ATHENA THERAPEUTICS

Targeting cancer at its core…

Presenter:

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Associate Professor, Department of Therapeutic Radiology
Co-Director, Yale Brain Tumor Center

ATHENA THERAPEUTICS

Targeting cancer at its core…

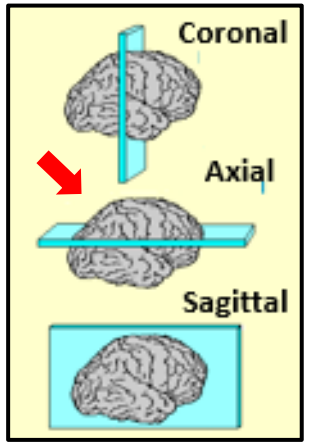
Mission Statement:

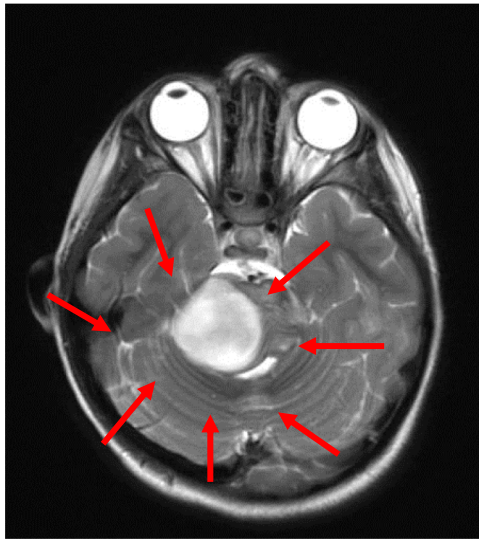
Translate the most innovative, cutting-edge science into biomarker-driven, novel therapeutic strategies for brain tumors… and beyond…

What's the clinical problem?

