Emerging immune therapeutics targeting glioma-mediated immune suppression

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Neurological Surgery
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• Laboratory and Clinical Studies: National Institute of Health, American Association of Neurological Surgeons, American Brain Tumor Foundation, National Brain Tumor Foundation, Dr Marnie Rose Foundation, Bullock Research Fund, AstraZeneca

• Paid Consultant: Celldex Therapeutics, Bristol Meyers Squibb

• Stock/Equity: Celldex Therapeutics

• Licensing Fees: Celldex Therapeutics/Pfizer

• Patents: EGFRvIII peptide vaccine (CDX-110), WP1066
Companies that are in Phase II/III vaccine/immunotherapy development

- Advaxis
- AEterna Zentaris/Keryx
- Alfacell
- Anosys
- Antigenics
- Aphton
- Argos Therapeutics
- Avantogen
- AVAX Technologies
- AVI BioPharma
- Biomira
- BioVex
- Bristol Meyers Squibb
- CancerVax
- CancerVac (Prima BioMed)
- Celldex Therapeutics
- Cell Genesys
- Cytos Biotechnology
- Dendreon
- Favrique
- Genitope
- Genzyme
- Geron
- GlaxoSmithKline
- IDM Pharma
- Immutep
- ImmunoCellular Therapeutics
- Introgen Therapeutics
- LipoNova
- Ludwig Institute for Cancer Research/CSL
- Medarex
- Merck and Co
- Northwest Biotherapeutics
- NovaRx
- Onyx
- Oxford BioMEdica
- Pharmexa
- Pfizer
- Progenics
- Sanofi-aventis
- Stressgen Biotechnologies
- Therion Biologics
- The Vaccine Company
- Transgene
- Tvax Biomedical
- Vical
- Xenova (Celtic Pharma)
- YM BioSciences
<table>
<thead>
<tr>
<th>Agent delivered/Site</th>
<th>Sponsor or Centers Involved</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEP-3-KLH + GM-CSF (ACTIVATE)/Systemic</td>
<td>The Univ. of Texas M. D. Anderson Cancer Center/Duke University Medical Center</td>
<td>Median survival = 2.3 years Newly diagnosed; n=18</td>
</tr>
<tr>
<td>PEP-3-KLH + GM-CSF with temozolomide (ACT II)/Systemic</td>
<td>The Univ. of Texas M. D. Anderson Cancer/Duke University Medical Center</td>
<td>Median survival = 2.3 years Newly diagnosed; n=22</td>
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<tr>
<td>Dendritic cells + PEP-3-KLH/Systemic</td>
<td>Duke University Medical Center</td>
<td>Median survival = 1.8 years Newly diagnosed; n=14</td>
</tr>
<tr>
<td>Dendritic cells + autologous tumor lysates/</td>
<td>University of Leuven and Wurzburg</td>
<td>Median survival from relapse = 0.8 years Recurrent GBM; n=56</td>
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<tr>
<td>Dendritic cells + tumor homogenate/ Systemic</td>
<td>Cedars Sinai Medical Center</td>
<td>Median survival = 1.8 years for immune responders vs 1.2 for non newly diagnosed GBM; n=11</td>
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<tr>
<td>Dendritic cells + acid eluted tumor peptides/Systemic</td>
<td>UCLA</td>
<td>Median survival = 1.6 years for immune responders vs 1.1 for non recurrent GBM; n=21</td>
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<tr>
<td></td>
<td></td>
<td>Median survival = 2.0 years Newly diagnosed and recurrent GBM patients; n=12</td>
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</table>
Epidermal Growth Factor Receptor Mutation

Wild Type Amino Acid Sequence

LEU-GLU-GLU-LYS-LYS-VAL-CYS-...-PRO-ARG-ASN-TYR-VAL-VAL-THR-ASP-HIS

Wild Type cDNA Sequence

CTG-GAG-GAA-AAG-AAA-GTT-TGC-...-CCC-CGT-AAT-TAT-GTG-GTG-ACA-GAT-CAC

Variant III cDNA Sequence

CTG-GAG-GAA-AAG-AAA-GGT-AAT-TAT-GTG-GTG-ACA-GAT-CAC

Variant III Amino Acid Sequence

LEU-GLU-GLU-LYS-GLY-ASN-TYR-VAL-VAL-THR-ASP-HIS
Saline + GM-CSF  
(Every 2 weeks i.d.)

