Celphedia

CELPHEDIA, a French Research Infrastructure, a reference center for animal research on rare diseases

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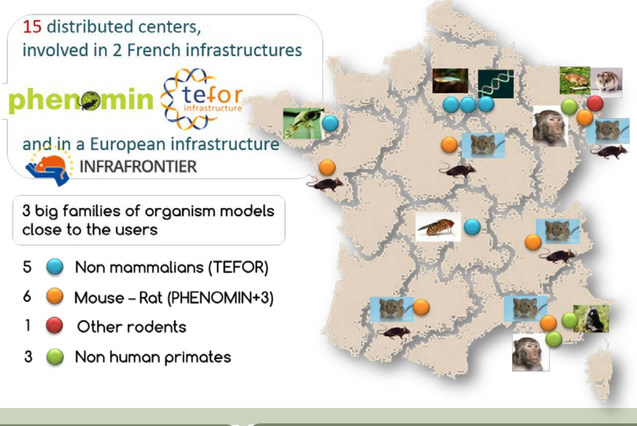
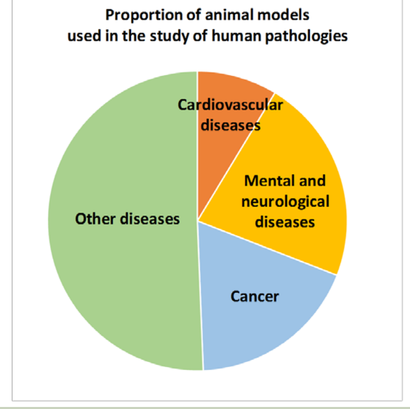
The best animal model to accelerate the comprehension of our genome and of human diseases

With 15 centers distributed over France, CELPHEDIA has developed innovative, standardized and massively parallel technological approaches:

- to accelerate the comprehension of the genome
- to generate human disease models
- to promote therapeutic innovations through validation of molecular targets

An unique access to 3 big families of model organisms to chose the best model to answer the questions of modern biology.





CELPHEDIA, a combination of expertise and skills

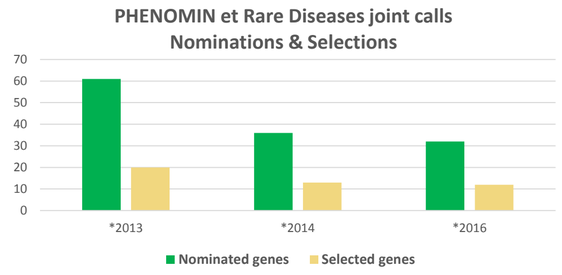
A remarkable palette of expertise, skills and knowledge unique in Europe.
This unique access enables:

- scientific and technological multi-model approaches
- integrated comparative functional analyzes
- better cross-functionality of the results from a model organism to another.

Mouse models and Rare Diseases

Rare Disease Foundation and PHENOMIN have launched 3 calls for joint research projects since 2013.
http://www.phenomin.fr/rare-diseases/

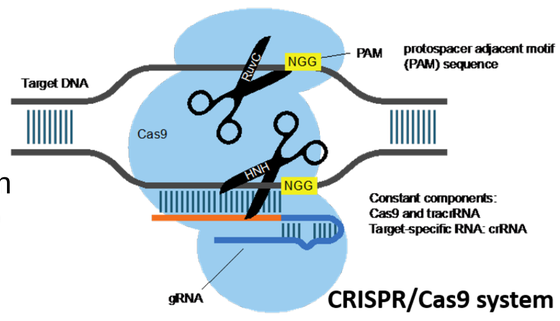
phenomin FONDATION maladies rares



Genome modification and creation of models

Design and production of genetically modified models, humanized mouse models, human pathology models, immunodeficient mice and rats :

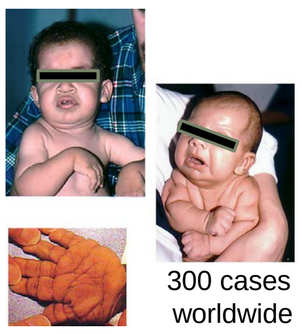
- o targeted mutagenesis : Knock-out (KO), conditional KO, Knock-in (KI), conditional mutations, deletion, duplication
- o pronuclear injection, ES cells microinjection
- o genome editing nucleases : CRISPR/Cas9



