CELPHEDIA, the French national reference infrastructure for animal research on rare diseases

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

With 13 centers throughout France, CELPHEDIA has developed innovative, standardized and massively parallel technological approaches to:

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

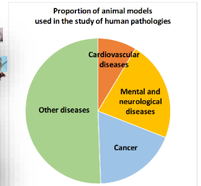
An unique access to 3 major families of model organisms allowing the selection of the most appropriate model to answer the questions of modern biology.

13 distributed centers,
involved in 2 French infrastructures
tefor infrastructure phenomin

and in a European infrastructure
INFRAFRONTIER

3 big families of organism models close to the users

3 Non mammalians (TEFOR)
6 Mouse – Rat (PHENOMIN+3)
1 Other rodents
2 Non human primates



Involvement in European and international projects

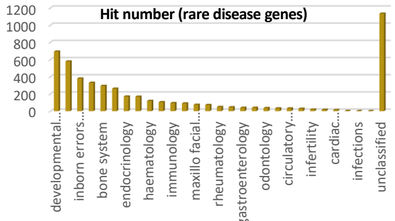
Celphedia — Distributed French infrastructure Reference center for animal research

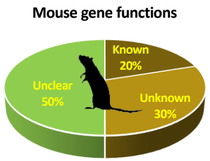
phenomin — French infrastructure of phenogenomic

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

IMPC — International 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





CELPHEDIA, a combination of expertise and skills

A wide range of expertise, skills and knowledge that is unique in Europe:

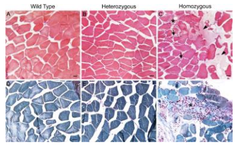
- multi-model scientific and technological approaches
- integrated comparative functional analyses
- a better cross-functionality of results from one model organism to another.

Zebrafish as a model of human rare disease

Bethlem's myopathy: an incurable human collagen VI disease. The zebrafish GA line was obtained using TALE nucleases and mimics a human mutation in an essential splice donor site of the *col6a1* gene, causing an in-frame skipping of exon 14.

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

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

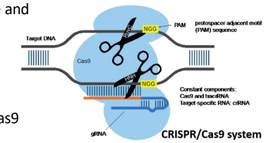


Hematoxylin-eosin-safran (A-C) or Masson's trichrome (D-F) staining.

Genome modification and creation of models

Design and generation of genetically altered (GA) models like humanized mouse models, human pathology models, immunodeficient mice and rats:

- targeted mutagenesis: constitutive and conditional knock-out, knock-in, conditional mutations, structural variants...
- ES cells in mouse
- pronuclear injection and CRISPR/Cas9 genome editing in mouse and rat

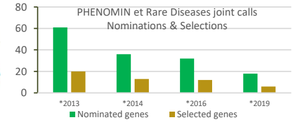


CRISPR/Cas9 system

Mouse models and Rare Diseases

Rare Disease Foundation and PHENOMIN have launched 4 calls for joint research projects since 2013.
http://www.phenomin.fr/rare-diseases/

phenomin FONDATION maladies rares

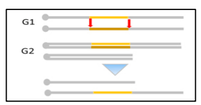


The rat to model human rare diseases

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

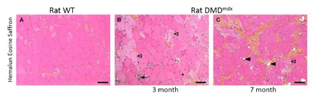


GA MRD7 rats: deletion of a *Dyrk1a* allele by CRISPR/Cas9

Duchenne myopathy

GA rats are deficient in dystrophin

Femoral biceps muscle collected at 3 and 7 months from WT control and DMD^{mdx} rats.



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

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	3%	**>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

The mouse to model human rare diseases

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

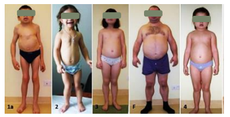
CLINICAL SIGNS	« COSTELLO » PATIENTS	« COSTELLO » MICE
POST-NATAL GROWTH DELAY		?
RHABDOMYOSARCOME		?
HAIR/FUR ABNORMALITIES		?
SKIN ABNORMALITIES		?
FACIAL FEATURES (MACROCEPHALY, ...)		
HEART ABNORMALITIES		
REDUCED MUSCLE STRENGTH		
REDUCED LOCOMOTOR ACTIVITY		
REDUCED COORDINATION		
LEARNING		

300 cases worldwide

T. Sorg's team

phenomin EXCELLENCE IN MOUSE PHENOGENOMICS

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 GA mice by CRISPR/Cas9 targeting helix 12 of the receptor

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human & mouse wt THRA
                NNKRKNNIPHFWPKLLMKVTDLRMIGACHASRFLHMKVECPTELFPPLFLEVFEDQEV
                                                Helix 11          Helix 12
human mutations in C-term :
E403X           NNKRKNNIPHFWPKLLMKVTDLRMIGACHASRFLHMKVECPTELFPPLFLK
E403K           NNKRKNNIPHFWPKLLMKVTDLRMIGACHASRFLHMKVECPTELFPPLFLKVFEDQEV
F397fs406X      NNKRKNNIPHFWPKLLMKVTDLRMIGACHASRFLHMKVECPTELFPPTLPRGL
P398R           NNKRKNNIPHFWPKLLMKVTDLRMIGACHASRFLHMKVECPTELFRPLFLEVFEDQEV
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F. Flamant's team, UMS3444/US8 SFR BioSciences, Lyon

CNRS — Université de Strasbourg — Institut thématiques Inserm institut national de la santé et de la recherche médicale — Celphedia

http://www.celphedia.eu