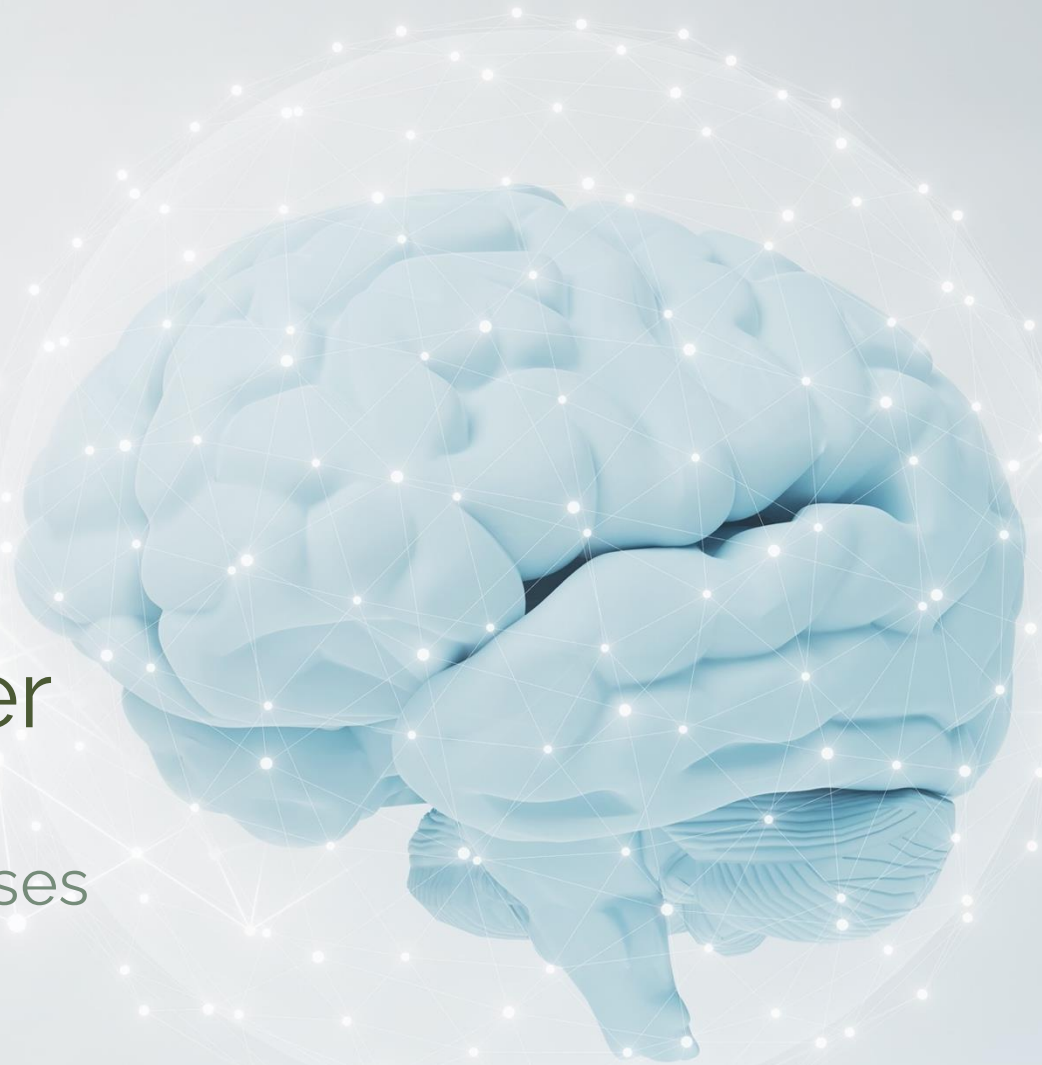
B^3 Therapeutics

Bypassing the blood brain barrier

For the treatment of primary CNS tumors,
brain metastases, and debilitating genetic diseases

