Research on animal model organisms funded by the European Commission's framework programmes

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Recognising the crucial role of model organisms in exploring the causes of human disease and in developing safe treatments, the European Commission has invested €180 million in collaborative research projects on model organisms since 2002. Further financial support is planned for the future. Projects supported by the European Commission are playing an important role in structuring the research landscape in Europe and creating the knowledge base to understand health and disease. Furthermore, they are generating important and freely available data and/or animal resources that will catalyse progress in biomedical research. This paper focuses on animal model organisms and includes the rodents, mouse and rat, other vertebrates such as zebrafish and frog, and also invertebrates such as nematodes. Research on other model organisms, including yeast, bacteria and plants, is also being supported and this is providing knowledge on basic cellular and molecular processes, as well as on host-microorganism interactions.

The European Commission supports research through multiannual framework programmes (FPs). FP6 covered the period 2002-2006 with a budget of roughly €20 billion, whereas FP7 is currently running for 7 years from 2007 to 2013 with a budget of €50 billion. During FP6, funding for model organisms was granted mainly through the health thematic priority, which had a budget of €2.5 billion. Approximately €180 million was allocated to research on model organisms in FP6, with the majority of the funding being for mouse functional genomics. Most projects in this area are large-scale integrated projects that usually combine the multidisciplinary expertise of about a dozen (or more) groups from different European member states and other countries. The European Commission funding for each project is on average €10-11 million, and the duration of funding is typically 4-5 years. Smaller research projects and coordination actions have also been funded and usually complement the bigger initiatives. A complete catalogue, including details of most of the projects on model organisms, entitled 'From fundamental genomics to systems biology: understanding the book of life' will be published soon by the office for official publications of the European Communities.

Initiatives and resources

Mouse

The mouse is often the model organism of choice for research on human disease, for several reasons: (1) its genome is well characterised; (2) it is genetically very closely related to humans (about 99% of human genes are found in the mouse genome and vice versa); and (3) most of its genes can be inactivated (or modified) in time- and space-dependent manners, allowing a precise analysis of the genetic networks underlying human health and disease.

In FP6, several large-scale mouse functional genomics initiatives (including EUCOMM, EUMODIC, EURExpress, EuTRACC and MUGEN) were funded and are still in progress (see Table 1). Some of these projects, which generate resources for the biomedical scientific community, are briefly described below. Other projects, using the mouse to understand fundamental biological processes that are relevant to human health and diseases, are described in the catalogue 'From fundamental genomics to systems biology: understanding the book of life'.

The EUCOMM project plays a pivotal role in integrating European skills, resources and infrastructure to produce mutations, using systematic high-throughput tools, throughout the mouse genome. In this project, a collection of more than 10,000 conditionally mutated genes will be generated in mouse embryonic stem (ES) cells. The mutant ES cell production is coordinated at an international level with three complementary initiatives. The North American Conditional Mouse Mutagenesis (NorCOMM) project in Canada, the NIH-sponsored Knockout Mouse Project (KOMP) and the Texas Institute for Genomic Medicine (TIGM) in the USA, together with EUCOMM, form the International Knockout Mouse Consortium (IKMC), which is expected to inactivate each one of the 25,000 mouse genes. Building on this resource, 650 mutant mice will be established, and systematically and extensively phenotyped by EUMODIC using the EMPReSS standardised phenotyping protocols that have been developed by the EUMORPHIA project (funded at the end of FP5). Archiving and distribution of mutant mice is achieved through the EMMA project. EUCOMM will also generate a limited set of mice expressing the Cre recombinase in a tissue- and/or time-dependent manner. This part of the work is complemented by FLPFLEX, a smaller scale project. Together, EUCOMM and FLPFLEX are expected to deliver 24 Cre mouse lines, which will become a valuable resource that will allow the inactivation of any gene in specific tissues, or at certain stages during development or after birth. The design of new Cre mice will be facilitated by the EURExpress project that is carrying out a systematic molecular phenotyping analysis. The project will result in an expression atlas of 20,000 mouse genes during embryonic development and in adult tissues.

