



Brain Tumor Immunotherapy: *Against All Odds*

Linda M. Liaw, MD, PhD, MBA

Professor & Vice Chair

UCLA Department of Neurosurgery

Jonsson Comprehensive Cancer Center

David Geffen School of Medicine

Los Angeles, California



BRAIN
RESEARCH
INSTITUTE
UCLA

Disclosures

- Research support from:
 - Northwest Biotherapeutics, Inc.
- Consultant for:
 - Arbor Pharmaceuticals
 - Actuate Therapeutics

Western Neurosurgical Society (1997)



WNS Lanai, HI; 1996

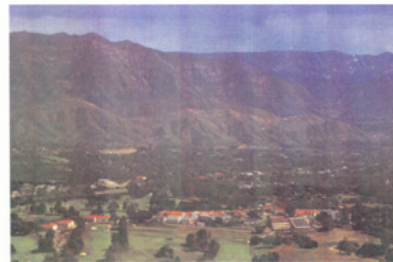


WNS Ojai, CA; 1997

THE WESTERN
NEUROSURGICAL SOCIETY



1997



Ojai Valley Inn
Ojai, California

10:00 - 10:30
COFFEE BREAK with Exhibitors

SESSION V
Moderator: Martin Weiss

- 10:30
15. **Time-lapse Imaging of Mossy Fiber Sprouting in Hippocampal Slices using Two-Photon Laser Scanning Microscopy**
Adam Mamelak, Steven M. Potter, David Kantor, Erin M. Schuman, Scott E. Fraser
- 10:45
16. **Retroviral Vector-Mediated Transfer of an Antisense Cyclin G1 Construct Inhibits Glioma Growth and Augments Thymidine Kinase Tumor Killing**
Mark D. Krieger, Erlinda M. Gordon, Berislav V. Zlokovic, Frederick L. Hall, W. French Anderson, Martin H. Weiss
- 11:00
17. **Treatment of Intracranial Gliomas with Bone Marrow-Derived Dendritic Cells Pulsed with Tumor Antigens**

11:15
PRESIDENTIAL ADDRESS
ROBERTE FLORIN
A Consultation and Prescription for Neurosurgery
Introduced by: Gail Magid

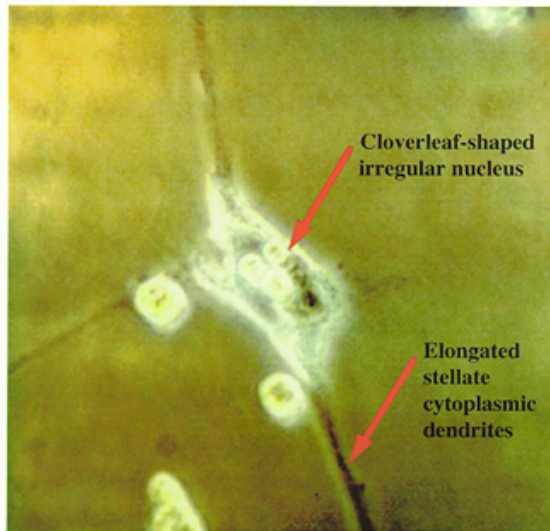
12:00
ADJOURN

**Resident Award Paper

“Treatment of intracranial gliomas with bone marrow-derived dendritic cells pulsed with tumor antigens”



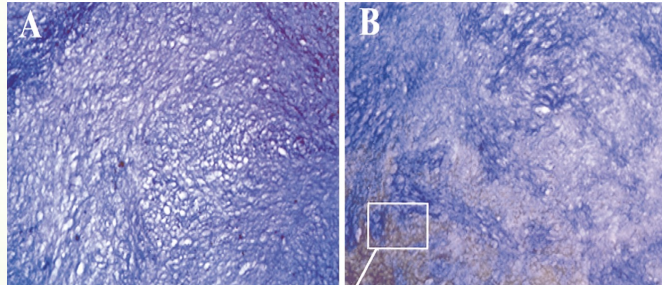
Journal of Neurosurgery



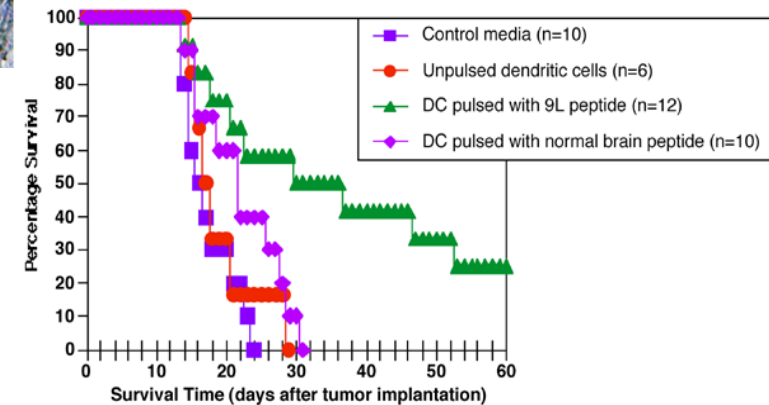
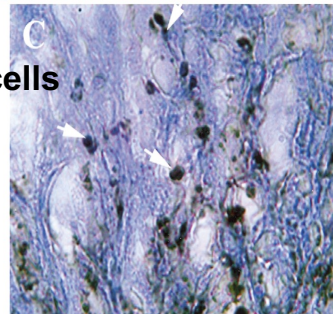
JUNE 1999 Volume 90, Number 6

