



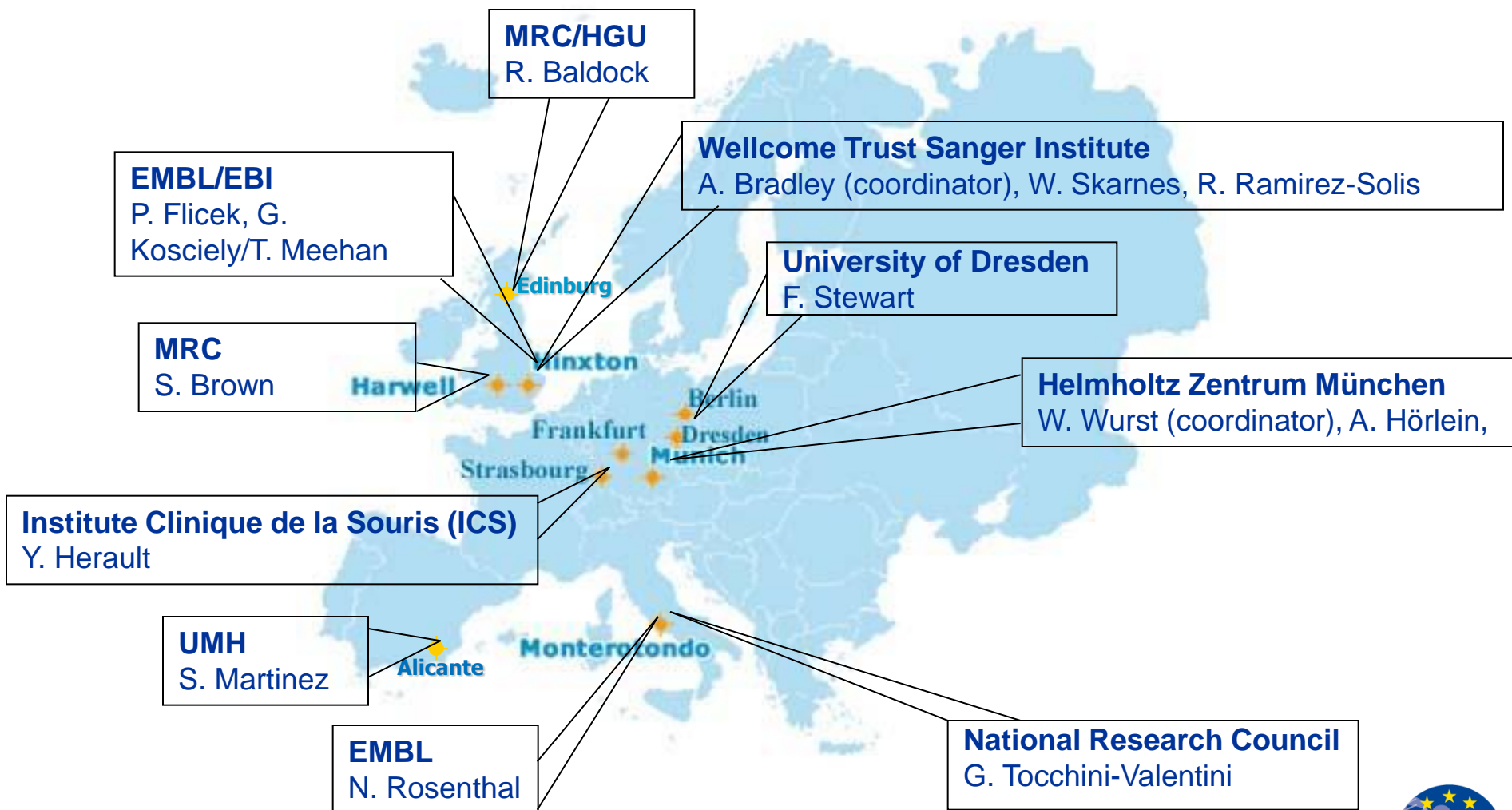
Infrafrontier

Munich, 8-9th May, 2014

EUCOMMTOOLS – IKMC Mutant ES Cell Resource
Wolfgang Wurst



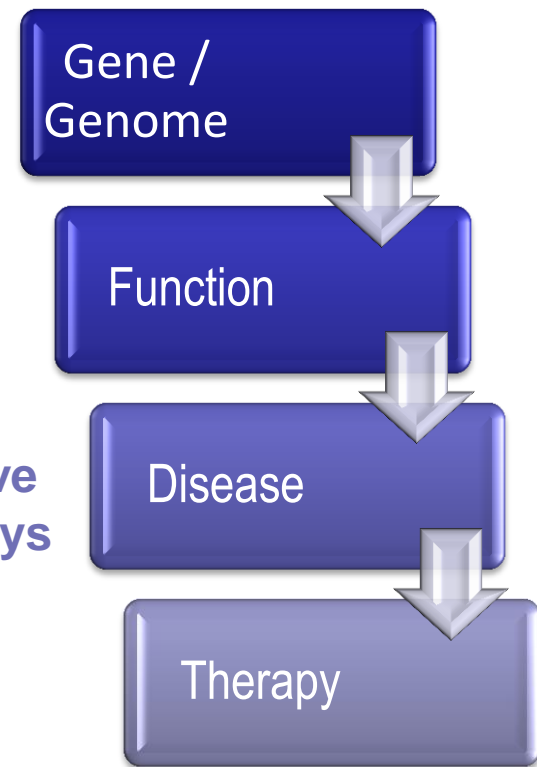
EUComm – TOOLS for
Functional Annotation of
the Mouse Genome





Challenges for the functional annotation of the mammalian genome

- » **IKMC: Generation of conditional mutations in every gene of the genome**
- » **IMPC: Characterization of the phenotype of every mutated gene**
- » **Generation of models for human disease – comparative analysis of disease relevant protein/metabolic pathways**
- » **Basis for individualised therapy development**





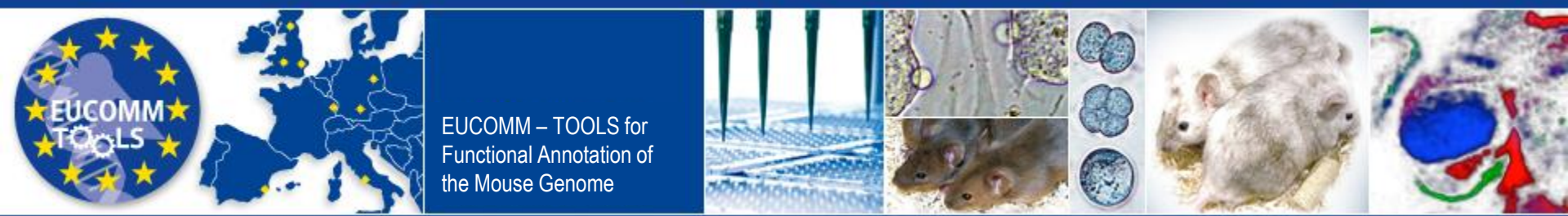
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International Knock-out Mouse Consortium (IKMC): *EUComm, KOMP, NorCOMM, TIGM*

Objectives:

- » Providing mutations of all 20.000 protein coding genes (conditional) in ES cells
- » Providing genetic tool-kit to modify each locus
- » Generation of mutant mouse lines for all 20.000 genes (IMPC)
- » Archiving and distribution of mutant ES cells and mice (germplasm, embryos)
- » Common web portal – one-stop-shop





EUComm/EUCommTOOLS Objectives:

- » Generation of **11.500 conditional gene knockouts**
- » Generation of **350 transgenic mouse line**
- » Establishment of **250 Cre/CreERT driver transgenic mouse lines** covering all organs and major cell types
- » Develop **new conditional technologies**
- » **Archiving and distribution** of vectors and ES cells by EuMMCR and mice by EMMA

