The mouse ascending: perspectives for human-disease models

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The laboratory mouse is widely considered the model organism of choice for studying the diseases of humans, with whom they share 99% of their genes. A distinguished history of mouse genetic experimentation has been further advanced by the development of powerful new tools to manipulate the mouse genome. The recent launch of several international initiatives to analyse the function of all mouse genes through mutagenesis, molecular analysis and phenotyping underscores the utility of the mouse for translating the information stored in the human genome into increasingly accurate models of human disease.

Mice and humans share most physiological and pathological features: similarities in nervous, cardiovascular, endocrine, immune, musculoskeletal and other internal organ systems have been extensively documented. Comparative analyses of mouse and human genomes have provided insight into our common features and have guided powerful genomic manipulations in the mouse to generate models of human pathologies. These mice can then be subjected to biomedical experimentation not possible in patients. As more is learned about human diseases that mice do not usually contract, a growing armamentarium of experimental approaches is being applied to 'humanize' mouse physiology and mimic our clinical manifestations.

How did the mouse ascend to such prominence in biological research? Compared with other mammals that contract our diseases, the mouse is cheap, easy to maintain and straightforward to breed in captivity . Mice also have a long history of cohabitation with humans[1]. Our chequered relationship with the mouse has its roots in the battle over agriculture and food stores in Africa more than 10,000 years ago. The subsequent domestication of the house mouse is likely to have originated in China and Japan, where the first 'fancy' mouse breeds were developed. By the late 1800s, these mutants attracted the attention of mouse collectors and distributors in Europe and the United States. Unusual coat colours and other variations in visible features attracted Victorian mouse fanciers to these animals, many of which are the direct forebears of today's standard laboratory mouse strains. The economics of supplying inbred strains to mouse fanciers was soon dwarfed by a burgeoning investment in mammalian genetics, as researchers noted a striking resemblance between the characteristics of some mouse mutants and certain human diseases.

To many scientists in the 1930s, mice were the obvious choice for genetic experimentation[2]. Small, docile, rapid and prolific breeders, they were also readily available from the fancy mouse collectors of the day. Since then, the mouse has attracted the attention of biologists and biomedical researchers, and a new billion-dollar industry has sprung up in response, breeding and shipping over 25 million mice to research laboratories each year. Repositories routinely distribute hundreds of unique inbred mouse strains[3] to laboratories around the world, as well arranging the transport of genetically engineered mutants prone to different cancers, heart disease, hypertension, diabetes, obesity, osteoporosis, glaucoma, blindness and deafness, neuropathologies such as Huntington or Lou Gehrig disease, and behavioural disturbances including anxiety and depression[4,5]. Mice with various immunodeficiencies are particularly valuable for studying tumour growth and infectious diseases, and can act as hosts to human tissues and cells[6]. Metabolic, physiological and behavioural stresses can be tested on mice models, the results of which can be compared directly with human clinical information. Through these advances, the lowly mouse, once vilified as vermin and agricultural pests, has now emerged as the premier mammalian model system for biomedical exploration.

New tricks of the mouse trade

The mouse's current appeal as a model for human disease has its origins in the historical selection and breeding initiatives used for producing offspring with specific traits. Numerous mutants were generated by exposing mice to radiation or DNA-damaging chemicals[1,2]. Although rapid and relatively inexpensive, these early approaches introduced multiple unknown genomic alterations that required extensive follow-up work to locate and characterize. More recently, researchers have generated single targeted mutations using an array of innovative genetic technologies that produce specific genomic changes[5]. For example, transgenic mice, in which the gene of interest is injected into a fertilized mouse egg, produce offspring with extra copies of the transgene; this transgene is often engineered to be expressed in a tissue-specific pattern or to be inducible with certain drugs.