Control

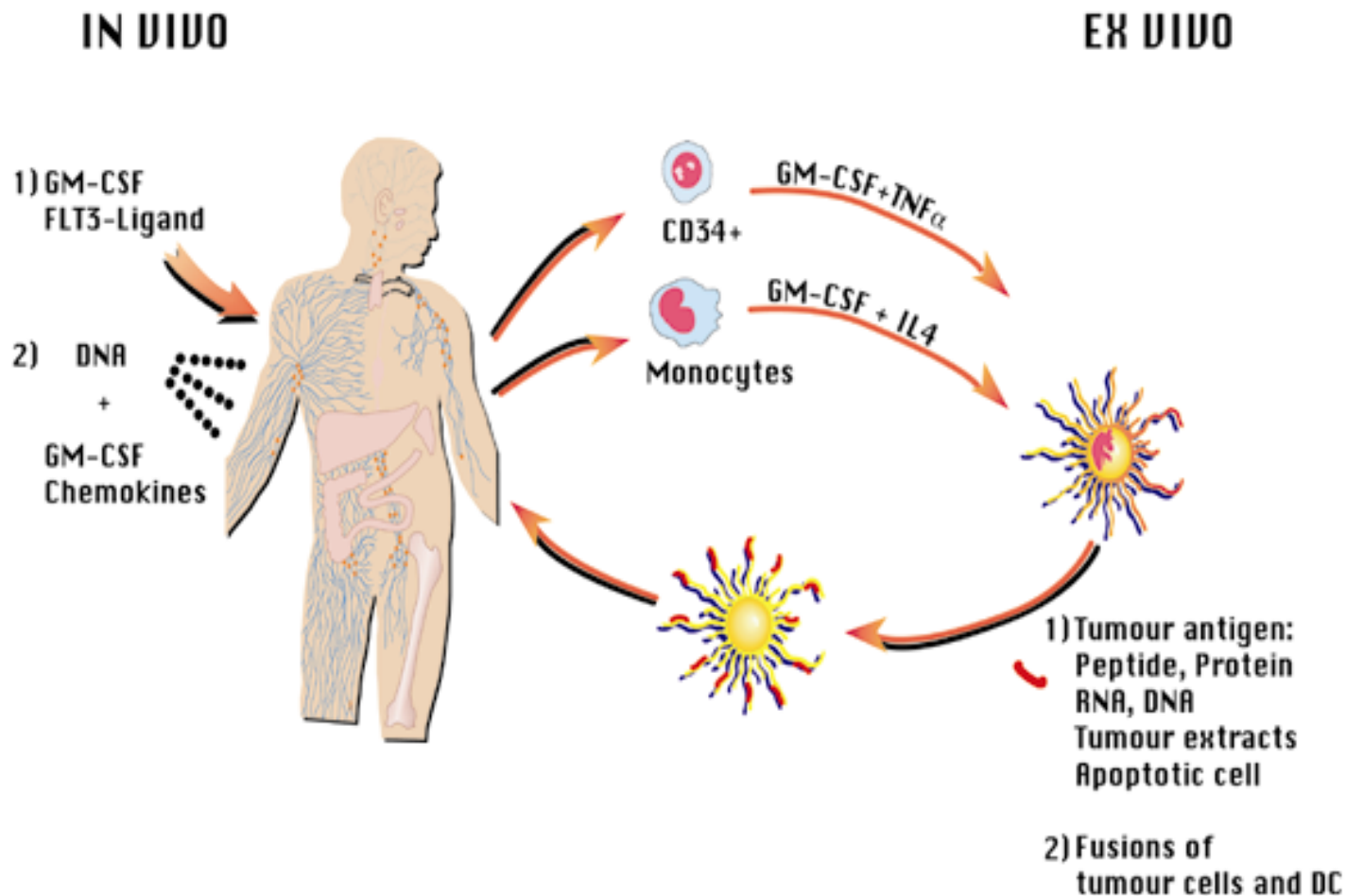
DC treated



CD8+ T cells

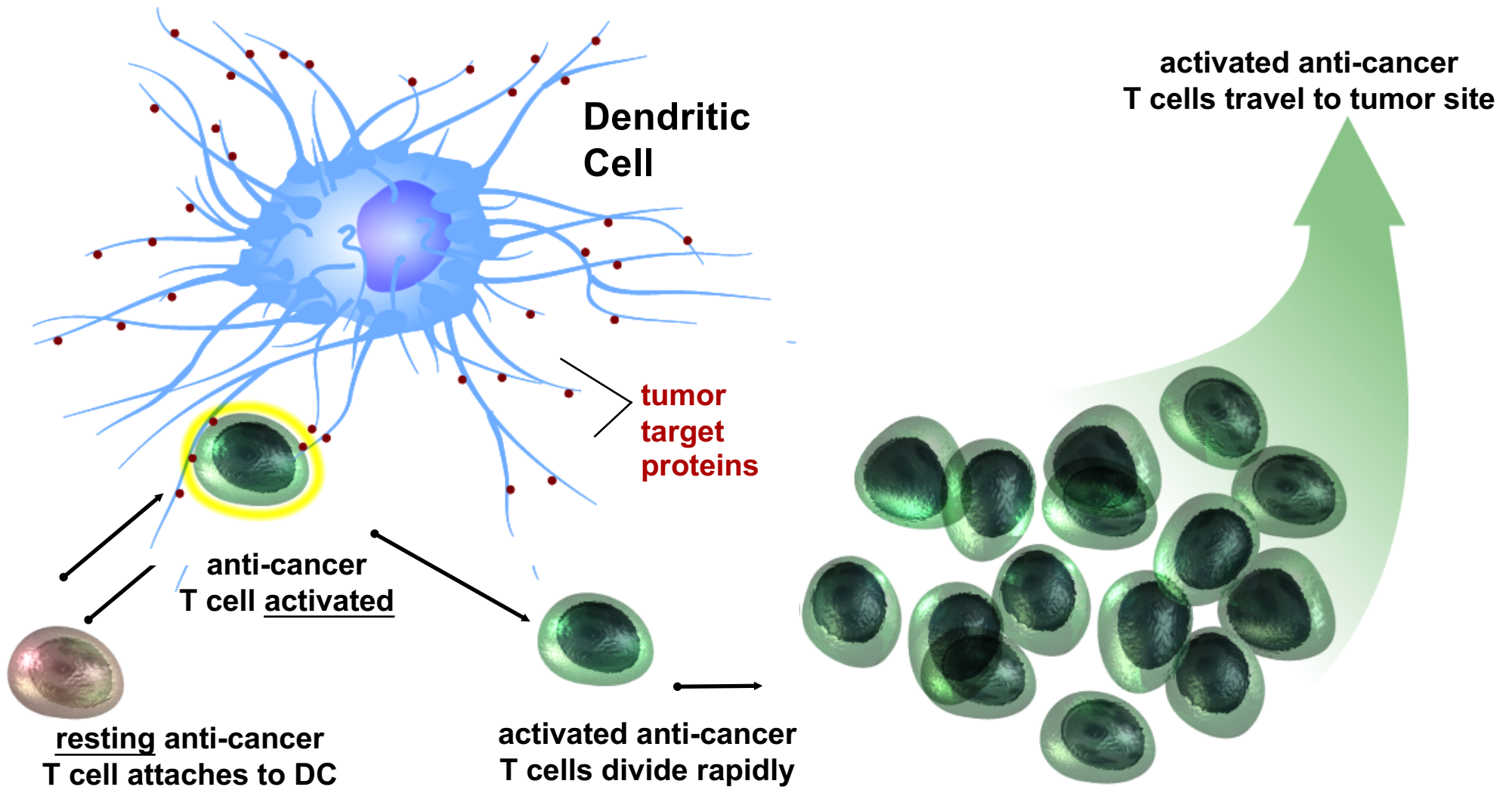


First-in-human treatment of a patient by vaccination with autologous dendritic cells pulsed with glioma peptides



WNS Mauna Lani, 2000

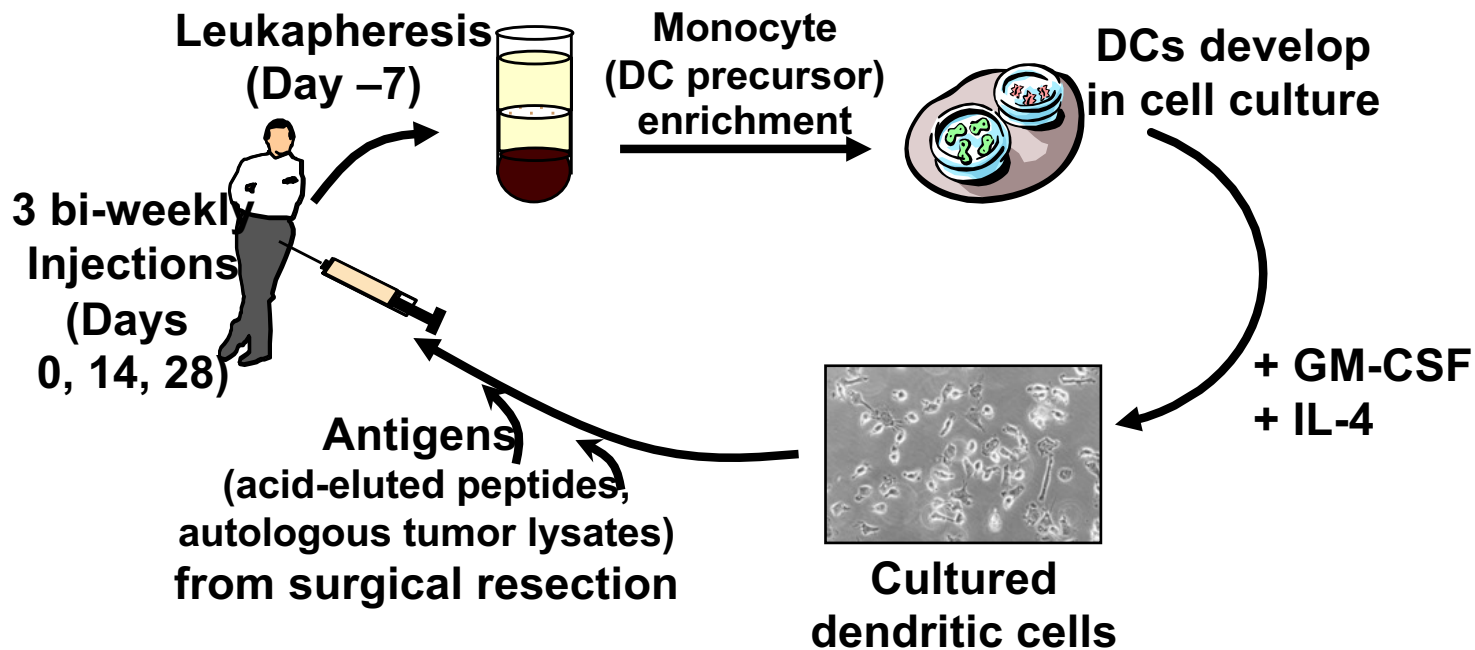
DC-based vaccine: Each “Educated” Dendritic Cell Activates Hundreds of Anti-Cancer T Cells



