Rima Al-awar, Madridge J Pharm Res. 2016
http://dx.doi.org/10.18689/2638-1591.a1.002

Discovery and optimization of novel antagonists of the WDR5-MLL interaction

Rima Al-awar
Drug Discovery Program at Ontario Institute for Cancer Research, Canada
Department of Pharmacology and Toxicology, University of Toronto, Canada

Histone methylation is a key component of epigenetic signaling and transcriptional regulation. The Mixed Lineage Leukemia (MLL) genes encode a family of histone methyltransferases that activate gene expression through the methylation of histone H3 on lysine 4 (H3K4). Rearrangement and amplification of the MLL1 locus are drivers of leukemogenesis, accounting for 10% of AML in adults and nearly 70% of ALL in infants. In addition, MLL1 mutations are common in a variety of solid cancers, including breast, colon, lung, and bladder. WD40 repeat protein 5 (WDR5) is a component of the multiprotein MLL1 complex that is essential for its methyltransferase activity, and disruption of the WDR5/MLL1 interaction may therefore present a viable therapeutic option for the treatment of MLL-dependent leukemias.

We conducted a medium throughput screen that identified micromolar drug like hits. Following several rounds of optimization using a structure-based approach and focused virtual library design we were able to identify OICR-9429, a nanomolar, highly selective and cell permeable inhibitor of the WDR5-MLL interaction. OICR-9429 is the first highly potent small molecule antagonist of the WDR5-MLL1 interaction and will serve as a valuable molecular probe for further exploration of WDR5 function.

Biography:

Dr. Al-awar earned a PhD in synthetic organic chemistry from North Carolina State University working on Lycopodium Alkaloids and did a post-doctoral fellowship focused on natural products synthesis at the University of North Carolina at Chapel Hill prior to joining Eli Lilly and Company in 1995. While at Lilly, she was an active medicinal chemist in the oncology area working in multidisciplinary teams on the antimicrotubule agent Cryptophycin and later on several kinase focused efforts. In 2002, while at Lilly, Dr. Al-awar took on administrative responsibilities as Head in Discovery Chemistry Research and Technologies and later as Head, Route Selection, in Chemical Product Research and Development prior to joining the Ontario Institute for Cancer Research to build a Drug Discovery Program in July 2008.