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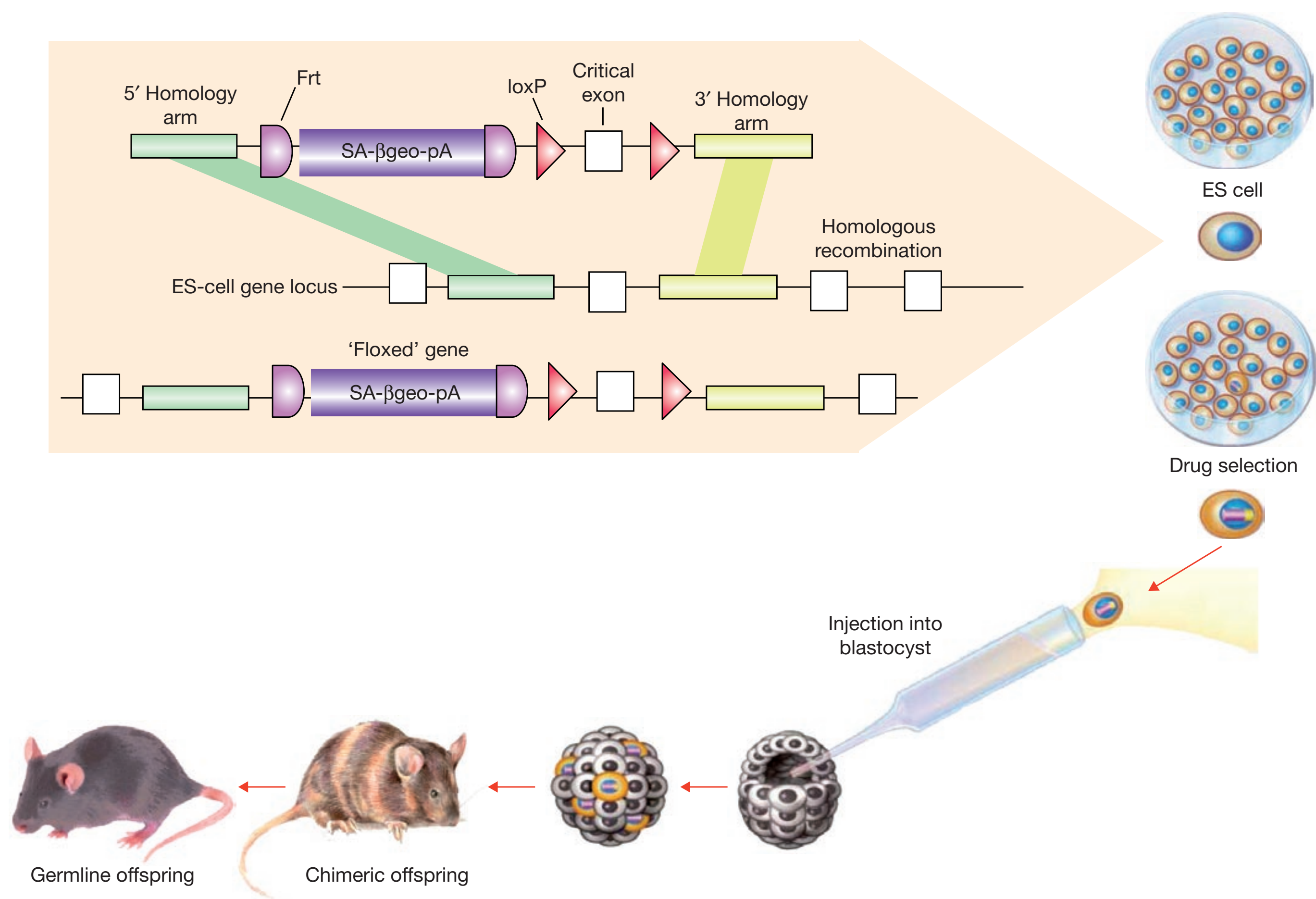

Figure 1 Large-scale strategy for mutagenesis of the mouse genome: a conditional knockout vector is created for each gene and introduced into mouse embryonic stem (ES) cells. The exon of the target gene is flanked by DNA motifs (loxP) that are recognized by a specific bacterial Cre recombinase. Homologous recombination between the cellular gene and the knockout vector flanking DNA sequences (green and yellow) results in the incorporation of the vector into the host ES-cell genome. The presence of a drug-resistance and marker gene (β-geo; purple) in the knockout vector allows targeted ES cells to survive drug selection, but these markers can be removed by a second recombinase (Flp) that recognizes a unique sequence (known as FRT). Mutant ES cells are injected into a host mouse blastocyst, which, when implanted into a foster mother, gives rise to chimeric offspring. This effect can be seen in their coat colour. Incorporation of mutant ES cells into germ cells results in germ-line transmission of the ES-cell genome to subsequent offspring.

