Multidisciplinary Approach to Cancer Treatment: Computationally Guided Discovery of Novel PRMT5 Inhibitors

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Disruption in the regulation of gene expression has been described as a factor promoting the development of cancer. Protein Arginine Methyltransferases (PRMT) are a group of enzymes that methylate arginine residues in histones and other proteins. PRMT5 symmetrically dimethylates histones 3 (H3R8) and 4 (H4R3), epigenetic marks that are associated with transcriptional silencing of genes involved in cell cycle regulation, thus promoting increased cell proliferation and growth. Overexpression of PRMT5 has been noted in numerous cancers such as glioblastoma, EBV-driven cancers, diffuse large B-cell lymphoma and mantle cell lymphoma (MCL). Given that PRMT5 remains a target involved with oncogenesis, a collaborative group at OSU has developed a first-in-class PRMT5 inhibitor. Prior work has shown that PRMT5 knockdown with shRNA leads to decreased growth and viability of numerous cancer cell lines. Mantle Cell Lymphoma cell lines were initially screened via MTS assay, a light colorimetric assay at assesses cell metabolic activity and cellular proliferation, with the 1st generation PRMT5 inhibitor Compound 5. Two cell lines, cc-mcl and mino, were chosen as the primary cell lines for screening new compounds based on their susceptibility to Compound 5-induced growth arrest. In addition to the biological assays, one approach to optimizing PRMT5 inhibitors was analyzing Compound 5 through molecular modeling tools such as UCSF Chimera and Autodock Vina. UCSF Chimera and Autodock Vina provide structural analysis of chemical bonds by measuring specific affinity levels between the inhibitor and protein. Based on computational analysis, molecular optimizations of Compound 5 were conducted to develop a second generation of PRMT5 inhibitors. Of these novel inhibitors, Compound ICD18 exhibited significant anti-cancer activity during MTS screening. Novel compounds were optimized based on ICD18 to produce a third generation of PRMT5 inhibitors that could outcompete PRMT5's cofactor, S-adensyl methionine (SAM). These compounds will be screened through MTS to examine the specificity and selectivity of inhibiting PRMT5 activity. Our immediate goal is to select lead PRMT5 inhibitors for further optimization in in vitro and in vivo preclinical cancer models. Our ultimate goal will be to identify key lead PRMT5 inhibitor drugs for preclinical efficacy, PK and toxicity studies allowing for filing an investigational new drug application (IND) with the FDA and move this new class of compounds forward for clinical investigation treating patients with diverse cancers.