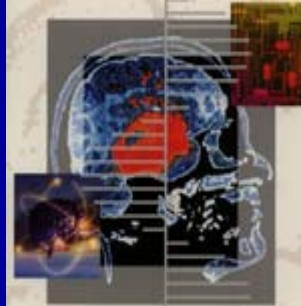


Cancer Vaccines



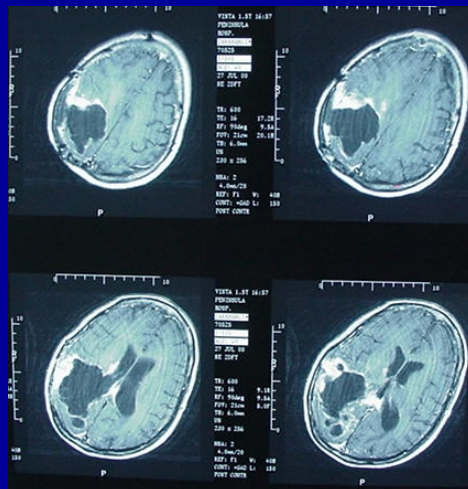
John S. Yu, M.D.

Director, Surgical Neuro-Oncology

Department of Neurosurgery,

Cedars-Sinai Medical Center, Los Angeles, CA

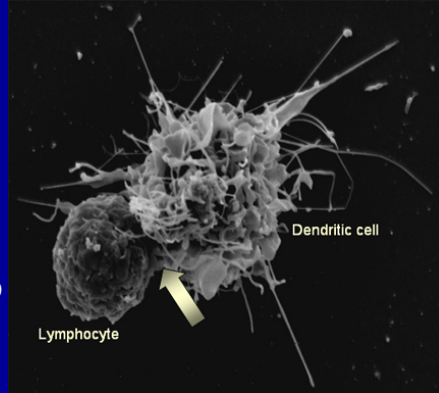
What are the problems in brain tumor therapy?



- Survival for glioblastoma remains a year
- Tumor cells spread in normal brain tissue
- Eats away at that which makes us human
- Brain tumors suppress normal immune responses

Immune Status of Glioma Patients

- Pt's with gliomas demonstrate impaired immune function.
- Dendritic cells (antigen presenting cells) are pulsed with tumor protein to make a vaccine.
- DC introduces tumor associated antigen (TAA) to T-cells.
- Activation of T-cells to eliminate tumor cells.



History of Immunotherapy

- 1796 Jenner introduces cowpox immunization to prevent smallpox infection
- 1879-1886 Pasteur introduces weakened chicken cholera bacterium and rabies
- 1954 Salk introduced live attenuated polio
- 1982 Ab to treat human B-cell lymphoma
- 1988 TAA



Immune Status of Glioma Patients

- Suppressed function of immune cells
- Lower number of immune cells
- Higher number of suppressor cells

Antigen Presentation

- Glioblastoma cells are poor antigen presenters to the immune system
- Tumor-Infiltrating antigen presenting cells are defective



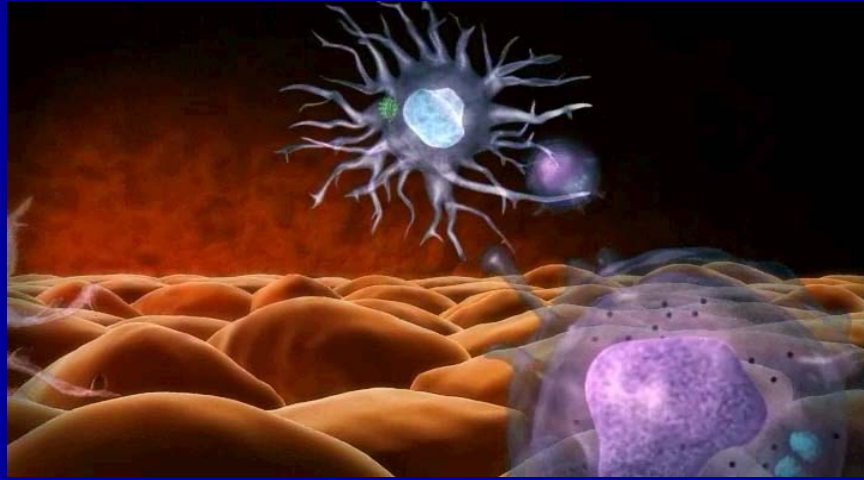
What are Dendritic Cells?

- ⌘ Small Component of white blood cell population,
- ⌘ Antigen presenting cells that possess highest T cell stimulatory capacity
- ⌘ Gives the bloodhound the scent of the criminal's clothes. T cells are the bloodhounds that track down the tumor cells.

