Translating Brain Cancer Immunotherapy to Clinical Practice

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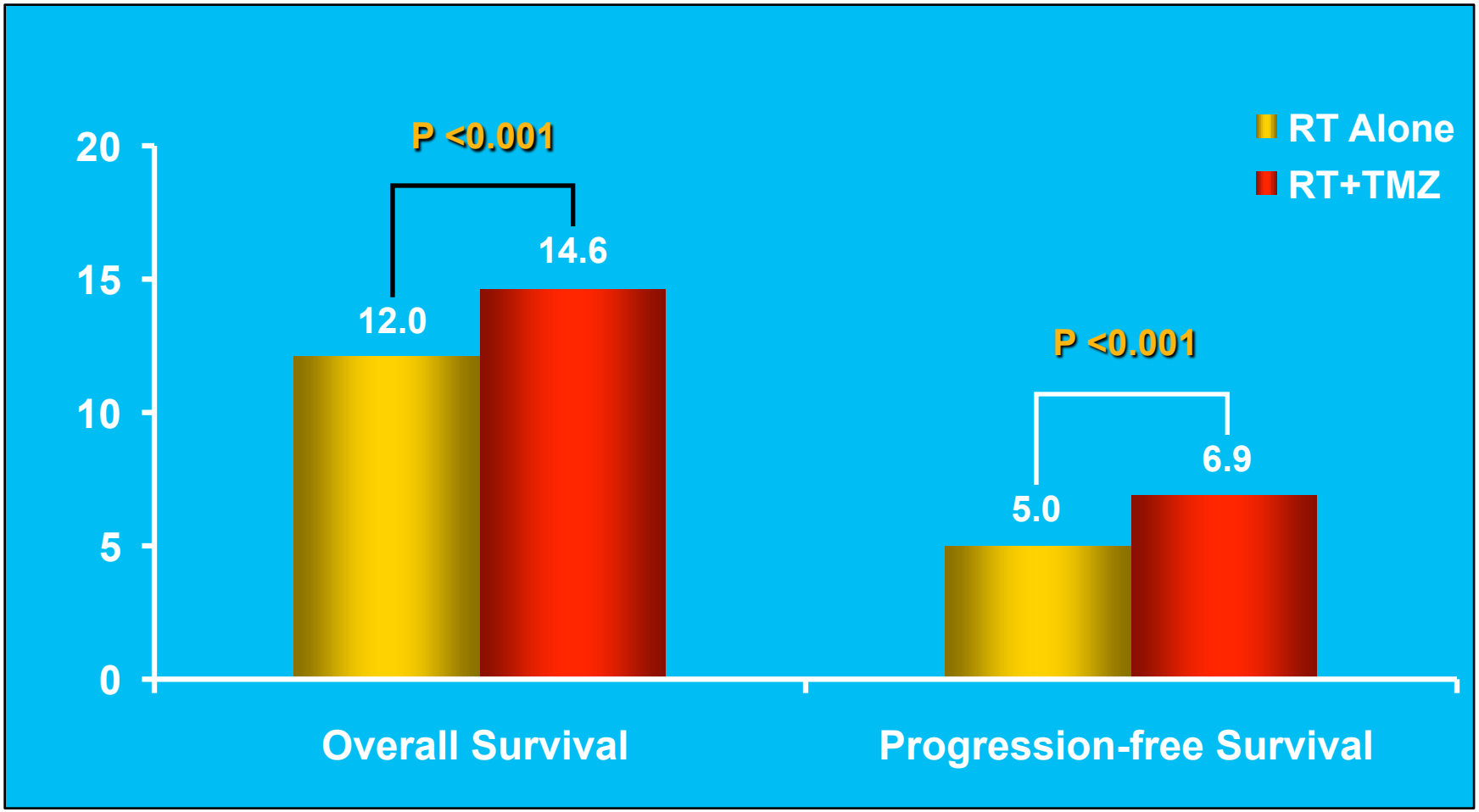
AANS/CNS Evidence-Based Guidelines for the Treatment of Newly Diagnosed Glioblastoma

- Surgery
- Radiation Therapy
- Chemotherapy

Radiotherapy +Temozolomide for Glioblastoma: Current SOC



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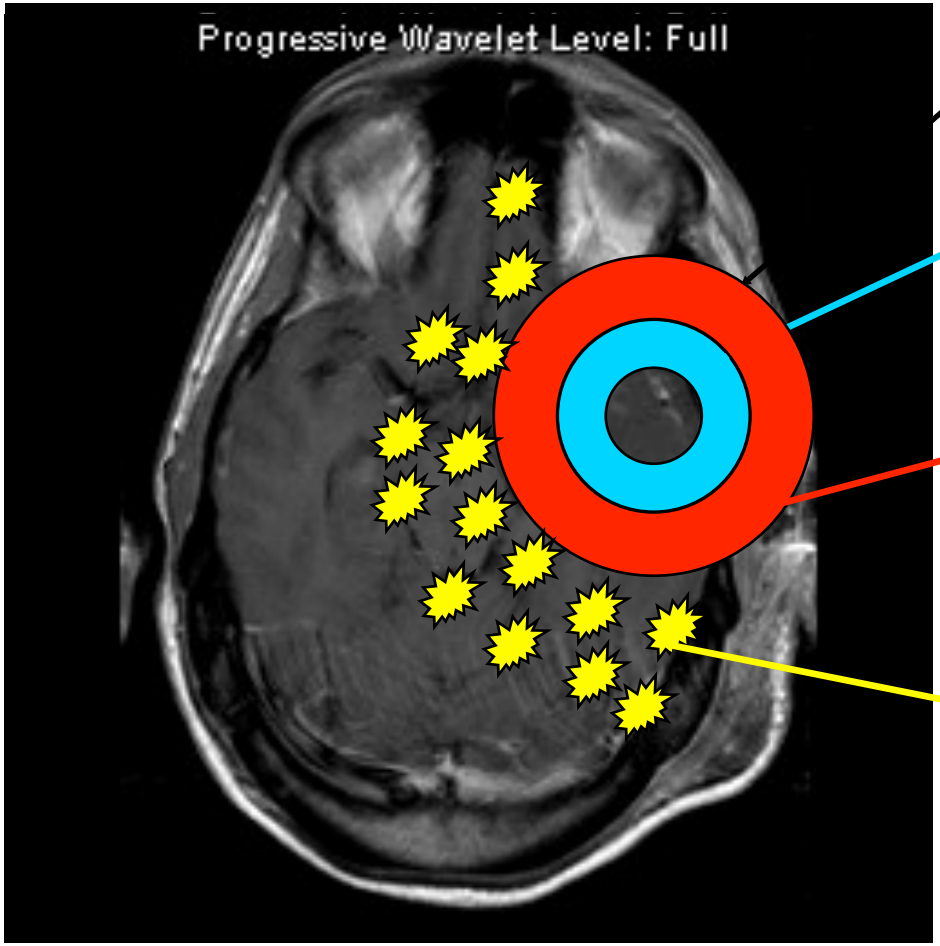
Stupp R, et al. ***N Engl J Med.*** 2005; 352:987-996.

Immunotherapy potentially can target infiltrating glioma cells



Surgery

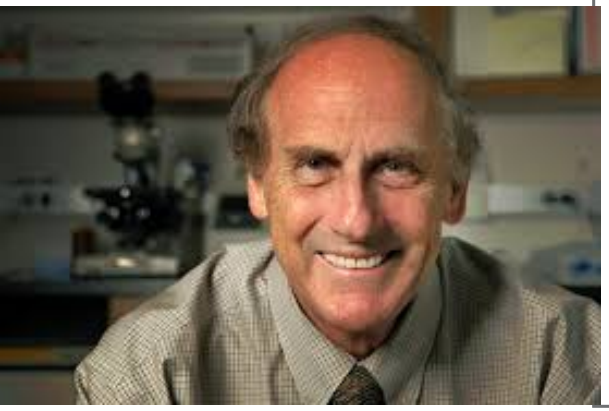
Radiation therapy

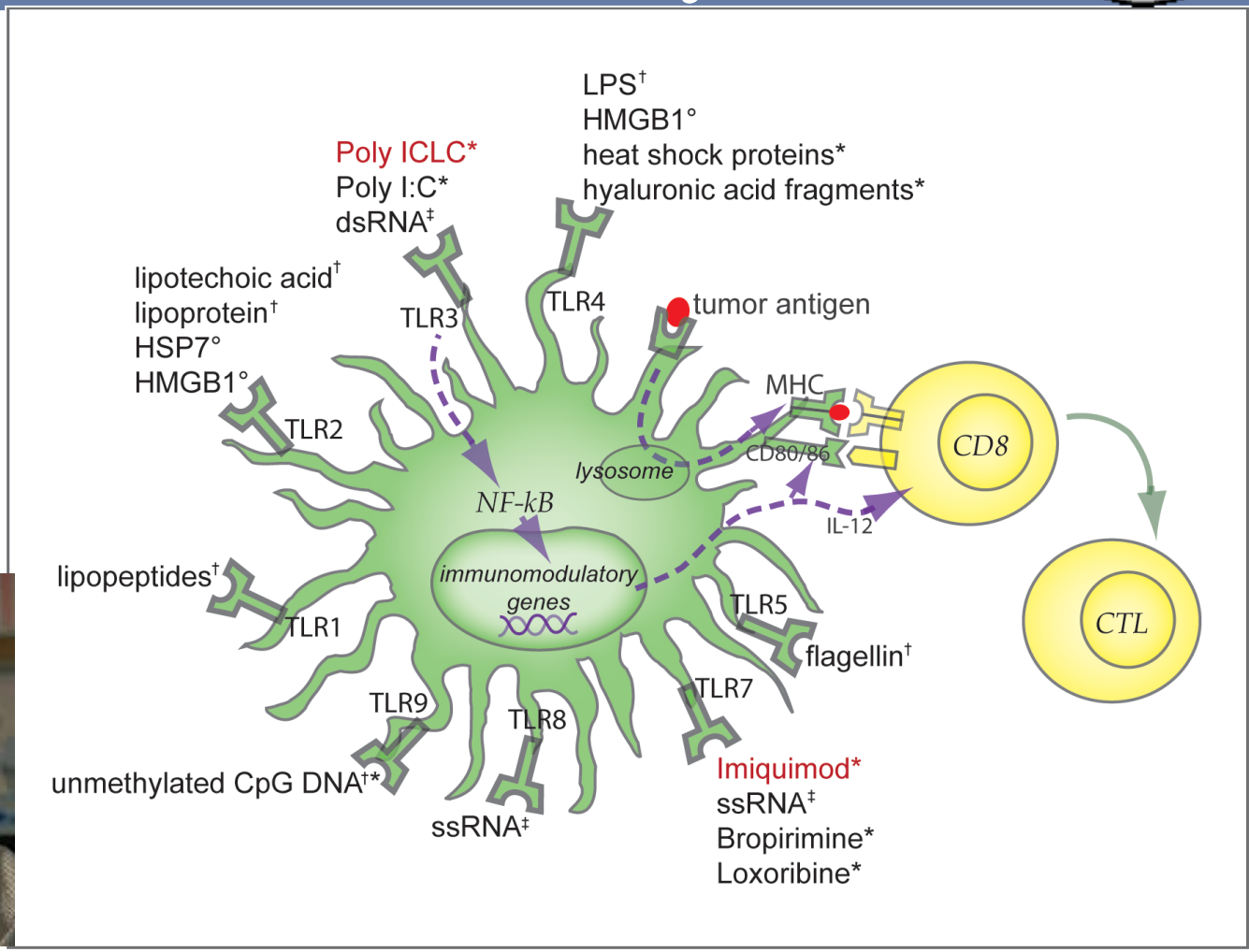
Chemotherapy

Immunotherapy

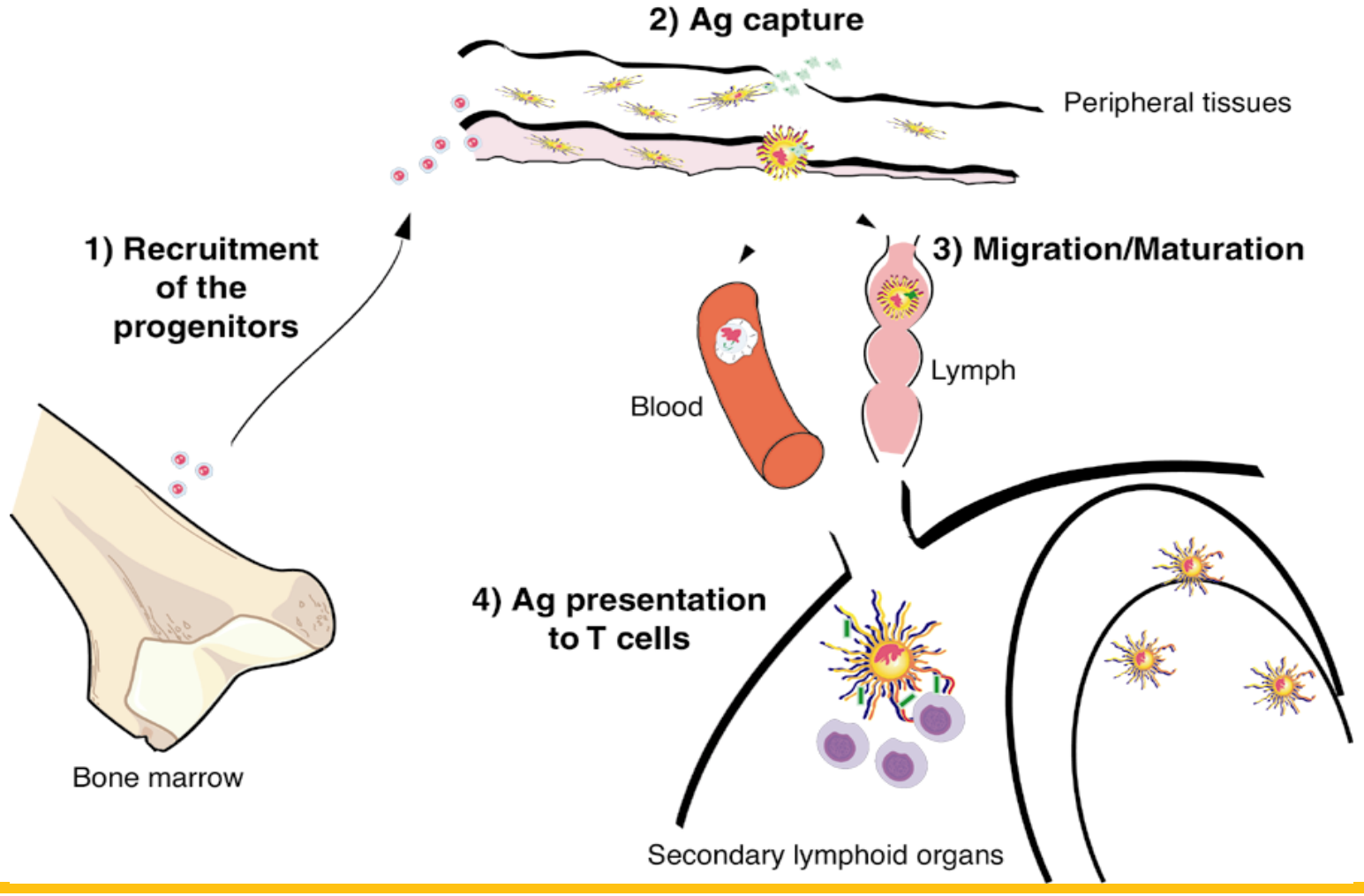
Dendritic Cells (DC): master regulators of immunity

Ralph Steinman, M.D.
2011 Nobel Prize





Dendritic Cells: "Professional" Antigen-presenting Cells (APC)



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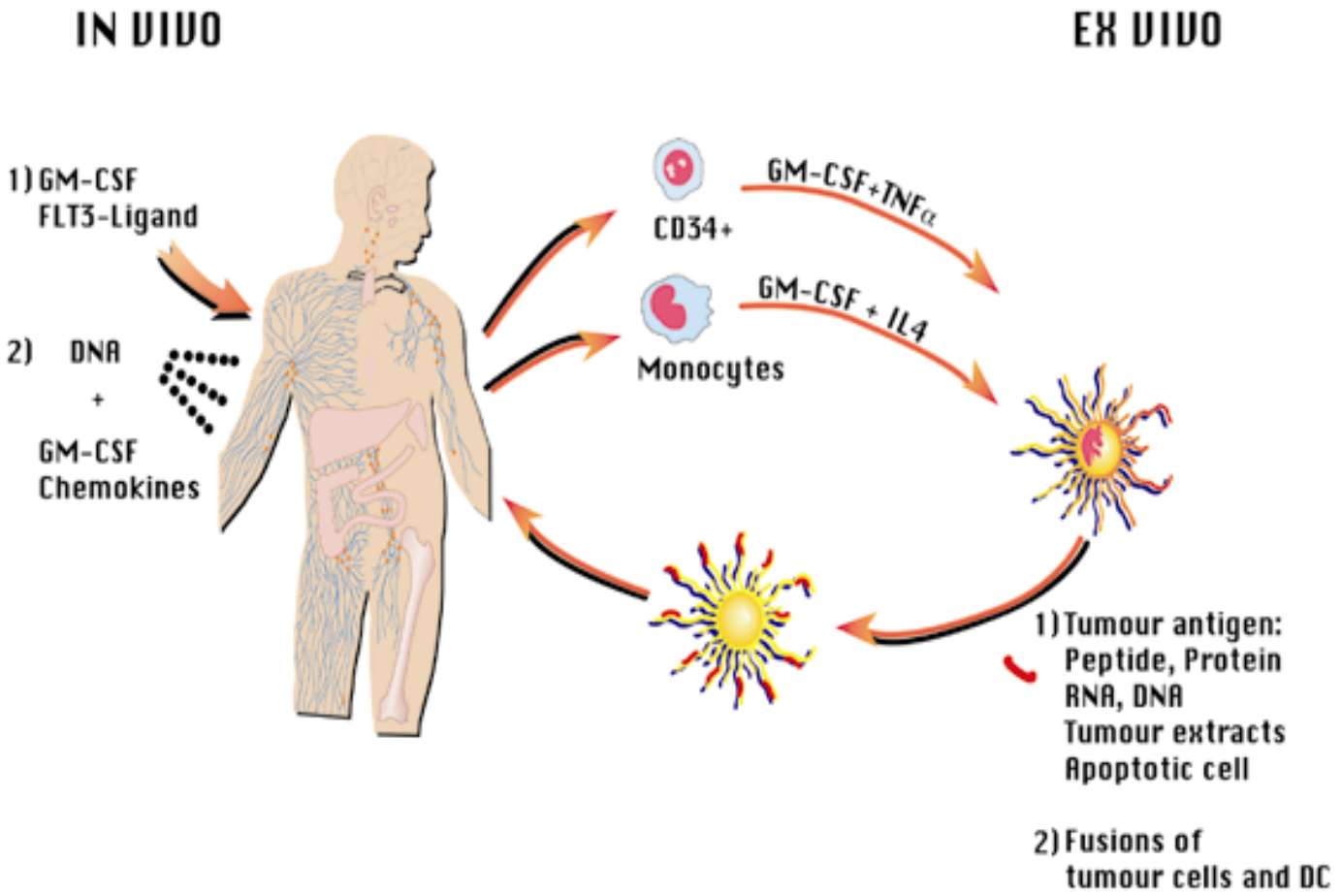
Liau LM et al., ***Brain Tumor Immunotherapy*** (Humana Press, 2001)

