Activity Report, 2019

phenomin

EXCELLENCE IN MOUSE PHENOGENOMICS

1. Introduction

Rodent Models are essential in research to gain knowledge on fundamental biological processes and veterinary and biomedical progress. They are essential to decipher and understand the integrative physiology or the expression of a genetic character in its environment. This statement is supported by many scientific academia, including the French Academy of Science in 2018.

As science moves forward with ethical aspects being increasingly important, there is a growing concern need to reinforce data reproducibility and robustness[1]. Whether some data irreproducibility is inevitable, the following items should be determined and used regularly, such as quality certified biological resources, a controlled environment, monitoring of the experimental and biological variations, mindful study designs, use of cross-validated protocols, data analysis and reporting.
To take into account this issue, PHENOMIN has undertaken several strategies which are willing to be pursued in the coming years. Indeed, the creation of models, their analysis, their preservation and their distribution are processes requiring the use of certified resources, validated, robust and standardized methods. The attentive study design guarantees the quality of the genetic modifications carried out, the statistical power and reproducibility of functional analyses, ensuring the quality and the sustainability of data and models preserved for future research. This animal research must be carried out respecting ethics, expressed in the 3'R rules, by reducing the number of animals linked to the refinement of tests and developing complementary methods using isolated cells or organs.

The objective of PHENOMIN is thus **to develop and maintain innovative, standardized and parallel methodologies, functional analysis and comparative genetics for rodent models, according to the community's needs**. PHENOMIN will allow research teams to carry out comparative and integrative functional analysis and to ensure a better translation of results to human.

PHENOMIN aims for the next 5 years period:

- To develop and improve tools to advance basic research in mammals and better respond to the ethical demands of the society on the use of animals in research (Welfare and Ethic) by harmonizing and sharing practices among partners, through high level technological developments in the fields of mutagenesis, zootechnics, cryopreservation, functional analysis, data analysis and preclinical research, while complying with ethical rules and animal welfare.

- To improve the impact of preclinical innovative mouse models in immuno-oncology, inflammation, infection, development, neurobiology, rare diseases for the development of therapies in humans

- To decipher the function of the mammalian genome and the consequences of genetic variations in both coding and non-coding sequences to underpin future concepts in biology, in physiology and disease with major insights in precision medicine, rare disease, clinical genetics, and healthy living.

[1] *Freedman, L. P., Venugopalan, G. & Wisman, R. Reproducibility2020: Progress and priorities. F1000Res 6, 604, doi:10.12688/f1000research.11334.1 (2017) AND Freedman, L. P., Cockburn, I. M. & Simcoe, T. S. The Economics of Reproducibility in Preclinical Research. PLoS Biol 13, e1002165, doi:10.1371/journal.pbio.1002165 (2015).*

PHENOMIN wants to continue its involvement in the national and international exchanges and access to models of interest through the European ESFRI infrastructure INFRAFRONTIER and the IMPC, in order to:

- **Contribute** to the international effort of the functional annotation of the genome and understanding of human diseases. Y. Hérault has been elected in the executive committee of the IMPC and PHENOMIN-ICS has hosted the Chief Operating Officer of the IMPC from April 2019.
- **Improve and lead** the development and harmonization of procedures and protocols, guaranteeing the regulation of efficiency, reliability and reproducibility. PHENOMIN has played a major role in INFRAFRONTIER and IMPC, participating or leading task forces with such an endeavour.

