Antagonism of Peroxisome Proliferator Activated Receptor Alpha (PPARα) by TPST-1120 Suppresses Tumor Growth and Stimulates Anti-Tumor Immunity

Chan C. Whiting1, Nick Stock2, Davorka Messmer2, Austin Chen2, Traci Olafson2, Allison Gartung3, Karin Stebbins4, Lisa Rahbaek5, Catherine Lee2, Chris Baccei6, Alex Broadhead2, Ryan Clark2, Dan Lorrain2, Alicia Levey1, Derek Metzger1, Amanda Enstrom1, Jennifer McDevitt1, David Spaner3, Peppi Prasit2, Dipak Panigrahy4

1Tempest Therapeutics, Inc., San Francisco, CA; 2Inception Sciences, San Diego, CA; 3Sunnybrook, Toronto, Canada; 4Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

ABSTRACT

TPST-1120 is a first-in-class selective antagonist of human PPARα, a transcription factor that induces expression of fatty acid oxidation (FAO) genes. Tumor metabolic adaptations promote its own survival and suppress tumor-specific immunity by upregulation of FAO. PPARα blockade has tumor intrinsic and extrinsic effects, and inhibits tumor cell growth and induces tumor-specific immunity, demonstrated among multiple syngeneic and xenograft mouse models.

Methods

TPST-1120 efficacy as a monotherapy or in combination with chemotherapy or anti-PD1 was evaluated in multiple syngeneic mouse models including B16 melanoma, MMTV mammary carcinoma, MC38 colon, Lewis lung carcinoma, Pan02 pancreatic cancer, and xenograft models of CLL, melanoma, melanoma and AML. To characterize its mechanism of anti-tumor immunity, TPST-1120 was evaluated in knock-out models of CCL2, MBL, TSP-1, STING and Batf3. Immune modulation was characterized by M2M1 macrophage flow cytometry phenotyping and ELISA measurement of plasma and tumor matrix proteins (thrombospondin-1 (TSP-1)), which is involved in granulocyte migration and angiogenesis.

Results

TPST-1120 mediated PPARα antagonism resulted in potent anti-tumor immune responses and significant tumor regression, either as a monotherapy or in combination with chemotherapy or anti-PD1. TPST-1120 showed anti-tumor efficacy against syngeneic models of breast, lung, colon, pancreatic and melanoma in addition to xenograft models of CLL, AML, melanoma and pancreatic cancers as a monotherapy or in combination with chemotherapy and anti-PD1. TPST-1120 demonstrated cytostatic effect on tumor cells in vitro. In a pancreatic and breast cancer model, TPST-1120 combination chemotherapy gemcitabine and eribulin, respectively, had additive effect on tumor growth. TPST-1120 combination with anti-PD1 in an ovarian orthotopic (ID8) and colon (MC38) models showed suppression of tumor growth and complete remission in some mice. Moreover, mice receiving the combination treatment conferred protections against autologous tumor re-challenge in the ID8 model, strongly suggesting immunological T cell memory against the primary tumor. Preliminary studies in genetic knock-out mice, suggest macrophages and antigen cross-presenting dendritic cells are targets for TPST-1120. To characterize its mechanism of anti-tumor immunity, TPST-1120 was evaluated in knock-out models of CCL2, MBL, TSP-1, STING and Batf3. Immune modulation was characterized by M2M1 macrophage flow cytometry phenotyping and ELISA measurement of plasma and tumor matrix proteins (thrombospondin-1 (TSP-1)), which is involved in granulocyte migration and angiogenesis.

Conclusions

Through its unique mechanism of restricting FAO, TPST-1120 targets a metabolic pathway that is critical for the survival of both tumor cells and of suppressive immune cell populations infiltrating the tumor microenvironment. TPST-1120 represents a promising new approach for evaluation in patients with advanced malignancies.

INTRODUCTION

- TPST-1120 is a first-in-class, orally administered, small molecule selective antagonist of the human peroxisome proliferator-activated receptor alpha (PPARα).
- PPARα is a transcription factor which induces the expression of genes that regulate fatty acid oxidation (FAO) and inflammation (Figure 2).
- PPARα and FAO gene signatures can be enriched in metastatic tumors (Figure 1).
- FAO supports the metabolism of immune suppressive cell populations that inhibit anti-tumor immunity.
- The growth and progression of diverse tumor types are completely suppressed in PPARα-deficient mice.
- TPST-1120 has significant anti-tumor activity as a monotherapy and in combination with chemotherapy or anti-PD1 antibodies.
- Anti-tumor activity of TPST-1120 is mediated through: 1) direct tumor cell killing; 2) release of immune suppression; and 3) restoration of TSP-1 to homeostatic levels.

METHODS

- Efficacy as a monotherapy or in combination with chemotherapy or anti-PD1 was evaluated in multiple syngeneic mouse models.
- TPST-1120 was evaluated in knock-out models of TP-1, String and Batf3 to characterize its mechanism of anti-tumor immunity.
- ELISA was used to measure plasma and tumor matrix protein TP-1 and Fg21.
- Gene expression analysis was performed by quantitative RT-PCR.

RESULTS

TPST-1120: PPARα Target Validation and Target Engagement

- TPST-1120 directly inhibits proliferation of primary CLL tumor cells (Figure 5).
- TPST-1120 directly inhibits proliferation of primary CLL tumor cells in a dose dependent manner after 48 hours of incubation. Cells were obtained from consented patients (n=14).

TPST-1120 CONCLUSIONS

- A first-in-class PPARα antagonist provides anti-tumor efficacy as a monotherapy or in combination with chemotherapy or anti-PD1.
- Directly inhibits tumor proliferation.
- Requires both innate and adaptive immunity for anti-tumor efficacy.
- Anti-tumor efficacy is TP-1 dependent.
- A Phase 1/1b open-label, dose-escalation and dose-expansion study of TPST-1120 as a single agent or in combination with systemic anti-cancer therapies in subjects with advanced solid tumors is planned to initiate in early 2019.

REFERENCES