Development of Effective Treatments for Malignant Brain Tumors

Keith L. Black, MD

- World Health Organization (WHO)
- 120 different types of Brain Tumors
- 200,000 New Brain Tumor Cases in U.S. each year
- 170,000 Metastatic Brain tumors
  - Lung, Breast, Colon, Melanoma
- 30,000 Primary
- 15,000 Astrocytic/Glial
- 9,000 GBM

Subtypes Predict Prognosis and Response to Treatments

- GBM De Novo – prognosis significantly worse than GBM that converted from lower grade glioma
- Longer History better prognosis
- Higher Function better prognosis
- Oligio component better prognosis
- 1p 19 q deletion better response to PCV

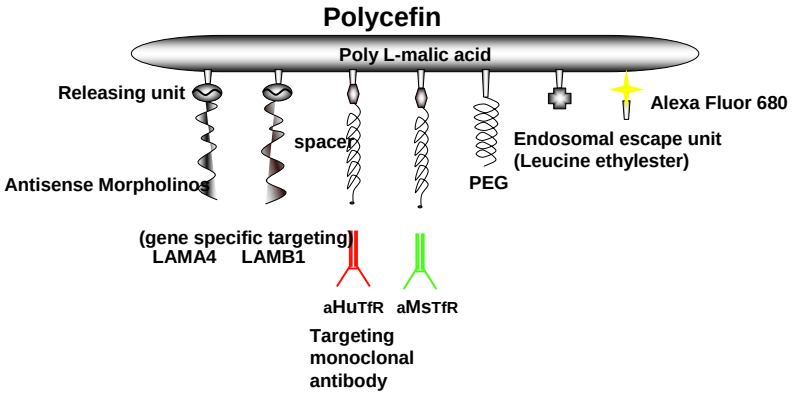
Subtypes of Glioma

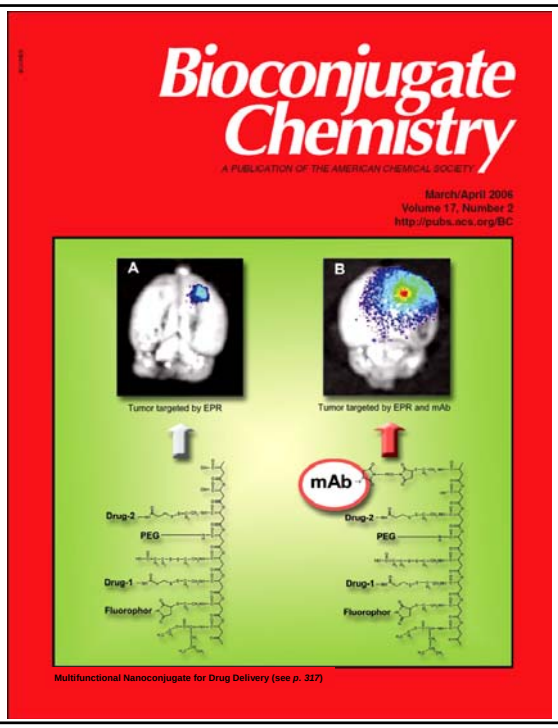
- Age is strongest predictor of survival and strong predictor of response to treatment
- Multiple reasons for correlation suggested
- Example of Bedside to Bench
- Chris Wheeler, PhD Immunologist at MDNSI demonstrated that the age correlation is entirely due to higher number of naive immune T cells in younger patients

Subtypes of Glioma

- Example of Bedside to Bench and back to Bedside
- Julia Ljubimova MD, PhD at MDNSI used gene arrays to identify certain laminins that are over-expressed in Gliomas. Ratio of laminin 8 to laminin 9 is highly predictive of prognosis for GBM. Has developed a nano-drug that blocks laminin 8 and increases survival in rat models of glioma.

To increase the specificity of anti-cancer treatment and to reduce the drug side effects, we have been developing a novel nanoconjugate for transporting active antisenses to tumor cells.





