



# **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.**

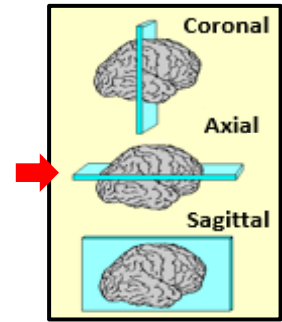
Graduate Student  
Department of Biomedical Engineering  
Yale University

**Philip Kong, Ph.D.**

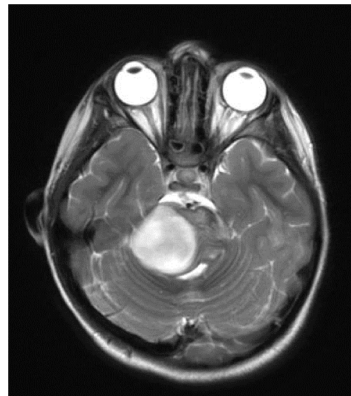
Blavatnik Fellow  
Yale University

# Defining the Clinical Problem

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

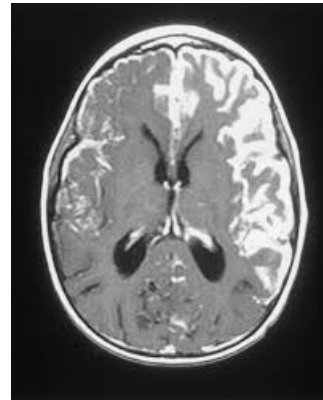


**Diffuse Intrinsic Pontine Glioma (DIPG)**



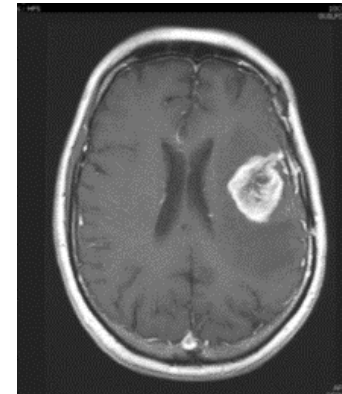
**Median Overall Survival:  
4-17 months**

**Recurrent Medulloblastoma and Ependymoma**



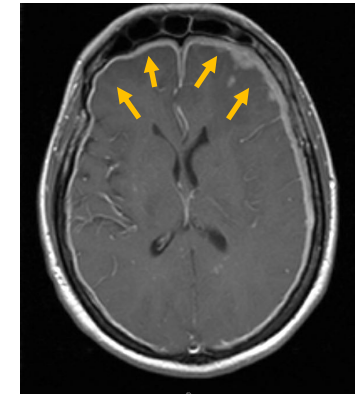
**Median Overall Survival:  
6 months-2 years**

**Recurrent Glioblastoma**



**Median Overall Survival:  
6-12 months**

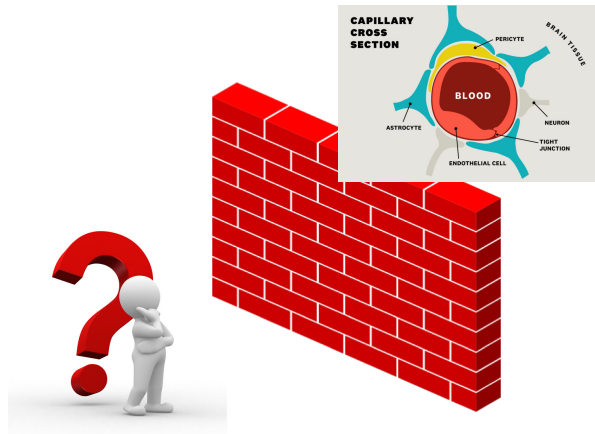
**Brain and Leptomeningeal Metastases**



**Median Overall Survival:  
3-12 months**

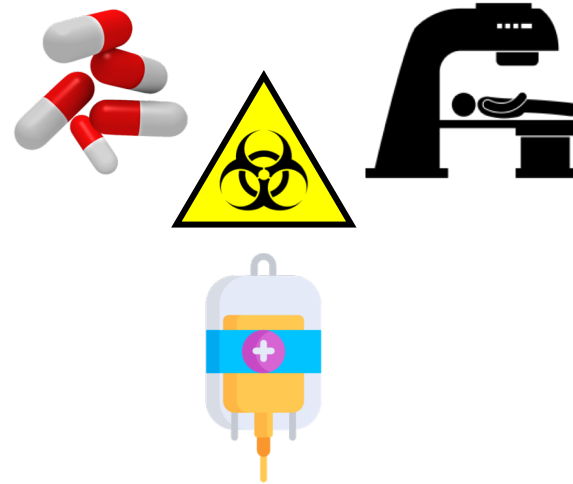
# What are the barriers to effective therapies for these tumors?