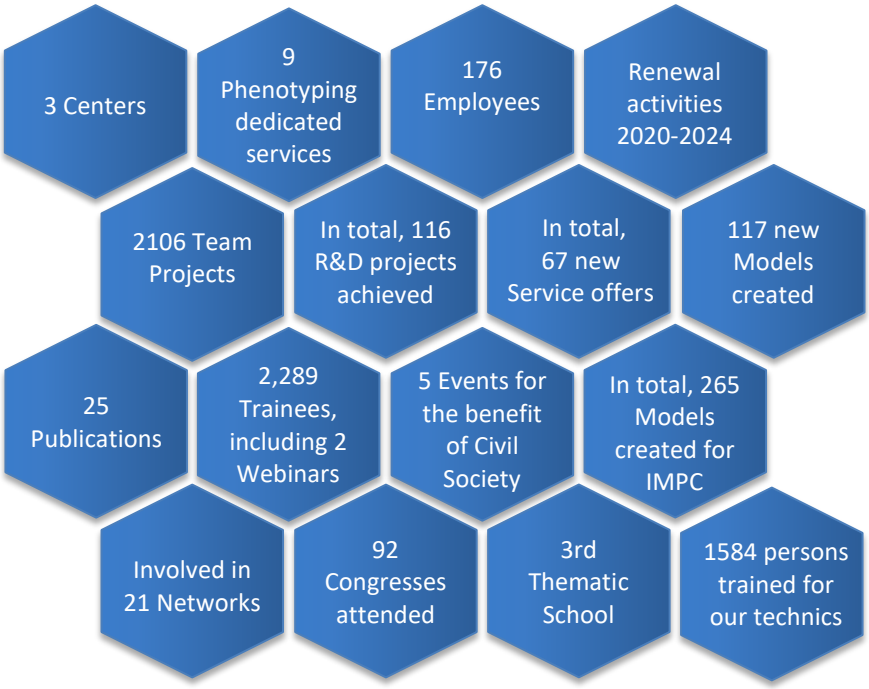
As such, PHENOMIN embraces the 3 goals of IMPC:

- Goal 1: **Complete the generation of a null mouse mutant resource for the coding genome** that delivers a comprehensive catalogue of mutant strains available to study mammalian gene function.
- Goal 2: **Design and produce a genome-wide mouse strain resource of human disease-associated coding variants associated with rare diseases** that can be used for validation of putative functional variants and insight into disease mechanism(s).
- Goal 3: **Design and generate mouse strains that model genetic variation in the non-coding genome** for the IMPC and the global research community to use in a collective effort to assess functionality and mechanism(s) in health and diseases.

Finally, PHENOMIN has continued to organise animal research in France, being one of the central node of the national research Infrastructure CELPHEDIA. This step was done with the approval of the Institutions and in collaboration with TEFOR, the second infrastructure for animal models. Both PHENOMIN and TEFOR will lead CELPHEDIA to develop innovative, standardized and massively parallel technological approaches, in order to accelerate the understanding of the genome and the generation of animal disease models.

PHENOMIN aims to continue strengthening the organisation of the community and strongly encourages the research teams to rely on the PHENOMIN infrastructure to ensure the creation of rodent models, their standardized analysis, their preservation and their distribution to the scientific community.

2. 2019 with numbers



3. Highlights

3.1. The PHENOMIN renewal 2020-2024: the international jury assembled by the ANR makes a very favorable evaluation of PHENOMIN

On June 16th, 2019, the PHENOMIN infrastructure defended its activity report for the period 2011-2018 and its proposal for 2020-2024 in front of an international jury convened by the ANR. After 15 minutes of presentation, an in-depth discussion on progress and future developments continued between the 3 PHENOMIN representatives and the panel of experts for 45 minutes. The evaluation of PHENOMIN was sent to us in August 2019 with the following general comment:

“The face-to-face meeting with representatives of the PHENOMIN supported the excellent report/application and the panel can state that PHENOMIN is mature, excellent research infrastructure of great importance to research community of France and with global impact. PHENOMIN has already established a realistic plan for future sustainability that is mostly based on the quality of services provided. Representatives of the RI explained also the PHENOMIN’s further development within the CELPHEDIA, where the PHENOMIN should take a lead as a central element, increasing its impact scientific community working with animal models, also other than rodents, thus disseminating their knowledge and expertise over the broad French and international research community.”

The Directors of the PHENOMIN Centers, as well as all the managers of work programs, would like to thank and congratulate all their colleagues for this evaluation which will commit us to a new period of activity of 5 years to serve the scientific community. We will all face new challenges and as Centre Directors we are confident that we can meet them together to provide better services and new tools to the scientific community.