Blavatnik 2024-2025 | Ranjit Bindra, MD, PhD



Seasoned Founding Team

Expertise spanning the bench to bedside to biotech

Mark Saltzman, PhD

Goizueta Foundation Professor
Yale School of Biomedical Engineering

Leader in nanoparticle engineering and novel drug delivery systems

Ranjit Bindra, MD, PhD

Harvey and Kate Cushing Professor
Yale School of Medicine Therapeutic Radiology, Neurosurgery

Leader in brain tumors and DNA damage repair

Kevin Rakin

Partner - HighCape Capital

Experienced Serial Entrepreneur and investor

YALE VENTURES

Shannon Anderson, PhD, Business Development

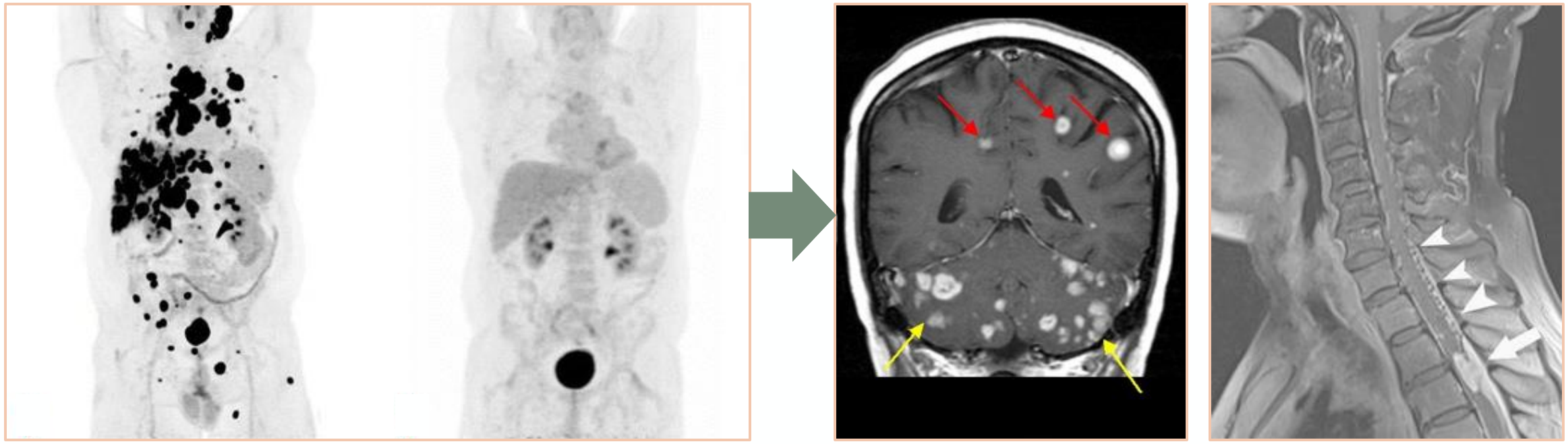
Robert Williams, PhD, Blavatnik Fellow

The Problem: Controlling Cancer Spread in the CNS

>5% of all cancer patients develop CNS metastases, accounting for ~100-200,000 new patients diagnosed each year

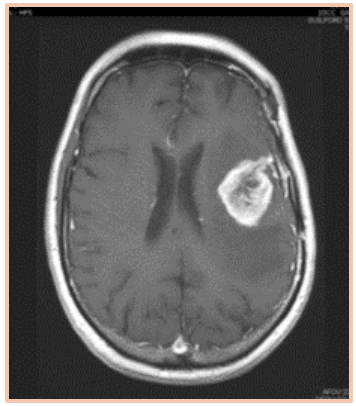
Remarkable systemic tumor control → **Lethal CNS metastases emerge**

Baseline Scan **Post-PD1 (3 mo)** **Brain** **Spine**



Urgent Unmet Need: effective therapies for brain tumors

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



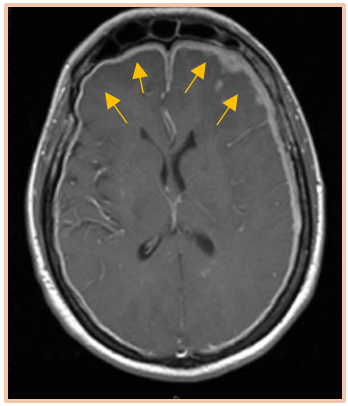
Glioblastoma and other Primary Brain Tumors