The mouse to model human rare diseases

Costello syndrome: mouse model HRAS G12S reproduces most of the phenotypic characteristics observed in patients

CLINICAL SIGNS	« COSTELLO » PATIENTS	« COSTELLO » MICE
POST-NATAL GROWTH DELAY		?
RHABDOMYOSARCOME		?
HAIR/FUR ABNORMALITIES		?
SKIN ABNORMALITIES		?
FACIAL FEATURES/ MACROCEPHALY		
HEART ABNORMALITIES		
REDUCED MUSCLE STRENGTH		
REDUCED LOCOMOTOR ACTIVITY		
REDUCED COORDINATION		
LEARNING		



300 cases worldwide

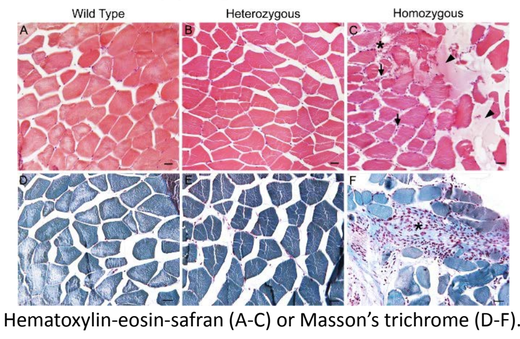
T. Sorg's team phenomin EXCELLENCE IN MOUSE PHENOGENOMICS

The zebrafish to model human rare diseases

Bethlem myopathy : an incurable human collagen VI-related disease
The zebrafish line reproduces a human mutation within an essential splice donor site of *col6a1* gene using TALE nucleases, provoking an in-frame skipping of exon 14.

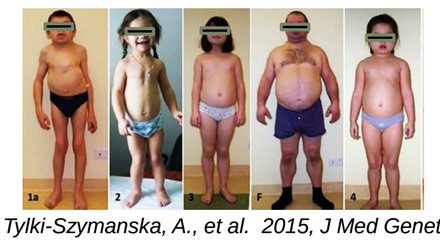
- Progressive disorganization of the muscle
- Co-dominantly inherited abnormal myofibers
- Enlarged sarcoplasmic reticulum
- Altered mitochondria
- Misaligned sarcomeres
- Development of fibrosis (* on C & F)
- Hypoxia-response behavior (locomotion tests)

Radev Z, et al. PLoS One. 2015 - F. Sohm's team tefor infrastructure EMAGE



Hematoxylin-eosin-safran (A-C) or Masson's trichrome (D-F).

RTHα genetic disease: mutations in the THRA gene coding the thyroid hormone receptor TRα1 generating various phenotypes



Tylki-Szymanska, A., et al. 2015, J Med Genet.

Generation of genetically modified mice at helix 12 of the receptor by CRISPR/Cas9

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human & mouse wt THRA
                NHRKHNIPHFWPKLLMKVTDLRMIGACHASRFLHMKVECPTELFPPLFLEVFEDQEV
                          Hélix 11                  Hélix 12

human mutations in C-term :

   E403X        NHRKHNIPHFWPKLLMKVTDLRMIGACHASRFLHMKVECPTELFPPLFLE
   E403K        NHRKHNIPHFWPKLLMKVTDLRMIGACHASRFLHMKVECPTELFPPLFLKVFEDQEV
   F397fs406X   NHRKHNIPHFWPKLLMKVTDLRMIGACHASRFLHMKVECPTELFPPTLPRGL
   P398R        NHRKHNIPHFWPKLLMKVTDLRMIGACHASRFLHMKVECPTELFRPLFLEVFEDQEV
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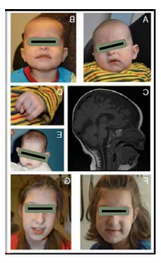
F. Flamant's team, UMS3444/US8 SFR BioSciences, Lyon

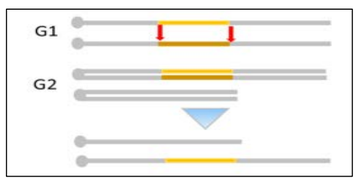
The rat to model human rare diseases

MRD7 syndrome

Clinical signs identified from 7 months to 7 years: microcephaly, growth delay, skeletal abnormalities, difficulty with nutrition, language delay, intellectual deficit, anxiety, aggressiveness, autism...

