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"Title of Project"
Dual-Platform Screening of Compound Libraries to Identify Novel Inhibitors of Histone Lysine Demethylase PHF8

The Jumonji C domain containing histone lysine demethylase PHD finger protein 8, or PHF8, has been characterized to be involved in various cellular processes including cell cycle progression, inflammatory responses, and hypoxic response. Furthermore, PHF8 dysregulation is shown to be causative of tumor proliferation and therapeutic resistance in human cancers. Despite PHF8 emerging as a versatile target for cancer treatment, little has been done in identifying small molecules that inhibit PHF8 activity with therapeutic potential.

We employed a dual-platform screening strategy to identify novel PHF8 inhibitors by repurposing previously characterized small molecules with known epigenetic activity. A virtual screen of a small molecule library containing 1,221 compounds was conducted using AutoDock Vina to predict binding affinities to the JumonjiC domain of PHF8, which is responsible for its demethylase activity. In parallel, we used AlphaScreen as an in vitro assay to evaluate the inhibitory activity of the 1,221 compound-library towards PHF8. Our virtual screening platform identified 140 small molecules that displayed potential for efficient binding the PHF8 active site. Upon inspection of these hits, we observed that pan JumonjiC targeting and PHF8 specific inhibitors, Daminozide and iPHF8, were shown to be amongst the top hits providing validation of the accuracy of our virtual screening approach. Intriguingly, virtual screen hits Oxamflatin and Belinostat showed percent inhibitions of 87.29 and 32.93, respectively, on our first set of AlphaScreen assays, indicating that our dual platform method performs with high accuracy and provides a structure-function basis for PHF8 small molecule inhibition.

Using our dual platform virtual and in-vitro screening highlights an encouraging methodology in identifying novel inhibitors for PHF8 with therapeutic potential. These findings provide a promising foundation for the development of PHF8-targeted therapy and a generalizable workflow for screening epigenetic inhibitors.