Alternative methods for mutagenesis rely on the manipulation of mouse embryonic stem (ES) cells. At present, a number of mutagenesis strategies based on ES cells are used, all of which use homologous recombination to alter genes in their original location, producing either 'knock outs' to cripple gene function or 'knock ins' to introduce an altered gene version. Knockout technology is extraordinarily powerful and generally produces loss-of-function mutations, which disrupt the earliest role of a gene in embryogenesis, but this often confounds the analysis of gene dysfunction at later stages of development or adulthood, which is when many human diseases are manifest. Further refinements to these manipulations include the conditional induction of genomic changes (Fig. 1). By crossing a mouse bearing a recombinase effector gene with one carrying the target gene, a mutation is induced by recombination in a spatially and temporally controlled way (Fig. 2). Because most common human diseases are acquired later in life, the generation of new mouse models of human disease currently relies heavily on this conditional mutagenesis technology that limits gene mutation to specific tissues or to a specific life stage.

To meet the growing demand for conditional mutant models, internationally coordinated initiatives have been established for the systematic generation of mouse mutants on a large scale using various strategies[7,8,9] (Table 1). The majority of these initiatives are committed to the production of mutant mouse ES-cell lines, each of which carries an altered — or 'floxed' (Fig. 1) — allele of a particular gene that harbours Cre recombinase sites. These mutant ES-cell mutations can be readily transformed into mice by using blastocyst injection, and the mutation is activated by crossing with the desired Cre recombinase driver strain.

As a complementary strategy, forward genetics — where the observation of a phenotype is followed by the identification of the responsible genetic loci — has been valuable for discovering new and unexpected gene–function relationships. In common with the early random-mutagenesis strategies, more recent methods for unbiased, random mutation in the mouse rely on post-mutagenesis detection of the sequence change, which has now been streamlined with the advent of positional cloning, haplotype maps, single-nucleotide polymorphisms (SNPs) and high-throughput genome sequencing. Newly developed reagents for mutagenesis include the reconstructed

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Table 1 International mouse genetics and genomics initiatives

Consortium		Mission and aims	URL
EUCOMM	European Conditional Mouse Mutagenesis Programme	Genome-wide mouse mutagenesis	www.eucomm.org
KOMP	Knock-out Mouse Project	Genome-wide mouse mutagenesis	www.nih.gov/science/models/mouse/knock-out/
NorCOMM	North Americam Conditional Mouse Mutagenesis Programme	Genome-wide mouse mutagenesis	www.norcomm.org
IMMC	International Mouse Mutagenesis Consortium	Coordinating the worldwide efforts of mouse mutagenesis consortia (above)	http://www.informatics.jax.org/mgihome/other/phenoallele_commun_resource.shtml#pointer1
FIMRe	Federation of International Mouse Resources	Coordinating activities and setting standards for repositories worldwide	www.fimre.org
IMSR	International Mouse Strain Resource	One-stop shop for searching archives across the globe for mutants of interest	www.informatics.jax.org
EMMA	European Mouse Mutant Archive	European network of repositories, archiving and distributing mutants to genetic community	www.emmanet.org
EUMODIC	European Mouse Disease Clinic	Pilot network for large-scale systematic phenotyping of mouse mutants	www.eumodic.org
Collaborative Cross	Complex Trait Consortium	A large panel of recombinant inbred strains derived from a genetically diverse set of founder strains, designed specifically for complex trait analysis	http://www.complextrait.org/

