

**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.**

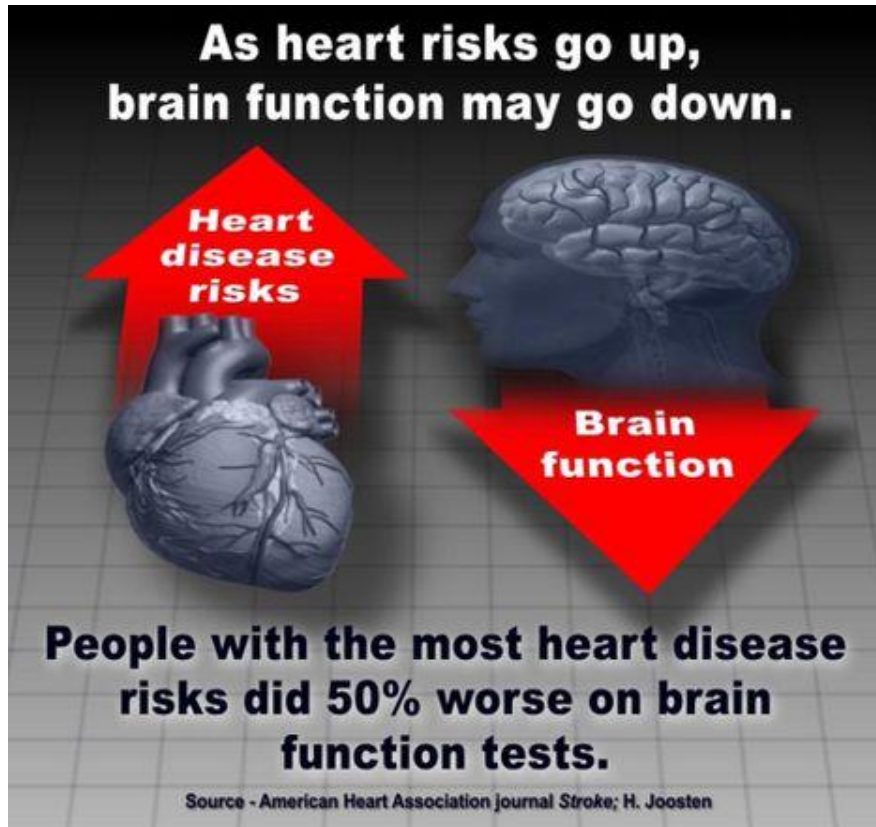


The Problem:

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.



American Heart Association journal Circulation: Heart Failure

The Impact:

