



National
Brain Tumor
Society

Therapeutic Vaccines Targeting CMV Antigens in Glioblastoma

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Treatment Paradigm

- Several advantages of immunotherapy with recent clinical successes in phase III trials (safety, systemic activity, tolerability)
- Our program leverages a novel and extraordinarily potent immunotherapy platform approach that employs a synergistic use of chemotherapy and vaccination (JCO 2010, Blood 2011)
- CMV antigens are expressed in high proportion (>90%) of GBM tumors and represent a novel and well-characterized immunogenic target for cancer immunotherapy
- CMV has been reported to be expressed in other tumors (colorectal CA, prostate CA, and breast CA) and thus therapeutic CMV vaccines may have broad applicability

Biology

[CANCER RESEARCH 62, 3347–3350, June 15, 2002]

Advances in Brief

Human Cytomegalovirus Infection and Expression in Human Malignant Glioma¹

Charles S. Cobbs,² Lualhati Harkins, Minu Samanta, G. Yancey Gillespie, Suman Bharara, Peter H. King, L. Burt Nabors, C. Glenn Cobbs, and William J. Britt

Surgical Service, Veterans Affairs Medical Center, Birmingham, Alabama [C. S. C., L. H., M. S.]; and Department of Surgery, Division of Neurosurgery [C. S. C., G. Y. G., S. B.], Department of Neurology [P. H. K., L. B. N.], Department of Medicine, Division of Infectious Diseases [C. G. C.], and Department of Pediatrics [W. J. B.], University of Alabama at Birmingham, Birmingham, Alabama 35294

Sensitive detection of human cytomegalovirus in tumors and peripheral blood of patients diagnosed with glioblastoma

Duane A. Mitchell, Weihua Xie, Robert Schmittling, Chris Learn, Allan Friedman, Roger E. McLendon, and John H. Sampson

Division of Neurosurgery, Department of Surgery (D.A.M., W.X., R.S., C.L., A.F., J.H.S.), and Department of Pathology (R.E.M., J.H.S.), Preston Robert Tisch Brain Tumor Center at Duke; Duke University Medical Center, Durham, NC, USA

Neuro-Oncology 10(1):10-18, 2008.

Detection of human cytomegalovirus in different histological types of gliomas

Michael E. Scheurer · Melissa L. Bondy ·
Kenneth D. Aldape · Thomas Albrecht · Randa El-Zein

Acta Neuropathol (2008) 116:79-86.

Cytomegalovirus Immunity after Vaccination with Autologous Glioblastoma Lysate

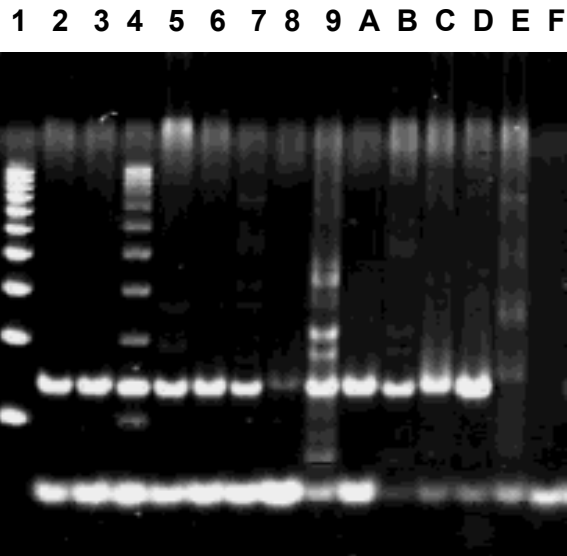
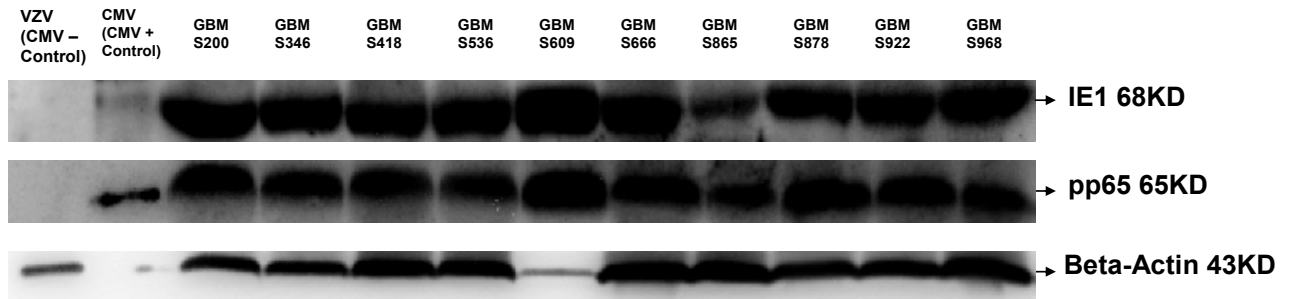
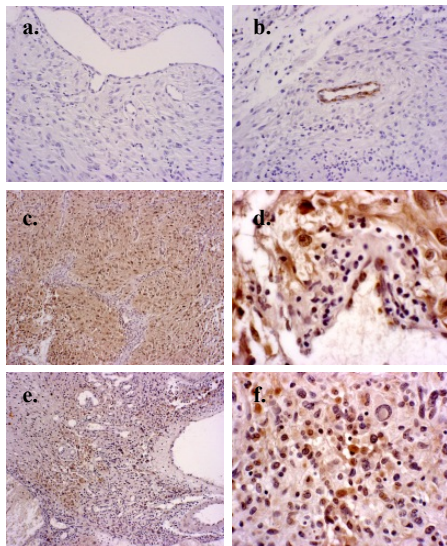
Prins et al. 2008, NEJM 359(5):539.

