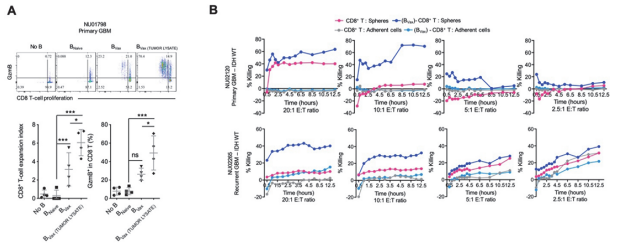
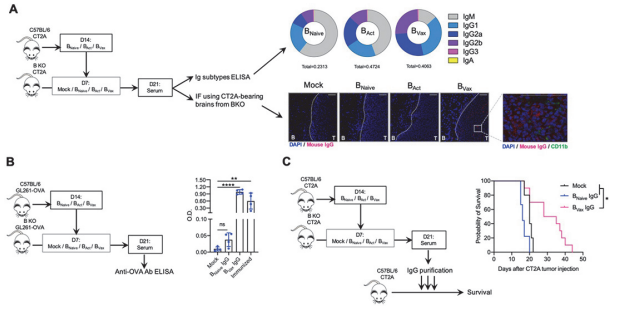


Abstract 167 Figure 3 GBM patient-derived BVax
GBM patient-derived BVax promote anti-tumor CD8+ T cells. (A) Paired fresh peripheral blood and tumor were collected from newly diagnosed GBM patients (n=4). BVax were generated and pulsed with tumor lysates and co-cultured with autologous eFluor450-labeled CD8+ T cells. CD8+ T-cell activation was assessed by cell proliferation (eFluor450 fluorescence dilution measured as expansion index) and intracellular expression of GzmB. (B and C) Paired samples from primary GBM IDH WT (case NU 02120, B) and recurrent GBM IDH WT (NU02265, C). BVax-activated autologous CD8+ T cells were obtained as shown in (A) and tested for their ability to kill autologous glioma cells. Cell killing measurement were taken periodically for 12.5 hours using the IncuCyte S3 Live Cell Analysis System. Statistical significance is depicted as ns: no statistically significant, *p<0.05, **p<0.01, ***p<0.001.



Abstract 167 Figure 4 BVax produce anti-tumor IgG
BVax produce tumor-reactive antibodies with therapeutic effect. (A) Schema of BVax-derived serum immunoglobulin (Ig) obtainment. BNaive, BAct and BVax-derived IgG were tested for IgG subtype (top) and their reactivity to B KO tumor bearing-brains (bottom). Top: Diagram representing the distribution of different Ig subtypes from serum antibodies derived from BNaive, BAct and BVax. Ig subtype measurement of serum samples was performed by ELISA, and mean total Ig concentration is shown in the bottom of the diagram (mg/ml). The experiment was performed in 7 mice/group. Bottom: B-cell subsets IgG reactivity was measured by immunofluorescence. Serum samples were incubated on tumor-bearing brains sections from B KO. Binding IgG was detected using anti-mouse IgG Cy5 (red) secondary antibody. Nuclei was detected using DAPI (blue), and myeloid cells were evaluated by using anti-mouse CD11b AF488 antibody (green). Bars represent 100 mm. Shown, a representative experiment of serum obtained in 4 mice/group, performed twice independently. (B) BNaive, BAct and BVax were generated from GL261 overexpressing ovalbumin (GL261-OVA) tumor-bearing mice. B cells were allowed to produce antibodies in GL261-OVA-bearing B KO. Serum samples were collected and IgG were purified and tested for their reactivity against OVA peptide SIINFEKL by ELISA. Semi-quantitative measurement is shown as optical density (O.D). Serum from B-cell deficient mice and C57BL/6 SIINFEKL-immunized mice were used as negative and positive control respectively (n=4/group). (C) Purified IgG were tested for their therapeutic effect in the CT2A model. IgG were delivered intracranially for 3 consecutives days (12.5 mg/mouse/injection). Untreated mice (black line) were used as controls. Experimental groups received either BNaive-derived IgG (BNaive IgG, blue line) or BVax-derived IgG (BVax IgG, pink line). The experiment was performed using n=10 mice/group. Statistical significance is depicted as ns: no statistically significant, *p<0.05, **p<0.01, ***p<0.001.

Acknowledgements In conclusion, BVax tackles GBM immunosurveillance escape by using both cellular (CD8+ T-cell activation) and humoral (anti-tumor antibody production) immunity. Our study provides an efficient alternative to current immunotherapeutic approaches that can be readily translated to the clinic.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0167

168 A NOVEL PROSTATE-RESTRICTED TUMOR-ASSOCIATED ANTIGEN: A POTENTIAL THERAPEUTIC TARGET

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Background Prostate cancer is the second leading cause of cancer related death in men in the United States, mainly due to disease progression to metastatic castration-resistant prostate cancer (mCRPC). Although immunological treatment with the FDA-approved vaccine sipuleucel-T extends survival for 2–4 months by targeting the prostate-restricted antigen PAP, the identification of more immunogenic tumor-associated antigens (TAAs) continues to be an unmet need.

Methods We evaluated the differential expression profile of the subset of epithelial cells reported to give rise to CRPC from mice following an androgen deprivation/repletion cycle. The expression levels of a set of androgen-responsive genes was further evaluated in prostate, brain, colon, liver, lung, and skin normal tissues from murine and human databases. The expression of a novel prostate-restricted TAA was then analyzed in primary tumors across all human cancer types in The Cancer Genome Atlas (TCGA). Finally, the immunogenicity of this novel prostate-restricted TAA was evaluated in vitro by autologous co-culture assays with cells from healthy donors and in vivo by antibody profiling (PhIP-Seq) in the sera of a cohort of prostate cancer patients treated with AR blockade alone or in combination with the cell-based vaccine GVAX.

Results Here, we discovered a set of androgen-responsive genes exclusively expressed by the putative cell-of-origin for prostate cancer. We confirmed prostate-restricted enrichment of these androgen-responsive genes in normal tissues from murine and human databases. Among these prostate-restricted genes, we identified PAP, PSA, and a novel non-mutated TAA. This novel TAA was confirmed to be expressed in prostate cancer. Furthermore, its expression was associated with survival in patients with primary prostate cancer. Interestingly, we found that pro-inflammatory activated TBET+ EM CD8 and CD4 T cells were expanded by moDCs pulsed with our novel TAA to a greater extent than moDCs pulsed with either PAP or PSA were used. An IgG antibody response to this novel TAA was detected in 30% of vaccinated patients, while fewer than 8% of vaccinated patients developed antibody responses to PSA or PSMA.

Conclusions Taken together, these results suggest we have found a novel immunogenic prostate-restricted TAA that represents a promising therapeutic target for treating mCRPC.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0168