IS01-2 **Rational Drug Discovery and Chemical Biology of HIF Pathway Inhibitors as Novel Anticancer Agents**

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HIF-1 is a key transcription factor that functions as a mast regulator in the response of growing tumor to hypoxia. Especially HIF-1α plays a major role in activating gene transcription and is important for maintaining homeostasis in solid tumors. In an attempt to develop a novel small molecule inhibitor targeting HIF-1α, we performed HTS screening using a cell based HRE reporter assay and chemical library. This resulted in the identification of several hits and we further conducted phenotype-based structure-activity relationship study on this series identified LW6 that potently inhibited HIF-1α accumulation by degrading HIF-1α without affecting the HIF-1α mRNA levels under hypoxia. To develope more potent and efficient HIF-1α inhibitors, we performed structural modifications of LW6, which in turn led to the development of LW7 as a clinical candidate.

In parallel, we designed and synthesized a variety of chemical probes in trimodular mode for direct target identification. Using bioprobes with photoactivable group and/or clickable group, we observed the mitochondrial localization and identified malate dehydrogenase 2 (MDH2) as a target protein. Further, we confirmed that it binds to MDH2 in TCA cycle, thereby inhibiting mitochondrial respiration and increasing the local oxygen tension. This is the first report that MDH2 regulates HIF-1α accumulation in cancer, which also suggest that well designed chemical probes provide a reliable platform for the identification of direct target protein in drug discovery.

Related reference: 1) K. Lee et al. Identification of the HIF Inhibitor LW6 using Multifunctional Chemical Probes. *Angew. Chem. Int.* **2013**, *125*, 10476-10479. 2) Naik et al. Synthesis and Structure–Activity Relationship of (E)-Phenoxyacrylic Amide Derivatives as Hypoxia-Inducible Factor (HIF) 1α Inhibitors. *J. Med. Chem.* **2012**, *55*, 10564-10571. 2) Lee, K et al. (Aryloxyacetylamino)benzoic Acid Analogues: A New Class of Hypoxia-Inducible Factor (HIF)-1 Inhibitors *J. Med. Chem*. **2007, 50(7),** 1675-1684.