In Vitro Findings

- Detection of multiple CMV antigens in GBM specimens by IHC, PCR, Western Blot, and immunofluorescence
- Immunologic recognition and killing of GBM tumors expressing endogenous levels of CMV antigens
- Capacity to stimulate CMV-specific effector cells from patients with GBM using autologous dendritic cells pulsed with RNA or CMV-specific peptides *in vitro*

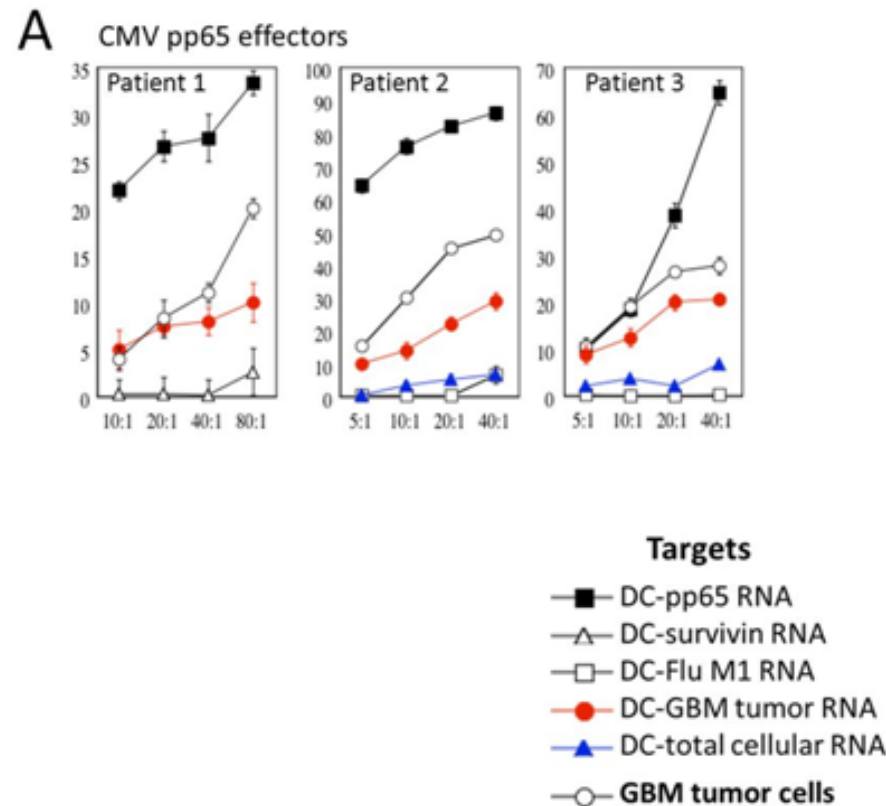
In Vitro Findings

Expression of CMV antigens in Glioblastoma (GBM)



- Cobbs et al., *Can. Res.*, 2002
- Mitchell et al., *Neuro Onc.*, 2008
- Scheuer et al., *Acta Neuro.*, 2008
- Prins et al., *NEJM*, 2009
- Lucas et al., *J. NeuroOnc.*, 2010
- Slinger et al., *Sci. Signal.*, 2010
- Dziurzynski et al., *ClinCanRes* 2011
- Soroceanu et al., *CanRes* 2011
- Bhattacharjee et al., *J. Virol* 2012