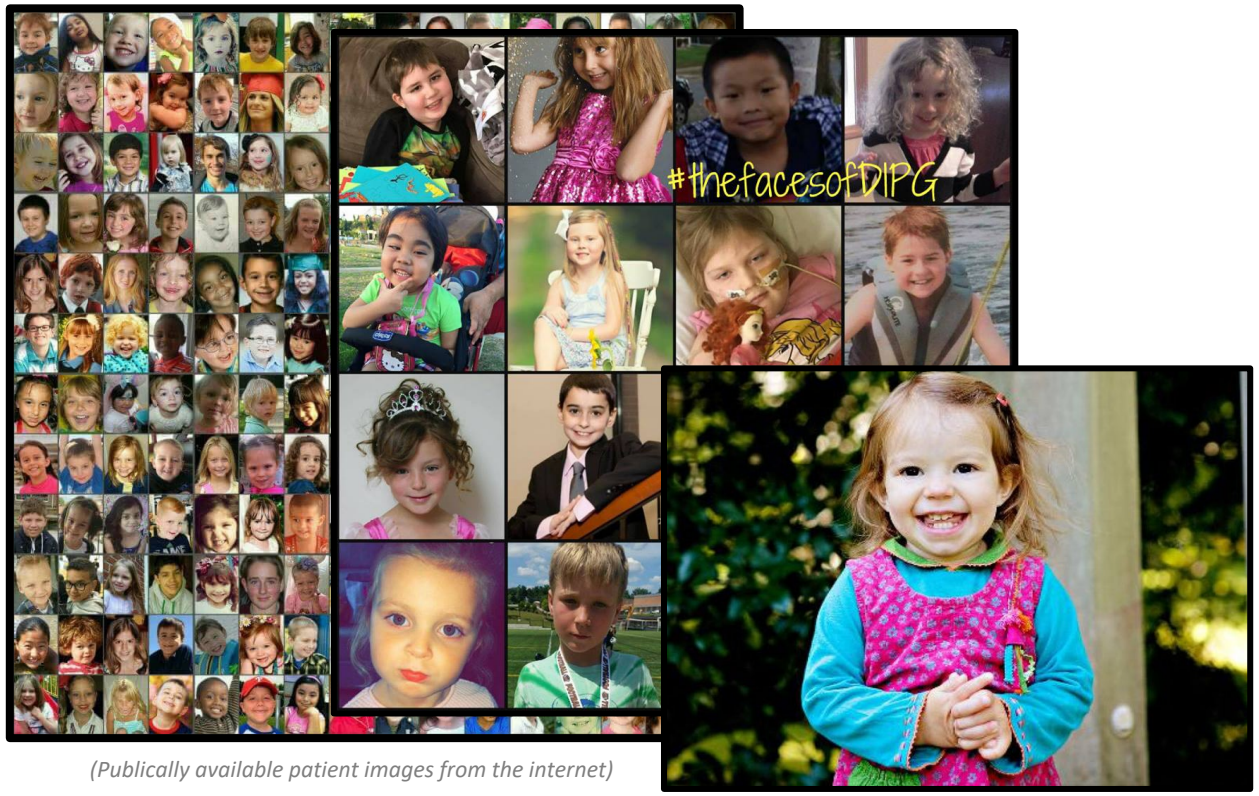
Incurable Gliomas

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





3 yo F with DIPG
Axial T2-weighted MRI

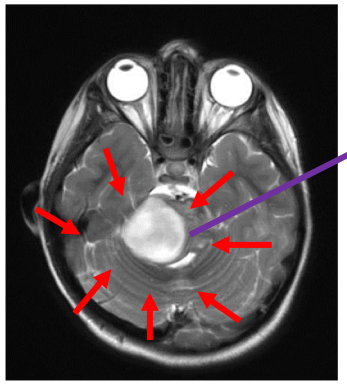


(Publically available patient images from the internet)

- 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

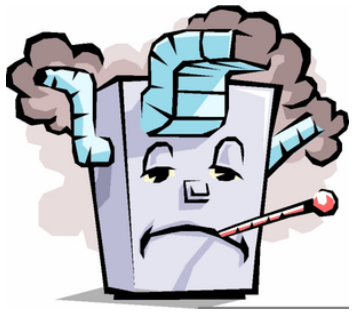
Images from
https://twitter.com/ReflectsOfGrace/status/1045705892874866688
https://patch.com/new-jersey/parsippany/cancer-victims-parents-helping-look-for-a-cure
https://www.facebook.com/dipgkids/photos/a.304246256608047/432840630415275/?type=3&theater

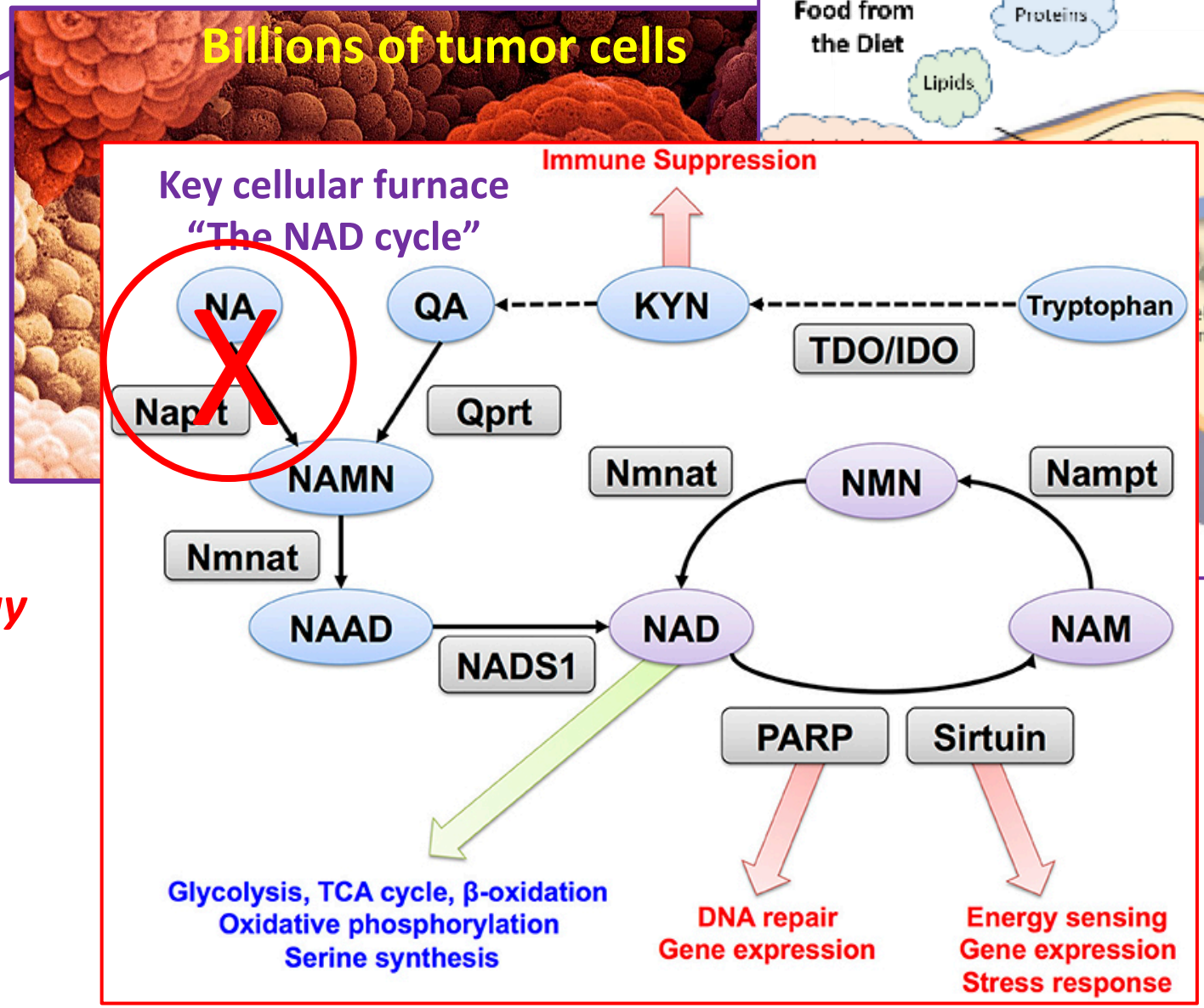
How can Athena solve this problem?

