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Single Cell Oncogenesis.

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It is believed that cancer originates from a single cell that has gone through generations of evolution of genetic and epigenetic changes that associate with the hallmarks of cancer. In some cancers such as various types of leukemia, cancer is clonal. Yet in other cancers like glioblastoma (GBM), there is tremendous tumor heterogeneity that is likely to be caused by simultaneous evolution of multiple subclones within the same tissue. It is obvious that understanding how a single cell develops into a clonal tumor upon genetic alterations, at molecular and cellular levels, holds the key to the real appreciation of tumor etiology and ultimate solution for therapeutics. Surprisingly very little is known about the process of spontaneous tumorigenesis from single cells in human or vertebrate animal models. The main reason is the lack of technology to track the natural process of single cell changes from a homeostatic state to a progressively cancerous state. Recently, we developed a patented compound, photoactivatable ("caged") tamoxifen analogue 4-OHC and associated technique called optochemogenetic switch (OCG switch), which we believe opens the opportunity to address this urgent biological as well as clinical question about cancer. We propose to combine OCG switch with genetically engineered mouse models of head and neck squamous cell carcinoma and high grade astrocytoma (including GBM) to study how single cells, when transformed through acute loss of tumor suppressor genes PTEN and TP53 and gain of oncogenic KRAS, can develop into tumor colonies with cellular and molecular heterogeneity in these tissues.