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A pre-clinical breast cancer stem cell model based on MMTV-PyMT Mice for testing nanoparticle directed therapy

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Abstract

The stem cell model of cancer predicts that cancer treatment failure can be overcome if treatment is directed to the self-renewing cancer stem cell (CSC). Most therapeutic approaches are directed to the proliferating cells of the tumor and not the tumor stem cells. In order to advance therapy to tumor stem cells, we need models of cancer in which the stem cells can be identified, targeted and treated. Cells comprising the microenvironment (stem cell niche) of CSCs also play a defining role in optimal tumor initiation potential and are a second target for treatment. We used the MMTV-PyMT transgenic mouse model of spontaneous breast cancer to identify both CSCs and tumor supporting mesenchymal cells. Female mouse mammary cancer (FFMC) cell lines consisting of two major populations were generated from primary breast cancers: $CD24^{+}CD29^{+}CD44^{low}CD49f^{+}Sca\text{-}1^{low}$ TICs and $CD24^{-}$ tumor-derived mesenchymal stem cells (TDMSCs). $CD24^{+}$ 419II cells at 1 x 10^{3} consistently initiated mammary gland tumors, whereas the $CD24^{-}$ TDMSCs failed to initiate such tumors at $1x10^{7}$ cells. Co-transplantation of TDMSCs and CD24+ TICs resulted in a significant increase in TI to the level of a single CSC. Knock-down of Bmi-1, a polycomb group protein and stem cell transcriptional promoter, by shRNA prevented 419II cells from initiating tumors. TI was restored when Bmi-1 was reintroduced via an expression vector. We now propose to use anti-CD49f coated nanoparticles containing shRNA to inhibit Bmi-1 and/or docetaxol to target therapy to the CSCs. Future experiments are planned to direct therapy to the TDMSCs as well as the CSCs.

Biography

Dr. Sell began research as a medical student at the University of Pittsburgh, in the Department of Pathology. After a pathology residency at Massachusetts General Hospital, and post doctoral fellowships at NIH and Birmingham England he returned to the University of Pittsburgh for 5 years before moving to the University of California at San Diego. After 12 years at UCSD, Dr. Sell became Chair of Pathology and Laboratory Medicine at the University of Texas (UT) at Houston for 14 years before moving to Albany Medical College as Director of the Division of Experimental Pathology. As of February 2003 he has been a senior scientist at Wadsworth Center. Awards received: Rudolph L. K. Virchow Award; Legacy Laureate of the University of Pittsburgh; Abbott Award of the ISOBM.