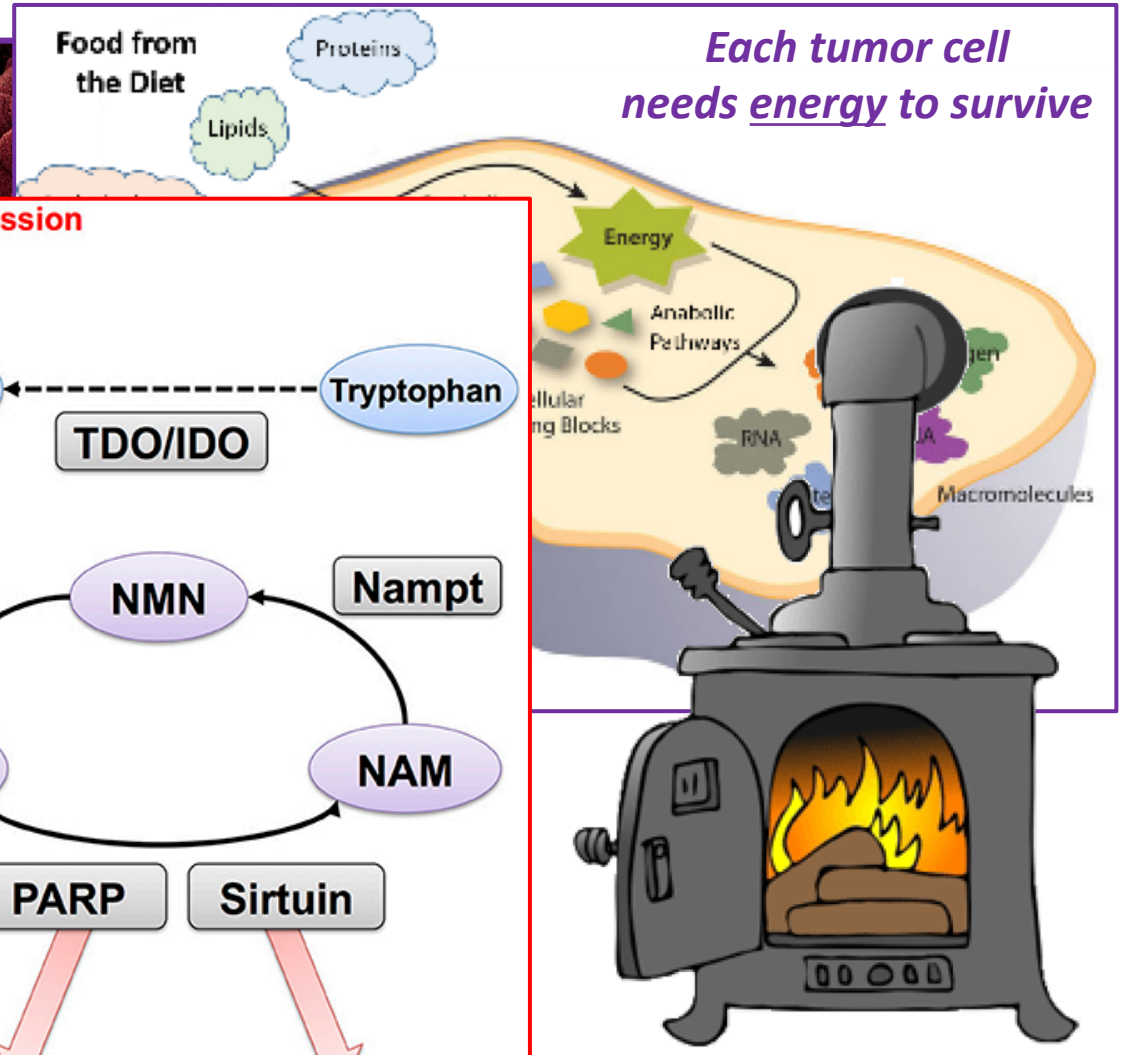


3 yo F with DIPG
Axial T2-weighted MRI

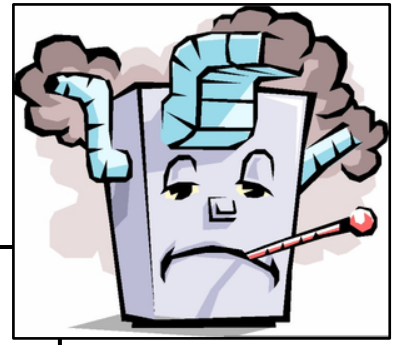
We found that many brain tumors <u>have lost</u> this pathway (furnace=broken)





