

FPT155: A first-in-class therapeutic CD80-Fc fusion protein that augments T cell co-stimulation

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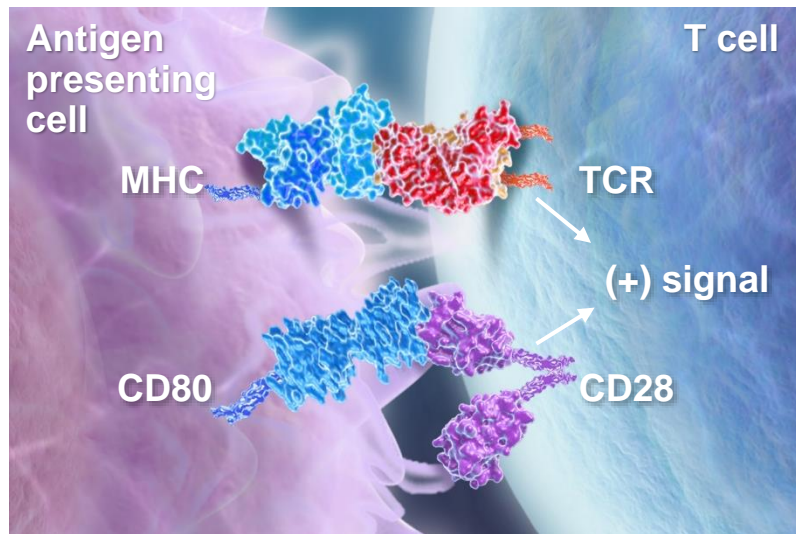
Five Prime Therapeutics, South San Francisco, CA

Disclosure Information

- I have the following financial relationships to disclose:
 - I am an employee of Five Prime Therapeutics
 - I am a stockholder in Five Prime Therapeutics
- I will not discuss off label use and/or investigational use in my presentation

FPT155: First-In-Class CD80-Fc Fusion Protein Engineered to Activate T Cells Through Multiple Pathways

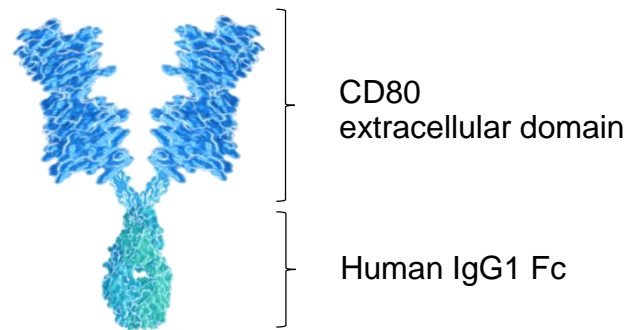
Normal T cell activation via CD80



CD80 is a co-stimulatory molecule expressed on antigen presenting cells

FPT155 uses the binding interactions of CD80 to:

- Directly engage CD28 to enhance its co-stimulatory activity (*without super agonism*)
- Block CTLA-4 from competing for endogenous CD80, allowing CD28 signaling to prevail in T cell activation

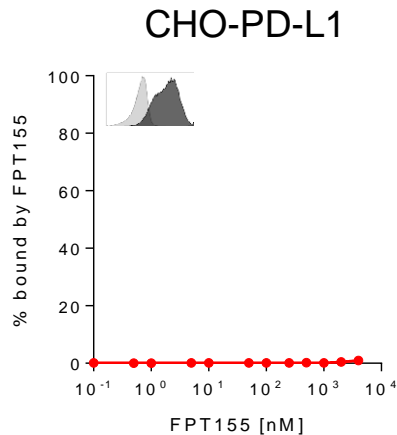
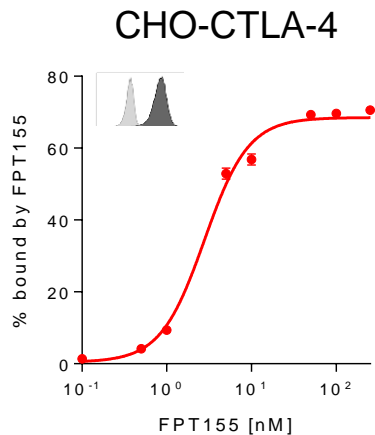
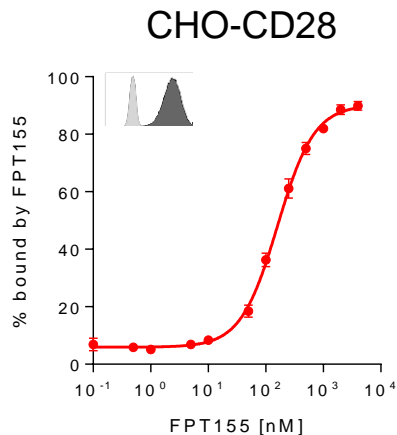


