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## A Knockout at the Nobels

The last 50 years have witnessed an explosion in basic research that has transformed the way we live our lives, understand ourselves, and interact with the world around us. Last month, the Nobel Foundation recognized some of the most important work with the naming of this year's Nobel laureates. While many scientists are worthy of such an honor, this event gives us an opportunity to reflect on the extraordinary contributions of this year's winners.

The winner of the Nobel Prize in Physiology and Medicine went to Mario R. Capecchi at the University of Utah, Martin J. Evans of Cardiff University, and Oliver Smithies at the University of North Carolina, Chapel Hill, for "their discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells".

These achievements resulted from the merging of two independent lines of study. In the 1980s, Drs. Capecchi and Smithies were investigating ways to manipulate the mammalian genome in live cells. Separately, they each discovered that genes could be specifically targeted by the process of homologous recombination, whereby pieces of foreign DNA could effectively be swapped for the homologous endogenous region.

At the same time, Dr. Evans was conducting seminal work with mouse embryonic stem (ES) cells. He successfully cultured these cells in a dish, infected them with a retrovirus, and then introduced them into growing embryos where the infected cells would give rise to all tissues in the body in a sporadic pattern. That included germ cells, and mating of these "mosaic" mice led to offspring that contained viral DNA in every cell.

The next step was to bring these two methods together and target a gene for homologous recombination in ES cells. These efforts were ultimately successful, and the first "knockout" mice were born in 1989. Such animals provide valuable information about the function of the gene in question, and this strategy has been used to develop mouse models for human diseases, including atherosclerosis and hypertension. To date, more than 10,000 genes have been disrupted independently in mice, and limitless possibilities exist for future studies in which multiple genes are knocked out and/or novel gene variants are introduced.

As for the future, ES cells have also shown promise for the treatment of many human diseases, including diabetes, Parkinson's disease, and heart disease. However, the manipulation of human stem cells has lagged far behind the work conducted in mouse cells by Dr. Evans 20 years ago, largely because of difficulties in culturing them. That will surely be resolved in the coming years as more scientists are focusing their research efforts on this front. One can only imagine what yet-to-be-discovered findings will garner the Nobel Prize a mere 20 years from now.



Eric Martens  
Senior Editor, *ACS Chemical Biology*