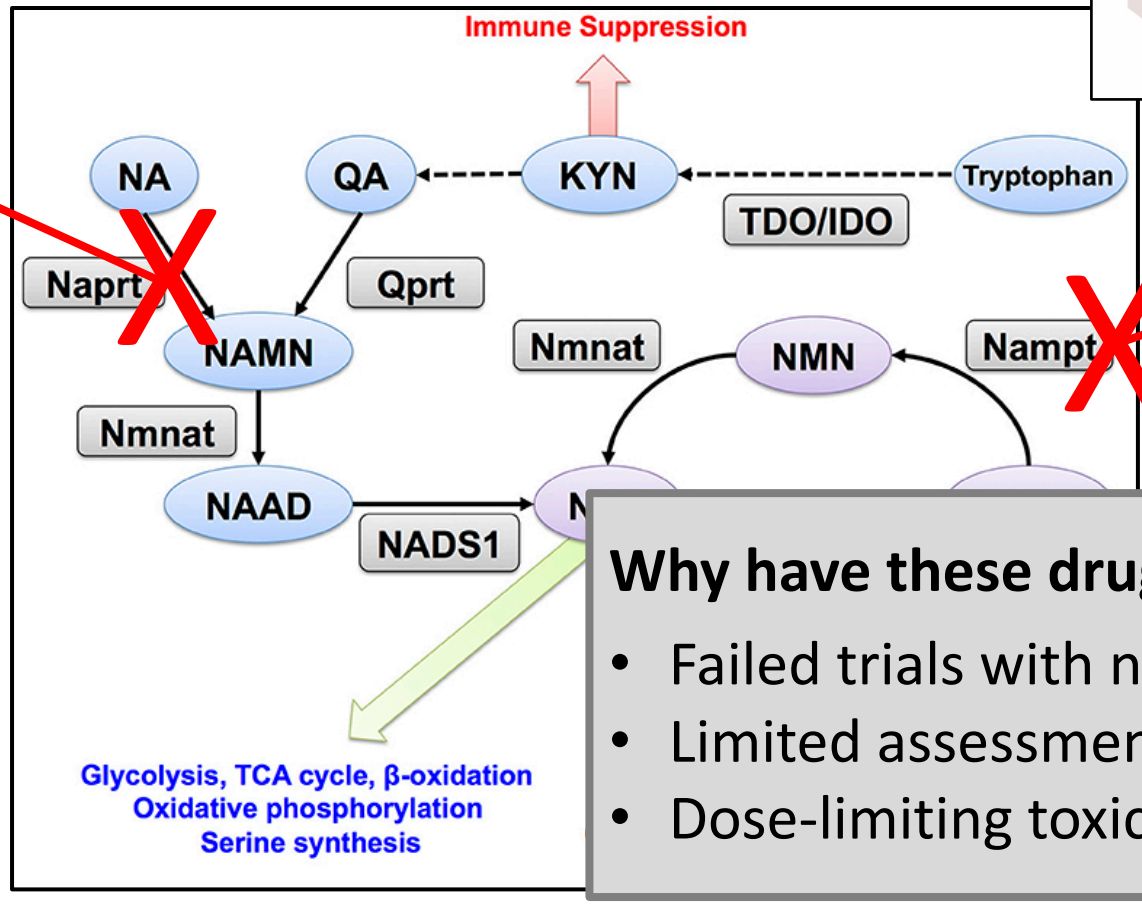


How can Athena solve this problem?



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)

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-11732-6 OPEN

PPM1D mutations silence NAPRT gene expression and confer NAMPT inhibitor sensitivity in glioma

Nathan R. Fons[1,2], Ranjini K. Sundaram[2], Gregory A. Breuer[1,2], Sen Peng[3], Ryan L. McLean[2], Aravind N. Kalathil[2], Mark S. Schmidt[4], Diana M. Carvalho[5], Alan Mackay[5], Chris Jones[5], Ángel M. Carcaboso[6], Javad Nazarian[7], Michael E. Berens[3], Charles Brenner[4] & Ranjit S. Bindra[1,2]

(*Patent Filed: 62/748,911)

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?

https://webstockreview.net/explore/sick-clipart-furnace/
https://freedesignfile.com/493962-color-cartoon-bookshelf-vector-material/