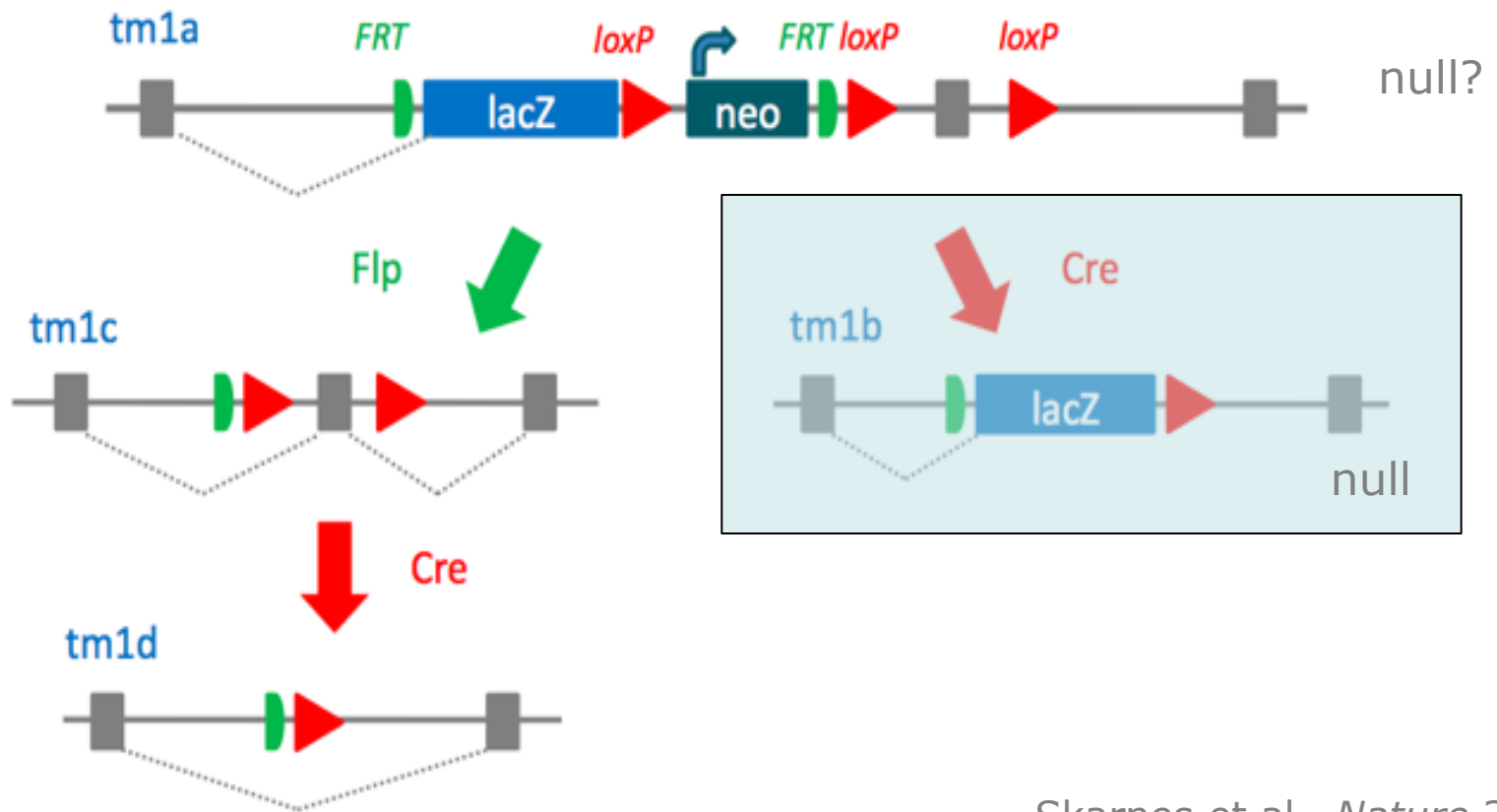


» New Technologies:

- » Universal reporter cassettes
- » Improvements of CreERT2 ligand binding
- » Flp, Dre switches implemented
- » Evaluate limitations of conditional targeting designs (LoxP distance)
- » Flp-ER^{T2}, Dre-ER^{T2} established and validated
- » TALEN/CRISPR/CAS to LoxP and Frt sites designed and generated



Knockout-first allele* EUComm/TOOLS



Skarnes et al., *Nature* 2011



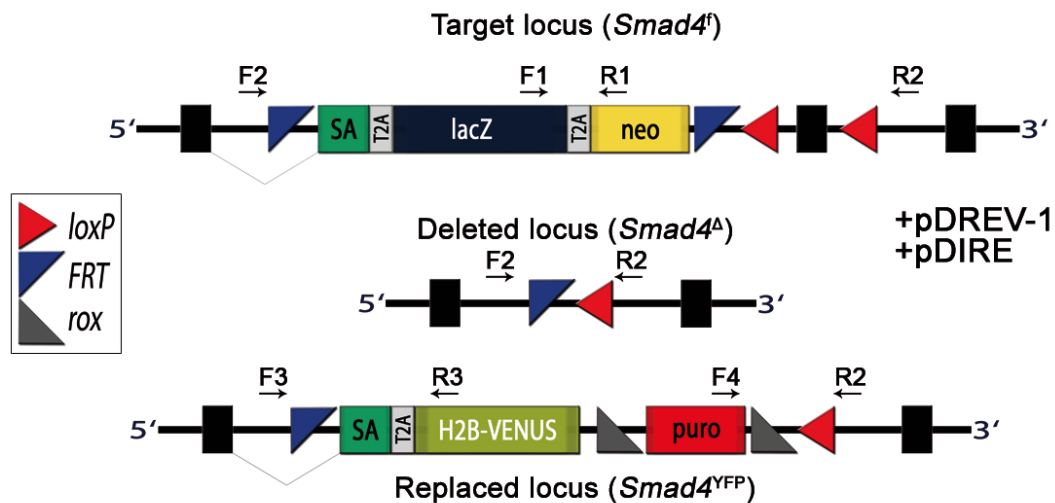
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IKMC alleles

