

**FORTY YEARS WITH HOMOLOGOUS RECOMBINATIONS****OLIVER SMITHIES***Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, NC, USA*

In thinking ahead towards the future, it is often useful to look back to find what factors have allowed us to reach our present state of knowledge. In my 50 years as a scientist at the bench, three factors have been important. CHANCE has been one of these factors. Its influence on the development of a new way of separating proteins will be illustrated by laboratory notebook entries from over 40 years ago. Curiosity is also a prime mover in science, and so out of curiosity the new protein separation method was tested with blood plasma. Those tests in due course led to the discovery of complicated genetic differences between the plasma proteins of different persons. At this stage, the second factor came into play. There was now an OPPORTUNITY to disentangle these complex new

findings. The solution to this genetic problem revealed new examples of the frequent occurrence of homologous recombination in biology. The third factor, PLANNING, had the most important consequences – it proved possible to plan to alter genes in living cells by homologous recombination (gene targeting). The subsequent extension of this idea to altering genes in animals has been hugely successful. The message for the future that comes from this backwards look is that we must make sure that the next generation of scientists will also have the freedom to take advantage of their scientific chances. We must make sure also that they have the opportunity to develop their findings in ways that improve human welfare.