DC-based Brain Tumor Vaccines

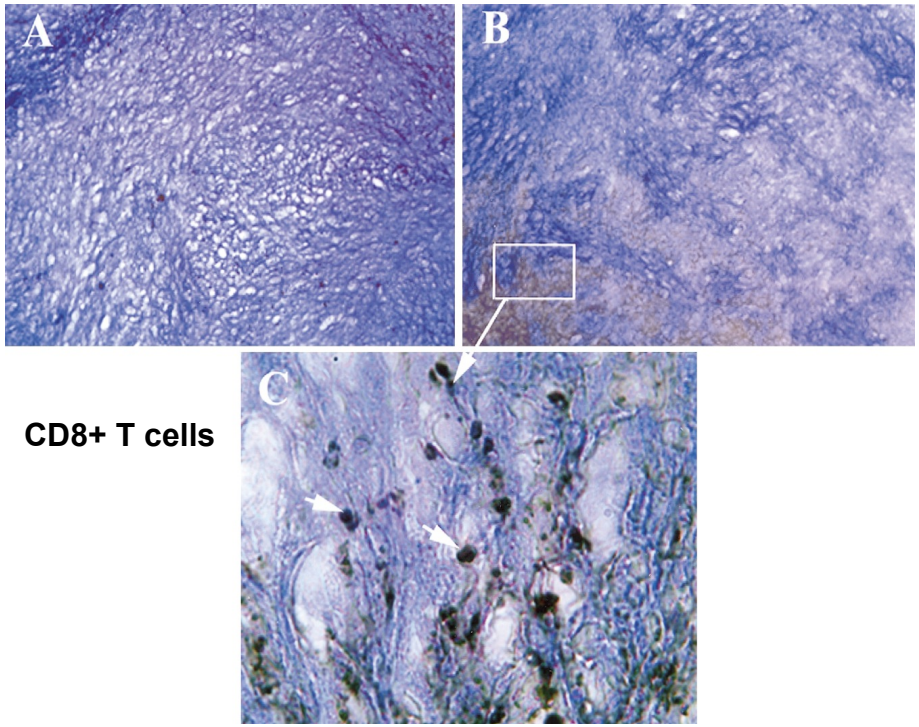


from Liau LM et al., ***Brain Tumor Immunotherapy*** (Humana Press, 2001)

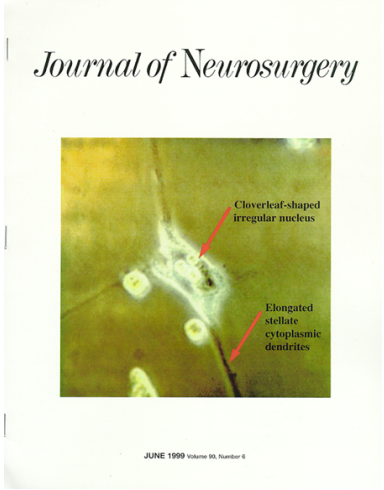
Treatment of intracranial gliomas with dendritic cells pulsed with autologous tumor antigens led to T-cell infiltration into brain tumors and prolonged survival *in vivo*

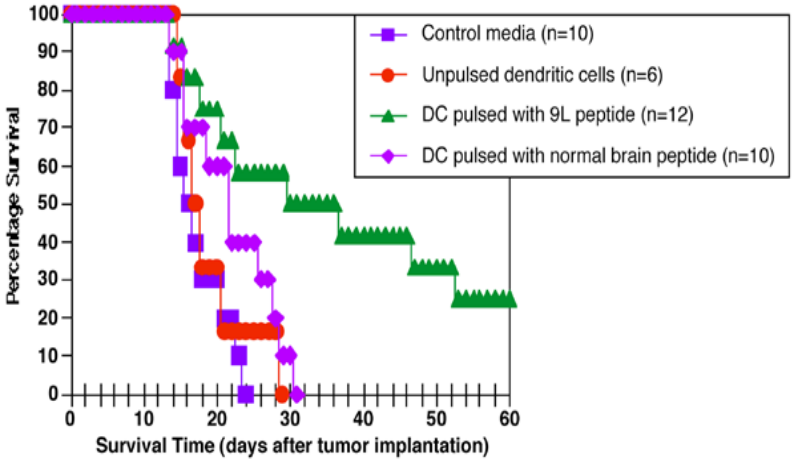
Control

DC treated



CD8+ T cells





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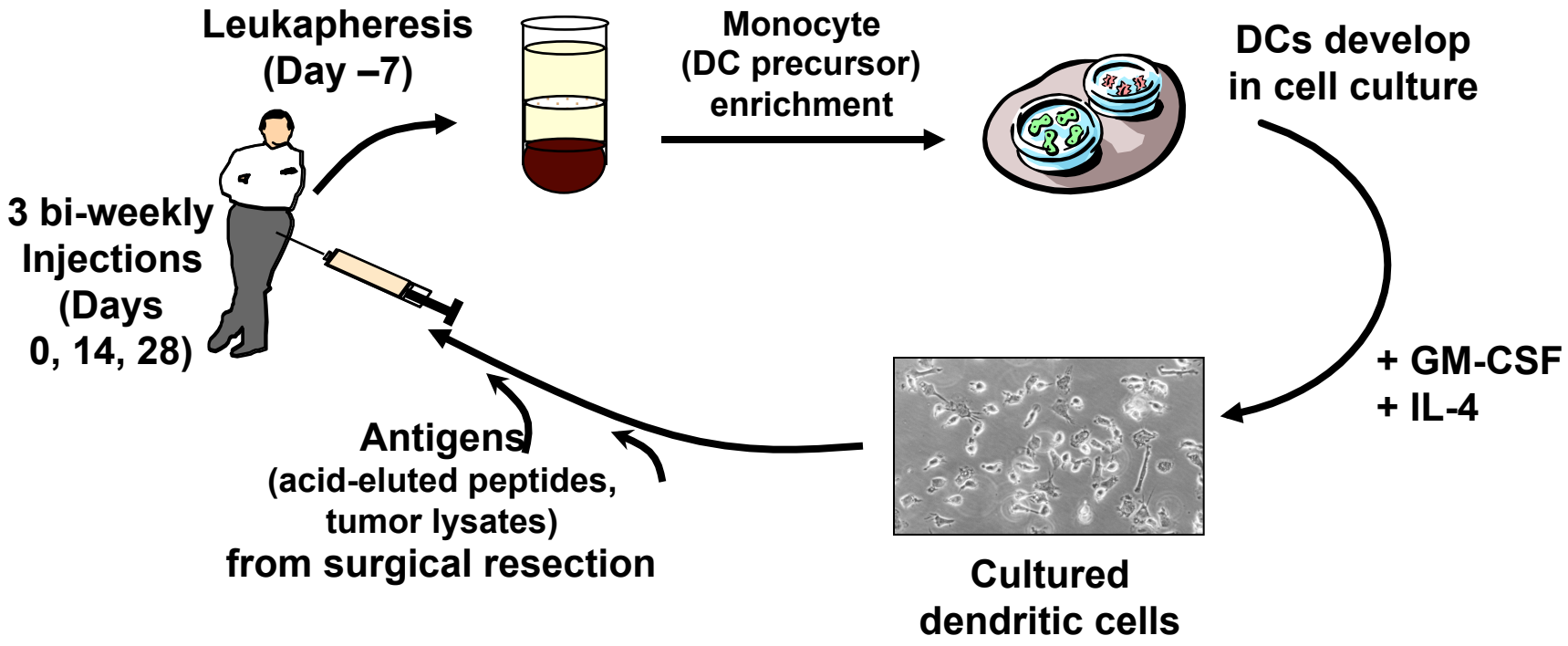
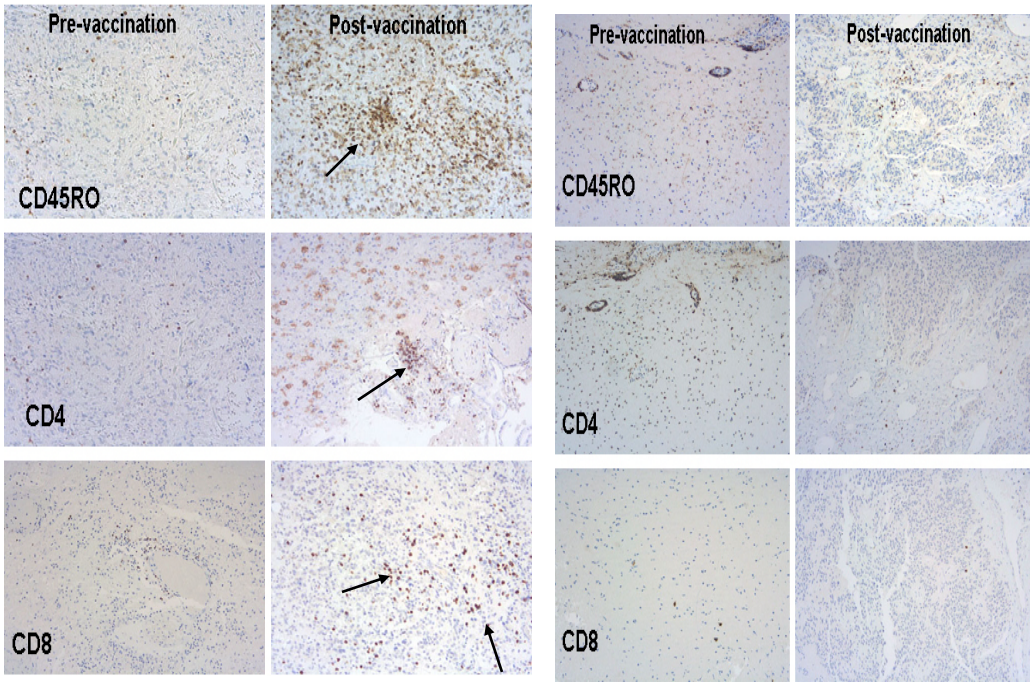
Liau LM et al, *J Neurosurg,* 1999

Phase I Clinical Trials: Preparation of Autologous DCs



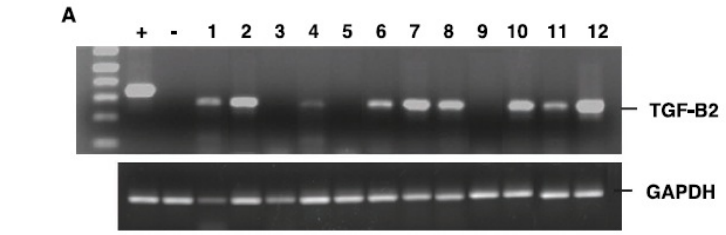
DC vaccination in glioblastoma patients induces systemic and intracranial T-cell responses modulated by the local CNS brain tumor microenvironment

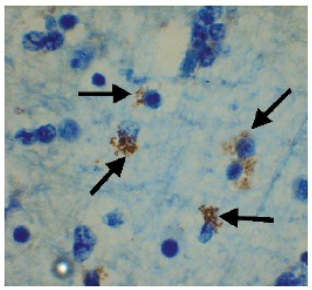


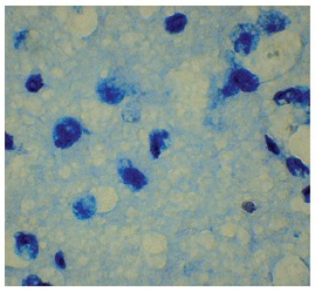
Patient #1: OS = 30.2 mos

Patient #2: OS = 11.4 mos

Increased $CD8^+$ T-cell infiltration correlated with <u>increased</u> survival







Patient #12: OS = 9.3 mos.

Patient #5: OS > 120 mos.

Increased TGF-β expression correlated with <u>decreased</u> survival

Liau LM et al., *Clin Cancer Res,* 2005.

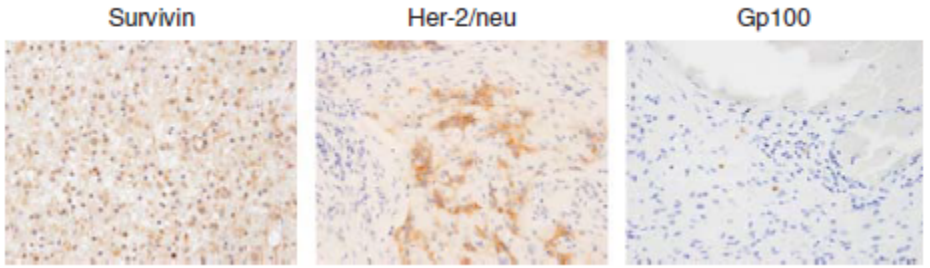
Comparison of DC-GAA vs. DC-tumor lysate vaccination in malignant glioma patients

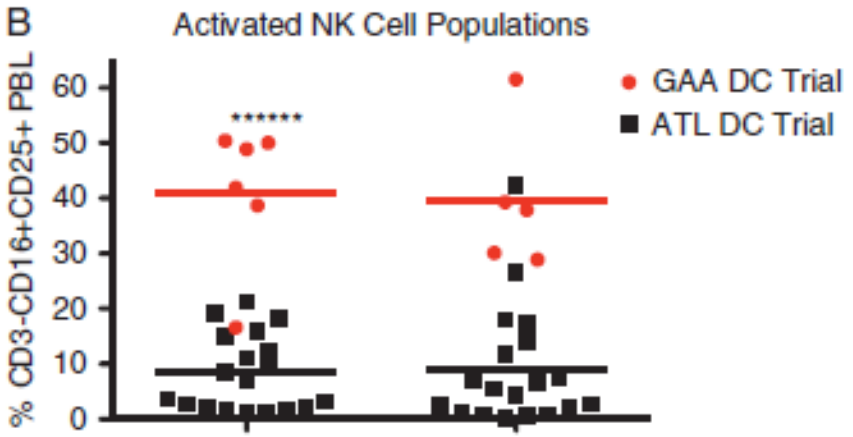
TABLE 1. Demographic and Baseline Clinical Characteristics

Characteristic	ATL-DC (N = 28)	GAA-DC (N = 6)
Age (y)	49	44
Sex		
Male	20	6
Female	8	0
KPS (at DC vaccination)	90	80
Tumor pathology		
Glioblastoma (WHO grade IV)	23 (82.1)	4 (66)
Anaplastic glioma (WHO grade III)	5 (17.9)	2 (33)
Tumor characteristics		
IDH1 (% mutated)	17	50
Time to Treatment* (mo)	4.9 ± 4.1	4.4 ± 1.8
Survival characteristics		
OS (mo)	34.4	14.5
PFS (mo)	18.1	9.6

*Time interval from the date of surgery until date of first DC vaccination in months ± SD.

KPS indicates Karnofsky performance scale; PFS, progression free survival.





