



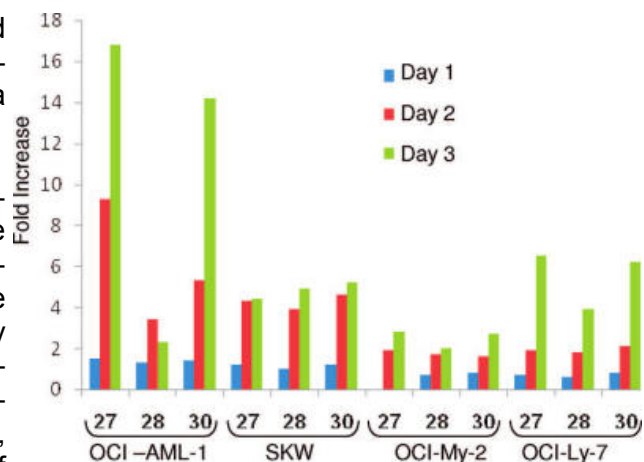
ODCase Inhibitors as Novel Anti-Cancer Agents

Overview of Technology:

Researchers at UHN have developed a novel family of small molecule cancer therapeutics that target the Orotidine-5'-Monophosphate Decarboxylase enzyme (ODCase) enzyme. ODCase activity is required for the de novo biosynthesis of essential nucleotides. Despite the existence of a nucleotide salvage pathway that can adequately supply nucleotides in quiescent or slowly replicating cells - the high demand for nucleotides in rapidly replicating cancer cells requires use of the de novo biosynthesis pathway. This requirement has led to previous efforts by several groups to develop cancer therapeutics targeting ODCase, however, these efforts did not succeed—likely due to a lack of understanding of the mechanism of action and structural details of ODCase.

World-leading structural studies of ODCase at UHN and use of structure based design tools have led to the creation of a novel class of nucleotide derivatives with a unique mechanistic activity targeting this enzyme.

This program is developing agents that target hematopoietic malignancies. Several compounds developed have shown potent inhibition in cell based assays against various hematopoietic cancer cell lines, with IC_{50} 's in the nanomolar to low micromolar range. Additionally, they have been shown to induce apoptosis in different leukemia and lymphoma cell lines. These first-in-class compounds can be synthesized rapidly and inexpensively, are stable, and can easily cross membranes. Many of these compounds are also new chemical entities (NCE's). Initial animal testing of this class of compounds has indicated good tolerability and bioavailability profiles. Lead compounds developed under this program have shown promising activities specifically against multiple myeloma (MM) and acute myeloid leukemia (AML), and exhibit superior anticancer activities without activating the JAK/STAT pathway.



Apoptosis as a result of treatment with three ODCase Inhibitors (27, 28, and 30) in various hematopoietic cancer cell lines in comparison to control cells when treated with each compound on days 1, 2, and 3. From Bello et al. *J. Med. Chem.* 2009, 52, 1648–1658

Related Publication:

Bello, A. M., et al. *Structure-Activity Relationships of Orotidine-5'-Monophosphate Decarboxylase Inhibitors as Anticancer Agents*, *J. Med. Chem.* 2009, 52, 1648–1658

Patents:

PCT/CA2006/001620 - Filed October 3, 2006 - National phase entry in: US, Europe, Canada, India, China (NCE claims), and US12/522,511 - Filed July 8, 2009 - (Method of treatment)

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