Development of BP-80, a soluble CD80 dimer (CD80-Fc) for cancer treatment

Miguel A. Lopez-Lago[1,2], Suzanne Ostrand-Rosenberg[3], Markus D. Lacher[1], Giuseppe del Priore[1,2], and William V. Williams[1,2]

*[1]**BriaPro** Therapeutics Corp., Philadelphia, PA; [2]**BriaCell** Therapeutics Corp., Philadelphia, PA; [3]Dept of Pathology, **University of Utah**, Salt Lake City, UT*

SITC 2026 Abstract **#404**

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BACKGROUND

Despite great advances in cancer immunotherapy, e.g., with immune checkpoint inhibitors, most patients fail to respond, or develop resistance. Soluble CD80-Fc fusion proteins with either the IgV-like (IgV) domain or the full extracellular domain (ECD) of CD80 may facilitate T cell activation not only by co-stimulating CD28 but also by blocking the inhibitory activities of CTLA-4 and PD-L1. We are developing BP-80, a CD80-Fc fusion protein with the full wild-type CD80 ECD, thereby differing from davoceticept (ALPN-202), a potency-enhanced CD80 IgV-Fc fusion protein associated with severe cardiac toxicity. The Fc portion of BP-80 incorporates the L234A/L235A "LALA" mutation to reduce ADCC, ADCP, and CDC.

METHODS

We have characterized BP-80 (**Figure 1**) in CD80/CD28 co-stimulation and CTLA-4 cell inhibition assays, both requiring the co-culturing of target and engineered Jurkat reporter cells with IL-2 promoter-driven luciferase. We also addressed BP-80's toxicity and pharmacokinetics in cynomolgus monkeys, at doses of 0 (vehicle), 0.5, 5, and 50 mg/kg.

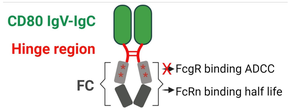


Figure 1. BP-80 structural features.

Preclinical Toxicity Study

According to the protocol, 40 cynomolgus monkeys (20 males and 20 females) were administered vehicle (20 mM Histidine, 87 mg/mL Trehalose, 0.05% PS80, pH 5.0) or test article (BP-80) via five weekly slow-bolus IV injections (**Table 1**). Two male and two female animals were retained and observed for a post-dosing recovery period of two weeks.

Group	Test Article	Dosage (mg/kg)	Males	Females
1	Vehicle	0	5	5
2	BP-80	0.5	5	5
3	BP-80	5	5	5
4	BP-80	50	5	5

Table 1. BP-80 doses.

RESULTS

Sample \ Target	CD28	PD-L1	CTLA-4
Positive control (mAb)	+++	+++	+++
CD80-Fc	+	Very weak	+++

Figure 2. BP-80 (CD80-Fc) binding activity.

BP-80 (CD80-Fc) binding to CD28, PD-L1, and CTLA-4 was assessed by surface plasmon resonance (SPR). BP-80 bound strongest to CTLA-4, weaker to CD28, and very weakly to PD-L1 **(Figure 2).**

RESULTS cont'd

BP-80 dose-dependently enhanced the luciferase signal in the presence but not absence of target cells (CHO-K1 cells engineered to express CD32b (FcγRIIb)), consistent with a mechanism of action in which BP-80:CD28 co-stimulation was dependent on Fc receptor (FcR) engagement (**Figure 3**). Similarly, in a CTLA-4 blockade reporter assay using Raji cells expressing CD80/CD86, BP-80 elicited a dose-dependent reporter response comparable to that of an anti-CTLA-4 antibody (Yervoy biosimilar), but only in the presence of anti-Fc antibody. BP-80 therefore functionally reversed CTLA-4 engagement by membrane CD80/CD86 in an Fc-crosslinking-dependent manner, consistent with avidity-enhanced competition for CTLA-4 binding (**Figure 4**). In cynomolgus macaques (cynos), the no observed effect level (NOEL) was 50 mg/kg/day and the half-life of BP-80 ranged from (8.08 to 8.92) hours **(Figure 5)**.