## Blood Brain Barrier (BBB)



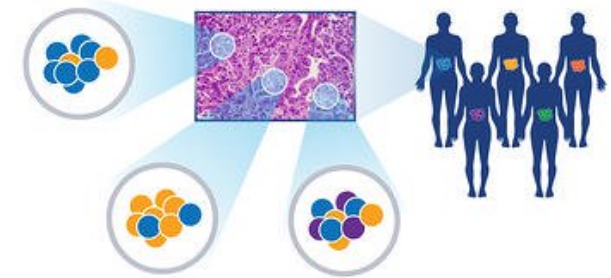
*>98% of small molecules cannot penetrate the BBB, thus better approaches are needed to enhance CNS exposure*

## 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*

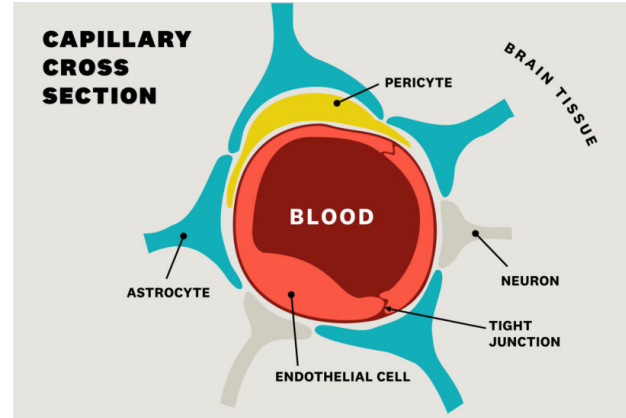
## Tumor Molecular Heterogeneity



*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

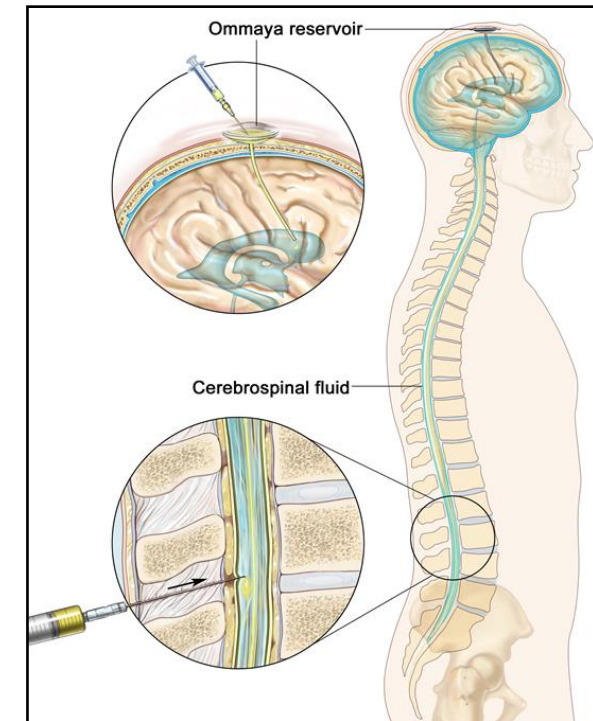
>98% of small molecules do not penetrate the BBB



## Convection-Enhanced delivery (CED)



## Intrathecal (IT) Infusion



Direct injection into the CNS has been tested as a solution

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

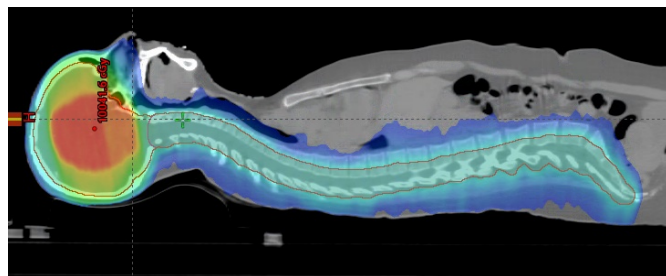
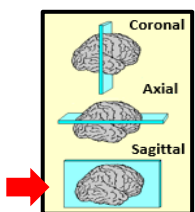
Sample IT Infusion half-lives