Our data/discoveries

ARTICLE
https://doi.org/10.1038/s41467-019-11732-6 OPEN
nature COMMUNICATIONS
PPM1D mutations silence NAPRT gene expression and confer NAMPT inhibitor sensitivity in glioma
Nathan R. Fons[1,2], Ranjini K. Sundaram[2], Gregory A. Breuer[1,2], Sen Peng[3], Ryan L. McLean[2], Aravind N. Kalathil[2], Mark S. Schmidt[4], Diana M. Carvalho[5], Alan Mackay[5], Chris Jones[5], Ángel M. Carcaboso[6], Javad Nazarian[7], Michael E. Berens[3], Charles Brenner[4] & Ranjit S. Bindra[1,2]

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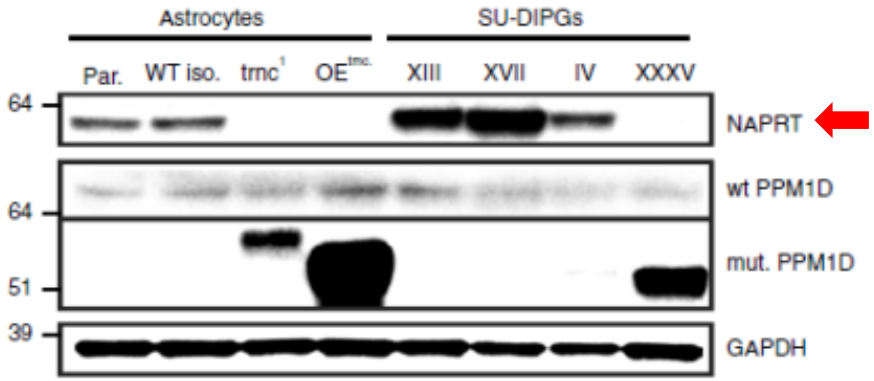
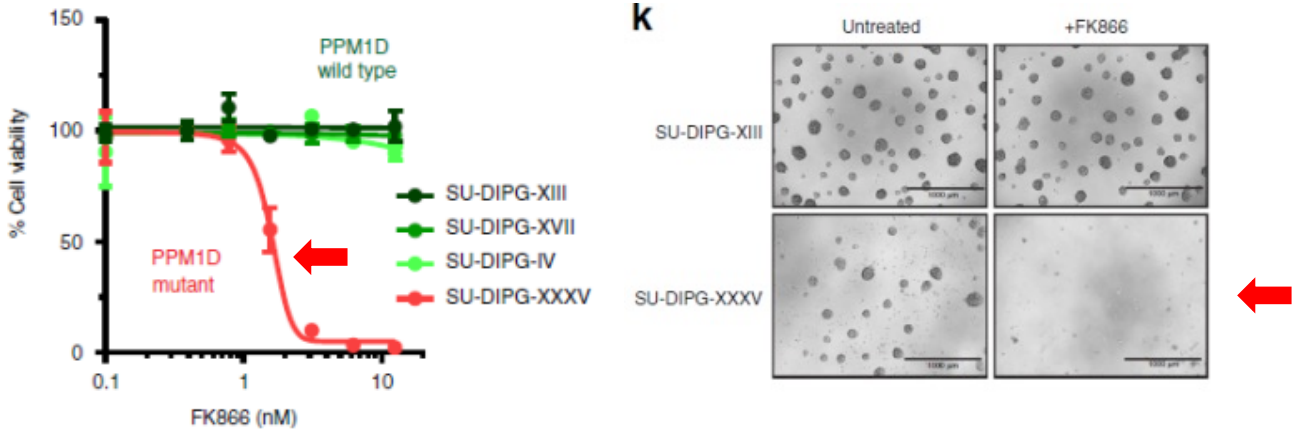
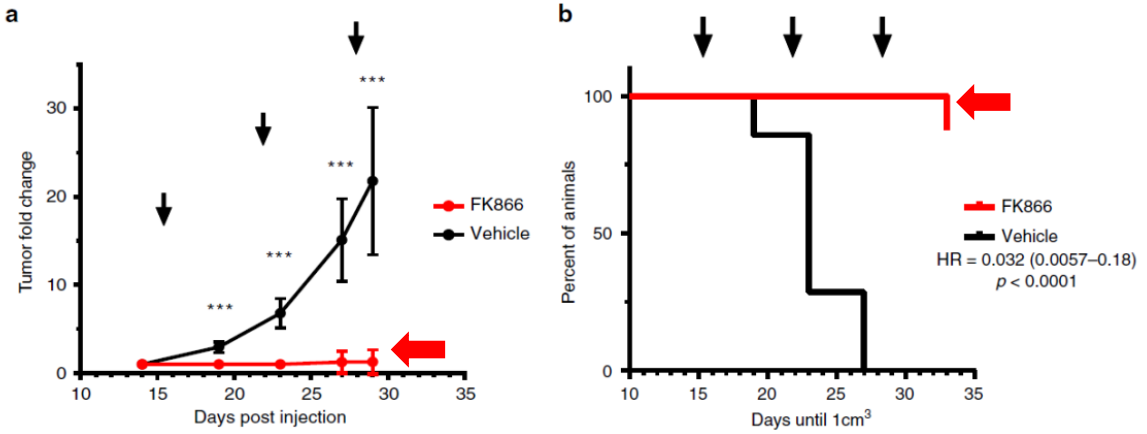
1. PPM1D mutations confer silence the expression of NAPPRT, a key NAD metabolism gene