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Table 1. Acronyms and web sites of the cited European projects

Name	Definition	Web site
CASIMIR	Coordination and Sustainability of International Mouse Informatics Resources	www.casimir.org.uk
EMMA	The European Mouse Mutant Archive	www.emmanet.org
EUCOMM	The European Conditional Mouse Mutagenesis Program	www.eucomm.org
EUMODIC	The European Mouse Disease Clinic: a distributed phenotyping resource for studying human disease	www.eumodic.org
EUMORPHIA	European Union Mouse Research for Public Health and Industrial Applications	www.eumorphia.org
EURATools	European Rat Tools for Functional Genomics	http://euratools.eu
EURExpress	A European consortium to generate a web-based gene expression atlas by RNA in situ hybridization	www.eurexpress.org
EuroSyStem	European Federation for Systematic Stem Cell Biology	www.eurosystemproject.eu
EuTRACC	European Transcriptome, Regulome & Cellular Commitment Consortium	www.eutracc.eu
FLPFLEX	A flexible toolkit for controlling gene expression in the mouse	
FunGenES	Functional Genomics in Embryonic Stem Cells	www.fungenes.org
HEROIC	High-throughput Epigenetic Regulatory Organisation In Chromatin	
Intrafrontier	The European infrastructure for phenotyping and archiving of model mammalian genomes	www.infrafrontier.eu
Med-Rat	New tools to generate transgenic and knockout mouse and rat models	http://medrat.abc.hu
Molecular Imaging	Integrated technologies for in vivo molecular imaging	www.molimg.gr
MUGEN	Integrated functional genomics in mutant mouse models as tools to investigate the complexity of human immunological disease	www.mugen-noe.org
NemaGENETAG	Nematode Gene-Tagging Tools and Resources	http://elegans.imbb.forth.gr/nemagenetag
Plurigenes	Pluripotency-associated genes to de-differentiate neural cells into pluripotent cells	www.plurigenes.org
PRIME	Priorities for Mouse Functional Genomics Research Across Europe: integrating and strengthening research in Europe	www.prime-eu.org
STAR	A SNP and haplotype map for the rat	
TransCode	Novel tool for high-throughput characterisation of genomic elements regulating gene expression in chordates	
X-OMICS	Xenopus Comparative Genomics: coordinating integrated and comparative functional genomics for understanding normal and pathologic development	
ZF-MODELS	Zebrafish Models for Human Development and Disease	www.zf-models.org
ZF-TOOLS	High-throughput tools for biomedical screens in zebrafish	

Some projects will develop (or use existing) mouse mutants to address more focused biological questions relevant to human health and disease. The EuTRACC project develops and applies high-throughput protein tagging technology for knock-in mice. The methodology introduces affinity tags in hundreds of transcription factors in mouse ES cells, some of which will also be converted into null mutations. This will allow the genetic circuitry that controls the formation of neural tissues and the blood system to be mapped. MUGEN is another major research initiative of FP6 that uses functional genomics tools to analyse more than 200 mouse mutant strains, in a standardised way, showing immune system defects. These animal models are being used to identify new genes that regulate immune processes and diseases.

Such mutant resources will be of crucial importance for health research, since they allow scientists to more accurately dissect gene functions within a living organism. They will also allow scientists to decipher molecular mechanisms of human disease, and in some cases, to provide a foundation for the development of diagnostic, prognostic and therapeutic strategies.

In addition to these research initiatives in FP6, the European Commission has also financed two coordination actions. PRIME aims to coordinate research activities and policies, across Europe, in the field of mouse functional genomics, whereas CASIMIR will deliver recommendations for the coordination, interoperability and sustainability of databases that support mouse functional genomics in Europe (Fig. 1).