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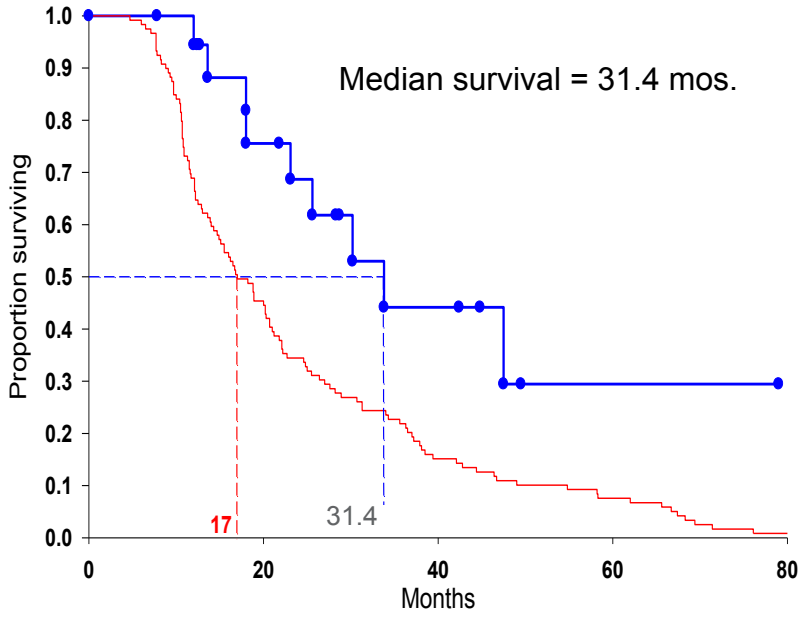
Prins RM & Liau LM, ***J Immunotherapy,*** 2013

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

	% alive at		
Patient population	**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	



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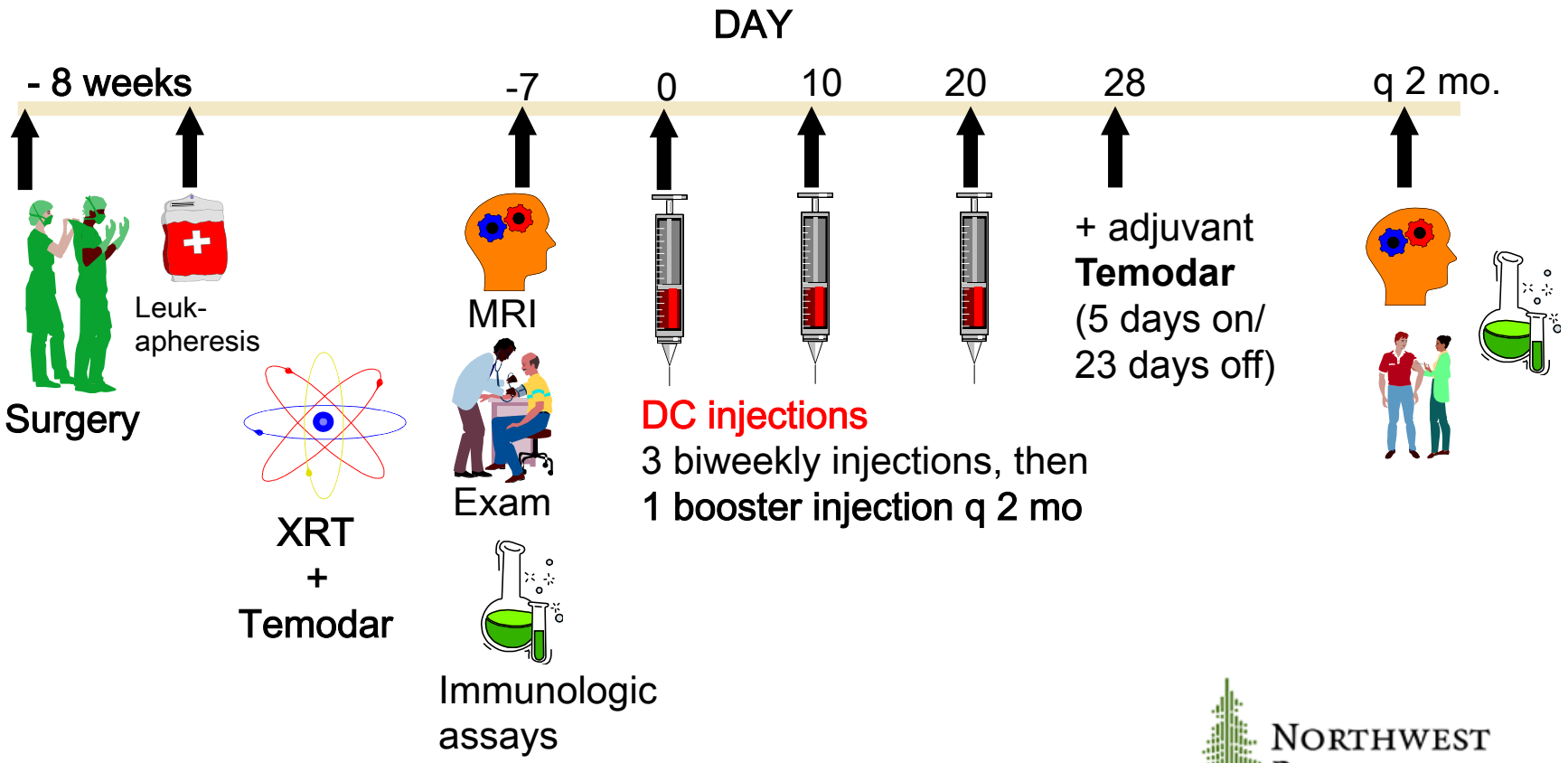
Prins RM et al, ***Clin Cancer Res,*** 2011

Phase III multi-center, randomized clinical trial of DCVax-Brain™ for newly diagnosed GBM (n=312)



NORTHWEST BIOTHERAPEUTICS

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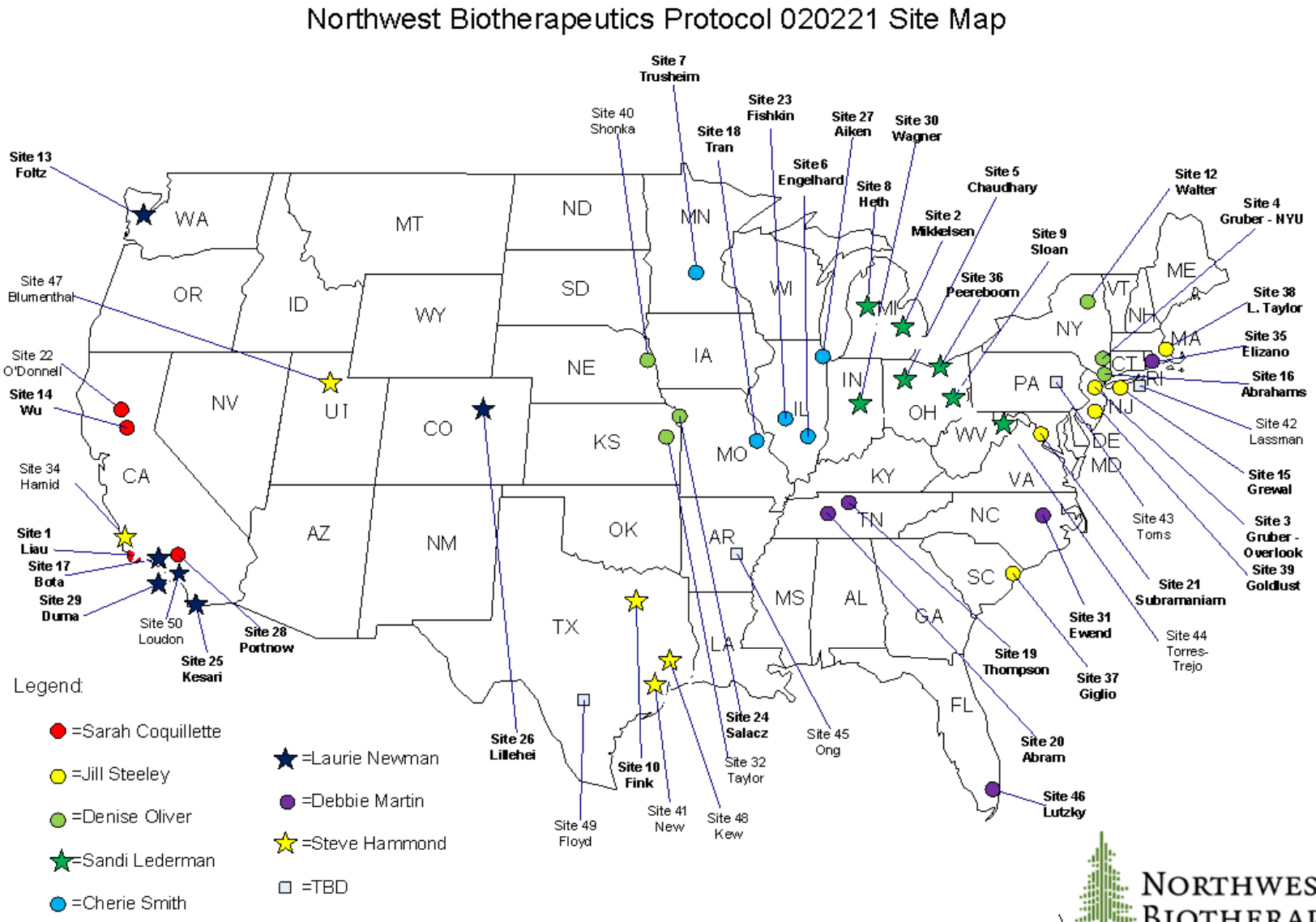
Phase III multi-center, randomized clinical trial of DCVax-Brain™ for newly diagnosed GBM (n=312)



NORTHWEST BIOTHERAPEUTICS

Enhancing effects of tumor vaccines with immune modulators

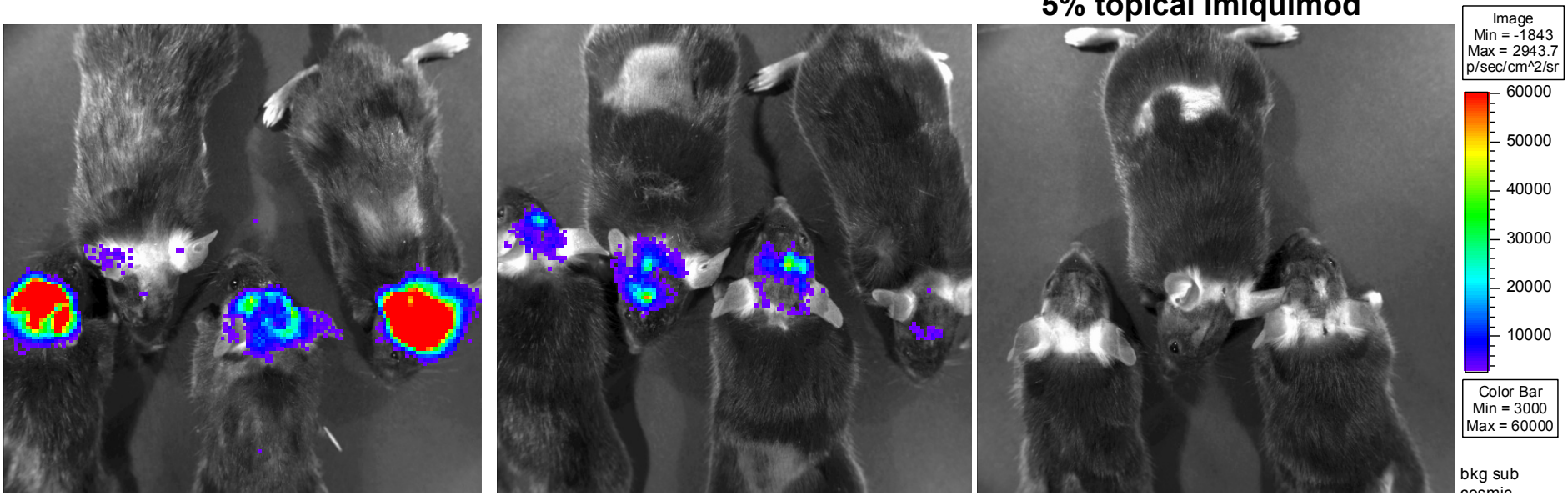
- TLR-7 agonist, imiquimod
- TLR-3 agonist, poly-ICLC
- CTLA-4 antibody, ipilimumab
- PD-1 antibody, nivolumab

TLR-7 agonist, Imiquimod, promotes anti-tumor immunity to CNS tumors

NP pulsed DC

gp100/TRP2-pulsed DC

gp100/TRP2-pulsed DC + 5% topical Imiquimod



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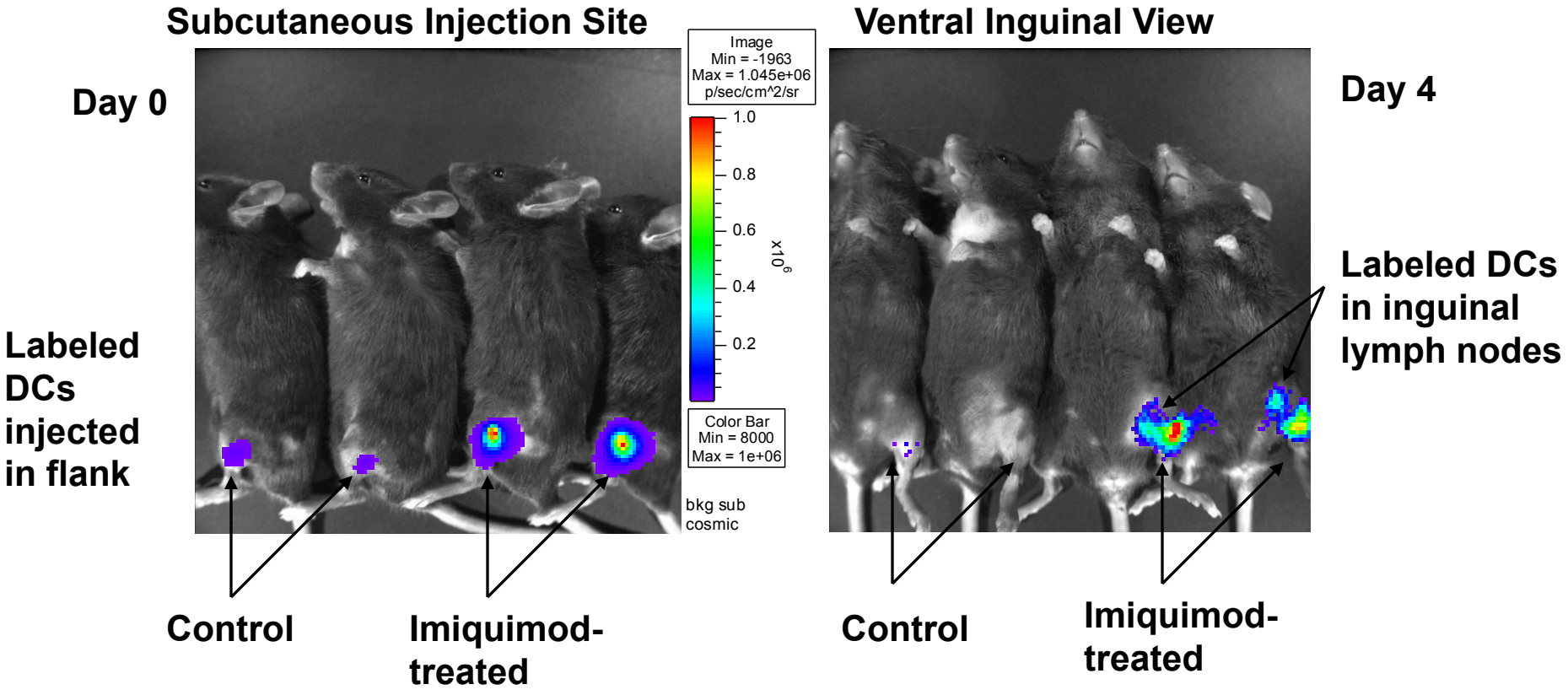
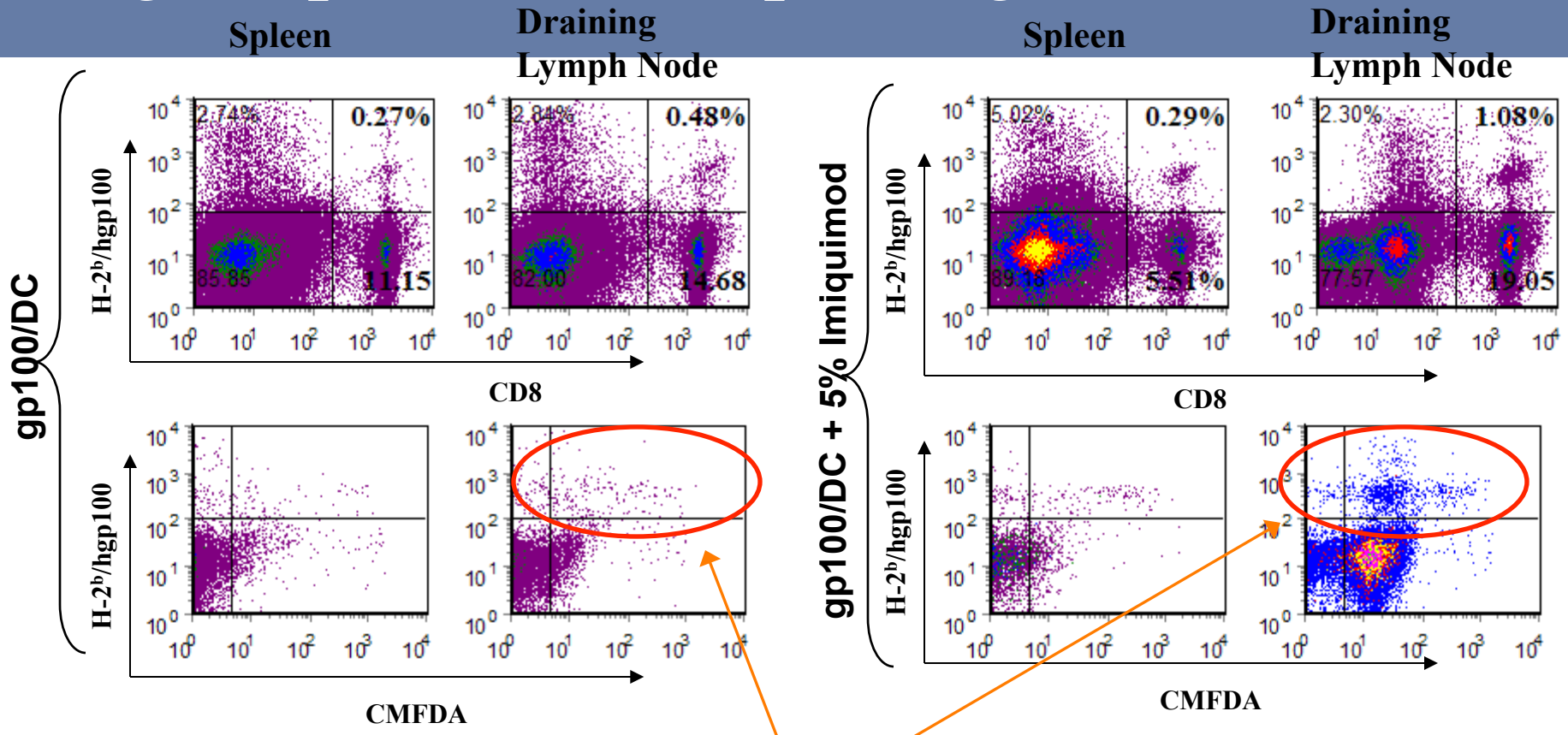
Prins RM et al., *Journal of Immunology,* 2006.