First in Human phase 1a/1b trial initiated in Nov 2018

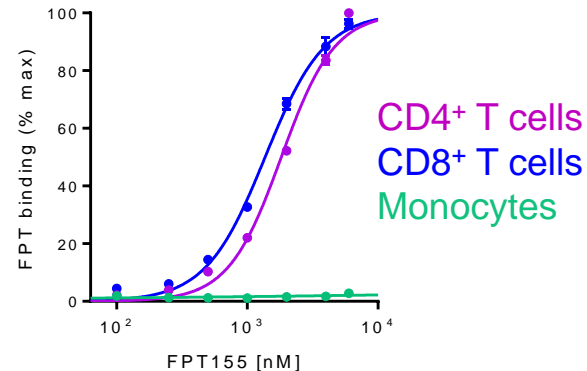
FPT155 Binds to Cell-Surface CD28 and CTLA-4

- Flow cytometry-based assays indicate that FPT155 binds to cells via CD28 and CTLA-4 but not via PD-L1
- FPT155 binds to primary T cells and *in vitro*-expanded T cells but not to hematopoietic subsets that express only PD-L1 (e.g. monocytes)

Binding to cell lines that express a single ligand

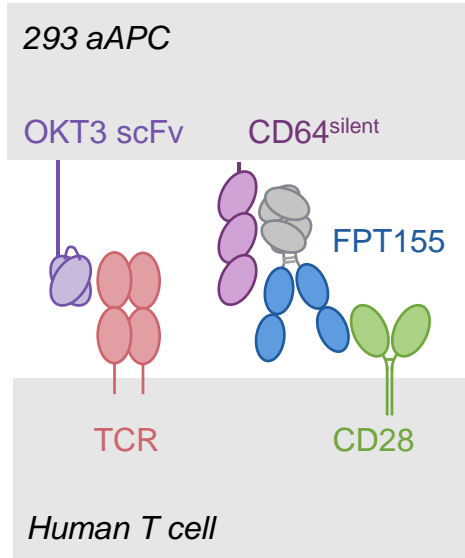


Binding to human PBMC

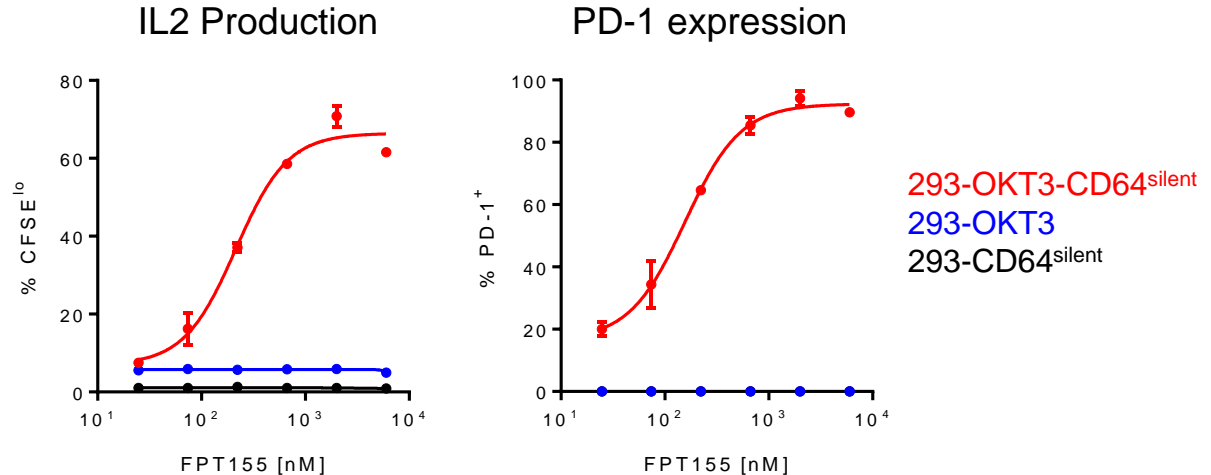


