CMV gB/pp65 eVLPs Formulated with GM-CSF as a Therapeutic Vaccine Against Recurrent GBM

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ATIM-14

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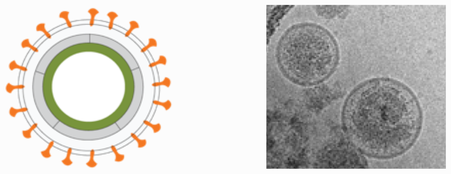
Background

- Cytomegalovirus (CMV) antigens are reported in >90% of GBMs
- 'Foreign' tumor-associated viral antigens are naturally immunogenic
- gB and pp65 antigens are the most frequent CMV targets for CD4 and CD8+ T-cells
  - gB is the viral fusion protein for APC uptake and is a major CMV antibody target, expressing multiple CD4 T-cell epitopes
  - pp65, the primary CD8 T-cell target, in its full-length overcomes HLA restriction
- Targeting CMV as a foreign viral antigen has the potential to harness and re-stimulate pre-existing anti-CMV immunity to clear CMV+ tumors
- VBI-1901 is a bivalent gB/pp65 enveloped virus-like particle (eVLP) formulated with GM-CSF and given as an intradermal injection
- VBI-1901 is currently in a Phase I/IIa clinical trial in recurrent GBM patients (NCT03382977)

About VBI-1901

Rationally-designed immuno-therapeutic vaccine for CMV+ solid tumors

Schematic *Virus-like structure stimulated innate immunity & promotes uptake by Antigen Presenting Cells (APCs)*	
Antibody Target	gB
T Cell Targets	gB ($CD4^+$), pp65 ($CD8^+$)
Target Indication	Treatment of CMV+ solid tumors, notably glioblastoma
Rationale	Targets multiple antigens, each with multiple epitopes, to promote broad immunity & avoid tumor selection/escape
Adjuvant	Co-administered with GM-CSF via intradermal route

Phase I/IIa Trial Design

Two-part, multi-center, open-label, dose-escalation study of VBI-1901 in patients with recurrent GBM

Part A: Dosing and safety
- Recurrent GBM (any # of times)
- N = up to 18 patients (6/cohort)

Low : 0.4µg of pp65 → **Mid :** 2.0µg of pp65 → **High :** 10.0µg of pp65

Part B: Extension Study
- Optimal dose selected from Part A *(defined as ≤1/6 DLT, ≤ MTD)*
- 1st recurrent GBM
- Tumor to 1-3cm in size
- N = up to 10 additional patients

→ Optimal Dose Level

Rolling Immunogenicity Data: Immunogenicity/biomarker measures → 6 mo & 12mo survival

Treatment
- Vaccination every 4 weeks until tumor progression
- Safety visit/immunogenicity measure : 2 weeks post each vaccination
- MRI : every 6 weeks at screening

Eligibility Criteria (Part A – *currently accruing*)
- Any # of recurrences
- Age 18-70 years, KPS ≥ 70, Dex ≤ 4mg/d
- No subependymal disease/lepto
- No HCMV viremia
- No immunodeficiency/autoimmune disease

Primary Outcome
- Safety & tolerability

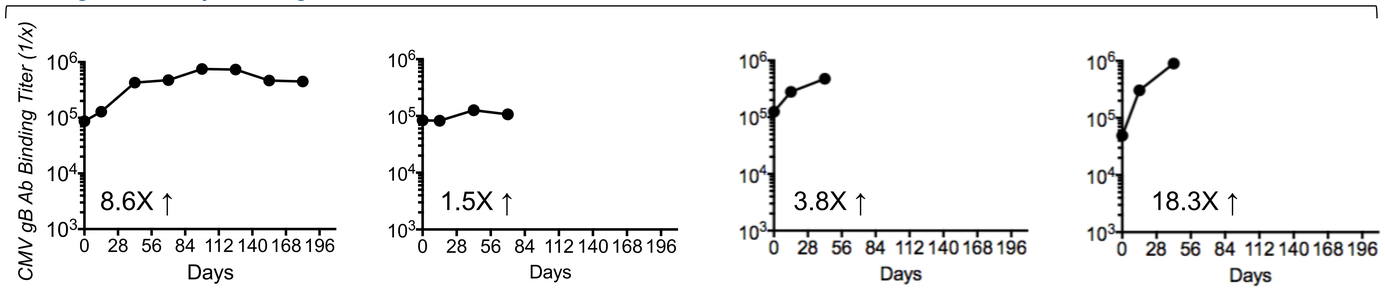
Secondary Outcomes
- Immunogenicity:
  - T-cell immunity (CD8 & CD4)
  - Serum anti-gB antibody titers
  - Other immune correlates & biomarkers
- Change in quality of life compared to baseline, including reduction in steroid use
- 6 and 12 month progression-free survival (PFS) and overall survival (OS)

Impact of Vaccination on CMV-Specific Immunity – Patient-Specific Data of Responders