Laminins

- Inhibition of laminin 411 also inhibits angiogenesis and glioma cell migration
- Avastin – anti-angiogenic Ab that binds to VEGF may decrease use of steroids and improve survival for GBM

Role of Surgery for Gliomas

- Number One – Need to achieve Image Complete Resection (ICR) of enhancing tumor to impact prognosis. Attempt 2 log kill
- Reserve incomplete resections for diagnosis or buying time for other therapies to have effect

Critical for effective treatment of primary brain tumors

- Treatment must reach **entire** volume of CNS. Glioma is not a local disease. It is a diffuse disease.
- Should not be toxic to normal brain cells. Normal Brain Tissue is Sacred
- Should limit the development of resistance to the therapy, and should reactivate tumor killing if or when there is a recurrence
- Reason localized treatments, i.e., Surgery, Radiosurgery, local infusion of Chemotherapy fail is that they do not meet these **critical** requirements

Immunology of Gliomas

- Our current understanding of tumor immunity is compelling that immunity is important in progression of gliomas.
- Immune Cells are not able to recognize gliomas. Gliomas “Cloak” themselves to killer T immune cells.

Immunology of Gliomas

- Not only do gliomas cells use “Cloaking”
- They actively suppress killer immune cell responses by release of immuno-suppressive chemicals.
- In fact, we have shown that the greater the immune response to the tumor, the greater the release of immunosuppressive chemicals by the tumor

- Tumors also actively kill immune cells infiltrating into the tumor
- Also, we have shown that the strong association of patient age with survival in glioma is entirely due to higher numbers of naïve T cells in younger patients.

Advantages of using Cellular Immune Therapy for Brain Tumors

- Activated immune cells can survey entire CNS
- Activated Immune Cells Cross the BBB.
- T Cell Immune killing is Selective and not toxic to normal brain
- Should retain memory for tumor killing. Should Reactivate when/if recurrence occurs

Brain Cancer Vaccines Can enhance immune response

- 1994-we showed prolonged survival rat glioma models post DC vaccine
- 2001-we reported first phase I study in glioma patients using dendritic cell vaccine

Can Res 61:842-847, 2001

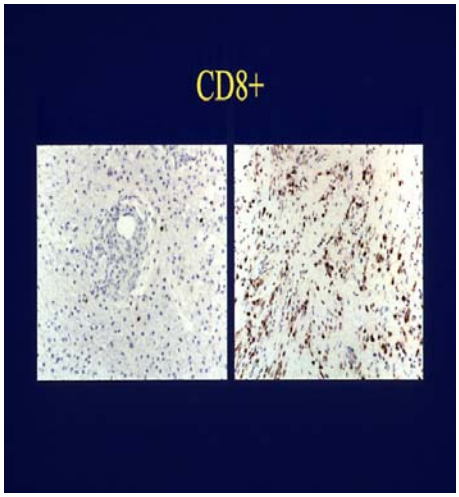
Glioma Vaccines Development at Cedars-Sinai

We have treated patients with:

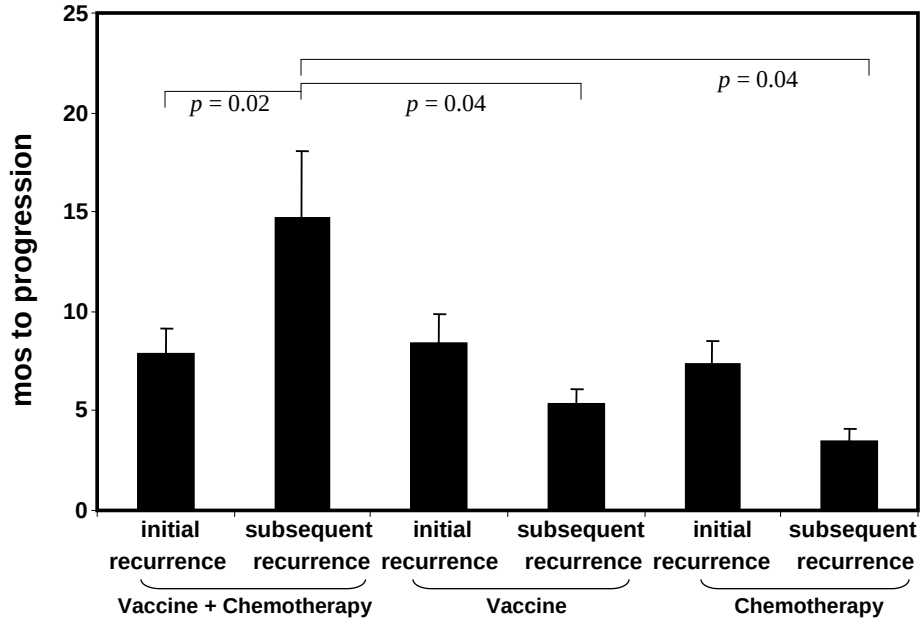
- TGFb antisense glioma vaccines
- GM-CSF genetically engineered vaccines
- **Dendritic Cell Vaccines**: Using Antigens from both tumor cell culture and tumor lysate.
- Advantages with dendritic cells: most potent way to present tumor antigens to immune system.
- Do not need to know specific glioma tumor antigens. Dendritic cells select the important tumor antigens. Also Decrease risk of immune resistance by activation of multiple tumor antigens