FPT155 Activity Requires Co-Presentation with TCR Stimulus

- 293-based “artificial APC” express an OKT3 scFv to provide TCR stimulation and/or a truncated FcγRI to cluster FPT155 in the cellular synapse
- Activity observed with FPT155 requires TCR signal and Fc-mediated clustering

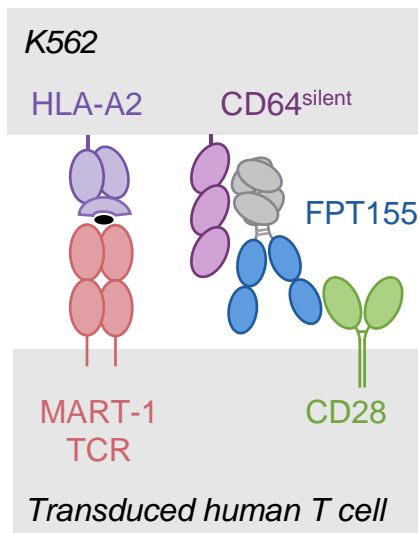


Naïve CD4⁺ T cells + 293 aAPC



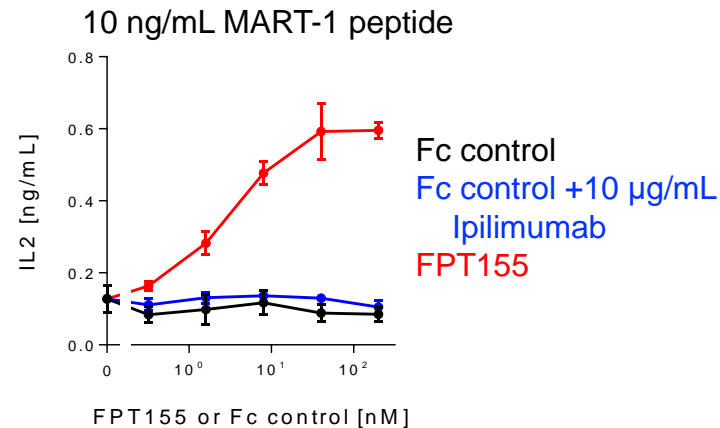
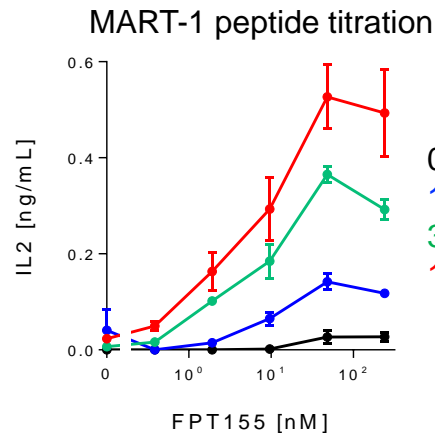
FPT155 Co-Stimulates T Cells in the Context of Antigen-Specific TCR Stimulation when CD28 Ligands are Limiting