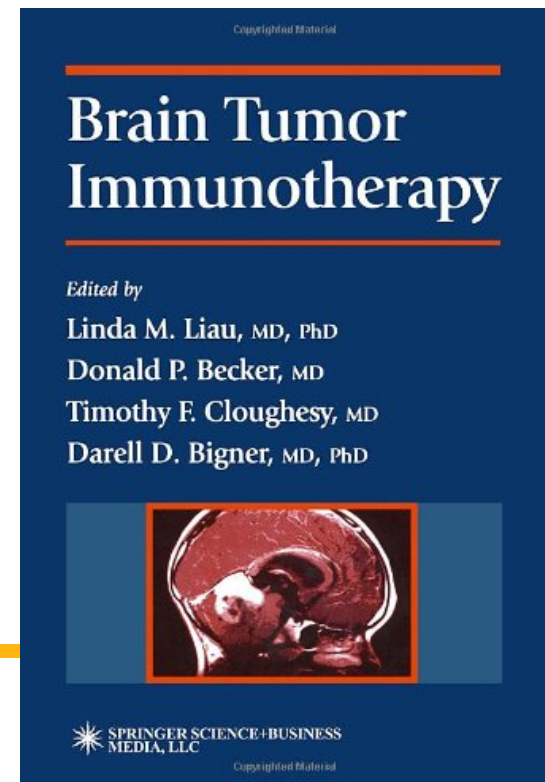
FDA IND #8434: Phase I Clinical Trial of DC Immunotherapy for Malignant Gliomas



Bianca born 2001



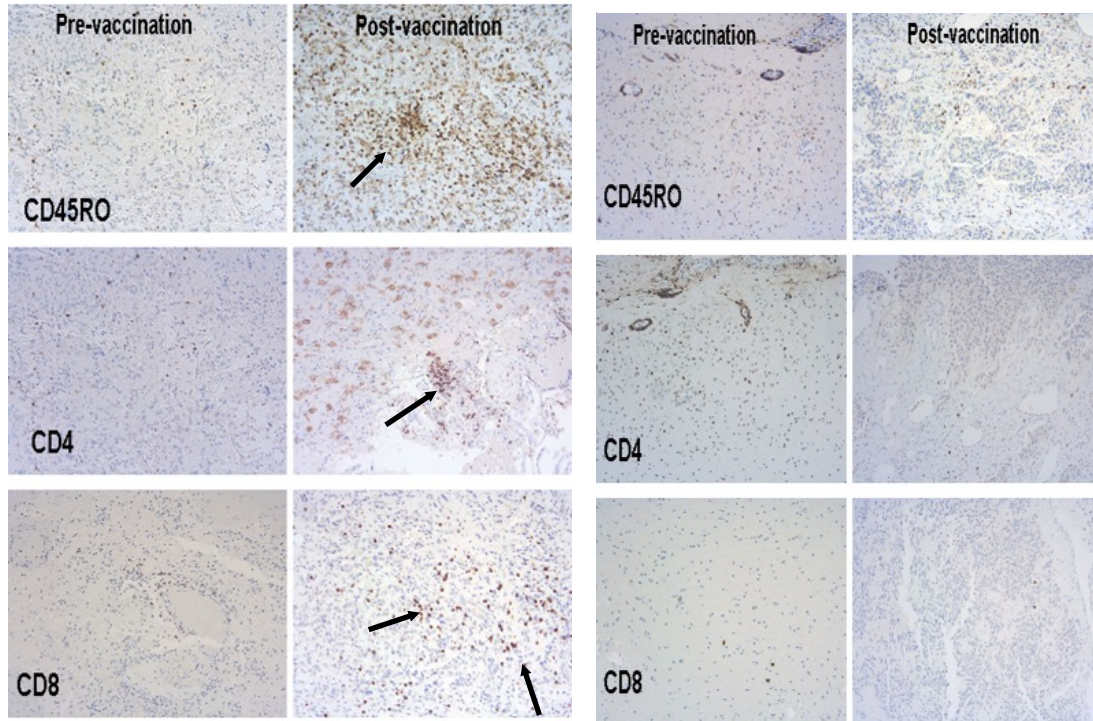
NIH R21-CA91545 (2001)



First in human clinical trial of brain cancer vaccine



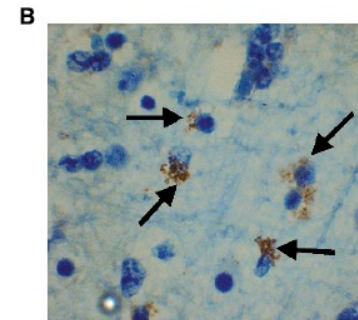
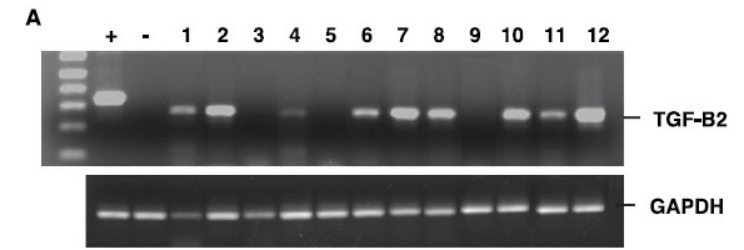
DC vaccination in glioblastoma patients induces systemic and intracranial T-cell responses modulated by the local CNS brain tumor microenvironment



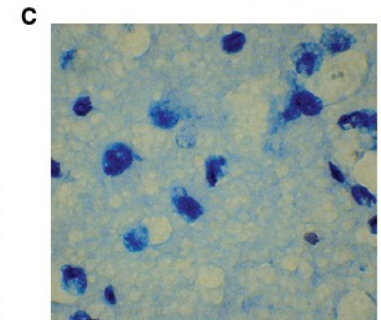
Patient #1: OS = 30.2 mos

Patient #2: OS = 11.4 mos

Increased CD8⁺ T-cell infiltration correlated with increased survival



Patient #12:
OS = 9.3 mos.

