



BPR1R Series: Novel CSF1R inhibitors as Cancer Immunomodulatory Agents

INDICATIONS:

- ✓ Solid tumors
- ✓ Giant-cell tumor of the tendon sheath

PATENTS:

US, ROC (Taiwan) application

DEVELOPMENT STATUS:

Lead optimization to candidate

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INVENTION DESCRIPTION

Colony-stimulating factor 1 receptor, CSF1R, is a type III receptor tyrosine kinase (RTK) that plays an important role in differentiation and survival of macrophages. Tumor cells rely on CSF1/CSF1R signal to induce the formation of immunosuppressive M2-like tumor-associated macrophages (M2-TAMs), thereby suppressing cytotoxic T cell-mediated immune responses. Thus, blockade of CSF1/CSF1R signals could shift M2-TAMs toward M1-like macrophages with anti-tumor functions and reprogram tumor microenvironment (TME).

NHRI-IBPR research team is experienced in drug discovery and has identified a series of BPR1R compounds as highly selective CSF1R inhibitors with excellent oral bioavailability. *In vivo*, oral administration of BPR1R compounds delayed murine colon tumor growth and reversed the immunosuppressive TME with increased M1/M2 ratio. The US & PCT patent application including more than 160 novel compounds was filed in April 20, 2020. Several potential compounds are undergoing candidate assessment for further preclinical studies.

COMPETITIVE ADVANTAGES OF BPR1R SERIES

- Tumor growth inhibition (TGI) = 69% without body weight loss [TGI of pexidartinib = 57% at the same dose]
- Brain penetration: brain-to-Plasma (B/P) ratio = 31%.
- Concise synthesis within 5 to 7 steps [10 g scale].
- Oral bioavailability (*F*) up to 38%.
- High kinase selectivity: $S(35) = 0.035$ @ 1 μ M against 403 kinases.
- High M2 TAM specificity: IC_{50} ratio against M1/M2 TAM > 200 fold.

MARKET POSITIONING/OPPORTUNITY

According to the Taiwan Institute of Economic Research's report, the global market value of CSF1R inhibitors will reach US\$ 23.8 billion by 2024. Currently, pexidartinib is the only CSF1R inhibitor approved so far as an orphan drug for treatment of tenosynovial giant cell tumor.

- > **Immune therapy possesses a huge opportunity** – agents that block CSF1/CSF1R signaling pathway represents an immunotherapeutic approach distinct from T-cell immune checkpoint inhibitors (ICIs). Our BPR1R inhibitors with high selectivity and low toxicity have the potential to combine with T-cell ICIs or cytotoxic agents to increase anti-tumor efficacy and anti-tumor immune responses.
- > **Potential Treatment for Alzheimer's Disease (AD) and Parkinson's Disease (PD)** – CSF1R is a promising target for AD and PD. Treatment of brain disorders requires drugs across the blood-brain barrier. Our compounds possessing excellent brain-penetrating ability provide a great opportunity as first-in-class agents for treatment of AD and PD.

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