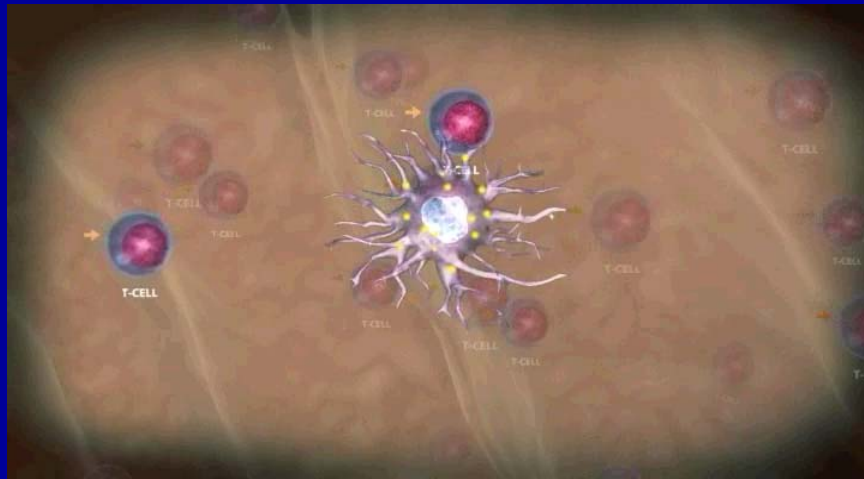
Dendritic cells: Initiators of the Immune Response