Opioid Drug	Half-life in CSF	Duration of action
Morphine	90 min	12-24 hrs
Meperidine	68 min	1-3 hrs
Sufentanil	100 min (after epidural)	1-3 hrs

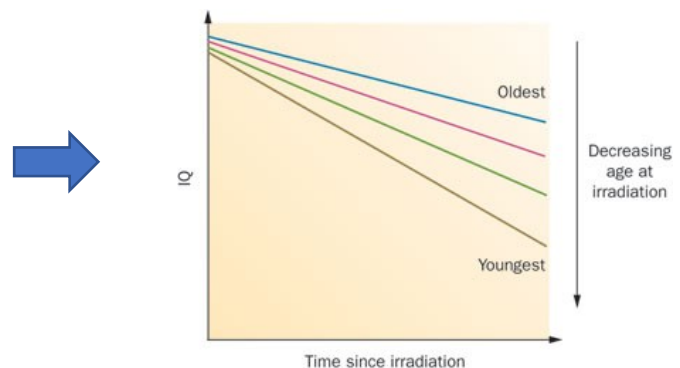
# Dose-Limiting Local and Systemic Toxicities

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

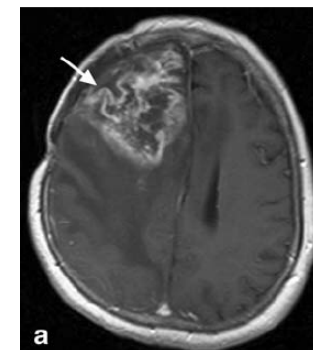
Craniospinal irradiation (CSI)



Severe cognitive decline over time

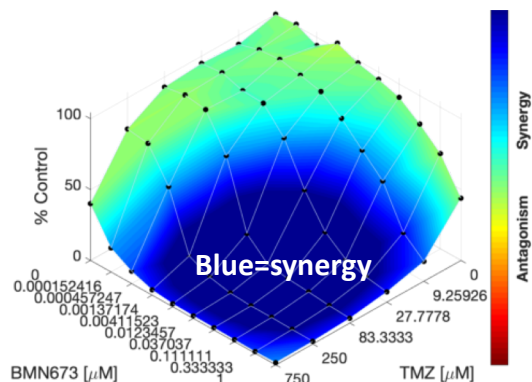


Radiation necrosis



## 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*



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ORIGINAL RESEARCH

Risk of severe hematologic toxicities in cancer patients treated with PARP inhibitors: a meta-analysis of randomized controlled trials

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



<https://www.nature.com/articles/nrneuro.2012.182/figures/1>  
[https://www.researchgate.net/figure/Radiation-necrosis-close-to-the-site-of-the-primary-tumor-in-a-50-year-old-woman-after\\_fig2\\_26243361](https://www.researchgate.net/figure/Radiation-necrosis-close-to-the-site-of-the-primary-tumor-in-a-50-year-old-woman-after_fig2_26243361)  
<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.reddit.com/r/interestingasfuck/comments/cwu12s/the_lethal_dose_of_fentanyl_2_milligrams_compared/)