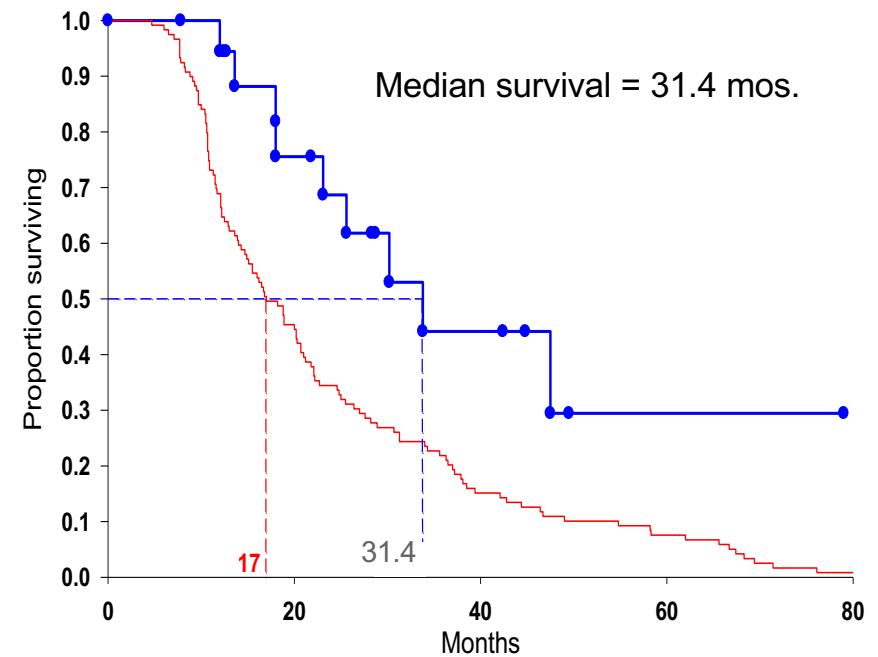


Patient #5:
OS > 120 mos.

Increased TGF-β expression correlated with decreased survival

Phase I/II clinical trial of DC-tumor lysate vaccine: Survival of glioblastoma patients from time of diagnosis

Patient population	% alive at		
	1 year	2 years	3 years
DC vaccine treated (n=23)	91	55	47
Institutional controls (n=119)	69 (p<0.02)	34 (p<0.05)	21
Stupp et al. 2005 (n=287)	61	26 (p<0.001)	20
Mirimanoff et al. RPA III		32	
Mirimanoff et al. RPA IV		19	



Liau LM et al, *Cancer Res*, 2000
 Liau LM et al, *Cancer Res*, 2002
 Liau LM et al., *Clin Cancer Res*, 2005
 Prins RM & Liau LM, *NEJM*, 2008

NIH funding

- R01-CA112358
- R01-CA121131
- R01-CA123396
- K01-CA111402 (mentor)



WNS, Hawaii 2007

Collaboration with Industry: Clinical Development of DCVax-L[®]



Linda Powers, CEO

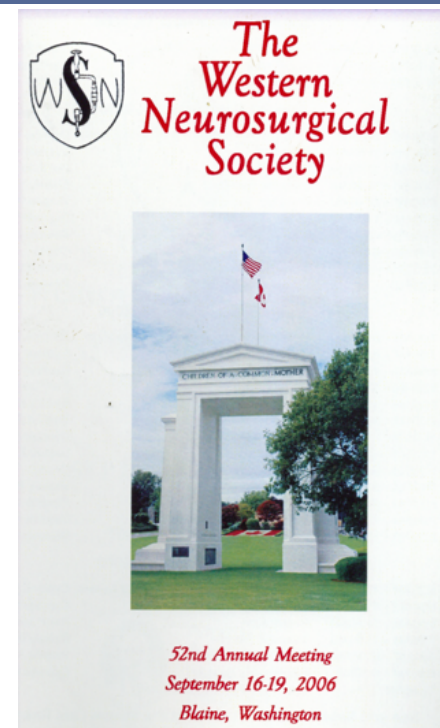


Non-blinded,
randomized

**First Phase I
trial in GBM at
UCLA
2000-2002**

**Second Phase
I/II trial in
GBM at UCLA
2003-06¹**

**Multi-
center
Phase
II
Trial
2007**



↑
**FDA grants
first IND**

↑
**Collaboration with
Northwest
Biotherapeutics, Inc.**

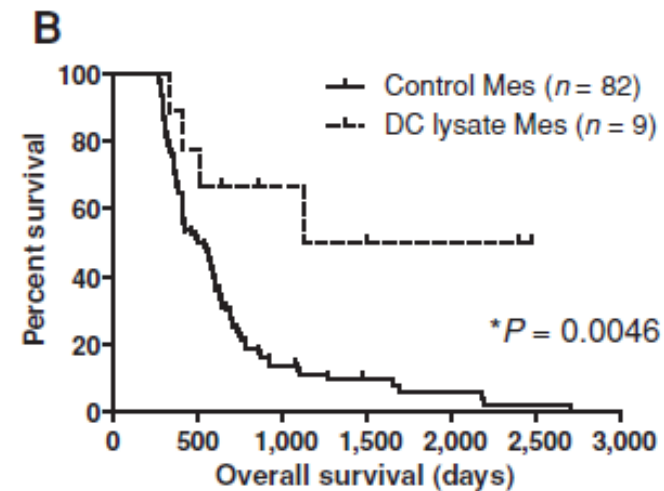
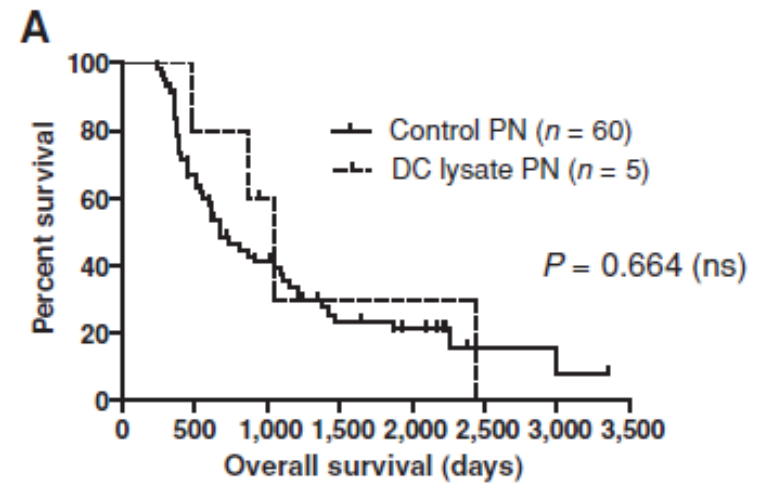
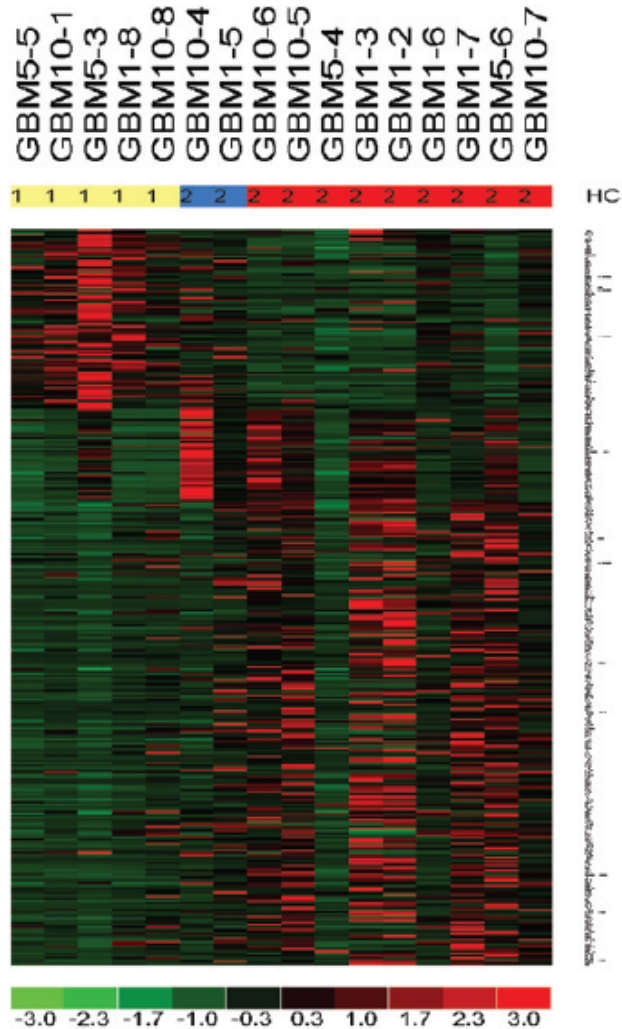
Western Neurosurgical Society Anchorage, Alaska (2008)



