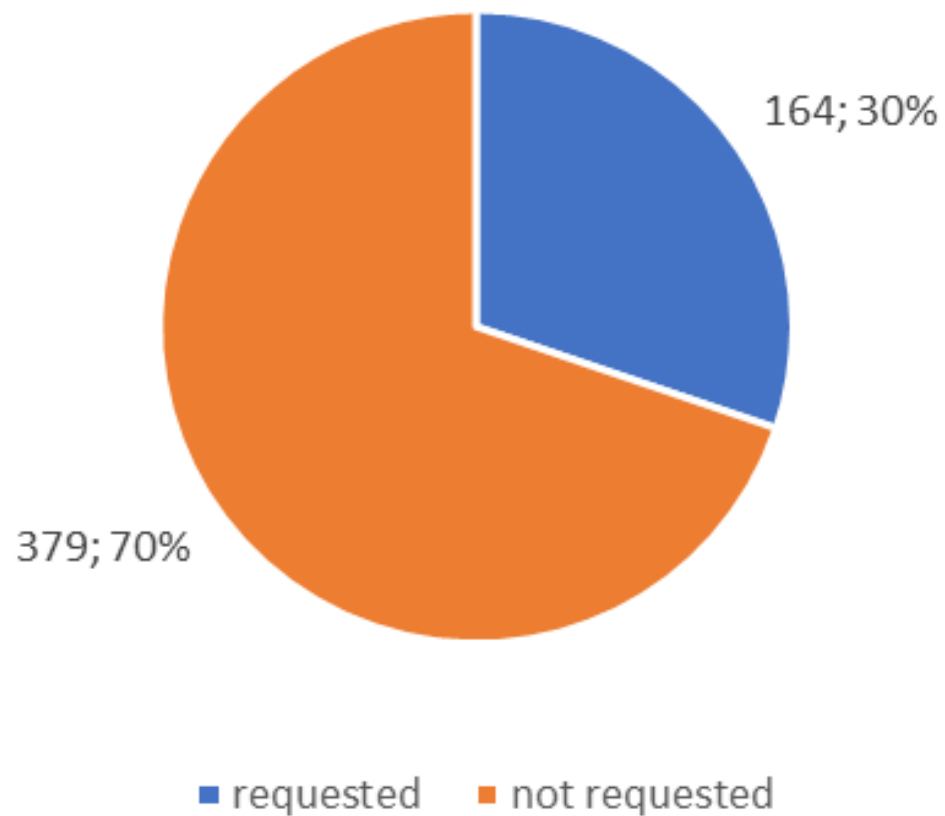
www.user.cnb.csic.es/criocnb/



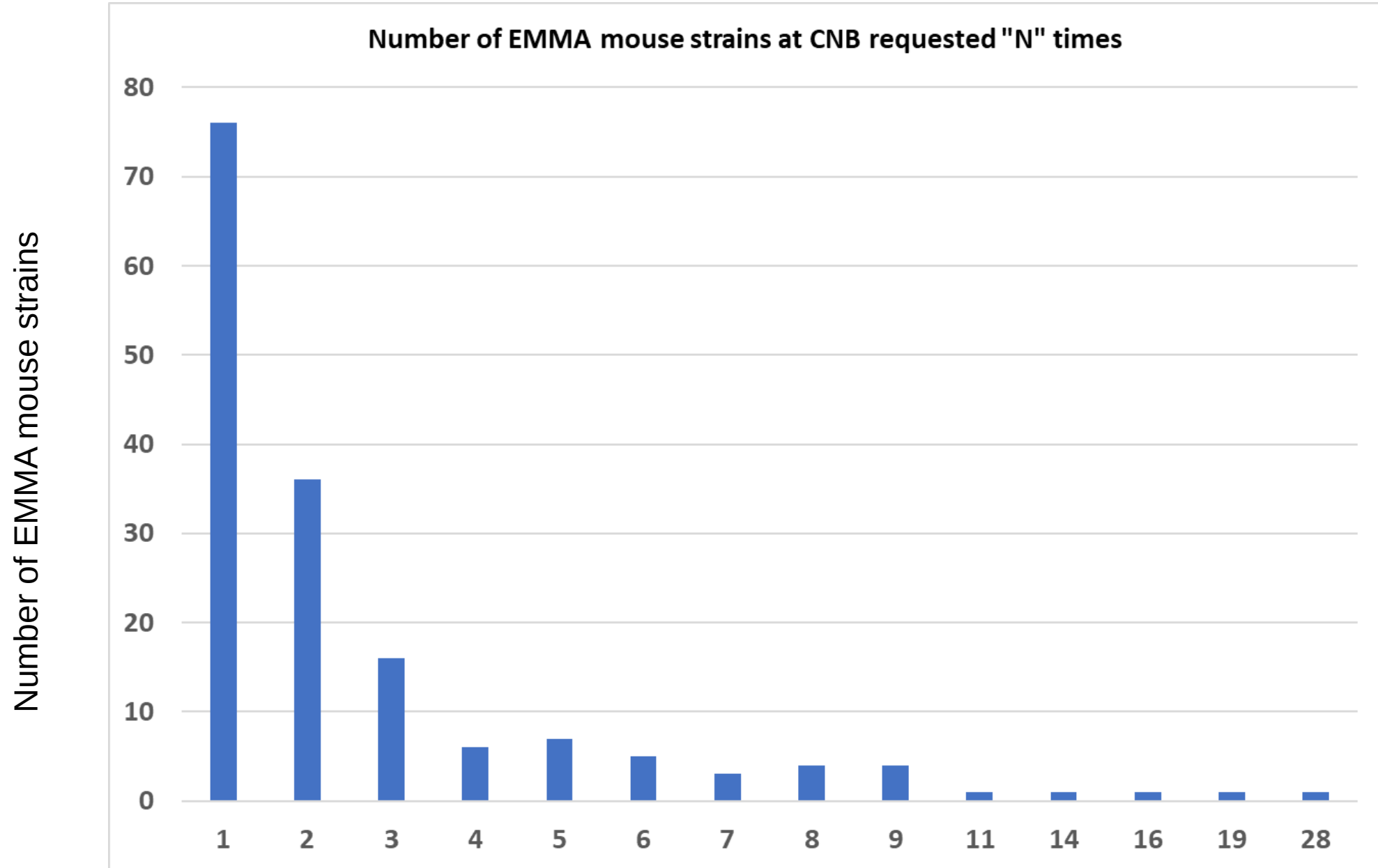
Infrafrontier and CRISPR licensing



EMMA Infrafrontier mouse lines at CNB



EMMA lines in total: 7708
EMMA lines at CNB: 543



164 mouse lines requested

Number of times requested

Impact of INFRAFRONTIER on ANIMAL WELFARE

- Number of animals “saved” (not bred, not born, not used) because they are cryopreserved
- ~50 animals/year needed to maintain a colony
- ~ 7.000 mouse lines archived in EMMA-INFRAFRONTIER
- Up to 350.000 mice per year

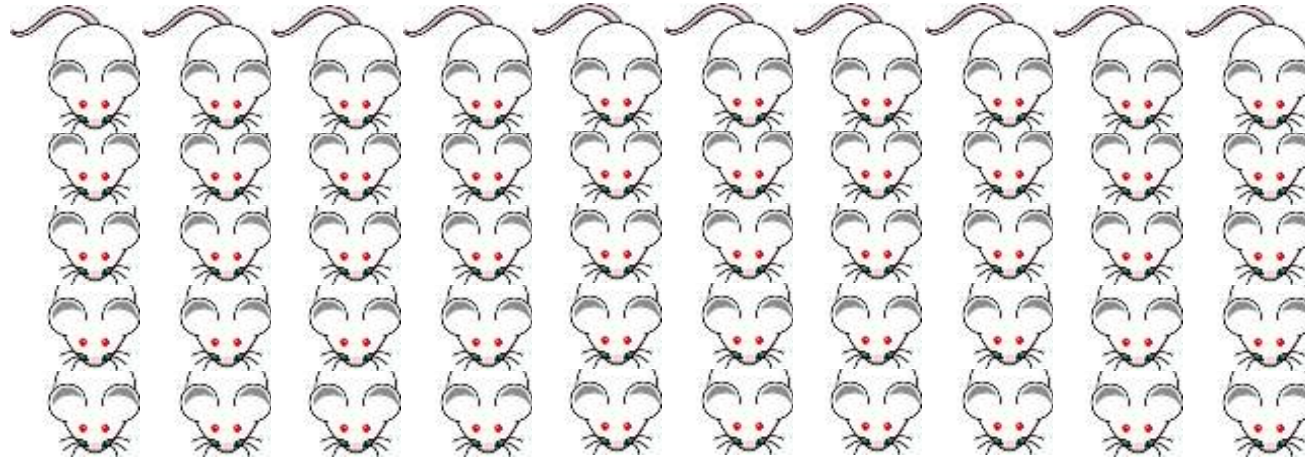
REDUCTION

BEFORE: to cryopreserve **ONE** mouse line

We required 8-10 males from the mouse line to be cryopreserved



We crossed the males 1:1 once per week during **5-6 weeks**



REDUCTION

TODAY: to cryopreserve **ONE** mouse line

We require 2-5 males from the mouse line to be cryopreserved



We obtain oocytes from 2-5 females for IVF



IVF and Cryopreservation methods extremely refined (CARD, Univ. Kumamoto)

From **60-70** mice to **4-10** mice in **1 day** per **ONE** line to be cryopreserved

REFINEMENT

Transgenic Res
DOI 10.1007/s11248-015-9897-1



TECHNICAL REPORT

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

**Ferdinando Scavizzi · Edward Ryder · Stuart Newman · Marcello Raspa ·
Diane Gleeson · Hannah Wardle-Jones · Lluís Montoliu · Almudena Fernandez ·
Marie-Laure Dessain · Vanessa Larrigaldie · Zuzana Khorshidi · Reetta Vuolteenaho ·
Raija Soininen · Philippe André · Sylvie Jacquot · Yi Hong ·
Martin Hrabe de Angelis · Ramiro Ramirez-Solis · Brendan Doe**

Received: 25 March 2015 / Accepted: 9 July 2015
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**CNB Mouse Embryo
Cryopreservation
Facility
Spanish EMMA node**

Julia Fernández
María Jesús del Hierro
Marta Castrillo
Cristina Bernal
Inés Arroba
Lluís Montoliu



INFRAFRONTIER
mouse disease models



www.user.cnb.csic.es/criocnb/



Marta
Castrillo

M^a Jesús
Del Hierro

Inés
Arroba

Julia
Fernández

Cristina
Bernal



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