**Therapeutic Vaccination Against Glioblastoma Multiformae Using CMV gB/pp65 eVLPS Formulated With GM-CSF**

**ABSTRACT**

Glioblastoma multiforme (GBM) is presently an incurable brain tumor with 70% of patients dead two years after diagnosis. Approximately 15,000 new GBM diagnoses arise in the US each year, and 2-3 people (100,000/year) in most European countries. A limitation of past immunotherapeutic research against GBM has been the difficulty in inducing a potent tumor-specific response, due at least in part to the inherent immunosuppressive activity of tumor-associated antigens, the route of vaccination delivery of the vaccine, or a combination of both.

We have demonstrated a novel enveloped synthetic particle (eVLP) vaccine for treatment of GBM. Our eVLPS are produced after transfection of HEK-293 cells with plasmid encoding canine herpes virus (30% gB) and plasmid-based to deliver the CMV gB antigen, which gives rise to the particles. Plasmid expressing CMV gB antigen is co-transfected with particles having human GM-CSF under the control of CMV promoter. eVLPS and GM-CSF secretion into the supernatant.

Using peripheral blood mononuclear cells (PBMCs) from healthy subjects, we have found that gB/pp65 eVLPS stimulate cytokine secretion from CMV (CMV-EBV) immune cells in all subjects evaluated (50% to 70% of donors tested). GM-CSF secreted by the human GM-CSF plasmid stimulates a second wave of cytokine secretion. Therefore, eVLP production in combination with GM-CSF is underway.

A mouse study is underway to determine optimal doses, route of administration, and formulation of GM-CSF eVLPS. A phase I trial is planned with FDA in Q4 2015.

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**CMV as a NeoAntigen**

**CMV Antigens are Over-Expressed (>90%) in Multiple Solid Tumors, Including:**

- Glioblastoma (GBM)
- Breast cancer

**Clinical Evidence Suggests CMV Vaccination Can Be Successful (Duke Data):**

- Dendritic cell priming combined with CMV vaccination significantly extended overall survival of GBM patients relative to Scd.

**GBM Unmet Medical Need**

- Over 20,000 new patients diagnosed each year
- Only 40% survive longer than 6 months
- GB Research predicts a market size of $600M+ million by 2020

**Design of GBM CMV eVLP Vaccine Candidate**

**Rationale for vaccination components/mechanisms of action**

- gB envelope protein - “homologous”
- CMV gB, pp65: Potent CD4+ and CD8+ T-cell responses
- eVLP formulation with GM-CSF: Argon tumor-specific IFN-γ and IL-2 responses
- Cytokine data demonstrates IFN-γ and IL-2 as key bioluminescence tumor immunity plasmids (et al., 2006)

**Results**

- Bivalent gB/pp65 eVLPS stimulate both CD4+ and CD8+ Human T-cell Responses *in vivo*

- Bivalent gB/pp65 eVLPS formulated with GM-CSF induce desired immunity in mice

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**CMV eVLP “NeoAntigen” Strategy vs Alternate Cancer Vaccine Approaches**

- eVLPS Balance Potent Delivery of Diverse Antigens with Ease of Manufacturing

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DE Anderson, C Square, J Bozic, B Onitsuka, T Ahmed, A Diess, M Yorke, A C Flickiger, and M Kirchmeier

Corporate Headquarters: 222 Third Street, Suite 2241, Cambridge, MA 02142; Research Operations: 310 Hunt Club Road East, 2nd Floor, Ottawa, Ontario, K1V 1C1