Patients treated with DC Vaccine at Cedars-Sinai

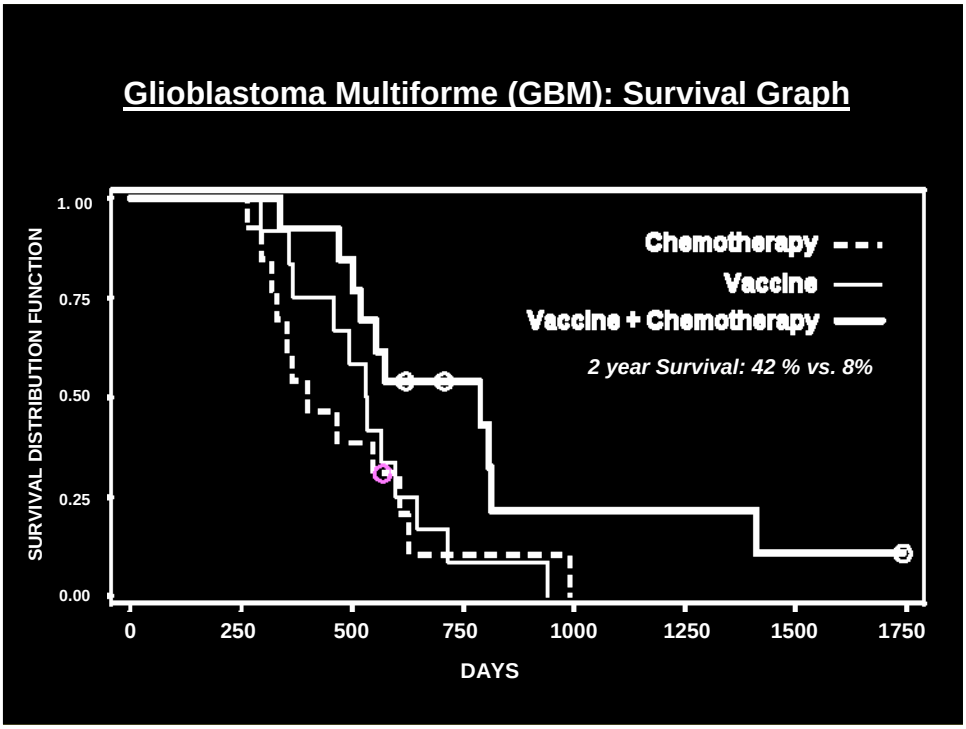
- Post-vaccination CTL positive in **60%** of patients
- **50%** of patients with CD8 and CD45RO T cell infiltration post-vaccination
- No auto-immune toxicity noted