TLR-7 agonist, Imiquimod, enhances dendritic cell survival and migration



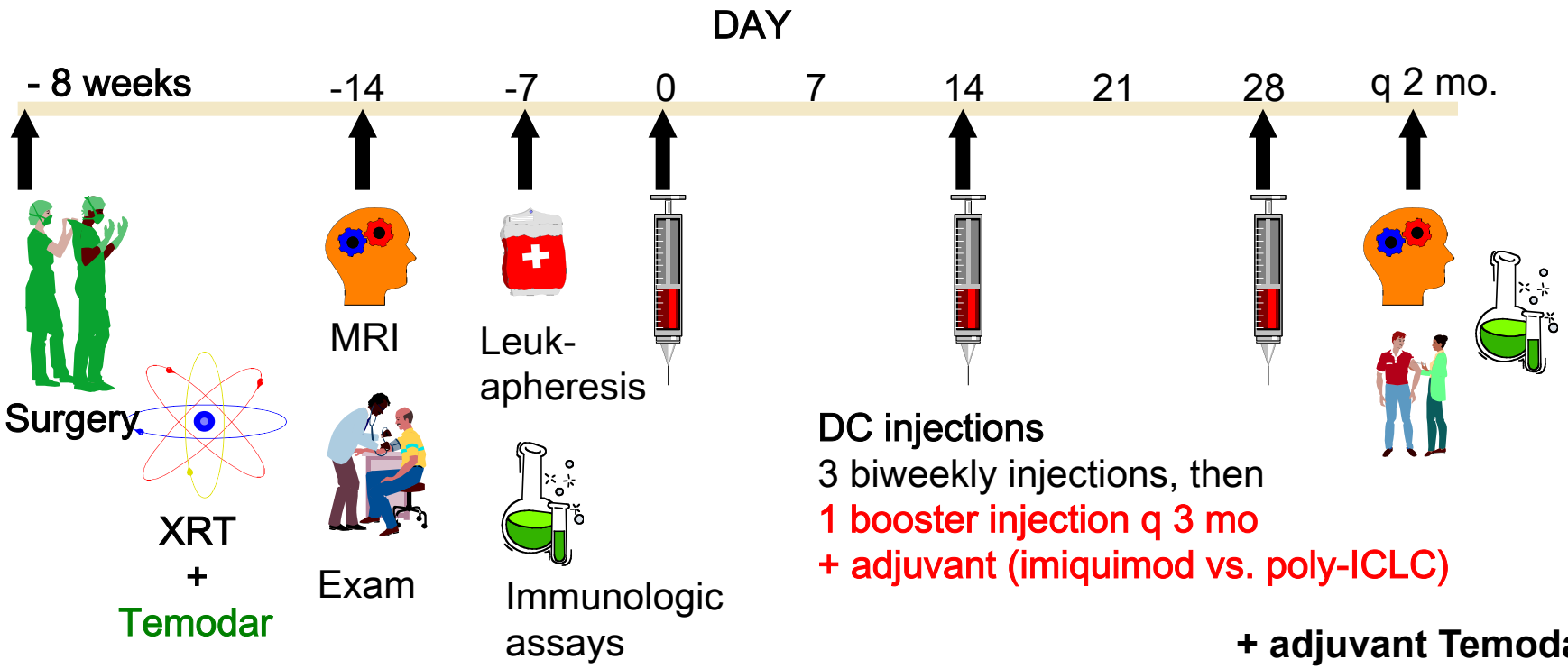
Prins RM et al., *Journal of Immunology,* 2006.

TLR-7 agonist, Imiquimod, promotes tumor antigen-specific T-cell priming



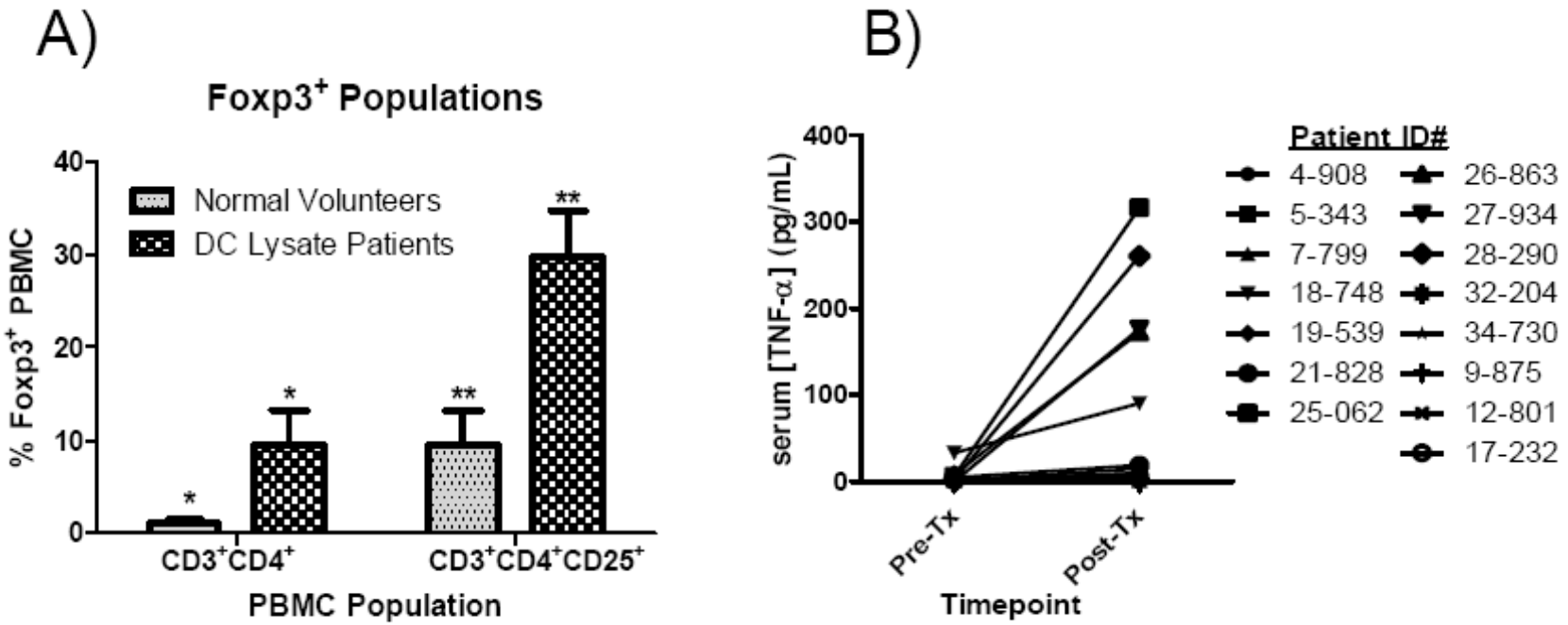
Increased accumulation and proliferation of gp100-specific T cells in the draining lympmph nodes after DC vaccination + 5% imiquimod treatment

Phase II clinical trial of autologous tumor lysate-pulsed DC + immune adjuvants (FDA IND 11053, 2003)



NIH RO1-CA112358

Immune monitoring data



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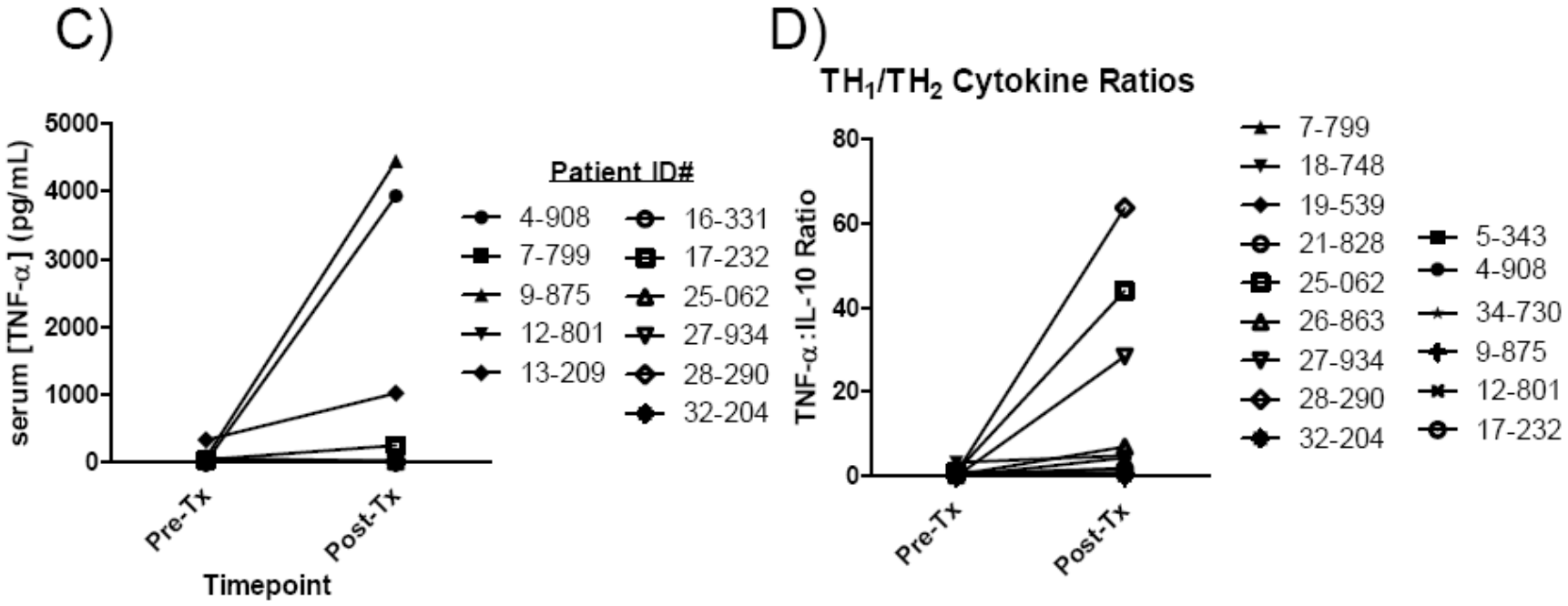
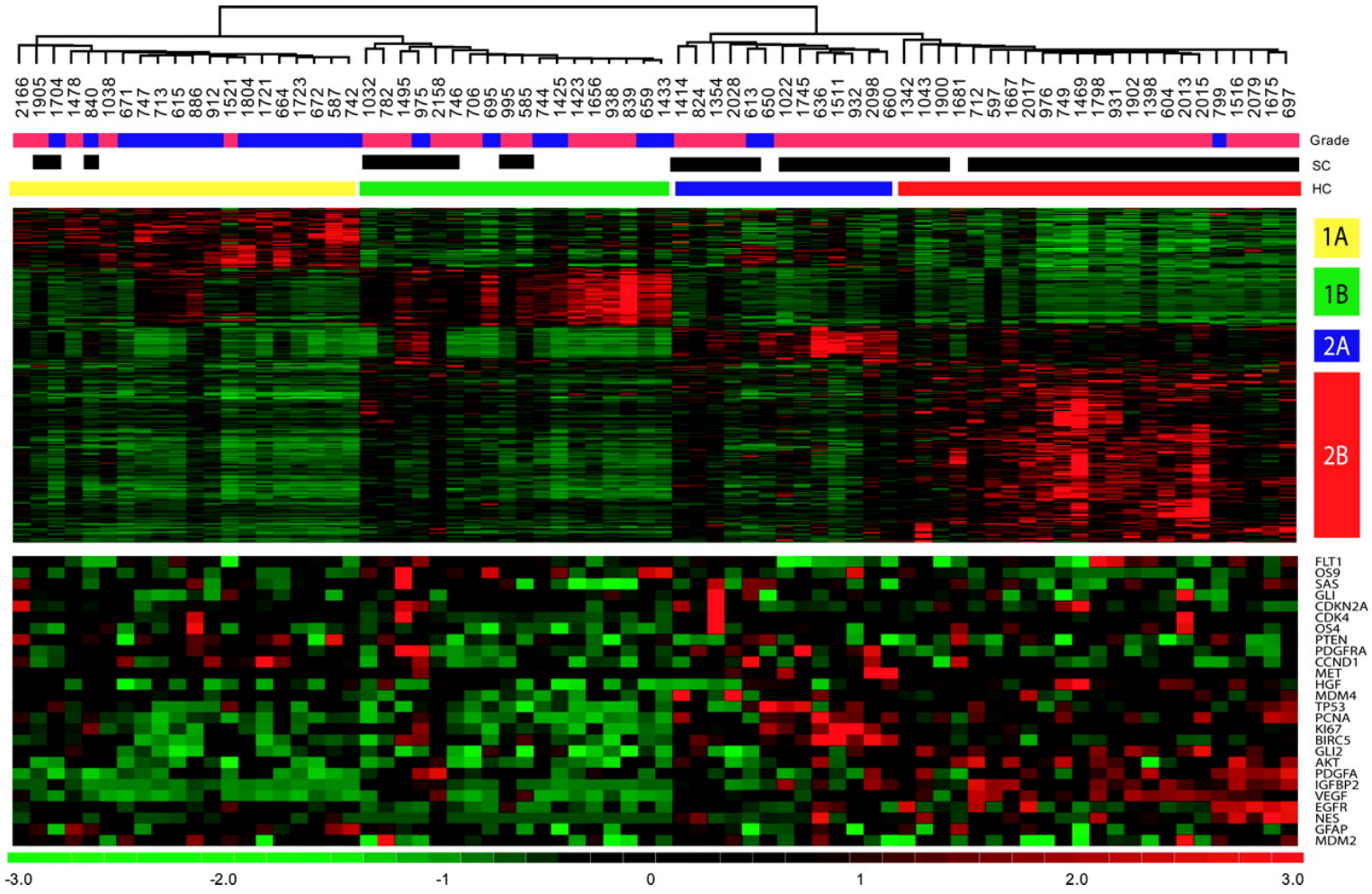


Gene expression profile of glioblastoma predicts survival



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Freije W A et al. ***Cancer Res,*** 2004