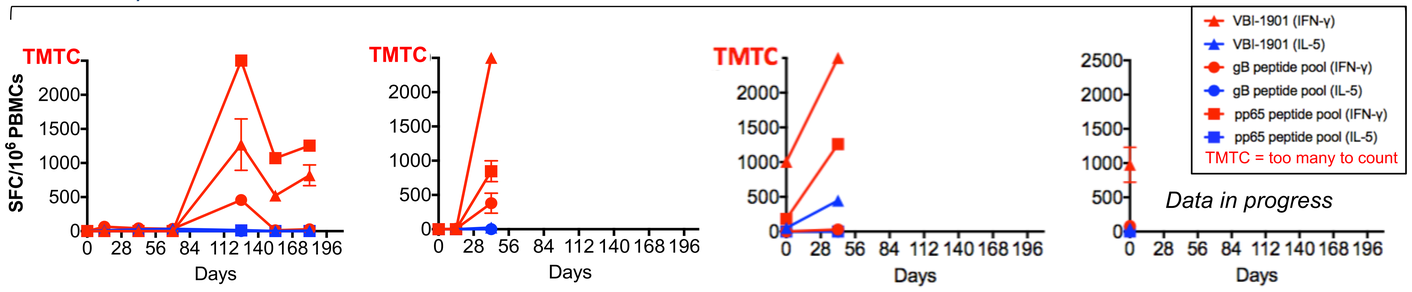
Low-Dose Cohort (0.4µg of pp65) | **Mid-Dose Cohort (2.0µg of pp65)**

Subject 01-003 2 recurrences | **Subject 01-007** 3 recurrences | **Subject 01-012** 2 recurrences | **Subject 03-002** 1 recurrence

CMV gB Antibody Binding Titers



T-Cell Responses



Enrollment Status

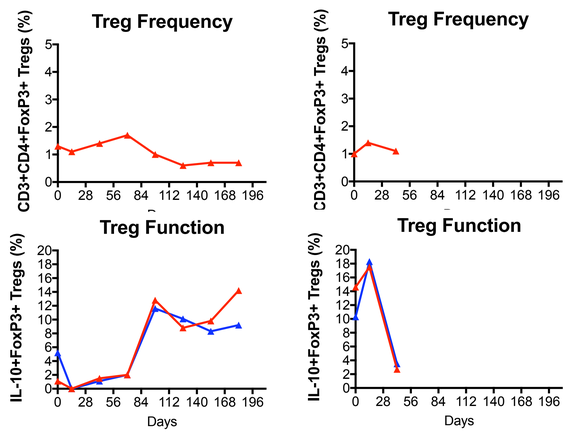
As of Nov. 14, 2018

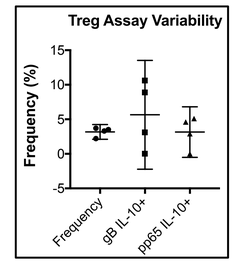
Dose Level	pp65 Content	N Treated	DLTs
Low	0.4µg	6	0
Mid	2.0µg	6	0
High	10.0µg	4	0

Low- and Mid-dose cohort patient details:
- Median age : 53.5 year (Range 39 – 66 yrs)
- Gender : 8 (67%) Men, 4 (33%) Women

Exploratory Analysis of Treg Frequency/Function

Subject 01-003 | **Subject 01-012**



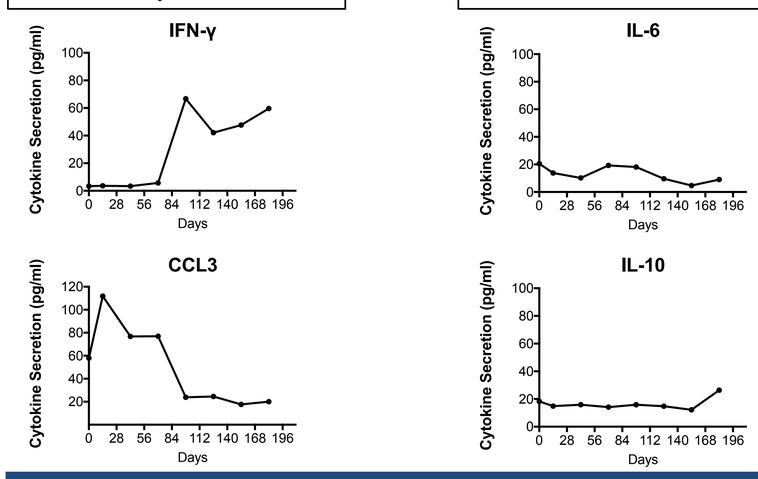


PBMCs from a CMV+ Healthy Subject are thawed each time a Treg assay is run with patient samples and are handled in the same manner. The geometric mean and 95% CI are plotted.

Exploratory Analysis of Plasma Biomarkers

Subject 01-003

Associated with pro-inflammatory vaccine effect | Associated with tumor growth and immunosuppression



Conclusions

- No DLTs observed to-date, including in the four subjects already dosed in the highest dose cohort (10.0µg)
- VBI-1901 induces CMV-specific, and more global, immune activity
- Enrollment/accrual is ongoing in the high-dose cohort