**Using heterokaryons to understand pluripotency and reprogramming**

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Reprogramming of differentiated cells towards pluripotency can be achieved by different experimental strategies including the forced expression of specific ‘inducers’ and the transfer of differentiated nuclei into enucleated oocytes or fertilized eggs. While these offer unparalleled opportunities to generate stem cells and advance disease modeling, the relatively low levels of successful reprogramming achieved (1-2%) makes any analysis of early molecular events associated with productive reprogramming very challenging. Here we used an alternative approach - generating transient heterokaryons between human differentiated cells (such as lymphocytes or fibroblasts) and mouse pluripotent stem cell lines. Under these conditions differentiated nuclei undergo a series of remodeling events before initiating human pluripotent gene expression and silencing differentiation associated genes. When combined with conditional ES mutant cell lines, RNAi-based approaches and high-throughput screens, heterokaryon studies can provide some important new insights into the factors and mechanisms required to direct the conversion of unipotent cells towards pluripotency.