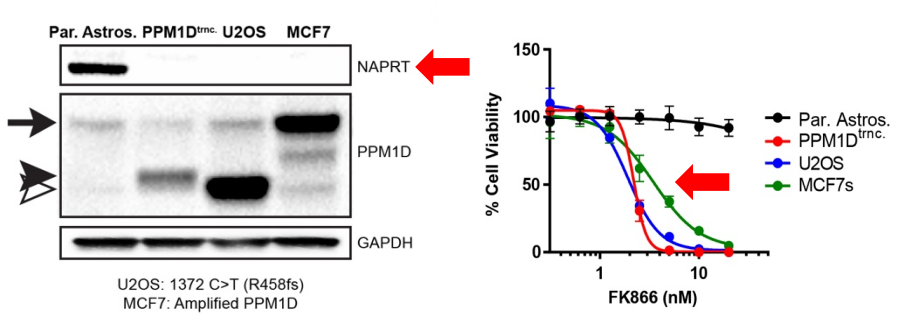
2. PPM1D mutations confer NAMPTi sensitivity in patient-derived glioma models *in vitro*



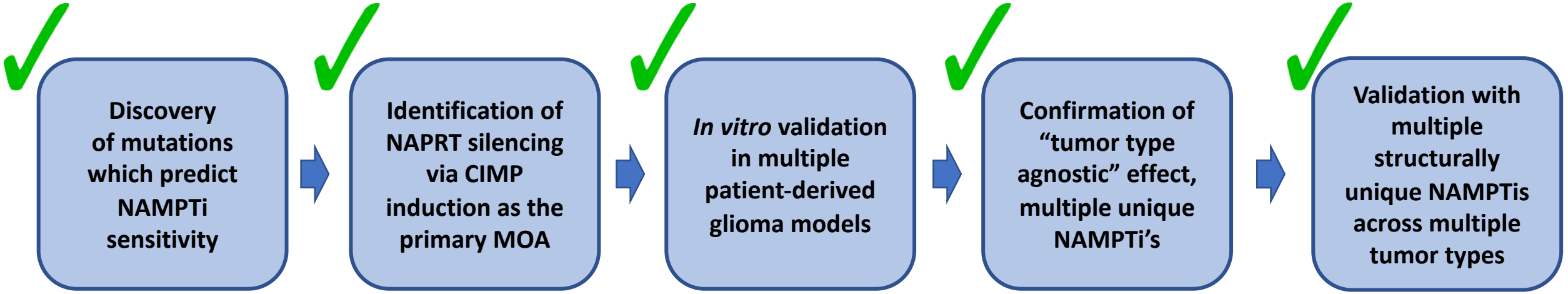
3. PPM1D mutations induce NAMPTi sensitivity *in vivo*



4. PPM1D-induced NAMPTi sensitivity occurs across multiple tumor types



Our data/discoveries – Summary of our academic work



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

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The team behind Athena…

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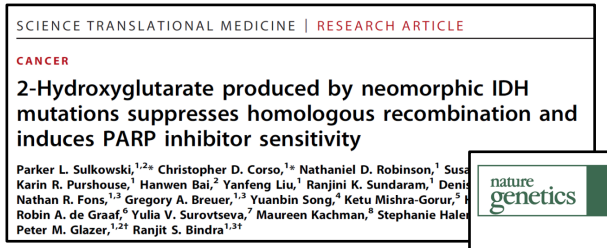
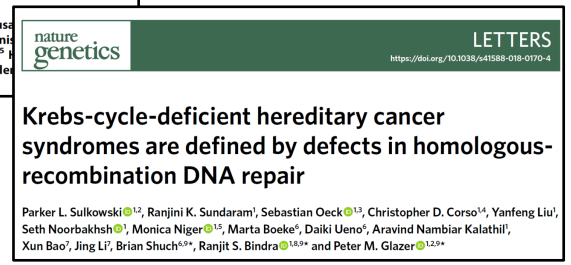
Experience in exploiting metabolic defects


SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

2-Hydroxyglutarate produced by neomorphic IDH mutations suppresses homologous recombination and induces PARP inhibitor sensitivity

Parker L. Sulkowski, Christopher D. Corso, Nathaniel D. Robinson, Susa… Karin R. Purshouse, Hanwen Bai, Yanfeng Liu, Ranjini K. Sundaram, Deni… Nathan R. Fons, Gregory A. Breuer, Yuanbin Song, Ketu Mishra-Gorur, … Robin A. de Graaf, Yulia V. Surovtseva, Maureen Kachman, Stephanie Hale… Peter M. Glazer, Ranjit S. Bindra


nature genetics — LETTERS

https://doi.org/10.1038/s41588-018-0170-4

Krebs-cycle-deficient hereditary cancer syndromes are defined by defects in homologous-recombination DNA repair

