

Therapy for Pantothenate Kinase-Associated Neurodegeneration (PKAN)

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Founder

Professor of Medicine, Microbial Pathogenesis and Pathology

Yale

Confidential

Rare neurodegenerative disease

- Parkinsonism
- Dementia
- Inability to control muscle function
- Death

Autosomal recessive:

- Pantothenate Kinase 2 (*PANK2*)



<https://www.dailymail.co.uk>

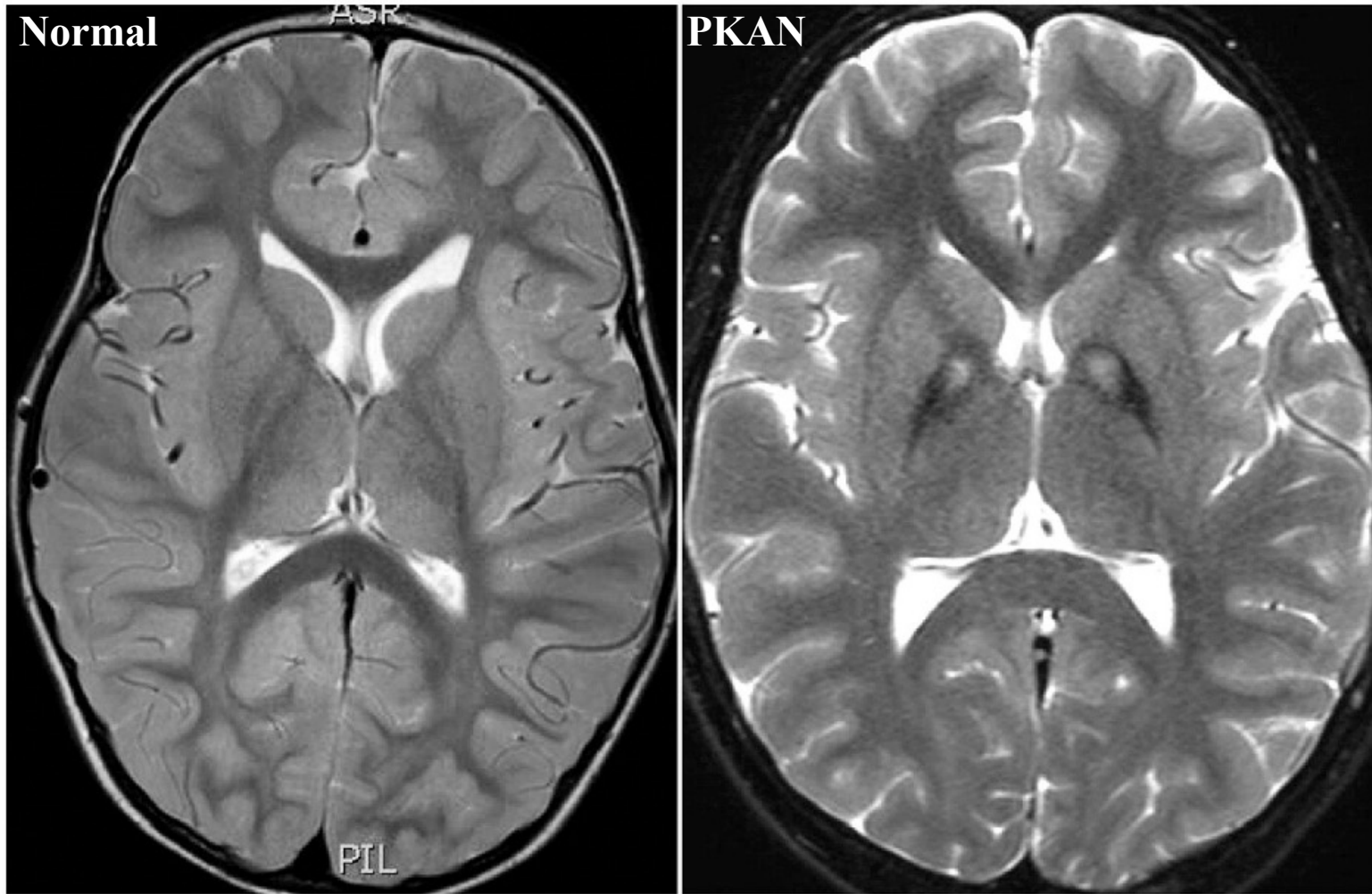
NBIA Conference Houston 05/ 2023



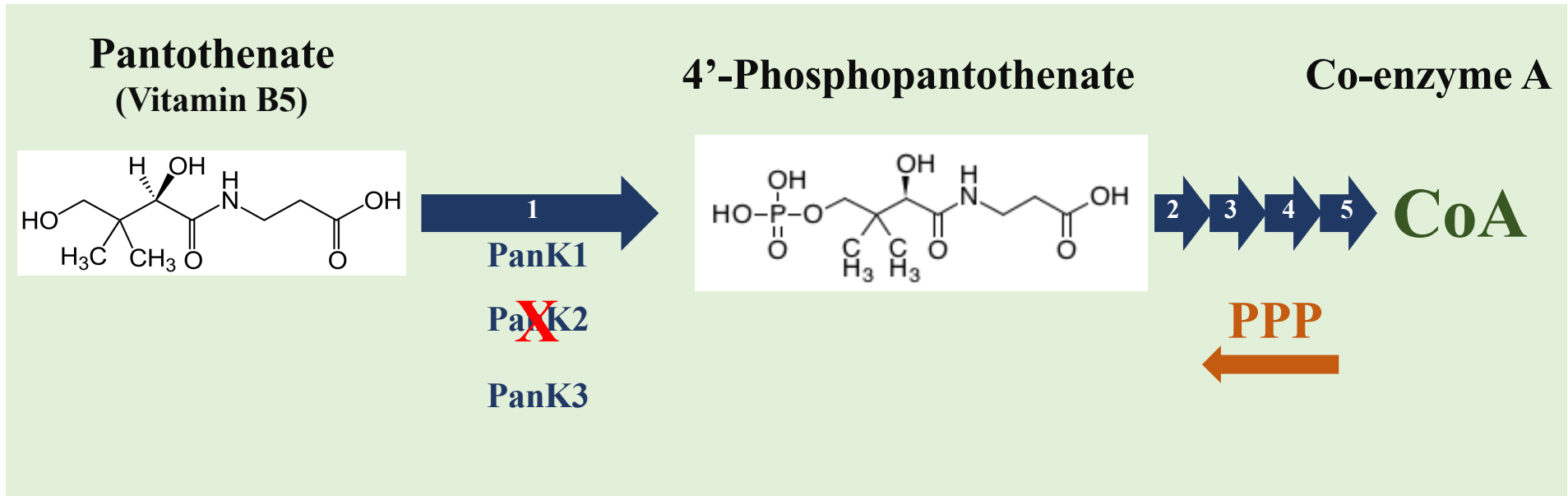


PKAN – NBIA

Iron accumulation in basal ganglia



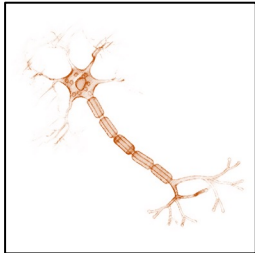
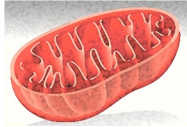
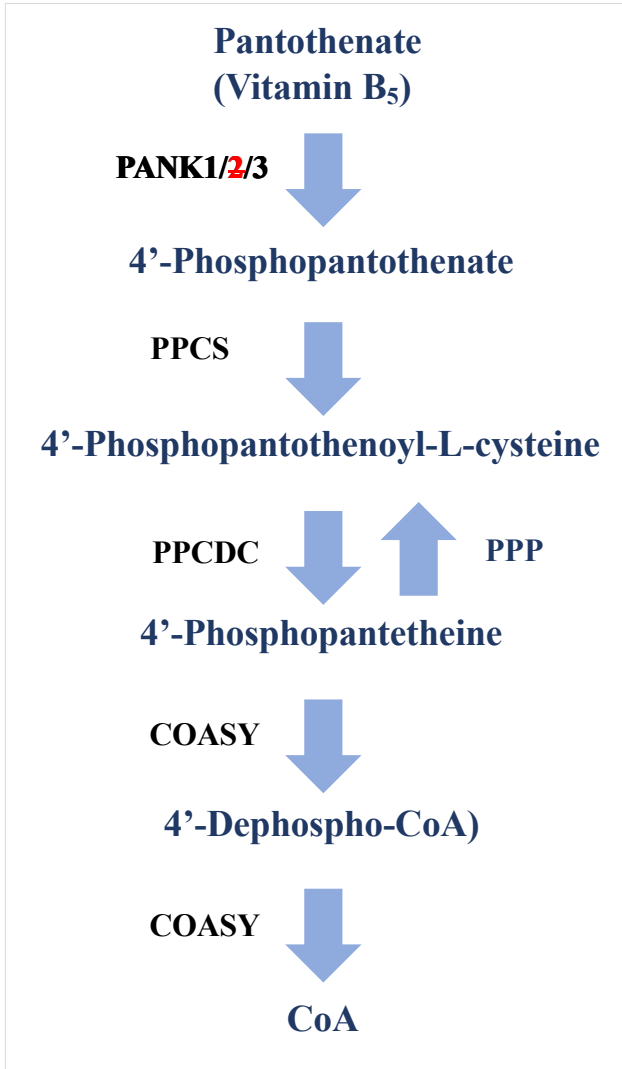
PanK2 loss of function → PKAN