# How will CNS-directed nanoparticles address these issues?



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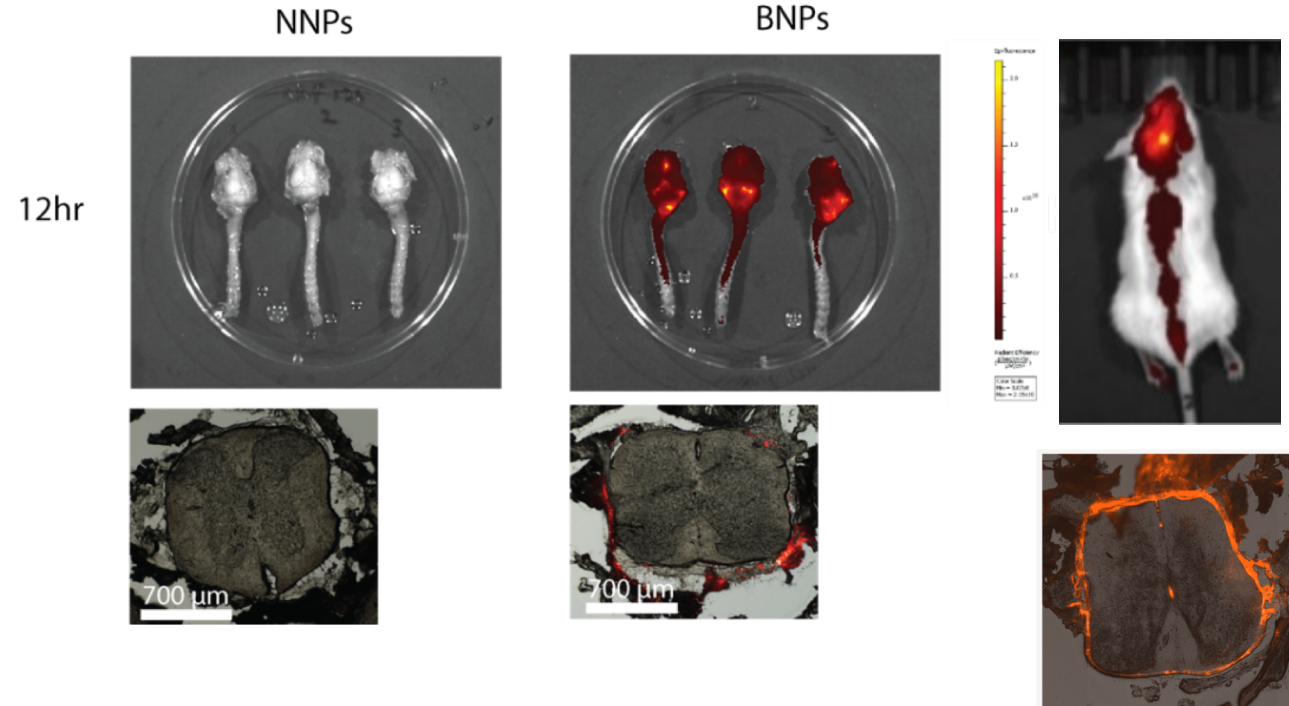
## Advantages of our proposed approach

- Higher doses in the CSF and brain will be possible
- Minimize systemic drug exposure/toxicity
- Allows combinations with systemic drugs