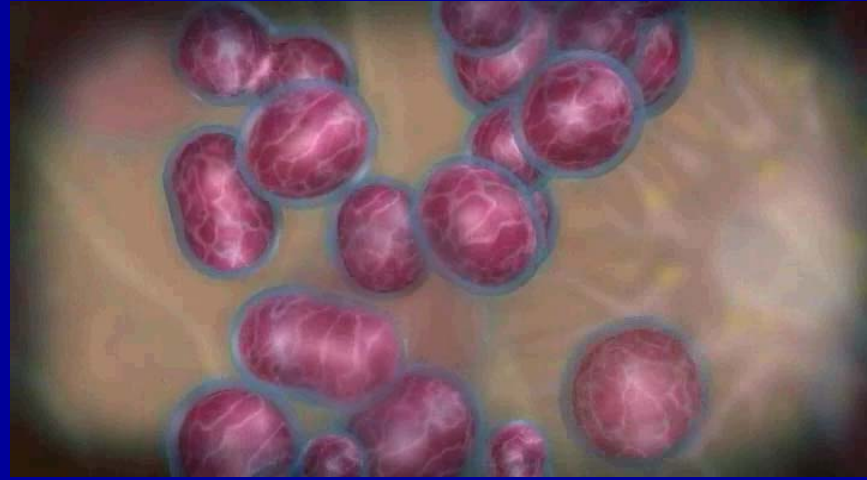
Antigen presentation from tumor cells



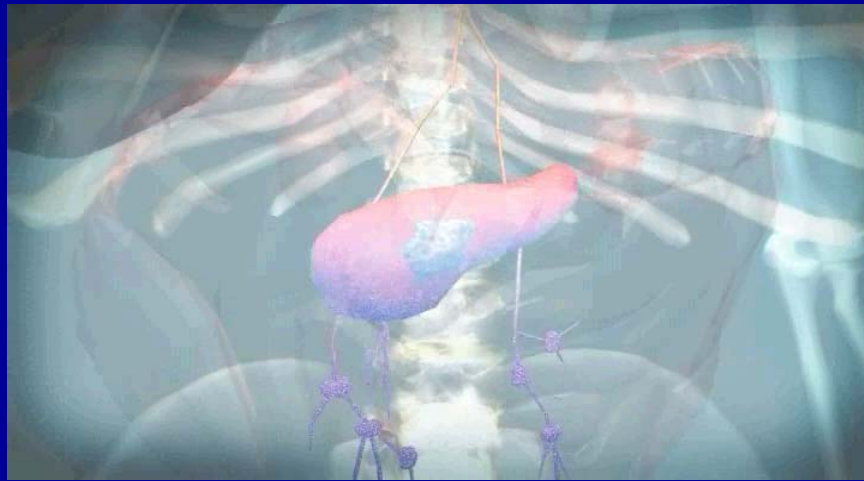
Presentation to T cells in lymph node



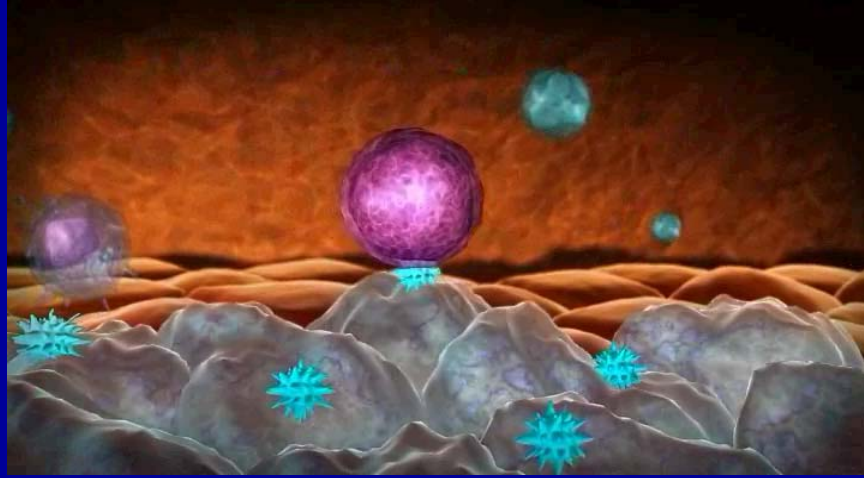
T cells multiply



T cells migrate from lymph node to tumors



T cells kill tumor cells

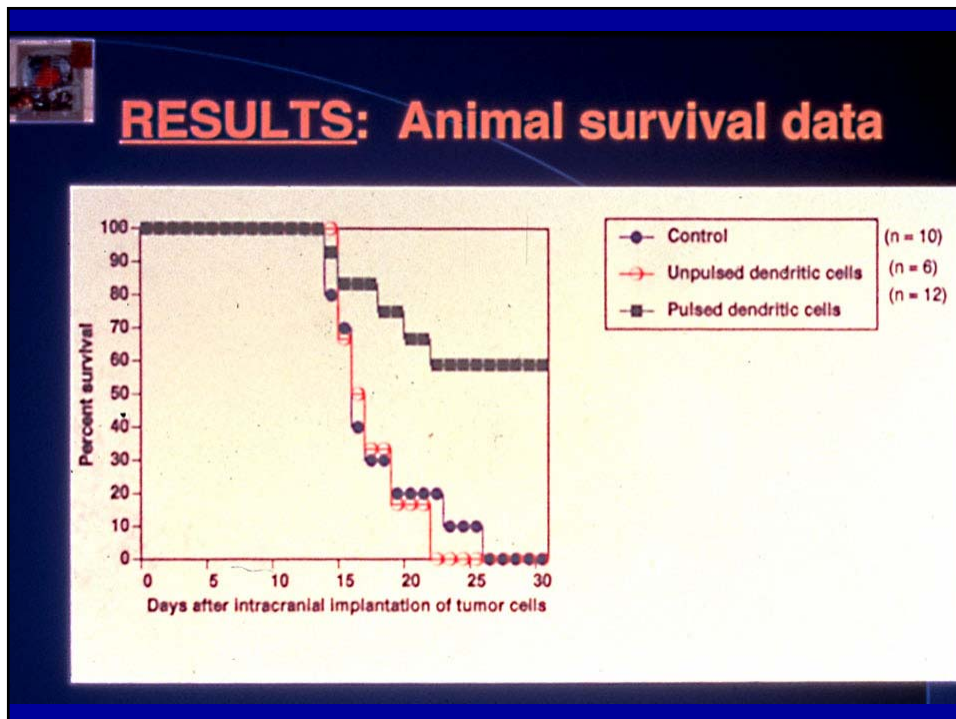


Rationale for DC vaccination

- **Optimization of dendritic cell activity and maturation.**
 - Greater dendritic cell yield
 - Enhanced antigen processing, presentation activities

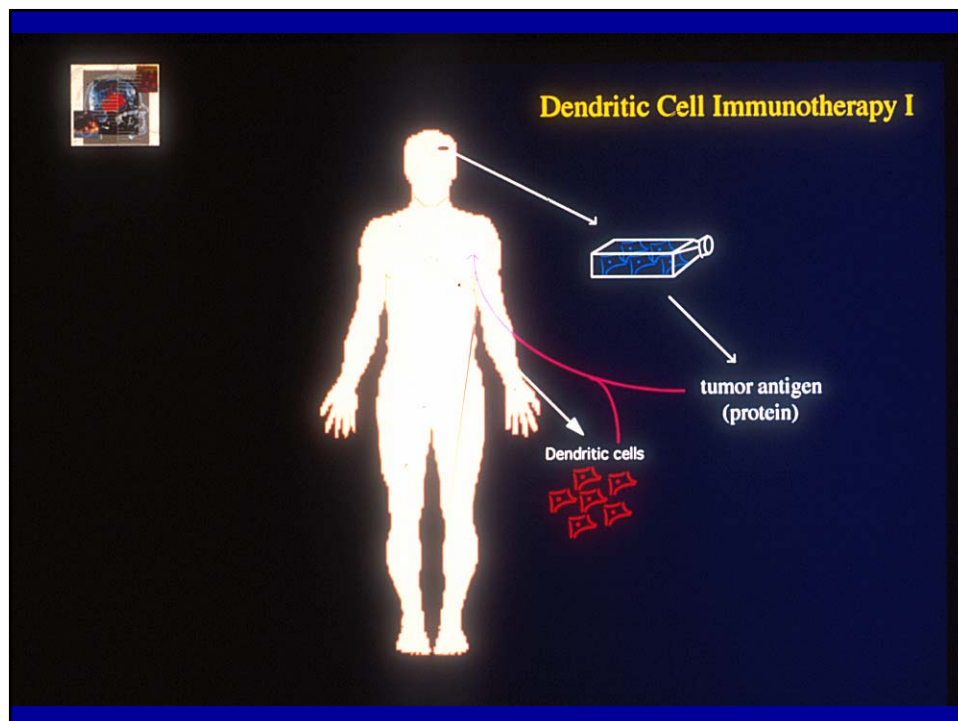
Preliminary Studies

- Vaccination with antigen pulsed DC prolongs survival in rat glioma model
- Allogeneic DC vaccination in a patient with brainstem glioma



