by which specific genes could be introduced or removed from genome with certainty. This technique was the homologous recombination and it was independently developed by Mario Capecchi and Oliver Smithies.

In 1980, Mario Capecchi developed the method of injecting DNA directly into the nucleus of mammalian somatic cells. In an experiment he noted that injection of DNA with gene for thymidine kinase (*tk*) in a cell line deficient in *tk* resulted in acquisition of *tk* function by a few cells. His anlaysis showed that such injected DNA must have undergone homologous recombination in mammalian somatic cells. Similar event had earlier been shown to be present in bacteria. He proposed that this machinery is conserved in mammalian cells as well and that it can be utilized for homologous recombination between the introduced DNA and host DNA and thus predetermined gene(s) could be removed or added. His grant proposal was rejected by the National Institutes of Health citing the unlikeliness of such an event. In 1986, he showed it was possible with a probability of 1 in 1000 cells.

In parallel, Oliver Smithies had also found in 1980 that homologous recombination does occur in mammalian cells and in 1985 he replaced the defective β-globin gene in the host cell with functional β-globin gene. He had developed the method of using plasmid DNA sequences for introducing DNA into host via homologous recombination and the strategy to identify such transfected cells.

Both Capecchi and Smithies developed the methods of introducing DNA onto host DNA in a predetermined and specific manner while Evan developed the method by which ES cells could be used as vehicle to generate living animals with such genetic changes. As it happened, Evans visited Smithies laboratory on invitation and literally carried the embryonic stem cells in his pocket for Smithies without any formal collaboration. Later, Capecchi also learnt the technique of ES stem cell transfer to blastocyst at Evans laboratory in UK. Together they generated the first knockout mice in 1989. Since then hundreds of knockout mice have been generated and the technology has been further refined to selectively remove the gene from the genome at later stages of development (knockdown). The therapeutic potential of correcting gene defects in patients is immense and the contribution by Capecchi, Evans and Smithies has laid down the path towards such endeavours.

Mario R Capeechi is currently the distinguished Professor of Human Genetics and Biology at University of Utah, USA and is studying the role of *hox* genes in developmental biology. Martin J Evans is the Professor of Mammalian Genetics and the Director of the School of Biosciences, Cardiff University, UK and currently studying the difference between mouse ES cells and inner cell mass using gene array technology. Oliver Smithies is the Excellence Professor of Pathology and Laboratory Medicine University of North Carolina, USA and is continuing to develop animal models for complex diseases like hypertension and hemoglobinopathies.

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