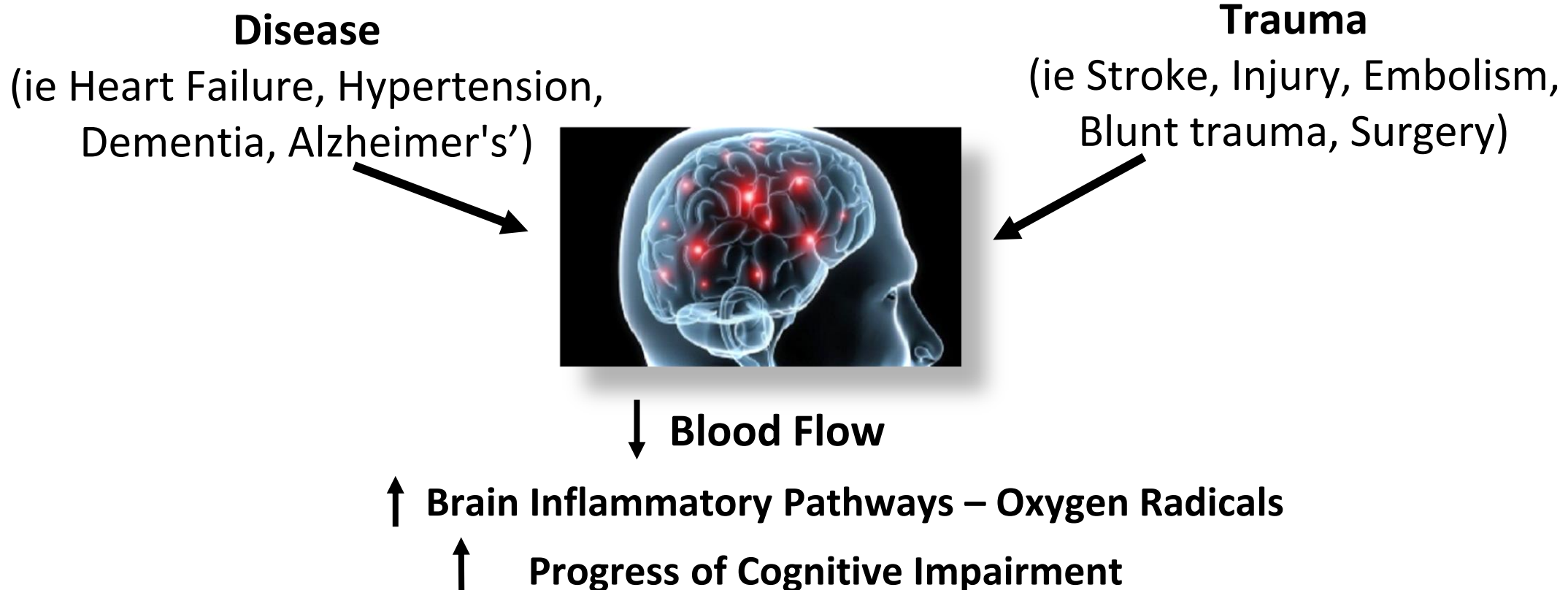
- Patients with vascular and heart disease with cognitive impairment are known to have hospital readmission rates ranging from 40 to 50% within 6 months.
- Increased duration of hospitalization.
- Impaired long-term quality of life.



Clinical Therapy:

Currently there are no FDA approved therapies to treat or prevent memory loss due to inflammation or vascular dementia.

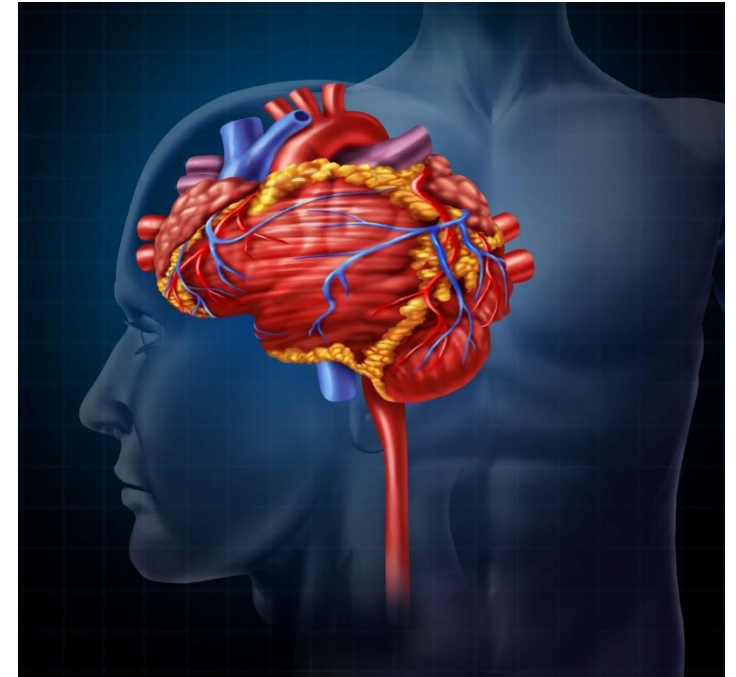
Approach: What is the Possible Mechanism of Action?