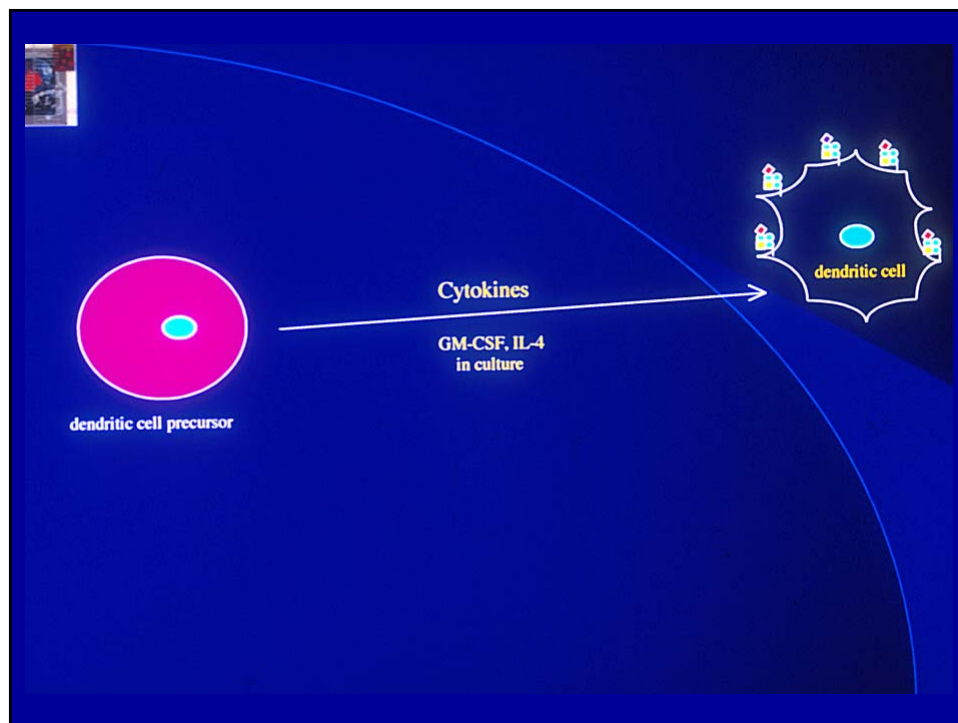
Hypotheses

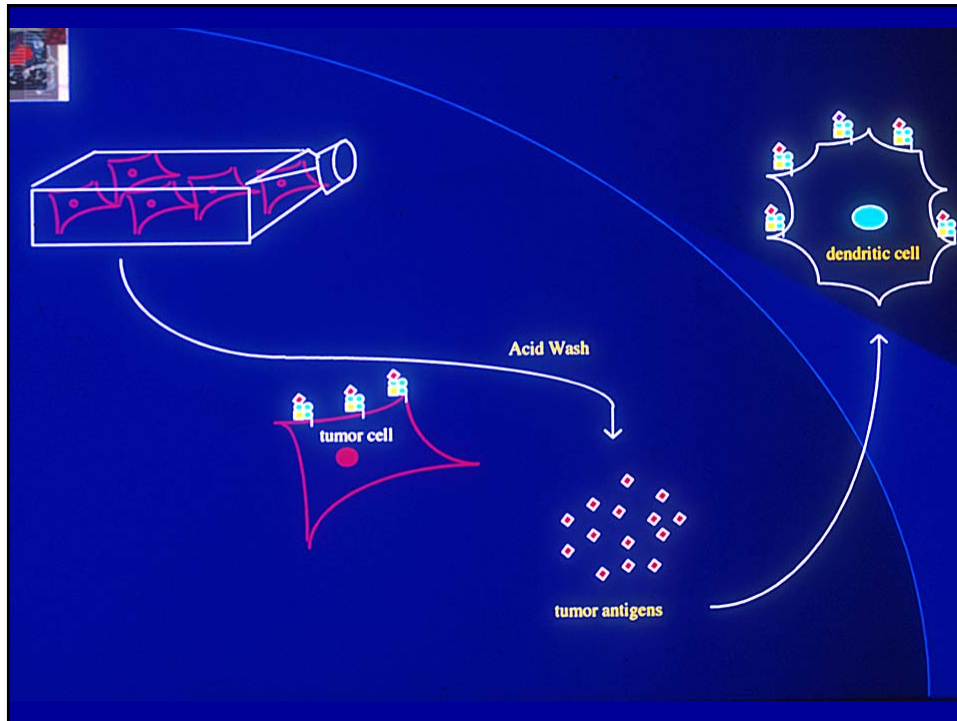
1. DC vaccination will elicit peripheral T cell cytotoxicity.
2. T cells will migrate into and kill intracranial tumor.
3. DC vaccination will prolong survival in malignant glioma patients.



Phase I Trial of Antigen Pulsed DC Vaccination

- 10 patients with newly diagnosed GBM or AA
- Proteins eluted from cell surface of tumor grown in culture
- Mononuclear cells isolated by phlebotomy and differentiated to DC
- 3 vaccinations with antigen pulsed DCs