Rat

Europe also has a large community of researchers using the rat as a model organism. Over the last 50 years, the rat has been intensively used by physiologists to investigate the molecular determinants of diseases such as diabetes. The availability of the rat genome sequence in December 2004 (Gibbs et al., 2004) and genome-scale technologies, along with the ability to clone fertile adult rats, has substantially advanced the potential for functional genomics research in the rat model.

The EURATools project aims at developing integrated genomic tools that will generate knowledge on the genetic basis of susceptibility to highly prevalent complex diseases in Europe. Med-Rat and STAR are two complementary smaller scale projects that will develop new tools with which to generate transgenic and knockout rat mod-

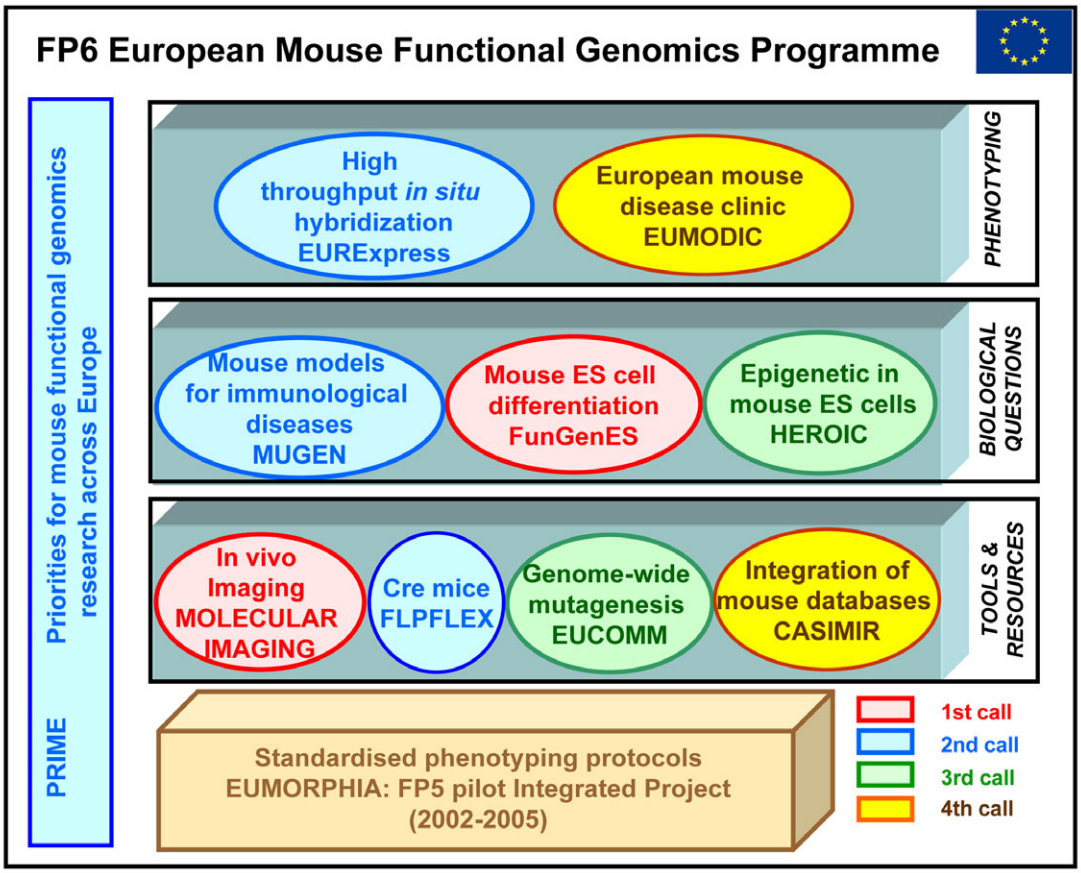

Fig. 1. European mouse functional genomics programme. In FP5 and FP6, the European Commission has invested substantially in mouse functional genomics. All projects are ambitious and highly complementary, thereby creating an integrated European research programme in mouse functional genomics. By joining forces at the European level via these collaborative projects, Europe is now at the forefront of international research in mouse functional genomics.

els (Med-Rat), or establish a single nucleotide polymorphism (SNP) and haplotype map for the rat model (STAR).