Deadliest and most common adult brain cancer

Median Overall Survival: 8-12 months (GBM)

Standard of Care: surgery, radiotherapy (RT) chemotherapy, Bevacizumab

Prevalence: **25,000** new cases per year in USA



Brain Metastases and Leptomeningeal Disease (LMD)

Occurs in 5% of all cancer patients

Median Overall Survival: 3-9 months

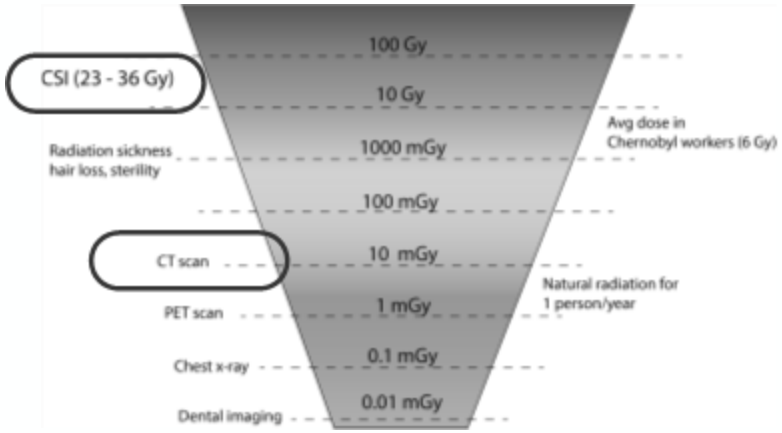
Standard of Care: radiotherapy, intrathecal + systemic chemotherapy

Prevalence: **200,000** new cases/yr in USA

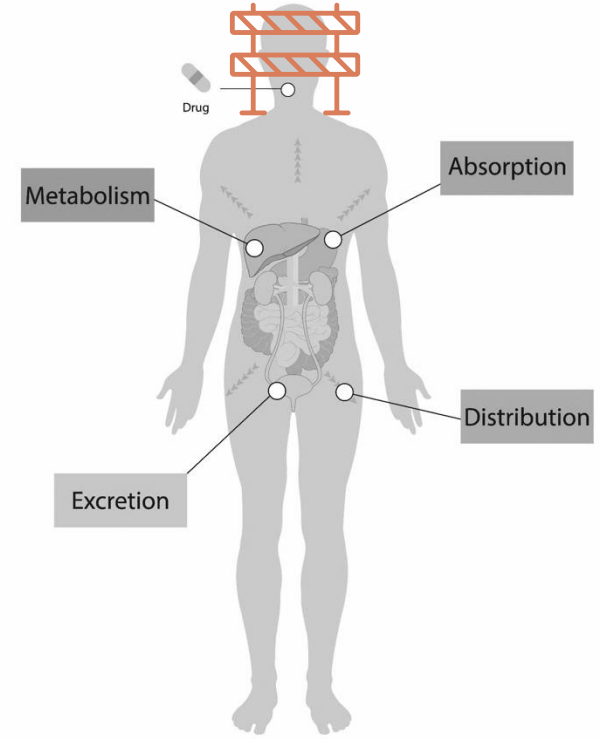
Limited treatment options for CNS tumors with poor overall survival

