Dual antagonism of prostaglandin receptors EP2 and EP4 by TPST-1495 suppresses tumor growth and stimulates antitumor immunity

Chan C. Whiting1, Kim Fischer2, Bryan Laffitte2, Lisa Rabhaek2, Davorka Messmer2, Austin Chen2, Traci Olafson3, Natalie Nguyen2, Alejandro Dariel2, Yalda Bravo2, Joe Nagamizo2, David Powell2, Joyce Wu4, Bob Gomez4, Tao Sheng4, Jim Ding4, Amanda Enstrom2, Derek Metzger1, Brian Francia1, Dingzhi Wang5, Raymond Dubois5, Dipak Panigrahy1, Glnna Laport1, Peppi Prasit1, Thomas Dubensky1

1Tempest Therapeutics, Inc., San Francisco, CA; 2Inception Therapeutics, San Diego, CA; 3College of Medicine, Medical University of South Carolina, Charleston, SC; 4Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; 5Inception Sciences, Vancouver, BC, Canada

ABSTRACT

Background

Prognosis of diverse malignancies is promoted by elevated levels of Prostaglandin E2 (PGE2). High PGE2 levels result from dysregulation of Cyclooxygenase-2 (COX-2), the enzyme that produces this lipid. PGE2 stimulates tumor cell proliferation, survival, evasion and metastasis along with host angiogenesis. PGE2 suppresses anti-tumor immunity through inhibiting the function of critical anti-tumor immune effectors such as NK and T cells, and macrophages, while promoting the activity of suppressive immune cells including myeloid derived suppressor cells (MDSCs) and regulatory T cells. PGE2 signals through a family of four homologous E-prostanoid (EP) G-coupled receptors (GPCRs), and activates four distinct signal transduction pathways.

Methods

The effects of TPST-1495 as monotherapy or in combination with anti-PD1 were evaluated in the syngeneic mouse colon models CT26 and ApcMin/+ as well as Lewis Lung Carcinoma. The mechanism of anti-tumor immunity of TPST-1495 was evaluated using in vitro primary dendritic cell (DC) differentiation and activation assays. Characterization of in vitro differentiated immune cells or tumors infiltrating lymphocytes were performed using flow cytometry. ELISA was used for measurement of cytokine production.

Results

Treatment with TPST-1495 reversed PGE2 immune suppression in vitro and in vivo compared to antagonist of EP4 alone or all 4 EP receptors. TPST-1495 prevented PGE2 inhibition in vitro of DC differentiation and activation from human donor monocytes; single EP2 or EP4 antagonists were sub-optimal in this assay. Significantly, combination with EP1 and EP3 antagonists reversed the effect of EP2 and EP4 blockade on PGE2 immune suppression, suggesting that COX-2 inhibition is not optimal for blocking the effects of PGE2. TPST-1495 induced potent anti-tumor immune responses and significant tumor regression as a monotherapy in different murine tumor models colon cancer, CT26 and ApcMin/+.

Conclusions

TPST-1495 is a differentiated highly potent selective dual antagonist of EP2 and EP4 that overcomes prostaglandin-mediated immune suppression and promotes anti-tumor efficacy.

INTRODUCTION

- TPST-1495 is a first-in-class, orally-administered, small molecule, selective dual antagonist of the human prostaglandin E2 (PGE2) receptors, EP2 and EP4
- PGE2 signals through four homologous E-prostanoid, G-protein coupled receptors (GPCRs): EP1, EP2, EP3 and EP4, which activate distinct signal transduction pathways
- TPST-1495 is a first-in-class, orally-administered, small molecule, selective dual antagonist of adenosine monophosphate; IP3: inositol triphosphate
- NSAIDs: nonsteroidal ant-inflammatory drugs; COX: cyclooxygenase; PGG2: prostaglandin G2; PGH2: prostaglandin H2; PGEs: prostaglandins

FIGURE 1: Signaling Pathways Associated with PGE2 receptors: Rationale for Inhibiting both EP2 and EP4 Receptors with a Dual Antagonist

FIGURE 2: TPST-1495 is Significantly More Potent Than EP2- or EP4-Selective Single Antagonists in Reversing PGE2-mediated Immune Suppression

FIGURE 3: TPST-1495 has Significant Monotherapy Activity in Lewis Lung Carcinoma Model

FIGURE 4: TPST-1495 has Potent Single Agent Anti-tumor Activity Associated with Increased T Cell Infiltration in the TME


FIGURE 6: TPST-1495 Combination with Chemotherapy Enhances Anti-tumor Response in Lewis Lung Carcinoma

FIGURE 7: TPST-1495 Combination with Anti-PD1-1 Enhances Anti-tumor Response in the Mouse CT26 Colon Cancer Model

FIGURE 8: Multiple Tumor Types Express Elevated Levels of EP2 Pathway Genes

FIGURE 9: Multiple Tumor Types Express Elevated Levels of EP2 and EP4 PGE2 Receptors

TPST-1495 CONCLUSIONS

- First-in-class dual antagonist of both EP2 and EP4 receptors
- Significantly more potent than EP4-selective single antagonists in clinical development
- Antagonism of both EP2 and EP4 receptors required for optimal reversal of PGE2-mediated immune suppression
- Potent single agent activity in multiple preclinical tumor models and enhances anti-tumor efficacy with chemotherapy and anti-PD1 Abs
- Increases infiltration of effector T lymphocytes into the TME
- TCGA analysis reveals multiple tumor types that appear reliant on EP2/EP4 pathway, informing clinical development
- A Phase 1b/2 open-label, dose-escalation and dose-expansion study of TPST-1495 monotherapy or in combination with anti-PD-1 mAb is planned to initiate in early 2020

REFERENCES