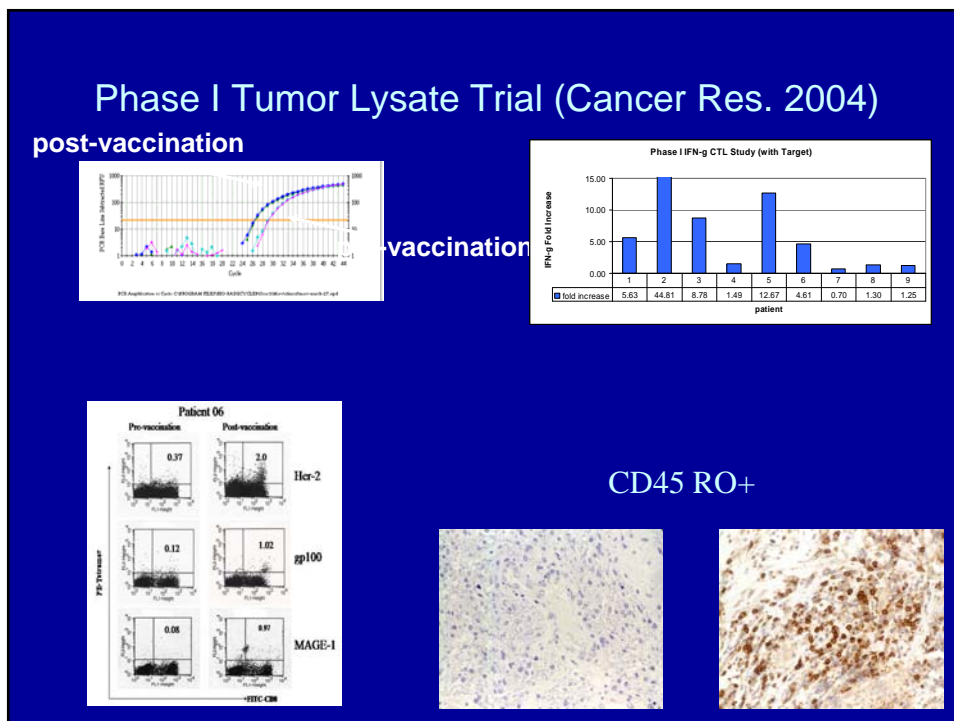
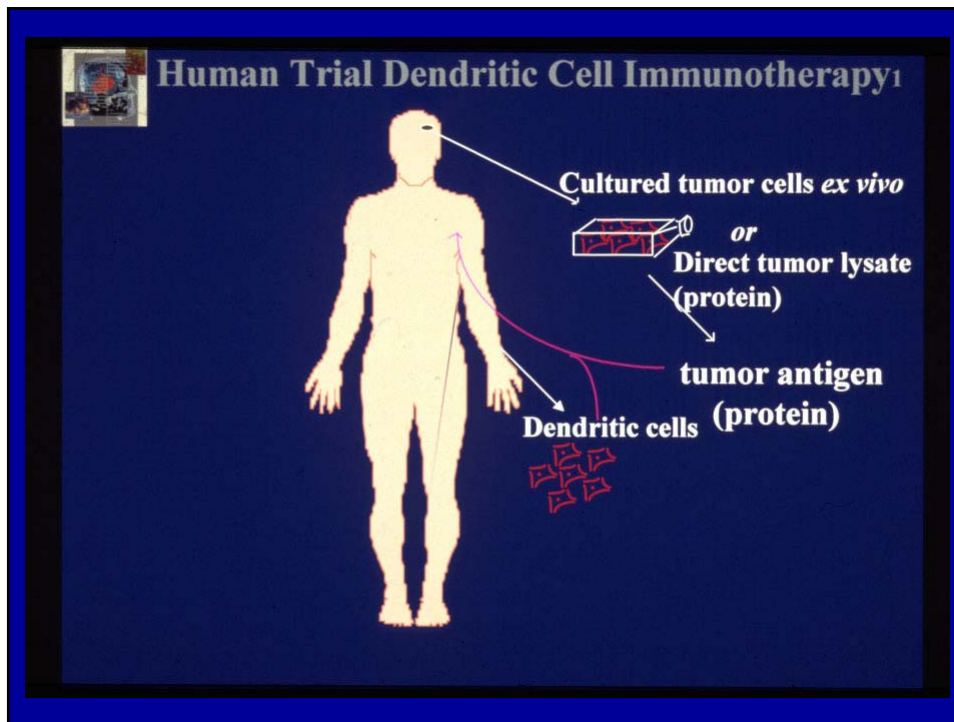




Peptide-pulsed DC Phase I trial

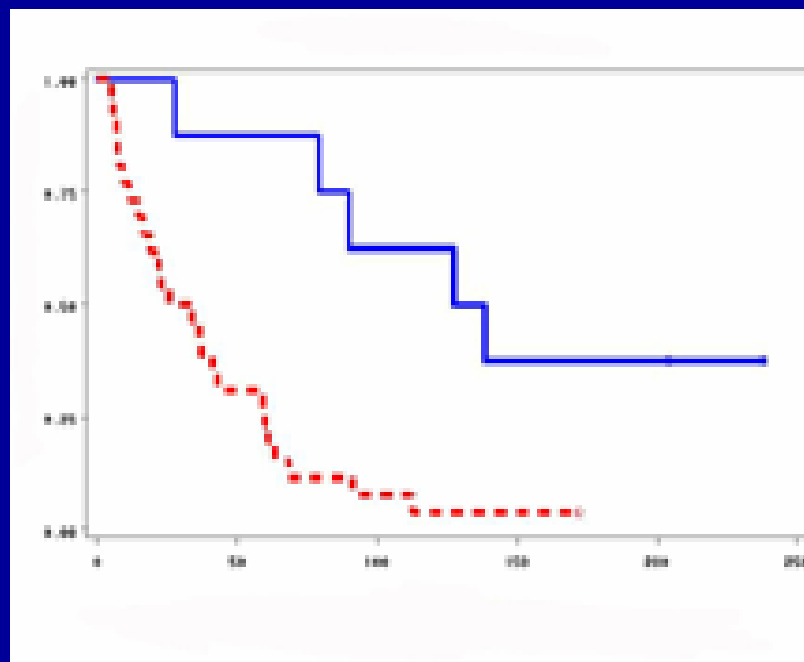
1. Peptide pulsed Dendritic Cell vaccination is safe.
2. DC vaccination elicits peripheral T cell cytotoxicity in 4/6 patients.
3. T cells migrate into intracranial tumor in 2/4 patients.
4. DC vaccination prolongs survival in malignant glioma patients compared to RTOG controls.





