



BRIGHT PEAK
THERAPEUTICS

Generation of a Highly Potent, *Cis*-signaling PD1-IL2 Immunocytokine Using a Novel Chemical Synthesis and Conjugation Platform

Jean-Philippe Carralot, M. Arévalo Ruiz, R. Alvarez Sanchez, R. Tam, L. Gremlich, A. Chi, V. R. Pattabiraman, B. Kreft
Bright Peak Therapeutics Inc., Basel, Switzerland & San Diego, CA. Email: science@brightpeaktx.com

Poster #1195

10) Immuno-Conjugates and Chimeric Molecules
c. Bispecific Molecules



INTRODUCTION

- Immunocytokines (IC) simultaneously engage distinct and complementary mechanisms of action using antibodies to deliver cytokine payloads to the surface of the same immune cell ("*cis*-signaling") resulting in enhanced anti-tumor activity.¹
- To generate ICs, we developed an entirely novel approach based on site-specific, chemical conjugation of engineered cytokines to existing, unmodified antibodies (Ab).¹
- We utilized LZM-009, an anti-PD-1 Ab in late-stage clinical development, for generation of proprietary multi-functional PD-1 targeted ICs in order to inhibit the dominant immune checkpoint pathway and target PD-1⁺ antigen-experienced T cells.
- Using our unique cell-free, chemical engineering platform, we generated a PD1-IL2 IC (BPT331) to target an α -dead IL-2 to tumor resident PD-1^{high} effector T cells while simultaneously releasing these cells from PD-1-mediated immune suppression.

CONCLUSIONS

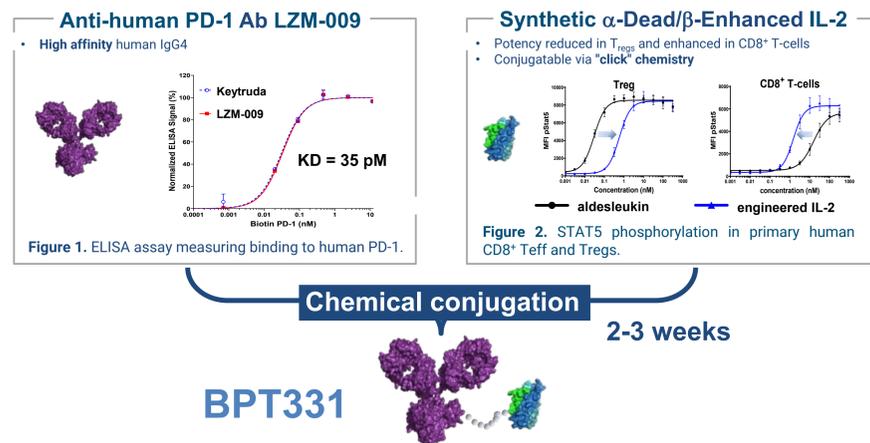
- Our ability to rapidly generate ICs from existing Abs enables highly efficient screening of cytokine payloads and antibody-cytokine combinations.
- We identified an optimized α -dead/ β -enhanced IL-2 payload to generate BPT331, a potent PD1-IL2 with high selectivity for PD-1^{high} cells.
- In vivo*, BPT331 triggers the selective expansion of PD-1^{high} effector memory CD8⁺ T (TEM) cells within tumors.
- Specific expansion of PD-1^{high} CD8⁺ TEMs in the tumor vs blood and tumor-specific retention of PD1-IL2 but not of non-targeted Her2-IL2 provide a rationale for tumor selectivity of BPT331.
- BPT331 exhibits potent *in vivo* efficacy in multiple tumor models including those resistant to anti-PD-1 treatment.
- BPT331 *in vivo* efficacy is likely achieved by simultaneous blockade of PD-1 and enhanced IL-2 signaling *in cis*.

