

Generation of customized genetically engineered rats

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Introduction

The Institut Clinique de la Souris - ICS (Mouse Clinical Institute - MCI) is a research infrastructure of excellence for translational research and functional genomics. ICS is part of PHENOMIN, the National research infrastructure that combines the capacity of generating mutant mice on a large scale with a high-throughput and comprehensive phenotypic analysis of the animals. Research programs focused on mutagenesis, transgenesis, archiving, zootechny and clinical phenotyping are also developed to provide state of arts technologies. ICS was also a key partner in Gencodys, a research consortium dedicated to discover the functions and dysfunctions of the brain. We have generated and phenotyped more than 40 mouse models for mental retardation. Based on our mouse expertise, we are currently developing the Rat model as a genetically modified organism.

Why Rats?

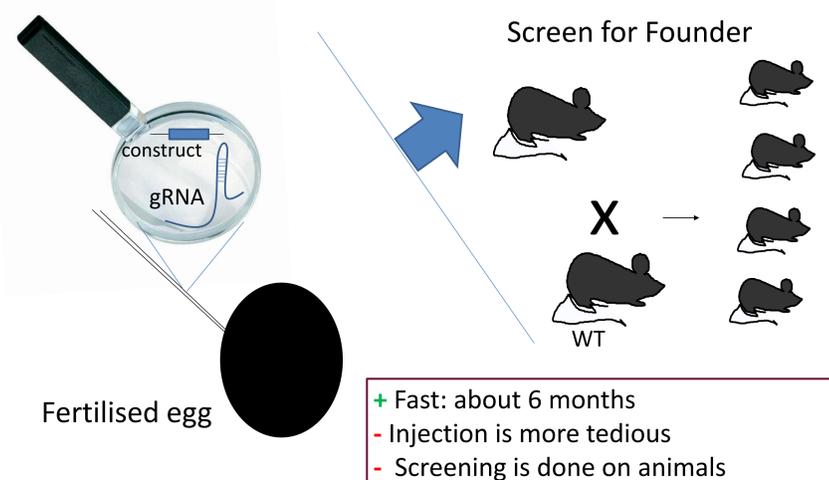
As mice:

- Anatomy, physiology, genetic similarities to humans
- Easy breeding in captivity
- Accelerated lifespan
- Efficient Assisted Reproduction Technologies (ARTs)
- Genome totally sequenced
- Mutagenesis tool box

Further advantages of the rats

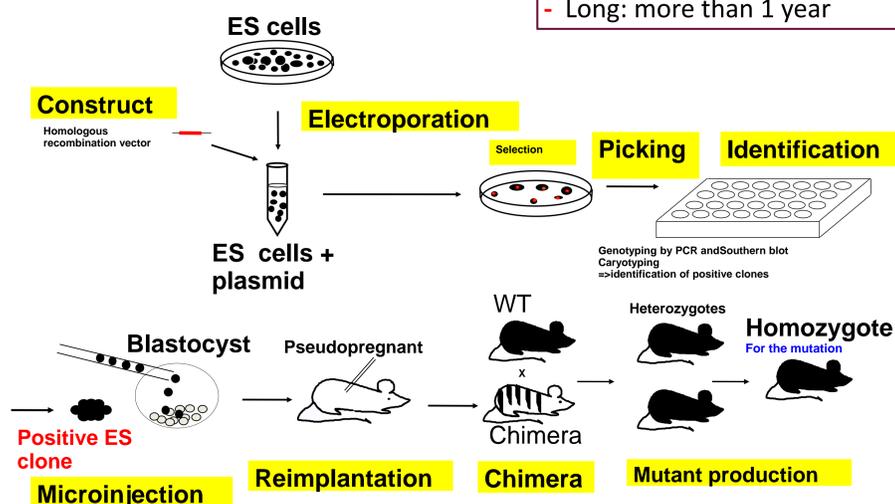
- Size (300-500g): Surgery, blood pressure, blood volume, brain
 - More advanced behavioral tests
- => Rats correspond to 15 % of model animals used in research to study behavior, physiology, neurosciences and pathology, including tumor biology, transplantation, and toxicology

CRISPR/Cas9 via injection in fertilized oocytes

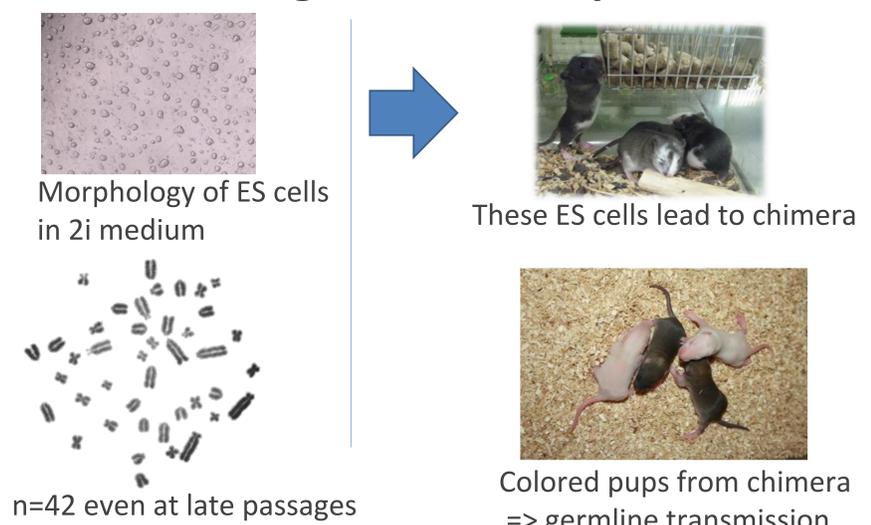


The ES route

- + Most of the screening is done on ES cells
- + coat color avoid some genotyping
- Long: more than 1 year



Our ES cells derived from Dark agouti rats are germline competent



Present pipeline: pilot projects

Pilot projects via injection in fertilized eggs (CRISPR/Cas9)

- First success with Knock-Out (KO) projects
- Improvement of the conditions for more complex projects

Pilot projects via ES route

- ES cells with germline competence have been obtained
- Homologous recombination achieved
- Males chimera obtained in iCS animal facility are currently breeding with WT females at TAAM animal facility

PHENOMIN & the Rats for the future

- Gene inactivation via CRISPR/Cas9 technology: call for projects will open soon.
- Gene editing via ES or CRISPR/Cas9 route: offers will available as soon as pilot experiments have succeeded.
- A rat phenotyping service will open soon.



Perspectives : Thanks to ES cells and CRISPR/Cas9 technologies, the rat model will enable major discoveries in human genetics and pathologies.