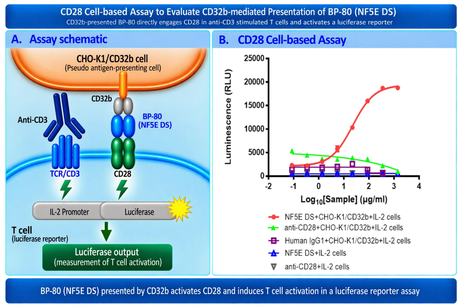
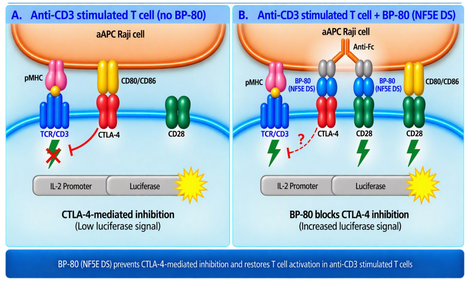


Figure 3. A) Schematic. **B)** CHO-K1/CD32b cells were co-cultured with Jurkat-IL2-luc cells (IL-2 cells) in the presence of increasing concentrations of BP-80 (NF5E DS), anti-CD28 antibody or human IgG (control). N=3.



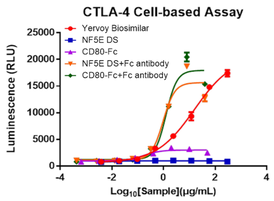


Figure 4. A, B) Schematic. **C)** Raji APC cells were co-cultured with Jurkat CTLA-4 effector cells in the presence of increasing concentrations of anti-CTLA-4 antibody (Ab) (Yervoy biosimilar), BP-80 (NF5E) ± anti-Fc Ab, or commercially available CD80-Fc ± anti-Fc Ab.

Preclinical Pharmacokinetics

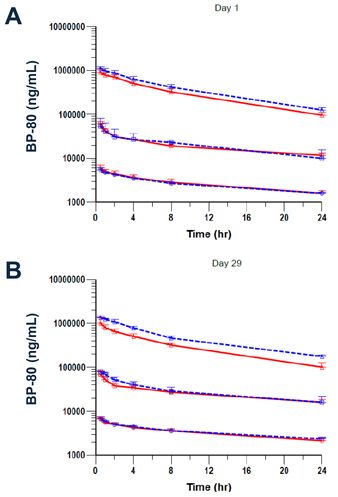


Figure 5. BP-80 (Bria-80) serum levels in cynomolgus monkeys. Mean half-life values ranged from 8.08 to 8.92 hours on Days 1 (**A**) and 29 (**B**) at the 5 and 50 mg/kg dose levels; half-life was not calculable at the 0.5 mg/kg dose level. Half-life (t1/2) was only calculable for one animal at 5 mg/kg on Days 1 and 29 and most t1/2 values were calculable for the 50 mg/kg dose level.

- Female; 0.5 mg/kg
- Female; 5 mg/kg
- Female; 50 mg/kg
- Male; 0.5 mg/kg
- Male; 5 mg/kg
- Male; 50 mg/kg

Preclinical Toxicity

- No BP-80-related mortalities, macroscopic observations, organ weight alterations, or microscopic observations.
- Procedure-related findings: minimal to mild mononuclear infiltration, minimal to mild mixed cell infiltrate, minimal erosion/ulceration, and/or minimal to moderate hemorrhage.
- In a few instances, microscopic findings of hemorrhage correlated with macroscopic observations of "discoloration, dark"
- A No Observed Effect Level (NOEL) of 50 mg/kg/day was observed, representing the total human equivalent doses (HEDs) shown in **Table 2**.

