



## SINGLE-MOLECULE EPIGENETICS: ILLUMINATING THE HISTONE CODE IN CANCER

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Different combinations of histone modifications have been proposed to signal distinct gene regulatory functions, but are poorly addressed by existing technologies. We recently published a novel high-throughput single-molecule imaging technology to decode combinatorial modifications on millions of individual nucleosomes (Shema et al., Science, 2016). We apply this technology to elucidate the epigenetic events that drive tumorigenesis in cancers carrying mutations in critical epigenetic pathways. Specifically, we study diffuse midline gliomas (DIPG), aggressive and deadly pediatric brain tumors harboring point mutations in the histone H3 Lysine 27. We combine the single-molecule proteomic platform with single-molecule DNA sequencing technology to simultaneously determine the modification states and genomic positions of individual nucleosomes. **Our single-molecule epigenetic profiling technology is a transformative new tool for functional genomics with the potential to unravel the contribution of epigenetic alterations to tumorigenesis.** We also harness this technology to reveal the tissue-of-origin of cell-free DNA circulating in our blood in the form of nucleosomes, and apply it to devise novel strategies for early detection of cancer and other diseases.