mariner element Sleeping Beauty[10] and piggyBac (PB), a transposon from insects that functions in mammals. Based on the principle of gene trapping (in which a genetic locus is disrupted by a reporter that simultaneously provides a readout of the disrupted gene's expression pattern), these DNA elements insert randomly into the genome and maintain the capacity to relocate and integrate at different genomic sites, generating tagged mutations on a large scale[11]. In a recent innovation, a PB-transposon-based mutagenesis strategy was combined with Cre-loxP recombination to mediate efficient *trans*-allelic recombination *in vivo*[12]. This facilitates the generation of large germline deletions, duplications or translocations between nonhomologous chromosomes. In principle, this system can be used for large-scale functional genomic analysis by systematically mutating extensive regions of the mouse genome simply through breeding.

Phenotype-driven, forward-genetic screens using the random chemical mutagen *N*-ethyl-*N*-nitrosourea (ENU) have been instrumental over the past decade in identifying a plethora of disease models and identifying novel genes and pathways[13]. With the advent of high-throughput genome sequencing, ENU is likely to enjoy continuing popularity. ENU introduces point mutations and can therefore generate alleles with a range of effects including loss-of-function, gain-of-function and dominant-negative mutations (see Box 1). Some of the alleles generated will have modest effects and be more similar to the genetic variation underlying complex disease in the human population. Moreover, large parallel archives of DNA and sperm from mice with mutations caused by ENU have been generated at several research centres. As genome re-sequencing costs plummet, it will become feasible to generate comprehensive datasets of ENU mutations for every gene in every mouse from the archive. Point mutations in any gene of interest can be readily recovered from the parallel sperm archive, providing an extraordinary new mutant resource for gene–function studies.

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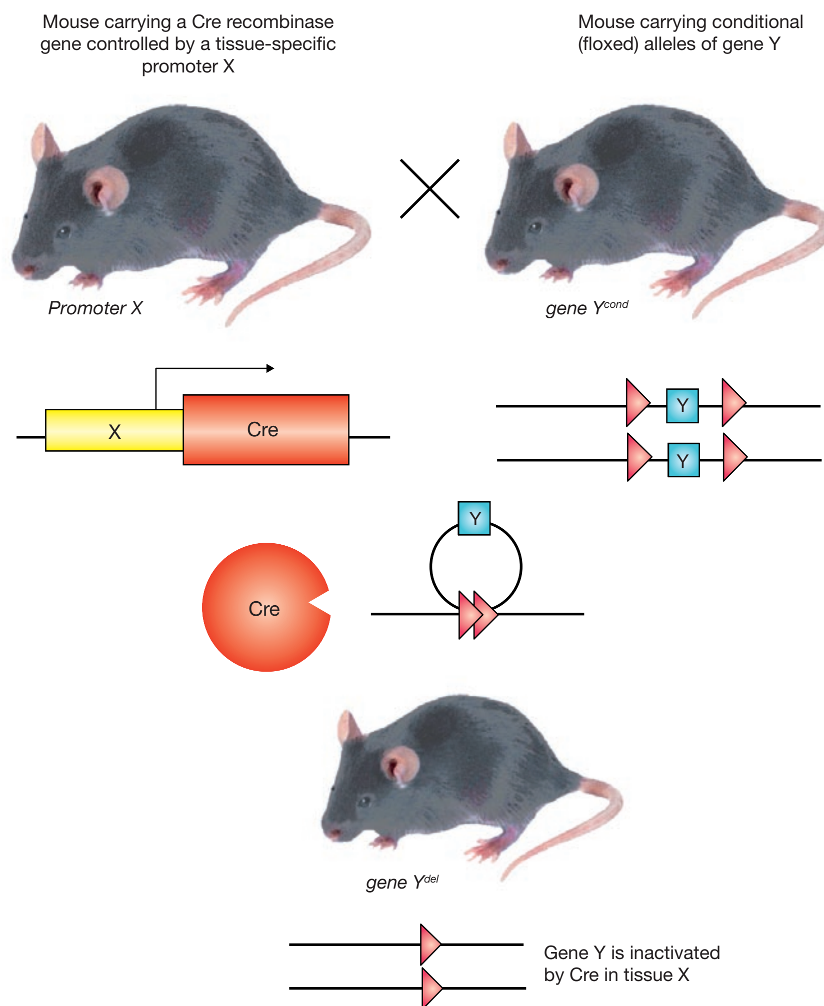

