Small Molecule Inhibitors of Thioredoxin Reductase as Cancer Therapeutics

ID 951

Background
Thioredoxin-1, a redox protein involved in regulating cell division, is often overexpressed in tumors. This overexpression results in growth of the cancerous tissue and is associated with a decrease in patient survival. Due to the role of Thioredoxin-1 in the growth and survival of tumors, small molecule inhibitors targeting Thioredoxin reductase may be potential anti-cancer agents.

Thioredoxin reductase may also play an important role in other disease states including diabetic neuropathy, rheumatoid arthritis, Sjogren’s syndrome, AIDS, and reperfusion injury.

Technology Description
Investigators have developed PX-916, a water soluble prodrug of Palmarumycin CP1, a natural product inhibitor of Thioredoxin reductase. In its natural form, the utility of Palmarumycin CP1 is limited by its water solubility, which therefore impacts its bioavailability. PX-916 is converted to active drug at physiological pH but is stable at acid pH. PX-916 demonstrates excellent antitumor activity both in vitro and in vivo in multiple human tumor xenograft models.

Advantages
• Candidate first in class molecule targeting Thioredoxin reductase
• Water soluble prodrug that is rapidly converted into the active drug at physiological pH and in plasma
• Active against multiple human tumor types
  o Breast Cancer
  o Rhabdomyosarcoma
  o Small Cell Lung Cancer

Stage of Development
• Activity in three human tumor xenograft mouse models
• Preclinical pharmacokinetics, toxicity and stability of lead compound have been defined

Applications
1. Anti-cancer agent active against multiple tumor types

US Patent Application 20090131511
European Patent Application EP1933820
Canadian Patent Application CA2622674

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Research Interests

- Total Synthesis of Natural Products
- Organometallic Chemistry
- Heterocyclic Chemistry
- Combinatorial Synthesis
- Computational Prediction of Macroscopic Properties

Publications


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