Current options are ***ineffective*** for CNS tumor control

Radiotherapy is ineffective and significantly reduces cognitive performance

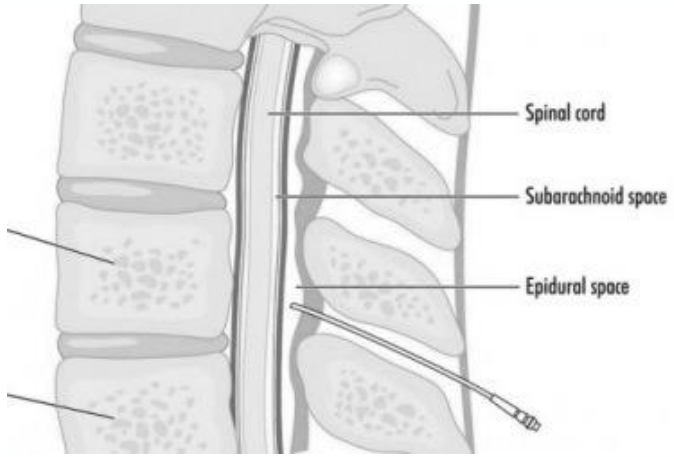


> 98% of all drugs delivered systemically do not reach the brain



Systemic chemotherapy is ineffective and accompanied by severe side effects

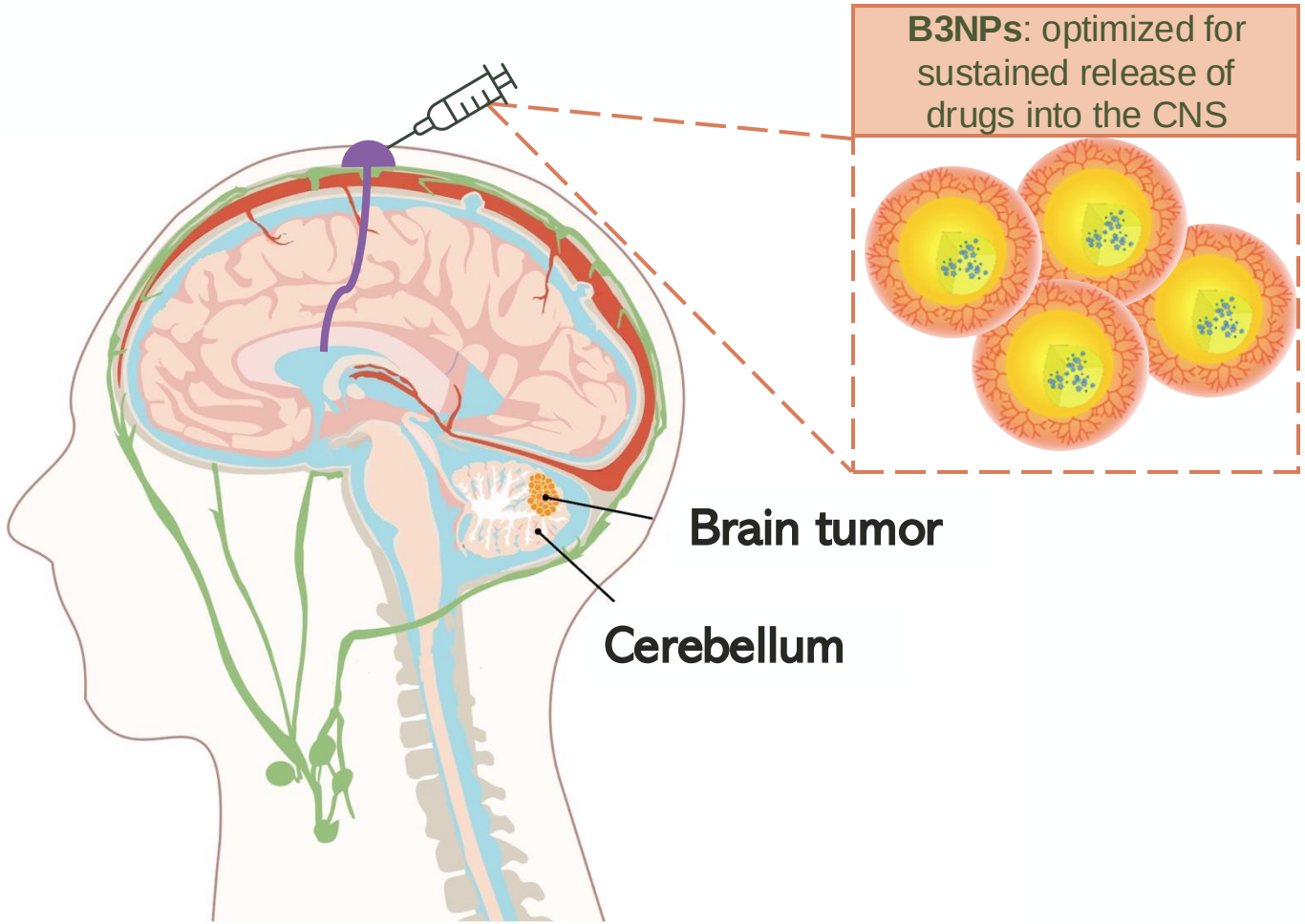
Drugs are cleared rapidly when administered directly into the CSF