REFERENCE

1. Carralot et al., proceedings of the annual meeting AACR 2022; New Orleans. Abstract #4223.

UNIQUE TECHNOLOGY PLATFORM

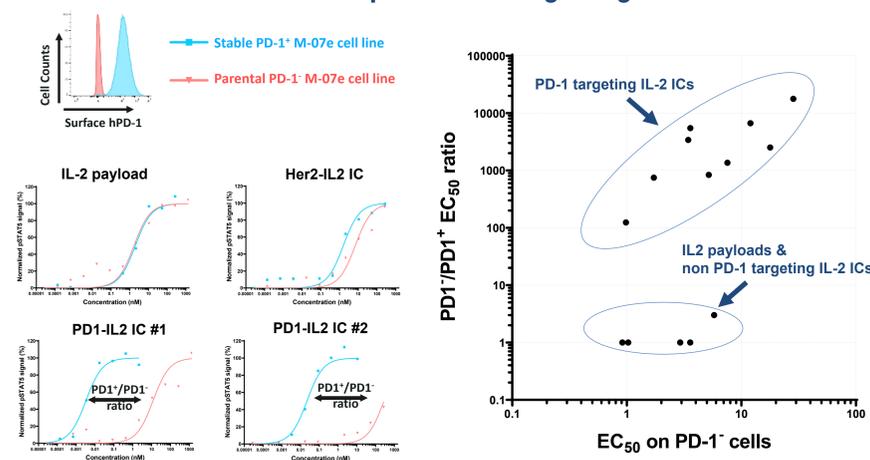
Rapid Generation of Immunocytokines via Chemical Conjugation



- "Off-the-shelf" human IgG antibodies, **no antibody engineering** required.
- **Site-specific conjugation** to defined lysine residue within Fc domain.
- Controlled drug-antibody ratio (DAR).
- No significant impact on antibody or cytokine (payload) functional properties.

RATIONAL DESIGN

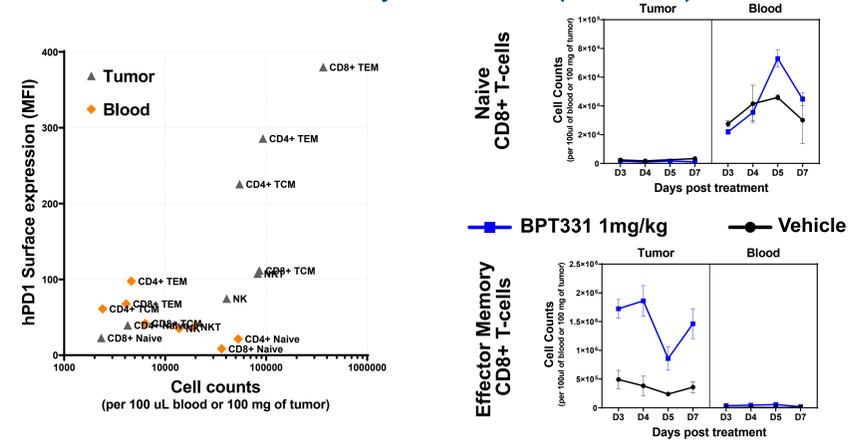
IL-2 Payload Screening and Selection to Maximize PD-1-Dependent *Cis*-Signaling



- Platform enables **rapid screening of IL-2 payloads** in the context of a PD1-IL2.
- Results in **optimal Ab-payload combination** for enhanced selectivity & potency.
- PD1-IL2 exhibits **>500-fold selectivity** for PD-1⁺ cells.

PHARMACODYNAMIC EFFECTS

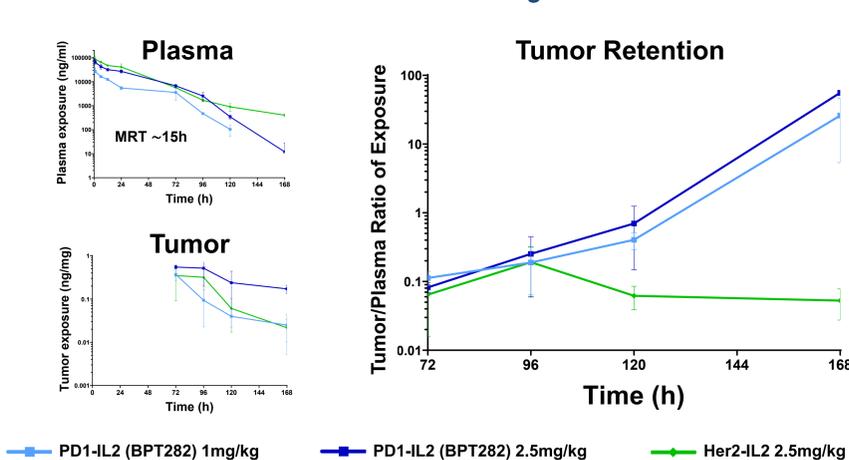
BPT331 Specifically Expands PD-1^{high} Intratumoral Effector Memory CD8⁺ T Cells (CD8⁺ TEM)



- MC38 tumors are **highly infiltrated with PD-1^{high} CD8⁺ TEM**.
- BPT331 **specifically expands PD-1^{high} CD8⁺ TEM** within the tumor with minimal effect on blood CD8⁺.