Survival Study

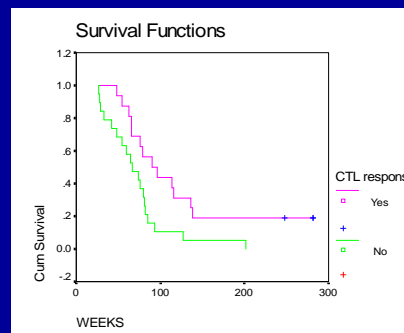
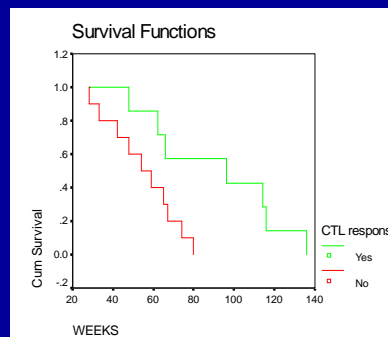
- 7 study patients vs. 51 control patients
- Median survival 133 weeks vs. 30 weeks
- Long Rank $p=0.003$



Conclusions

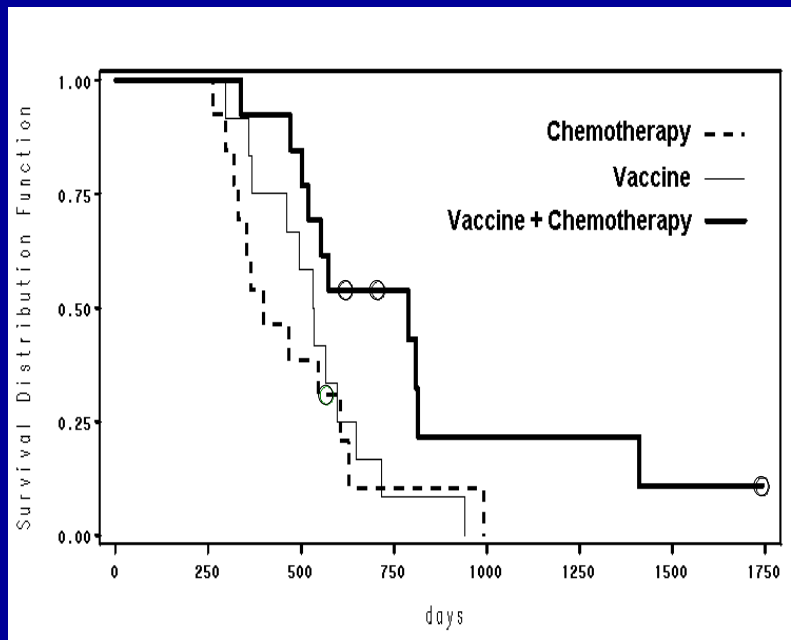
1. Tumor lysate pulsed Dendritic Cell vaccination is safe.
2. DC vaccination elicits peripheral T cell cytotoxicity.
3. T cells migrate into intracranial tumor.
4. DC vaccination prolongs survival in recurrent malignant glioma patients.

Survival of CTL responders

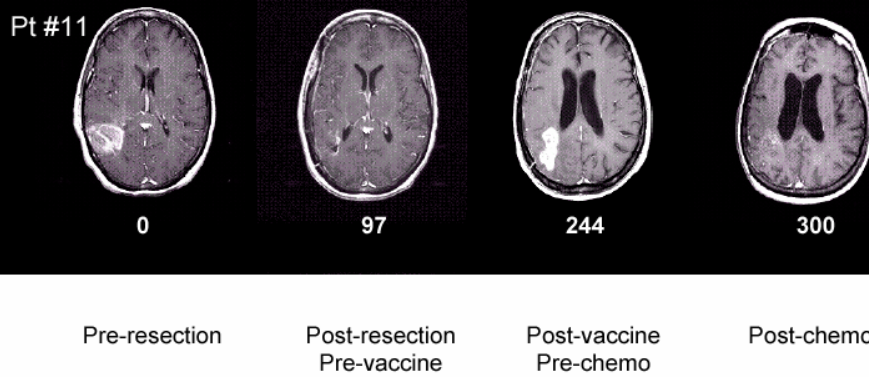


CTL response	Sample size	Median weeks	Statistical difference
No	10	54	
Yes	7	96	P=0.017

CTL response	Sample size	Median weeks	Statistical difference
No	19	67	
Yes	16	90	P=0.014