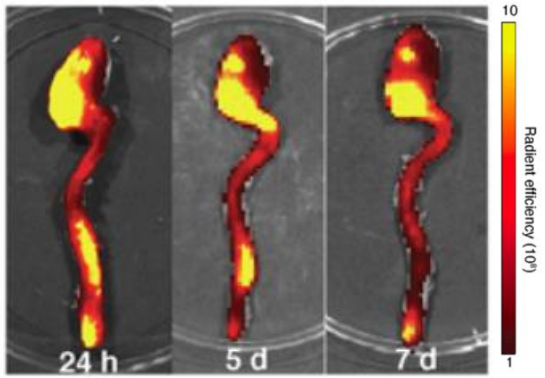
Opioid Drug	Half-life in CSF	Duration of action
Morphine	90 min	12-24 hrs
Meperidine	68 min	1-3 hrs
Sufentanil	100 min (after epidural)	1-3 hrs

Solution: CNS-directed, sustained release nanoparticles (NPs)

B3NPs distribute throughout the brain and spinal cord following intrathecal (IT) administration



- Composed of a biodegradable polymer based on materials ***widely used in FDA products***
- Distributed throughout the CNS and ***retained for >3 weeks*** after one injection
- Limited systemic exposure
- Compatible with multiple drug modalities



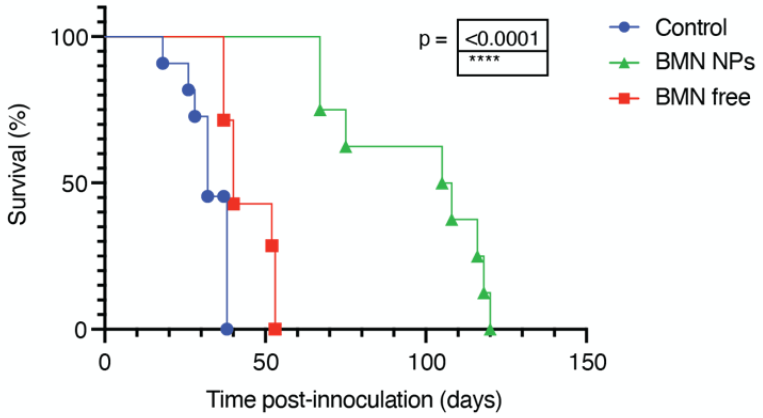
Khang et al, Science Translational Medicine 2023

PCT US 2016/031890 (treatment of gliomas, exp. 2035); PCT US 2023/079181 (leptomeningeal tumors, exp. 2042)

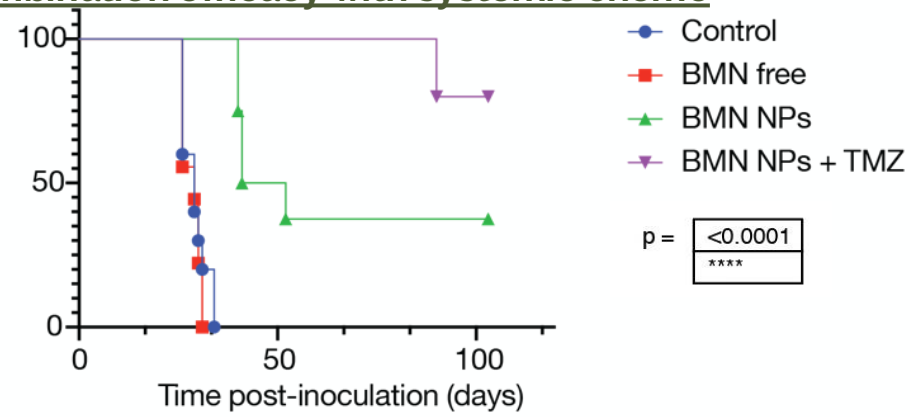
Administration of PARPi encapsulated in B3NPs significantly improves survival

