“Elucidating Mechanisms of ETS-mediated Oncogenesis in Prostate Cancer and Gastrointestinal Stromal Tumor (GIST)”

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Abstract: Recurrent genetic fusions involving ETS family transcription factors (e.g., *ERG, ETV1, ETV4, ETV5*) occur in ~60 percent of prostate cancers (Tomlins *et al*., 2005). This fusion event leads to overexpression of the targeted ETS protein, activating a downstream transcriptional program that drives prostate carcinogenesis. In an ongoing collaboration between the Sawyers and Allis laboratories, we uncovered a previously unrecognized role for ETV1 in gastrointestinal stromal tumors (GIST) (Chi *et al*., 2010). In brief, ETV1 functions as a master regulator (in the absence of gene amplification, translocation or mutation) of interstitial cells of Cajal (ICCs) that are the cell-of-origin for GIST. Furthermore, ETV1 is required for maintenance of GIST tumors in mice. The fact that ETV1 plays an oncogenic role in both prostate cancer and GIST provides an opportunity to dissect the mechanisms governing transcription factor binding, transcriptional output and pathogenesis in two distinct tissue types. We hypothesize that the transcriptional output of ETV1 (and ERG) expression will be governed by collaborating transcription factors and the chromatin landscape. Using several well-characterized prostate and GIST model systems, we will characterize the ETV1 and ERG transcriptional programs (Aim 1), their "cistromes" or global genomic binding sites (Aim 2) and the local epigenome that governs ETV1 or ERG binding and resultant transcriptional output (Aim 3). Preliminary data implicating the histone acetyltransferase (HAT) PCAF suggests that this line of investigation will have translational implications since these histone modifying enzymes can be targeted pharmacologically.