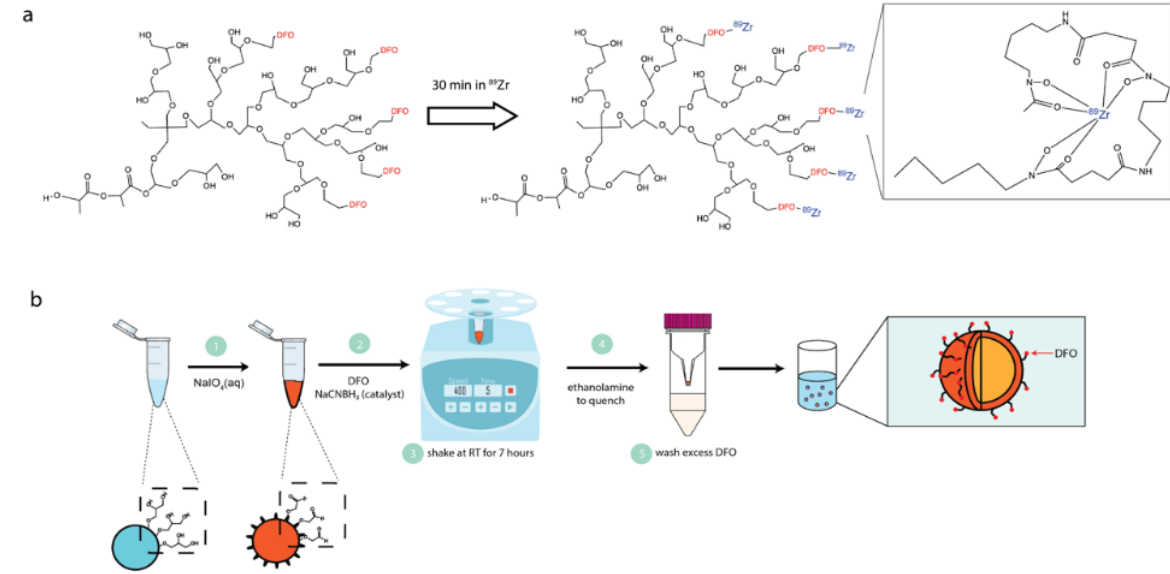


# Sample Data: Successful Development of IT Nanoparticle Delivery Strategies...

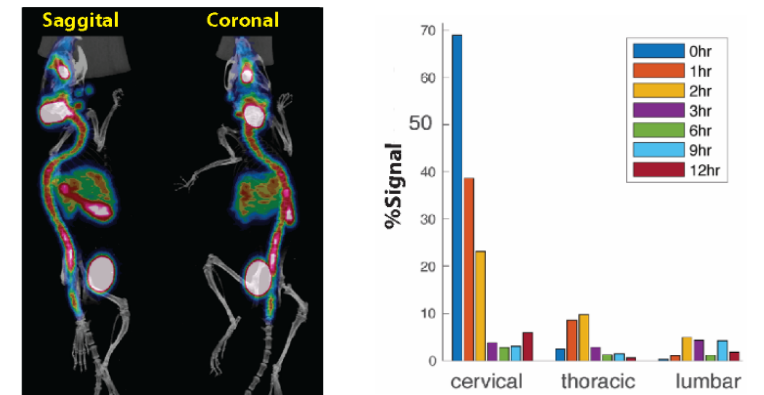
## 1. We can now deliver NPs into the CSF space



## 2. PET tracers for nanoparticle tracking



## 3. Detection of IT NPs *in vivo*

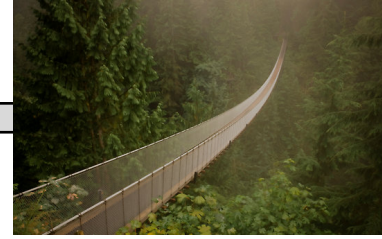


Minsoo Khang  
Grad Student  
(Saltzman Lab)

# Why our team?



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

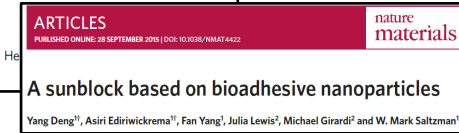
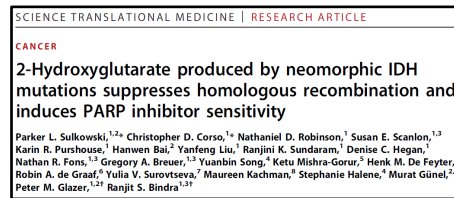
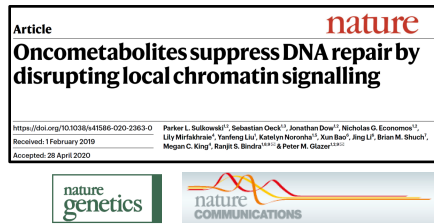


*Bridging the realms of translational cancer research and nanomedicine*

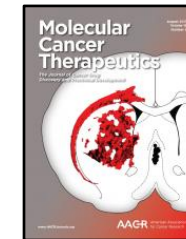
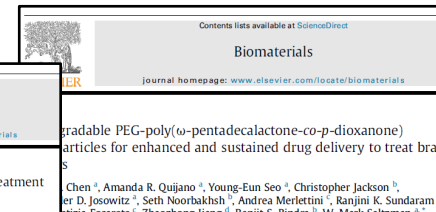
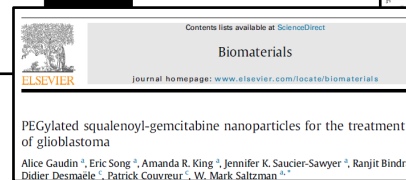
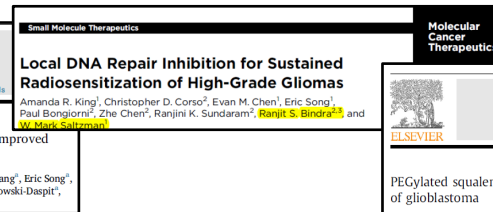


**W. Mark Saltzman, Ph.D.**  
Professor  
Yale Biomedical Engineering

**High-Impact Scientific Publications**



**Innovative Academic Collaboration**



**Biotech Start-up Veterans**



**STRADEFY BIOSCIENCES**

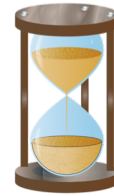


# BrainStorm's Overall Strategy

Identify shelved & off-patent drugs



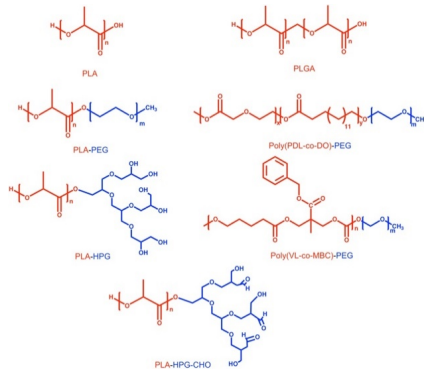
Identify drugs with patents expiring soon



