International Mouse Phenotyping Consortium - IMPC

A GLOBAL NETWORK UNDERPINNING STUDIES OF THE GENETICS OF DISEASE

About

The International Mouse Phenotyping Consortium (IMPC, https://www.mousephenotype.org) is an international effort to identify the function of every protein-coding gene in the mouse genome and provide the foundations for the functional analysis of human genetic variation. Launched in 2011, the consortium consists of 20 research institutes across four continents with funding provided by the NIH (USA), European, Australian and Asian national government funding agencies and the partner institutions. IMPC is generating a knock out mutation for every single gene in the mouse genome and undertaking comprehensive phenotyping (including embryonic, haematological, metabolic, cardiovascular parameters among others[1]) of each mutant line, thus linking each gene to disease traits. In the last 8 years, the IMPC has already generated over 8,500 mutant lines and phenotyped over 6,500, representing over one-third of the mouse genome. By 2021, IMPC expects to have analysed half of the genome. Both the data and the mice strains **are open to the scientific community at large**, and are already having a transformative impact on our understanding of the genome landscape and its role in disease. Within Europe, the development, output and impact of the IMPC from European mouse genetics centres is significantly enhanced by the investment in infrastructure for mouse genetics through the Infrafrontier programme.

2021 will mark the tenth anniversary of the IMPC, which is now preparing for the next phase. IMPC has laid out a new strategic plan for 2021-2030 (https://www.mousephenotype.org/wp-content/uploads/2019/05/IMPC_Strategy_2021-30.pdf) and will focus on providing insights into the functional analysis of human genetic variation, providing a critical underpinning to the interpretation of human genetic variants and a deeper understanding of disease mechanisms that will have a significant translational impact.

In this prism, the IMPC is preparing to capitalize on and grow our collaborations with consortia in human and clinical genetics and build new synergies with genetics societies and patient organisations.

[1] Throughout all its scientific work, the IMPC not only complies with all ethical and welfare rules for animal research but additionally strives for welfare improvements and the 3Rs principle –reduction, refinement and replacement

Success stories

- Results of the consortium already include a number of major scientific publications, many in high impact journals such as *Nature*, *Nature Genetics* and *Nature Comms*
- The IMPC has been recognised by the G7 Science Ministers as an exemplary global Infrastructure (http://ec.europa.eu/research/infrastructures/pdf/gso_progress_report_2017.pdf)

Key goals of IMPC for 2021–2031

1. *Complete the functional annotation of the coding genome*. With almost half of the mouse genes studied by 2021, the IMPC aims to secure funding to continue its efforts and complete the full functional analysis of the remaining (another ~9,000 human orthologous genes in mice) unstudied genes.
2. *Enable functional assessment of genomic variation and of the noncoding genome*. Null deletions can reveal function of protein-coding genes. However, the number of variants of unknown significance is increasing dramatically and is not being met by a commensurate analysis of variant function. Moreover, the coding region only constitutes 3-5% of the mammalian genome, with the remaining 95% of the genome playing many roles across a variety of biological processes (DNA replication, gene expression and regulation etc). The IMPC aims to develop programmes for the rapid creation and analysis of mouse models of human coding variants and of conserved noncoding elements in order to fully explore the *in vivo* function of the darkest part of the genome.
3. *Translate functional knowledge to clinical knowledge*. The emerging field of genomic medicine relies on the ability to interpret the potential pathophysiological consequences of genetic variation in patients and apart from the academic/research considerations, there exists a long-term financial investment in translating human genetic variation to functional phenotypes and disease mechanisms, projected to rise to as high as US$200billion in 10 years. The study of the mouse (and other models) can generate gene function data to inform clinical databases and enable insight into genetic variation and disease to catalyze future developments in genomic and human medicine.

4. *Integrate functional testing in clinical decision-making*. Ultimately, phenotyping data generated from the study of mutant mouse models should be readily available to inform diagnostic decisions, drug selection, and disease prevention strategies. To do so, clinicians should be able to request mouse models as testing platforms and review the obtained result to guide their clinical decision-making. In turn, mouse genetic experts should be able to perform quick and reliable targeted mouse phenotyping of mouse models. Use of mouse functional data must be optimized by ensuring that stakeholders support testing

of mouse models as human patient avatars and making available mouse data in the electronic medical record.

The IMPC has established a formidable network and operation for the large-scale analysis of mammalian gene function and the dissection of the functional role of human genetic variation. It is open to collaborations, new memberships and networking. Apart from its scientific excellence and state-of-the-art technologies and infrastructures in mouse genetics, it can also be a key partner to provide expertise on ICT aspects of big data management, storage and analysis.