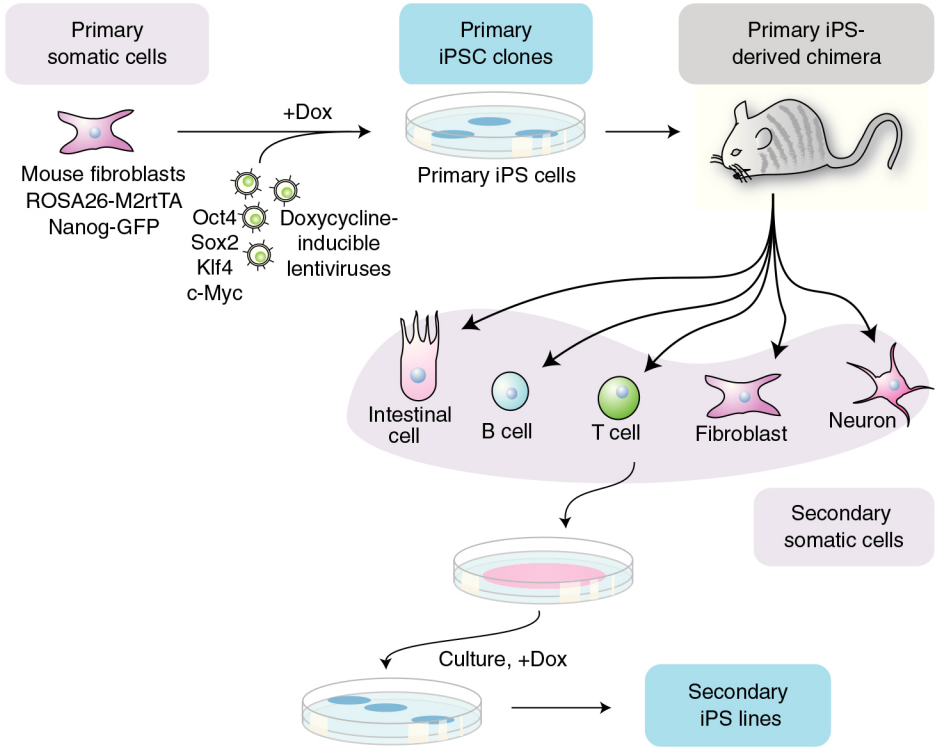

Figure 4. Generation of genetically homogeneous cell cultures for epigenetic reprogramming. Scheme for obtaining genetically homogeneous somatic cells that are more efficient at pluripotency induction. Primary somatic cells with stable integrations of a Nanog-GFP (green fluorescent protein) marker and reverse tetracycline transactivator (M2rtTA) are infected with DOX-inducible lentiviruses encoding the four reprogramming factors. Primary iPSCs are generated by culturing the cells in DOX to activate the factors. After DOX withdrawal, the primary iPSCs are injected into mouse blastocysts and "secondary" somatic cells carrying the DOX-inducible vectors are cultured in the presence of DOX to produce secondary iPSCs. The key advantage of this system is that reprogramming can be induced without new virus infection at a much higher efficiency. (Modified, with permission, from Hanna et al. 2008a.)