

Title: Targeting APOBEC3B with Second-Generation Small Molecule Fragment Ligands

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APOBEC3B (A3B) is a deaminase enzyme that converts cytosine to uracil in single stranded (ss) DNA. It is part of a larger family of APOBEC3 enzymes that possess similar activity, which were discovered as viral restriction factors. A3B plays a significant role in tumor progression and drug resistance in cancers by deaminating genomic DNA to induce oncogenic mutations. For these reasons, A3B is an attractive target for therapeutic inhibition; however, a selective small molecule modulator or mechanistic chemical probe for A3B has not been developed. Our lab previously initiated a fragment-based drug discovery campaign on the catalytically active C-terminal domain (ctd) of A3B using a biophysical NMR approach. This screen led us to characterize a thiophene chemical series that binds weakly by surface plasmon resonance (SPR). These compounds were later advanced to an indole scaffold to improve physiochemical properties. Promising 7-azaindole analogues were identified with improved affinity for A3Bctd by SPR; however, their location of binding to the enzyme remains unclear. Further optimization of these analogues is ongoing with the overarching goals of (i) improving solubility, (ii) enhancing ligand-A3Bctd binding affinity, and (iii) identifying an optimized compound that will be suitable for NMR structural studies and covalent probe design to conclusively annotate the mode of binding. Progress towards accomplishing these goals will be presented, which will serve as the basis for a well-optimized, small molecule A3B inhibitor that we hypothesize would extend the therapeutic window of many current cancer therapies by slowing or preventing the evolution of drug resistance mutations.