

## LATEST NEWS



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### RESEARCH must go on !

It has been a year now that we are living with the pandemic. In this context, we have decided more than ever to celebrate the 10th anniversary of the PHENOMIN infrastructure which is a valuable support in the use of mouse models for your research. Animal models that make sense in COVID-19 research, which has accelerated around important national and international efforts over the past year, and are already bearing fruit. [Such specific resources for Covid-19 research can be found online.](#)

We have again successfully renewed our quality management certification, in line with our desire to improve PHENOMIN infrastructure coordination and management. This highlights the special attention we pay to your satisfaction.

The research and user projects go one, thanks to all our staff on the front line who have shown great flexibility and commitment, particularly during the pandemic. [PHENOMIN's 10th anniversary will be an opportunity to share with you our and your successes.](#) We look forward to seeing you online!

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## French TRANSPARENCY and OPENNESS in animal research

France is the fifth country in Europe - after the United Kingdom, Spain, Portugal and Belgium – in which institutions have signed a [national agreement committing themselves to speak openly to policy makers, the media and the general public about the use of animals in biomedical studies](#). Initiated by the French Ministry of Higher Education, Research and Innovation, and coordinated by GIRCOR, an associative organization that informs the public about animal research, the national charter make four commitments:

1. To explain the reasons and conditions for using animals for scientific and regulatory purposes
2. To disseminate information to the general public and the media
3. To ease information flow with the general public and the media
4. To produce an annual document outlining the progress regarding public information

Have a look at the interview of Dr Y. Hérault, director of PHENOMIN and ICS, done by our European partner about the national agreement: <https://www.infracontier.eu/news/french-transparency-charter-why-openness-key-animal-research-europe>

## DESIGN & DATA ANALYSIS: OUR VISION



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## Challenges in research REPRODUCIBILITY

The reproducibility of scientific results remains one of the major challenges in 21-century science, especially in our field of phenogenomics. To ensure reproducibility, each scientist must not only be an expert in his/her field but master other skills that are sometimes far outside his/her education. For example, mathematical notions and more particularly statistics have become indispensable for good data analysis. A researcher is also required to use unfamiliar methods and technologies to answer his or her scientific question. He/she is expected to understand methods limits and biases for protocols that he sometimes uses for the first time.

PHENOMIN-ICS speakers were invited by Charles River Laboratory to participate to their Fast Tracks event: free Quick Insights In Animal Health learning series features short, on-demand presentations (each no more than 15 minutes). Three PHENOMIN-ICS webinars are available [on-demand](#):

- In the microbiome track: Dr G. Pavlovic presented "Reproducibility with 16S metagenomics" focusing on technical challenges that are to be considered to ensure good quality and reproducibility for in vivo bacteria identification and quantification using 16S
- In the emerging hot topics track: Dr G. Pavlovic presented "CRISPR/Cas9 genome editing: challenges for research reproducibility and clinical safety" and Dr S. Jacquot presented "Improve reproducibility and

animal welfare with better genotyping practices" focusing respectively on understanding the nature of mutations observed when using genome editing especially CRISPR/Cas9 and on good genotyping practices to guaranty animal identification and non-invasive sampling methods for 3R improvement.



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## Our work to improve the reproducibility of rodent models

For many years, PHENOMIN has been committed to publishing or participating in reviews and protocols focusing on technology questions. Some of these papers are based on years of data, allowing great robustness of the proposed protocols.

- The use of genome editing particularly CRISPR/Cas9 for the creation of structural variants "Efficient and rapid generation of large genomic variants in rats and mice using CRISMERE" ([Birling MC et al., 2017](#)) and humanization of rodents "Modeling human disease in rodents by CRISPR/Cas9 genome editing" ([Birling MC et al., 2017](#))
- The variability in genome editing outcomes and how it impacts research reproducibility ([Teboul L et al., 2020](#))
- Reliable protocols and tricks and tips for PCR genotyping ([Jacquot S et al., 2020](#)), blastocyst genotyping ([Scavizzi F et al., 2015](#)), Southern Blotting ([Codner GF et al., 2020](#)), digital PCR (and RT-ddPCR) ([Lindner L, et al., 2020](#)) or digital karyotyping ([Codner GF et al., 2016](#))
- New model creation tools like improvement of the FLEx approach for the generation of conditional point mutation models ([Scekcic-Zahirovic J et al., 2016](#) and [Gillet JG et al., 2020](#)) or Cre and FlpO deleters ([Birling MC et al., 2012](#))
- The functional validation of genetically altered rodents ([Lindner L et al., 2021](#))

