Mitochondria-Targeted Metformins: Potent Anti-Pancreatic Cancer Compounds

**Background**

Mito-Metformins (Mito-Mets) are novel, mitochondria-targeted metformin derivatives that exhibit surprisingly potent inhibitory activity against human pancreatic cancer cells, but not normal cells. Due to the apparent mechanism of action, the inventors believe that Mito-Mets may also be used to treat cancers of the colon, lung, liver, breast, prostate, cervix, skin, and brain.

Metformin is a widely prescribed antidiabetic drug that was found unexpectedly to exert anticancer effects in diabetic individuals with pancreatic cancer. It is believed that both the antidiabetic and antitumor effects of metformin are due to its ability to sequester into mitochondria, where it inhibits complex I in the mitochondrial electron transport chain, elevates the intracellular AMP/ATP ratio, and activates the 5′-AMP–activated protein kinase (AMPK)/mTOR pathway—a critical pathway involved in regulating cellular metabolism, energy homeostasis, and cell growth.

Taking advantage of much higher mitochondrial membrane potential (more negative inside) in tumor cells as compared to normal cells, the inventors enhanced the mitochondrial uptake of metformin by attaching a lipophilic cationic moiety, triphenylphosphonium (TPP⁺), to metformin via alkyl linkers of varying lengths (2-12 carbon atoms), thus creating a set of mitochondria-targeted metformins, i.e., Mito-Mets (Cheng et al. 2016. Cancer Res 76:3904–15).

**Description of the Invention:**

**In vitro potency:** Mito-Met analogues are approximately 1000-times more potent than metformin in their ability to inhibit human pancreatic ductal carcinoma cell (PDAC) proliferation in vitro.

**In vivo efficacy:** In a mouse model for human pancreatic cancer, treatment with Mito-Metformin-C₁₀ (Mito-Met₁₀) significantly reduces tumor burden and results in markedly smaller primary tumors relative to untreated controls and metformin-treated animals.

**Low toxicity:** Mito-Met₁₀ accumulates in tumor tissues with negligible liver or kidney toxicity after two weeks of daily dosing (1 mg/kg). In vitro data indicate selectivity of Mito-Met₁₀ towards pancreatic cancer cells relative to non-tumorigenic cell lines.

**Mechanism of action:**

- Like metformin, Mito-Met₁₀ inhibits mitochondrial complex I and stimulates superoxide formation and AMPK activation in pancreatic tumor cells, but does not appear to affect normal, nonmalignant cells.
- Mito-Met₁₀ potently triggers G1 cell-cycle phase arrest in PDAC cells.
- Mito-Met₁₀ represses expression of a key gene involved in cell-cycle regulation, the redox-responsive transcription factor FOXM1. FOXM1 is a proto-oncogene whose upregulation occurs in the majority of solid cancers, including those of the pancreas, colon, lung, liver, breast, prostate, cervix, skin, and brain.