DBPR22998：A Potent QPCTL (IsoQC) Inhibitor Targeting CD47-SIRPα Axis for Cancer Immunotherapy

INDICATIONS:

- ✓ Solid tumors
- ✓ B-cell lymphoma
- ✓ Leukemia

PATENTS:

US, ROC (Taiwan) and PCT Granted:US10,584,120B2, TWI715156

DEVELOPMENT STATUS:

Candidate determination/ preclinical stage

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INVENTION DESCRIPTION

CD47-SIRPα "Do-not-eat- me" signaling axis is myeloid-specific innate immune checkpoint. Cancer cells express CD47 on the cell surface enable them to evade detection by the innate immune system and thus avoid destruction by macrophages. Inhibition of CD47-SIRPα axis triggers phagocytosis by macrophages. Glutaminyl-peptide cyclotransferase-like protein (QPCTL, or isoQC) is a Golgi-resident enzyme that catalyzes the cyclization of N-terminal glutamine and glutamic acid residues on target protein into a pyroglutamate residue (pGlu). Pyroglutamation on CD47 is important for SIRPα binding. We have identified a potent isoQC inhibitor with isoQC inhibitory activity at sub-nanomolar range. DBPR22998 significantly reduced the binding of anti-CD47 antibody on cell surface and prevented the interaction of human SIRPα-Fc with cell surface CD47 in both solid tumors and hematologic cancer cell lines tested. In addition, DBPR22998 in combination with anti-CD20 antibody rituximab enhanced antibody-dependent cellular phagocytosis in a human B-cell lymphoma Raji cells. *In vivo*, oral administration of DBPR22998 in combination with rituximab induced tumor regression and prolonged mean survival time compared to anti-CD20 antibody rituximab alone in Raji xenograft tumor model. DBPR22998 compound exhibited excellent pharmacokinetic properties and good oral absorption (F >30%) in mice and rats.

COMPETITIVE ADVANTAGES OF DBPR22998

- ➤ An orally bioavailable small molecule isoQC inhibitor modulating CD47-SIRPα "Do not eat me" cancer immune checkpoint activity
- ➤ Target post translational modification process of CD47 protein synthesis
- ➤ Demonstrate potent inhibitory activity of isoQC enzyme and effective blocking of CD47 and SIRPα interaction in CD47-expression cell lines in vitro
- ➤ Demonstrate antibody-dependent cellular phagocytosis (ADCP) in human monocyte-derived macrophage ex vivo culture
- ➤ Demonstrate anti-tumor efficacy in combination with antibody therapeutics in solid tumors and hematologic cancers
- ➤ Demonstrate more potent isoQC inhibitory activity in vitro and greater anti-tumor efficacy in vivo than those of the current clinical agent

MARKET POSITIONING/OPPORTUNITY

Anti-CD47 monoclonal antibodies are the most extensively studies for cancer immunotherapy. As opposed to antibody approaches in clinical development, our small molecule isoQC (QPCTL) inhibitor DBPR22998 is a best-in-class and innovative therapeutic approach for boosting the efficiency of cancer immunotherapy.

There are several advantages of targeting isoQC over therapies targeting CD47: 1. IsoQC inhibitors do not expect to cause hemolysis (lysis of red blood cells) and thrombocytopenia (loss of platelets), 2. IsoQC inhibitors would not suffer from the "antigen sink" problems of anti-CD47 therapy, 3. Small molecule inhibitors of isoQC can be administrated by oral route, which may be particularly beneficial for treating solid tumors.

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