Y. Herault's team phenomin EXCELLENCE IN MOUSE PHENOGENOMICS

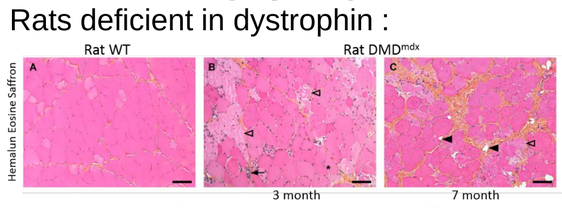




Rat model MRD7: Inactivation of a *Dyrk1a* allele with deletion of a gene sequence by CRISPR/Cas9

Duchenne myopathy

Rats deficient in dystrophin :



◄ centers of small regenerating centronucleated fibers;
◅ fibrous necrosis; ★ fibrosis;◄ adipose tissue

Femoral biceps muscle collected at 3 and 7 months from WT control and DMDmdx rats.

Comparaison of pathological and functional characteristics between patients and model animals

	DMD patient	GRMD dog	DMD pig	HFMD cat	Mdx mouse	*Dmd*^{mdx} rat
Muscle histopathology						
Revertant fibers	1 to 3%	<1%	ND	ND	5%	**5%**
Necrotic fibers	0.5 to 3.5%	2%	absent	present	5%	**>10%**
Regeneration	ND	15%	ND	present	10%	**10%**
Calcification	mild	mild to marked	ND	severe	mild	**absent**
Fibrosis	marked	present	present	diaphragm mainly	late & mainly diaphragm	**marked**
Lipomatosis	severe	absent	absent	absent	absent	**mild**
Cardiomyopathy	marked, major cause of death	mild	absent	present	absent or late	**marked**
Muscle function						
Strength reduction	marked	marked	ND	ND	mild	**marked**
Locomotion	severely impaired	impaired	impaired	ND	normal	**impaired**

doi:10.1371/journal.pone.0110371.t002

I. Anegon's team tefor infrastructure trip

CELPHEDIA at an international level

Involvement in European and international projects

Celphedia — Distributed French infrastructure Reference center for animal research

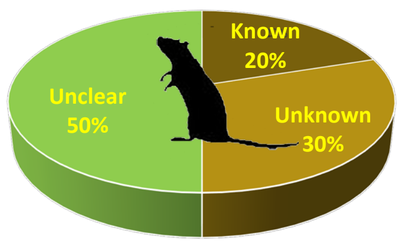
phenomin — French infrastructure of phenogenomic

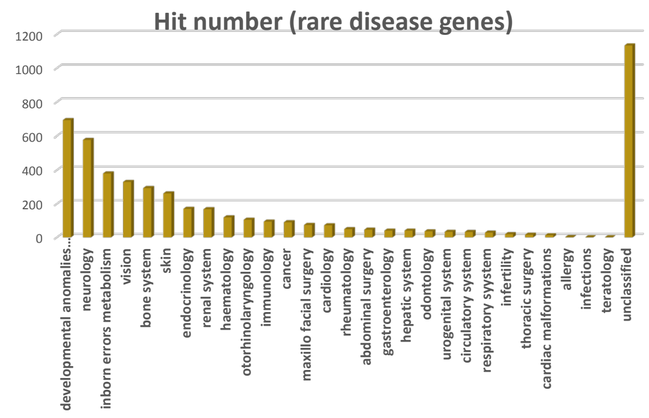
INFRAFRONTIER — European network of phenotyping, archiving and distribution of mouse models

IMPC International Mouse Phenotyping Consortium — International consortium of mouse phenotyping
9 countries
16 mouse clinics

- ❑ To undertake broad based primary phenotyping of about 20,000 mutants
- ❑ To determine the function of every gene in the mouse genome

Mouse gene functions





http://www.celphedia.eu