PHARMACOKINETICS

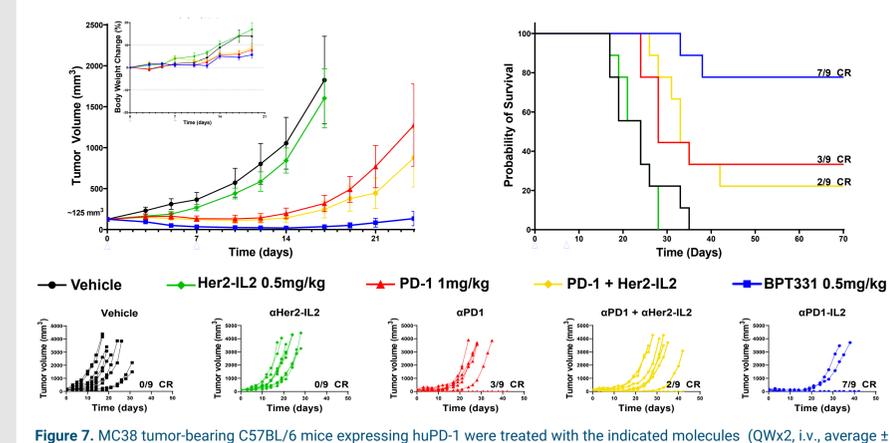
PD1-IL2 is Efficiently and Selectively Retained in Tumors vs Plasma and vs a Non-Targeted Her2-IL2



- PD1-IL2 and Her2-IL2 show similar clearance in the blood.
- Over time, **PD1-IL2 but not Her2-IL2 is retained in the tumor**.

IN VIVO EFFICACY

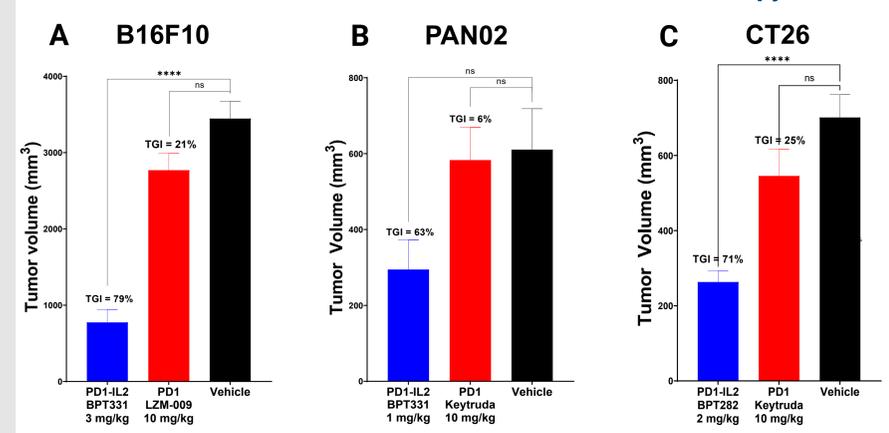
BPT331 Exhibits Potent Anti-Tumor Efficacy That is Superior to the Combination of anti-PD-1 Ab Plus Non-Targeted Her2-IL2



- **BPT331 is highly potent (78% CR)** and **well tolerated** in mice.
- Efficacy of BPT331 is **superior to anti-PD-1 Ab**, to non-targeted Her2-IL2, and to the combination of these two agents.
- Enhanced efficacy of BPT331 appears to be **achieved by simultaneous blockade of PD-1 and enhanced IL-2 signaling *in cis***.

EFFICACY IN PD-1 RESISTANT TUMORS

PD1-IL2 Overcomes Resistance to Anti-PD-1 Therapy



- PD1-IL2 shows **significant efficacy in models resistant to anti-PD-1 therapy**.
- Superior efficacy is achieved at **3-10x lower doses compared to anti-PD-1 Ab**.