Small Molecules that Inhibit the β-catenin/BCL9 Interaction

Aberrant Wnt pathway signaling is thought to be important for the growth of triple negative breast cancer stem cells and bulk cancer cells. The β-catenin/BCL9 protein-protein interaction (PPI) is thought to be near the end of the Wnt pathway and is therefore considered to be a good target with minimal side effects. There is also some recent evidence to suggest that activation of the Wnt/β-catenin pathway may help cancer cells avoid a T-cell based anti-tumor immune response. Drug-like and selective β-catenin/BCL9 PPI inhibitors have been developed with an IC_{50} of at least 0.87 uM. The parent compound has excellent microsomal stability and pharmacokinetic properties with an oral bioavailabiity (F) of 83%, and triggers rapid apoptosis of cancer cells with hyperactive β-catenin signaling.

COMMERCIAL OPPORTUNITY

- There were estimated to be about 221,270 new cases of breast cancer in 2019. Triple negative breast cancer is found in about 10–20% of breast cancer patients. TNBC is highly metastatic, less responsive to standard treatment, and associated with a high rate of cancer recurrence. Data have indicated dramatic hyperactivation of canonical Wnt signaling in TNBC.
- Compelling basic and clinical studies demonstrate that hyperactivation of β-catenin signaling promotes hallmark characteristics of metastases in several cancers including triple negative breast cancer (TNBC). WNT/β-catenin signaling is also emerging as a key pathway that promotes immune evasion and resistance to immunotherapies.
- The inhibitors of the upstream effectors of the Wnt/β-catenin signaling pathway are less desirable, because those inhibitors have no efficacy for cancer cells harboring more downstream APC and Axin loss-of-function mutations, and β-catenin activation mutations. The upstream inhibitors also disturb noncanonical Wnt signaling pathways.
- BCL9/BCL9L provides the structure for scaffolding the 'WNT enhanceosome' and couples β-catenin and Pygos to the T-cell factor (Tcf) and lymphoid enhancer-binding factor (Lef) family of transcriptional factors to transcribe downstream target genes. Many studies have recognized the β-catenin-BCL9-Pygo axis is the key driver of malignancy, facilitating the switch from non-invasive to invasive cancer, provoking cancer progression and metastasis, and promoting immune suppression.

TECHNOLOGY

Drug-like β-catenin/BCL9 inhibitor derivatives of a parent compound have been designed and synthesized. AlphaScreen assays indicated that the parent compound disrupted the β-catenin/BCL9 PPI with a Ki of 0.76 ± 0.044 μM and exhibited 220-fold selectivity for disrupting β-catenin/BCL9 over β-catenin/E-cadeherin PPIs. A battery of biochemical and cell-based studies have demonstrated that this parent compound is the first drug-like inhibitor that binds with β-catenin, disrupts the β-catenin-mediated transcriptional complex, selectively inhibits β-catenin signaling activation, regulates Wnt target genes, and triggers rapid apoptosis of cancer cells with hyperactive β-catenin signaling. The parent compound has cell-based IC_{50}s around 10 uM.

PUBLICATION/PATENT

- Provisional patent application filed September 20, 2019 for Dr. Ji.

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