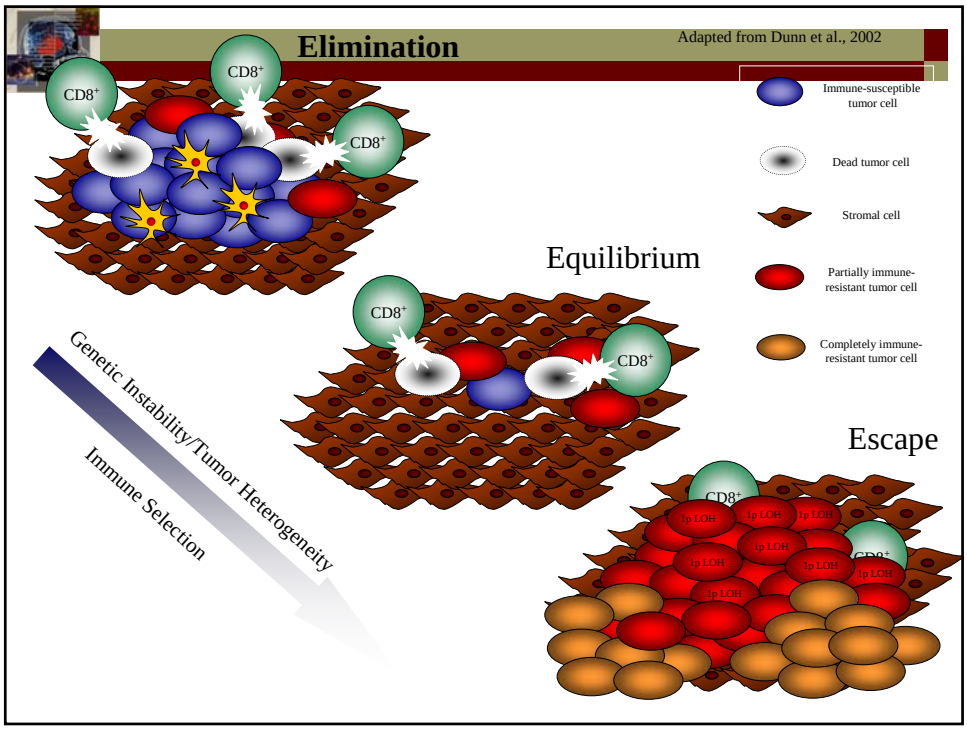


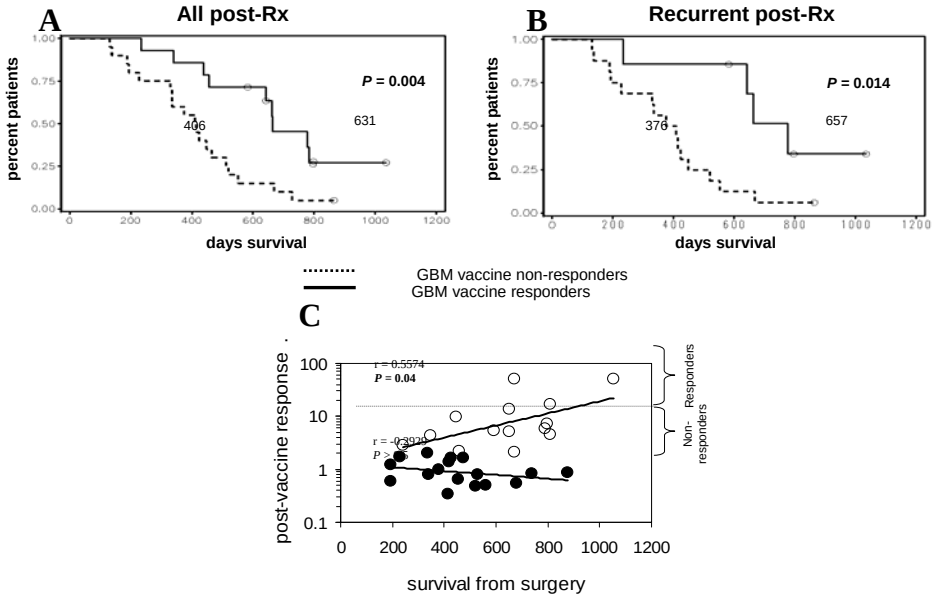
Glioblastoma Multiforme (GBM): Time to Progression



Glioblastoma Multiforme (GBM): Survival Graph







What Have We Learned

- About half of patients have an immune response to vaccine
- Those that respond have improved survival
- Enhanced response to chemotherapy post vaccine
  - Immune editing

