Update: Development of Novel Angiotensin (1-7) Derivatives: For Treatment of Brain Inflammation Related Memory Impairment

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Speaker Disclosure Statement

Dr. Meredith Hay has the following financial conflicts of interests:

• Founder and major stockholder of ProNeurogen, Inc

• Scientific Consultant for ProNeurogen, Inc

• ProNeurogen, Inc holds exclusive licensing rights from UA to technology discussed herein.
The Problem:

Cognitive impairment is a common neurological complication in patients with systemic inflammatory disease such as heart failure, hypertension, and diabetes.

Affects approximately 50-70% of HF patients.

Due to growing aging population, the number of people with HF could increase 46 percent from 5 million in 2012 to 8 million in 2030.
The Impact:

• Patients with vascular and heart disease with cognitive impairment are known to have hospital readmission rates ranging from 40 to 50% within 6 months.

• Increased duration of hospitalization.

• Impaired long-term quality of life.
Clinical Therapy:

Currently there are no FDA approved therapies to treat or prevent memory loss due to inflammation or vascular dementia.
**Approach: What is the Possible Mechanism of Action?**

**Disease**  
(ie Heart Failure, Hypertension, Dementia, Alzheimer's')

**Trauma**  
(ie Stroke, Injury, Embolism, Blunt trauma, Surgery)

**Blood Flow**

↑ Brain Inflammatory Pathways – Oxygen Radicals

↑ Progress of Cognitive Impairment

Increase in inflammatory cytokines and reactive oxygen species in the brain leads to cognitive dysfunction.
The Ideal Drug Candidate

✓ Would interrupt this inflammatory cascade.

✓ Work at both sides of the blood-brain barrier 

*inhibiting inflammation* at both:

- Brain vascular endothelium
- Neurons and microglia.

✓ *Improve cerebral blood flow.*
Our Drugs: Angiotensin 1-7 Agonists: Mas Receptor Target

Ang-(1-7) → MasR → PI3K/Akt

- e-NOS (brain vasculature)
- NADPH NOX-4
- Ib1a,ERK1/2,NF-κβ

Increased Brain Blood Flow
Decreased ROS
Anti-inflammatory
Neuroprotection

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NEUROPROTECTION & DECREASED DEMENTIA RISK
OUR APPROACH: Develop Angiotensin-(1-7) derivatives as a novel platform for neuroprotection.

*Long-Range Drug Development Plan:* Administration of Ang-(1-7) receptor agonist will attenuate cognitive dysfunction in patients whose cognitive impairment is clinically associated with an increase in inflammation in the central nervous system.
Angiotensin 1-7: Mas Receptor Target

**Ang-(1-7) Mas Receptor:**

- Highly expressed in brain and hippocampus
- Increases endothelial nitric oxide (NO) release = vasodilation and improved blood flow
- Decreases reactive oxygen (ROS) formation and NOX2 in brain
- Improves circulating inflammatory profile and pro-neuroregeneration profile
- Rescues cognitive impairment in cardiac disease model
- Decreases amyloid load in mouse Alzheimers model
- Ang-(1-7) Therapy Safe in humans
Leveraging Cross-Disciplinary Teams

Heart

Brain

Pharmacology
We have **developed and patented** novel glycopeptide-based **Angiotensin-(1-7) derivatives** that show:

- Increased blood-brain barrier penetration,
- Improved serum ½ life
- Cognitive protective.

**PNA5 and PNA6** are our lead compounds.
Glycosylated Ang-(1-7) = Improved Half-life and Brain Penetration

![Graph showing serum concentration and CSF dialysate over time for various glycosylated Ang-(1-7) derivatives.](image-url)
Step 1 Preclinical Phase

- Develop a preclinical mouse model of HF induced cognitive impairment.
- Document spatial memory and object recognition impairment in CHF.
- Treat animals with Ang-(1-7) peptides and retest memory function.
- Design a 2nd generation peptide with improved BBB penetration and half-life.
Change in Ejection Fraction Post MI

Baseline 4 weeks 8 weeks 12 weeks
Sham (n=4) MI (n=4)

Give drug 3 weeks
Novel Object Recognition Test

This task takes advantage of the well-known tendency of rodents to explore novel objects more than familiar ones.

Memory impaired animals will not distinguish familiar objects from novel ones.

**Familiar Test, 2 hour delay, Novel vs Familiar Test**

\[
\text{DRatio} = \frac{(t \text{ novel} - t \text{ familiar})}{(t \text{ novel} + t \text{ familiar})}
\]

A **positive score** indicates more time spent with the novel object,
A **negative score** indicates more time spent with the familiar object,
A **zero score** indicates a null preference

\* = p< 0.05, \# = p< 0.05. ANOVA + posthoc Tukey test
PNA5 – Rescues HF-Induce Cognitive Impairment- Object Memory Test

*P = .009

**P = .0005

#P = .0008

D ratio +/- SE

HF + Saline (n= 11)
HF + PNA5 (n= 11)
Control + PNA5 (n= 5)
Control + Saline (n= 6)
Heart Failure Impairment of Spatial Memory

Week 4 post CHF Induction, Sham (n=4) vs MI (n=10)

Significant Spatial Memory Impairment

- MI
- Sham

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PNA5 Attenuates HF-Induced Spatial Memory Impairment

Mice are 12 weeks post MI or Sham Surgery.
11 mice were MI + Ang(1-7)
10 mice were MI + saline
6 mice were Sham + Ang (1-7)
Alzet pumps with either Ang(1-7) or saline were implanted sq.
Morris WM test performed 4 weeks post pump implant.
Step 2: Clinic Phase

- Patents: U.S. PATENT 9,670,251, PATENT 9,796,759, JAPAN 6254692
- Startup ProNeurogen, Inc
- FDA IND Approved for native 2015
- Develop Nasal Formulation/Autoinjector

Phase Ila Clinical Trials:
- Cardiac Bypass Patients: Funded U01 $3M, NHLBI, 2017: enrolling
- Phase II Clinical Trial for HF patients: enrolling
Product Development Timeline

1st Gen Peptide – PNA1-Proof-of-Concept
**Cardiac Bypass /Heart Failure**
Clinical Trial Phase 2a

2nd Gen peptide – PNA5
IND Enabling Studies - Phase I safety

2nd Gen Peptide – PNA5
**Vascular Dementia/Heart Failure**
Clinical Trial Phase 2a, 2b

Identify Pharma Partner for Phase 3 Trials, Marketing and Sales

- **2018**
- **2020**
- **2022**

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Thank you.

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