Pipeline	Targeted Genes	Mice
EUComm/EUTOOLS*	8,715	1,572
EUCommTools-Cre*	350	51
KOMP-CSD	5,642	1,266
KOMP-REGN	4,134	830
NorCOMM	594	26
mirKO	243	10
All	19,328	3,755
Unique (gene)	15,481	3,748

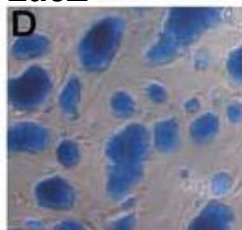
*active pipeline

TOOLKIT EXAMPLE: RMCE KNOCK-IN



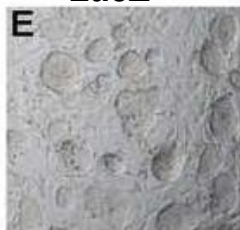
Target Line

LacZ

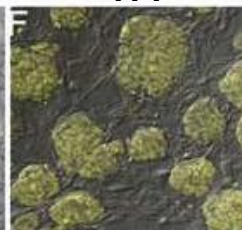


Correct RMCE Clones

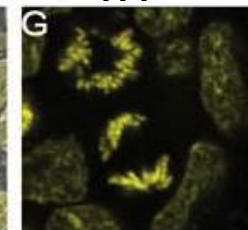
LacZ



YFP



YFP

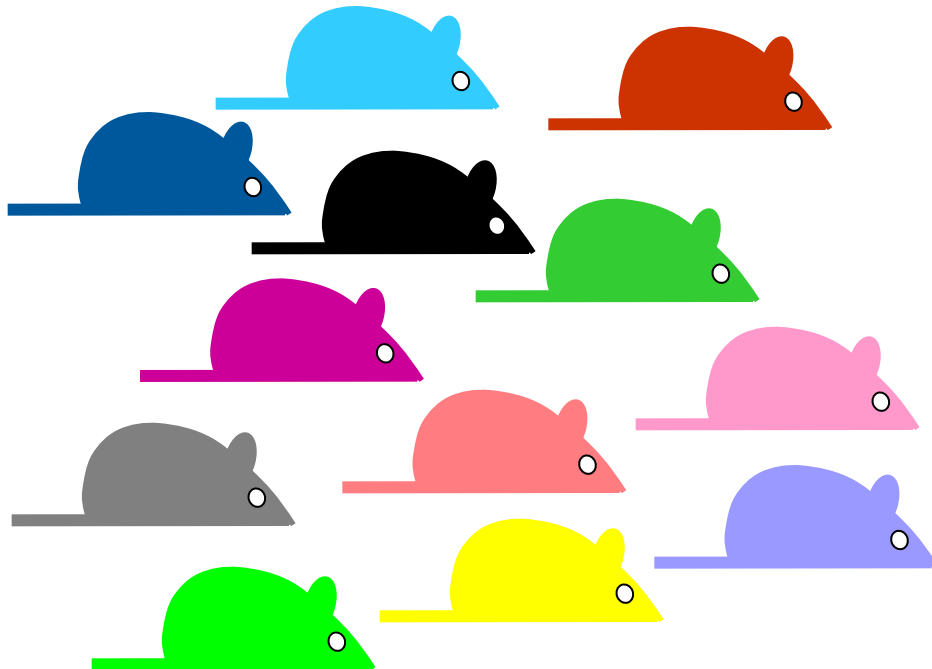


Javier Lopes-Rios, Rolf Zeller



Tissue/cell specific gene inactivation

- 20,000 floxed alleles
- Integrated database
- Hundreds of Cre driver strains
- Scattered databases
- Various background





