Personalized neoantigen cancer vaccine assembled on DC targeting antibody improves cancer immunity

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Background

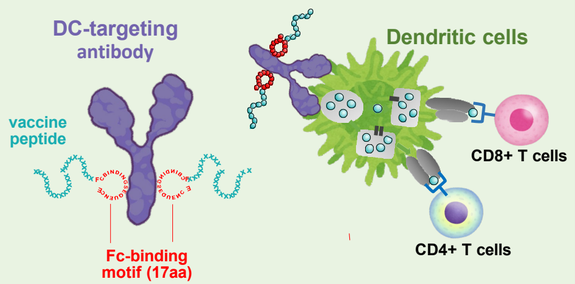
Personalized neoantigen cancer vaccines have demonstrated robust tumor-specific immunity and preliminary evidence to cure patients with melanoma and other cancers. To improve the efficacy of personalized cancer vaccine, we herein, describe a novel vaccine platform using neoantigen peptides that contain a high affinity binding motif for dendritic cell (DC)-targeting antibodies.

Methods

We developed a novel vaccine platform (BP1209 vaccine) in which we employed peptides consisting of a neoantigen-epitope and an IgG binding motif. The peptides form a divalent peptide complex per antibody molecule by simply mixing with therapeutic antibodies in physiological condition. Initially, we selected ovalbumin (OVA) as a model antigen and evaluated the efficacy of this vaccine format in combination with DC-targeting antibodies in vivo. Next, we generated series of neoantigen peptides in both human and murine origins using in-house bioinformatic algorithms and evaluated the advantages of this vaccine platform.

*The study was approved by IRBs and GDS at both National Cancer Center Japan and BrightPath Biotherapeutics.

Schematics of BP1209 vaccine



Fc-binding motif (17mer in red) non-covalently binds to Fc-region of DC-targeting antibodies, resulting efficient antigen delivery to DC.

Results

Peptide-antibody binding is critical for enhanced therapeutic potential of BP1209 vaccine

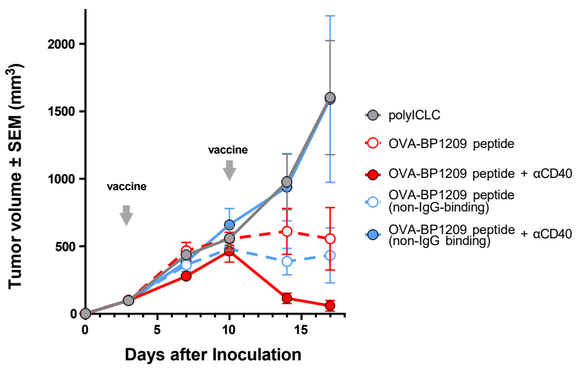


Fig. 1 BP1209 OVA-peptide or BP1209 OVA-peptide with mutations that impairs IgG binding capacity were administrated EG.7 tumor baring mice with or without anti-CD40 Ab on day 3 and day10. The mice treated with BP1209 vaccine with anti-CD 40Ab exhibited tumor regression in all the mice tested, while the vaccine lacking IgG binding property + anti-CD40 Ab did not induce complete tumor regression, suggesting that enhanced antitumor efficacy results from the assembly of peptide-antibody complex.

BP1209 neoantigen vaccine exerted robust antitumor effect in therapeutic setting

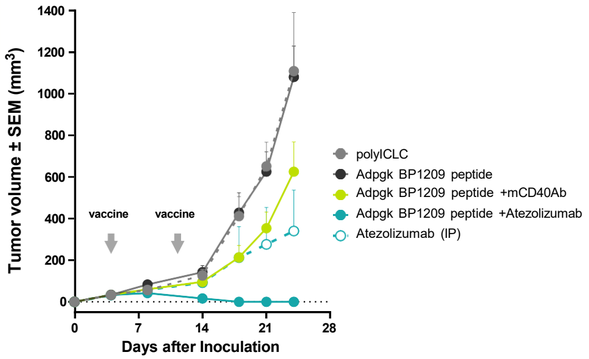


Fig. 2 Mice were subcutaneously inoculated with MC-38 cells on day 0. Anti-CD40 Ab or Atezolizumab were subcutaneously administrated with or without BP1209 neoantigen vaccine peptide for Adpgk on day 4 and 11. The mice treated with BP1209 vaccine exhibited delayed tumor growth. Notably, Atezolizumab conjugated BP1209 vaccine maintained complete tumor regression in all the mice until study end (n=9).