3.2. 12th call for mouse model nomination addressed to the French scientific community

In 2019, PHENOMIN launched its 4th call for mouse model nomination in collaboration with the "Fondation Maladies Rares" for the generation and characterization of mouse and rat models in order to i) gain a better understanding of the pathophysiological mechanisms involved **in rare diseases** whose defective genes have been identified, ii) test and validate therapeutic proofs of concept, at the pre-clinical *in vivo* level.

The French Foundation for rare diseases "Fondation Maladies Rares" and the French National Infrastructure PHENOMIN launched 3 successive joint calls "Mouse models and rare diseases" (in 2017, 2015 and 2013, respectively) and the last joint call in collaboration with the Infrastructure CELPHEDIA "**new experimental animal models of rare diseases"** (2019) addressing rare disease issues.

In total, **50 projects for new mouse models** and **3 projects for new rat models** have been or are being realized from 145 submissions**.** All generated models are publicly available to the scientific community after 2 years embargo.

Late in 2018 and in 2019, PHENOMIN was involved in the trans-national open access call through its partnership with the European infrastructure INFRAFRONTIER and its involvement in IMPC program. Up to now 8 calls have been launched and then **248 projects have been or are being realized by PHENOMIN from supporting mouse (236) or rat model (3) generation, specialized neurobehavioral (3) and immuno-phenotyping (3), and the derivation of germ-free mouse line (3)**.

3.3. Integration of new research programs and partnerships

In 2019 PHENOMIN experts and teams have been integrated in 3 new research programs and partnerships: EarlyCause, GO-DS21 and PATHBIO.

These projects complete the list of active PHENOMIN projects and partnerships: Jackson laboratory partnership, PAIN-Net, TheraHCC, ANR (COSMIT, Enterocyte purge recovery, NACID) and ERC projects, CELPHEDIA, INFRAFRONTIER, IMPC, CanPathPro, CRL partnership, ImmGen, Magenta, Marseille Immunopole, MSDAVENIR, Fondation Maladies Rares, Fondation Bettencourt Schuller, Fondation Jerome Lejeune.

3.4. Organizing the 33rd International Mammalian Genome Conference: IMGC 2019

The main purpose of the International Mammalian Genome Society is to promote and stimulate research in mammalian genetics from sequencing to functional genomics, mutagenesis and mutant analysis, and to represent the concerns of its members in their professional activities. The company's activities have grown with the growing awareness of the important and unique role of rodent species in biomedical research and current genetics.

The perpetual evolution of mammalian genomics is the main focus of IMGS' annual conferences. The two organizers of the 33rd edition were Yann HERAULT (director of PHENOMIN-ICS, Strasbourg and Elected member of the IMGS Secretariat) and Xavier MONTAGUTELLI (head of the Mouse Laboratory, Institut Pasteur, Paris).

This event was a great success, and welcome nearly 200 participants from all over the world, and has contribute as expected, to promote and to recognize the hard contribution of the students, postdoctoral fellows and junior faculty to the annual meeting.

3.5. Quality management certification

Late in 2019, PHENOMIN has prepared the renewal of its certification obtained in March 2017 for the management and strategic steering of the Infrastructure under ISO 9001:2015 norm. This certification concerns the management/coordination (the 3 centers are independently certified for their service activities) and is dedicated to the satisfaction of PHENOMIN interested parts (administrative supervisors and funding body, governance, service offer evaluation (user committee) and scientific evaluation (SAB)). The permanent interaction between strategy, coordination and other processes ensures reactivity and strategy adjustments if needed.

3.6. 3rd Thematic school

PHENOMIN has organized its 3rd European thematic school on mouse phenogenomics in May 2019. It gathered 27 European experts and 18 participants (researchers and PhD candidates) from 7 countries (12 nationalities) around the mouse as model organism. This school aims at disseminating and transferring technological and ethical knowledge as well as good practices regarding animal welfare through presentation and working group sessions. Next edition will be organized in collaboration with the European Infrastructure INFRAFRONTIER in 2021.

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