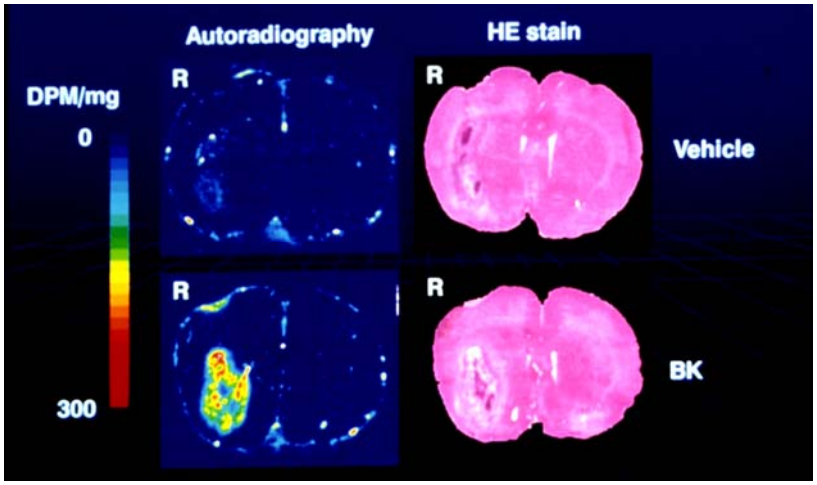
Potential Vaccine Improvements

- Development of DC Vaccine that Targets GBM Cancer Stem Cells – John Yu MD
- Clinical Phase I Trial underway using DC Vaccine and tumor antigens with ICT Inc. – John Yu MD
- Combine Danger signals/TLR with DC cells
- Exploit Chemo effect with Trial using combination of high dose chemotherapy

Blood-Brain Barrier

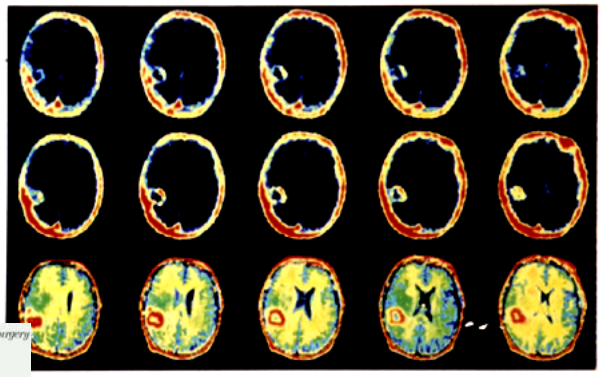
- **BBB protects brain from toxic substances**
- **Primarily small, lipophilic molecules readily cross the BBB**
- **98% of potential CNS therapeutics, including monoclonal antibodies, most chemotherapeutics don't cross BBB in sufficient quantities to be effective**
- **Misconception that blood-brain tumor barrier does not impair drug delivery to brain tumors**
- **None of the major pharmaceutical companies have a brain drug delivery division**

Effects of BK using [^{14}C] Dextran



Phase 1 RMP-7 Clinical Trial

RMP-7 Selectively Increased Delivery of Compound to Patients with Brain Tumors



Baseline PET Image

Post 100 ng/kg RMP-7 PET Image

Co-registraton of Baseline MRI with RMP-7 PET Image

Cover **J Neurosurg** 86:603-609, 1997

CEREPORT

- Alkermes 028 Study
  - 79 patient study in metastatic lung cancer
  - All patients had measurable CNS mets
  - No CNS radiation
  - Treated with CEREPORT and iv carboplatin (monthly courses)
  - First 53 patients treated with “standard” dose of 300 ng/kg
  - 26 additional patients treated in standard dose escalation format to MTD
  - Fully QA’d IND study; multi-institutional (Europe)

CEREPORT Results-2

Response by dose (All patients)

Dose range (ng/kg):	300	450 - 1050	1200 - 1800
Number Treated:	53	13	13
CR	1	-	1
PR	5	2	4
Mx			1
CR + PR	6 (11.3%)	2 (15.4%)	5 (38.5%)

Response by dose (All patients) Segregated at mean dose

Dose range (ng/kg):	300-900	1050 - 1800
Number Treated:	62	17
CR	1	1
PR	7	4
Mx	-	1
CR + PR	8 (12.9%)	5 (29%)