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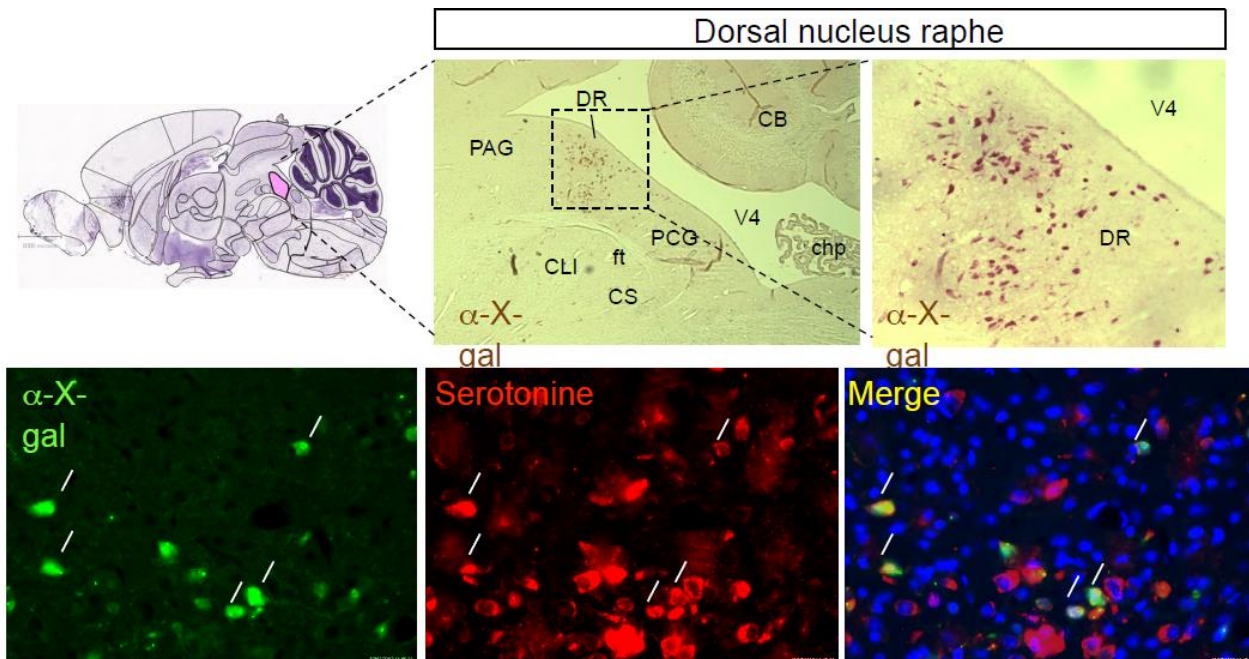
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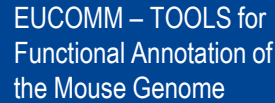
CRE DRIVER RESOURCE

Targeting vector



Ppm1a: protein phosphatase 1a





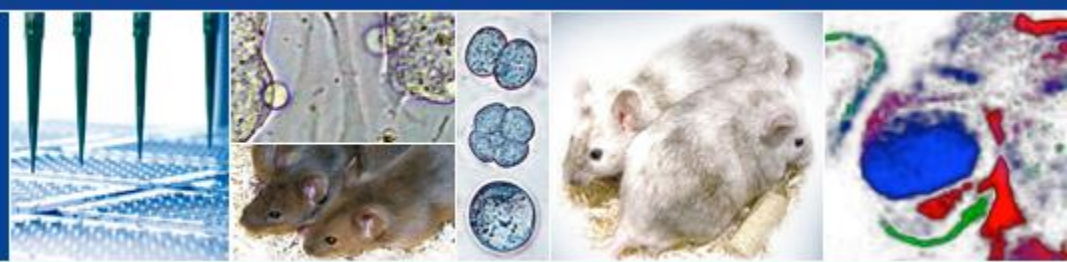
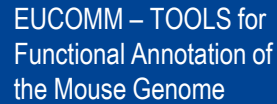
- organ system
- nervous system
- central nervous system
- brain
- forebrain
- diencephalon
- thalamus
- dorsal horn

anterior thalamic group +
dorsal thalamus medial thalamic group (37 gene expression)
basal ventral medial thalamic nucleus
central medial thalamic nucleus
medial dorsal thalamic nucleus
geniculate thalamic group +
intralaminar thalamic group +
lateral thalamic group
midline thalamic group +
posterior thalamic group +

ONTOLOGY COMPARATIVE ANALYSIS:
 MGI vs EUCOMMTOOLS/ALLEN (brain)
 BODY: MGI/EUREXPRESS=EUCOMMTOOLS
EUCOMMTOOLS CELLULAR LEVEL!!!