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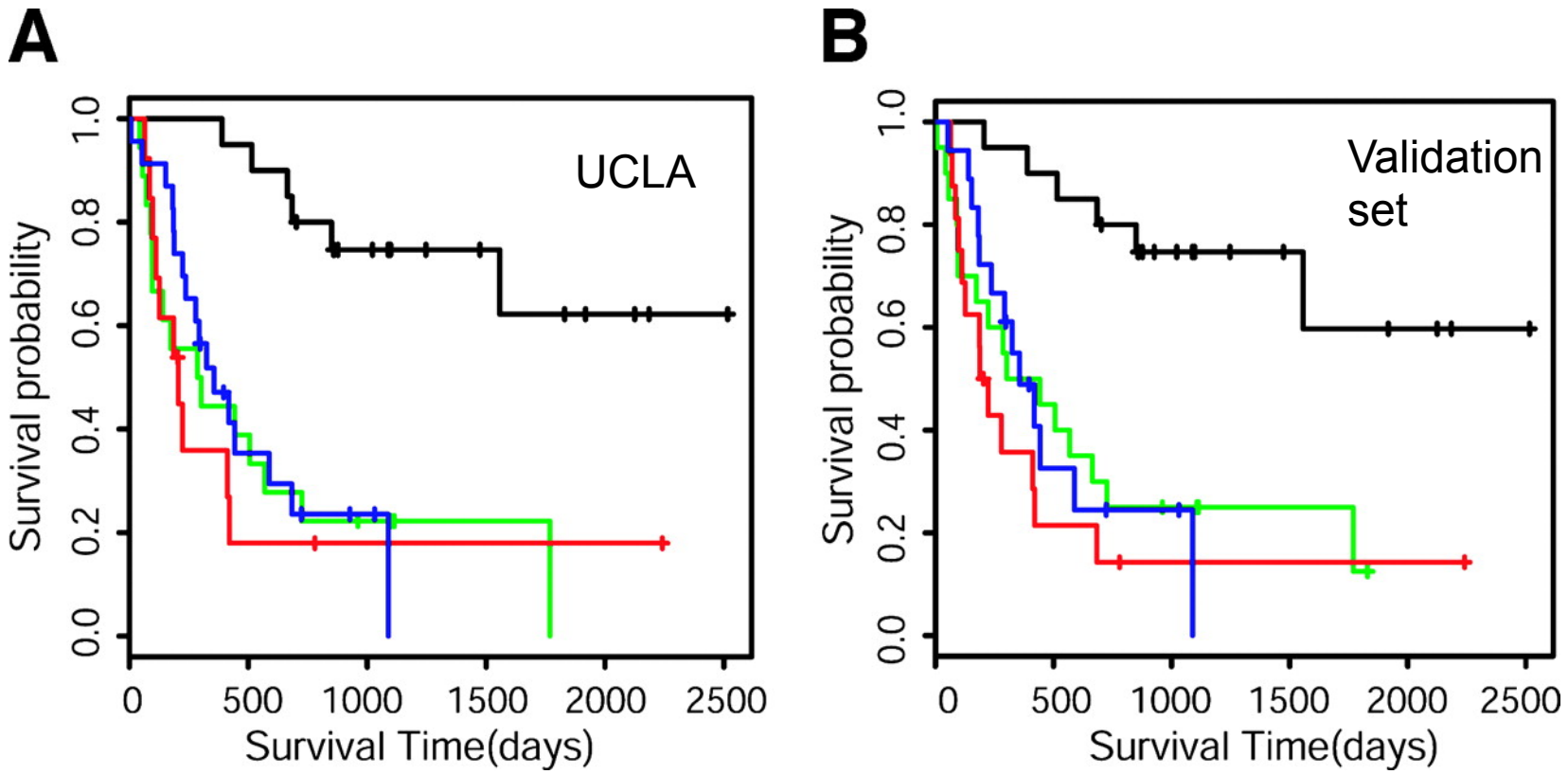
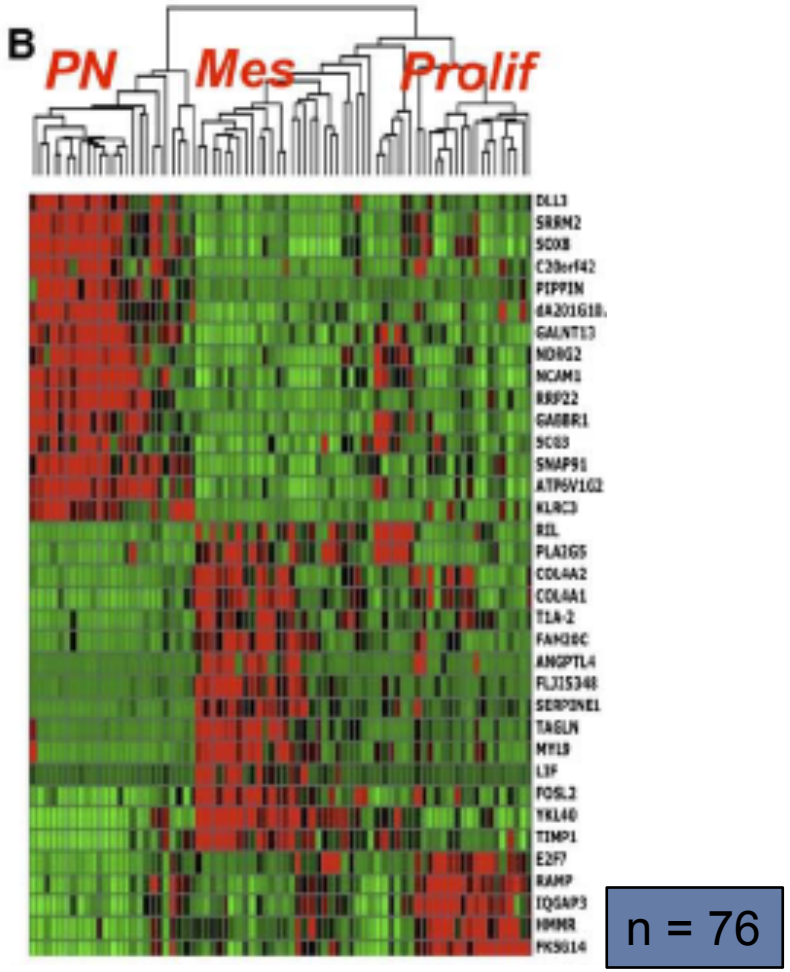
n = 74

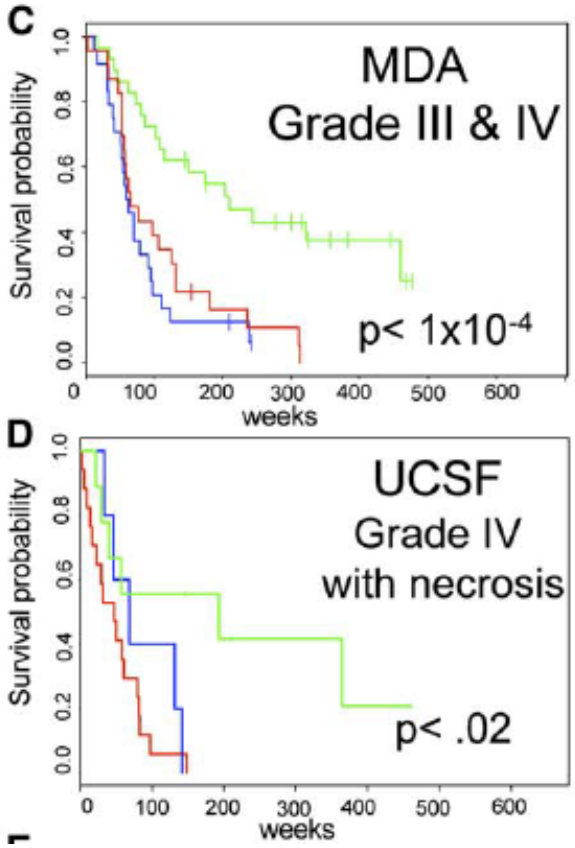
Survival analysis of glioblastomas grouped by gene expression



Freije W A et al., ***Cancer Res,*** 2004

Molecular subclasses of high-grade glioma predict prognosis





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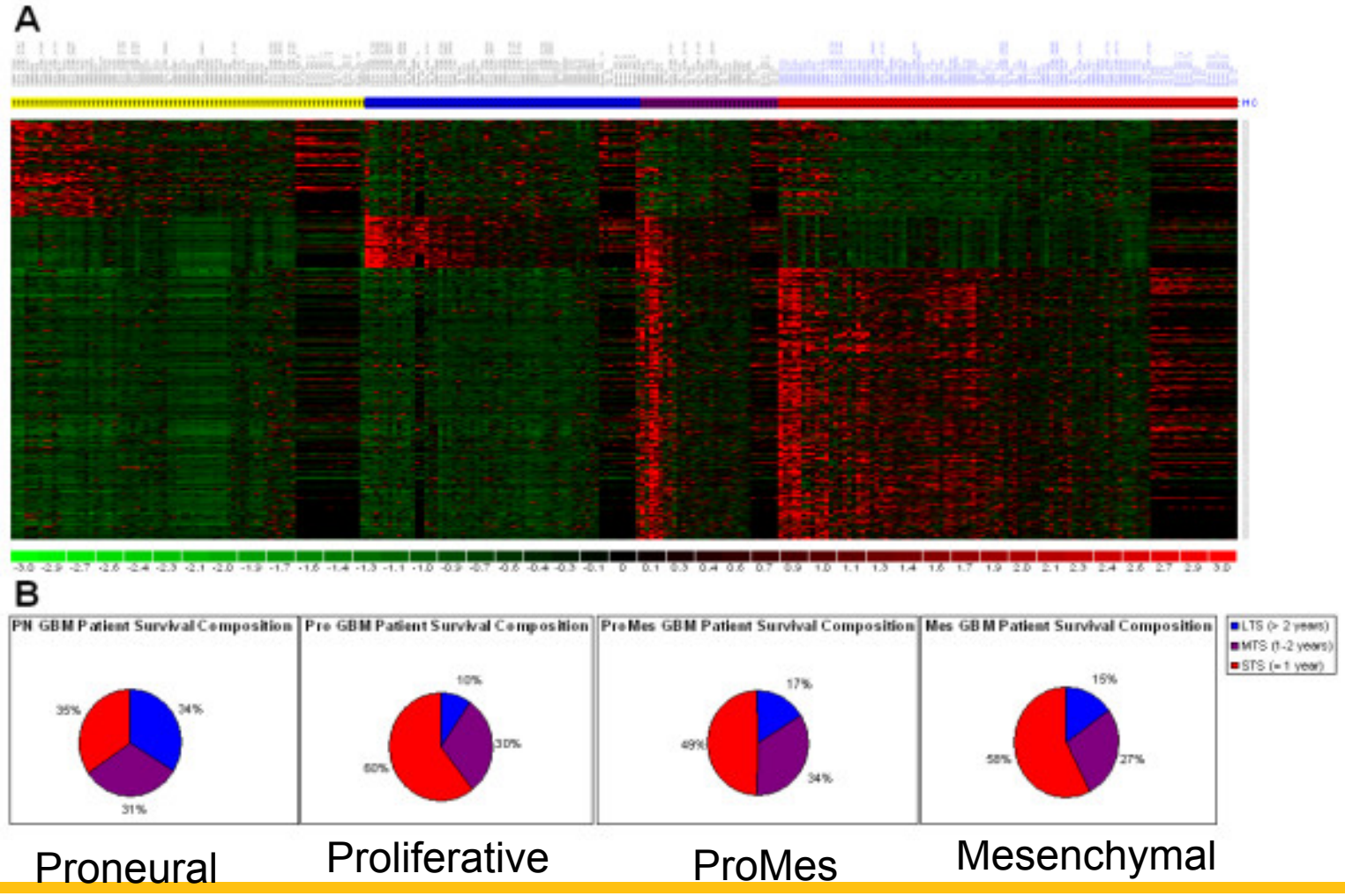
Phillips HS et al, ***Cancer Cell***, 2006

Gene expression profile related to survival



Proneural | Proliferative | ProMes | Mesenchymal

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Lee Y et al, ***BMC Medical Genomics,*** 2009

n=267

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

	% alive at		
Patient population	**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
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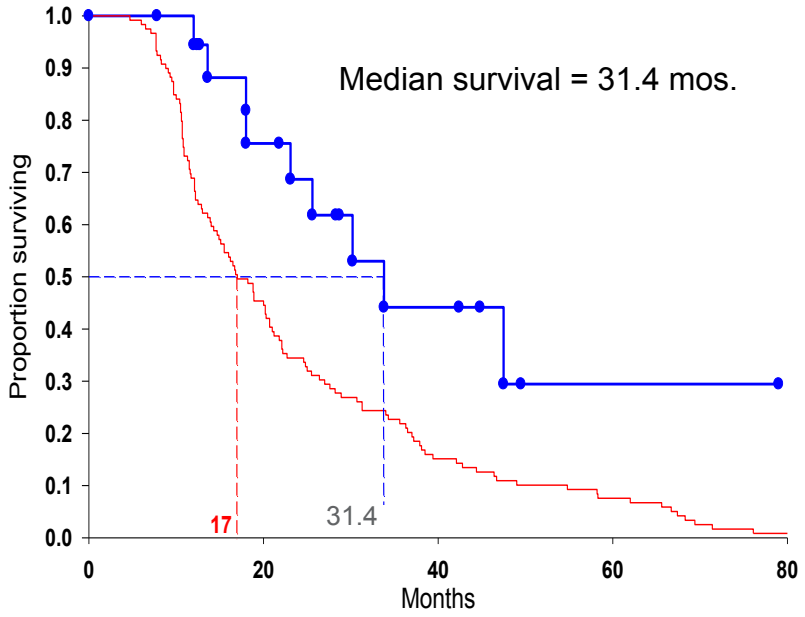

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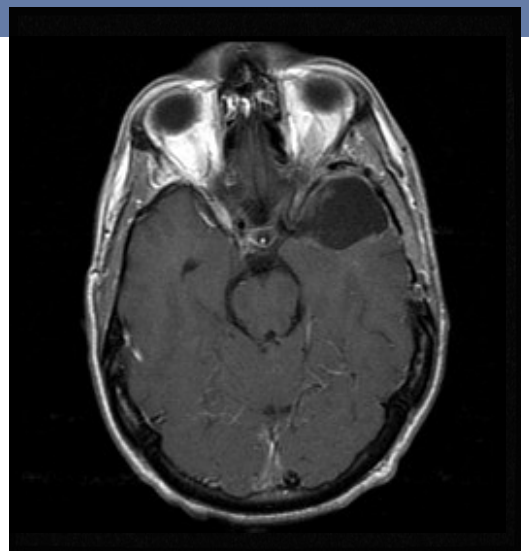
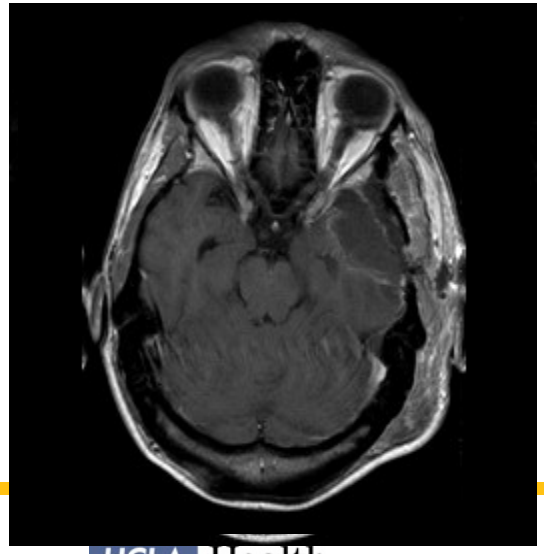
Prins RM et al, ***Clin Cancer Res,*** 2011

Tale of Two Tumors





XRT (60 Gy)
+
Temozolomide

FDA IND #11053 (2003)

Phase I trial of tumor lysate-pulsed DC vaccination for GBM

Patient ID	Tumor pathology	Age	Gender	KPS	OS (mo)
GBM1-1	GBM	39	M	90	33.83
GBM1-3	GBM	34	M	90	>91.3

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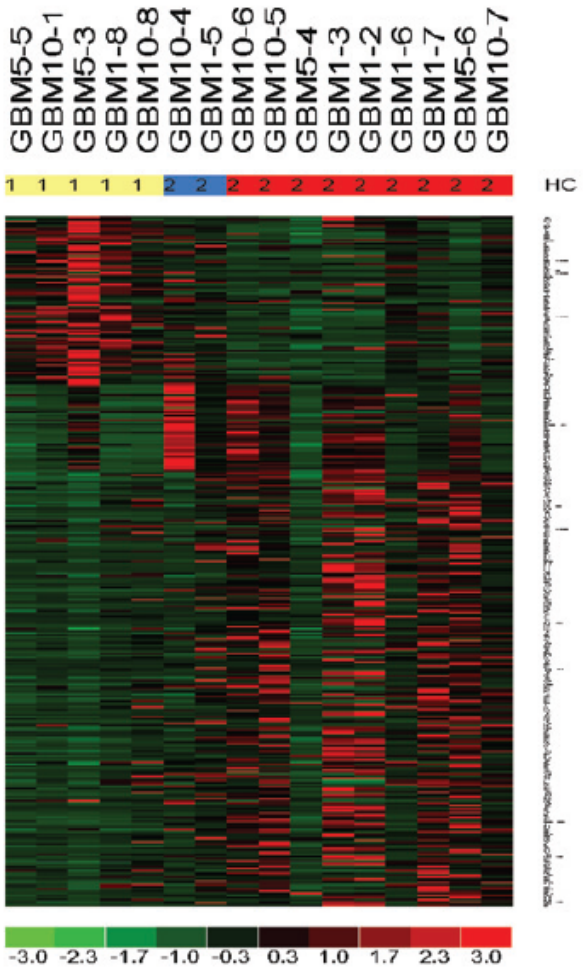
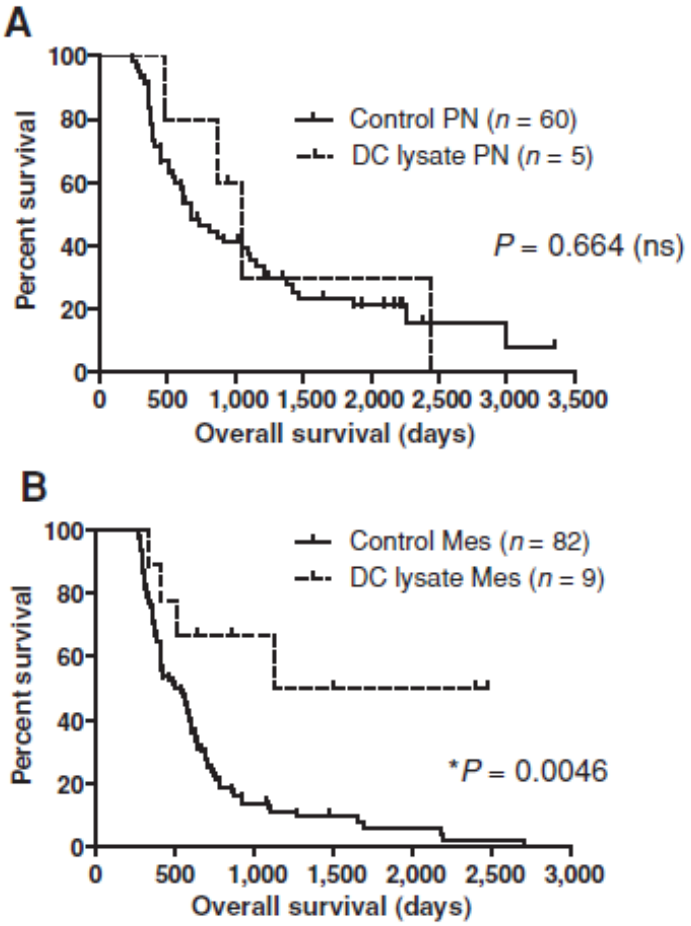
Prins RM et al, ***Clin Cancer Res,*** 2011