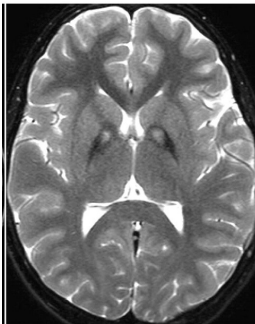
PANK2

- Mitochondrial PanK enzyme
- The major active PANK isoform in the human brain

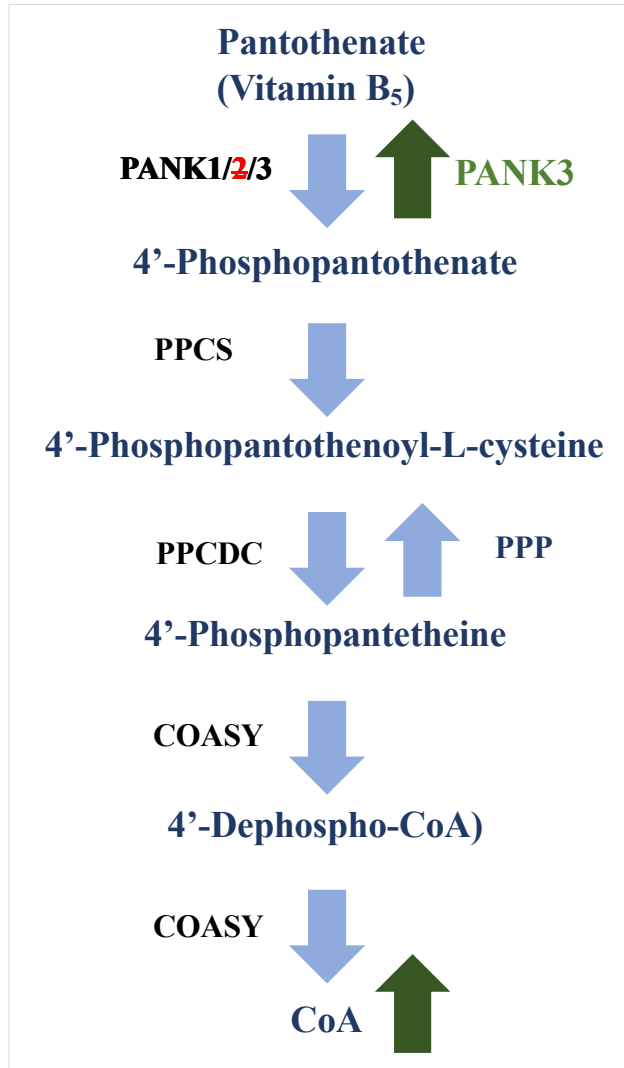
PROBLEM



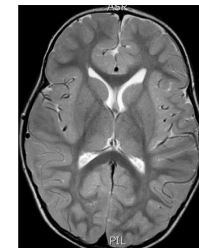
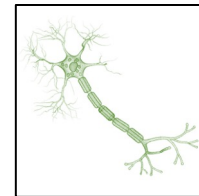
Disrupted



