Autologous tumor cell immunotherapeutic platform, with evidence of clinical activity in glioblastoma, induces in vitro immune responses in both glioblastoma and endometrial cancer

Christopher Uhl[1], Jenny Zilberberg[1], Mark A. Exley[1]

[1]Imvax, Inc., Philadelphia, PA.

Abstract #: A001

Background

Imvax is developing a novel personalized immunotherapeutic platform combining irradiated, patient-derived tumor cells and insulin-like growth factor type-1 receptor antisense oligonucleotide (IMV-001) in biodiffusion chambers (BDC; 0.1-micron pores). The combination product IGV-001 was evaluated in a newly diagnosed glioblastoma (GBM) phase 1b clinical trial [1]. Median overall survival of highest exposure IGV-001-treated 'Stupp-eligible' patients [2] was 38.2 months compared with 16.2 months in recent standard-of-care-treated patients (P=0.044) [1]. We have now manufactured the endometrial cancer product analog to IGV-001, IEC-001, using patient-derived endometrial tumors and developed an assay using matched peripheral blood mononuclear cells (PBMCs), to evaluate the *in vitro* immunostimulatory activity of both IEC-001 and IGV-001, as a precursor to future translational studies.

Methodology

Nine IEC-001 and three IGV-001 patient-matched PBMCs co-culture assays were evaluated. Patient-derived tumor cells (0.5-1x10^6) treated with IMV-001 were loaded into BDCs, spiked with more IMV-001, and irradiated (5-6 Gy). Co-cultures were established with direct IEC-001 or IGV-001-PBMC contact and via Transwell® to mimic BDC membranes separating product from immune cells (Fig. 1) at a 1:10 ratio of IEC-001 or IGV-001:PBMC (2.5x10^4 : 2.5x10^5 cells). Flow cytometric analyses were conducted to evaluate dendritic cell maturation, T cell activation (CD69 and CD107a markers) and memory subsets (effector memory CD197$^+$CD45RA$^-$ and central memory CD197$^-$ CD45RA$^-$) on days 3, 7, 14 &/or 21. Some co-cultures were re-stimulated on day 21 with fresh tumor and analyzed 7 days later. Increase in the expression of a particular cell population above PBMCs (blue dash line) is denoted by a red dash rectangle.

Fig. 1: Co-Culture Assay Overview

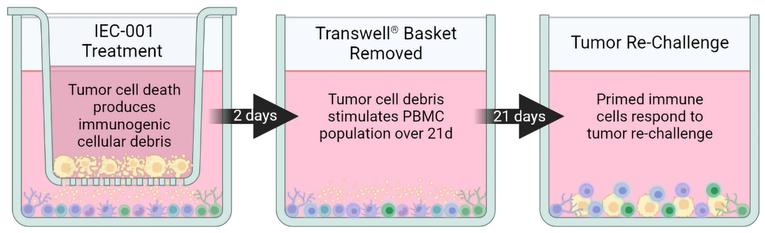


Fig. 2: Dendritic Cell Maturation: CD11c$^+$HLA-DR$^+$ (% Gated – Day 3)

Representative data from 4 patients

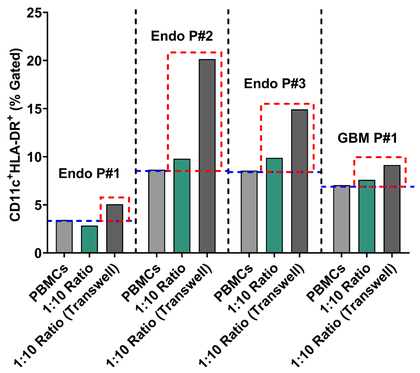
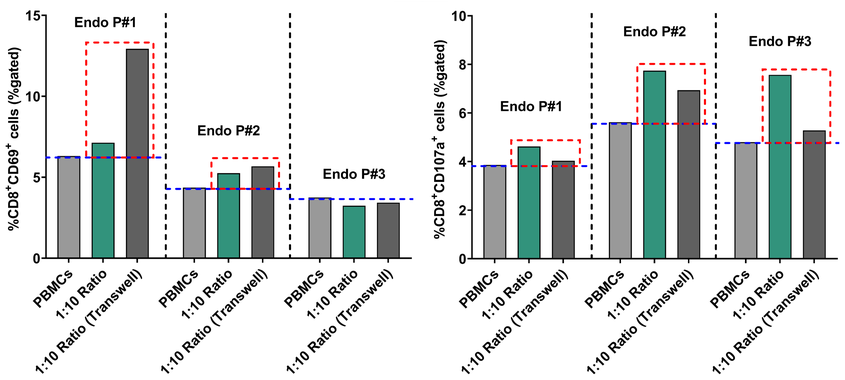


Fig. 3: T Cell Activation: CD69$^+$ & CD107a$^+$

Representative data from 3 patients

Day 7



Day 14

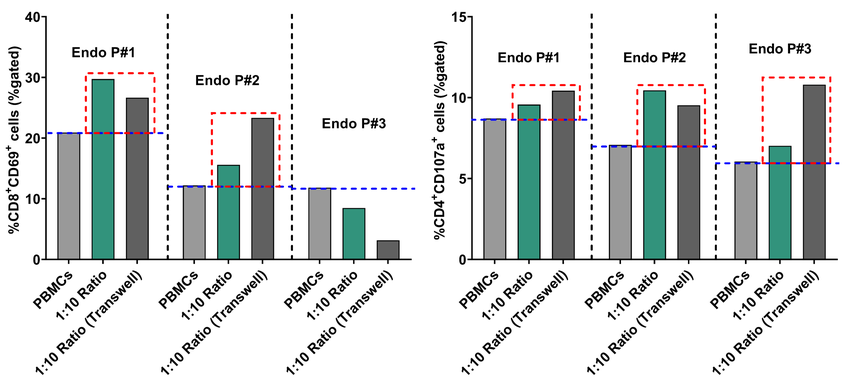


Fig. 4: CD4$^+$ Effector Memory T Cells (Day 21)