anterior nuclei			
anterodorsal nucleus			
↓			
	Neurons		
		Projection neurons	
		Interneurons	
	Glia		
		Astrocytes	
		Oligodendrocytes	
		Microglia	
anteroventral nucleus			
↓			
	Neurons		
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		Microglia	
anteromedial nucleus			
↓			
	Neurons		
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		Interneurons	
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		Microglia	



[illegible]



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*active pipeline



www.eummc.org



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Welcome to the EuMMCR - European Mouse Mutant Cell Repository

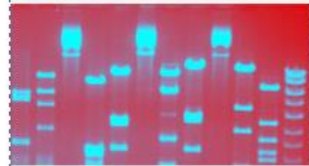
EuMMCR is the distribution unit of EUCOMM. EuMMCR is located at the Helmholtz Zentrum München in Munich, Germany. » [more](#)

Search Genes & Products



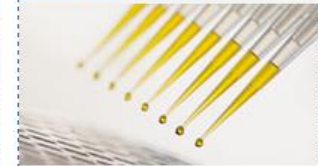
HelmholtzZentrum münchen
German Research Center for Environmental Health

Final Vectors



Final targeting vectors are designed to generate conditional gene mutations. » [more](#)

Intermediate Vectors



Intermediate vectors are building blocks for user-specific vector designs. » [more](#)

Mutant ES Cells



Mutant ES cell clones from the EuMMCR are ready for the generation of conditional knock-out mice. » [more](#)

Chimera Production



EuMMCR intends of offer a Chimera Production Service to generate mice from the EUCOMM ES cell resource. » [more](#)

Distribution of Mice



Mice produced from the EUCOMM ES cell resource are being distributed by the [European Mouse Mutant Archive \(EMMA\)](#). » [more](#)

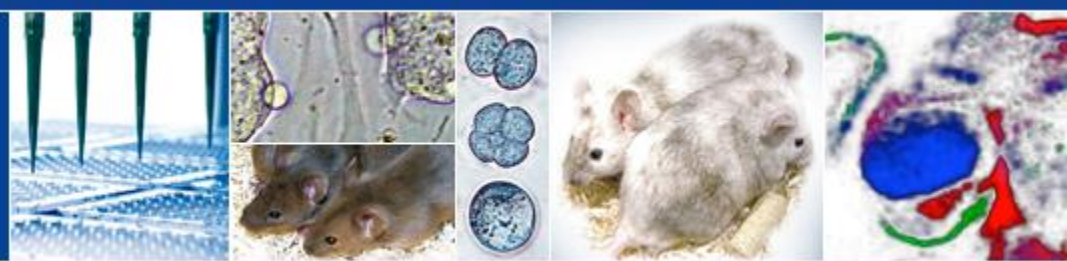
Wild Type C57BL/6N ES Cells



Wild type ES cell strains used for the EUCOMM project are offered for gene targeting experiments. » [more](#)

