Therapy for Pantothenate Kinase-Associated Neurodegeneration (PKAN)

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Yale
Rare neurodegenerative disease
- Parkinsonism
- Dementia
- Inability to control muscle function
- Death

Autosomal recessive:
- Pantothenate Kinase 2 (*PANK2*)

[https://www.dailymail.co.uk](https://www.dailymail.co.uk)
With permission from the families
PKAN – NBIA
Iron accumulation in basal ganglia
PanK2 loss of function $\rightarrow$ PKAN

Pantothenate (Vitamin B5)

1. PanK1
2. PanK2
3. PanK3

4’-Phosphopantothenate

Co-enzyme A

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

Pantothenate (Vitamin B₅)

\[ \text{PANK1/2/3} \]

4’-Phosphopantothenate

\[ \text{PPCS} \]

4’-Phosphopantothenoyl-L-cysteine

\[ \text{PPCDC} \]

4’-Phosphopantetheine

\[ \text{COASY} \]

4’-Dephospho-CoA)

\[ \text{COASY} \]

CoA

Disrupted
PROBLEM & SOLUTION

Pantothenate (Vitamin B_5)

- PANK1/2/3
- 4’-Phosphopantothenate
- PPCS
- 4’-Phosphopantothenoyl-L-cysteine
- PPCDC
- 4’-Phosphopantetheine
- COASY
- 4’-Dephospho-CoA)
- COASY
- CoA

PANK3 activators VTAC1-14

Restored
HUMAN PANK3 ACTIVATORS
VTACs

PanK Modulators
Screening cascade

156,593 Compounds
Hits: 268
Inhibition of Fungal PanK
No inhibition of Human PanK3
Med. Chem. Triage: 76
Chemotypes: 12
415 analogs
86 PTZ
9 ACT

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 →

Confidential
VTACs Modes of Activation

**Active site activator**
- AC_{50} = 49 nM
- cLogP = 2.18
- MW: 382.466
- No toxicity

**Allosteric activator**
- cLogP = 2.28
- MW: 297.361
- No Toxicity
VTACs superiority over pantazines (Direct vs Orthosteric activators)

A

Without Ac-CoA

% Activity vs Log [ drug ] (μM)

B

hPANK3 Activity (Fold Change)

AcCoA + + + +

Modulator - PZ-2891 VTAC-1 VTAC-2
VTACs: Long half life and CNS exposure

VTAC-1 brain PO

VTAC-2 brain PO
Cell-based Assays and Animal Models

In vivo efficacy ongoing

**Relative Luminence unit (RLU)**

- WT
- WT+CO-NLUC
- KO
- KO+CO-NLUC
- KO+TF-NLUC

**DNA Gel Electrophoresis**

- pank2^{-/-}
- 446 bp
- 344 bp

**Relevant**

- **RLU**
- **pangk2^{-/-}**
SUMMARY

Novel Activators

Novel mode of action

Novel strategy

IP → 2040

Series A

Milestone IND + Phase I

Goal Treatment for PKAN
With permission from the families
HOPE IS A WAKING DREAM

ARISTOTLE

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Thank You

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