Representative data from 4 patients

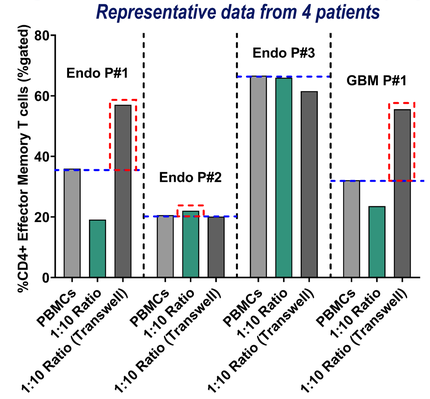


Fig. 5: Endometrial Tumor Re-challenge T Cell Activation & Memory Responses (Day 28)

Representative data from 1 of 2 patients

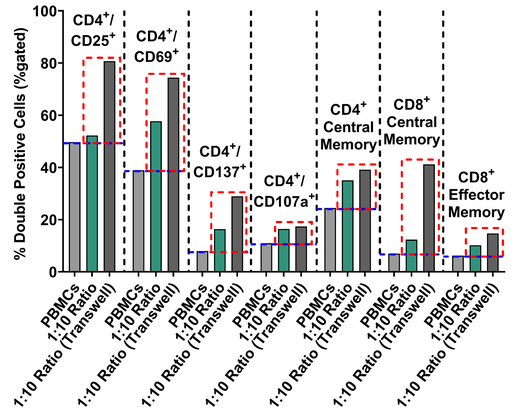


Fig. 6: Response Frequency in Endometrial Co-Culture

Day #	Flow Cytometry Markers	Total Response	Response %
3	CD11c$^+$/CD80$^+$	5	56
	CD11c$^+$/CD86$^+$	5	56
	CD11c$^+$/HLA-DR$^+$	9	100
7	CD4$^+$/CD25$^+$	6	67
	CD8$^+$/CD25$^+$	3	33
	CD4$^+$/CD69$^+$	8	89
	CD8$^+$/CD69$^+$	7	78
	CD4$^+$/CD137$^+$	4	44
	CD8$^+$/CD137$^+$	2	22
	CD4$^+$/CD107a$^+$	7	78
	CD8$^+$/CD107a$^+$	8	89
14	CD4$^+$/CD25$^+$	6	67
	CD8$^+$/CD25$^+$	3	33
	CD4$^+$/CD69$^+$	6	67
	CD8$^+$/CD69$^+$	4	44
	CD4$^+$/CD137$^+$	7	78
	CD8$^+$/CD137$^+$	4	44
	CD4$^+$/CD107a$^+$	8	89
	CD8$^+$/CD107a$^+$	3	33
21	CD4$^+$ Central Memory	4	44
	CD8$^+$ Central Memory	6	67
	CD4$^+$ Effector Memory	3	33
	CD8$^+$ Effector Memory	5	56

Results

Co-culture of PBMCs with either matched-IEC-001 or IGV-001 showed an overall increase in immunological activity: **(1)** Increased dendritic cell maturation was observed in direct and indirect co-cultures; expression of HLA-DR beyond that of PBMC controls was observed in 9/9 IEC-001 experiments (Fig. 2, 6). **(2)** Elevated activation markers in both CD4$^+$ and CD8$^+$ T cells were observed for both co-culture conditions (direct and Transwell®) after 7 days with sustained activation on day 14 (Fig. 3). Of note, CD69 and CD107a were upregulated in ~80% of IEC-001 cultures (Fig. 3, 6). **(3)** Increased effector memory CD4+ T cell subset was also observed by day 21 in 67% of the experimental setups (Fig. 4, 6). **(4)** Day 28 analyses showed that T cell activation and memory responses were potentiated upon re-challenge (Fig. 5, 6). **(5)** CD11c$^+$HLA-DR$^+$, CD4$^+$CD69$^+$, CD4$^+$CD107a$^+$, & CD8$^+$CD107a$^+$ populations were shown to respond most consistently across all co-cultures (Fig. 6).

Conclusions

- Dendritic cell maturation, CD4$^+$ & CD8$^+$ T cell activation, and increases in central & effector memory T cells were observed *in vitro* in response to IEC-001 and IGV-001.
- *In vitro* IEC-001 data supports the immunostimulatory activity of Imvax's platform.
- Favorable IEC-001 pre-clinical data, together with GBM clinical results using IGV-001 [1], supports a path forward to evaluate IEC-001 in clinical studies.

[1] Andrews, David W et al. "Phase 1b Clinical Trial of IGV-001 for Patients with Newly Diagnosed Glioblastoma." Clinical Cancer Research vol. 27,7 (2021): 1912-1922. doi:10.1158/1078-0432.CCR-20-3805l

[2] Stupp, Roger, et al. "Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma." New England Journal of Medicine vol. 352,10 (2005): 987-996. doi:10.1056/NEJMoa043330

Imvax, Inc.
601 Walnut Street
Suite 440 W
Philadelphia, PA 19106
Telephone: 267-900-4110
E-mail: contact@imvax.com