- FPT155 potently co-stimulates the activation of MART-1 antigen-specific T cells *in vitro*
 - The effect is sensitive to peptide concentration, indicating that TCR-induced signals are critical for activity
- Activity is observed at lower concentrations than are required to detect soluble binding, and lower than are expected to saturate CTLA-4
 - Absence of activity with Ipilimumab suggests that FPT155 may be efficacious when co-stimulation is limiting



MART-1 TCR⁺ panT cells + K562 aAPC

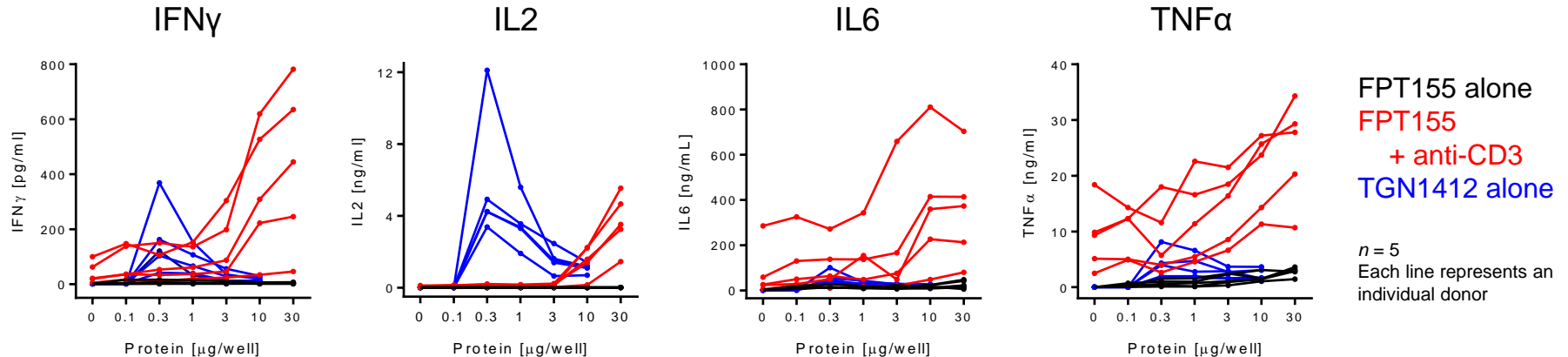
IL2 production



FPT155 is Not a T Cell Superagonist

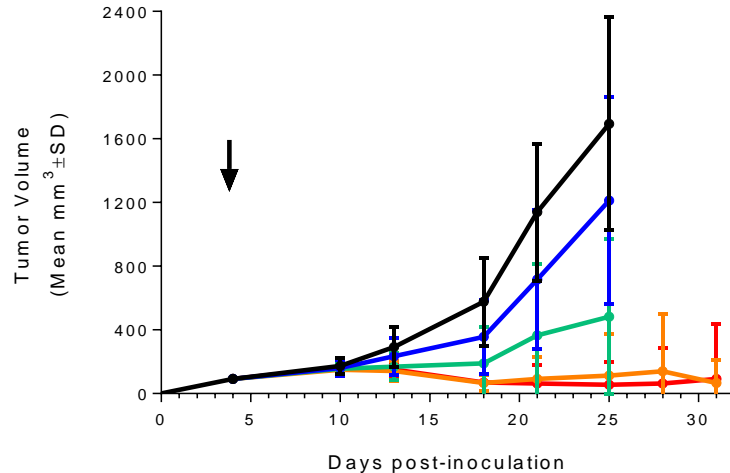
- The CD28 superagonist antibody TGN1412 induces spontaneous cytokine release by PBMC when immobilized on plastic
 - The cytokine profile matches that of clinical cytokine release syndrome
- FPT155 alone does not induce spontaneous cytokine release in this format
 - Cytokines are produced when FPT155 is co-immobilized with anti-CD3, indicating that FPT155 is functionally active in this assay format, but requires co-engagement with the TCR for T cell activation

