



## CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:  
RP170407

Project Title:  
Role of HDAC8 and higher order chromatin structure in melanoma metastasis and therapy

Award Mechanism:  
Individual Investigator

Principal Investigator:  
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Entity:  
The University of Texas M.D. Anderson Cancer Center

### Lay Summary:

Metastatic spread of cancer cells makes is the most deadly stage of cancer progression. Most tumors are clinically manageable if they are contained within the site of their origin. Therefore, there is a great value in understanding the biological processes that regulate a cancer cells ability to metastasize. Melanoma is a highly metastatic disease whose incidence is rising over the years and the five-year survival rates are dismal. Although immunotherapy agents are showing tremendous promise for management of melanoma in the clinic, they are efficacious in only a subset of patients and therefore other strategies are needed for better treatment of this disease. Epigenetic processes drive cellular fate transitions and have been shown to impact cancer progression in recent years. Therefore, a number of novel targeted therapeutic strategies have been developed against epigenetic enzymes. The role of these processes in regulating cancer metastasis is not well understood and a thorough understanding of epigenetic processes will help us devise better therapeutic strategies in highly metastatic tumor types such as melanoma. Motivated by our preliminary results, our proposed studies will provide a systematic interrogation of alterations in higher-order chromatin structure and chromatin states in metastatic tumors compared to their primary counterparts. Further, we will directly assess role of HDAC8, a histone deacetylase, in regulating these pro-metastatic alterations. HDAC8 is a readily targetable enzyme with multiple specific inhibitors in development and therefore we will test whether HDAC8 inhibition alone or in combination with immune-checkpoint blockade agents could provide better efficacy and response. A detailed understanding of role of epigenetic processes and proteins such as HDAC8 in metastasis may propel other pre-clinical and clinical studies for epigenetic inhibitors including those specific to HDAC8.