PROBLEM & SOLUTION



**PANK3 activators
VTAC1-14**



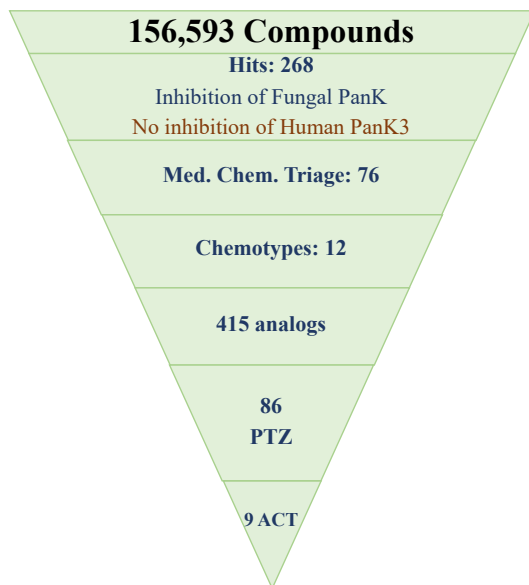
Restored

HUMAN PANK3 ACTIVATORS

VTACs

PanK Modulators

Screening cascade



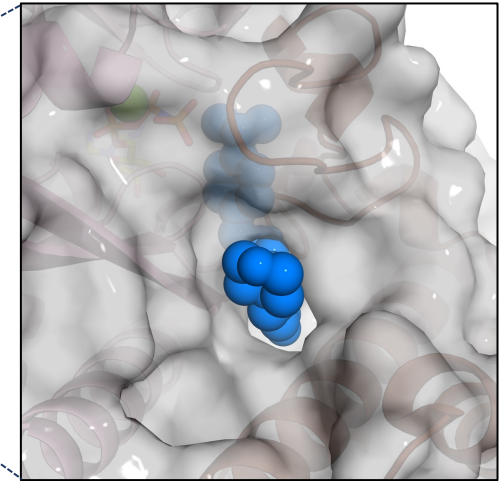
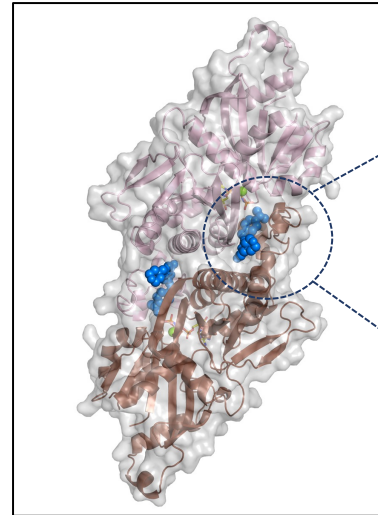
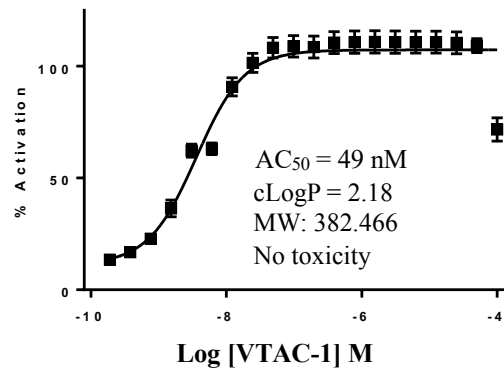
IP: Yale 63/043,534
valid until 2040

1 Completed	Assay Development Developed ATP-based high-throughput screen
2 Completed	PanK modulators 156,000 compounds screened
3 Completed	Lead Identification 14 activators of human PanK3 VTAC1-14: AC ₅₀ in the nM range
4 In Progress	Preclinical Studies Cell-based assays Animal models of PKAN
5 Future	Clinical Testing Conduct clinical trials

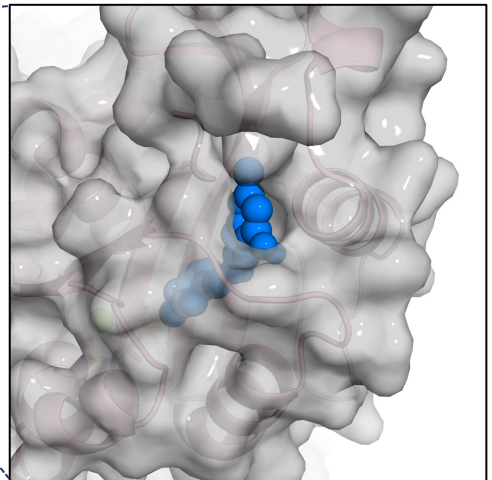
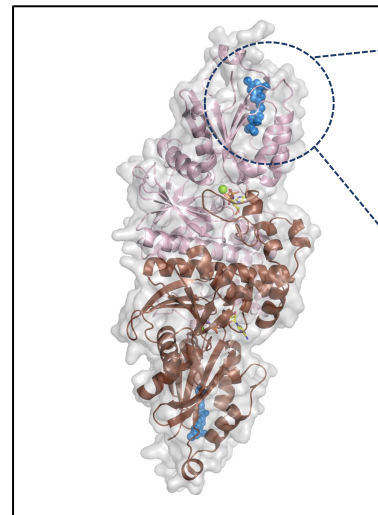
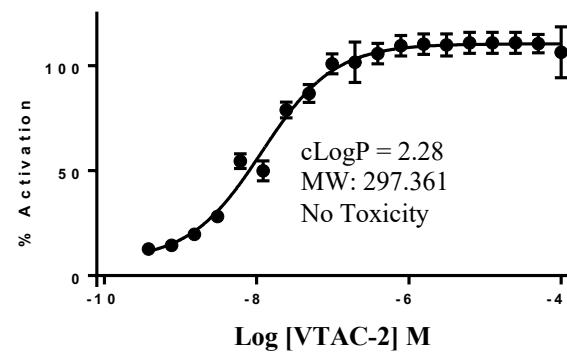
FUNDING
Program in Therapeutics for CT Health 2017 - 2020 (\$736,000)
YBFI \$300K: 07/21 – 07/24 NDF: \$700K: 07/23–06/25
Series A 2023 →