CEREPORT Results-3

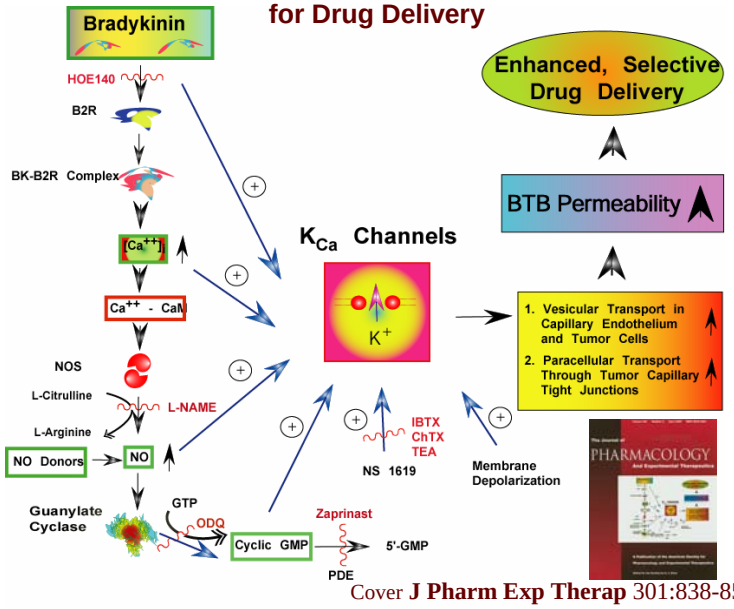
Response by dose (NSCLC Patients)

Dose range (ng/kg):	300	450 - 1050	1200 - 1800
Number Treated:	42	10	8
CR	-	-	-
PR	4	1	3
Mx			1
CR + PR	4 (9.5%)	1	3 (37.5%)

Response by dose (SCC Patients)

Dose range (ng/kg):	300	450 - 1050	1200 - 1800
Number Treated:	11	3	5
CR	1	-	1
PR	1	1	1
Mx	-	-	-
CR + PR	2 (18.8%)	1	2 (40%)

Biochemical and Cellular Mechanisms for Drug Delivery



Cover **J Pharm Exp Therap** 301:838-851, 2002

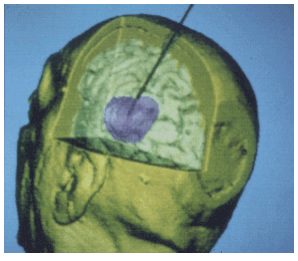
PDE5 Inhibitors

- Levitra significantly increases drug delivery to Brain Tumors in Rat Models
- Combination of Levitra and Chemotherapy improves survival in rat brain tumor models

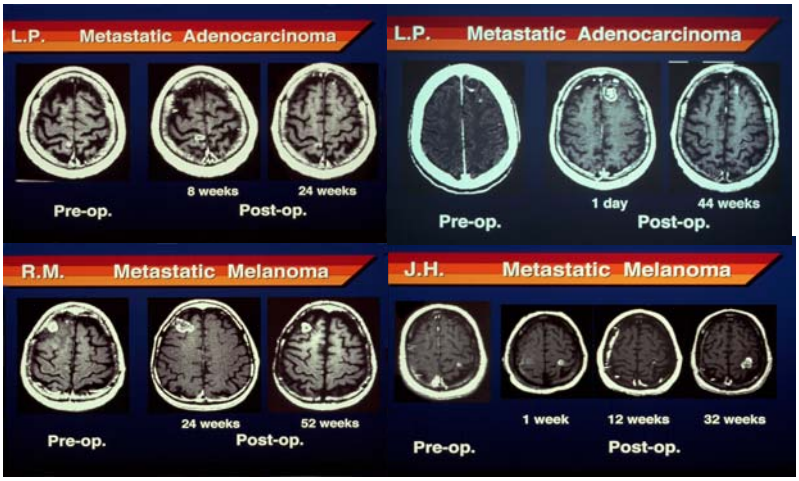
The MicroWave Device

Focused Microwave Ablation Device

- **Minimally invasive**
  - **Probe fits in biopsy tract**
  - **Out-patient procedure**

