BrainStorm Cancer Therapeutics

Redefining blood-brain barrier penetration

W. Mark Saltzman, Ph.D.
Goizueta Foundation Professor
Department of Biomedical Engineering
Yale University
Head, Jonathan Edwards College
Yale University

Ranjit S. Bindra, M.D., Ph.D.
Professor
Department of Therapeutic Radiology
Yale School of Medicine
Co-Director, Brain Tumor Center
Yale Cancer Center

Minsoo Khang, M.S.
Graduate Student
Department of Biomedical Engineering
Yale University

Philip Kong, Ph.D.
Blavatnik Fellow
Yale University
Defining the Clinical Problem

Many adult and pediatric CNS cancers are difficult to treat, and patients rarely survive more than 1-2 years...

Diffuse Intrinsic Pontine Glioma (DIPG)  
Median Overall Survival: 4-17 months

Recurrent Medulloblastoma and Ependymoma  
Median Overall Survival: 6 months-2 years

Recurrent Glioblastoma  
Median Overall Survival: 6-12 months

Brain and Leptomeningeal Metastases  
Median Overall Survival: 3-12 months
What are the barriers to effective therapies for these tumors?

**Blood Brain Barrier (BBB)**

>98% of small molecules cannot penetrate the BBB, thus better approaches are needed to enhance CNS exposure.

**Local and Systemic Toxicity**

Drug combination therapies can effectively target CNS tumors, but local and systemic toxicities are dose-limiting...direct injection into the CNS is a potential solution.

**Tumor Molecular Heterogeneity**

Intra- and inter-tumor heterogeneity is common in CNS cancers and brain metastases, suggesting a need for drug regimens with activity across many tumor types.
The Blood Brain Barrier is a Treatment Efficacy Barrier

>98% of small molecules do not penetrate the BBB

Convection-Enhanced delivery (CED)

In both cases, drug washes away rapidly after injection...

<table>
<thead>
<tr>
<th>Opioid Drug</th>
<th>Half-life in CSF</th>
<th>Duration of action</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>90 min</td>
<td>12-24 hrs</td>
</tr>
<tr>
<td>Meperidine</td>
<td>68 min</td>
<td>1-3 hrs</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>100 min (after epidural)</td>
<td>1-3 hrs</td>
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Intrathecal (IT) Infusion
Dose-Limiting Local and Systemic Toxicities

1. Radiation therapy is active against many CNS tumors, but it is locally toxic, and typically not curative.

   - Craniospinal irradiation (CSI)

   - Severe cognitive decline over time

   - Radiation necrosis

2. Combinations of chemo and systemic therapies can increase efficacy, but systemic toxicity is dose-limiting.

   - PARP inhibitor + TMZ chemotherapy
     - synergy in medulloblastoma cells *in vitro*

   - BMN673 (PARPi) doses over 1 mg are severely toxic to the bone marrow

https://www.nature.com/articles/nrneurol.2012.182/figures/1
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5648323/
https://www.reddit.com/r/interestingasfuck/comments/cwu12s/the_lethal_dose_of_fentanyl_2_milligrams_compared/
https://www.cancer.gov/article/2014-10-09/figure2
How will CNS-directed nanoparticles address these issues?

Smart Drug Combinations + Brain penetrating Nanoparticles + Direct CNS Delivery

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Advantages of our proposed approach
- Higher doses in the CSF and brain will be possible
  - Minimize systemic drug exposure/toxicity
  - Allows combinations with systemic drugs
Sample Data: Successful Development of IT Nanoparticle Delivery Strategies...

1. We can now deliver NPs into the CSF space

2. PET tracers for nanoparticle tracking

3. Detection of IT NPs *in vivo*
Why our team?

Ranjit S. Bindra, M.D., Ph.D.
Professor
Yale Radiation Oncology

W. Mark Saltzman, Ph.D.
Professor
Yale Biomedical Engineering

High-Impact Scientific Publications

Innovative Academic Collaboration

Biotech Start-up Veterans

Why our team?

Bridging the realms of translational cancer research and nanomedicine

STRADEFY BIOSCIENCES

Veterans

Innovative Academic Collaboration

Biotech Start-up

Why our team?

High-Impact Scientific Publications
BrainStorm’s Overall Strategy

1. Identify shelved & off-patent drugs
2. Identify drugs with patents expiring soon
3. Partnerships for on-patent, non-CNS penetrant drugs

Create NP formulations, in vitro/vivo validation
(leverage Saltzman Lab expertise in NP formulation)

IND-enabling work (in-licensing as indicated)

Translate into phase I trials...
(Leverage Bindra Lab brain tumor biomarkers + bench-to-bedside expertise)
# How a Blavatnik Award will help launch BrainStorm

<table>
<thead>
<tr>
<th>Year</th>
<th>Pre-Seed/Seed Round</th>
<th>Seed/Series A Round</th>
</tr>
</thead>
<tbody>
<tr>
<td>2021</td>
<td></td>
<td></td>
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<tr>
<td>2022</td>
<td></td>
<td></td>
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<tr>
<td>2023</td>
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<tr>
<td>2024</td>
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## Blavatnik Award Period

### Demonstrate feasibility/scale-up at a contract research organization (CRO)

- **Milestone 1 ($75K)**
  - Initial NP Formulation (Months 1-3)
  - PLA-HPG NP Synthesis (with PAIP1 encapsulation)
  - Purify drug-loaded NPs

- **Milestone 2 ($75K)**
  - Convert to bioadhesive NPs (Months 4-6)

- **Milestone 3 ($150K)**
  - NP Characterization (Months 7-12)
  - Characterization (size, z-potential)
  - Drug loading
  - Release Kinetics
  - Cellular Uptake

~12 months, ~$300K
Why Now?

**DNA Damage Response (DDR) Inhibitors as a Case Study**

- **2000**: DDR inhibitors (DDRI’s) created/patented
- **2010**: DDRi optimization, trials, approvals
- **2020**: Yale Intellectual Property Generated Around Our NPs
- **DDRI’s going off-patent**

**Key CED/Intrathecal (free drug) Trials Completed**

- **Opportunity to rapidly advance CNS-directed NPs into the clinic**

Fundamental academic studies which validate the potential for CNS-directed NPs
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