Weight (kg/lbs)	HED (mg)	Weight (kg/lbs)	HED (mg)	Weight (kg/lbs)	HED (mg)	Weight (kg/lbs)	HED (mg)
40/88	649	60/132	973	80/176	1297	100/220	1622
50/110	811	70/154	1135	90/198	1459	110/243	1784

Table 2. Total HEDs at NOEL of 50 mg/kg in cynos for different human weights. Based on Eq. 2 (HED (mg/kg) = Animal dose (mg/kg) x (Animal K_m/Human K_m)) and Table 1 of Nair AB, Jacob S. J Basic Clin Pharma 2016;7:27-31, using K_m of Rhesus monkey for cyno.

PROPOSED MECHANISM OF ACTION OF BP-80

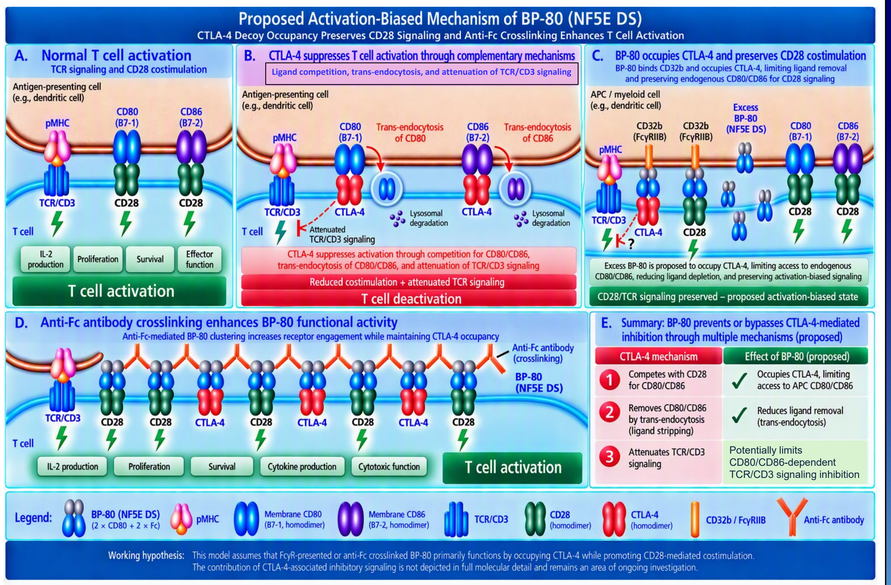


Figure 6. Proposed Mechanism of Action (MoA) of BP-80. A) T cell activation in the absence of CTLA-4. Peptide-MHC (pMHC):TCR (Signal 1) and CD28 stimulation via CD80 or CD86 (Signal 2) are required. **B) Negative effects of CTLA-4 on T cell activation.** CTLA-4 may, 1), act as a decoy receptor for CD80 and CD86, preventing CD28 stimulation, 2), remove CD80 and CD86 by trans-endocytosis, and 3), inhibit TCR/CD3 signaling. **C) Role of BP-80.** Despite its "LALA Fc mutation", BP-80 may crosslink Fc receptors such as CD32b with CTLA-4 or CD28, thereby promoting T cell activation directly (via CD28), or indirectly by preventing trans-endocytosis of endogenous CD80 or CD86 by blocking CTLA-4. **D) Proposed effect of crosslinked BP-80.** Anti-Fc antibodies may crosslink BP-80 molecules, thereby providing a high-avidity complex effectively co-stimulating T cells via CD28. **E)** Summary of proposed BP-80 MoA. *This figure was generated with Microsoft 365 Copilot.*

CONCLUSIONS

- **BP-80 antagonized the T cell-inhibitory activities of CTLA-4 and reactivated the CD28 pathway, confirming biological activity.**
- **BP-80 demonstrated dose-proportional pharmacokinetics in cynos with no dose limiting toxicities with a no-adverse effect human equivalent dose of 973 mg for a 60 kg (132 lbs) patient while the projected biologically active dose is 50 mg, suggesting a wide therapeutic margin.**

ACKNOWLEDGEMENTS

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