Gary Felsenfeld, National Institute of Health, Maryland : *"The Evolution of Epigenetics"*

ABSTRACT: The term 'epigenetics' was first used to denote the series of events that govern the transformation of the fertilized egg into the adult organism. It was clear that during development individual tissues and cells acquired distinct phenotypes, but it was a mystery as to how the initial genetic information contained in a single cell could be used to determine the architecture of a complex organism. Studies in *Drosophila* in the 1930s by H. J. Muller showed that rearrangements that moved a chromosomal segment to a different position could result in changed phenotypes. But perhaps most important was the demonstration in 1970 by Gurdon that the DNA in somatic cell nuclei could be used to reprogram an enucleated oocyte and lead to development of a complete organism. Since differentiation did not involve loss of DNA sequences, it must reflect targeted activation and repression of cell type specific genes. The term epigenetics thus began to refer to these mechanisms, and particularly to the ways in which modifications of DNA such as methylation, or interactions of DNA with protein complexes, could create an 'inheritable' state that could survive cell division. This change in point of view has resulted in considerable confusion and disagreement about what definition of epigenetics would be most useful. It has also tended to obscure the chain of events that initiates gene activation or repression. However recent results from Yamanaka and others have provided detailed information about the mechanisms that govern the transformation from a single pluripotent stem cell to a complete organism, perhaps returning us to the original definition, but this time with a detailed understanding of the associated biochemical events.

While reviewing this history, I will discuss various regulatory mechanisms that can contribute to maintaining cell type specific gene expression once it is established, particularly histone modifications, DNA methylation and their effects on chromatin structure. It is now becoming clear that large scale architecture within the nucleus may also be important in transmitting epigenetic information. The more we know about how things work, the less important a definition becomes.