Today, [15 papers are available](#) in the field of the creation of genetically modified rodents and answer different technological questions. Please have also a look to the [Study design page](#).



PHENOMIN-CIPHE © Guilhem Malissen

## REPRODUCIBILITY AND SAFETY of your model colonies

As a follow-up to the previous topic along to past few years, most important questions underline the interplay between experimental design and implementation of the 3Rs in practice. Improving experimental quality and optimizing scientific data also goes hand in hand with improving the protocols and techniques we apply in animals or on samples from animal research, which will be processed for data analysis, and especially with reducing the number of animals used. [Most we are increasing the robustness of our method more we preserve our mouse lines.](#)

PHENOMIN-ICS has recently illustrated 3 topics on rodent models which highlight the crucial positive impact in using the best practices in general and especially in 16S rRNA gene studies performed for bacteria identification and quantification in vivo, explaining how recent work from animal and cell models demonstrates the importance of extensive validation for the risk assessment of genome editing and its impact on cell integrity, and showing that non-invasive sampling methods for genotyping becomes a refined and a more robust method regarding genotyping errors.

All both were presented as a learning series features from Charles River short training session during Spring 2021; you can find [on-demand](#) the presentations (each no more than 15 minutes) across six different tracks.

- The microbiome: G. Pavlovic had presented "Reproducibility with 16S metagenomics"
- Emerging hot topics: G. Pavlovic had presented "CRISPR/Cas9 genome editing: challenges for research reproducibility and clinical safety" and S. Jacquot had presented «Improve reproducibility and animal welfare with better genotyping practices"

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### USER'S OPINION MATTERS



### OUR AIM: to satisfy you!

We are pleased to announce, especially this year, that one hundred percent of our users recommend us to the scientific community and are satisfied or even very satisfied of PHENOMIN.

The positive feedbacks of our users and their complete satisfaction is a true testimony to the great work and service that we want to provide. Below, some recent unsolicited positive users feedback:

".....For my project, I plan to generate 3 mouse lines - 2 knock-in (inserting Cre to 3'-UTR of my marker genes) and one conditional mutant allele. All the PIs in IGMM recommended me that ICS has the best expertise for mouse transgenesis in France....." . MK, March 2021

"Thank you very much for the very detailed report. It is really unfortunate that the rats are not viable with this mutation (certainly interesting, though). I really appreciate your dedication and effort to first try to make this work, and later obtain an explanation as to why the model cannot be created....For my part, it

has been great working with all of you, and I really appreciate the effort and availability to communicate and discuss results. Thank you very much!" . DDC, Dec. 2020

Thank you for your trust!

*ENS Paris, Caraway Therapeutics. Sanofi, Oslo University Hospital, , IBENS-PARIS, IGBMC-Strasbourg, IMGG-Montpellier, I2MC – Inserm / UT3 Paul Sabatier, UMR 7369 – MEDyC, Odimma, Université Paris sud, Czech Centre for Phenogenomics, CPTP-INSERM-Toulouse, Francis Crick Institute, Interdisciplinary Institute for Neuroscience - UMR CNRS 5297-Bordeaux, UCBLyon1.*