VTACs Modes of Activation

Active site activator

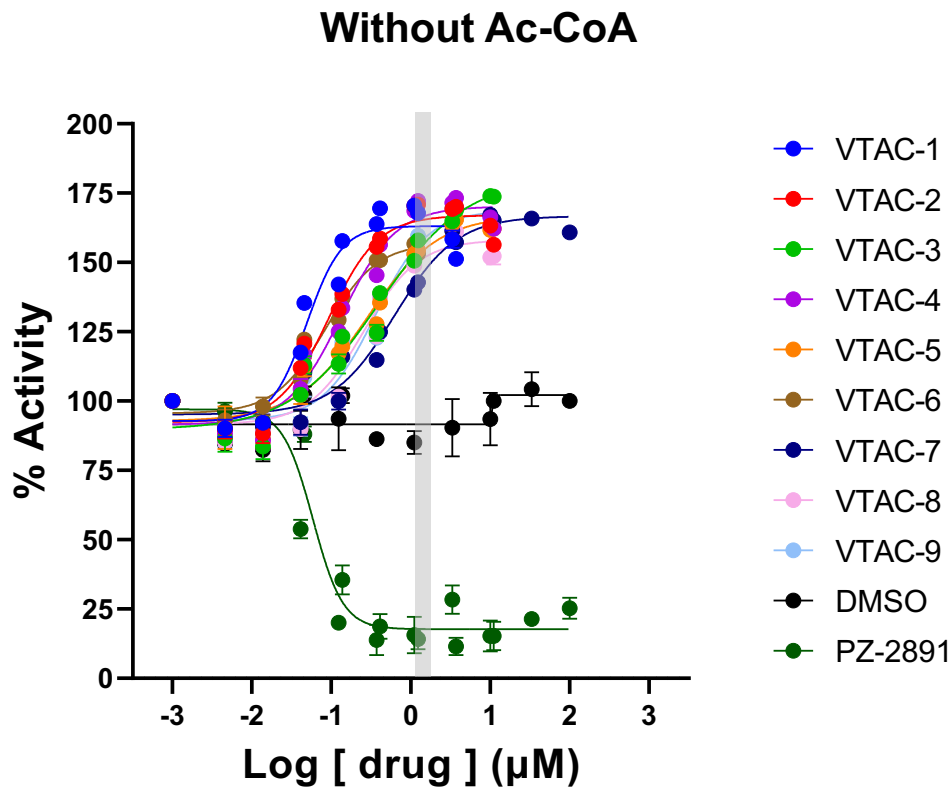


Allosteric activator

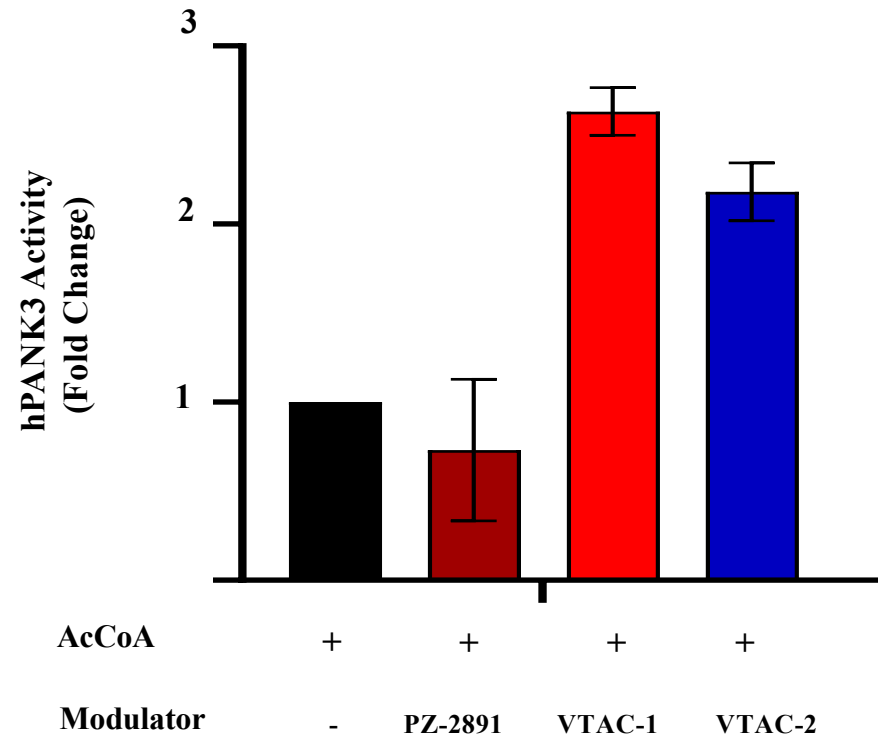


VTACs superiority over pantazines (Direct vs Orthosteric activators)