WNS, Alaska, 2008

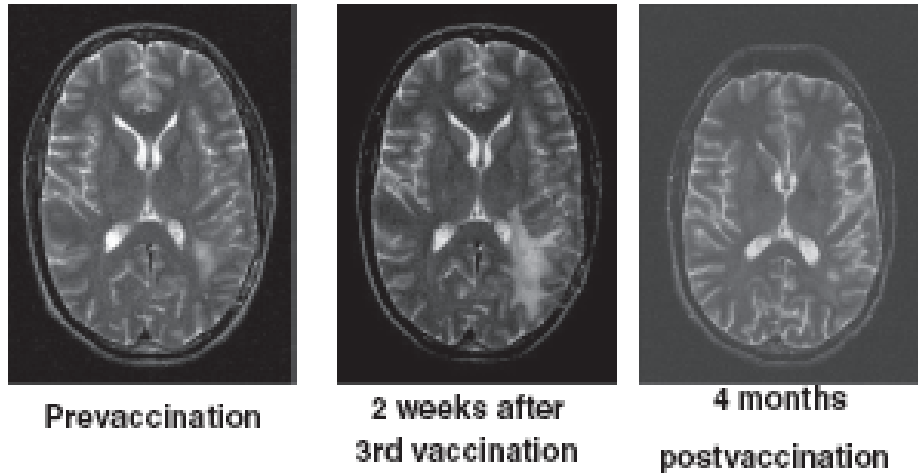


Gene expression profile correlates with increased survival in glioblastoma patients vaccinated with DC immunotherapy

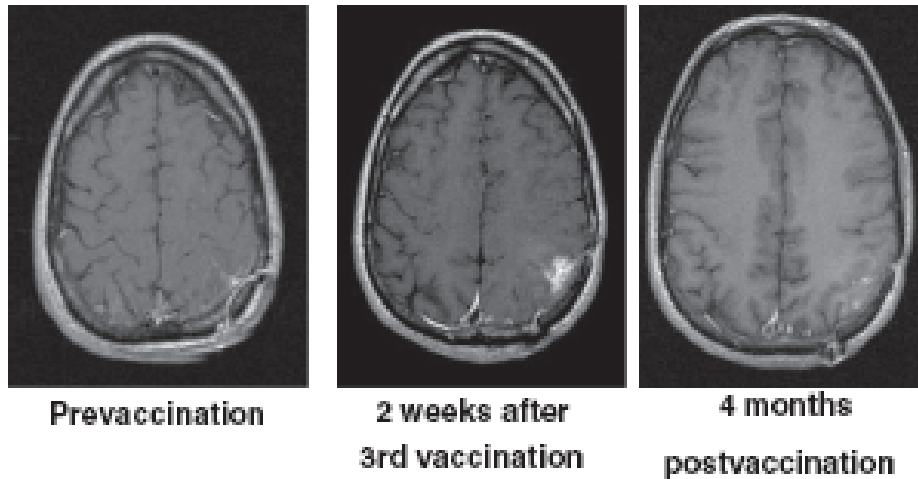


“Mesenchymal” gene expression signature associated with increased tumor-infiltrating lymphocytes

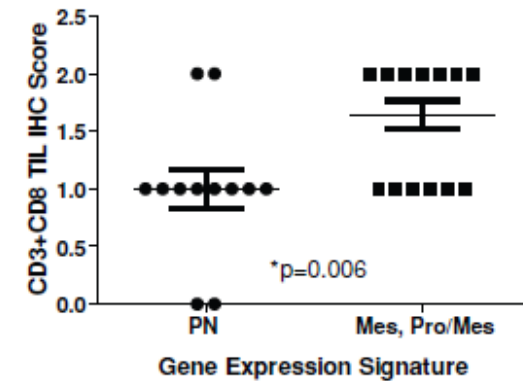
A



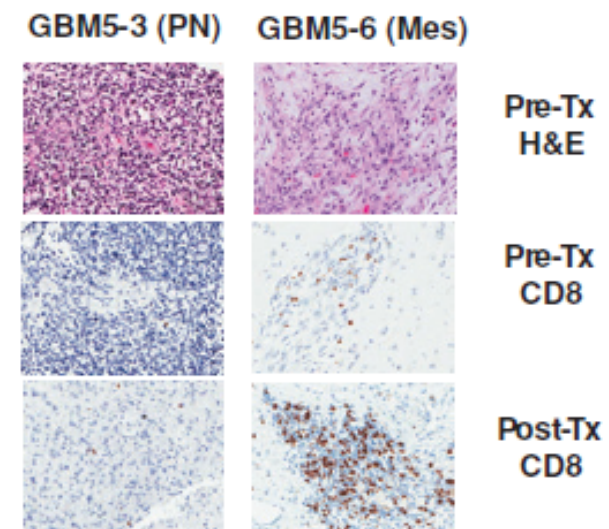
B



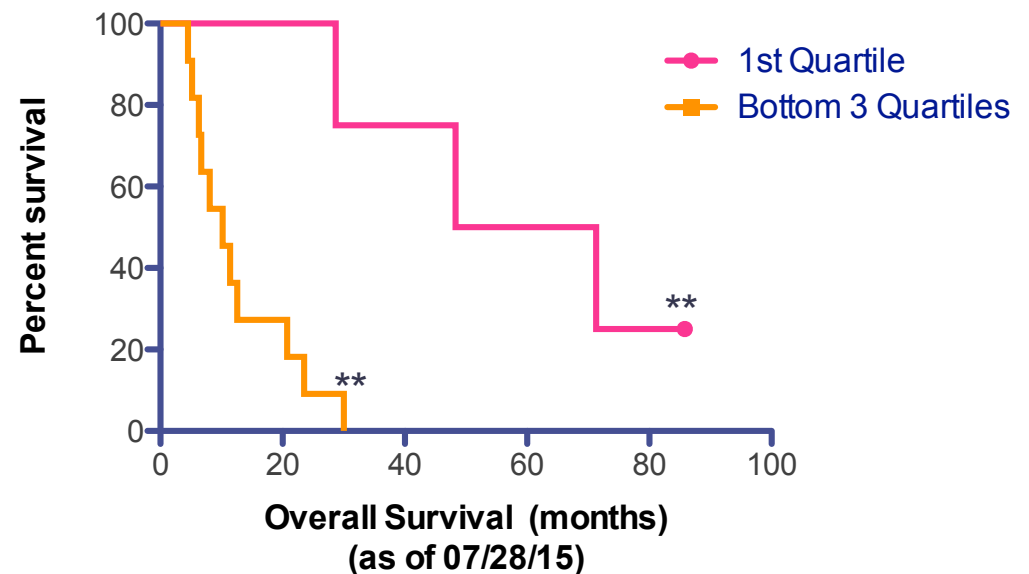
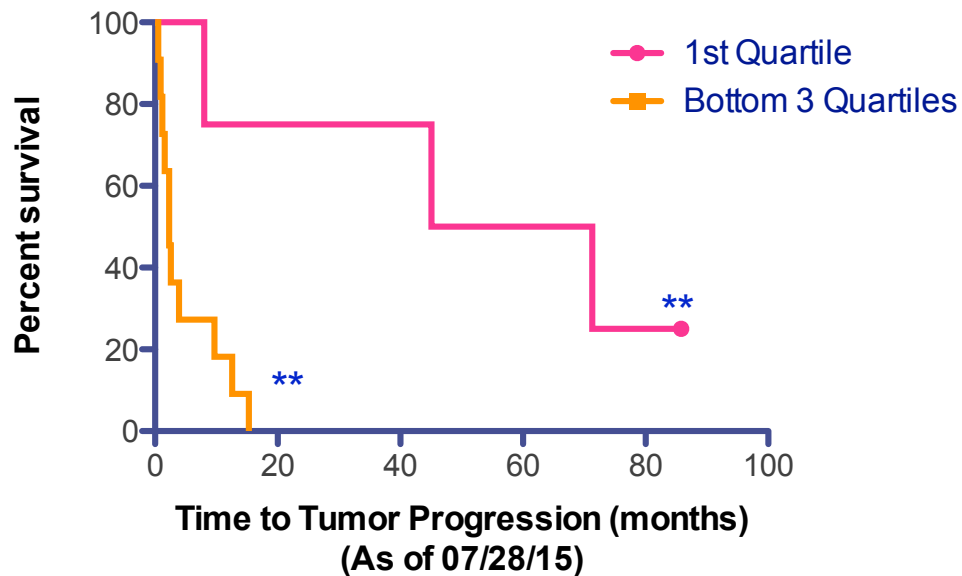
A



