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Monocarboxylate Transporter (MCT) Inhibitors to Treat Hypoxic Tumors (20120012)

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MCT Inhibitors Disrupt Hypoxic Tumor Metabolism

Certain tumors, such as triple negative breast cancer and gliomas, are especially difficult to treat due to unique metabolic features of these tumors. In particular, tumor hypoxia in these cancers can lead to treatment failure, relapse, and patient mortality as these cells are resistant to standard chemo- and radiation therapy.

Hypoxic areas develop when tumor metabolism rate outpaces development of vascularization, leaving areas with densely packed cells that are low on oxygen. These cells are metabolically different from their non-hypoxic counterparts and are therefore difficult to treat by traditional anticancer agents. Because of the unique metabolism of these tumors, metabolic pathways have become targets for treating these resistant hypoxic areas. Monocarboxylate transporters (MCTs) are targets for treatment because they transport lactate across the cell membrane. Lactate is a key chemical compound in cell metabolism and if transport is blocked, cell function will suffer. Tumor cells up-regulate these transporters for their unique metabolic needs, so targeting MCTs should lead to minimal damage to healthy cells while maintaining activity against tumor cells.

MCT Inhibitors as Anti-cancer and Immunosuppressive Agents

A group of small molecules that are potent MCT1 and MCT4 inhibitors have been designed. These molecules are potential anticancer and immunosuppressive agents that can be developed as targeted single agent anticancer agents or complimentary agents in combination with primary chemotherapeutic agents.

Because tumor cells up-regulate these transporters specifically for their unique metabolic needs, it is expected that normal cells will be tolerant to the chemotherapeutic actions, thereby leading to minimal side effects. Because the tumor cells' metabolism will be influenced by these inhibitors, tumor cells will have a harder time generating energy and will therefore have lower survival rates.

BENEFITS OF INHIBITING MONOCARBOXYLATE TRANSPORTER (MCT)

- MCT inhibitors provide an effective way to specifically treat hypoxic areas within tumors
- Disrupting the metabolism of tumor cells will decrease survival rates of the tumors
- These compounds have potential applications as immunosuppressive agents
- In vivo data showing tumor regression and improved survival
- Animal experiments demonstrated minimal side effects
- Lead compounds target both MCT1 and MCT4
- High oral bioavailability of compounds
- Easy to synthesize compounds

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Category
Life Sciences/Diagnostics & Imaging
Life Sciences/Pharmaceuticals

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Phase of Development Several very potent hydrophilic and lipophilic MCT inhibitors have been identified for further therapeutic applications. Experiments in various animal cancer models are ongoing. Early toxicology screenings completed.

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External Link (www.pharmacy.umn.edu)