Therapy for Pantothenate Kinase-Associated Neurodegeneration (PKAN)

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VIRTUS MANAGEMENT

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Yale
PKAN Genetic Disorder

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

- First report: 1922
- 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)

- PanK1
- PanK2
- PanK3

**4’-Phosphopantothenate**

1. $\rightarrow$ Co-enzyme A

- **PANK2**
  - Mitochondrial PanK enzyme
  - The major active PANK isoform in the human brain

11/9/21
PROBLEM

Pantothenate (Vitamin B₅)

\[
\text{PANK1/2/3} \rightarrow 4'-\text{Phosphopantothenate}
\]

\[
\text{PPCS} \rightarrow 4'-\text{Phosphopantothenoyl-L-cysteine}
\]

\[
\text{PPCDC} \rightarrow 4'-\text{Phosphopantetheine}
\]

\[
\text{COASY} \rightarrow 4'-\text{Dephospho-CoA}
\]

\[
\text{COASY} \rightarrow \text{CoA}
\]

Disrupted PanK4 4PPP
PROBLEM & SOLUTION

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

PanK3 activators VTAC1-9

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

Active site activator

$AC_{50} = 2.2 \text{ nM}$
$cLogP = 2.18$
$MW: 382.466$
No toxicity

Allosteric activator

$AC_{50} = 4.9 \text{ nM}$
$cLogP = 2.28$
$MW: 297.361$
No Toxicity
VTACs 1-9 → *In vitro* Screening Cascade → Humanized Mouse Model → Clinical Candidate

- Biochemistry
- Structural Biology
- Medicinal Chemistry
- Cell Biology
Market Size: ~$360M/year

U.S.:
- 320 – 1000 patients

EU:
- 350 – 1300 patients

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
# 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) Failed</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)

11/9/21
SUMMARY

VIRTUS TECHNOLOGY AND COMPETITIVE ADVANTAGE

Novel Activators

Novel mode of action

Novel strategy for treatment of PKAN

Competitive advantage (IP to 2040)
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