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## OUR RESEARCH SPOTLIGHT



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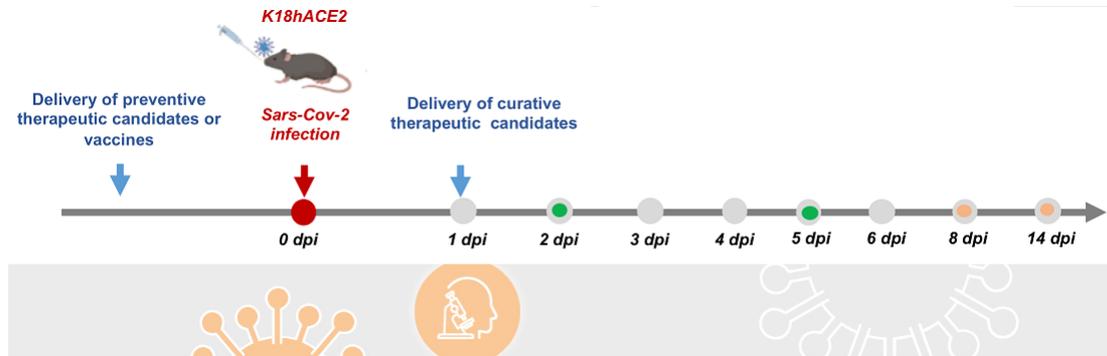
### A resource of targeted mutant mouse lines for 5,061 genes (Nat Genet 53, issue 4, April 2021)

This April, an article in Nature Genetics highlights the major contribution of PHENOMIN-ICS in the International Mouse Phenotyping Consortium (IMPC) for the implementation of a comprehensive quality control strategy for alleles in targeted embryonic stem (ES) cells clones produced by high throughput. More than 5,000 resulting mouse lines were generated with these ES cell clones through a collaborative effort of the different IMPC centers. All of them have the great advantage of having been established in the same C57BL/6N genetic background. Almost 3,700 have a versatile allele that has the advantage of being able to be transformed either into a conditional knockout or into a knockout bearing a LacZ reporter gene. The conditional allele remains a tool of choice for all scientists wishing to perform more detailed analyzes. The total number of genes with a potential conditional allele has been nearly doubled thanks to the effort of the IMPC.

The ultimate goal of IMPC is to generate and phenotype in a standardized manner the KOs of all protein-coding genes to provide key information for the biology and understanding of the development of human diseases. We were able to show that 72% of the KO lines show at least one phenotype, thus revealing a significant pleiotropy. This proportion includes the 39 % showing partial or total lethality. Thanks to this tremendous effort, almost half of the mouse genome is now targeted. Since 2015, the production of KOs from ES cells has been replaced by simple KOs obtained by CRISPR/Cas9 technology. Even in the new era of genome editing, this ES cell-derived collection remains of unique value, as it offers particularly sophisticated and quality-controlled alleles representing a cornerstone of the collective development of a resource of null alleles for the complete genome of mammals.

[Marie- Christine Birling et al., 2021 - Nat Genet.](#)

## OUR RESOURCES and NETWORKS



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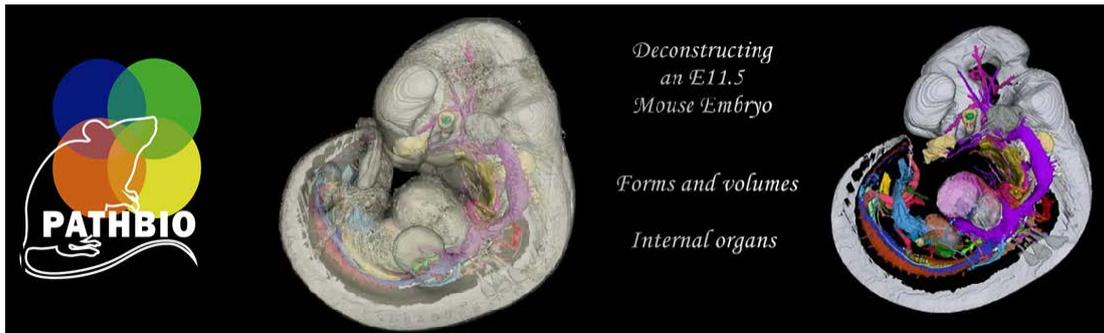
### Record participation in COVID-19 Open Call

The expert teams of [PHENOMIN-CIPHE](#), coordinating the COVID-19 TA Call, and the contributing partner CCP in Prague are happy about the high value of the submitted projects. Ana Zarubica, PHENOMIN-CIPHE Deputy Director and the PI supervising the COVID-19 Therapeutics Pipeline, says: "The relevance and quality of all proposals was excellent. They are all addressing fundamental clinical issues."

