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 $\rightarrow$ PKAN

**Pantothenate**
(Vitamin B5)

-Pantothenate $\rightarrow$ PanK1 $\rightarrow$ PanK2 $\rightarrow$ PanK3 $\rightarrow$ 4’-Phosphopantothenate $\rightarrow$ Co-enzyme A $\rightarrow$ CoA

**PANK2**
- Mitochondrial PanK enzyme
- The major active PANK isoform in the human brain
Pantothenate (Vitamin B₅)

PANK1/2/3 → PanK3

4’-Phosphopantothenate

PPCS → 4’-Phosphopantothenoyl-L-cysteine

PPCDC → 4’-Phosphopantetheine

COASY → 4’-Dephospho-CoA

COASY → CoA

PanK3 activators VTAC1-9

Disrupted

stored

11/12/21 Confidential
HUMAN PANK3 ACTIVATORS

**PanK Modulators Screening cascade**

1. **1 Completed**
   - Assay Development
     - Developed ATP-based high-throughput screen

2. **2 Completed**
   - PanK modulators
     - 156,000 compounds screened

3. **3 Completed**
   - Lead Identification
     - 9 activators of human PanK3
     - VTAC1-9: 2.2 nM - 268 nM

4. **4 Pending**
   - Preclinical Studies
     - Cell-based assays and mouse models of PKAN

5. **5 Future**
   - Clinical Testing
     - Conduct clinical trials

**FUNDING**

**PITCH**

2017 - 2020

($736,000)

**SEED FUNDING**

(Blavatnik)

**VENTURE CAPITAL**

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

Active site activator
AC₅₀ ~2.6 nM
cLogP = 2.18
MW: 382.466
No toxicity

Allosteric activator
AC₅₀ = 4.9 nM
cLogP = 2.28
MW: 297.361
No Toxicity
**USE OF FUNDS & MILESTONES**

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

- Synthetic Chemistry
- VTAC - hPanK3
- DMPK
  - MDR1-MDCK
  - Permeability $>1 \times 10^{-6}$ 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

Carter A.  https://news.ohsu.edu/2019/10/29/

Jameson M., 2yo  www.thebaynet.com/ NBIAcure

In memory of Riley
Thank You
VIRTUS MANAGEMENT

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

Choukri Ben Mamoun, PhD. Yale
Professor of Medicine and Microbial Pathogenesis
Founder

Akansha Bhargava, MD
Blavatnik Fellow, Yale
Manager

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

Jaime Grutzendler, MD Yale
Professor of Neuroscience and Neurology
Scientific advisor

Tom Gerson: Ex-CFO of 3 biotech companies (2 Yale spinoffs)
Advisor: Finance, business strategy and operations

Mark S. Plummer, PhD
Scientific Manager
Advisor: Chemistry

John Puziss, Yale
OCR contact
## PKAN Therapies in Development

<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 (deferiprone)</td>
<td>ApoPharma</td>
<td>Iron chelating agent (Thalassemia)</td>
<td>Phase 3 (efficacy modest)</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)

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<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>$&lt; 100 \text{ nM}$</td>
</tr>
<tr>
<td>$AC_{50}$ hPanK1/hPanK2</td>
<td>$&lt; 100 \text{ nM}$</td>
</tr>
<tr>
<td><strong>Selectivity</strong></td>
<td></td>
</tr>
<tr>
<td>$IC_{50}$ hPanK1/2/3</td>
<td>$&gt; 100 \times AC_{50}$</td>
</tr>
<tr>
<td>$IC_{50}$ human protein kinases</td>
<td>$&gt; 100 \times EC_{50}$</td>
</tr>
<tr>
<td><strong>Cyto-toxicity</strong></td>
<td></td>
</tr>
<tr>
<td>$CC_{50}$ HepG2, HEK293, HeLa, THP1 and hTERT</td>
<td>$&gt; 100 \times AC_{50}$</td>
</tr>
<tr>
<td><strong>in vitro ADME</strong></td>
<td></td>
</tr>
<tr>
<td>Kinetic Solubility (pH 7.4)</td>
<td>$&gt; 10 \text{ µM}$</td>
</tr>
<tr>
<td>Metabolic Stability (liver microsomes)</td>
<td>$t_{1/2} &gt; 1 \text{h} @ 0.1 \text{ µM}$</td>
</tr>
<tr>
<td>Permeability (Caco-2)</td>
<td>$&gt; 3.0 \times 10^{-6} \text{ cm/s}$</td>
</tr>
<tr>
<td><strong>Off-target</strong></td>
<td></td>
</tr>
<tr>
<td>hERG binding</td>
<td>$&lt; 50% @ 30 \text{ µM}$</td>
</tr>
<tr>
<td>CYP binding (8 CYPs)</td>
<td>$&lt; 50% \text{ inhibition} @ 100 \text{ µM}$</td>
</tr>
<tr>
<td><strong>PK</strong></td>
<td></td>
</tr>
<tr>
<td>IV and PO dosing</td>
<td>$[\text{drug}]<em>{\text{plasma}} &gt; EC</em>{99}$</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 $[\text{drug}]<em>{\text{plasma}} &gt; AC</em>{99}$</td>
<td>Tx of PANK1$^{-/-}$PANK2$^{-/-}$ results in: Body weight: wild type level ($&gt;3x$ vehicle ($~5g$ KO vs $15$ to $30g$ WT)) Survival: wild type $%$ survival (50 days KO vs 150 days WT) CoA in forebrain: WT level ($~40$ pmol/mg/wet weight KO vs $~55$ pmol/mg/wet weight WT) CoA in hindbrain: WT level ($~60$ pmol/mg/wet weight KO vs $~110$ pmol/mg/wet weight WT) % Time Moving: WT level ($~5%$ KO vs $~75$ WT) Path traveled (m): WT level ($~1m$ KO vs $~15m$ WT)</td>
</tr>
</tbody>
</table>
IN VITRO SCREENING CASCADE

VTACs 1-9

PKAN Fibroblasts:
- CoA
- IRON Levels

In vitro assays
- MDR1-MDCK1 Permeability assay

Co-crystallization SAR & New design

Go / No-Go

NO-GO

GO
PK and *in vivo* screening cascade

**In vivo PK Safety**

**Go**

**PKAN humanized mouse model**

**Go / No-Go**

**Humanized mouse model of PKAN**

- *Pank2*^{n/n}
- *mPank3*^{−/−}
- *HuPank3*^{+/+}
- SynCre+

**Lead Clinical candidate**

**No-Go**

**SAR**

**Brain biomarkers**
- CoA, dopamine…

**Survival**

**Movement & distance traveled**

**Behavioral**

**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

Present 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.