Spontaneous PBMC cytokine release *in vitro*

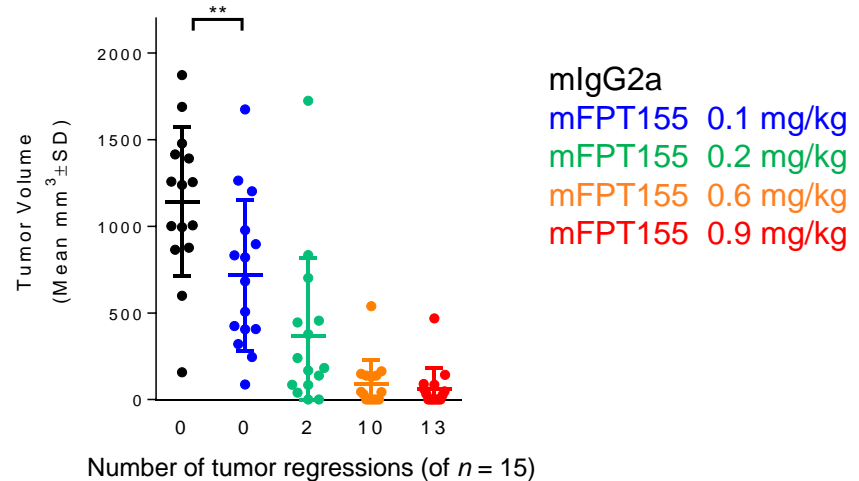


The Murine Surrogate mFPT155 Can Induce Complete Tumor Regression After a Single Dose at 0.2 mg/kg

CT26 tumor growth



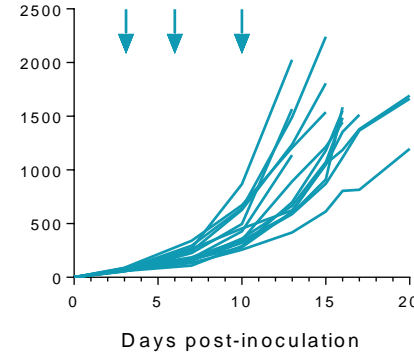
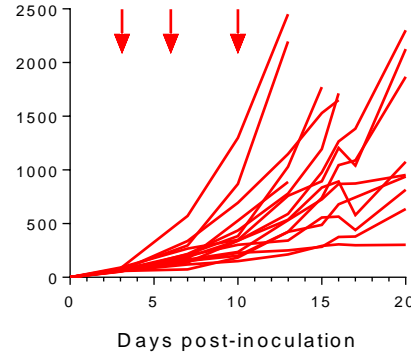
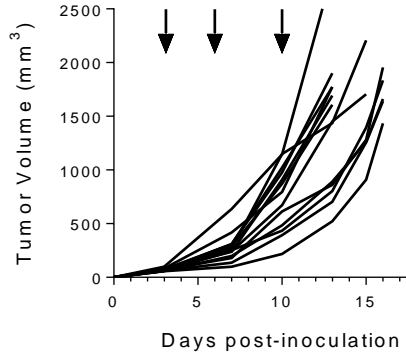
Day 21 tumor volume



- mFPT155 exerts monotherapy anti-tumor activity in multiple tumor models including CT26, MC38, EMT6, A20, and WEHI164[‡]
- Mice that reject tumors in response to mFPT155 are protected from subsequent re-challenge
- mFPT155 exhibits synergistic activity in combination with anti-PD-1 in the CT26 model

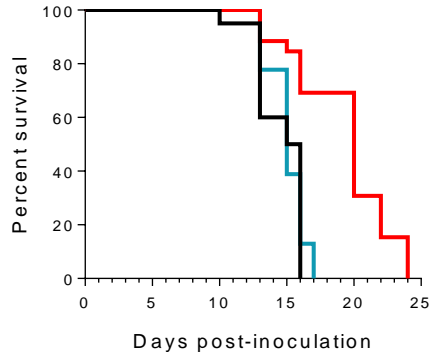
mFPT155 is Efficacious in Tumor Models Typically Refractory to IO Treatment