Figure 2 Principles of conditional mutation. The gene cassette encoding Cre recombinase is usually engineered in a separate mouse strain. When Cre recombinase (red circle) is introduced, either as a transgene by crossing into a mouse line carrying the targeted gene locus or on a viral vector, the DNA between the loxP sites (red triangles) is removed, thereby inactivating the gene.

Delving deeper into disease mechanisms

The mechanisms underlying the developmental origins of disease remain poorly defined. Epigenetic tagging of genes, through DNA methylation and histone modification, controls the function of the genome at different levels and maintains cellular memory after many cellular divisions. Importantly, tagging can be modulated by the environment and is involved in onset of diseases such as cancer[14]. It is becoming clear that epigenetic changes are involved in the human disease as well as in normal development. A unifying theme of disease epigenetics is a defect in phenotypic plasticity. (Plasticity is the cells' ability to change their behaviour in response to internal or external environmental cues). This model proposes that hereditary disorders in the epigenetic apparatus lead to developmental defects, that cancer epigenetics involves disruption of the stem-cell programme, and that common diseases with late-onset phenotypes involve interactions between the epigenome, the genome and the environment. Increased understanding of epigenetic-disease mechanisms could lead to disease-risk stratification for targeted intervention and to targeted therapies[15].

Increasing evidence from functional analysis of mammalian genomes reveals important regulatory roles for non-coding sequences. Recent comprehensive analysis of a small portion of the human genome[16] suggests that a much higher proportion of the mammalian genome is transcribed into RNA than previously recognized. Over a third of mammalian coding transcripts are silenced by microRNAs (miRNAs), potent negative regulators of gene expression that are increasingly implicated in the establishment and maintenance of genetic programmes[17] and are a likely source of significant phenotypic variation underlying complex traits[18]. Mutations in non-coding transcripts such as miRNAs may cause a significant number of disease phenotypes (see Box 2) and are likely to be key regulators of disease mechanisms that can only be modelled in a mammalian context such as the mouse. *In vivo* application of emerging technologies involving endonuclease-mediated RNA cleavage and ligation[19] in mice might permit conditional repair of genetically defective transcripts that contain a loss-of-function sequence, and, in principle, could be applied to destroy, modify or restore the formation of regulatory noncoding RNA species such as miRNAs.

The challenges of mouse-mutant characterization and distribution

Despite the remarkable toolkit available for generating mutations in mice, the biggest

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BOX 1 NEW MOUSE MODELS OF COMPLEX HUMAN DISEASES

Inflammation of the middle ear, known as otitis media (OM), is the most common cause of hearing impairment and surgery in children. Recurrent OM and chronic OM have a strong genetic component, but nothing is known of the underlying disease-causing genes in humans. Two new dominant mutants, *Jeff* and *Junbo*, have been identified from ENU-mutagenesis screens, and mice carrying these mutations develop a conductive deafness caused by chronic suppurative OM that recapitulates the human pathology. The *Jeff* mutant carries a mutation in an F-box gene, *Fbxo11*, a member of a large family of proteins that are specificity factors for the SCF E3 ubiquitin-ligase complex[30]. Initial studies of *FBXO11* SNPs in human OM families have uncovered nominal evidence of association, indicating the genetic involvement[31] of human *FBXO11* in chronic OM with effusion and recurrent OM. *Junbo* carries a mutation in the *Evi1* transcription factor, a gene previously implicated in myeloid leukaemia. *Evi1* represses the TGF-β signalling pathway by binding to *Smad3*. The *Junbo* mutation provides *in vivo* evidence implicating this pathway in the development of OM[32].

challenge faced by the mouse-genetics community is determining the phenotype of each mutant[20,21]. A profound understanding of the systems biology of the mouse will require a comprehensive phenotypic description of every mutant generated. However, even a primary but systematic characterization of biochemical, physiological and developmental phenotypes for mutants for every gene in the mouse genome is an enormous undertaking. Standardization of phenotyping procedures will be crucial to generate comparable sets of data from phenotyping centres around the world (Table 1). In addition, there is a pressing need to develop appropriate ontologies to describe the phenotypes and to relate them in a systematic and coherent way to the equivalent human disease state[21].