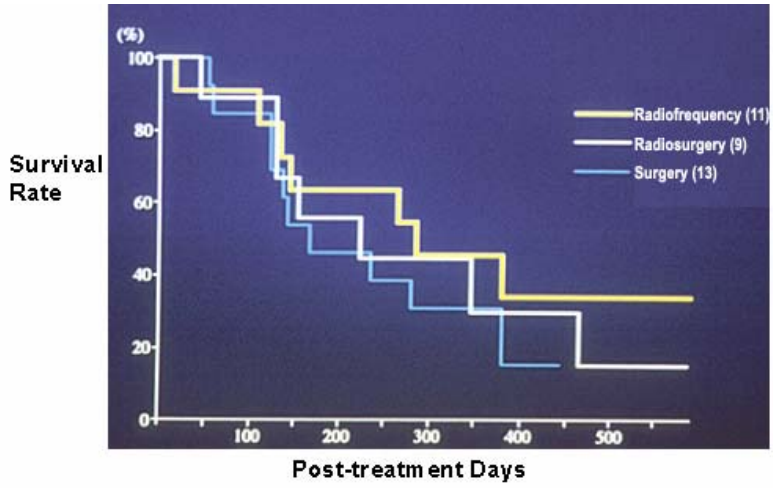


RFA Study



RFA Study Results

Survival Rates Are Virtually Identical

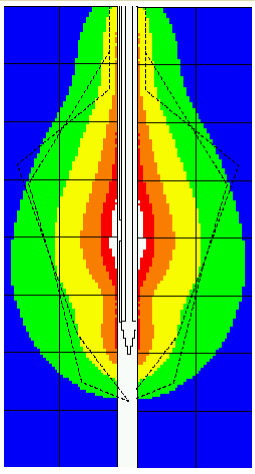


Ablation is Future of Brain Surgery

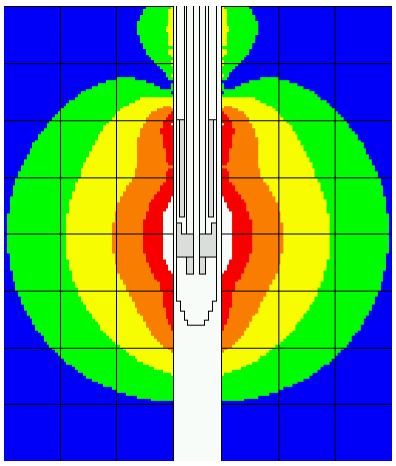
One of These People Had Brain Surgery
5 Minutes Ago

Probe Heating Pattern Models

RF "Football"



MicroWave Sphere



Keith Black RFA Study

Patient "TK" with Malignant Glioma in Speech Area of Brain, 1 Tumor Treated with RFA

MicroWave and Immune Therapy

- Infusion of DC cells into ablated tumor
- Danger Signals TLR ligands
- Potential synergy with systemic vaccines
- Synergy in chemotherapy with BBB modulation

Brain Tumor Quality Data

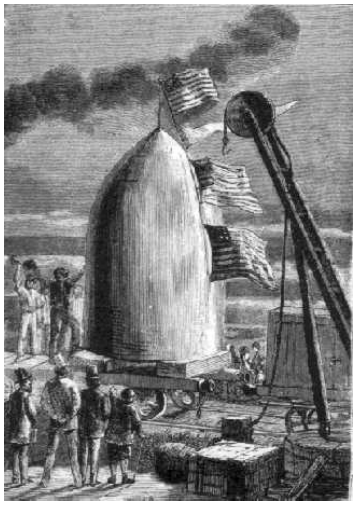
In-Patient Hospital Averages	Cedars-Sinai Brain Tumor 2006 (N = 164)	National Average 2006	Cedars-Sinai Brain Tumor 2007 (N = 164)	National Average 2007
For patients undergoing **brain tumor resection**, the median **mortality rate** was:	0.00%	1.52%	0.06%	1.57%
For patients undergoing **brain tumor resection**, the median **length of stay** following surgery was:	5.7	5.4	4.8	5.1
For patients undergoing **brain tumor resection**, the median **ICU Days** following surgery was:	1.9	N/A	1.6	N/A

Brain Tumor Quality Data

Brain Tumor Survival Rate	Cedars-Sinai Brain Tumor 2002-2006	State of California Average	National Average
One Year Survival:	75.9%	49.8%	46.6%
Two Year Survival:	61.1%	31.7%	29.3%
Three Year Survival:	55.9%	26.4%	24.4%
Four Year Survival:	51.4%	23.5%	21.8%
Five Year Survival:	50.1%	21.7%	19.8%

Impossible Mission

- Think Out of The Box
- Tumors Behave more Like Terrorists
- Need Bold New Thinking



In Jules Verne's 1866 book "Novel From Earth to the Moon"

Actual Lunar Landing 1969

APOLLO 11 ASTRONAUT BUZZ ALDRIN WALKS ON MOON

Buzz Aldrin,
Col., USAF
Apollo XI Mission
Lunar Module Pilot