

## Advances in Embryonic Stem Cells

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### 2007 Nobel Prize Medicine

2007 was a very fruitful year for the field of genetic research. During this year, Mario R. Capecchi, Martin J. Evans and Oliver Smithies were awarded the Nobel Prize in Medicine or Physiology.

Capecchi, Evans and Smithies won the Nobel Prize for their discovery regarding the principles in introducing specific gene modifications in mice by the use of embryonic stem cells.

#### Stem Cell Research

There were two vital discoveries in their research. First is homologous recombination wherein DNA sequences are exchanged within two homologous chromosomes, one from the mother and the other from the father. The second key discovery is the use of embryonic stem cells. Embryonic stem cells can grow and differentiate into any type of tissue present in the body of the organism from which it was taken.



The banner features a bright orange background. At the top center is a white icon of a flask with a flame, followed by the word "EXPLORABLE" in a white, sans-serif font. Below this, the phrase "Quiz Time!" is written in a white, cursive font. Underneath are three white-bordered boxes, each containing a different image and a quiz title. The first box shows a pair of red roller skates on a wooden deck, with the text "Quiz: Psychology 101 Part 2". The second box shows a fan of colorful pencils, also with the text "Quiz: Psychology 101 Part 2". The third box shows a Ferris wheel at sunset, with the text "Quiz: Flags in Europe". In the bottom right corner of the banner, the text "See all quizzes =>" is written in white.

### The Three Brilliant Minds

Mario Capecchi was born 1937 in Italy. During high school, his primary inclination was sports. He was varsity of football, soccer and baseball. During college, he initially took political science but switched to physical science physics and chemistry. He finished his PhD in Biophysics in 1967 at Harvard University. He then became Howard Hughes Medical Institute Investigator and Distinguished Professor of Human Genetics and Biology at the University of Utah.

Martin Evans was born on the 1st of January 1941. As early as prep school, he was already exposed to

biology. During middle school, chemistry, physics and biology are his inclinations. During college in Cambridge, he took up biochemistry, finished his PhD in Anatomy and Embryology in 1969 in London. He then became Director of the School of Biosciences and Professor of Mammalian Genetics in Cardiff University.

Oliver Smithies was born prematurely on the 23rd of June 1925 in England. He initially planned to take up physics in college but ended up in a medical school. He then finished his PhD in Biochemistry in 1951 in Oxford University and became a professor of pathology and laboratory medicine in the University of North Carolina at Chapel Hill.

## Route to Nobel Prize of 2007

The concept of genetically introducing gene modifications in mice via embryonic stem cells has a pretty straightforward method: create a targeted gene modification in a chromosome of the embryonic stem cell and use these cells to grow mice that can transmit the chromosomal changes to their offspring. This method is highly dependent on two genetic principles: the exchange of specific chromosomal DNA sequences by homologous recombination, and development of embryonic stem cells that will allow genetic inheritance.

During the process of fertilization, the haploid sperm cell and the haploid egg cell unite to form a diploid zygote which has a new pair of chromosomes, one from the egg and one from the sperm. As the zygote develops, the chromosomes recombine with their homologues derived from the two parents and this process is called homologous recombination. Homologous recombination provides continuous genetic variation as the species pass their gametes to the succeeding generations.

In 1985, Oliver Smithies attempted to introduce DNA sequence from the human beta-globin locus into an erythroleukemia cell line and he found that specific exchange of the introduced gene with the homologous sequence in the erythroleukemia cell line is possible. This experiment of Oliver Smithies proved that targeted recombination of genetic materials is possible.

During the same time of Smithies discovery, Mario Capecchi was able to devise a method to introduce DNA directly into the nucleus of the target cell by the use of a glass pipette. The method developed by Capecchi allowed efficient transfer of genetic materials into random chromosomal locations which also leads into homologous recombination. This was a key discovery since Capecchi was able to prove that homologous recombination can occur in somatic cells. In his succeeding studies, he was able to perfectly rescue a genetically mutant cell by introducing a functional copy of the dysfunctional gene.

The next challenge was to be able to ensure heritability of the genetic modifications so that the changes can be passed on to future generations. The only solution to this problem was to use a cell line of embryonic origin. Smithies and Capecchi looked into the work of Martin Evans for the solution. Martin Evans discovered that [embryonic stem cells](#) [1] can be taken directly from early mouse embryos. His next step was to test whether his embryonic stem cells can actually contribute to the germ line, thus, allow heritability. He proved this by injecting blastocysts with cultured embryonic stem cells that were infected with a retrovirus since retrovirus integrates their genes into the chromosome. He found that the retroviral DNA was detectable in both somatic and germ-line cells of the developed blastocysts.

The collaboration of the three great minds initially aimed to repair defects in the 'hprt gene'. They identified and selected cells that have undergone homologous recombination thereby eliminating the defective gene. This was then implanted into a surrogate mother who gave rise to a mice strain that is homozygous to the inert gene which they called a [knockout mouse](#) [2]. This work wherein gene targeting is done by homologous recombination while ensuring heritability of the genetic changes led to the understanding of the function of the genes present in our genomes.

## Clinical Implications

This method became a norm in genetic research. A lot of researches were done using this method to explore the functions of different genes. This development made it possible to study the function of almost any gene in a living animal. Furthermore, given the high degree of similarity between the mouse and human genomes, this technology of gene manipulation has important clinical implications. Considering the success of gene targeting in the genome of mice and its similarity with our genome, it is reasonable to envision clinical applications of a similar strategy used in medical settings. Maybe it is possible to genetically modify stem cells to restore the function of a dysfunctional gene in specific tissues. Maybe we can eliminate genes which are vital in the development of life-threatening diseases like cancer, diabetes, heart disease, stroke and a lot more. Maybe this discovery is the key to the ultimate goal of medicine, the eradication of all human diseases.

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### Links

[1] <http://www.newscientist.com/article/dn12748-stem-cell-pioneers-scoop-nobel-prize>

[2] <http://www.genome.gov/12514551>