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



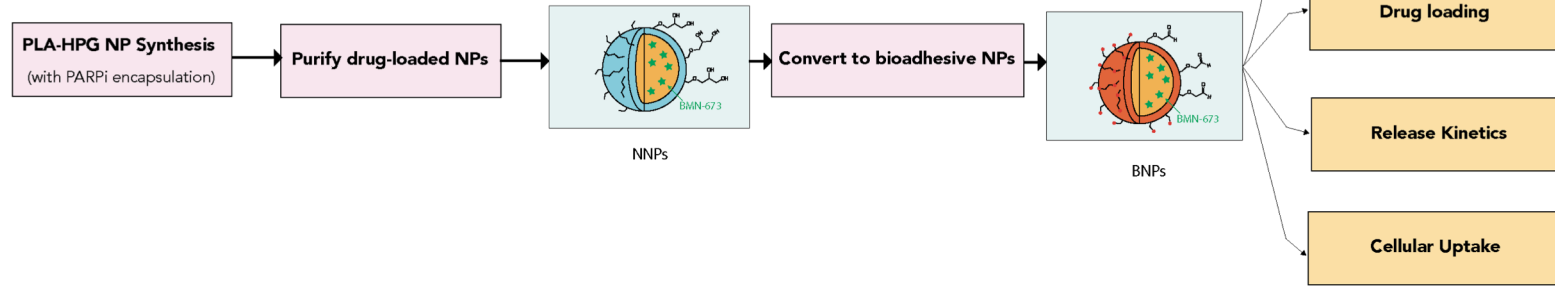
**Demonstrate feasibility/scale-up at a contract research organization (CRO)**

*~12 months, ~\$300K*

**Milestone 1 (\$75K)  
Initial NP Formulation  
(Months 1-3)**

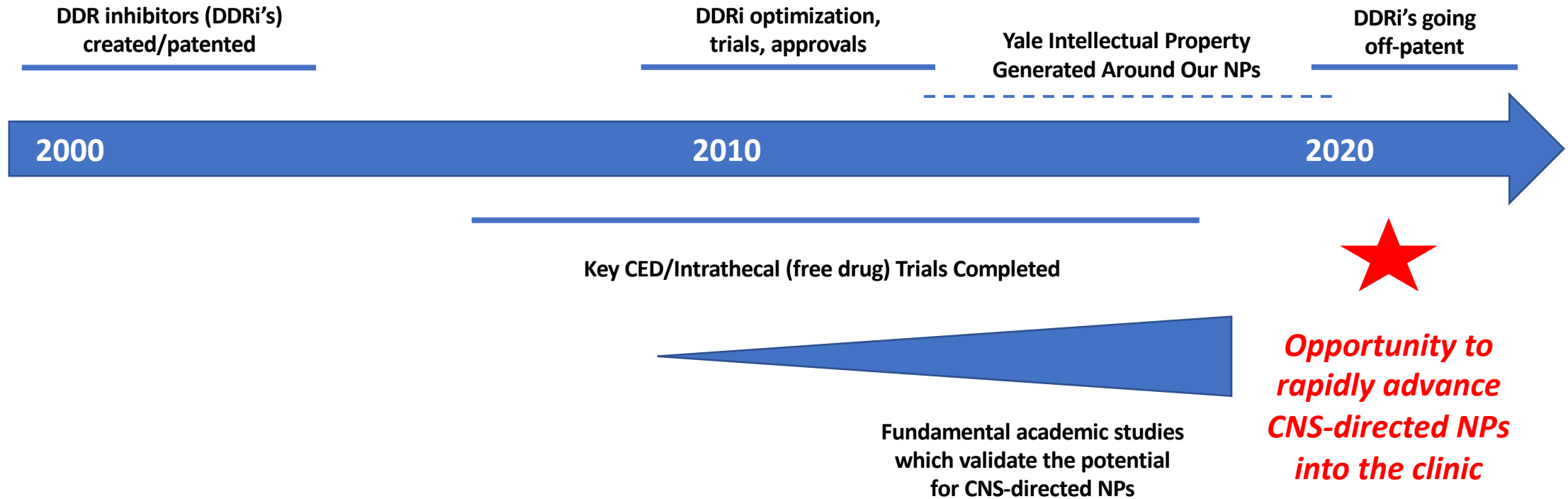
**Milestone 2 (\$75K)  
Convert to BNPs  
(Months 4-6)**

**Milestone 3 (\$150K)  
NP Characterization  
(Months 7-12)**



# Why Now?

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





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