Novel carbamoylphosphonates regulating tumor microenvironment (Yissum)

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Self targeting to the extracellular fluid gives ideal drugs

Categories	Cancer, metastasis, drug, zinc enzyme inhibitor
Development Stage	Drug at preclinical stage
Patent Status	PCT published (WO2010/089752)
Market Size	Global oncology drug sales are projected to reach $55 billion in 2009

Background

- Current estimates regarding the global incidence of cancer predict that by year 2020, the number of new cancer cases diagnosed each year will increase to 15 million and that the disease will be responsible for more than 12 million deaths. Despite recent advances in surgical techniques, and development of molecularly targeted therapies, most deaths due to cancer result from the progressive growth of metastases that eventually turn resistant to current therapies.
- The process of cancer metastasis consists of a series of sequential events that requires deregulated proliferation and eventually distal dissemination involving detachment from the extracellular matrices and invasion of the surrounding normal tissue
- Proteases are important for multiple processes during malignant progression and are hallmarks in tumor angiogenesis, local and distal invasion and cellular dissemination by acting as part of an extensive multidirectional network. Among them, matrix metalloproteinases occupy central nodes of this process. Localized proteolysis at the tumor-matrix interface signifies the transition from a benign state to a malignant one. Therefore the events in the microenvironment of the transformed cell play a critical role in the progression to malignancy.
- The enhanced proliferative capacity of tumor cells creates oxygen and nutrient deficient environment. The hypoxia condition initiates several enzymatic pathways including those of specific carbonic anhydrases, enzymes involved in the regulation of intra and extracellular pH, and therefore essential for the survival and proliferation of the cancer cells.

Our Innovation

- A novel family of compounds that target two types of cancer-related zinc enzymes: 1) matrix metalloproteinases (MMP2 and 9) involved in tumor metastasis dissemination, and 2) two tumor related carbonic anhydrases (CIs IX and XII) that regulate the pH in the tumors' microenvironment. Our orally bioavailable novel compounds self-target only into the extracellular space where the zinc-dependent enzymes also operate. Being unable to enter the cells by crossing lipid cell-membranes due to their polar nature, there are no toxic side effects observed in the course of such joint anti-cancer action
- The unique zinc binding group (ZBG) of the ionic carbamoylphosphonates (CPO) assures solubility in the extracellular fluid where the target enzymes operate.
- The compounds are useful by once daily oral administration, they show no toxicity, including musculoskeletal side effects manifested by most other similar drug candidates.

Key Features

- Oral activity in cancer metastasis models.
- Water soluble
- Non toxic
- The ionic drugs concentrate in the extracellular fluid and do not cross cell membranes.
- Enzyme selective – our compounds inhibit only the metalloenzymes CAs & MMPs, which operate in the extracellular fluid and are directly involved in the disease.

Development Milestones

Modifying molecules in order to reach second generation compounds with optimized potency, affinity, and specificity toward CAs & MMPs.

The Opportunity

- The oncology market is the third largest drug market.
- The global cancer market is predicted to grow at a CAGR exceeding 10%

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