Advances in the manipulation of the mouse genome and characterization of mutant phenotypes have run in parallel with the development of an equally sophisticated set of technologies to preserve mouse mutants and to propagate strains with poor breeding capacity. Reproductive technologies, including cryopreservation of embryos and sperm, *in vitro* fertilization and ovary transplantation, have been modified for use in the mouse. Distributing the mouse mutants to research institutes presents another logistic barrier that the field is currently struggling to overcome. Laboratories that do not have access to the reproductive technologies necessary to derive mice from frozen embryos or sperm require receipt of live mice. However, transport of live animals is expensive and requires complex logistics, particularly when large distances, international boundaries and strict quarantine restrictions are involved. The establishment of centralized supply centres on several continents[22] (Table 1) promises to alleviate these problems, which are escalating as the large-scale mutagenesis programmes daily add more options to the list of available mutants.

Measuring mice against the competition

From a practical point of view, the mouse is by no means the easiest model system for discerning principles of body form and cellular function. Historically, the tractable genetics of yeast, worms and flies have proven extremely powerful for studying many basic aspects of organismal biology. The genetic and molecular underpinnings of many conserved cellular processes involving orthologues to human-disease genes have been elucidated in these invertebrate organisms. Metabolic pathways, cellular proliferation and dynamics, early embryonic inductive circuits and principles of morphogenesis have been elegantly elucidated by using the large-scale 'forward-genetic' mutagenic strategies possible in these organisms[23]. Owing to the considerably greater evolutionary timespans separating mammals from invertebrates, these popular models do not share with humans many of the structures and organs that are targeted in disease, making vertebrate models more desirable for studying many aspects of human biology.

Fish models represent particularly elegant genetic systems for the dissection of vertebrate organ formation and dysfunction. The initial popularity of the zebrafish and a related teloest, the medaka, derived chiefly from the transparency of its embryos, which permitted rapid visual screening for dysmorphologies of embryonic and larval stages produced by random mutagenesis. This has led to the rising popularity of the fish as a powerful model for mapping phenotype to single-gene disorders. Pharmacological applications also promise to be particularly appropriate for the zebrafish, which is becoming the preferred vertebrate model for the screening of chemical libraries[23]. However, directed manipulation of the fish genome still lags well behind that of the mouse. This is partly because the mouse enjoys obvious advantages in surgical manipulations of adult stages not yet possible in fish. Although obvious differences in fish-organ formation and physiology ultimately limit its applicability to the dissection of human disease, the value of the fish as a complementary vertebrate model for gene discovery and complex-trait analysis should not be underestimated. The rat is also an increasingly relevant disease model. Genetic studies in the rat continue to make significant contributions, providing important insights into disease genetics in areas such as cardiovascular disease and hypertension[24]. However, unlike the mouse, the genetic toolkit for generating new mutations is limited, and improving the available tools and genetic resources is a key goal of the rat-genetics community.