BP1209 vaccines allow CTL immune-induction of weakly immunogenic neoantigen epitopes

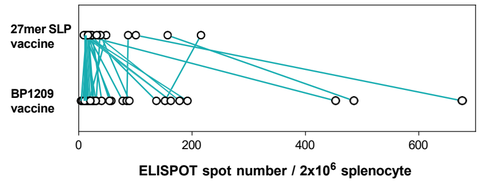
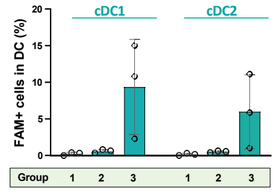


Fig. 3 We developed neoantigen prediction pipeline .
►Related Abstract was presented on Poster #1911/15

We predicted 30 neoantigen epitopes from the genomic sequence of MC-38 tumor cells. The neoantigen peptides in length of 27aa (SLPs) and 27aa with an IgG-binding motif (BP1209 vaccine) were synthesized. SLPs or anti-CD40 Ab-conjugated BP1209 peptides were administrated C57BL/6 three times at weekly intervals. CTL induction were analyzed by ELISPOT using spleens from these mice.

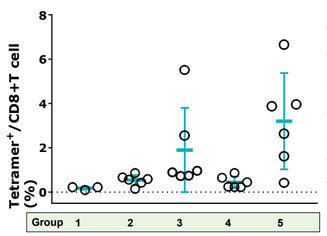
BP1209 vaccine accumulates in DCs in lympho-node via DC-targeting antibody



Group	1	2	3
FAM-peptide	-	+	+
α-CD40 Ab	-	-	+
polyICLC	+	+	+

Fig. 4 A fluorescent labeled BP1209 vaccine peptide was inoculated subcutaneously with or without anti-CD40 antibody. Six hours later, proximal lymph nodes were resected and the peptides uptake into cDC1 and cDC2 were quantified by flowcytometry.

BP1209 vaccine enhances in vivo CTL response by combining with DC-targeting antibodies



Group	1	2	3	4	5
OVA peptide (BP1209 format)	-	-	+	-	+
OVA peptide (non-IgG-binding)	-	+	-	+	-
αCD40 mAb	-	+	+	-	-
Atezolizumab	-	-	-	+	+
polyICLC	+	+	+	+	+

Fig. 5 BP1209 OVA vaccine exhibited an enhanced CTL induction when administrated with anti-CD40 Ab or atezolizumab. Vaccine peptides without antibody-binding property had limited response even administered with antibodies, suggesting that vaccine-antibody binding is critical for enhanced immune-induction.

BP1209 neoantigen vaccine strongly enhances Stem-like TEX infiltration into tumor

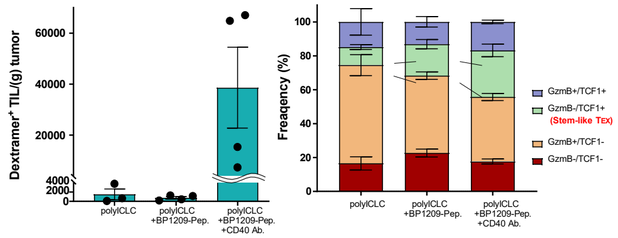


Fig. 6 BP1209 vaccine peptide against Adpgk were subcutaneously administrated to MC-38 tumor baring mice with or without anti-CD40 Ab. After two vaccinations at weekly intervals, tumors were harvested and used for TIL analysis. Mice treated with the BP1209 vaccine had a marked increase in Adpgk-specific TIL (Left). The BP1209 vaccine increased TCF1+ / Granzyme B- Stem-like exhaust T cells (TEX) (Right).

Conclusion

- BP1209 vaccine dramatically enhanced CTL induction compared to conventional vaccine and exhibited robust anti-tumor effect in vivo.
- Binding ability of peptides to IgG is essential for the enhanced antitumor efficacy.
- We developed neoantigen prediction pipeline and validated the accuracy by the analysis using patient derived neoantigen and HLA transgenic mice. (in detail, Poster #1911/15)
- BP1209 neoantigen vaccine promote stem-like TEX infiltration into tumor.
- **BP1209 vaccine provides an ideal option to improve neoantigen vaccine therapy.**

Disclosure

Mishima Y.: Employee of BrightPath Biotherapeutics

BrightPath Biotherapeutics