A single dose of B3NP-encapsulated, FDA-approved PARP inhibitor (BMN-673) significantly improves survival as a monotherapy or combined with chemotherapy in an orthotopic mouse model of medulloblastoma

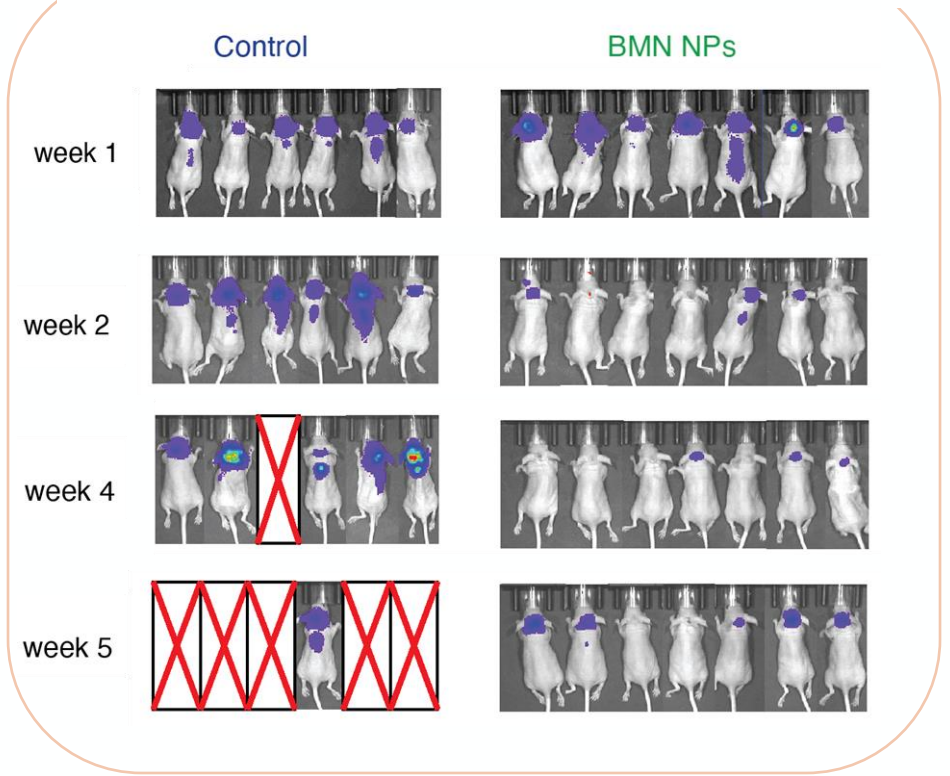
Monotherapy efficacy



Combination efficacy with systemic chemo



Remarkable monotherapy tumor control



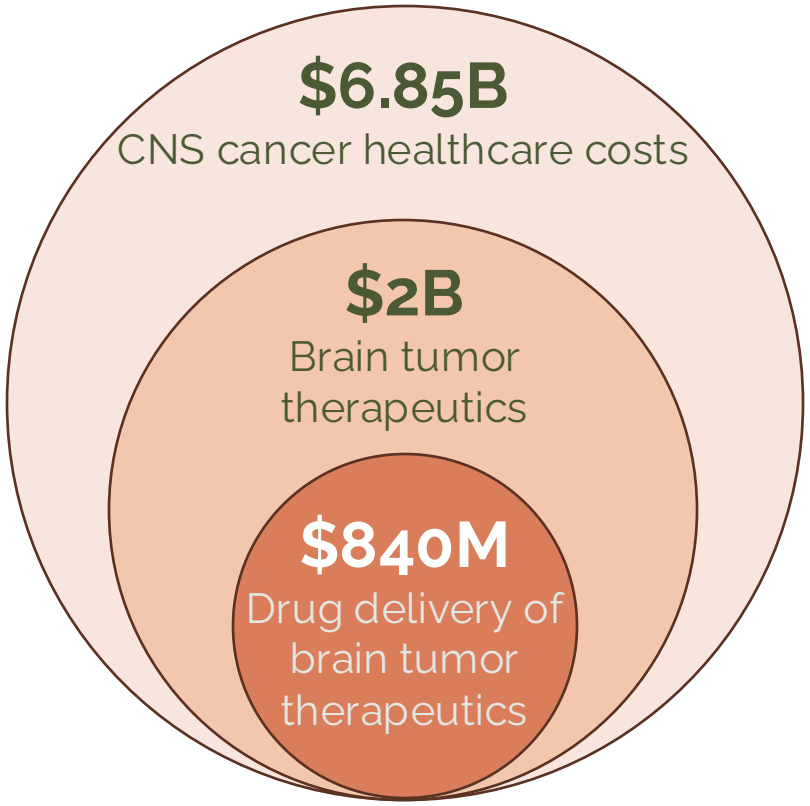
Khang et al, Science Translational Medicine 2023

