Special Organic Colloquium

Chemical Strategies for Regulating DNA-Interactive Proteins: Targeting APOBEC Cytosine Deaminases and the N-Myc Transcription Factor

Abstract: Our laboratory focuses on the development of small molecule ligands and enzymatic inhibitors of proteins that interact with nucleic acids. We utilize biophysical and biochemical assays to screen chemical libraries to discover protein-binding ligands, which are then optimized using iterative rounds of molecular design, synthesis, and biological evaluation. Our overarching goals are to develop chemical probes to enable the discovery of new biology by the biomedical research community, as well as develop novel and patentable therapeutic compounds for clinical development by a pharmaceutical partner. In this vein, two programs from our laboratory, the discovery of APOBEC inhibitors and N-Myc degraders, will be presented.

APOBEC enzymes are a family of 7 human DNA cytosine-to-uracil deaminases that degrade foreign DNA as part of the innate immune response to pathogen infection. However, APOBEC enzymes have been shown to contribute C-to-U/T mutations that enable virus and cancer cell genomic mutations that confer resistance to drug therapies. Consequently, small molecule APOBEC inhibitors may have utility as "anti-mutation" therapies that slow or prevent the evolution of resistance mutations that defeat targeted drug therapies. Our work to develop first-in-class APOBEC inhibitors will be presented.

The Myc family of transcription factors are master regulators of proliferation in the majority of human cancers. In the case of childhood neuroblastomas, which are the most prevalent cancer in children under 1-year of age, N-Myc is a validated therapeutic target and molecular diagnostic. A vulnerability of N-Myc in many neuroblastomas is that N-Myc is stabilized from proteolytic degradation by Aurora kinase A (Aurora-A). We have developed novel chemical degraders of Aurora-A, such as HLB-0532259, that elicit the degradation of Aurora-A and the concomitant degradation of N-Myc. HLB-0532259 also exhibits potent antiproliferative activity in neuroblastoma cells and xenograft mouse models. Our work to develop novel N-Myc degraders will be presented.

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