Human pluripotent stem cells (hPSCs) have generated a lot of interest in the scientific community based on their potential applications in regenerative medicine. Over the past decade, there has been enormous progress in developing propagation conditions for maintaining hPSCs in their undifferentiated state; and differentiation strategies for generating specialized cell types. However, challenges related to scalability and genomic stability need to be addressed prior to use in clinical applications. Work from our laboratory and others have demonstrated that amplification of chromosomal regions is correlated with increased gene expression. This talk will focus on selection models for studying culture conditions that reduce the appearance of genomically altered hPSCs, that aids in elucidation of a mechanism that act as a molecular switch during culture adaptation.