Of mice and men

Dr Lluís Montoliu, Research Scientist at the Spanish National Research Council (CISC), highlights the emerging role that the nation is playing in the study of the human genome...

Spanish scientists, unfortunately, did not participate in the genomic momentum, when the human and, subsequently, the mouse genomes were first revealed in 2001 and 2002, respectively. Other than punctual collaborations, Spain was not directly involved in one of the greatest recent revolutions in biology and biomedicine. Once the genomes were initially analysed, it became obvious that the number of genes we all carry had been largely overestimated. Today we know that a bit more than 20,000 genes appear to constitute the genome of a mammalian organism, including humans and mice.

Surprisingly, mice and human genes are extremely similar (95% homologous), both at the level of the sequences and also regarding their inherent functions. This high degree of conservation made it possible to study mouse genes to understand the human counterparts. The genomic comparative approach enabled the investigation of normal gene function, in physiological situations, and their abnormal behaviour, in pathological conditions. Collectively, all the approaches and strategies aiming to the comprehensive description of human genes, through research conducted on the mouse genes and using mice as animal models of human diseases, are known as 'mouse functional genomics'. Here, Spain had a second chance and claimed its deserved place in Europe, in the scientific world.

Since the early 90s, many genetically modified mouse strains, transgenic and knockout (mutants) had been created, engineered by the fantastic toolbox available to mouse geneticists, enabling them to devise precise gene alterations, in just one locus, leaving the rest of the genome untouched. These gene mutations could, in principle, be created for each one of the 20,000 genes, thereby addressing the function of the corresponding gene through the phenotypic analysis of the resulting mouse mutant. However, in spite of scientists' efforts, the statistics of the reference databases stated that only about half of the genes had ever been explored, and only about 1,000 human diseases had been ever modelled and investigated in mice.[1]

Of course, a few of the already investigated genes had been worked out by Spanish scientists at research centres of excellence such as CNB, CNIO, CRG, IRB, CNIC, at several universities, research institutions such as CSIC, ISCIII and CIEMAT or network biomedical initiatives such as CIBERER and CIBERNED.

In order to reverse the situation, several years ago key international researchers in biomedicine decided to systematically study the function of all mouse genes, by knocking all of them out, one after the other. Several international projects were assembled, eventually merging into the 'International Knock-Out Mouse Consortium' (IKMC, www.knockoutmouse.org). The rationale of this high-throughput approach was to discover the function and role of each of the human genes through the inactivation of the corresponding locus in the mouse genome, and, specifically, through the investigation of the resulting phenotype in the animal, its associated characteristics, which could shed light on the role of this gene in normal human physiology and its potential involvement in pathology.

Logistically, the IKMC is a challenging project. Not all biomedical research institutions can produce, store and analyse the 20,000 mouse mutations being generated, therefore archive repositories were created or boosted from their initial foundation plans. At these archives, all these newly engineered mouse strains could be safely cryopreserved in the form of frozen sperm or embryos, and eventually distributed to interested researchers. In Europe, the reference repository for mouse strains is the European Mouse Mutant Archive (EMMA, www.emmanet.org), established in 1999 by the European Commission; it was formed by several nodes across different countries where Spain, again, had not been historically involved. In Spain, in 2007, from the Centro Nacional de Biotecnología (CNB) and with the full support of the CSIC and the entire Spanish biomedical research community, we initiated a bottom-up strategy, contacting colleagues at national research institutions and requesting their support for the initiative.

Eventually, with the support received we approached the Spanish authorities (Ministry of Science and Education, MEC), which presented the case before the project coordinators and the European Commission. The entire

process led us to an invitation to join the EMMA project through the cryopreservation and animal facilities at the CNB (www.cnb.csic.es/~criocnb), thereby becoming the Spanish EMMA node and, hence, contributing to the archiving and distribution tasks of the many mouse mutants that are internationally being generated, requested and distributing. The Spanish EMMA node has been in operation since January 2009 and is engaged in the adequate cryopreservation and distribution of 200 mouse strains during the four years of the current European project. A good proportion of these mouse strains directly come from the European Conditional Mouse Mutagenesis (EUCOMM, www.eucomm.org) project, part of the IKMC.

However, the challenges of the IKMC project are not just about logistics, solved by archives such as EMMA, but also regarding the phenotypic analyses that must be conducted for each of the mouse mutant strains being generated. Irrespective of the research centre where these analyses are being carried out, there must be a uniform, standardised manner to explore a new mouse mutant. In Europe, pioneer projects, such as EUMORPHIA (www.eumorphia.eu), have defined a set of 'standard operating protocols' (SOPs) that could be applied universally, aiming to be able to compare results across the globe.

In EUMORPHIA, there was only one partner from Spain, the CNIO. The systematic phenotyping, through the use of SOPs, of all new mouse mutants being created by IKMC has become possible at the Mouse Clinics, where several pipelines of tests and medical examinations are applied to mice in an organised and comprehensive manner. One such Mouse Clinic will be built in Spain at the campus of the Universitat Autònoma de Barcelona (UAB). In Europe, a limited number of Mouse Clinics exist and are currently in operation (Munich, Strasbourg, Harwell, Hinxton, etc.). With the addition of the Spanish Mouse Clinic, and a few others that are already planned, the phenotyping capacity of Europe will be increased dramatically. At the Mouse Clinics, a pilot project (EUMODIC, www.eumodic.org) has already been initiated, aiming to phenotype 650 of the mouse mutants being generated. Spain is also part of EUMODIC through the Mouse Clinic at the UAB and the CNIO.

Therefore, in 2010, Spain is already part of the 'mouse functional genomics' core of Europe through its participation in the EMMA (Madrid) and EUMODIC (Barcelona and Madrid) programmes. Due to these implications in 'archiving' and 'phenotyping' tasks, the two nodes in Spain, the CNB-CSIC in Madrid and the UAB in Barcelona, were also invited to join the European Science Forum for Research Infrastructures (ESFRI) project Infrafrontier (www.infrafrontier.eu), whose preparatory phase started in 2008 and will finish in 2011.

Infrafrontier will organise two complementary and linked infrastructure networks: Phenomefrontier, for large-scale and comprehensive phenotyping; and Archivefrontier, for archiving mouse models, serving the European genetics and biomedical research community for the benefit of human health. At the current preparatory phase, Infrafrontier has identified initiatives in Europe that are planning to establish, or renew, archiving and phenotyping centres.

In Spain, two initiatives have been declared: in Barcelona, the Mouse Clinic, to be built at the UAB, focused on phenotyping tasks of new mouse models; and in Madrid, the Spanish Mutant Animal Archive for Research and Technology (SMAART) centre, to be built in the Madrid region, supported by universities (UAM and UCM), research institutions (CSIC, CIEMAT and ISCIII) and the governmental and autonomic scientific authorities. The SMAART centre will be oriented to archiving procedures.

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Therefore, in the last 10 years of the post-genomic era, Spanish scientists have not only contributed extensively to our understanding of the human genome, and to the progress of biomedicine through the creation and analysis of many new mouse models of human diseases, but have also managed to firmly connect Spain to continental and international initiatives on subject such as IKMC, EMMA and EUMODIC. Whatever future benefits these large consortia will hopefully bring to the biomedical research community, Spain will be part of the core, a contributing player and no longer a simple spectator.

[1] Mouse Genome Informatics, MGI; www.informatics.jax.org/mgihome/homepages/stats/all_stats.shtml

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