Competitive Advantage

	B3NP	Intrathecal Radioligand/Abs	Other NPs	Ab Transport Vehicles (Denali)	Systemic Chemotherapy
CNS Penetration	*high*	high	low	low	low
Duration of Effect	*high*	low-mid	mid	unknown	low
Toxicity	*low*	high	mid	unknown	high
Broad Applicability	*yes*	no	varies	yes	yes

Commercial opportunity

***Effective** brain cancer therapies and CNS delivery technologies are commercially viable*



ModifiBio
Modifying DNA to Eradicate Cancer

$1.3 B acquisition
Q4 2024

Preclinical

Merck acquired Modifi Bio to continue development of novel GBM small molecule therapy

ALIADA THERAPEUTICS

$1.4B acquisition
Q4 2024

Preclinical

AbbVie acquired BBB-accessing technology for $1.4B cash

DENALI

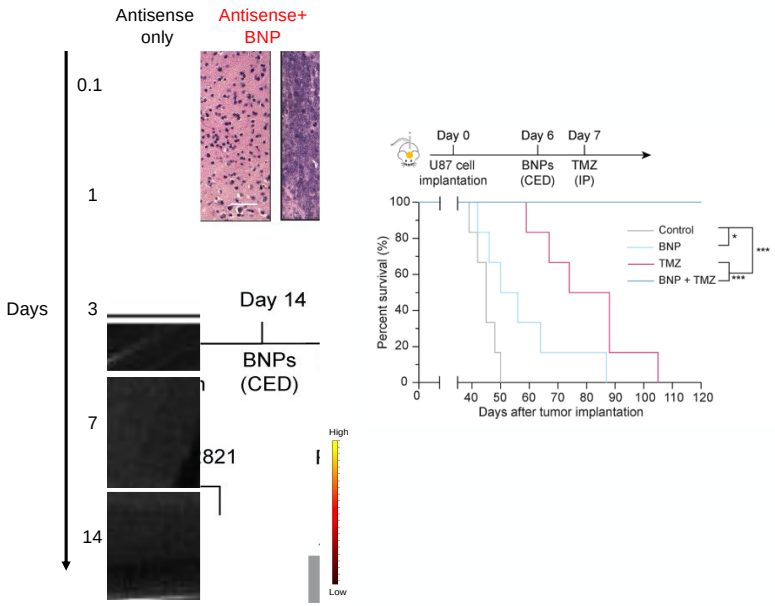
$471M acquisition
2018

Preclinical

Denali acquired F-star's CNS delivery technology

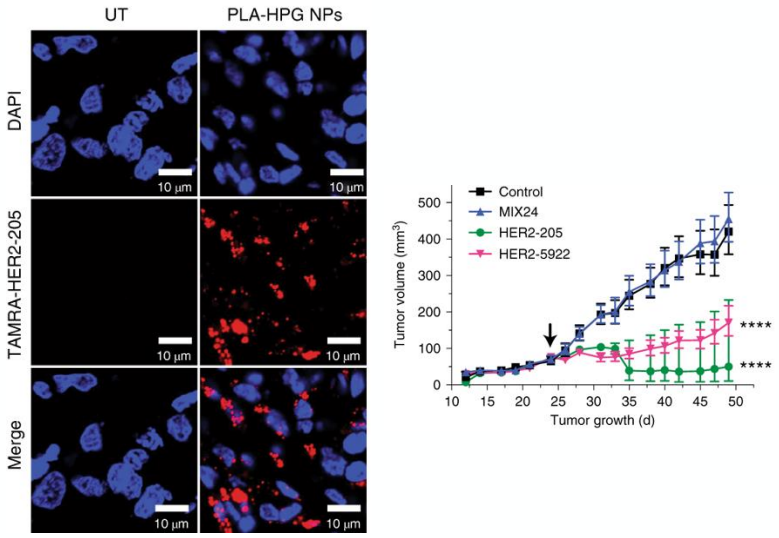
B3NPs are compatible with multiple therapeutic modalities

Anti-Sense Oligonucleotides



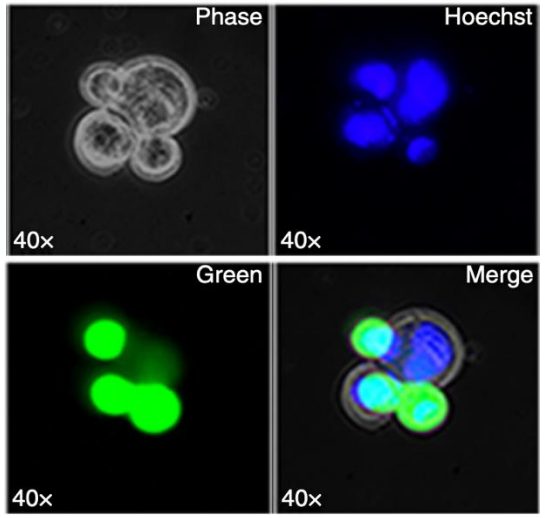
Science Advances, 2023

DNA Oligonucleotides



Nature Biotechnology, 2021

Plasmid DNA



Mol. Can. Ther., 2016

B3NPs also offer a sustained release advantage for IT-administered treatments for several diseases beyond cancer…

Broad Intellectual Property Protection

Protection for current B3NP and any future optimization; for use with any small molecule or nucleic acid
All Yale IP

Lead B3NP Formulation

Patent Family 1:
Foundational Compositions of Matter and Methods of Use
Published 2015

Patent Family 2:
Compositions and methods for treatment of Gliomas
National Phase filings begin May 2025
