Therapy for Pantothenate Kinase-Associated Neurodegeneration (PKAN)

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https://www.dailymail.co.uk
PKAN Genetic Disorder

Neurodegenerative disease that can lead to:
- Parkinsonism
- Dementia
- Inability to control muscle function
- Death

- First report: 1922 – No treatment to date
- Types: Classical (3.5 y) and Atypical (>10 y)
- Prevalence: 1-3/million people worldwide
- Autosomal recessive:
  - Pantothenate Kinase 2 (PanK2)

https://news.ohsu.edu/2019/10/29/
PanK2 loss of function → PKAN

Pantothenate (Vitamin B5)

\[
\text{\begin{align*}
\text{H}_3\text{C} & \text{CH}_3 \\
\text{HO} & \text{HO}
\end{align*}}
\]

4’-Phosphopantothenate

\[
\text{\begin{align*}
\text{HO-P} & \text{O} \\
\text{O} & \text{HO}
\end{align*}}
\]

Co-enzyme A

- PanK1
- PanK2 \(\times\)
- PanK3

PANK2

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

Pantothenate (Vitamin B₅)

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

PanK3 activators
- VTAC1-9

Disrupted

stored
## HUMAN PANK3 ACTIVATORS

### PanK Modulators Screening cascade

<table>
<thead>
<tr>
<th>Step</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1    | Completed | Assay Development  
Developed ATP-based high-throughput screen |
| 2    | Completed | PanK modulators  
156,000 compounds screened |
| 3    | Completed | Lead Identification  
9 activators of human PanK3  
VTAC1-9: 2.2 nM - 268 nM |
| 4    | Pending  | Preclinical Studies  
Cell-based assays and mouse models of PKAN |
| 5    | Future   | Clinical Testing  
Conduct clinical trials |

### FUNDING

**PITCH**  
2017 - 2020  
($736,000)

**SEED FUNDING**  
(Blavatnik)

**VENTURE CAPITAL**

**IP:** Yale 63/043,534 valid until 2040

**Funding**

**Assay Development:**  
- 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
HuPanK3 Activators:
1 Chemotype, 9 Compounds and 2 Modes of activation

Active site activator

\[ \text{AC}_{50} \approx 2.6 \text{ nM} \]
\[ \text{cLogP} = 2.18 \]
\[ \text{MW: 382.466} \]
No toxicity

Allosteric activator

\[ \text{AC}_{50} = 4.9 \text{ nM} \]
\[ \text{cLogP} = 2.28 \]
\[ \text{MW: 297.361} \]
No Toxicity
ASK: $300K - BLAVATNIK
USE OF FUNDS & MILESTONES

**AIM 1**
Chemistry, Structural Biology & Pharmacology

- Synthetic Chemistry
  - VTAC - hPanK3
- DMPK
  - MDR1-MDCK
  - Permeability >1 x 10^{-6} cm/s
  - *In vivo* pharmacokinetics
  - Brain and plasma c/c

**AIM II**
Cell-based efficacy in Pank2-deficient cells

- Cellular metabolism
  - CoA
  - Iron
  - Cysteine
  - Mitochondrial biogenesis

**AIM III**
Efficacy In Mice (Top 2 compounds)

- Humanized mouse model:
  - Create the first mPank2^{-/-} - hPANK3 mouse model
- Neurological and motor function analyses
  - Brain biomarkers
  - Survival
  - Movement
  - Behavioral analysis

$124K + $50K + $126K = $300K

**IND/Clinical Candidate**
Market Size: ~$360M/year

Potential pricing analogs, based on prevalence and disease severity:

- Vimizim (Morquio Syndrome) - ~$600 K/yr
- Vpriv (Type 1 Gaucher) - $320 K/yr
- Fabrazyme (Fabry’s Disease) - $295 K/yr
- Procysbi (Nephropathic Cystinosis) - $595 K/yr
- If approved, Ferriprox treatment may be priced at $50 – $150 K per year

Assuming ~1,200 patients and price of $300 K/year, market size is ~$360 M annually, and population may increase with improved care
APPLICATIONS

- PKAN
- CoA deficiencies
- Other neurological disorders
  - Parkinson’s disease
  - Alzheimer’s disease
- Anti-aging
SUMMARY