In Vitro Findings

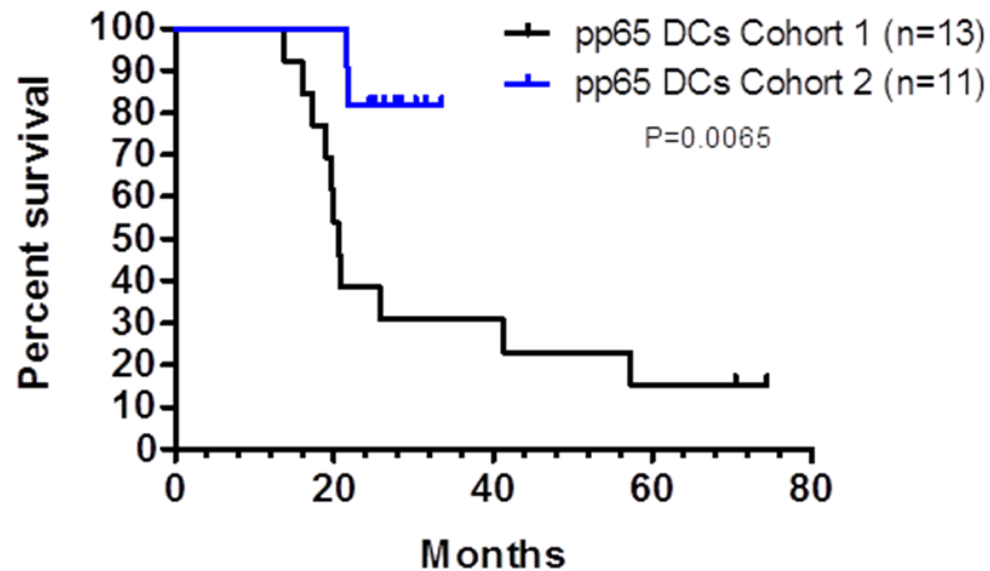


Pharmacology (PK/PD)

- FDA-approved INDs for CMV RNA-pulsed DC vaccines (FDA IND BB-12839) and multi-component CMV peptide vaccine (FDA IND BB-15379)
- Demonstrated immunogenicity, safety, and promising efficacy of DC vaccines targeting CMV antigens in patients with newly-diagnosed GBM
- cGMP multi-component peptide vaccine manufactured and clinical protocol FDA approved for phase I/II clinical trial

Promising Efficacy of DC Vaccines Targeting CMV pp65 in Patients with GBM

FDA IND BB-12839, Duke IRB 3877



Patient groups	Median PFS	Median OS	24-month survival
ATTAC Cohort 1 (n=13)	15.4 months	20.6 months	46.3%
ATTAC Cohort 2 (n=11)	25.3 months	Undefined	81.8%
Historical Cohort*	6.9 months	15-18 months	27-38%

*Lancet Oncology 2009. V10(5):p 459 (Stupp trial, 5-year analysis)

Cohorts 1 and 2 differ in TMZ regimen (standard vs dose-intensified TMZ) and DC vaccine/adjuvant formulations. Standard vs dose-intensified TMZ was shown to have no difference in clinical benefit in a recent phase III clinical trial in newly-diagnosed GBM (RTOG 0525). Efficacy (overall survival) was not different between the two TMZ regimens across all subgroups of GBM patients including extent of resection and RPA class. Differences observed between cohorts 1 and 2 are therefore unlikely attributable to TMZ treatment alone. A randomized phase II trial to confirm these results is currently planned.

Intellectual Property

Proprietary approaches to novel targets in brain cancer and other cancers (EGFRvIII, cytomegalovirus)

Intellectual property related to synergistic use of chemotherapy and vaccination to generate unheralded immunologic responses in patients with grade IV brain cancer

Contact Alan Herosian, MBA Office of Licensing and Ventures, Duke University

Appendix

- -Cobbs et al., *Can. Res.*, 2002
- -Mitchell et al., *Neuro Onc.*, 2008
- -Scheuer et al., *Acta Neuro.*, 2008
- -Prins et al., *NEJM*, 2009
- -Lucas et al., *J.NeuroOnc.*, 2010
- -Slinger et al., *Sci. Signal.*, 2010
- -Dziurzynski et al., *ClinCanRes* 2011
- -Soroceanu et al., *CanRes* 2011
- -Bhattacharjee et al., *J. Virol* 2012