Exploring the interactome of H3K27M to find therapeutic targets for DIPG

Section 2: Executive Summary

We now have a wealth of genetic and epigenetic information about DIPG. However, relatively little is known about the molecular consequences downstream from H3K27M mutations and how they can lead to cancer formation. It is known that, as well as DNA hypomethylation, H3K27M mutation leads to a global loss of the repressive chromatin mark H3K27me3. H3.3K27M has also been shown to interact more strongly than wild type (WT) H3.3 with the polycomb repressive 2 (PRC2) complex members EZH2 and SUZ12. However, beyond these observations relatively little is known about how H3K27M mutations might alter the histone code through changes in interactions with writers, erasers and readers. This is a critical step in understanding how the H3K27M mutation might drive DIPG pathogenesis and how to develop appropriate therapies for H3K27M mutant tumors.

To better our understanding of the effects of these H3K27M mutations, we are undertaking a novel approach to the problem by investigating the protein interactions that are altered by H3.3K27M and H3.1K27M. Histone binding partners whose histone affinity may change in the presence of H3K27M are likely to play a significant role in mediating this mutation's tumorigenicity. As well as extending our molecular understanding of DIPG, focussing on these interactors offers an attractive new avenue in the search for an effective therapy for this fatal disease. The structural and post-translational plasticity of histone tails means directly targeting H3K27M itself with small molecules is unlikely to be effective. However, understanding how this mutation alters the histone interactome offers a unique opportunity to specifically modulate the activity of those proteins immediately downstream from H3K27M. The goal of this project is to exploit novel proteomics technology (Bio ID) to gain new insight into the functional consequences of the H3K27M mutation. **We hypothesize that the H3K27M mutation leads to differential interaction with and function of multiple chromatin modifiers and nuclear proteins beyond PRC2**. This hypothesis is supported by our preliminary data and will be rigorously tested through the following specific aims:

Aim 1: To determine the differential protein interactions imparted by the K27M mutation on both H3.1 and H3.3

Aim 2: To characterize the H3K27M interaction landscape in DIPG model systems

Our project is the first to directly address the question of how the H3K27M mutation in both H3.1 and H3.3 impacts on the H3 protein-protein interaction landscape. A deep understanding how the protein landscape of DIPG changes will not only shed further light on the molecular basis of this disease, but it will also open a new approach for developing more effective treatment regimens for this universally fatal disease. The facilities and expertise at The Brain Tumor Research Centre and the Hospital for Sick Children as well as our close collaborations within the DIPG Registry Group will help us rapidly advance our findings through pre-clinical investigations and eventually into clinical trials.