Zebrafish

The zebrafish is a vertebrate model that offers certain advantages compared with the rodent models. The fish is smaller in size and less costly to breed and maintain. Several transgenic approaches are feasible, facilitating the study of highly conserved vertebrate genes that function in health and diseases. Furthermore, developmental processes can be easily observed since the embryo develops outside of the mother's body and is fully transparent.

The ZF-MODELS project uses the zebrafish model to harvest large data sets on the gene functions underlying development and disease. Fish with genetic disorders corresponding to human diseases are produced by chemical mutagenesis (forward genetics) or targeted knockout (reverse genetics), and are phenotypically characterised. These disease models should aid clinical researchers and the European pharmaceutical industry in the development of new therapies. This project has also contributed to basic knowledge of human development. A smaller project called ZF-TOOLS aims to develop a case study for an anti-tumour drug screening system, based on implantation of fluorescently labelled tumour cells into zebrafish embryos.

Other models

The European Commission is also supporting functional genomics research projects in other model organisms including Xenopus (X-OMICS, EuTRACC), ascidians (TransCode, Plurigenes) and nematodes (NemaGENETAG). Although not discussed here, major programmes are also in place for microorganisms and plants.

Future directions and funding opportunities through the FPs of the European Union

During FP7, research activities on model organisms will continue to receive substantial financial support. As a result of the first two calls for proposals published under the cooperation programme in the health priority, the EuroSyStem project, which uses mouse mutants to address the differentiation of stem cells, has received funding, and several contracts for other projects in support of mouse functional genomics are currently being negotiated. Intrafrontier is a project funded by the capacity programme of FP7 that brings together 15 European laboratories running large-scale infrastructures for mouse functional genomics. They form a coalition

with a significant number of funding agencies, in order to develop the prerequisites for a common European infrastructure for comprehensive phenotyping and archiving of mouse models.

In March 2007, a conference involving groups working in the area of mouse functional genomics was organised in Brussels by the European Commission, Genome Canada and the NIH. The aim was to discuss current and future approaches for mouse functional genomics, and to plan for the future use of mouse resources to facilitate translational research across the spectrum from basic biomedical sciences to experimental medicine. Recommendations put forth at this meeting are expected to be published soon.

The third call for proposals of the cooperation programme in the health priority was published in September 2008. It foresees funding for one or more large-scale integrating projects (European Commission funding of between €6-12 million) addressing a topic entitled: 'Large-scale functional genomics effort in multicellular organisms to elucidate the function of human gene products'. The projects should aim to understand the functions of human gene products, through systematic and multidisciplinary large-scale functional genomics in multicellular organisms that are relevant for human health and disease. The projects should, where possible, integrate with international efforts in this area. The deadline for submitting the proposals is 3 December 2008 and the evaluation will then proceed through a two-stage procedure. More details about the call can be found at: http://cordis.europa.eu/fp7/dc/index.cfm?fuseaction=UserSite.CooperationDetailsCallPage&call_id=141.

In 2009/10, the European Commission hopes to organise a workshop that will bring together experts in mouse functional genomics and other model organisms, with human clinicians and geneticists. The workshop will explore the ways in which these scientific and medical communities might best interact to take advantage of model organisms to elucidate the mechanisms of, and susceptibility to, human disease, and to develop more efficient therapies and diagnostic tools.

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COMPETING INTERESTS

The authors declare no competing financial interests.

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This article was written by a Scientific Officer within the European Commission. It is part of an ongoing series that will include the perspectives of agency officials on the qualities they look for in grant applications and their expectations for the field's future. These articles also present resources that their agency provides to support the larger community of medical scientists. Please see related article 'The baffling multitude of disease models for the study of human disease – how can the scientist navigate the huge amount of data and receive guidance?' in *DMM* Volume 1, Issue 2/3, pages 99-102.