ACTIVATE Trial

Immunologic Monitoring

Leukapheresis

Randomize

Saline + GM-CSF  
(Every 2 weeks i.d.)

Randomize

PEPvIII-KLH + GM-CSF  
(Every 1 month i.d.)

First patient treated in 7/04
Efficacy of PEP-3-KLH vaccine

**Progression-Free Survival**

- ACT III
- ACT II
- ACTIVATE
- Historical control

**Overall Survival**

- ACT III
- ACT II
- ACTIVATE
- Historical control

Matched controls went 3 months without progression
# Efficacy of PEP-3-KLH vaccine

<table>
<thead>
<tr>
<th>Clinical Sites</th>
<th>Median PFS from Diagnosis (months)</th>
<th>Median OS from Diagnosis (months)</th>
<th>OS at 24 Months</th>
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<tr>
<td>ACT III (n=65)</td>
<td>31</td>
<td>12.3</td>
<td>24.3*</td>
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<tr>
<td>ACT II (n=22)</td>
<td>2</td>
<td>15.3</td>
<td>24.4</td>
</tr>
<tr>
<td>ACTIVATE (n=18)</td>
<td>2</td>
<td>14.2</td>
<td>24.6</td>
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<tr>
<td>Matched historical control (n=17)</td>
<td>1</td>
<td>6.4</td>
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<tr>
<td>Standard of care radiation/TMZ (n=287)</td>
<td>85</td>
<td>6.9</td>
<td>14.6</td>
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</tbody>
</table>

- In all three rindopepimut trials, study treatment began ~3 months post-diagnosis.
- Historical controls were treated at M.D. Anderson and matched for eligibility (EGFRvIII-positive, KPS ≥ 80%, complete resection, radiation/TMZ and without progression through ~3 months post-diagnosis).
- Confidence intervals for median PFS and OS for vaccinated patients do not overlap with those for historical control and standard of care.
- Mature data for ACT II and ACTIVATE are presented.

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* ACT III survival data not yet final
Shifting the paradigm of the immune therapeutics for targeting malignancy

Tumors can be immunologically recognized/eliminated if global mediators of immune suppression are targeted.

Sufficiently potent immune responses need to be generated to overcome profound immune suppression and/or the immune suppression has to be negated/minimized (GTR).
Immunosuppression in Malignant Glioma Patients

Mechanisms

- Cytokines – IL-10, TGF, PGE2
- Lack of functional antigen presenting cells i.e. immunosuppressive microglia/macrophages (microglia, paucity of myeloid dendritic cells)
- Induction of T cell apoptosis (FasL; Galectin-3)
- Treg recruitment to the tumor
- Increase expression of immune regulatory molecules (B7-H1, HLA-G)
- Loss of antigen
- Decreased B2 microglobulin and/or HLA
- Induction of inappropriate T-helper function (skewing to Th2)
- Cancer stem cells/initiating cells
- Tumor hypoxia/HIF-1α

Manifestations

- Decreased delayed type hypersensitivity responses to recall antigens
- Diminished antibody responses
- Impaired T cell proliferation and responses to IL-2
- Impaired cytotoxic/effector T cell responses
- T cell anergy/unresponsiveness
## Enrichment of immune response in the mesenchymal subtype

### Immune suppressive gene % mRNA overexpression

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<th>Gene</th>
<th>Proneural</th>
<th>Mesenchymal</th>
<th>Classical</th>
<th>Neural</th>
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### Immune effector gene % mRNA overexpression

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<th>Gene</th>
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<th>Classical</th>
<th>Neural</th>
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<td>HLA-DPB1</td>
<td>9</td>
<td>38</td>
<td>6</td>
<td>17</td>
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</tbody>
</table>
Rationale for anti-CTLA-4 in GBM

