

timeline

The house mouse, *Mus musculus*, has been inextricably linked with humans since the beginning of civilization — wherever farmed food was stored, mice would be found. Many of the advances in twentieth-century biology owe a huge debt to the mouse, which has become the favoured model animal in most spheres of research. With the completion of the draft sequence of its genome published in this issue, the mouse promises to continue to provide us with an essential resource for all aspects of biology. In this timeline, we chart the key events in the history of the mouse that led to this landmark achievement.

75–125 million years ago A common ancestor of mice and humans



The common ancestor of mice and humans — a creature about the size of a small rat — lives alongside the dinosaurs. The picture above is 125-million-year-old *Eomaia scansoria*, the earliest known representative of the Eutheria lineage, which gave rise to all modern placental mammals.

~6 million years ago *Mus*



The genus *Mus* is established, although the name comes much later, via Latin, from the ancient Sanskrit word 'mush', meaning to steal. *Mus musculus*, the house mouse, does not appear as a distinct species until after the end of the last ice age, at about 8,000 BC. The picture shows an early depiction of the mouse in a detail from a Chinese zodiac dating from AD 877.

1900 Fancy mice become lab mice

Generations of 'fancy mice' are created during the nineteenth century, as hobbyists selectively breed the

house mouse.

These mice have a range of different coat colours, and among the mutations created are agouti and satin, both still used in research today. In 1900, Abbie Lathrop, a retired schoolteacher, turns her hobby of breeding fancy mice into a business, selling the animals from her farm in Granby, Massachusetts. Within two years, biologist William Ernest Castle (above) has begun buying mice from her to conduct experiments in his lab in nearby Harvard, testing Mendel's laws of inheritance on coat colours.



1909 Birth of the lab mouse



Clarence Cook Little (above), a Harvard biologist from William Castle's lab, develops the first inbred mouse strain, known as DBA (dilute brown non-agouti). He is convinced that studying a genetically pure breed will unlock the secrets of human diseases such as cancer. This event is subsequently hailed as the birth of the modern lab mouse, and DBA mice are still used in genetics labs today.

1921 C57BL

Clarence Little breeds the mouse strain C57BL from a female mouse code-numbered 57 bought from Abbie Lathrop's farm. C57BL becomes one of the most widely used and important mice to geneticists, and is the strain that will have its genome sequence completed and published in 2002.

1929 The Jackson Laboratory



Two car barons, Edsel Ford (son of Henry) and Roscoe Jackson, head of the Hudson Motorcar Company, provide backing for Clarence Little to set up the Jackson Laboratory in Bar Harbor, Maine. The lab grows into one of the world's most important research centres for mouse genetics.

1972 First computer database for mouse genetics

Mouse Genome Informatics

The Jackson Laboratory updates its card-file database for mouse genetics by designing the first computer database for mammalian genetics. It forms the precursor to the Mouse Genome Database, which will serve as the hub of mouse-genome sequencing projects.

1982 First transgenic mouse



A team led by Richard Palmiter and Ralph Brinster fuse elements of a gene that can be regulated by dietary zinc to a rat growth-hormone gene, and inject it into fertilized mouse embryos. The resulting mice, when fed with extra zinc, grow to be huge, and the technique paves the way for a wave of genetic analysis using transgenic mice.

1987–89 The first knockout mouse

Teams led by Martin Evans, Oliver Smithies and Mario Capecchi create the first 'knockout' mice, by selectively disabling a specific target gene in embryonic stem cells. The three receive the Lasker Award in 2001 for this achievement, and the technique goes on to be used to create several thousand knockout mice.

1998 Mouse clones

After Dolly the cloned sheep in 1997, a team in Hawaii produces Cumulina and her clones, the first cloned mice.

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The life history of the mouse in genetics



1999 The Mouse Genome Sequencing Consortium



At its inception in 1990, the Human Genome Project included the mouse as one of its five central model organisms to have its genome sequenced. In 1999, with the human genome sequence well under way, three major sequencing centres (the Wellcome Trust Sanger Institute, the Whitehead Center for Genome Research and Washington University Genome Sequencing Center) launch a concerted effort to sequence the mouse genome, under the title of the Mouse Genome Sequencing Consortium. By 2002, the consortium has expanded to embrace scientists from 26 institutes in six countries.

2001 Feb The human genome

The first drafts of the human genome are published. The publicly funded International Human Genome Sequencing Consortium publishes its draft sequence in *Nature*, going head-to-head with Celera Genomics, a US-based company led by Craig Venter, which publishes in *Science*. Both of these milestone achievements provide a panoramic view of our genomic landscape, estimating a



size of 3.2 billion base pairs (Gb) and predicting some 31,000 genes. Much work needs to be done to produce a complete sequence, but the collaborative effort of the public consortium coupled with the Celera sequence reflect an unprecedented achievement.

2001 June The private shotgun mouse genome



Celera sells its draft mouse sequence, which has been generated by whole-genome shotgun sequencing — a technique in which the entire genome is sequenced at once. Five-fold coverage of the mouse genome is made available to private customers for \$45,000 for a three-year contract. Celera's sequence is made up of four

strains of mouse, including DBA, but not C57BL/6J — the subject of the publicly funded sequencing effort.

2002 May Mouse chromosome 16

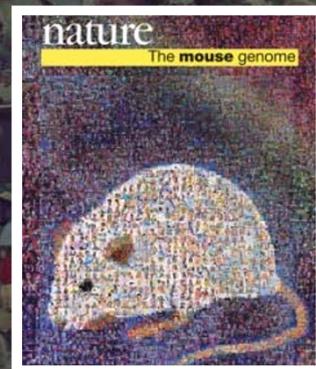
Using the sequence generated by Celera's private mouse genome, Richard Mural *et al.* publish an analysis of the sequence of mouse chromosome 16 in *Science*. They find that there is a large region with high genetic similarity to human chromosome 21, which has already been well characterized.

2002 Aug Physical map of the mouse genome



An international consortium provides the framework for the full determination of the mouse DNA sequence by building a physical map of the genome. Large blocks of correspondence between mouse and human sequences make it possible to lay out chunks of decoded mouse sequence and, conversely, the mouse map can be used to fill gaps in the human genome.

2002 Dec The mouse genome



The Mouse Genome Sequencing Consortium publishes the culmination of international efforts — a high-quality draft sequence and analysis of the genome of the C57BL/6J mouse strain. The estimated size is 2.5 Gb, smaller than the human genome, with less than 30,000 genes. About 40% of the human and mouse genomes can be directly aligned with each other, and about 80% of human genes have one corresponding gene in the mouse genome. Accompanying papers detail various other aspects of the genetic make-up of the mouse, and through the efforts of the RIKEN Genome Science Laboratory in Japan, many essential resources are made freely available.

For an extended, interactive version of this timeline, visit our Mouse Genome Web Focus at www.nature.com/nature/mousegenome, which also contains all of the articles on the mouse genome from this special issue, available free. These are accompanied by related articles from the archives of *Nature* and *Nature Reviews Genetics*, available free until 5 March 2003.