Discovery of APOBEC3B DNA Cytosine Deaminase Ligands by Protein Observed Fluorine NMR Screening

Michael J. Grillo†, William C. K. Pomerantz‡,†, Hideki Aihara§, and Daniel A. Harki†,‡,§,*

†Department of Medicinal Chemistry, ‡Department of Chemistry, §Department of Biochemistry, Molecular Biology & Biophysics, University of Minnesota, Minneapolis, MN 55455, United States

Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (A3) catalyzes C-to-U deamination in single-stranded (ss)DNA as a function of the innate immune defense against pathogenic DNA. A3s cause hypermutation leading to genomic instability and clearance by the host immune system. One A3 enzyme in particular, A3B, is overexpressed in various cancer types and is a source of genomic mutations that result in tumor evolution and the development of drug resistance. A3B is nonessential in humans making it an exciting new target for cancer therapy. High-throughput screening campaigns have identified covalent inhibitors of A3G, but no A3B small molecule inhibitors have yet been reported. Recently, a co-crystal structure of A3B with a fragment-sized molecule has been solved indicating that A3B can be targeted by fragments. Consequently, we have initiated a solution-phase fragment screening campaign to identify A3B-binding molecules. Our approach utilizes Protein Observed Fluorine (PrOF) NMR to identify A3B-binding ligands. PrOF NMR involves incorporating fluorinated amino acids into the target protein and observing changes in the 19F-NMR resonance shifts upon titration of ligands. These changes in resonance shifts not only indicates that a molecule is binding, but also gives information on where the molecule is binding, which yields a powerful tool for the discovery of enzyme ligands. This poster will highlight recent efforts to develop a PrOF-based assay for A3B ligand screening and preliminary chemical matter discovered through our efforts.