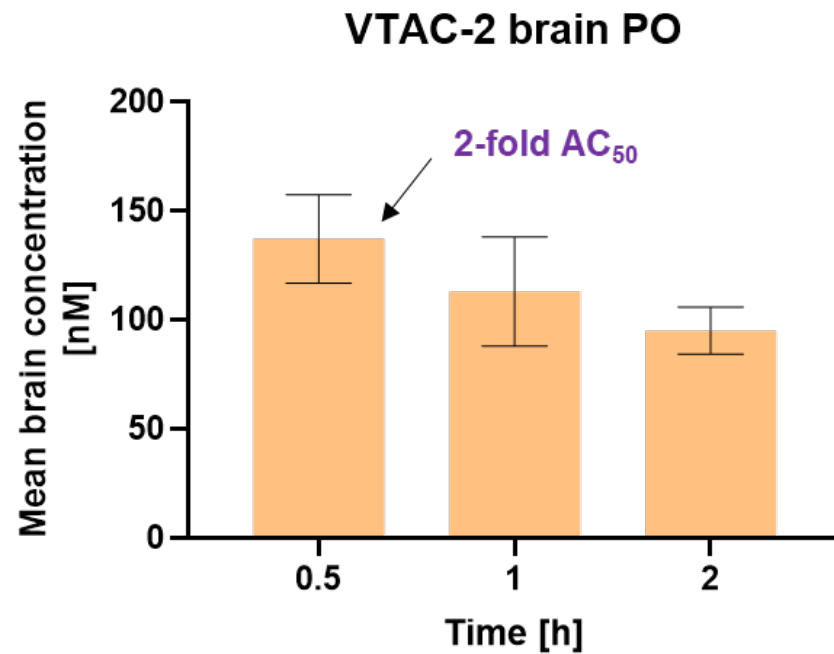
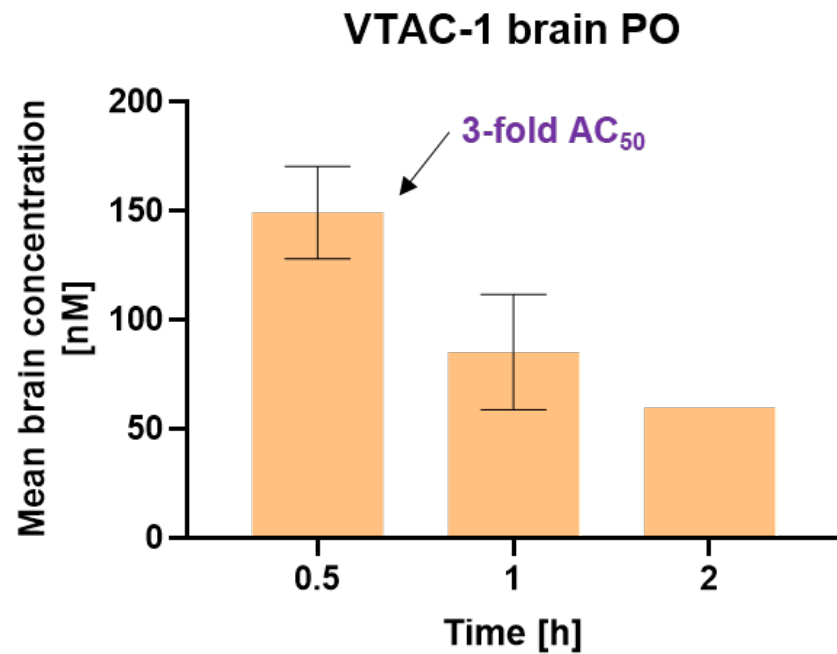
A