Parker L. Sulkowski, Ranjini K. Sundaram, Sebastian Oeck, Christopher D. Corso, Yanfeng Liu, Seth Noorbakhsh, Monica Niger, Marta Boeke, Daiki Ueno, Aravind Nambiar Kalathil, Xun Bao, Jing Li, Brian Shuch, Ranjit S. Bindra and Peter M. Glazer

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

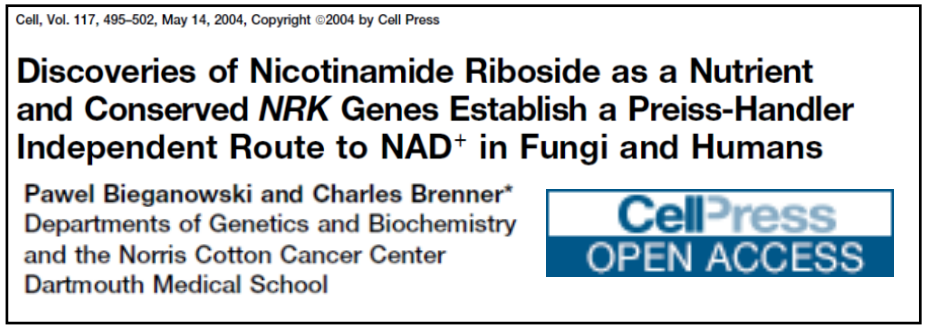
CYBREXA THERAPEUTICS

Helix Therapeutics — DNA Repair for Human Diseases

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

Discovered the NR pathway in NAD metabolism


Cell, Vol. 117, 495–502, May 14, 2004, Copyright ©2004 by Cell Press

Discoveries of Nicotinamide Riboside as a Nutrient and Conserved *NRK* Genes Establish a Preiss-Handler Independent Route to NAD+ in Fungi and Humans

Pawel Bieganowski and Charles Brenner*
Departments of Genetics and Biochemistry and the Norris Cotton Cancer Center
Dartmouth Medical School

CellPress OPEN ACCESS

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

ChromaDex

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.

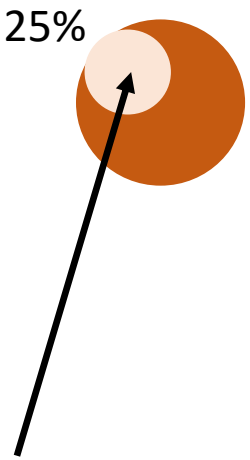
4. **Develop companion diagnostic (~$75K)**
   Goal? Establish CLIA NAPRT IHC biomarker
   Who? Multiple CROs being considered

**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…

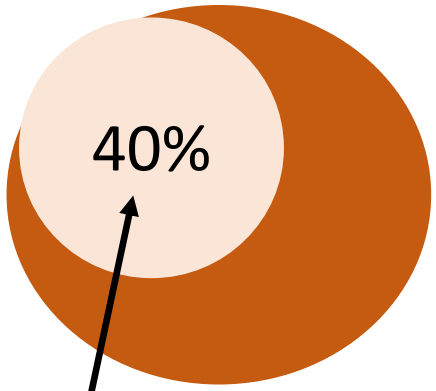
Multiple cancer types beyond glioma…

FIRST INDICATION
Pediatric BSG



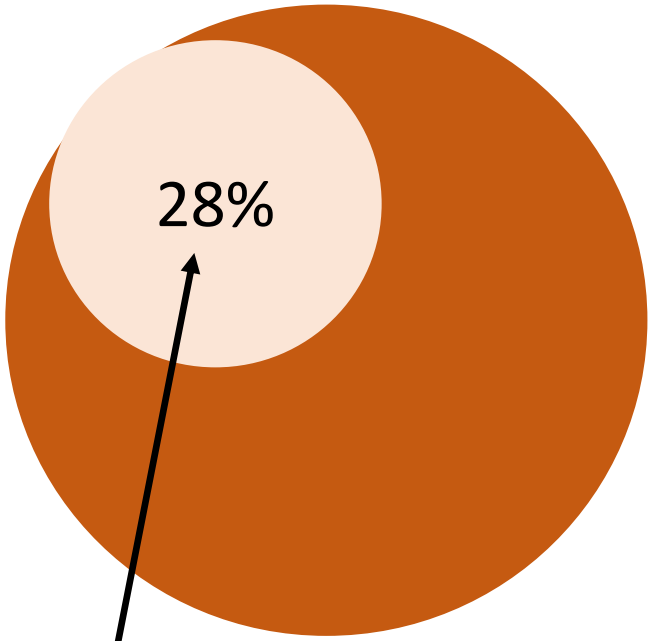
580 BSG patients per year
200+ WIP1 patients/year