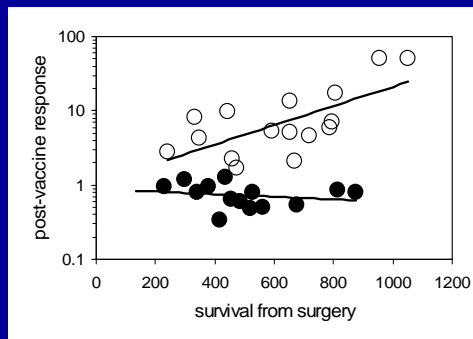


Patient 11 response to temozolomide



Biological Endpoint

- Level of immune response correlates highly with extension of survival



Antigens	HLA-restriction	Epitope Sequence	Detected Samples
MAGE-1	A1	EADPTGHSY	U-87, U-118, U-373, U-138, IR-801, IR-802, IR-803, Primary glioma cells
ATM-2 (Non-spliced)	A1	RSDSGQQARY	U-87, U-118, U-373, U-138, IR-802, Normal brain tissue, Primary glioma cells
(Spliced)	A1	Not shown	U-87, U-118, U-373, U-138, IR-802, Normal brain tissue, Primary glioma cells
gp100	A2	ITDQVPFSV	U-87, U-138, IR-801, IR-803 Normal brain tissue, Primary glioma cells
HER-2	A2	KIFGSLAFL	U-87, U-118, IR-801, IR-802, IR-803 Normal brain tissue, Primary glioma cells
TRP-2	A2	SVYDFVWL	Primary glioma cells
GALT-3	A2	TIMAFRWVT IMSRDLVPRI NLLKVNIII	B2-17, U-251, KINGS-1, T98-G, KALS-1, KNS60, KNS81, ONS76, Normal brain tissue,
ARF4L	A2	FLPHFQALHV ALHVVVIGL CTTFQVWDV	SF-126, B2-17, U-251, KINGS-1, T98-G, KALS-1, KNS60, KNS81, Normal brain tissue,
IL-13R α 2	A2	WLPFGFILI	U-251, SNB19, T98-G Normal brain tissue, Primary glioma cells
SART-1	A24	EYRGFTQDF	KNS-81, KALS-1, Normal brain tissue, Primary glioma cells
SART-3	A24	Not shown	Glioma cell lines, Normal brain tissue, Primary glioma cells

Table 1. CTL-recognizing TAAs in glioma cells

BSG TRIAL

Newly Diagnosed (N=16: GBM)

Progression Free Survival

6 Month PFS (95% CI): 93.8 (63.2, 99.1)

9 Month PFS (95% CI): 75.0 (46.3, 89.8)

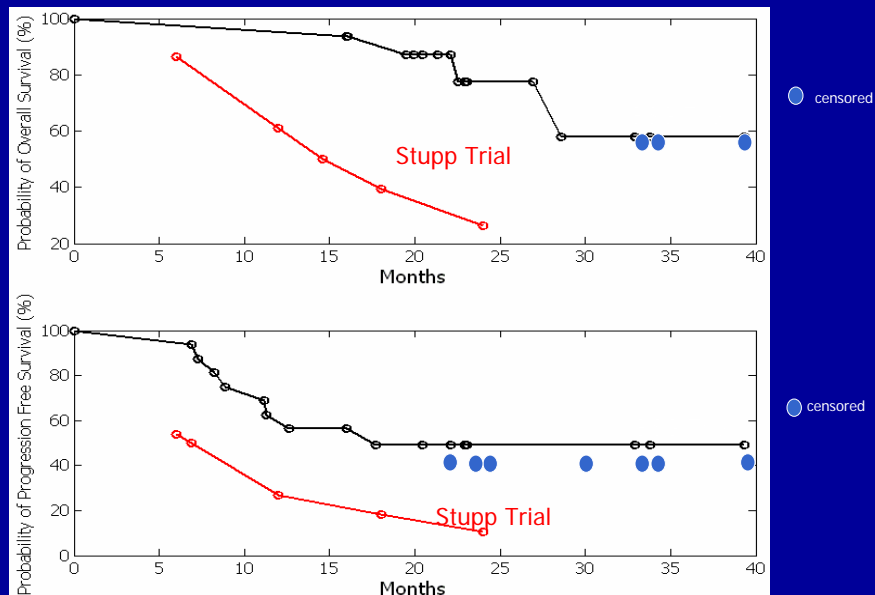
12 Month PFS (95% CI): 62.5 (34.9, 81.1)

Median PFS in Months: 17.7 (11.1, 39.3)

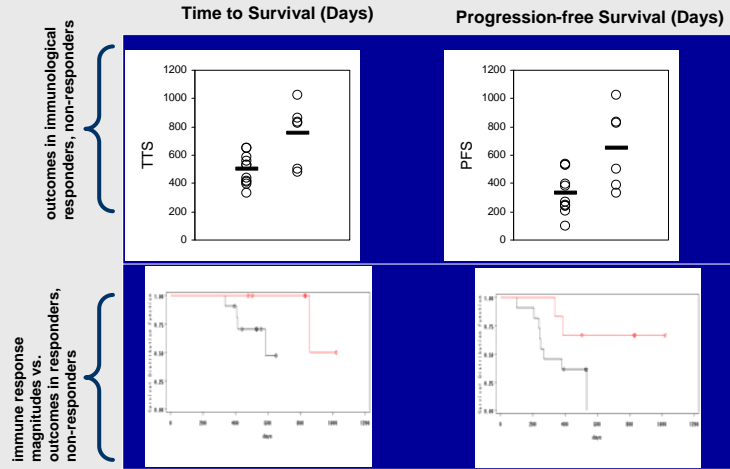
Overall Survival

Only 4 out of 16 individuals have died. Median OS has not been reached. However, the times to death for these individuals are 15.97, 19.52, 22.54, and 28.58 months (median=21.03) respectively from surgery.