B16-F10 tumor growth



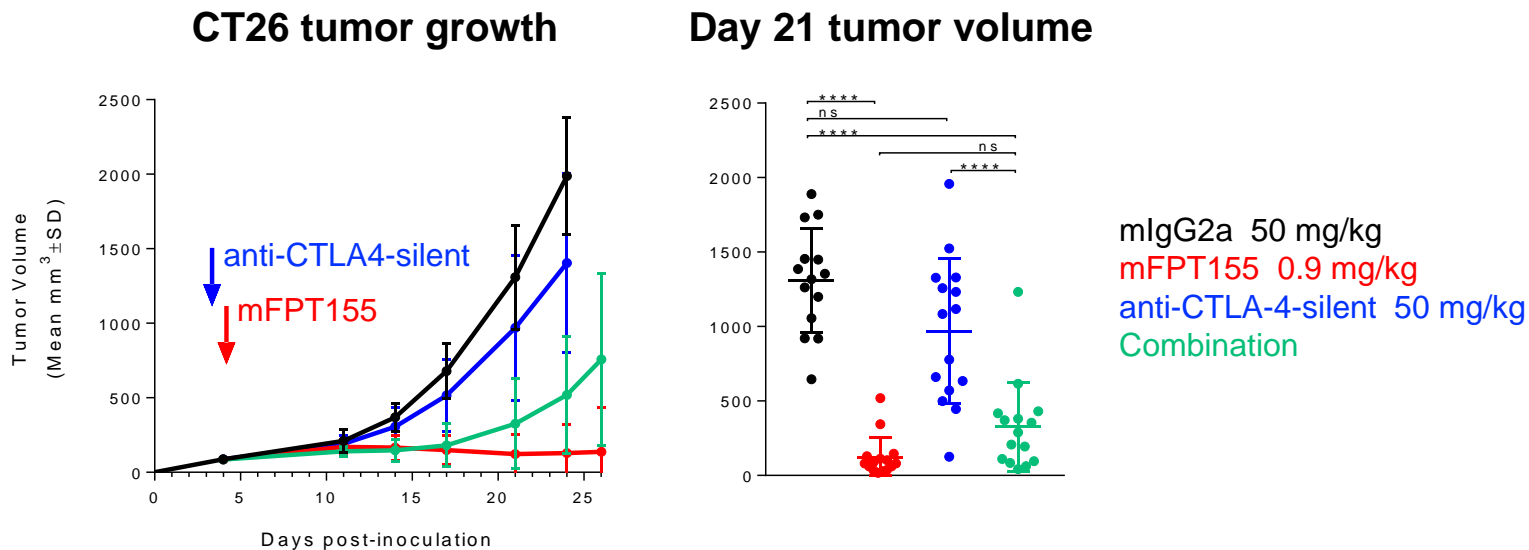
mIgG2b control
mFPT155 (mIgG2a)
3 mg/kg
anti-CTLA4 (mIgG2b)
10 mg/kg

B16-F10 survival



- mFPT155 also has significant activity in other refractory tumor models, including Renca and 4T1[‡]
- Activity in such tumor models suggests that FPT155 could have clinical activity in tumor types that respond poorly to IO therapies

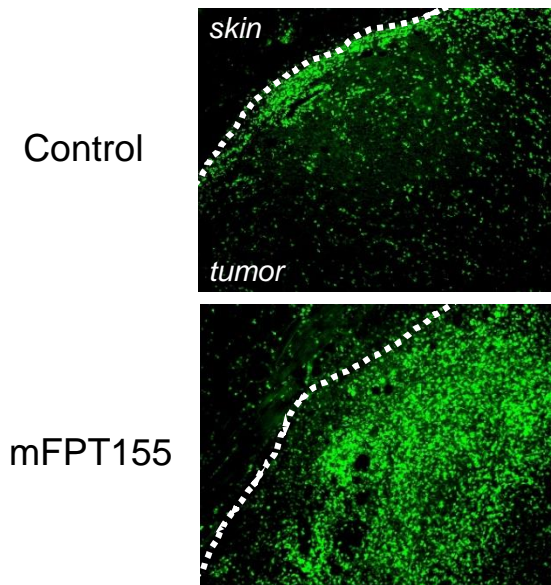
mFPT155 Retains the Majority of Its Activity in vivo Independent of Its Interactions with CTLA-4



