Prostate-Specific Membrane Antigen (PSMA) Activated Prodrug and Imaging Agents

Introduction

- Antiproliferative Chemotherapies have had limited success in the treatment of metastatic cancers.
- These therapies have significant toxicities that greatly limit the amount and duration of therapy.
- Targeted Therapies attack cancer specific targets while minimizing toxicity.
- Heterogeneity of target expression within tumor results in outgrowth of resistant cells.
- Limits the effectiveness of targeted therapies such as kinase inhibitors and monoclonal antibodies.

What is the unique feature of the Thapsigargin Prodrug Strategy?

The Thapsigargin Prodrug Strategy

- Identify a critical intracellular protein whose function is required for survival of all cell types.
- Resistance is unlikely as cells need continued expression of the target protein to survive.
- Prodrug is selectively activated within tumor tissues.
- Protease specific peptide substrate to create an inactive intracellular protein.
- Release of thapsigargin prodrug.
- Thapsigargin irreversibly inhibits a critical intracellular protein, the Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase (SERCA) pump, causing sustained elevation of intracellular calcium, activation of ER stress response and release of apoptotic factors.
- High levels of expression in normal prostate and in prostate cancer.
- No detectable expression in normal endothelium.
- Positive expression in anovascularize of large number of tumors.
- PSMA expression is upregulated following androgen ablation.
- Unique enzymatic activity.

G202 Kills PSMA-Positive Cells In Vitro

- Radiolabeled PSMA-Activated Thapsigargin Prodrug for Imaging Prostate Cancer

Efficacy Against Human Prostate Cancer Xenografts

- G202 Phase I Clinical Trial

Thapsigargin as Therapy For Cancer

- Radioabeled PSMA-Activated Thapsigargin for Imaging Prostate Cancer

Conclusions

- Preclinical studies demonstrate that G202 is a PSMA-activated prodrug that has broad spectrum anti-cancer activity against a panel of human cancer xenografts.
- G202 licensed to GenSpera, a startup biotechnology company based in San Antonio, TX (www.genspera.com)
- GenSpera has completed GMP manufacture of clinical grade G202.
- Toxicology studies completed in rats and monkeys.
- IND awarded in September 2009.
- Phase I clinical trials began at Johns Hopkins and University of Wisconsin 2010.

PSMA is a Folate Hydrolase

- Unique enzymatic activity.
- PSMA expression is upregulated following androgen ablation.
- Unique enzymatic activity.
- PSMA is a Folate Hydrolase.