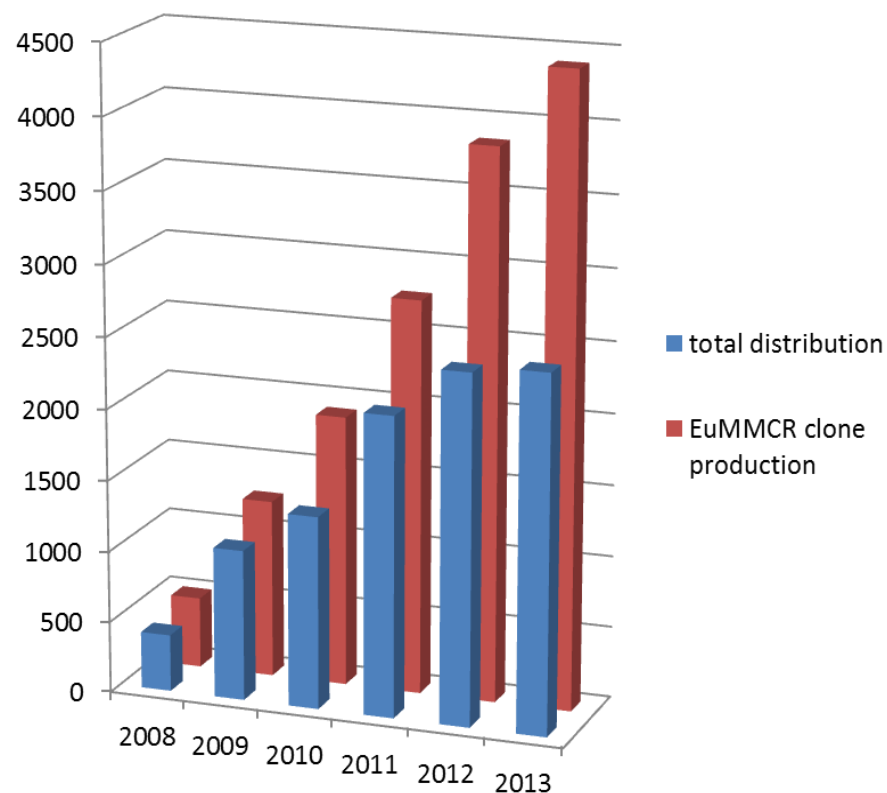


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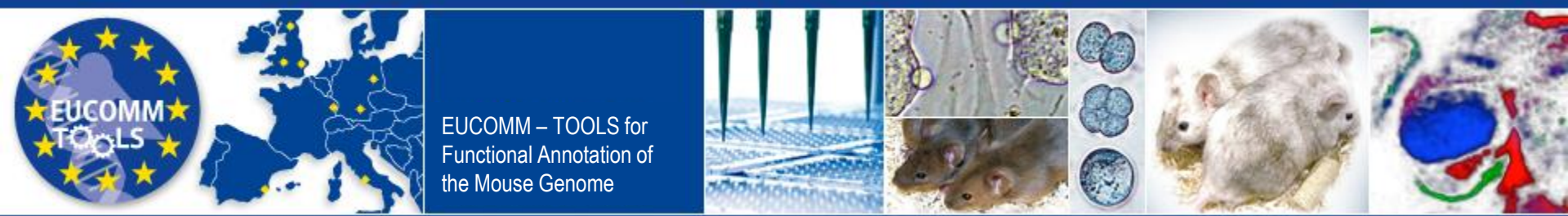
EuMMCR

production & distribution numbers 2008 – 2013

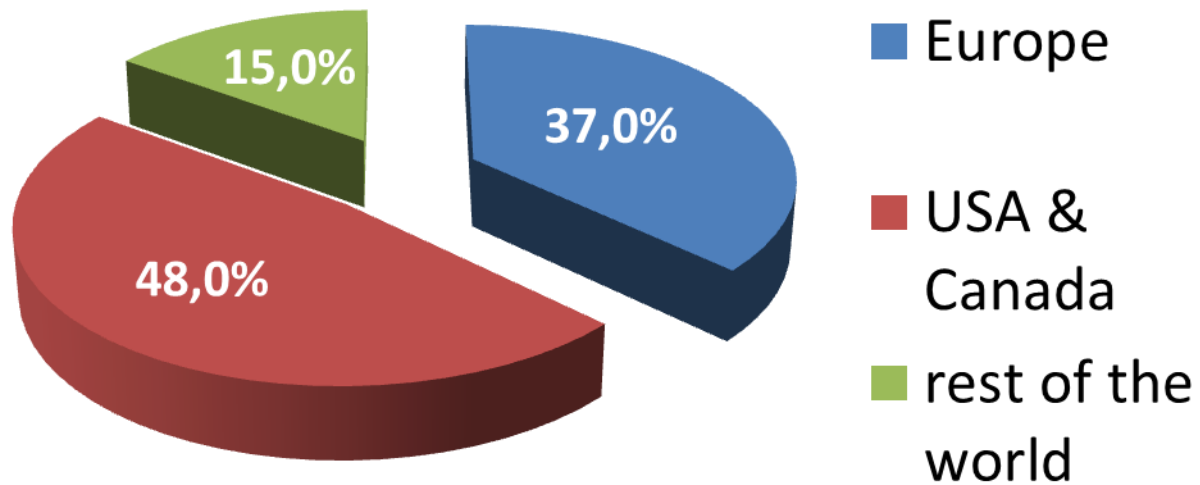


	2008	2009	2010	2011	2012	2013	Total
total distribution	398	1058	1353	2106	2451	2500	9866
EuMMCR clone production	495	1248	1899	2761	3848	4400	14651