VIRTUS TECHNOLOGY AND COMPETITIVE ADVANTAGE

- Novel Activators
- Novel mode of action
- Novel strategy for treatment of PKAN
- Competitive advantage (IP to 2040)

ASK
$300K
Milestone
Identify a clinical candidate
Goal
Treatment for PKAN
HOPE IS A WAKING DREAM
ARISTOTLE
Thank You
STRATEGIC PLANNING

Pre-clinical

2017-19

2020

2021

2022

2023

2024

2025

2026

2027

2028

2029

Clinical

Launch

PITCH

$736K

Private

funding

Strategic partner

Joint Venture

Acquisition

IPO
VIRTUS MANAGEMENT

Stephen Chang: CEO
Ex-CEO, president, chairman of the board of multiple biotech companies

Muhammad Munshi, Yale
Economics Major
Pre-Med
Undergraduate (Senior)

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Advisor: Finance, business strategy and operations

Mark S. Plummer, PhD
Scientific Manager
Advisor: Chemistry

John Puziss, Yale
OCR contact
<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Mechanism</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBP-671</td>
<td>CoA Therapeutics (BridgeBio)</td>
<td>Inhibitor of Acetyl-CoA feedback inhibition of PanK</td>
<td>Preclinical (reported toxicity)</td>
</tr>
<tr>
<td>CoA-Z</td>
<td>OHSU</td>
<td>4’-phosphopantetheine pPanSH</td>
<td>Phase 2 (recruiting)</td>
</tr>
<tr>
<td>Ferriprox</td>
<td>ApoPharma</td>
<td>Iron chelating agent (Thalassemia)</td>
<td>Phase 3 (efficacy modest)</td>
</tr>
<tr>
<td>(deferiprone)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosmet-PTT</td>
<td>Retrophin</td>
<td>Prodrug of PTT</td>
<td>Discontinued</td>
</tr>
<tr>
<td>TM-1803</td>
<td>TM3 Therapeutics</td>
<td>Prodrug of PTT</td>
<td>Discontinued</td>
</tr>
</tbody>
</table>

- Select patients with atypical disease have benefited from high doses of pantothenate
- Symptomatic to manage muscle spasms are available (e.g., baclofen, trihexyphenidyl)
## TARGET PRODUCT PROFILE

<table>
<thead>
<tr>
<th>Assay</th>
<th>Desired Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potency</strong></td>
<td></td>
</tr>
<tr>
<td>AC$_{50}$ hPanK3</td>
<td>&lt; 100 nM</td>
</tr>
<tr>
<td>AC$_{50}$ hPanK1/hPanK2</td>
<td>&lt; 100 nM</td>
</tr>
<tr>
<td><strong>Selectivity</strong></td>
<td></td>
</tr>
<tr>
<td>IC$_{50}$ hPanK1/2/3</td>
<td>&gt; 100 x AC$_{50}$</td>
</tr>
<tr>
<td>IC$_{50}$ human protein kinases</td>
<td>&gt; 100 x EC$_{50}$</td>
</tr>
<tr>
<td><strong>Cyto-toxicity</strong></td>
<td></td>
</tr>
<tr>
<td>CC$_{50}$ HepG2, HEK293, HeLa, THP1 and hTERT</td>
<td>&gt; 100 x AC$_{50}$</td>
</tr>
<tr>
<td><strong>in vitro ADME</strong></td>
<td></td>
</tr>
<tr>
<td>Kinetic Solubility (pH 7.4)</td>
<td>&gt; 10 µM</td>
</tr>
<tr>
<td>Metabolic Stability (liver microsomes)</td>
<td>t$_{1/2}$ &gt; 1h @ 0.1 µM</td>
</tr>
<tr>
<td>Permeability (Caco-2)</td>
<td>&gt; 3.0 x 10$^{-6}$ cm/s</td>
</tr>
<tr>
<td><strong>Off-target</strong></td>
<td></td>
</tr>
<tr>
<td>hERG binding</td>
<td>&lt; 50% @ 30 µM</td>
</tr>
<tr>
<td>CYP binding (8 CYPs)</td>
<td>&lt; 50% inhibition @ 100 µM</td>
</tr>
<tr>
<td><strong>PK</strong></td>
<td></td>
</tr>
<tr>
<td>IV and PO dosing</td>
<td>[drug]$<em>{plasma}$ &gt; EC$</em>{99}$</td>
</tr>
<tr>
<td>determine %F, AUC, t$_{1/2}$</td>
<td></td>
</tr>
<tr>
<td><strong>in vivo</strong></td>
<td></td>
</tr>
<tr>
<td>MTD</td>
<td>No toxicity</td>
</tr>
<tr>
<td>Efficacy: oral dose that delivers</td>
<td>Tx of PANK1$^{-/-}$ PANK2$^{-/-}$ results in:</td>
</tr>
<tr>
<td>[drug]$<em>{plasma}$ &gt; AC$</em>{99}$</td>
<td><strong>Body weight</strong>: wild type level (&gt;3x vehicle (~5g KO vs 15 to 30g WT)</td>
</tr>
<tr>
<td></td>
<td><strong>Survival</strong>: wild type % survival (50 days KO vs 150 days WT)</td>
</tr>
<tr>
<td></td>
<td><strong>CoA in forebrain</strong>: WT level (~40 pmol/mg/wet weight KO vs ~55 pmol/mg/wet weight WT</td>
</tr>
<tr>
<td></td>
<td><strong>CoA in hindbrain</strong>: WT level (~60 pmol/mg/wet weight KO vs ~110 pmol/mg/wet weight WT</td>
</tr>
<tr>
<td></td>
<td><strong>% Time Moving</strong>: WT level (~5% KO vs ~75 WT)</td>
</tr>
<tr>
<td></td>
<td><strong>Path traveled (m)</strong>: WT level (~1m KO vs ~15m WT)</td>
</tr>
</tbody>
</table>
IN VITRO SCREENING CASCADE