B

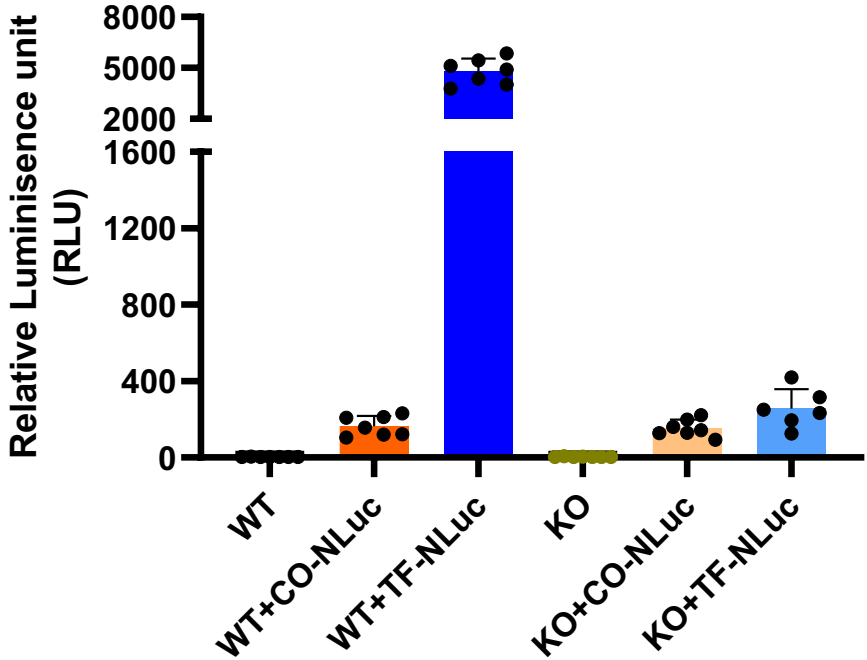


VTACs: Long half life and CNS exposure

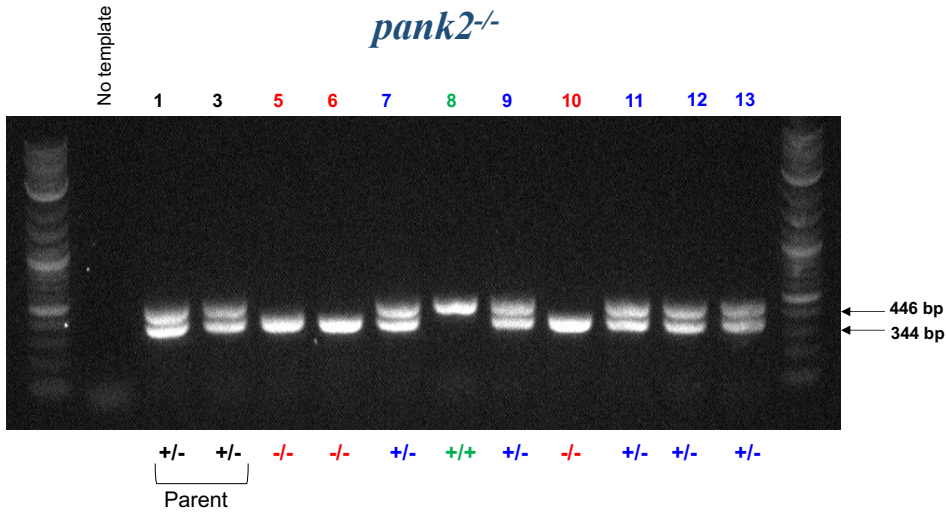


Cell-based Assays and Animal Models

In vivo efficacy ongoing

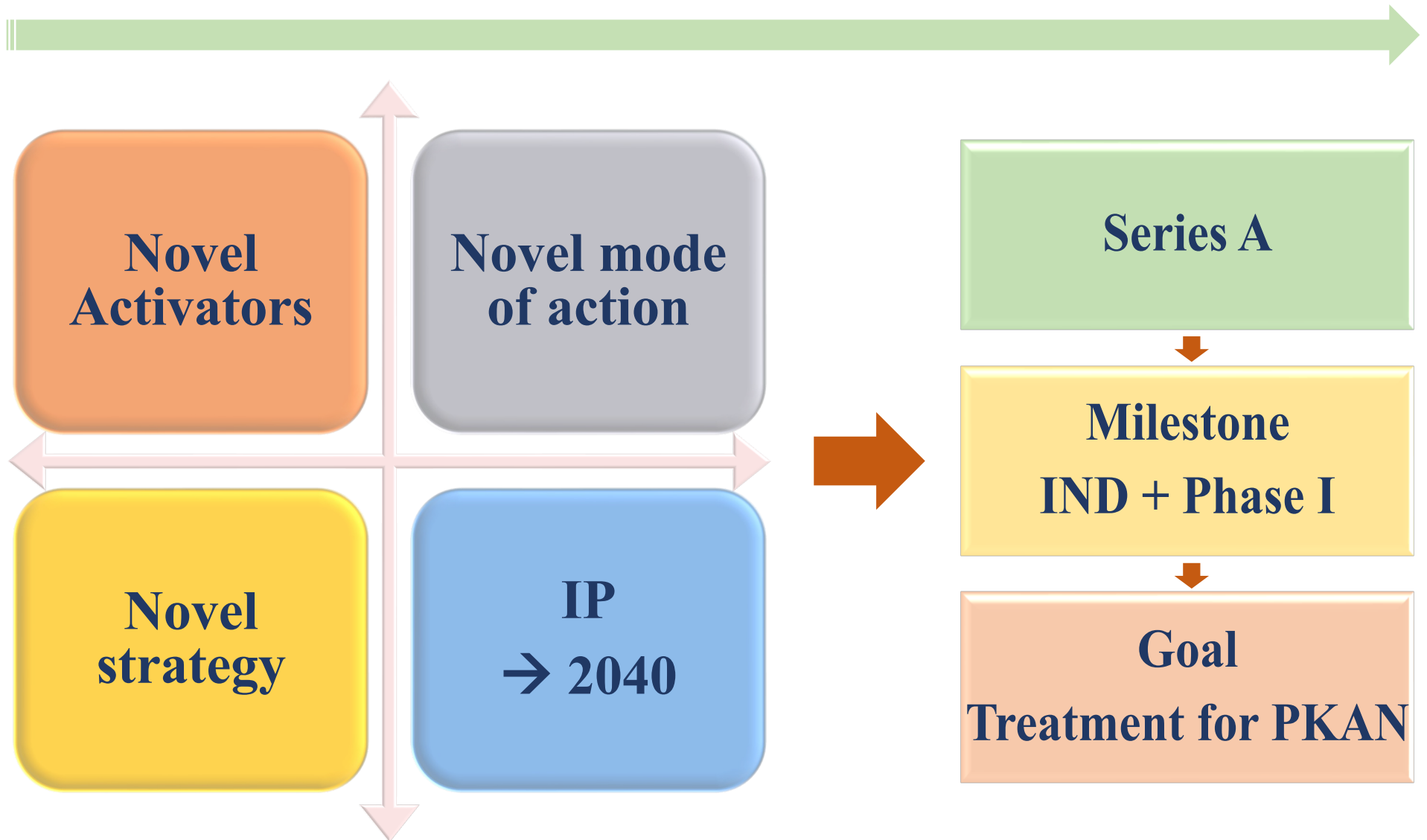


pank2^{-/-}





SUMMARY





