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Stem cell pioneers scoop Nobel Prize

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The Nobel Prize in Physiology or Medicine 2007 has been awarded to two Americans who pioneered ways of "knocking out" specific genes in mice to reveal their function and their impact on disease.

The prize also recognizes the discovery of embryonic stem cells (ESC) in 1981 by Martin Evans of Cardiff University in Wales. Evans proved that mouse ESCs are pluripotent, meaning they can mature into any possible tissue.

Human counterparts of ESCs discovered since then have opened up huge possibilities for regenerating and repairing a patient's organs and tissues. But the field has also been dogged by controversy because all human ESCs made so far have been created by destroying human embryos, a procedure opposed by pro-life campaigners.

"Martin Evans certainly was one of the pioneers, being the first to derive mouse ESCs in 1981," says Lyle Armstrong, of the Institute of Human Genetics at the University of Newcastle upon Tyne, UK. "It brings home the importance of stem cell biology for the future of medicine."

Evans shares the \$1.54-million prize with Italian-born Mario Capecchi, a Howard Hughes medical investigator based at the University of Utah in Salt Lake City, and British-born Oliver Smithies of the University of North Carolina at Chapel Hill, both of whom are now US citizens.

'Silencing' genes

Once Evans had worked out how to create live mice from embryonic stem cells, Capecchi and Smithies took the process a stage further in 1986 by learning how to genetically engineer the cells beforehand through a process called homologous recombination.

Thus, it became possible to create mice genetically engineered to have genes that do not work, or entirely new genes from other species, including humans.

This has since led to creation of thousands of "knockout" mice with specific genes "silenced" to see whether this results in disease in the mice. By knocking out genes that are vital to the healthy development of embryos in the womb, Capecchi used the technique to discover the genetic causes of abnormalities in babies.

Since the first "knockout mouse" was reported in 1989, more than 10,000 have been created – covering approximately half of the genes in the entire mammalian genome.

Evans and others have also used the technique to create mice with the counterparts of human diseases, including the inherited lung disease, cystic fibrosis. Mice have been engineered by Smithies to have the equivalents of high blood pressure and arterial disease in humans.

Knockout mouse technology has now advanced to the point where mutations can be activated at a specific time or in specific cells or organs, both in the developing embryo and in the mature animal.

Funding restrictions

"The development of gene-targeting technology in the mouse has had a profound influence on medical research," says Stephen O'Rahilly of the University of Cambridge, UK. "Thanks to this technology, we have a much better understanding of the function of specific genes in pathways in the whole organism, and a greater ability to predict whether drugs acting on those pathways will be beneficial."

Despite the huge progress in knockout mouse technology, development of human embryonic stem cells for the treatment of human disease has been held back by restrictions on funding for federal researcher in the US. In 2001, President George Bush restricted the number of ESC cultures that federally funded researchers were allowed to work on to about 20.

Although private US companies have continued researching embryonic stem cells, Bush is under increasing pressure to lift the restrictions on federally funded researchers.

"It's good to see that despite the controversy, embryonic stem cell research has been recognized with a Nobel Prize," says Armstrong. "It probably won't change Bush's personal viewpoint, but might prompt a future US government to release federal funds for ESC research."

"Bravo for Capecchi, Evans, and Smithies," says Bob Lanza, chief scientist at Advanced Cell Technology in Massachusetts, US. "The message to the world is loud and clear – despite the brouhaha and opposition surrounding stem cell research, the field has been recognized as being profoundly important to the advancement of science and medicine."