Whats New and Promising in the treatment of BRAIN CANCER

KEITH L. BLACK MD
Disclosures

- Founder, Chair of SAB, equity holder of ImmunoCellular Therapeutics
- Founder, Chairman, equity holder of NeuroVision
- Founder, equity holder of Arrogene NanoTechnologies

- This talk will discuss non FDA approved therapies and diagnostics for Glioblastoma and Alzheimer’s disease
Maxine Dunitz Neurosurgical Institute est. 1997

- To discover effective treatments for disorders that effect the human brain

- Glioblastoma Multiforme
Glioblastoma Multiforme

- Most common and fatal brain cancer
- About 11,000 new patients diagnosed each year in the United States
- 80% go through surgery (20% non-operable)
- Very few treatment options
- Cancer typically recurs within a year
- Survival rate only 26% after two years and 16% after 3 years
Glioblastoma Multiforme

- At time of diagnosis, malignant cells throughout the brain
- Local therapies fail: Surgery, Radiosurgery
- Resistant to Chemotherapy and Radiation Rx
- Multiple tumor cell clones that change with Rx
- Median survival has only improved from 9 months to 15 months in last 50 years
- Cannot get drugs into brain/BBB
- More difficult than landing a man on the moon and returning in 1968
Think and Imagine out of the Box

- 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 not allow the development of resistance, be able to kill multiple tumor cell clones, and therapy should reactivate tumor killing, if or when, there is a recurrence
Swim against the current

• Why not use the power of the immune system to fight brain cancer

• Told would not work by experts in field

• Brain has no immune system etc.

• Unique construct of the Neurosurgical Institute allow research to go forward despite high risk and lack of expert support of concept
Odd observations/mold on bread

- Activated immune cells can survey entire CNS
- Activated Immune Cells Cross the BBB
- T-Cell Immune killing is Selective
- Could retain memory for tumor killing
- Could reactivate when/if recurrence occurs and may kill multiple cell clones
Ah Ha moments

- Immunity IS important in gliomas.
- Immune Cells normally are not able to recognize gliomas.
- Gliomas “Cloak” themselves to killer immune cells. Hide antigens proteins on tumor cell surfaces that are important for immune recognition and killing.
Brain cancer acts like Sharks

- Not only do gliomas cells use “Cloaking”
- They actively suppress killer immune cell responses by release of immuno-suppressive proteins.
- Tumors also actively kill immune cells that get into the tumor by activation of a cell death program
The strong association of patient age with survival in glioma is entirely due to higher numbers of immune cells in younger patients.
Start of the Battle

- 1997: initiated at Cedars-Sinai clinical trial using DC vaccine
- 2001: we reported first phase I study in glioma patients using dendritic cell vaccine

Cedars-Sinai Clinical Trials

- Tumor lysate or cultured tumor cells obtained from surgical specimen
- Mononuclear cells isolated by leukapheresis and differentiated into DCs
- 3 to 4 vaccinations over 6 to 10 weeks with DCs pulsed with antigens from cultured tumor cells or lysate from whole tumor
Cancer Stem Cells: Good Guys Turned Bad

- Cancers originate in tissue progenitor or stem cells through dysregulation of the self-renewal process.
- Throughout tumorigenesis, CSCs drive tumor growth.
- Without killing CSCs, it is like spraying for weeds without killing the roots. The weeds (tumors) come back!

John Yu, MD
Vice Chair, Department of Neurosurgery
Director, Surgical Neuro-oncology
## ICT-107 Targets Cancer Stem Cells

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Tumor expression</th>
<th>CSC expression</th>
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<tbody>
<tr>
<td>gp100</td>
<td>melanoma, brain</td>
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<tr>
<td>MAGE-1</td>
<td>melanoma, brain</td>
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<td>IL-13αR2</td>
<td>brain, ovarian</td>
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<td>Her-2/neu</td>
<td>breast, ovarian</td>
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<tr>
<td>AIM-2</td>
<td>breast, ovarian, colon, brain</td>
<td>High</td>
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<tr>
<td>Trp-2</td>
<td>melanoma, brain</td>
<td>High</td>
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First Indication is Brain Cancer, but broad platform potential
Phase I Trial with ICT-107

- Nonrandomized, single-center study
  - Cedar-Sinai Medical Center
- Nineteen GBM patients
  - 16 newly diagnosed
  - 3 recurrent
  - ~75% fully resected
- Surgery and chemo-radiation followed with three vaccinations of ICT-107 every 2 weeks
Phase I Results

**Median OS**

38.4 vs. 14.6 months for standard of care*

*Surgery followed by radiation and temozolomide (TMZ).

ICT-107 Phase I Results
Newly Diagnosed GBM Patients

- RT/Chemo
- Vaccine
- PD

Months from Surgery

★ = Death
Phase II Trial Design

- 102 patients to be treated at 20 centers in US
- 160-170 patients to be enrolled
- 2:1 randomization, double blind
- Placebo: Unloaded dendritic cells
- Primary End Points: OS and PFS
- Secondary End Points:
  - OS/PFS at various time intervals
  - Immune Response
  - Safety
- Interim analysis (based on 50% events) in Q4, 2012
- Final analysis in Q3/Q4 2013

Chemo cycle 1
Chemo cycle 2
Chemo/Vaccine Until recurrence
Coming Soon

- CTLA 4
- PD1
- PD L1
- In combination with vaccines
- Vaccines for low grade gliomas
Ground Assault
Dr. Julia Ljubimova is developing a novel nanoconjugate for targeted drug delivery

Polycefin

Poly L-malic acid

- Releasing unit
- Antisense Morpholinos
- (gene specific targeting) LAMA4, LAMB1
- Targeting monoclonal antibody

- spacer
- PEG
- Endosomal escape unit (Leucine ethylester)

- aHuTfR
- aMsTfR

Alexa Fluor 680

Julia Ljubimova, MD, PhD
Director, Drug Delivery and Nanomedicine
Department of Neurosurgery
Multifunctional Nanoconjugate for Drug Delivery (see p. 317)
Dr. Pramod Butte is using optical imaging for intra-operative navigation.

Laser Pulse Excitation $x(n)$

Fluorescence Emission $y(n) = h(n) \ast x(n)$

Intrinsic tissue emission

$h(n) = \sum_{j=0}^{L-1} c_j b_j^\alpha(n)$

Laguerre deconvolution

Classification

Discriminant Function Analysis

Pramod Butte, PhD
Independent Investigator
Department of Neurosurgery
TRLIFS Portable Prototype

Portable Intra-operative
TRLIFS Prototype

TRLIFS probe being used on the brain to record fluorescence emission
## Department of Neurosurgery Researchers

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<tr>
<th>Drug Delivery and Nanotechnology (Julia Ljubimova – PI)</th>
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Support

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- Mashouf Family
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- Other NSI donors
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Thank You