VTACs 1-9 → PKAN Fibroblasts: CoA → MDR1-MDCK1 Permeability assay
IRON Levels → Go / No-Go

In vitro assays
GO

Co-crystallization SAR & New design
No-Go

11/1/2021 Confidential
PK and \textit{in vivo} screening cascade

\textbf{In vivo PK Safety} \hspace{1cm} \textbf{GO}

\textbf{PKAN humanized mouse model} \hspace{1cm} \textbf{Lead Clinical candidate}

\textbf{No-Go} \hspace{1cm} \textbf{Go / No-Go}

\textbf{Humanized mouse model of PKAN}

\texttt{Pank2}^{n/n} \hspace{0.5cm} \texttt{mPank3}^{-/-} \hspace{0.5cm} \texttt{HuPank3}^{+/+} \hspace{0.5cm} \texttt{SynCre+}

\texttt{Brain biomarkers CoA, dopamine…}

\texttt{Survival}

\texttt{Movement & distance traveled}

\texttt{Behavioral}

\texttt{MRI (no iron accumulation)}
• PZ-2891 --> BBP 671

• BridgeBio / CoA pharmaceuticals (subsidiary)

• IND-enabling studies ongoing
  • Planning to file in 2020 in Organic Acidaemias
  • Prevalence: 5 in 100,000 births (200,000 global patients)

• “In non-clinical toxicology studies, we have observed **dose-limiting corneal toxicity** in a 14 day repeat dosing experiment in dogs. This BBP-671 compound did not achieve a NOAEL* in these test subjects; however a NOAEL was achieved in rodents.” – most recent S-1 filed May 24, 2019

• *: No-observed adverse effect level
The lead pantazine, PZ-2891, inhibited PANK3 with nM affinity, whereas the inactive PZ-3067 had no effect (Fig. 2a).

Sharma et al., 2018 PMID: 30352999
PKAN

Presents in two forms:

- Classic:
  - Starts around age ~3 ½ and patients require a wheelchair by mid-teens.
  - Inability to walk between 10-15 years after the beginning of symptoms
  - When severe, PKAN can result in muteness, an inability to eat or control muscle twisting and contractions, as well as, ultimately, a loss of the ability to breathe

- Atypical:
  - Occurs after age 10 and within the 1st 3 decades of life
  - Inability to walk typically occurs 15 to 40 years after symptoms
  - Psychiatric symptoms

Currently, no disease-modifying therapeutic is available