Overall Survival and Progression Free Survival for BSG and Stupp Trial



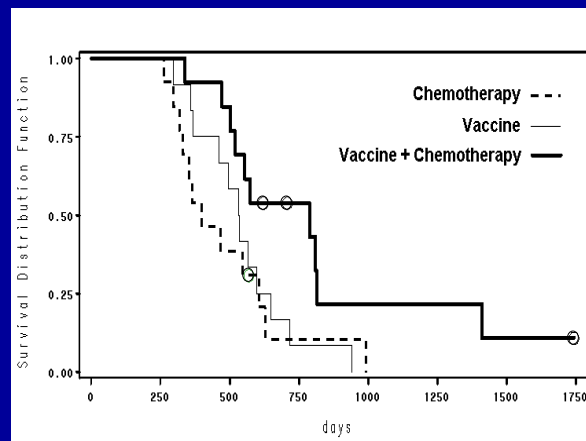
Immune Responses



35% response rate to date – lower than previous trials
 ≥1.5-fold increase IFN-g production after vaccination = “responder” (tetramer/FACS)
 27% non-responders (33% responders) deceased or lost to followup
 73% non-responders (33% responders) progressed
 255 d shorter time to survival (318 d shorter PFS) in nonresponders

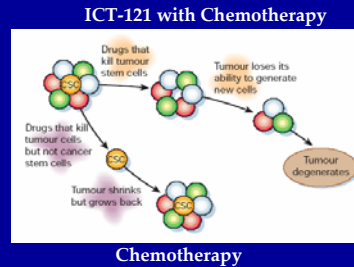
ImmunoCellular
 Immunocellular Therapeutics Ltd.

Vaccination and Chemotherapy



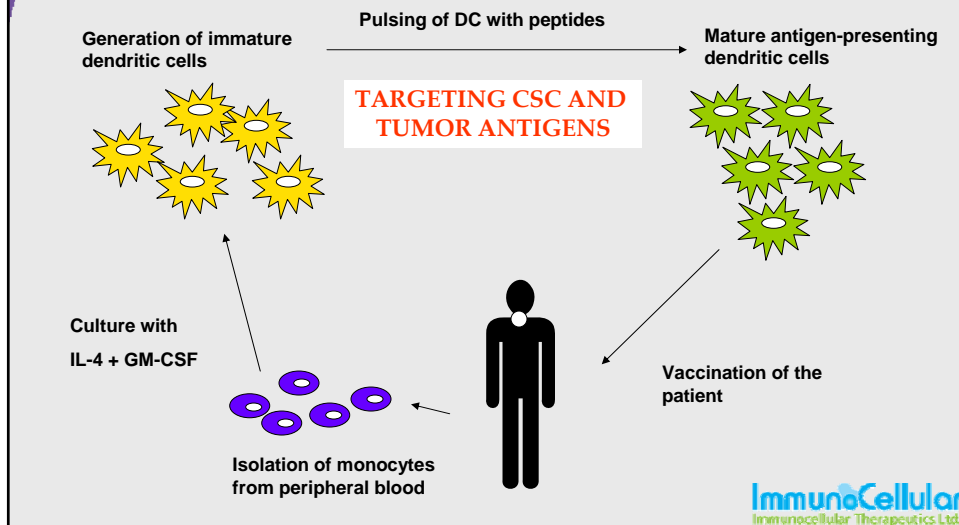
Targeting Cancer Stem Cells: A Paradigm Shift in Treatment

- Resistant to chemotherapy and radiation.
- Root of many tumors.
- Current therapies target proliferating and
Targeting CSCs may significantly delay or prevent disease recurrences
 tumor but not quiescent CSCs.

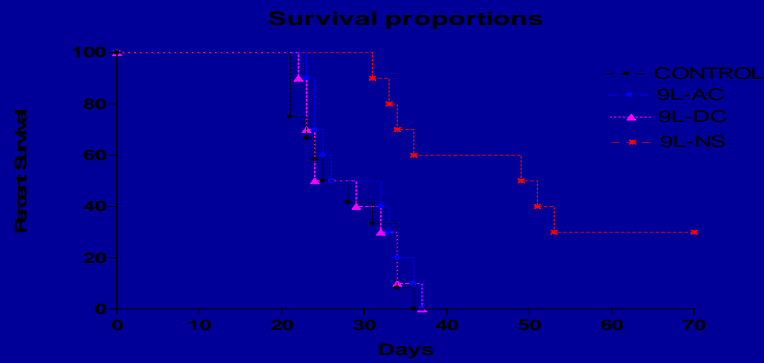


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Dendritic Cell Therapy for GBM



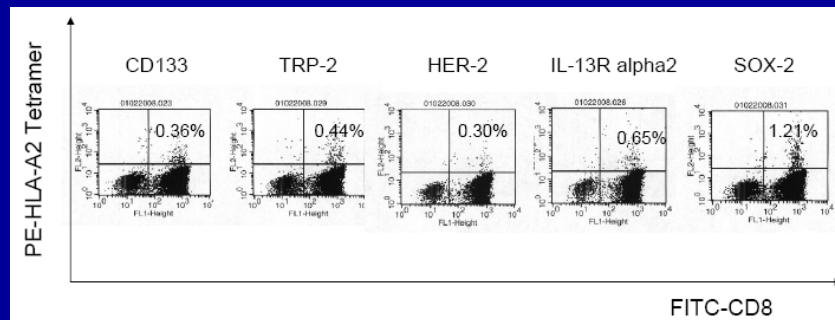
Survival of rats vaccinated against CSC or daughter cells



P=0.0015

Xu et al., Stem Cells, 2009

CSC primed T cells recognize Tumor-associated Antigens



Acknowledgements

Past

Moneeb Ehtesham
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Aruna Nalla
Jim Ji
Minlin Xu
Mia Mazer
HongQiang Wang
Xiangpeng Yuan



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Evan Snyder
Keith Black
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San Phuphanich
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Jangwon Lee
Maria Castro
Pedro Lowenstein
Daniel Farkas
Bindu Konda