[The COVID-19 TA Call surpassed expectations](#) and turned out to be the most successful open call organized by INFRAFRONTIER so far. 21 scientific institutions from eight countries applied to be one of the five research projects that an INFRAFRONTIER expert team will support in the framework of the EC-funded call. The five successful projects come from five different countries – France, Germany, Norway, Spain and the USA – and deal with various research areas in the fight against COVID-19. Some of them aim to re-purpose existing drugs to prevent cellular entry of the SARS-CoV-2 virus. Others target on developing completely new ways to defend the attacks of the virus or to heal and restore organs that are already infected.

Another very positive outcome of the Trans-national Access Call was that its promotion across the global scientific community proved the willingness among researchers to use well suited mouse models for their COVID-19 studies.

[More information](#)



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## Innovative teaching material in mouse development

The mouse is the most commonly used laboratory animal. Pathologists need to learn more and more the anatomy of mouse embryos in order to diagnose correctly congenital anomalies and diseases.

[The PATHBIO project](#) supports the design and the development of a list of innovative teaching materials for learning anatomy, histology, embryology, imaging and pathology of the mouse. [Three-dimensional \(3D\) imaging](#) is a useful tool to characterize morphological phenotypes, but also to describe the normal anatomy of embryos for educational purposes. The involved researchers from [IGBMC](#) (Institut de Génétique et Biologie Moléculaire et Cellulaire) and [PHENOMIN-ICS](#) (PHENOMIN-Institut Clinique de la Souris) provide to the whole scientific community the first annotated 3D representations of E11.5 mouse using HREM (high resolution episcopic microscopy) technology that provides images that are comparable to histology in terms of resolution. It shows forms, volumes, internal organs and cavities from global mouse embryo (E11.5), its nervous system, heart and vascular system, primitive gut, and urogenital system. Each image content is detailed and annotated, inspired by the texts of Karl Theiler (1972) and Matthew Kaufman (1992).

We are pleased that it is [now freely available on the web](#).

And congratulations to the teams!

1- Karl Theiler, The House Mouse © Springer 1972

2- Matthew H. Kaufman, The Atlas of Mouse Development © Academic Press 1992



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## IMPC has elected a New Senior Leadership Team

After the nice review of the 2020 highlights, [International Mouse Phenotyping Consortium](#) (IMPC) have announced the election of a new Senior Leadership Team. Radislav Sedláček Director of the [Czech Centre for Phenogenomics](#) (CCP) is the new Chair of the IMPC, and Yann Héroult, Director of the [Institute Clinique de la Souris](#) (PHENOMIN-ICS), the new Vice-Chair.

[Steve Brown, the former Chair of IMPC, commented:](#)

“Many congratulations to Radislav Sedláček and Yann Héroult! I know that they will bring a wealth of expertise, judgement and foresight to the leadership of IMPC, and all of us at IMPC look forward to working with them. The IMPC, in sept. 2021, will celebrate the 10th anniversary of its foundation and are now preparing to enter a new phase of our work. We will complete a functional catalogue of the mouse genome, and increasingly focus our endeavours on large-scale functional studies of human genetic variation. These are exciting times for IMPC!”

The new Chair will support the start of [the next 10 years strategy](#) “*that encompasses completion of Phase 2, and execution of Phases 3 and 4...*” The strategy document describes clearly the IMPC’s key ambitions and the concrete goals to go further into how mouse genetics and mouse models inform gene function, human disease, and clinical genetics. In particular, it provides an explanation of the crucial role of the mouse in facilitating “the challenges and complexities of interpreting human genetic variation in the context of gene dysfunction (disease): 1) as an informative and comparable mammalian model system for the analysis of human genetic variation, and 2) to provide robust models for hypothesis-driven discovery research, mechanistic insight, purpose-driven translational studies, preclinical safety and effect programmes, and molecular target testing platforms”.