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





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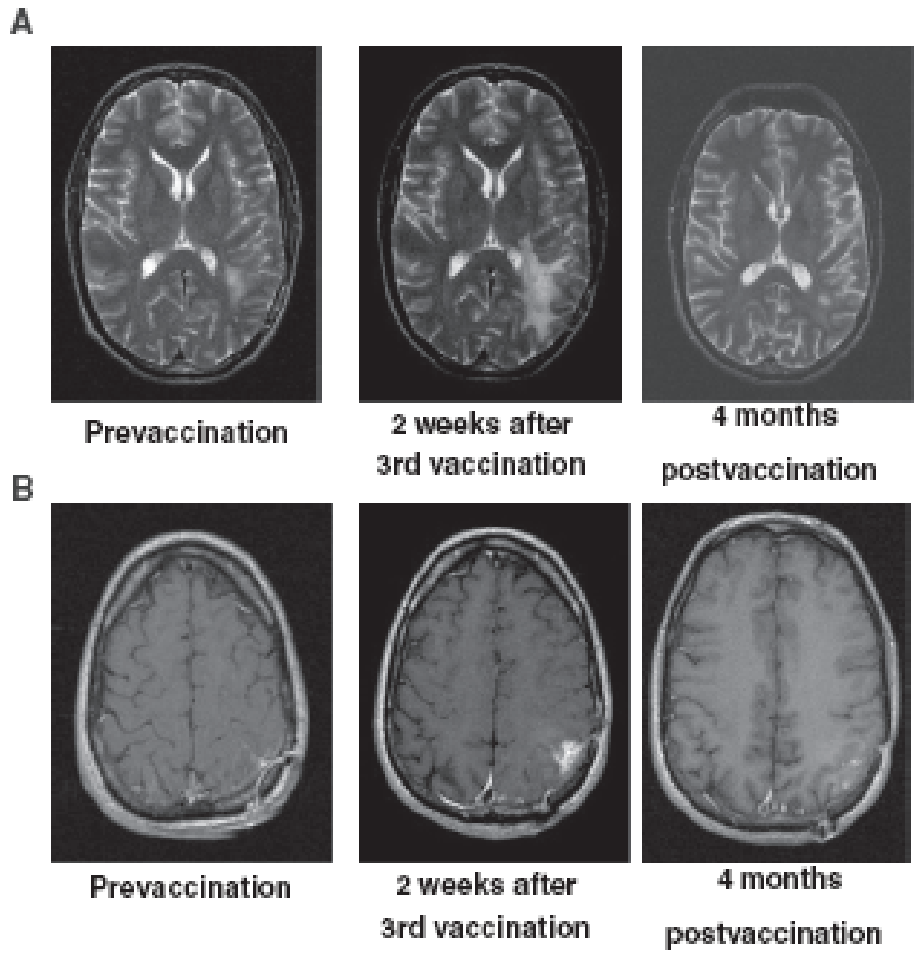
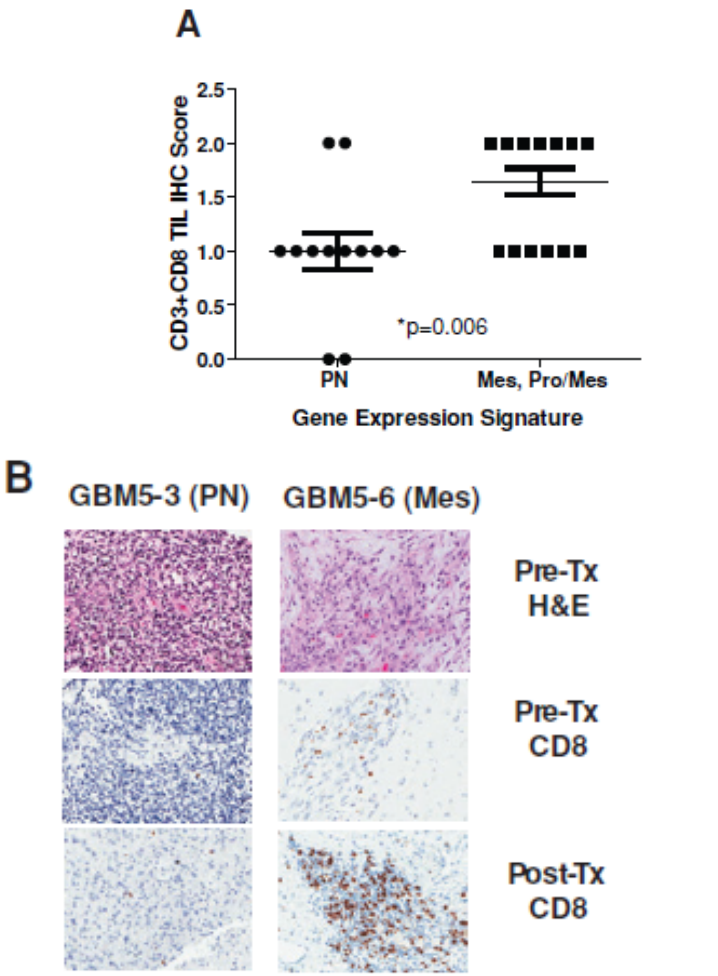
Prins RM, ***Clin Cancer Res***, 2011

"Mesenchymal" gene expression signature associated with increased tumor-infiltrating lymphocytes





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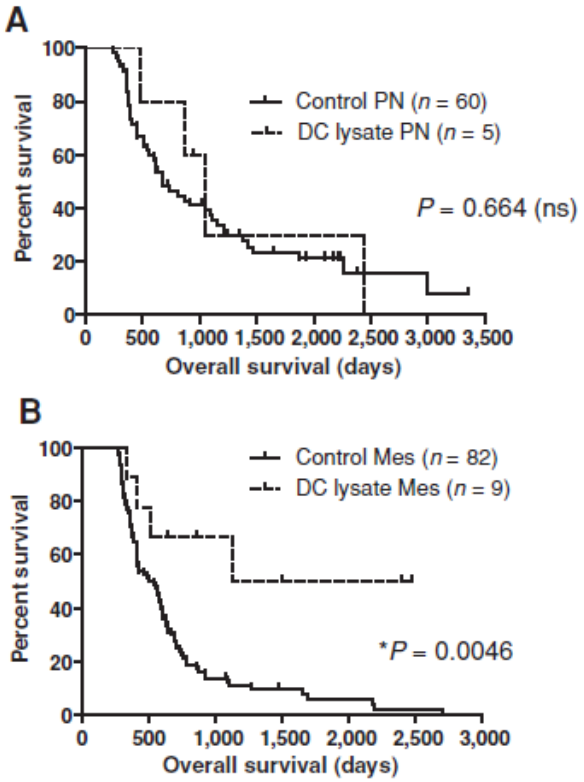
Prins RM et al., ***Clin Cancer Res,*** 2011

"Mesenchymal" glioblastoma subtype may be associated with modulation of immune pathways



Gene	Direction	Function	RATIO
YKL-40	Inflammatory	MGES; tissue re-model	6.3
Galectin-3	Suppressive	induces T cell apoptosis	4.5
IL-6	Dual	inhibits TNF-α, induces IL10	2.4
CCAAT binder enhancer protein	Inflammatory	cytokines & acute phase	2.2
CD11b	Inflammatory	Mϕ receptor	1.6
IL-18	Inflammatory	Induces IFNγ by Tcells	1.5
SOCS3		Inhibits STAT3	1.4
STAT3	Suppressive	Up regulates IL10, VEGF, Tregs, ↑TGFβ	1.4
TGF-beta	Suppressive	Tregs; block monocytes	1.3
gp130	Suppressive	IL6 receptor and activates STAT3	1.3
Granzyme B	Inflammatory	Target cell apoptosis	1.1
IFNαreceptor1	Inflammatory	phosph of STAT 1&2; antiviral	1.1
IL-12B	Inflammatory	induces Th1helper T cells	1.0
Foxp3	Suppressive	Treg marker	0.9
IFNγ	Inflammatory	Mϕ activator;	0.9
IL-12A	Inflammatory	NK & T cells, Th1 & Th2,	0.9
IL-2	Inflammatory	induction and prolif of T cells	0.9
IL-4	Inflammatory	induces Th2 helper T cells	0.9
JAK1	Dual	phosphorylation of STATs	0.9
MAPK11	Inflammatory	activated by pro-inflam.cytokines	0.9
T-bet	Inflammatory	controls expression of IFNγ	0.9
TNFα	Inflammatory	acute phase, apoptosis	0.9
PDGFRα		Entry for CMV	0.5

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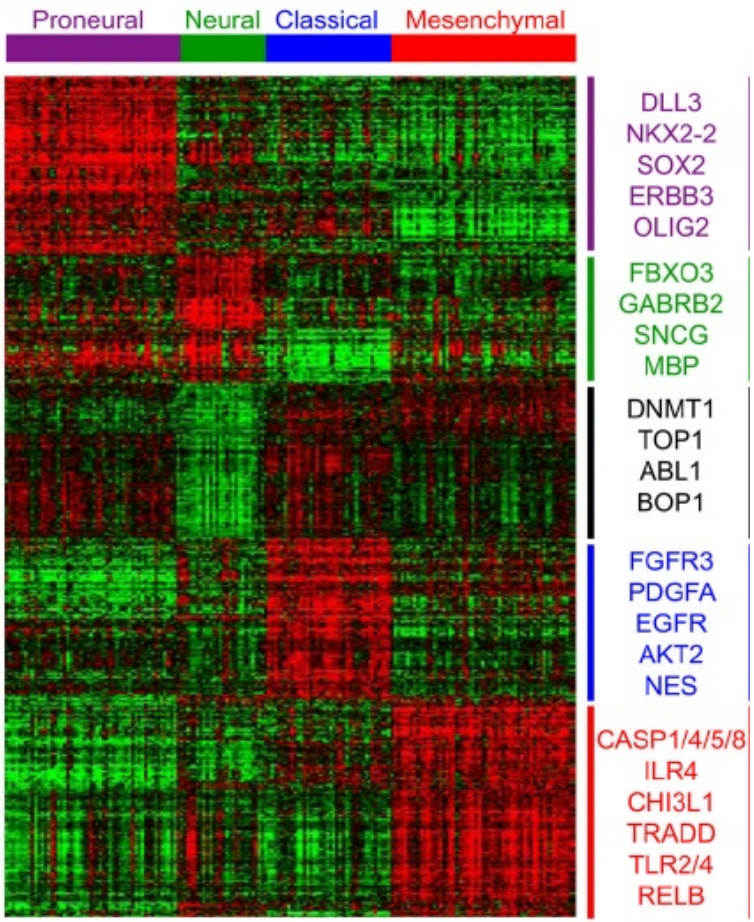
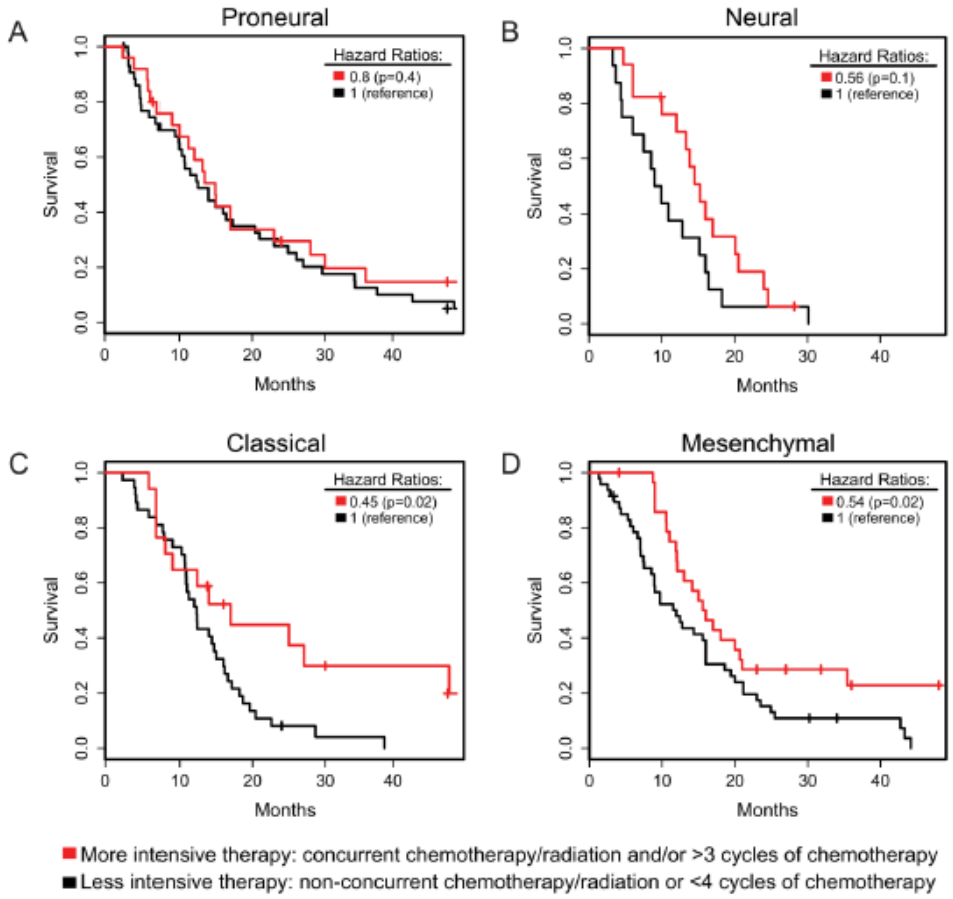
Gene list courtesy of Amy Heimberger & Ken Aldape (MDAnderson)

The Cancer Genome Atlas (TCGA)

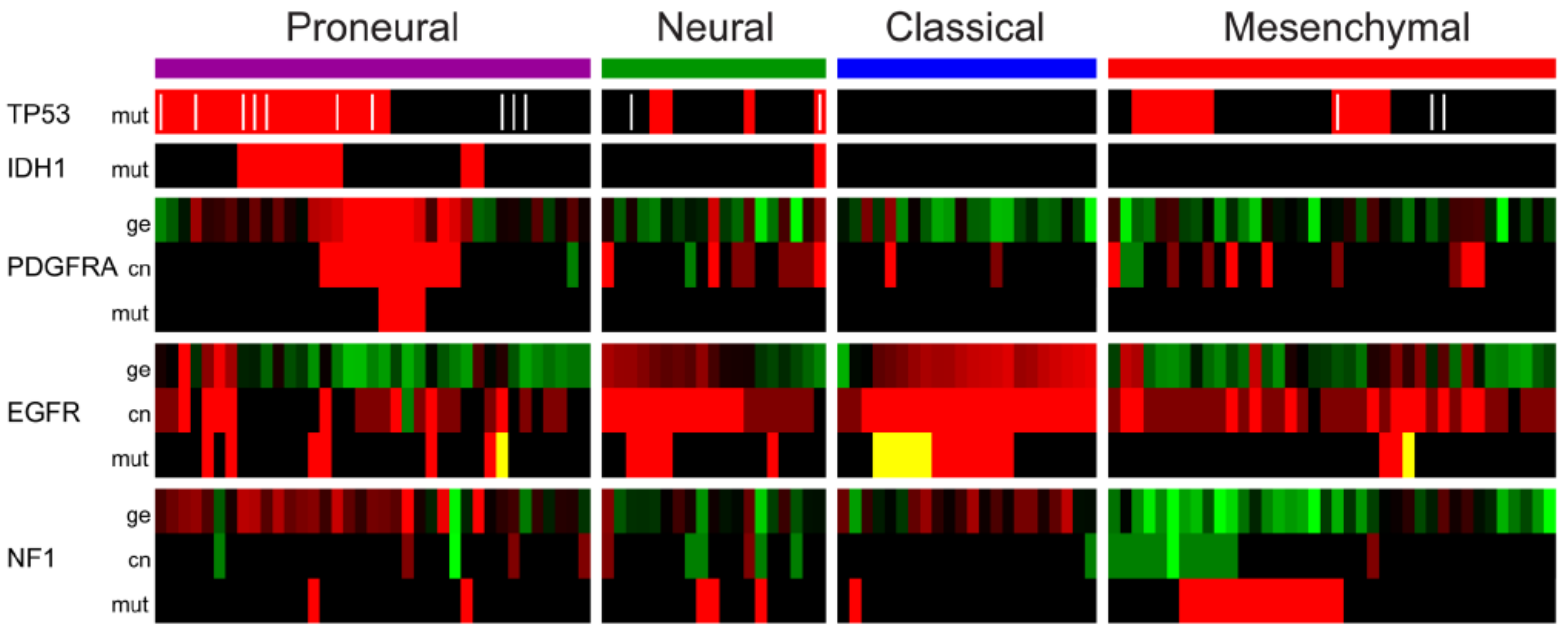




UCLA Health

TCGA, ***Cancer Cell,*** 2010

Genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in IDH1, EGFR, & NF1



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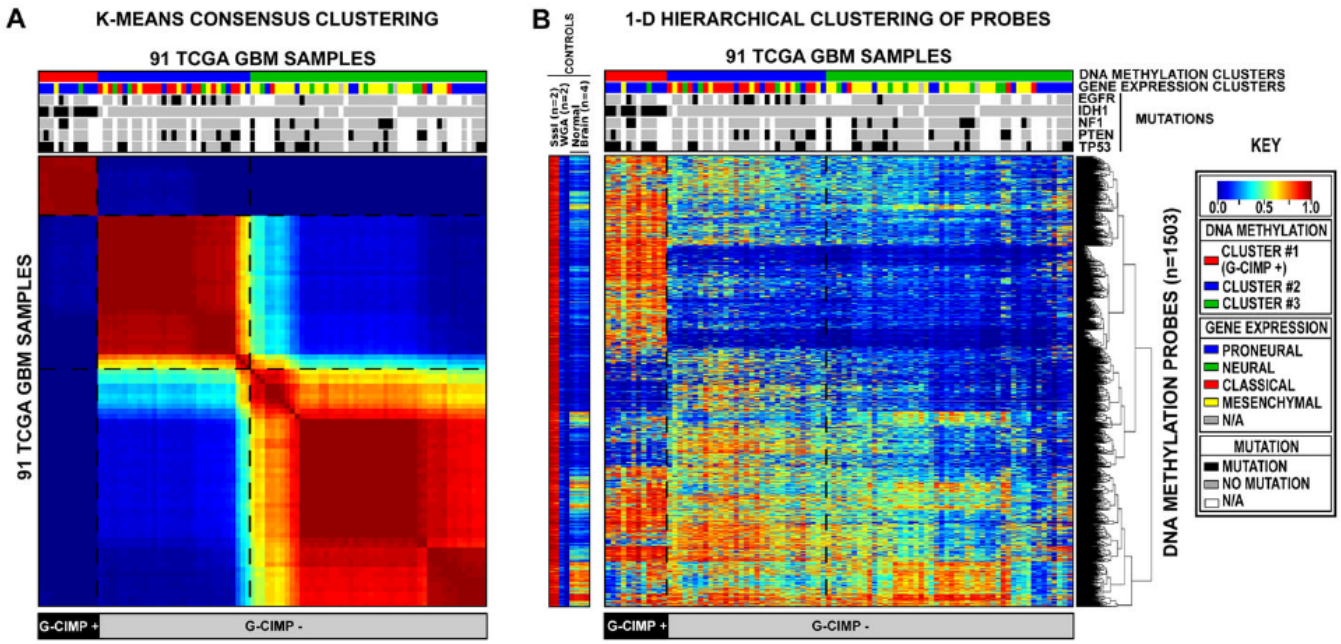
Verhaak RGW et al, ***Cancer Cell***, 2010