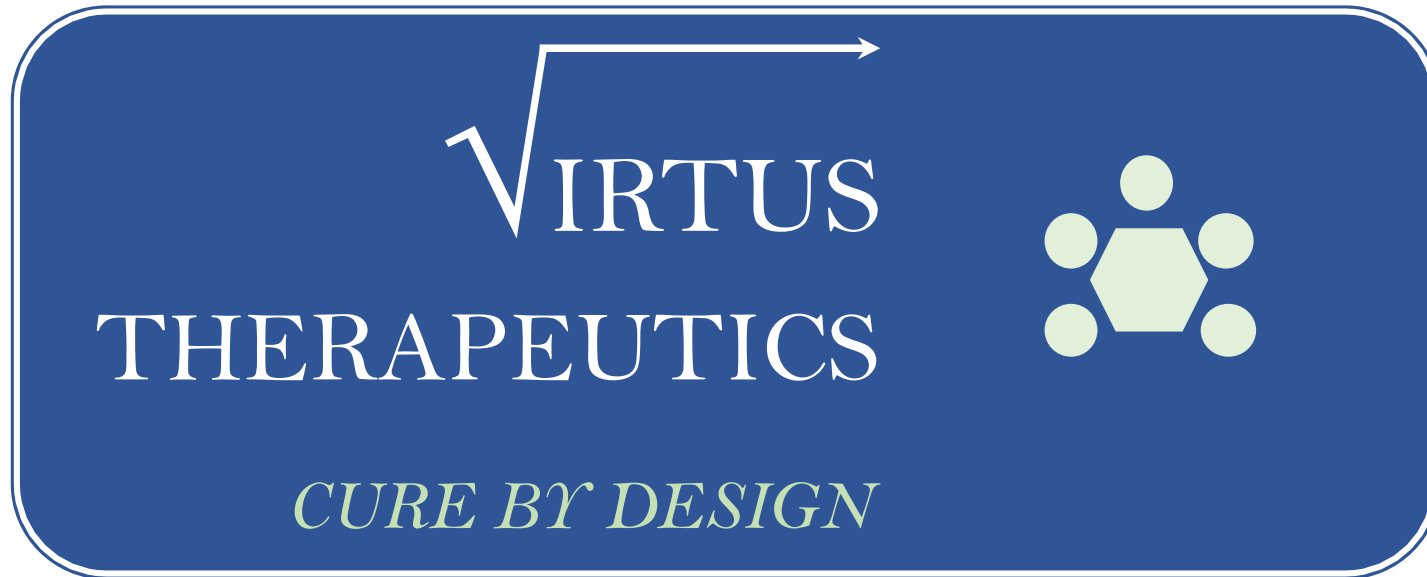
With permission from the families

HOPE IS A WAKING DREAM

ARISTOTLE



With permission from the families



Thank You

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VIRTUS STRUCTURE



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