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The overall goal of this proposal and my developing academic career is to assess whether chromatin remodeling (via histone deacetylase inhibitors (HDACIs) can mediate solid tumor differentiation into mature tissue. While significant pre-clinical and clinical effort has been dedicated to the study of HDACIs (e.g., SAHA) the majority of this effort has been exclusively focused on their cytotoxic effect, with relatively scarce attention, if any, given to their more "classical" roles as differentiation agents capable of reprogramming tumor cells to resume normal maturation pathways. *It is the hypothesis of this proposal that HDACIs have intrinsic differentiation capacity on solid tumors, but that this property has not been adequately studied, and would likely require different dosing schedules to achieve the appropriate biological end-point of tumor cellular differentiation.* Our hypothesis is based on our recent demonstration that (a) sarcomas arise from mesenchymal stem cells (MSCs) and can be reprogrammed to resume normal MSC differentiation pathways if specific MSC-like signaling patterns are first re-established; (b) that different stages of MSC differentiating along mesenchymal lineages are the likely precursors of different sub-types of that lineage; and (c) chromatin modifying agents can promote differentiation in sarcoma cell lines and in sarcoma mouse models. Our specific aims are: **Aim 1: To determine whether currently clinically used HDACIs at conventional (maximum tolerable doses, MTD) doses result in tumor chromatin modification in the tumors of treated patients.** Patients presenting with primary sarcoma will be enrolled on a Pilot Phase II study of neo-adjuvant treatment with the HDACI - SAHA (i.e., Vorinostat; LOI approved by Merck; PI Matushansky). Patients will undergo a diagnostic excisional biopsy followed by four weeks of SAHA treatment and then surgical excision. Paired samples will be histologically and immunohistochemically compared focusing on changes in chromatin modification and structure. *It is the hypothesis of this aim that chromatin modifying agents administered at the MTD will be sufficient to result in chromatin modification; but that differentiation will not be observed and may require a prolonged dosing schedule at doses tolerable over the prolonged treatment.* **Aim 2: To determine whether prolonged treatment with chromatin modifying agents results in tumor differentiation in the clinical setting.** Patients presenting post-surgical resection for high grade sarcomas will be enrolled on a Pilot Phase II of adjuvant treatment with the HDACI – valproate (Columbia IRB-AAAD4523; PI Matushansky). Patients will be required to obtain and/or authorize access for a panel of unstained slides of their excised tumor amenable to histological and immunohistochemical analysis. Patients will receive valproate for six months and followed until recurrence. Recurrent tumors will be diagnostically biopsied or surgically treated (if resectable). Recurrent tumors will be histologically and immunohistochemically compared focusing on changes in degree of tumor maturation. *It is the hypothesis of this aim that under such prolonged treatment conditions differentiation will be observed and will correspond to degree of chromatin modification.*