Therapeutic Potential of Targeting Amino Acid Metabolism in Pancreatic Cancer

INTRODUCTION

- Numanous cancers display an increased cellular demand for amino acids in order to sustain their increased proliferation.
- LAT1 overexpression in pancreatic cancer has been shown to be an important prognostic factor for the development of chemoresistance and survival in patients with pancreatic ductal adenocarcinomas (PDAC).
-LAT1-overexpression in pancreatic cancer has been shown to support the development of chemoresistance and survival in patients with pancreatic ductal adenocarcinomas (PDAC).

PROPOSED MECHANISM OF ACTION

- LAT1 is overexpressed in a wide variety of cancers including prostate, ovarian, and breast. Drugs that inhibit LAT1 activity are under investigation for the treatment of cancer.
- Several SMs (Korner et al.) have been reported to be important in EMT transition and mesenchymal cell defense mechanisms.
- SMs are novel anti-cancer agents that selectively target cancer cells by disrupting protein synthesis machinery, inducing oxidative stress, and decreasing defense mechanisms.
- Several D-amino acids have been shown to cause:
  - Transient overexpression of a tyrosine dehydrogenase is designed to leverage LAT1 overexpression for selective tumor targeting.
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ADDITIONAL POTENTIAL EFFECTS

- Catecholamine as a Cancer Target
  - The absence of SM 88 is known to inhibit tyrosine hydroxylase (Hayashi K et al.), thus the role of SM 88 in pancreatic cancer has been shown.
  - LAT 1 has been reported to be important in EMT transition and mesenchymal cell defense mechanisms.
  - Several D-amino acids have been shown to cause:
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ON-GOING AND PLANNED WORK

- Evaluation of the anti-cancer effects of SM 88 using in vitro (cell line), and in vivo ( xenograft) models of PDAC.
- Evaluation of SM 88 efficacy in models of additional cancer types.
- Determination of the contribution of the LAT and SM 88 isoforms to the immune effects of SM 88.
- Gated examination of patient systemic and tumor immunomodulatory effects in EMT.
- Use of pre-clinical models to evaluate SM 88 effects on migration, invasion, and metastatic potential.
- Combinations of SM 88 and standard therapies.

RESULTS AND CASE STUDIES

- Overall survival in patients with pancreatic cancer has been shown to be an important prognostic factor for the development of chemoresistance and survival in patients with pancreatic ductal adenocarcinomas (PDAC).
- LAT 1 has been reported to be important in EMT transition and mesenchymal cell defense mechanisms.
- Several D-amino acids have been shown to cause:
  - Transient overexpression of a tyrosine dehydrogenase is designed to leverage LAT 1 overexpression for selective tumor targeting.

CLINICAL TRIALS

- 10 patients with PDAC were enrolled in the First Human Study and showed subsequent compassionate use progression-free survival.
- These patients received 230 mg of SM 88 per day. Of the 10 patients, 9 obtained M2PS (melanin 50 μg, melanin 50 mg, and serotonin 2.5 mg per day).
- Nine patients with PDAC were enrolled in a compassionate use study, and were treated with SM 88 (melanin 50 μg, serotonin 2.5 mg, and melatonin 1 mg) for 30 days.
- SM 88 reduced resectability of catecholamines in patients with metastatic melanoma, in addition to improved survival in the treatment of melanoma.
- LAT 1 has been shown to be important in EMT transition and mesenchymal cell defense mechanisms.
- Several D-amino acids have been shown to cause:
  - Transient overexpression of a tyrosine dehydrogenase is designed to leverage LAT 1 overexpression for selective tumor targeting.

CONCLUSIONS/DISCUSSION

- Altered amino acid (LAT 1) metabolism has shown to be a negative prognosticator in pancreatic cancer survival and progression.
- Results from clinical studies of SM 88 suggest the therapy is well-tolerated and early signs of anti-tumor effects have been observed.
- Ongoing and planned pre-clinical studies with SM 88 could further clarify the mechanism and potential of this agent in the treatment of breast cancer.
- Future studies may clarify the potential utility of this approach in the treatment of pancreatic cancer.