CynAxis

Traversing the Blood Brain Barrier
Many Effective Therapies Cannot Cross the Blood Brain Barrier (BBB)

Brain Metastases are difficult to treat because either effective therapies cannot cross the BBB or cannot reach adequate concentrations in the microtumor environment.

- 10-20% of all patients develop brain metastasis
- Brain metastasis portends high mortality
  - 8.1% survival rate at 2 year
  - 2.4% survival rate at 5 year
- Neurosurgical excision and radiotherapy not possible or sustainable for some patients

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Incident Proportion of Brain Metastasis by Cancer Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>20%</td>
</tr>
<tr>
<td>Breast</td>
<td>5%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>7%</td>
</tr>
<tr>
<td>Renal</td>
<td>7%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>2%</td>
</tr>
</tbody>
</table>

Glioblastoma Remains Largely Incurable

- Gliomas Grade 1-4 includes astrocytic tumors, oligodendrogliomas, ependymomas, and mixed glioma
- Glioblastoma multiforme (GBM) IV is malignant
- Accounts for 50% of all gliomas in all age groups; 60% of all brain tumors in adults
- Poor prognosis; 14-15 month survival after diagnosis
- Main challenges in therapy of GBM are related with the location of the disease and its complex and heterogeneous biology

Asian Pac J Cancer Prev, 2017. 18 (1), 3-9
CynAxis can solve the problem

- CynAxis can engineer patient specific peptides to activate an adaptive immune response
- This enables transient and defined access of drugs and biologics to the CNS
- This technology can allow delivery any drugs or biologics to the CNS.

2017, LISA CLARK, The Scientist Magazine
CNS antigen-specific CD4⁺ T Cells Could Mediate BBB opening

**Step 1**
Stimulate CD4 T cells with specific peptides delivered to intranasally to the CNS.

**Step 2**
Interferon gamma secreted by CD4 T cells enable transient permeability of the BBB, enabling drugs and biologics to access the CNS parenchyma.

CD4 T cells were stimulated in the CNS and on days 1-6, BBB permeability was measured by albumin access to the CNS.

- MHC class II peptide will be delivered intranasally using a spray.
- Peptide will follow olfactory nerves to enter the CNS to stimulate CD4 T cells.
- CD4 T cells produce interferon gamma to open up the BBB for a few days.
Stimulation of T cells by Intranasal Peptide (IN) Enables Checkpoint Inhibitor Biologics to Access Brain Tissue and Treat Tumor

- Immunize -5 weeks
- Brain tumor inoculation day 0
- Checkpoint inhibitor 200µg (CPI) day 9 day 11
- Monitor survival

Day 7 Tumor burden prior to treatment

Graph showing survival over days with different peptide treatments:
- IN control peptide alone
- IN control peptide + CPI
- IN peptide + CPI
## Intervention Technology

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Technology</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Convection-enhanced delivery</strong></td>
<td>Catheters placed to infuse into a specified area of the brain</td>
<td>• Larger molecules have low Vd, hence limited efficacy</td>
</tr>
<tr>
<td><strong>Nanoparticles</strong></td>
<td>Various classes of particles types engineered to enhance delivery across BBB</td>
<td>• Relies on endocytosis so trafficking drug of interest to correct cellular compartments challenging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rapid particle clearance in systemic circulation</td>
</tr>
<tr>
<td><strong>Focused Ultrasound and Microbubbles</strong></td>
<td>Microbubbles are injected peripherally and ultrasound causes the bubbles to swell and contract.</td>
<td>• Effects on endothelial tissue integrity unknown and may increase risk of leaky endothelium,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increased risk thrombosis, infection</td>
</tr>
<tr>
<td><strong>Chemical Disruption</strong></td>
<td>Non-Ionic Amphiphilic compounds can traverse BBB via endothelial cells.</td>
<td>• Clinical trials to date have shown no efficacy</td>
</tr>
<tr>
<td><strong>Utilizing specific receptors or transporters</strong></td>
<td>Leverage a specific receptor or transporter that gates BBB access.</td>
<td>• Achieving sufficient concentrations in CNS via transport mechanism variable and unpredictable</td>
</tr>
<tr>
<td><strong>Osmotic diuretics</strong></td>
<td>Temporary dehydration of BBB endothelial cells, grants small and large molecules indiscriminate access to the brain for limited time</td>
<td>• Technology developed in 1970s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Osmotic BBB disruption results in transient cerebral edema</td>
</tr>
</tbody>
</table>
## CynAxis IP Estate

<table>
<thead>
<tr>
<th>Patent Title</th>
<th>Country</th>
<th>Application Type</th>
<th>Status</th>
<th>Application No.</th>
<th>Patent No.</th>
<th>Expiration Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition and Methods</td>
<td>US</td>
<td>Issued</td>
<td></td>
<td></td>
<td></td>
<td>2036</td>
</tr>
<tr>
<td>Utility and Formulation</td>
<td>US</td>
<td>Issued</td>
<td></td>
<td></td>
<td></td>
<td>2038</td>
</tr>
</tbody>
</table>
Cynaxis Timeline and Use of Proceeds

**Pre-Clinical Characterization**
- 2020
  - PK Studies
  - ADME
- 2021
  - GLP Toxicology Studies (Short and Long Term)
  - Estimate effective human dose
  - GLP toxicology and safety (2nd species)
- 2022

**Preclinical Proof of Mechanism (POM)**
- 2020
  - Metastatic Efficacy Model
  - CNS Rare Disease Efficacy Model

**CMC**
- 2020
  - API CMO Qualification
  - Formulation for inhalation
- 2021
  - Process Scale-up and Optimization
  - Analytical Method Development / Qualification
  - Initial cGMP Manufacturing
- 2022
  - Delivery Device evaluation

**Regulatory**
- 2020
  - Pre-IND

**Patent Estate**
- 2020
  - File Additional Method of Use Provisional

Budget reflects development costs only and excludes personnel, G&A

**2020**
- Go/No Go 1

**2021**
- Go/No Go 2

**2022**
- Go/No Go 3