A new platform of personalized neoantigen cancer vaccines directed by checkpoint inhibitor antibodies to improve cancer immunity

1005P

Y. Mishima[1], F. Isoda[1], N. Matsumoto[1], K. Hiranuka[1], T. Yamada[1], N. Fujinami[2], M. Shimomura[2], T. Suzuki[3], T. Nakatsura[2], N. Nakamura[1]

[1] BrightPath Biotherapeutics Co., Ltd., Kawasaki, Japan, [2] Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Chiba, Japan, [3] Department of Pharmacology, School of Medicine, Teikyo University, Tokyo, Japan

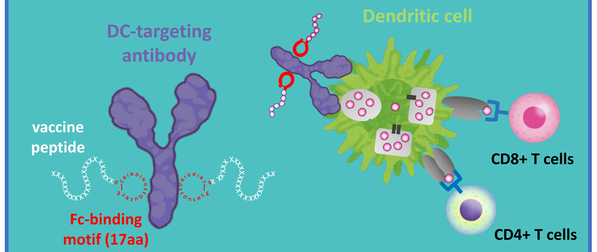
Background

Personalized neoantigen 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 cells (DCs)-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 dendritic cell (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.

Schematics of BP1209 vaccine



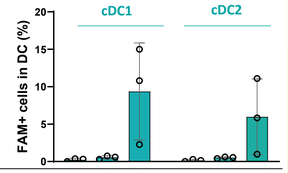
Fc-binding motif (17 mer in red) non-covalently binds to Fc-region of DC-targeting antibodies, resulting efficient antigen delivery to DC.

Results

BP1209 vaccine accumulates in DCs via DC-targeting antibody

BP1209 vaccine peptide was fluorescently labeled and inoculated subcutaneously with or without anti-CD40 antibody. Six hours later, proximal lymph nodes were resected and the peptide uptake into cDC1 and cDC2 in the lymph nodes was evaluated by flow cytometry, confirming enhanced uptake of the BP1209 vaccine into DCs (Fig. 1).

Fig. 1



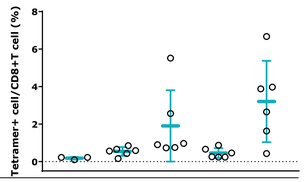
Group	1	2	3	1	2	3
Fluorescent vaccine	-	11.7	11.7	-	11.7	11.7
α-CD40 antibody	-	-	200	-	-	200
polyICLC	8	8	8	8	8	8

(μg/injection)

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

BP1209 OVA vaccine exhibited an enhanced CTL induction when administrated with anti-CD40 Ab or atezolizumab. Vaccine pepitde without binding ability had limited response even administered with these antibodies, suggesting that vaccine-antibody binding is critical for enhanced immune-induction (Fig.2)

Fig. 2



OVA peptide (BP1209 format)	-	-	10.5	-	10.5
OVA peptide (non-IgG-binding)	-	10.5	-	10.5	-
αCD40 mAb	-	200	200	-	-
Atezolizumab	-	-	-	200	200
polyICLC	8	8	8	8	8

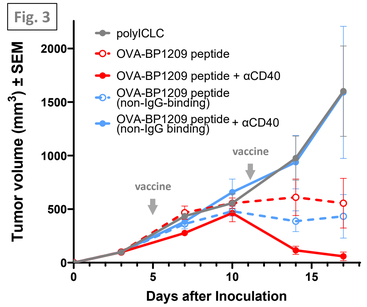
(μg/injection)

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

Mice were subcutaneously inoculated with EG.7 cells on day 0. Anti-CD40 Ab was subcutaneously administrated with BP1209 OVA-vaccine or BP1209 OVA vaccine with mutations that impair IgG binding capacity on day 4 and day11.

The mice treated with BP1209 vaccine exhibited tumor regression in all the mice tested, while the vaccine lacking IgG binding property did not, suggesting that enhanced antitumor efficacy results from the assembly of peptide-antibody complex (Fig.3).