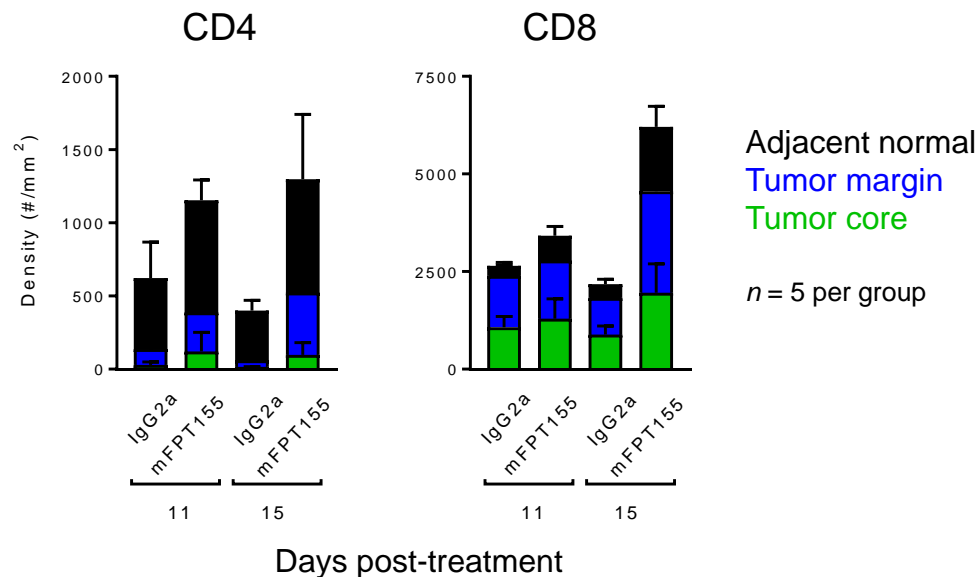
- CTLA-4 blockade via a Fc-silent antibody has minimal monotherapy activity against CT26
- Slight but non-significant loss of activity in combination suggests that mFPT155 has CTLA-4-mediated function independent of neutralization