Fecci, CCR, 2007
RTOG 1125 Trial: Phase II/III

Sample size: 815; 190 for the phase II component

**Primary Endpoints**
- Phase II: Progression-free survival
- Phase III: Overall survival

**Secondary Endpoints**
- Phase II: Treatment-related toxicities
- Phase III: Progression-free survival, Treatment-related toxicities
- Net Clinical Benefits (NCB): Symptom burden measured by the MDASI-BT; HRQOL measured by the EORTC-QLQ30/BN20 instrument; and neurocognitive function measured the Hopkins Verbal Learning Test

**Immune monitoring components: correlation with clinical responses**
- Baseline immune competency
- ALC recovery kinetics
- Serum chemokine and cytokine profiles (Multiplex and Meso scale)
- T cell subset and phenotypic analysis
- T cell immune responses (EPIMAX)
- TCR repertoire (NanoString)
- HLA
- Intratumoral immune response

Molecular profile

6000 cGy + TMZ

Randomize based on molecular profile

TMZ d 1-5 of 28-d cycle + Ipi iv q 4 wks 6 cycle maximum

Ipi IVq 3 months x 6 cycles

placebo IV q 3 months x 6 cycles
Immunosuppression in Malignant Glioma Patients

Mechanisms
- Cytokines – IL-10, TGF, PGE2
- Lack of functional antigen presenting cells i.e. immunosuppressive microglia/macrophages (microglia, paucity of myeloid dendritic cells)
- Induction of T cell apoptosis (FasL; Galectin-3)
- Treg recruitment to the tumor
- Increase expression of immune regulatory molecules (B7-H1, HLA-G)
- Loss of antigen
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Manifestations
- Decreased delayed type hypersensitivity responses to recall antigens
- Diminished antibody responses
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- Impaired cytotoxic/effector T cell responses
- T cell anergy/unresponsiveness

Is there a common pathway?
The STAT3 pathway is a key regulatory pathway in global immune suppression

- pSTAT3 becomes active in immune cells in the presence of malignancy.
- Induces the expression of immune suppressive cytokines
- STAT3 activity turns off antigen presenting cells like dendritic cells.
- STAT3 suppresses macrophage/microglia activation and function; induces M2 macrophages.
- STAT3 is a transcriptional regulator of FoxP3 in Tregs.
- Ablating STAT3 in hematopoietic cells in mice resulted in marked enhancement of immune responses and marked anti-tumor activity.
- STAT3 blockade in the immune cells from glioma patients can restore T cell proliferation and responses.
- Can be found in the peripheral blood of malignant glioma.
The STAT3 pathway is active in many cancers and especially within malignant gliomas

- Constitutive activation is observed in majority of many malignancies or can be induced by EGF, PDGF, IL-6, CMV.
- Upon phosphorylation of tyrosine$^{705}$ (p-STAT3), dimerization occurs and subsequent nuclear translocation.
- The p-STAT3 is a potent transcriptional factor that regulates key factors that mediate tumor proliferation and survival (e.g., cyclin D1, p53, BCL-XL), migration and invasion (e.g., MMP-2, MMP-9), and angiogenesis by VEGF, basic fibroblast growth factor, and HIF-1α.
- Is a negative prognostic factor for survival.
- Shown to mediate the proneural to mesenchymal transition.
- Maintains “stemness”.

---

**Diagram**: A schematic representation of the STAT3 pathway, showing interactions with other signaling molecules such as EGF, IL-6, and various transcription factors and downstream effectors.
p-STAT3 expression within anaplastic astrocytomas was a negative prognostic factor

(p = 0.02)

(p-STAT-3 Negative)

(median: 34.6 mo, 95% CI, 33.9 mo-NA)

(p-STAT-3 Positive)

(median: 12.2 mo, 95% CI, 6.2 mo-NA)

Abou-Ghazal, CCR, 2008
Induction of high-grade malignant gliomas in immune competent mice (Ntv-a model)

The RCAS/tv-a System

- **Transgene**
  - Nestin tv-a
- **Target**
  - Glioneuronal Progenitors
- **RCAS Vector**
  - gag, pol, env, PDGF-B, LTR

TV-A (ALV-A Receptors)

