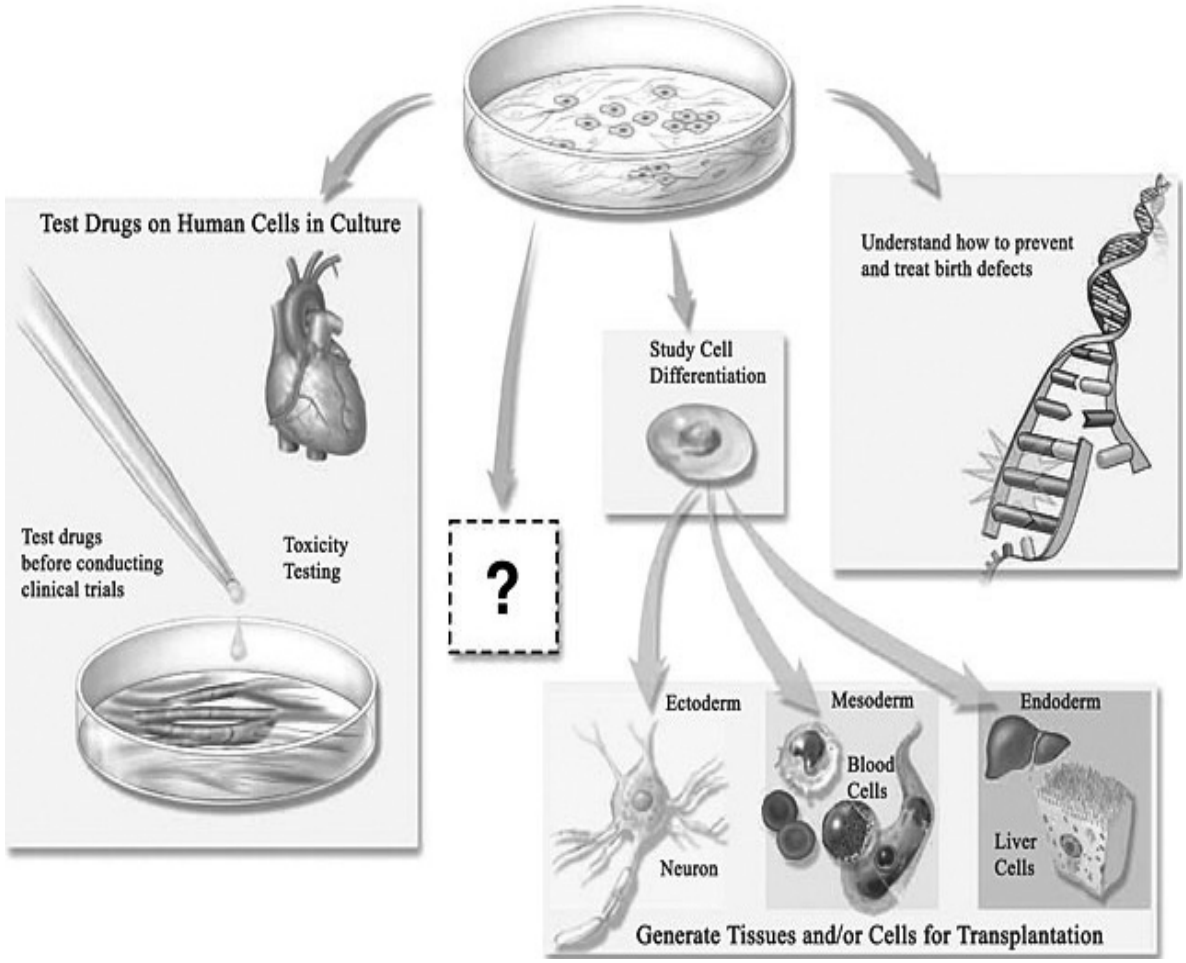
"Hotspots" of Failed Reprogramming to Pluripotency in Human Stem Cells

The induction of pluripotency from adult, terminally differentiated cells opens doors for the study of disease pathogenesis, with strong potential for clinically translatable therapies. Despite the vast somatic and germline differentiation potential of induced pluripotent stem (iPS) cells, it remains unclear the extent to which viral, RNA, or protein-based reprogramming techniques re-establish embryonic stem (ES) cell-like patterns of DNA methylation. Logically, ideal reprogramming would return an adult cell type to as close an ES-like state as possible genetically and epigenetically. Last year, George Daley and colleagues at Children's Hospital Boston reported on "epigenetic memory" in mouse iPS cells, and showed they could overcome this hurdle to reprogramming by long-term culture or differentiation (1).

By performing whole-genome, single base pair sequencing of methylation patterns in human cells, Lister, Pelizzola and colleagues report in Nature that, while there is indeed global similarity between human ES and iPS cell methylomes, iPS cells retain "memory" of the somatic cell type from which they were derived. They also contain distinct methylation patterns that are peculiar to iPS cells, as well as "hotspots" of megabase regions that, in different iPS cell lines, reveal methylation patterns resistant to reprogramming toward ES cells (2). The authors conclude that these epigenetic marks are passed on to the cells' progeny and differentiated derivatives. This study points toward important concerns in the development of strategies to fully reprogram adult cells to an ES cell state. It also raises the possibility of using epigenetic landmarks and sequencing techniques to assess the success of reprogramming efforts. Lastly, it remains to be assessed how significant these iPS cell-identifying marks are, both molecularly, and in influencing differentiation and clinical potential. H



▲ **Figure 1.** What are the possible applications of induced pluripotent stem cells?

credit: http://stemcells.nih.gov/info/media/promise.htm

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1. Kim, K. et al. (2010) Nature 467, 285-29.
2. Lister, R., Pelizzola, M. (2011) Nature (advance online publication).