Identification of CpG Island Methylator Phenotype (CIMP) that Defines a Distinct Subgroup of GBM



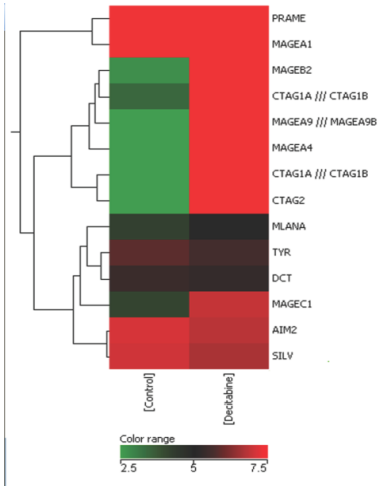
ALL TUMORS		G-CIMP		TOTAL
		–	+	
IDH1	Wild-type	184	5	189
	Mutant	0	18	18
TOTAL		184	23	207
PRIMARY TUMORS		G-CIMP		TOTAL
		–	+	
IDH1	Wild-type	171	4	175
	Mutant	0	12	12
TOTAL		171	16	187
RECURRENT TUMORS		G-CIMP		TOTAL
		–	+	
IDH1	Wild-type	12	0	12
	Mutant	0	4	4
TOTAL		12	4	16
SECONDARY		G-CIMP		TOTAL
TUMORS		–	+	
IDH1	Wild-type	1	1	2
	Mutant	0	2	2
TOTAL		1	3	4

UCLA Health

TCGA, ***Cancer Cell,*** 2010

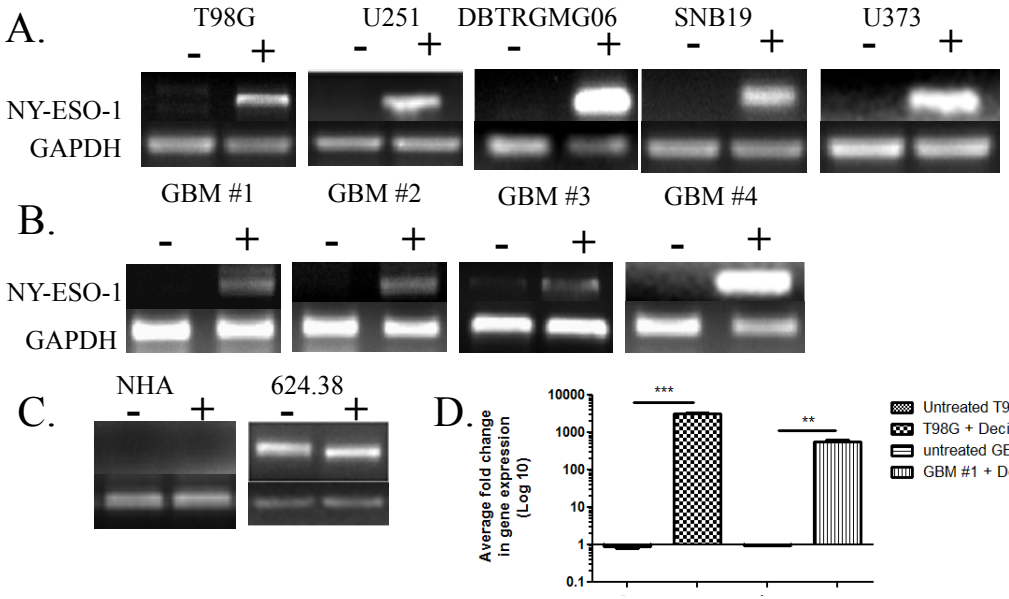
Epigenetic demethylating agents immunosensitize gliomas to immune attack

Decitabine upregulates cancer testes antigens (CTA) on human gliomas



Gene Symbol	Gene Title	Fold Induction
PRAME	Preferentially expressed antigen in melanoma	1.01
MAGE-A1	Melanoma antigen Family –A1	1.39
MAGE-B2	Melanoma antigen Family-B2	92.92
CTAG1A///CTAG1B	Cancer/testis antigen 1A/1B (NY-ESO-1)	376.59
MAGE-A9	Melanoma antigen Family-A9	83.45
MAGE-A4	Melanoma antigen Family-A4	248.02
CTAG1A///CTAG1B	Cancer/testis antigen 1A/1B (LAGE-2, NY-ESO-1)	57.90
CTAG2	Cancer/testis antigen-2 (LAGE-1, CAMEL)	654.87
MLANA	Melan-A/MART-1	1.86
TYR	Tyrosinase (oculocutaneous albinism 1A)	0.82
DCT	Dopachrome tautomerase (TRP-2)	0.94
MAGE-C1	Melanoma antigen Family-C1	7.03
AIM-2	Absent in melanoma-2	0.82
SILV	Silver homolog (gp100)	0.78

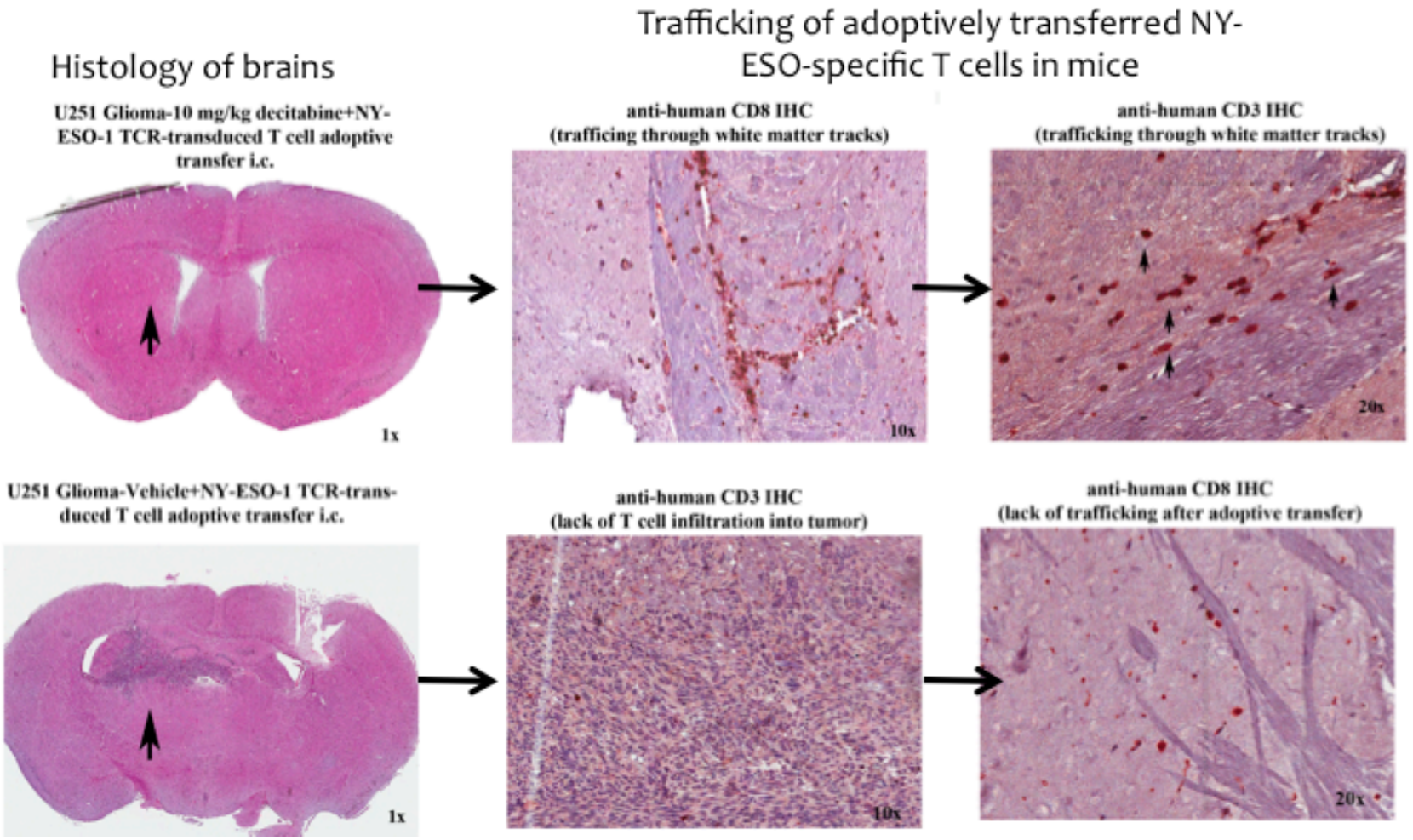
*(log_2 of normalized gene expression values)



UCLA Health

Konkankit VV et al., ***J Transl Med,*** 2011

Decitabine "immunosensitizes" gliomas to NY-ESO1-specific T-cell targeting

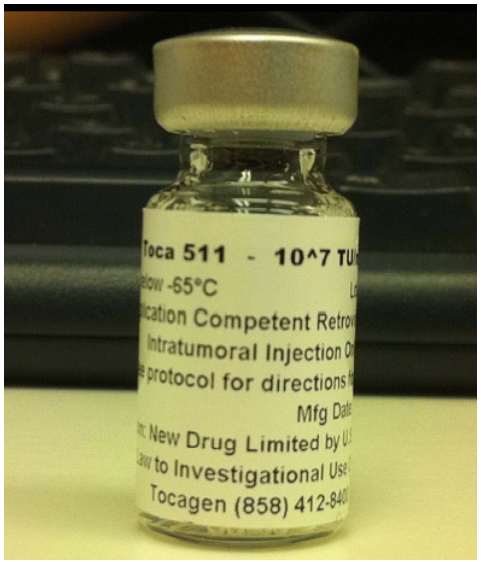


Viral gene therapy immunosensitizes gliomas to immune attack

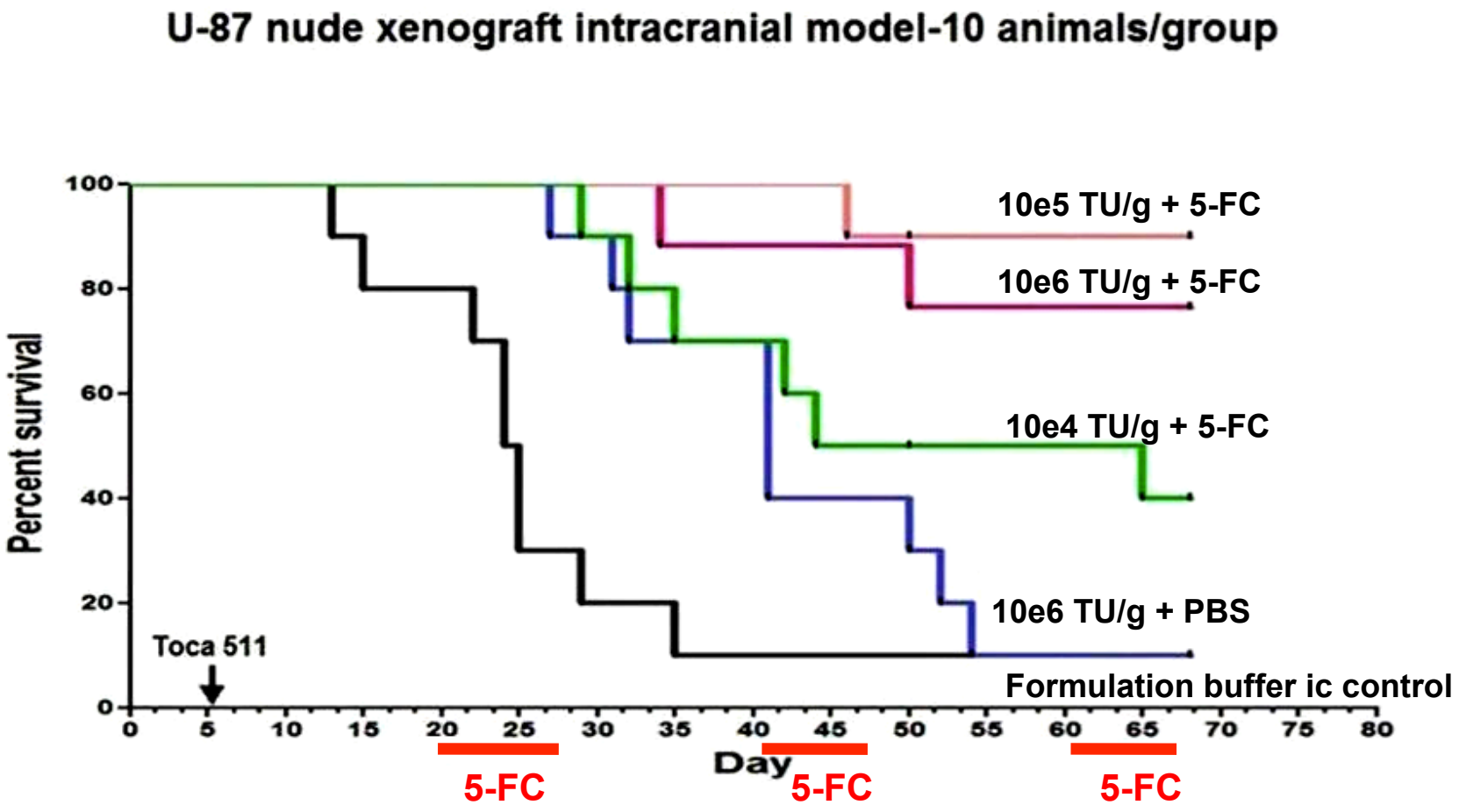
Phase I clinical trial of RRV gene therapy for recurrent malignant glioma