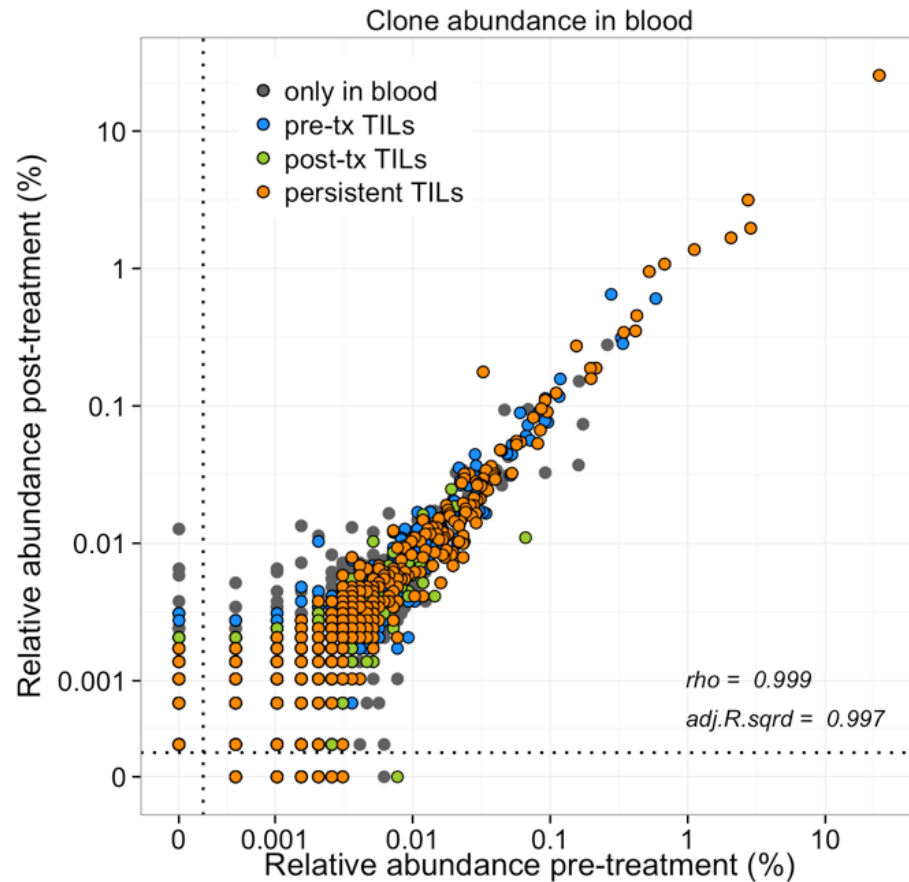
B



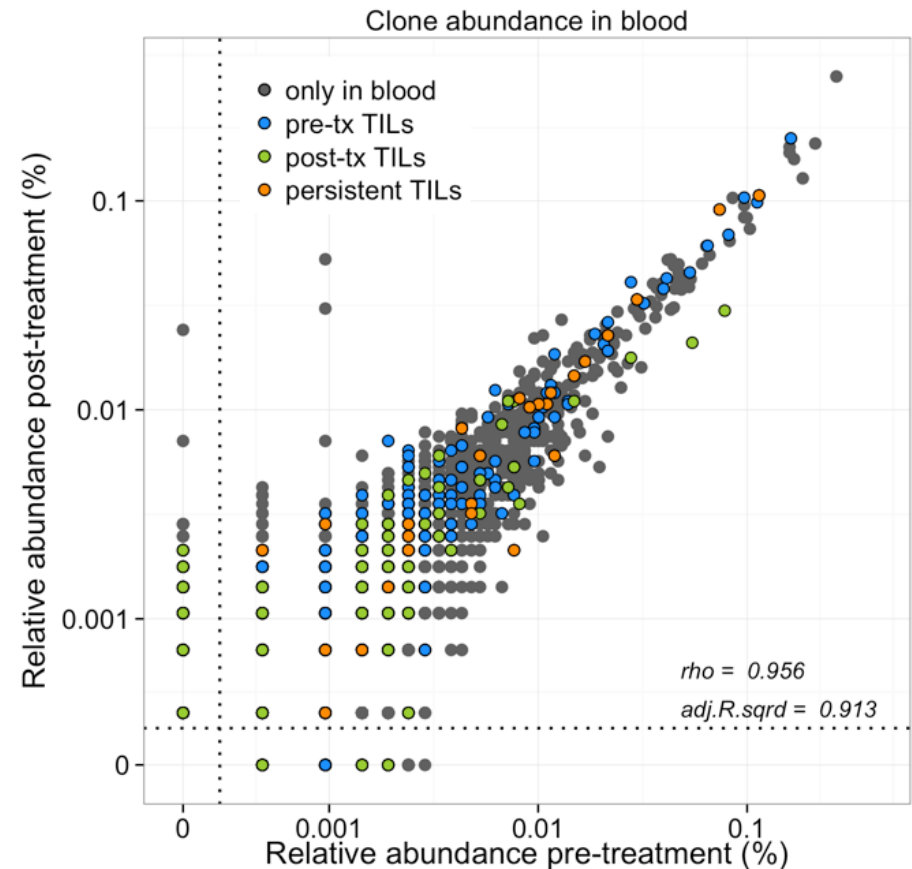
Tumor-infiltrating lymphocyte content is predictive biomarker of survival after DC vaccination



Increases in TCR overlap in tumor vs. peripheral blood leads to increased survival