mFPT155 Promotes Effector T Cell Recruitment into Tumors

CD3 staining in CT26 tumors



CD4 and CD8 staining in MC38 tumors

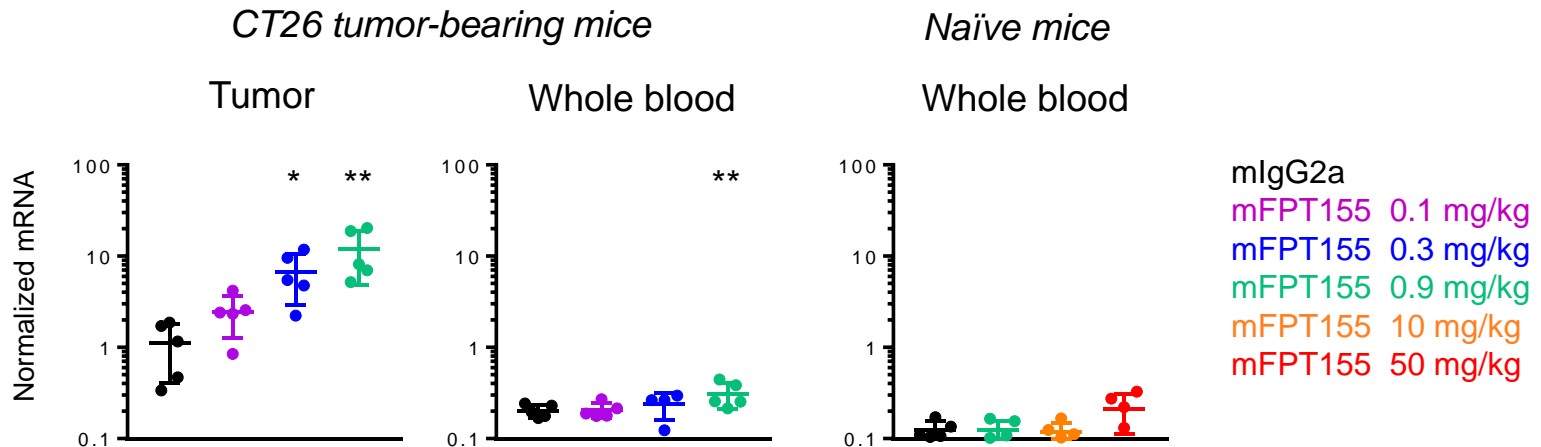


- mFPT155 treatment promotes recruitment and subsequent infiltration of T cells
- The response is specific to effector T cells and is not observed for T_{reg}

mFPT155 Induces T Cell Activation in Tumor-Bearing Animals at Projected Clinical Dose Levels

- mFPT155 preferentially induces effector T cell activation in the tumor as detectable by transcriptomics and flow cytometry
- Effect is observed in peripheral blood only in tumor-bearing animals, indicating that mFPT155 does not induce non-specific T cell activation at projected clinical dose levels

Gzmb expression 11 days after mFPT155 administration



Phase 1a/1b Clinical Trial to Evaluate FPT155 Monotherapy Activity

PHASE 1a

Dose Escalation

Any Solid Tumor

Exploratory Cohorts

Basket of Solid Tumors

Initiated
November 2018

PHASE 1b

Expansion at Chosen Dose

Select Solid Tumor Cohorts

Study Objectives

- Safety
- Objective response rate and duration
- Survival
- Baseline and on-treatment biopsies

- Trial initiated in Australia; expansion to other countries in Phase 1b
 - A conservative MABEL approach was used to select starting dose for dose escalation
- We are currently evaluating combination strategies

Biomarker Analyses to Monitor Safety, Efficacy, and MOA Endpoints

Real-Time Safety Assessments

- Local lab tests include complete blood count, full chemistry panel, and CRP on D2 and weekly in C1

Retrospective Analyses

- Tumor at baseline (archival)
 - Evidence of tumor immunogenicity (IHC, RNA, DNA)
- Tumor pre-/on-treatment biopsies mandated in 1a exploratory cohorts
 - Optional biopsy collection at progression
 - Immune infiltration and activation (IHC, RNA)
- Peripheral blood pre-/on-treatment
 - T cell phenotype (flow cytometry)
 - Peripheral cytokines, including CRS signature
 - Tumor mutation burden (ctDNA)

Summary

- FPT155 is a first-in-class CD80-Fc fusion protein engineered to activate T cells via engagement of CD28 and CTLA-4
- FPT155 does not have TCR-independent superagonist activity in nonclinical studies
- The murine surrogate (mFPT155) has potent anti-tumor activity in multiple murine tumor models, including models typically refractory to IO agents
 - mFPT155 has synergistic combination activity with anti-PD1
- mFPT155 promotes a favorable tumor immune contexture characterized by effector T cell infiltration and activation
 - mFPT155 preferentially activates T cells in the tumor microenvironment vs periphery
- Five Prime initiated a Phase 1a/1b clinical trial in November 2018

Acknowledgements

FPT155 Core Team

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Nallakkan Arvindan
Francis Sarena
David Smith

External

MART-1 TCR system: Steven Rosenberg, NCI

Patients and clinicians participating in the FPT155-001 trial