- **August 2, 2010:**

  First-in-man injection of RRV Toca 511 in glioblastoma patient at UCLA



Toca 511/5-FC treatment prolongs survival in immunosuppressed animals



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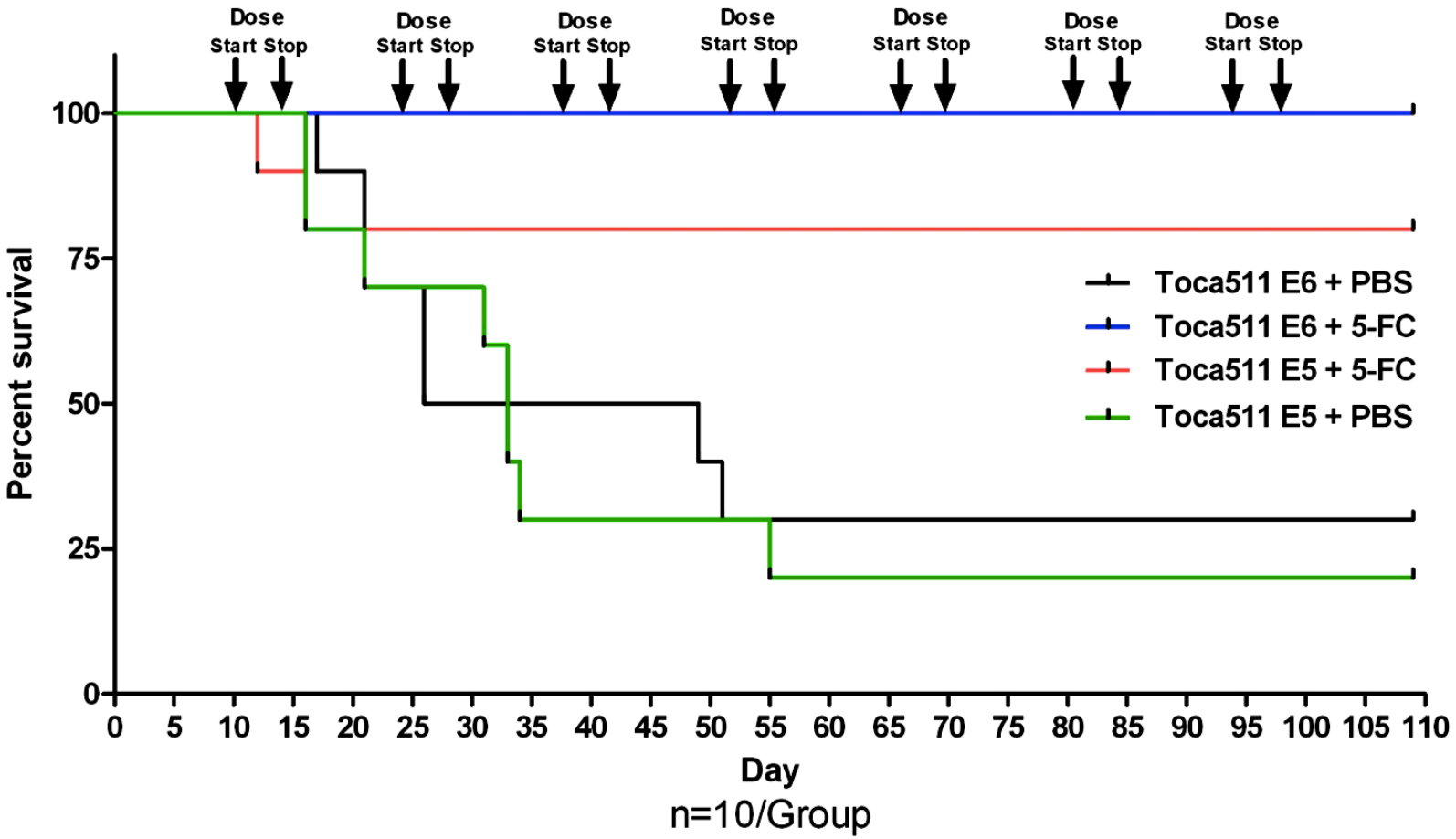
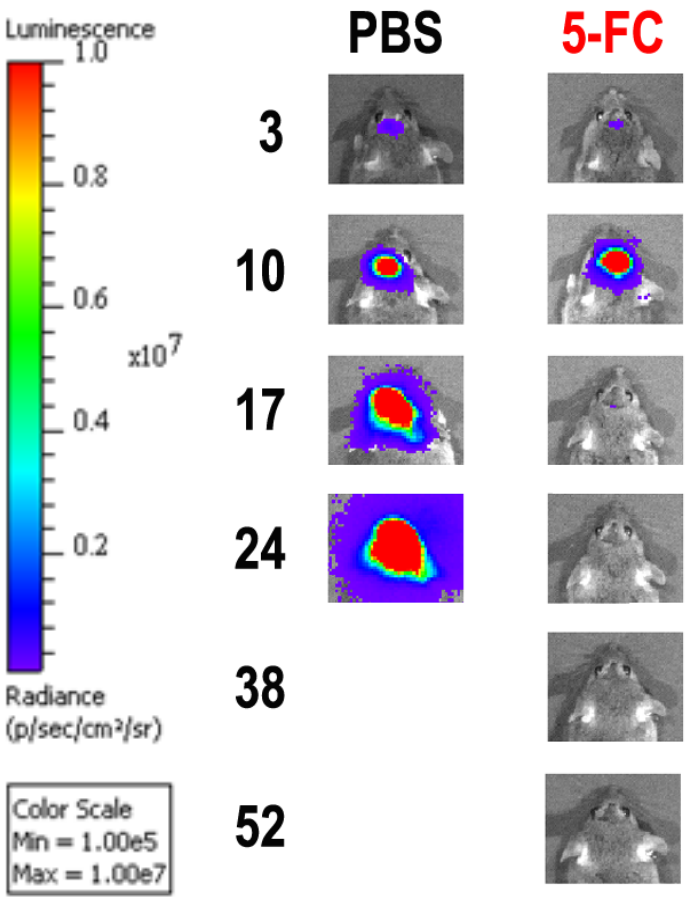
Kasahara et al., 2012

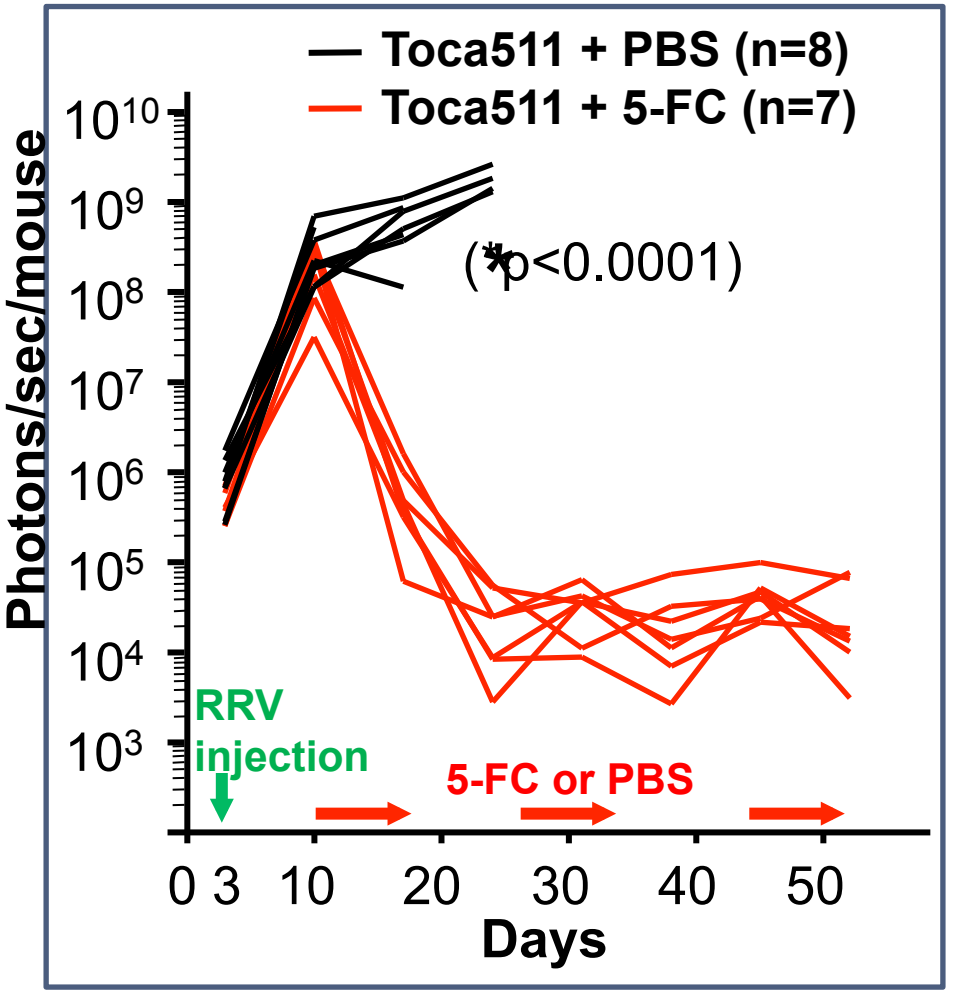
Toca 511/5-FC treatment eradicates tumors in immunocompetent animals



Kasahara et al., 2012

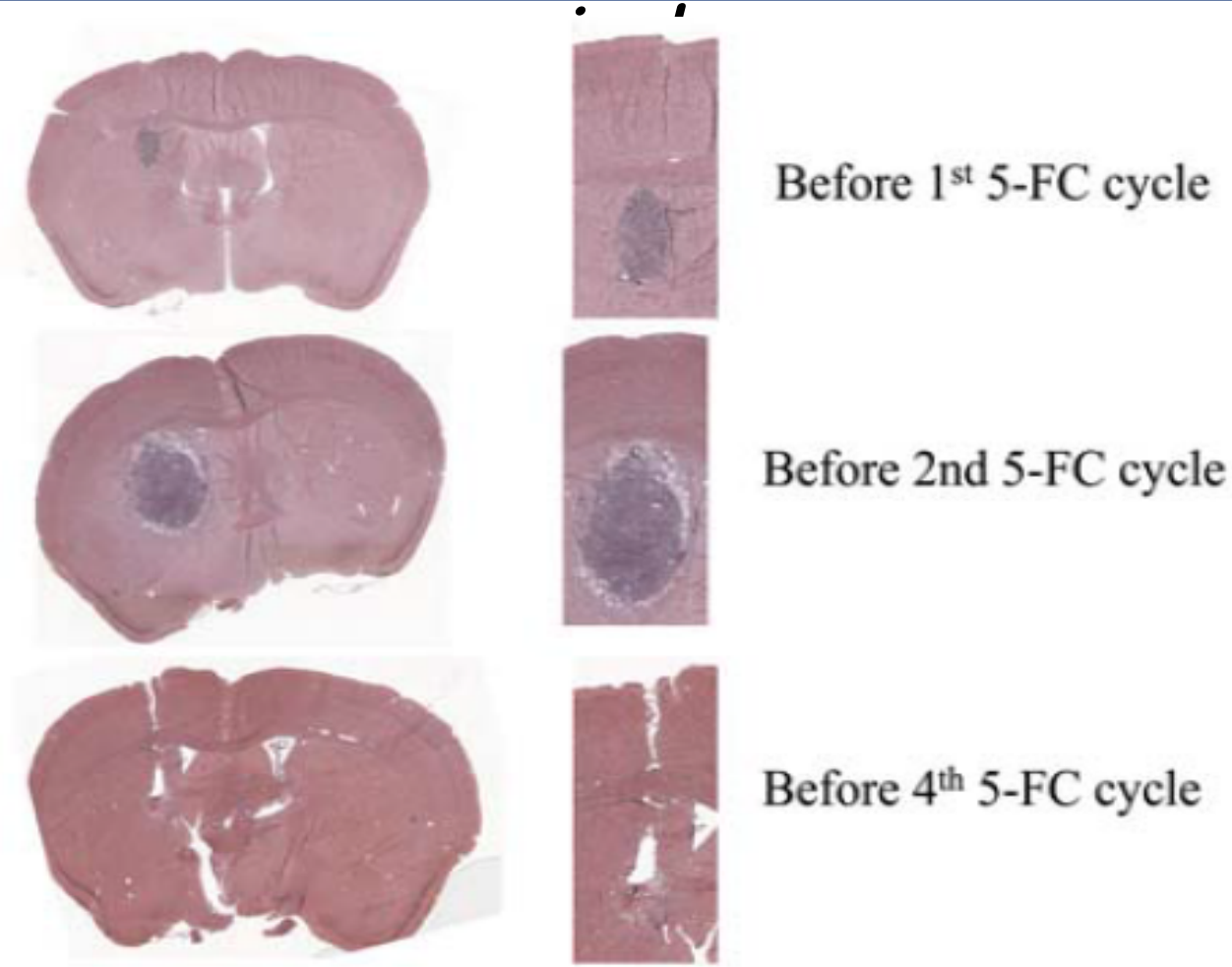
Eradication of Tu-2449 intracranial gliomas in syngeneic B6/C3 F1 mice after RRV-CD followed by multiple cycles of 5-FC





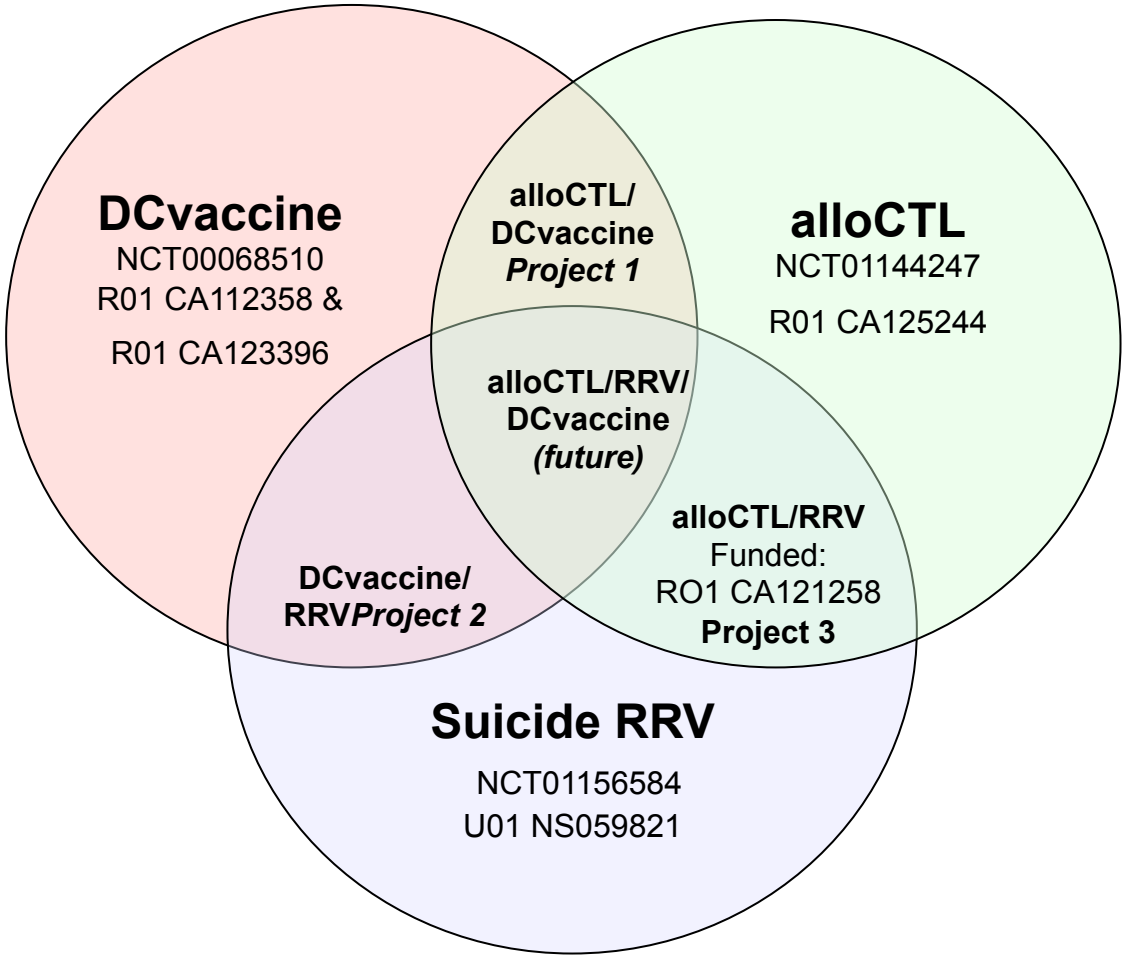
Eradication of intracranial gliomas after 4 cycles of 5-FC post-Toca511 vector injection:

Complete eradication is only seen in immunocompetent

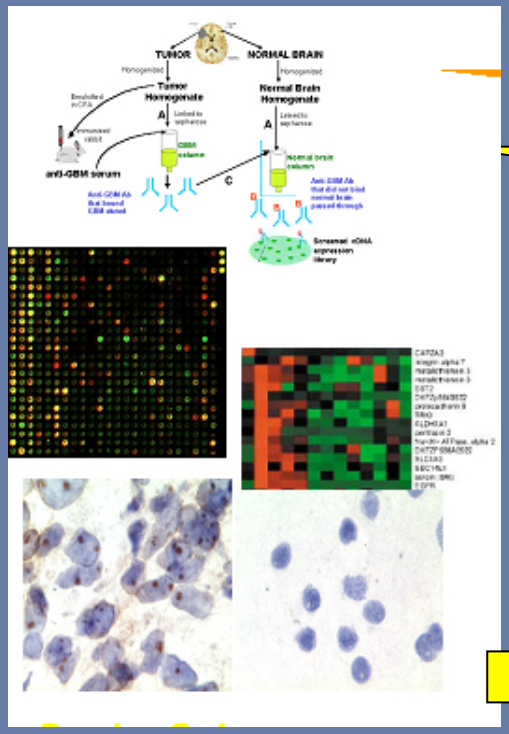


Kasahara et al., 2012

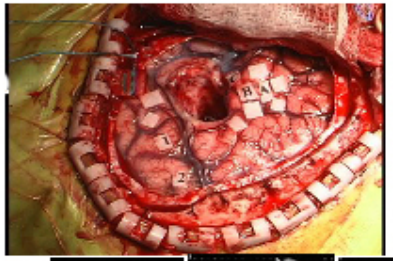
Combining immunotherapy and viral gene therapy for brain tumors

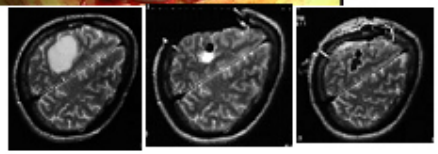


Translating Brain Cancer Data & Models to Clinical Practice: From Bench to Bedside and Back



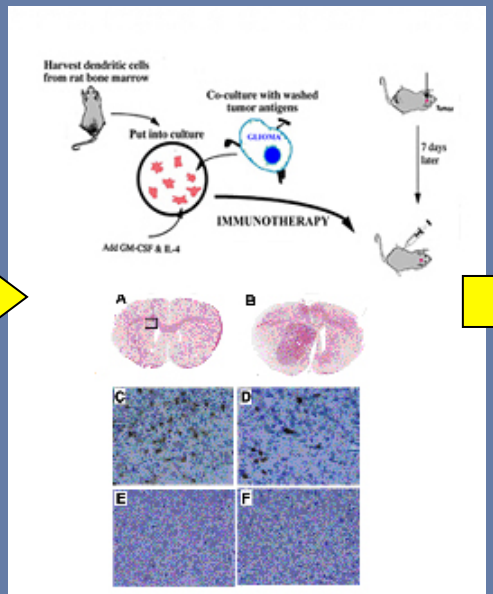
Human tissues collected back to lab





Translational Studies:

Studies of cancer immuno-therapy and gene therapy in animal models of brain tumor



Basic Science:

- Identification of novel oncogenes and mechanisms of gliomagenesis;
- Studies of neuro-immunology and CNS tumor immunology

Clinical Trials:

Phase I/II studies of novel brain tumor therapies;
Intra-op brain mapping studies of brain function

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THANK YOU!

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