Targeting cancer at its core...

Presenter:

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Co-Director, Yale Brain Tumor Center
Mission Statement:
Translate the most innovative, cutting-edge science into biomarker-driven, novel therapeutic strategies for brain tumors... and beyond...
What’s the clinical problem?

**Incurable Gliomas**
*(Diffuse Intrinsic Pontine Glioma, Glioblastoma, High Grade Gliomas)*

- Devastating adult and pediatric brain tumors, most common primary CNS cancer
- Survival ranges 1-3 years in most cases, no effective treatment options
- Recent “quantum leaps” in the molecular drivers behind these cancers

*Images from: https://twitter.com/ReflectsOfGrace/status/1045705892874866688*
*https://www.facebook.com/dipgkids/photos/a.304246256608047/432840630415275/?type=3&theater*

3 yo F with DIPG
Axial T2-weighted MRI

*Publically available patient images from the internet*
How can Athena solve this problem?

3 yo F with DIPG
Axial T2-weighted MRI

Billions of tumor cells

Key cellular furnace
“The NAD cycle”

- NA
- QA
- KYN
- TDO/IDO
- Tryptophan

We found that many brain tumors have lost this pathway (furnace=broken)

Glycolysis, TCA cycle, β-oxidation
Oxidative phosphorylation
Serine synthesis

DNA repair
Gene expression
Energy sensing
Gene expression
Stress response
How can Athena solve this problem?

We found that brain tumors have lost this pathway* (furnace=broken)

Key cellular furnace: “The NAD cycle”

Multiple drugs developed which target NAMPT (NAMPTi’s)

Why have these drugs stalled in the clinic?
• Failed trials with no molecular biomarkers
• Limited assessments of CNS penetration
• Dose-limiting toxicity at the highest doses

How can we exploit this NAD energy defect?

(*Patent Filed: 62/748,911)
Our data/discoveries

1. PPM1D mutations confer silence the expression of NAPPRT, a key NAD metabolism gene

2. PPM1D mutations confer NAMPTi sensitivity in patient-derived glioma models in vitro

3. PPM1D mutations induce NAMPTi sensitivity in vivo

4. PPM1D-induced NAMPTi sensitivity occurs across multiple tumor types
Our data/discoveries – Summary of our academic work

- Discovery of mutations which predict NAMPTi sensitivity
- Identification of NAPRT silencing via CIMP induction as the primary MOA
- In vitro validation in multiple patient-derived glioma models
- Confirmation of “tumor type agnostic” effect, multiple unique NAMPTi’s
- Validation with multiple structurally unique NAMPTis across multiple tumor types

The academic work has been completed... and we are now ready to translate this into a venture, in order to perform IND-enabling studies...
The team behind Athena...

Ranjit S. Bindra, MD/PhD

- Associate Professor, Yale Brain Tumor Center Co-director
- Adult/Peds CNS Radiation Oncology Attending, expertise in bench-to-bedside trials
- PI of a large, R01-funded drug screening laboratory at Yale
- Founded two biotechnology companies

Charles Brenner, PhD

- Professor and Head, Biochemistry, University of Iowa
- Discovered the nicotinamide riboside kinase (NRK) pathway & vitamin activities of NR and NAR
- Developed quantitative targeted NAD metabolomics
- Chief Scientific Advisor, ChromaDex

Jamison Langguth, MPH, MSED

- MPH in Health Management, Harvard University
- Blavatnik Fellow, Yale University
- 8 years of clinical trials operations experience (5 years in neuro)
- Co-founder, Aero Therapeutics
What will we do with the Blavatnik funding?

1. Patent Landscape analysis (~50K)
   Goal? Identify/In-license a NAMPTi
   Who? Yale Center for Mol Discovery

2. PK/PD Modeling (~$75K)
   Goal? Profile CNS exposure, model PK/PD
   Who? Karmanos PK Core Facility

3. Validate NAMPTi’s in PDXs (~$100K)
   Goal? Demonstrate efficacy at a CRO*
   Who? Charles River, Champions Onc.

4. Develop companion diagnostic (~$75K)
   Goal? Establish CLIA NAPRT IHC biomarker
   Who? Multiple CROs being considered

*validate that our biomarkers unlock NAMPTi efficacy with dose de-escalation...

The Blavatnik Funding will allow us to pass our first, and most critical value inflection point...
Multiple cancer types beyond glioma...

**FIRST INDICATION**

- Pediatric BSG
  - 580 BSG patients per year
  - 200+ WIP1 patients/year

**Ovarian Cancer**

- 22,540 OC patients per year
- 900+ WIP1 patients/year

**Breast Cancer**

- 268,000 breast cancer patients in 2019
- ~75,208 WIP1 patients/year

**Grade II/III Glioma**

- 9,200 glioma patients per year
- 6000+ IDH patients/year

25%

40%

28%

70%
Our 36 month strategy...

NAMPTi

- NAMPTi Landscape Analysis
- NAMPTi in-licensing
- NAMPTi NCE Investigations
- NAMPTi Preclinical Development

Build ATHENA Core Team

IND-Enabling Work

CMC Formulation

X-ATH 2.0 Preclinical Development

$300K Blavantik

2ND Candidate

- X-ATH 2.0 Design + Secure IP
- X-ATH 2.0 Preclinical Development
- X-ATH 2.0 IND-Enabling Work

CMC Formulation

Phase I Clinical Trial

IND

$5-15M Series A

C - Candidate Selection
P - Pre-IND Meeting

Q1 2020 Q2 2020 Q3 2020 Q4 2020 Q1 2021 Q2 2021 Q3 2021 Q4 2021 Q1 2022 Q2 2022 Q3 2022 Q4 2022
Why invest in Athena?

• Translating high-impact Yale science, directly to the clinic, for brain tumors and beyond

• Founders “on the leading edge”, with biotech and clinical trials experience

• Significant unmet need, potential for expansion into multiple tumor types

• NAMPTI’s have been de-risked in the clinic, but now need molecular biomarkers

• Fast path to market, possibility for priority review vouchers and orphan drug status
No child left behind...