

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 2.2 μ M.

COMMERCIAL OPPORTUNITY

- There are expected to be about 255,000 new cases of breast cancer in 2017. Breast cancer is the leading cause of cancer death in females worldwide. Triple negative breast cancer (TNBC; estrogen receptor, progesterone receptor and epidermal growth factor receptor 2-negative breast cancer) is found in about 10–20% of breast cancer patients. TNBC represents an important clinical challenge because it is highly metastatic, less responsive to standard treatment, and associated with a high rate of cancer recurrence.
- Currently, no targeted treatment option is available for this type of breast cancer. Compelling data have indicated dramatic hyperactivation of canonical Wnt signaling in TNBC. TNBC cells are heterogeneous and have a subpopulation of cancer stem cells that drive tumor growth, seed metastases, and induce cancer recurrence. These cancer stem cells are resistant to current treatments. They must be eradicated to achieve a durable remission. Canonical Wnt signaling is aberrantly overactivated in TNBC cancer stem cells, which maintains cancer stem cell self-renewal and resistance to current therapies.
- Significant efforts have been made to discover small-molecule inhibitors for the canonical Wnt signaling pathway. However, the inhibition of the upstream sites is less desirable because it can cause crossregulatory effects on the noncanonical Wnt pathways. The formation of the β -catenin/T-cell factor (Tcf), B-cell lymphoma 9 (BCL9), and CREB (cAMP response element-binding protein)-binding protein (CBP) supercomplex in the cell nucleus is the penultimate step of canonical Wnt signaling. The aberrant formation of this supercomplex is the major driving force for TNBC tumorigenesis.

TECHNOLOGY

Drug-like highly potent and selective β -catenin/BCL9 inhibitor derivatives of a parent compound have been designed and synthesized. The parent molecule has been shown in an AutoDock model to bind to the β -catenin protein. FP and AlphaScreen assays show that the parent compound can completely disrupt β -catenin/BCL9 PPIs with a K_i value of $2.4 \pm 1.1 \mu$ M and is more potent than carnosic acid in the parallel assay, and also exhibits 218-fold selectivity for disrupting β -catenin/BCL9 over β -catenin/E-cadherin PPIs. The MTs cell viability assay showed that the parent compound inhibited the growth of TNBC cells MDA-MB-231 and MDA-MB-436 with the IC_{50} values of 1.23 ± 0.25 and $1.69 \pm 1.37 \mu$ M, respectively.

PUBLICATION/PATENT

- Provisional patent application filed 1/9/2018 for Dr. Ji.

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LICENSING OPPORTUNITY