Refining the models: shared resources for common diseases

Despite recent exciting advances in animal modelling, the magnitude of the task of capturing the full spectrum of human disease is beoming increasingly obvious. Complex-trait analysis is being attacked on an international scale through establishment of The Collaborative Cross project by the Complex Trait Consortium[25] (Table 1), which aims to provide a common reference panel of 1000 recombinant inbred mouse strains that can be used to identify and map the loci and genetic interactions between the subtle gene mutations underlying many common disorders. These mutations can arise from disruption of multiple genes encoding proteins with interrelated functions. Alternatively a single mutant protein can cripple the multiprotein complex in which it acts. Yet, pathologies with seemingly unrelated clinical presentations can derive from different mutations in the same gene, when the protein it encodes is involved in multiple metabolic pathways. Human geneticists are already joining forces with bioinformaticians to model their findings. Systematic approaches

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BOX 2 REVEALING MECHANISMS OF MICRO-RNA-RELATED DISEASE IN THE MOUSE

In the mammalian heart, two myosin genes, *MHC*α and *β*, are regulated in an opposing pattern in development and during stress to the adult heart. Even the small increases in βMHC composition induced in cardiac hypertrophy and heart failure can compromise cardiac function. A recent study in mice (van Rooij *et al.* 2007) revealed that miR-208, an miRNA encoded by an intron of the mammalian αMHC gene, is responsible for this stress-dependent switch in MHC composition. Knocking out miR-208 sequences severely blunted cardiac βMHC expression in response to several hypertrophic insults to the adult heart. miR-208 operates, at least in part, by repressing expression of the transcriptional coregulator THRAP1, which in turn represses βMHC expression in the adult heart. These results suggest that therapeutic manipulation of miR-208 expression or interaction with its mRNA targets might improve cardiac function in heart failure.

to uncovering complex interactions between genes and phenotypes operating in human diseases have already revealed new relationships that are not apparent from gene-by-gene analyses[26,27].

Capturing the full complexity of the human 'diseaseome' will require sharing tools between areas of research that have traditionally been distinct. An encyclopaedic knowledge of the direct and indirect protein interactions that govern mammalian physiology will be necessary to dissect and test the postulated mechanisms underlying many acquired human disorders. Primed with the knowledge of the human genome, new consortia have been established to develop a comprehensive resource of well-characterized affinity reagents for analysis of the human proteome[28]. A parallel effort will be crucial to establish a systematic bank of affinity reagents and specific binding molecules directed against individual mouse proteins, including variant forms and modifications.

Finally, the escalating financial burden of providing useful mouse models of complex human diseases needs to be shouldered internationally. Despite the considerable efforts of international consortia that are generating and phenotyping mutants, over 70% of mammalian genes mutated in ES cells still do not have a corresponding mutant mouse line, and still fewer have an assigned phenotype. If these projects continue to be funded, the gap will close, resulting in a valuable catalogue of mutations underlying inherited mammalian traits. Distributed repositories for these models will also mean that the expense is best shared globally (Table 1). The research community as a whole must now consider the next steps if we are to capitalize wisely on the investment already made in the mouse. Prioritizing disease-gene candidates identified by linkage analysis or association studies in humans will require large-scale genetic suppressor and enhancer screens, against a background of known disease-causing mutations or inbred strains. Such sensitized screens are in their infancy in the mouse, but early results are promising[29]. However, given the costs, other model organisms such as fish will undoubtedly have a significant role in sensitized screening. A concerted approach exploiting the advantages of each model system is clearly the most rapid and cost-effective way to crack the big questions in human disease.

Future prospects for clinical application

The continuously evolving field of mouse-genetic manipulation has already made a profound impact on medical research, a trend that will only intensify in the years to come. Recent comparative analysis of human and mouse genomes has uncovered numerous novel gene pathways whose roles in human physiology and dysfunction can now be dissected through modelling in the mouse. This is a crucial step in understanding the underlying genetic susceptibilities to disease in human populations, and for identifying potential targets and designing tests for pharmaceutical intervention. Although the ultimate model for human maladies will always be man himself, the increasingly dynamic communication between mouse researchers and clinicians promises to provide invaluable insights into our own pathology while shedding light on areas where our evolutionary paths have diverged. These efforts have begun to address the remaining limitations of mouse models, by developing humanized mice that resolve differences in haematopoiesis, immunity, infection, cancer biology and neurobiology, to name just a few. As we have learned, the most pervasive human diseases are caused by the interplay of environmental influences and underlying complex traits, and the sophistication of our models must keep pace. The mouse is rising to the challenge.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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