- TVA
- Avian Leukosis Virus

**Olig 2**

- RCAS-PDGFB
- RCAS-PDGFB+RCAS-STAT3

**Notch1**

**VEGF**

- Tumor Incidence
- High Grade
- Low Grade

Doucette, Neuro-Oncology,
WP1066: Blocks nuclear translocation of dimerized p-STAT3

Caffeic Acid

WP1066

Courtesy of W Priebe
WP1066: Achieves preferential deposition in the CNS
Key Findings of *in vitro* WP1066

Potent inhibitor of STAT3

Inhibits cancer stem cells

Inhibits Tregs

Enhances tumor cytotoxicity

Enhances microglia function

Hussain, CR, 2007; Kong, CCR, 2008
WP1066 exerts potent in vivo efficacy against intracerebral melanoma and gliomas

Kong, CCR, 2008; Kong, CCR 2010; Doucette, NO 2012
WP1066 modulates the tumor microenvironment and immune response
The STAT3 pathway and therapeutic treatment failure

In collaboration with J. de Groot
WP1066 demonstrates minimal in vivo toxicity

Table 1  Systemic histopathological effects of WP1066 in C57BL/6 mice

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration Route</th>
<th>Total (mg/kg)</th>
<th>Pathology of Systemic Organs</th>
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<tr>
<td></td>
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<td>Spleen</td>
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<td>Vehicle</td>
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</table>

a  hemosiderin staining within macrophages  
b  autolysis  
c  chronic inflammatory infiltrate in connective tissue adjacent to the liver  
d  likely post-mortem bacterial endocarditis  
e  pulmonary congestion  
f  reactive lymphoid follicles with germinal center  
g  chronic inflammation
Investigational New Drug (IND) application

- Initial IND has been submitted (11-21-2011) with funding support from the SBIR I and II mechanisms and philanthropy

- Review call with the FDA has been completed (12-21-2011)
  - FDA is requiring second species toxicity and PK studies
  - FDA is requiring more detail on formulation and release criteria

Drug (API) is being made and formulated (CMC)

Anticipated (soon) submission of Phase I clinical trial to MDACC IRB
Key miRNAs down modulated in gliomas

<table>
<thead>
<tr>
<th>miRNA</th>
<th>relative down regulation</th>
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miR-124 expression is lost in all gliomas

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<td>Mixed Oligoastrocytoma</td>
<td>0/5</td>
</tr>
<tr>
<td>Anaplastic Oligodendroglioma</td>
<td>0/16</td>
</tr>
<tr>
<td>Anaplastic Mixed Oligodendroglioma</td>
<td>0/9</td>
</tr>
</tbody>
</table>
miR-124 targets STAT3
MiR-124 influences the immune biology of cancer stem cells
miR-124 blocks glioma growth
Scramble miR-124

Spenocytes: GL261

% Killing of GL261

Scramble control

miR-124

CD4

Scramble

miR-124

IFN-γ

Scramble

miR-124

CD8

IFN-γ

Scramble

miR-124

TNF-α

Scramble

miR-124
miR-124 exerts a therapeutic effect against heterogeneous gliomas
MiR-124 induces immune effector responses from GBM patients

IFNγ producing CD4+ T cells

IL-2 producing CD4+ T cells

TNFα producing CD4+ T cells

pSTAT3 positive CD4+ T cells

IFNγ producing CD8+ T cells

IL-2 producing CD8+ T cells

TNFα producing CD8+ T cells

pSTAT3 positive CD8+ T cells

**P** = 0.0088

**P** = 0.0009

**P** = 0.0026

**P** = 0.0702

**P** = 0.0184

**P** = 0.0078

**P** = 0.099

**P** = 0.0002
Key Considerations for Immune Therapeutic Clinical Trials

• Sufficiently potent immune responses need to be generated to overcome profound immune suppression and/or the immune suppression has to be negated/minimized (GTR)
• Agents that are targeted to a single immune suppressive mechanism are unlikely to have durable efficacy and will likely only treat a select subset of patients
• Targeting “drivers” of malignancy are more likely to be efficacious
• Immune suppression is heterogeneous and needs to be considered in patient stratification - patient specific tailored immune therapeutics based on tumor characteristics is a future goal
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