Leaping fish story: New mechanisms underlying iPSC induction

Funding by the National Natural Science Foundation of China, Prof. Fan Xianqun, Group leader of Ophthalmology in Shanghai Ninth Hospital at Shanghai Jiao Tong University and Stanford collaborators published their research findings "Intrachromosomal Looping Is Required for Activation of Endogenous Pluripotency Genes during Reprogramming" in *Cell Stem Cell* (**2013**, 13(1): 30–35).

The discovery of iPSC technology marks a promising breakthrough in regenerative medicine. The beauty of the technology is its ability to convert adult mature cells into embryonic stem cells through the expression of a cocktail of essential factor genes. The technology of iPSC induction, however, is in its infancy, and yet seven years after the initial breakthrough, the efficiency of iPSC induction is extremely low with all existing approaches. Without clearing these road blocks, it would be impossible to translate this technology to the clinic and ultimately help accelerate disease research in the near future.

The extremely inefficient process of iPSC induction implies the presence of a strong epigenetic block preventing cells from achieving pluripotency. They thus investigated the epigenetic mechanisms underlying the low efficiency of iPSC induction and found that the activation of the endogenous pluripotent factors, like OCT4, was the key in iPSC induction. In order to identify an epigenetic feature unique to iPSC, they collected iPSCs and un-reprogrammed cells (URCs). Comparison of local chromatin structure revealed that in each case, there was a cohesin-complex-mediated intrachromosomal loop that juxtaposes a downstream enhancer to the gene's promoter, enabling activation of endogenous stemness genes, a critical step towards the successful iPSC induction (Figure **A**). They also proposed a "Jump over model" to illustrate this finding: Unreprogrammed cells (URCs) that even expressed OSKM must jump over the epigenetic looping barrier for pluripotent destination. This scene is inspired by Chinese ancient legend "Carps jumping over the Dragon Gate", in which the carp that successfully jump rapids and leap over the gate, change into dragon (Figure **B**). These findings highlight the importance of chromosomal structure as critical epigenetic mediators of cell reprogramming and also suggest future directions to explore the epigenetic mechanisms in initiation and progression of eye-related cancer stem cells by concentrating on orchestrating chromatin structure.

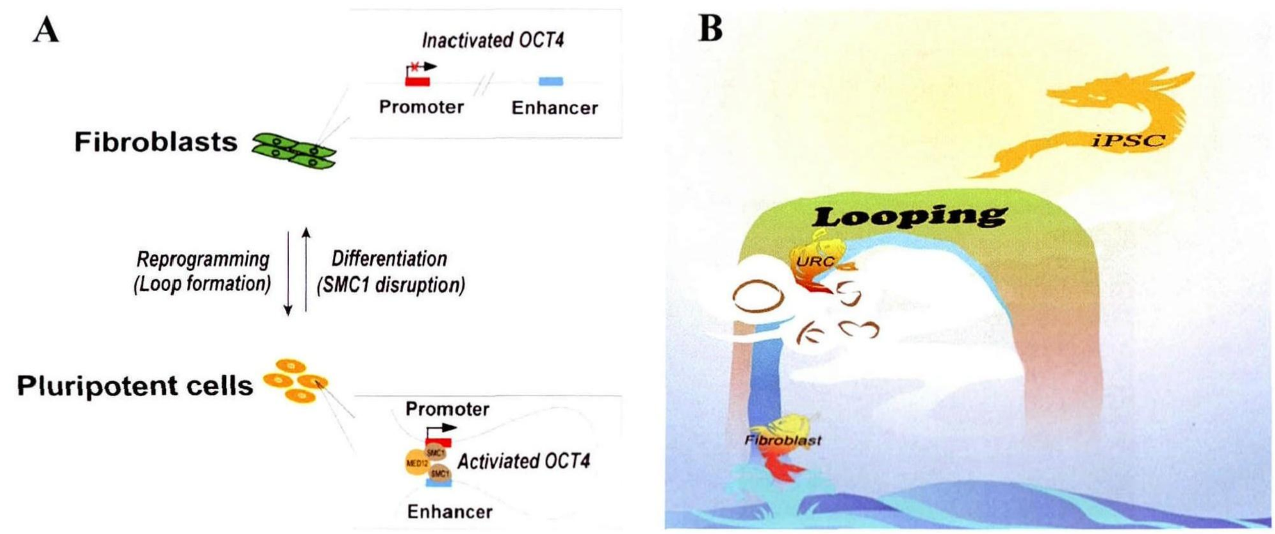

Figure **A** The epigenetic illustration of iPSC induction. **B** "Jump over model": The carp over the four clouds represents URC expressing OSKM, and the dragon represents iPSC.