Fig. 3

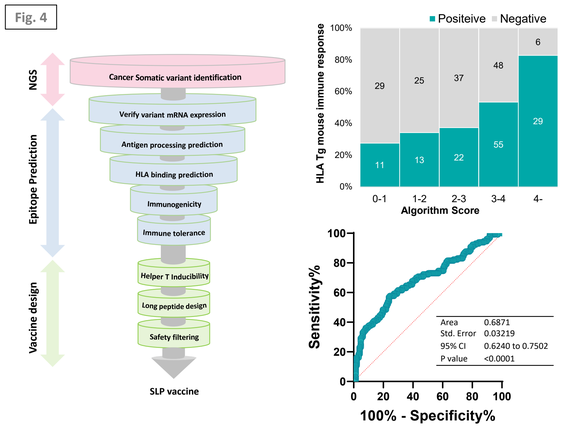


Development of tumor Neoantigen prediction pipeline and validation

We conducted neoantigen prediction from tumor tissues from patients with hepatocellular carcinoma (HCC) and metastatic colorectal carcinoma (mCRC) using our prediction pipeline (Fig.4 left) and validated its accuracy by in vivo vaccination experiments with four types of human leukocyte antigen (HLA) transgenic mice. By evaluation of a total of 275 epitopes, we successfully demonstrated capability of our pipeline to predict neo-peptides (AUC = 0.687, p<0.0001).

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

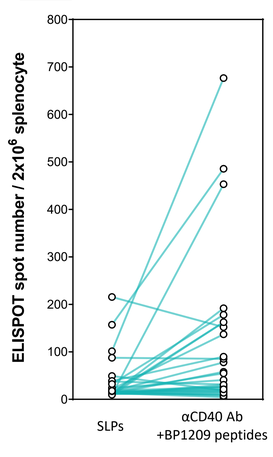
Fig. 4



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

We analyzed the genomic sequence of MC-38 tumor cells and predicted thirty neoantigen epitopes. Their peptides in length of 27aa with (BP1209 peptides) or without (SLPs) IgG-binding motif were synthesized. SLPs or anti-CD40 Ab-conjugated BP1209 peptides were immunized C57BL/6 mice with polyICLC three times at weekly intervals. CTL induction were analyzed by ELISPOT using spleens from these mice. The BP1209 vaccines substantially induced specific CTLs even in weakly immunogenic epitopes at SLP format (Fig. 5).

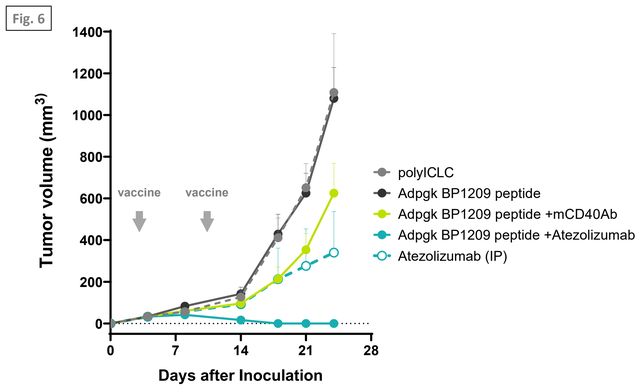
Fig. 5



BP1209 neoantigen vaccine exerted robust antitumor effect in therapeutic setting

Mice were subcutaneously inoculated with MC-38 cells on day 0, then anti-CD40 Ab or Atezolizumab were subcutaneously administrated with or without BP1209 vaccine against neoantigen of Adpgk gene on day 4 and 11. The mice treated with BP1209 vaccine exhibited delayed tumor growth (Fig.6). Notably, Atezolizumab conjugated BP1209 vaccine maintained complete tumor regression in all the mice until study end (n=9).

Fig. 6



Conclusion

- BP1209 vaccine dramatically enhanced CTL induction and exhibited robust anti-tumor effect in vivo.
- Enhanced antitumor efficacy required the binding ability of peptides to IgG.
- We developed neoantigen prediction pipeline and validated the accuracy by the analysis using patient derived neoantigen and HLA transgenic mice.
- BP1209 vaccine provides an ideal option to improve neoantigen vaccine therapy.

Disclosure

Mishima Y.: Employee of BrightPath Biotherapeutics

BrightPath Biotherapeutics