Ovarian Cancer
Clear Cell Carcinoma



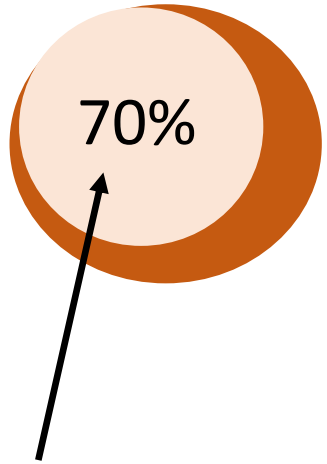
22,540 OC patients per year
900+ WIP1 patients/year

Breast Cancer



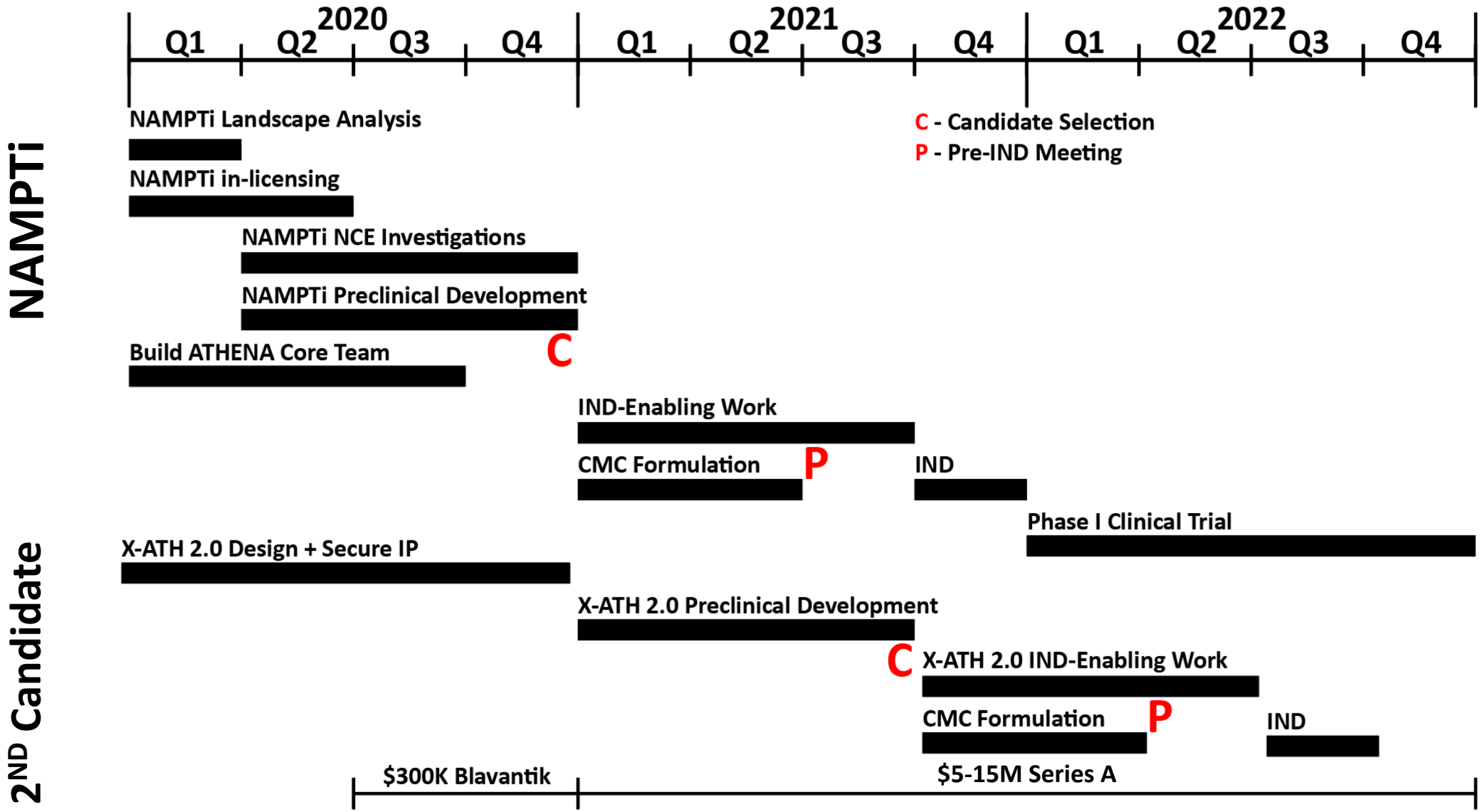
268,000 breast cancer patients in 2019
~75,208 WIP1 patients/year

Grade II/III
Glioma



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

Our 36 month strategy…



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**

ATHENA
THERAPEUTICS

No child left behind…