© IMPC /Mousephenotyping.org

## X-ray Annotation Mouse Atlas

[The IMPC](#) and its consortium members adhere to standardised phenotyping protocols to produce high-quality data. 2 members from the [Universitat Autònoma de Barcelona](#) and MRC Harwell Institute, have collaborated and provide you with a really great tool to investigate basic anatomical analysis skills from 152 X-ray images produced following an IMPC standardized phenotyping protocol. Exiting starting in 2021, with this [X-ray annotation mouse Atlas!](#)

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**UPCOMING EVENTS**



Phenomin celebrates **10** years

One short day online connection with you  
July 6<sup>th</sup> 2021

Opportunity to share our successes : Join us !

**phenomin**  
EXCELLENCE IN MOUSE PHENOMICS

PHENOMIN-ICS © Nathalie Maridet/Esperluette

## Special event

[10th anniversary of PHENOMIN: one short day online connection with you](#)

July 6th, 2021, online - [Join us to celebrate!](#)

Thanks to the support of the French government "Investissement d'avenir" obtained in 2011, and to the crucial effort of our staff, PHENOMIN is able to develop and maintain innovative, standardized and parallel methodologies of functional analysis and comparative genetics for rodent models, according to the needs of the community. That is, your needs!

The French infrastructure and its staff belonging to the 3 partner centers allow research teams to perform comparative and integrative functional analyses and to ensure a better translation of the results in humans. And we want to celebrate this with you!

10 years at your side and a desire to connect and share with you our successes and our future perspectives in functional genomics to support you in your research. [We invite you to join us on 6th July from 2pm to 6pm](#) to celebrate our achievements and share a vision for the future of PHENOMIN

[Delighted to meet you online!](#)



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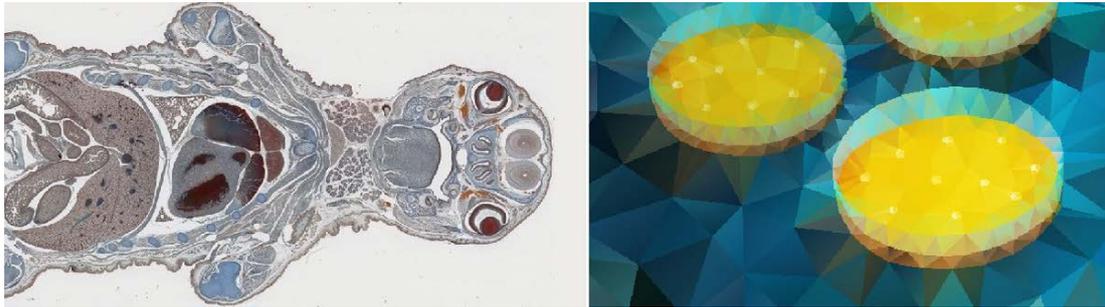
## Upcoming international training course

[3rd Imaging PATHBIO master class](#)

September 27th - October 5th, 2021, Online. [Registrations are open](#). The master class aims to provide graduate, master, PhD and postdoc students with basic and expert knowledge to phenotype morphologically mouse models of human diseases. It's a unique chance to understand the basic principles of several key methods from structural to functional imaging and to get an overview of the best practices including the 3'R rules to design scientific experiments. There is not fee for this course.

[In vivo CRISPR-Cas9 genome editing](#)

October 8th – 9th, 2021, Strasbourg, France. [Registrations are open](#). This training provides a general framework to get scientists started using CRISPR-Cas9 for in vivo gene editing in rodents. The training will be held online, for 3 consecutive mornings, on the same dates, only if sanitary conditions require it.



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## Upcoming French trainings

### [Introduction to Mouse embryology](#)

November 16 - 18, 2021, Online. [Registration are open](#). [This virtual training allows attendees to acquire a general knowledge of the major stages of the mouse embryonic development, to be able to design a first-line phenotyping experiment on mouse embryos & to determine a window of lethality in utero, and finally gets improved knowledge of imaging techniques adapted to mouse embryos.](#)

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