EuMMCR distribution, country distribution





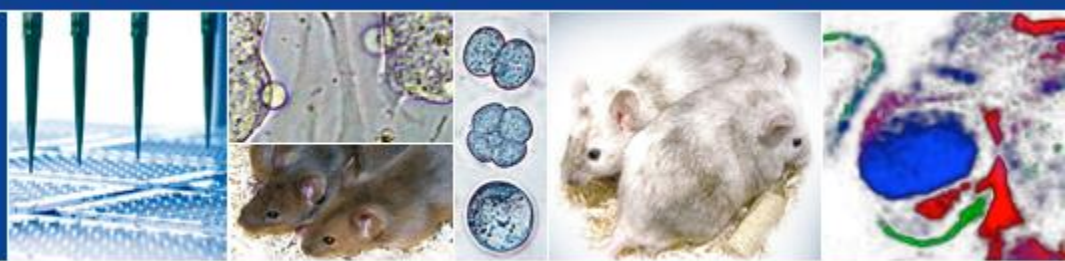
EUComm mouse lines for IMPC

Production center	Mice
WTSI	629
Harwell	249
HMGU	186
BCM	184
ICS	181
Monterotondo	96
TCP	59
JAX	42
MARC	26
UCD	15
Riken BRC	4
Unique (gene)	1606





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INFRAFRONTIER
mouse disease models

Contact

Infrafrontier Research Infrastructure

Resources and services

Procedures

Knowledgebase

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Deposit mice into the EMMA repository

General information

The European Mutant Mouse Archive (EMMA) welcomes submission of mutant mouse strains from all over the world, archives free of charge and facilitates global distribution.

[Read more](#) >

Submission form

After reading the general information about the EMMA archiving service, please use the online submission form to submit your strains to EMMA.

[Submit mice to EMMA](#) >

Resources and services

Deposit mice into the EMMA repository -

[General information](#) >

[Submission form](#) >

[Access to EMMA mouse resources](#) +

[Axenic service](#) +

[Free of charge Transnational Access services](#) +

[Training and consulting services](#) +

Online submission



EMMA

[Submit mice to EMMA](#) >

**EUComm/IKMC
mouse lines:**

Stored: 1,822

Ordered: 1,467

Distributed: 1,229



IMPC webportal

www.mouseknockout.org
www.mousephenotype.org



[HOME](#) [ABOUT IMPC ▼](#) [SEARCH](#) [NEWS AND EVENTS ▼](#) [CONTACT US](#) [MY IMPC ▼](#) [REGISTER](#)

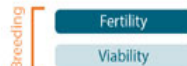
Welcome to the International Mouse Phenotyping Consortium

SEARCH IMPC DATA

Enter your favorite gene in the search box and register your interest or type a standard protocol name and retrieve the parameters measured in IMPReSS.



7M + 7F Mutant Adult Mice



[BROWSE GENE LIST](#)

Find out the latest status of your gene of interest



[REGISTER FOR GENE STATUS UPDATES](#)

Register to be kept up to date in the latest progress of your gene of interest



[PHENOTYPE PROTOCOLS \(IMPRESS\)](#)

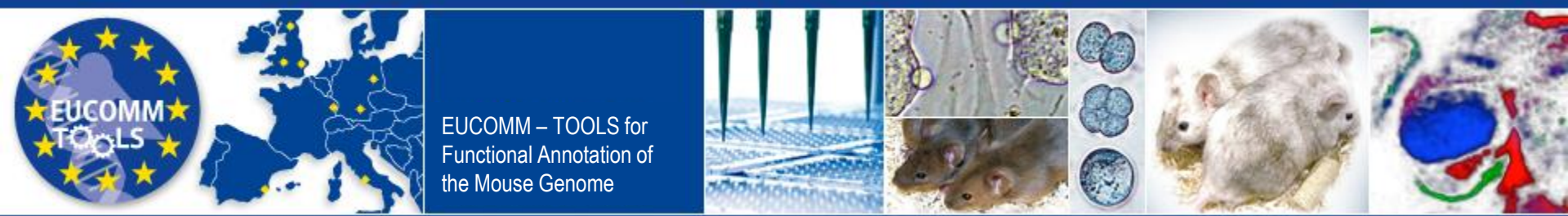
View Phenotype Procedures and Parameters held in the IMPReSS Database



[TRACK MOUSE PRODUCTION \(IMITS\)](#)

Follow microinjection progress and mouse production

Project Status



Outlook:

- Complete knock-out and Cre-driver resource
- Develop additional KO strategies (TALEN, Crisp/CAS)
- Introduce human mutations (cDNA, BAC, point mutations)
- Homozygous mutant ES, iPS cell resource (TALEN, Crisp/CAS)
- Proteine network analysis in vitro and and vivo (tagging)
- Phenotyping all mouse mutants (IMPC)



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EUCommTOOLS Consortium

Helmholtz Zentrum München

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Seisenberger • Antje Bürger**

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• Tony West • Derek Matthews • Haydn Prosser
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MRC-MGU Harwell

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Martin Fray**

MRC-HGU Edinburgh

Richard Baldock