Published 2017

Patent Family 3:
Compositions and methods of use for treatment of leptomeningeal tumors
Published 2024

Future filings:
Manufacturing, classes of compounds, additional disease areas

Additional B3NP Formulations

Patent Family 4:
Compositions of Matter:
PEG-based Bottlebrush Block Copolymers for the Formation of Long-Circulating Nanoparticles
Filed 2024

Patent Family 5:
Compositions of Matter:
Novel biodegradable and biocompatible polyethylene glycol ethylenebrassylate-co-dioxanone polymer for fabrication of nanoparticles in drug delivery
Filed 2024

Blavatnik award de-risks lead B3NP and enables development of additional formulations

Combining B3NP with FDA-approved, off-patent PARPi for an Orphan indication is cost- and time-efficient

Completed

- ✓ Lead B3NP polymer optimization
- ✓ In vivo Biodistribution
- ✓ In vivo efficacy as monotherapy and synergy with standard of care
- ✓ Varied payload delivery

$300k Blavatnik Full Award

$200k
Safety/tox of lead B3NP + PARPi; CMC scale-up

$50k
Efficacy evaluations with additional NP-encapsulated compounds

$50k
Optimization of additional B3NP formulations

NewCo Formation
$5-10M Seed Round

IND-enabling Studies

Series A Financing ($25-40M)

Phase Ia/Ib Trial

Solid tumor CNS mets (adult patients)

Appendix

Efficient Path to the Clinic

Combining B3NP with FDA-approved, off-patent PARPi for an Orphan indication is cost- and time-efficient

Completed:

- ✓ Lead B3NP polymer optimization
- ✓ In vivo Biodistribution
- ✓ In vivo efficacy as monotherapy and synergy with standard of care
- ✓ Payload encapsulation optimization