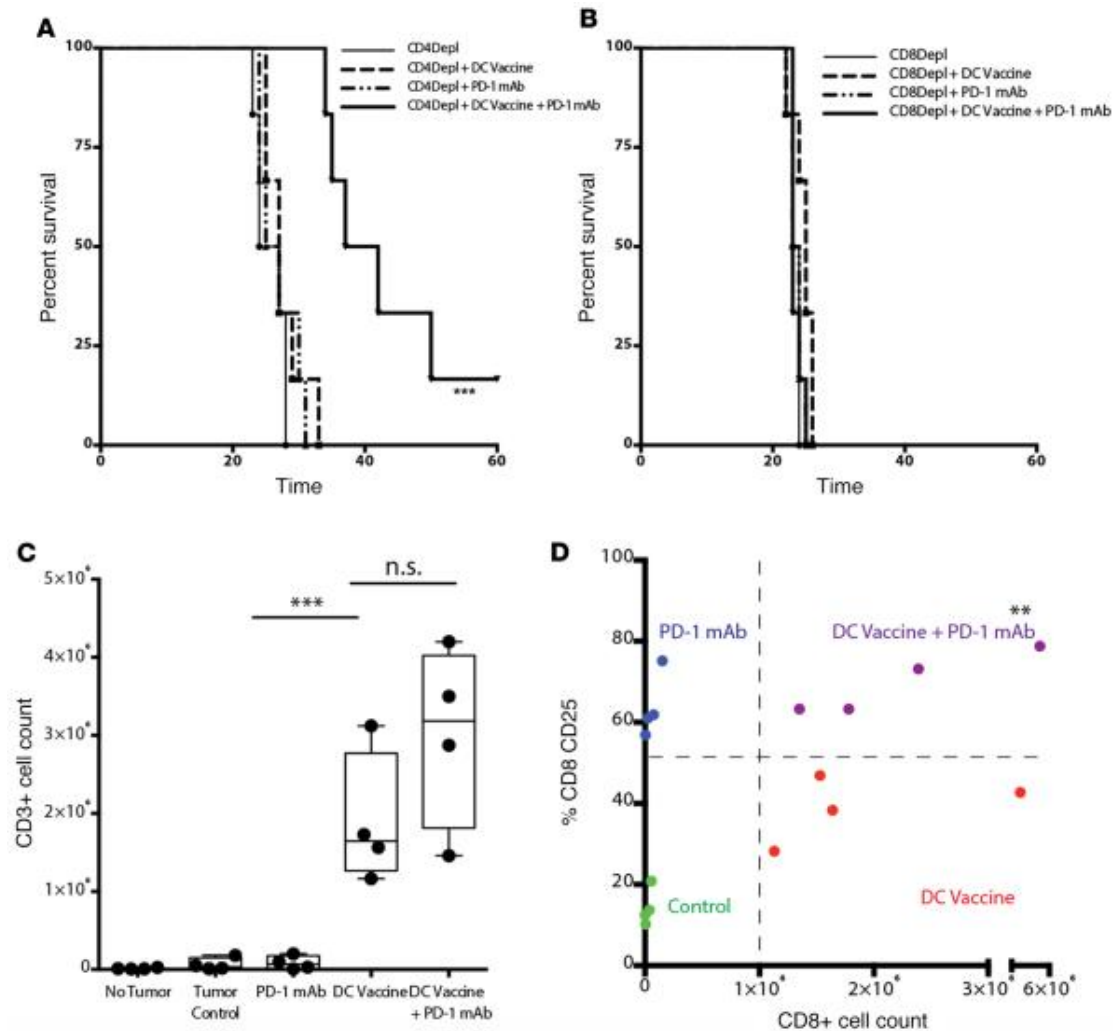


OS = 71.3 mos

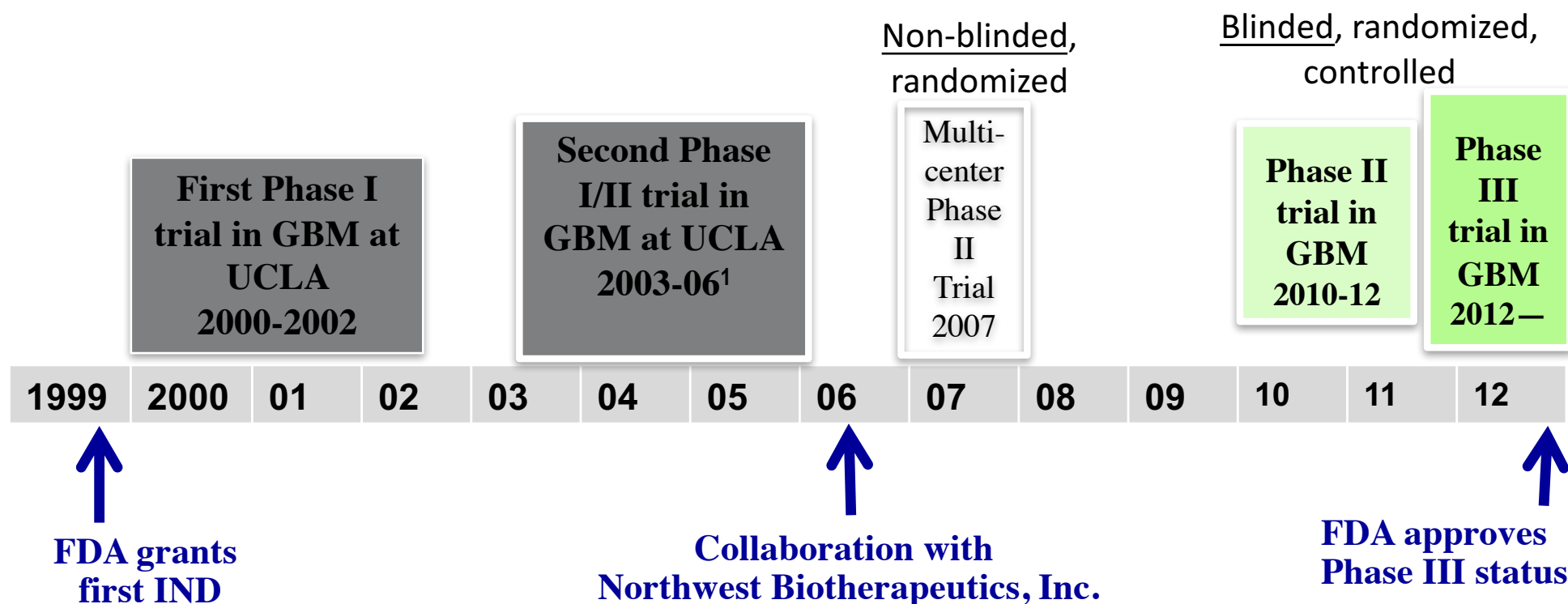


OS = 6.3 mos

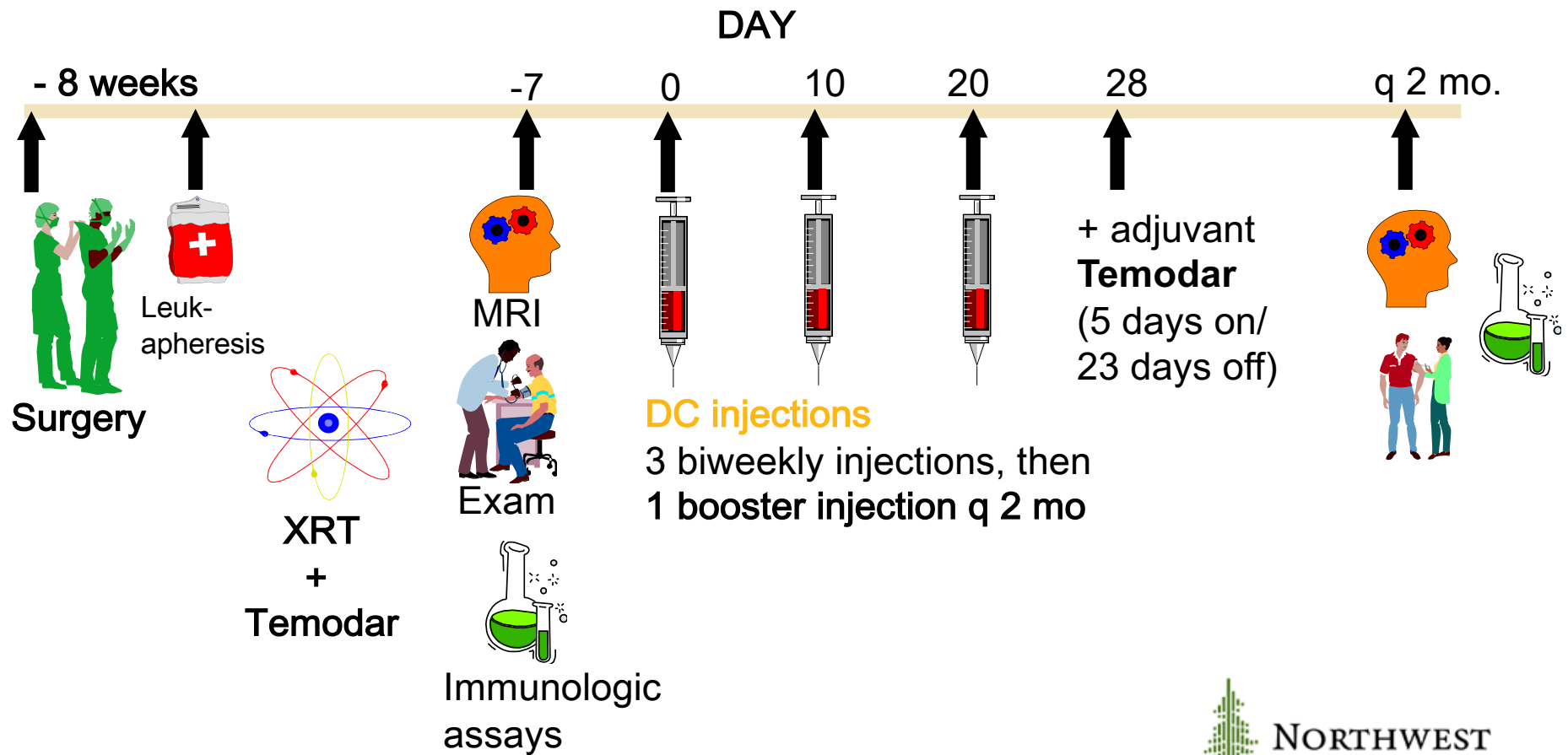
PD-1 blockade enhances vaccination-induced immune response in glioma



Collaboration with Industry: Clinical Development of DCVax-L®



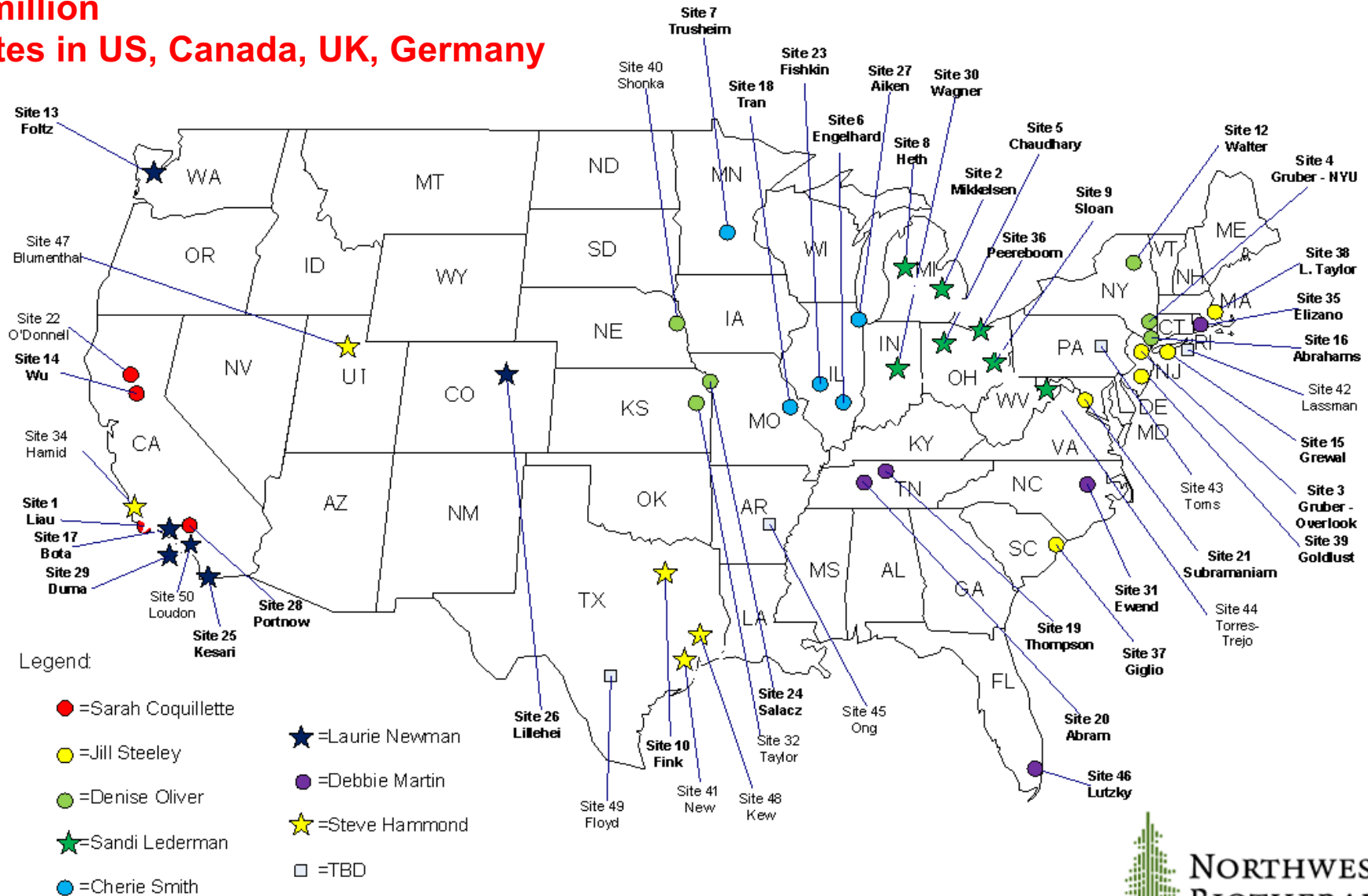
Phase III multi-center, randomized clinical trial of DCVax-Brain™ for newly diagnosed GBM (n=331)



Phase III multi-center, randomized clinical trial of DCVax-Brain™ for newly diagnosed GBM (n=331)

Northwest Biotherapeutics Protocol 020221 Site Map

\$50 million
50 sites in US, Canada, UK, Germany



Phase III DCVax-L[®] Trial Design

- Multi-center, double-blind, randomized, placebo controlled trial
- 348 newly diagnosed GBM patients, randomized 2:1 (treatment:placebo) with cross-over
- DCVax-L adjuvant to standard of care (surgery, radiation, Temodar); injections interspersed with adjuvant Temodar
- Centralized imaging review with reassessment of pseudo-progression
- **Primary endpoint:** Progression-Free Survival
- **Secondary endpoints:** Overall Survival, TTP, Immune Responses, Safety, Landmark analyses for survival

DCVax-L Phase III Trial for GBM – Projections

- Recruitment completed in U.S. (n = 331)
- Final analysis by early 2017 (depending on events)
- Regardless of efficacy of DCVax-L[®] for GBM, there will be a wealth of clinical information, centralized imaging, and tumor/blood samples for genomic subgroup analysis, development of immunological biomarkers, and new avenues of clinical research

THANK YOU!

UCLA Department of Neurosurgery

David Geffen School of Medicine