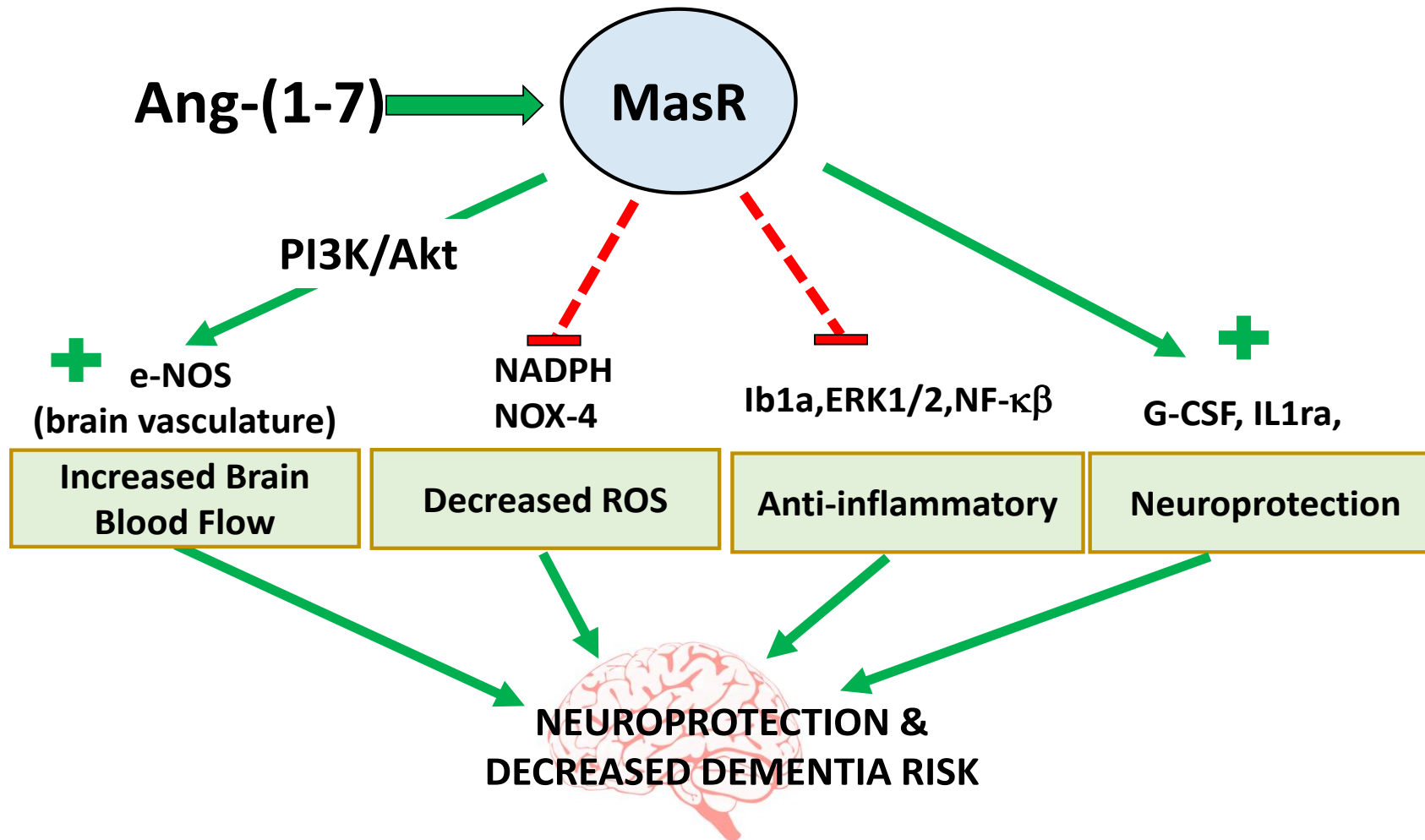
Increase in inflammatory cytokines and reactive oxygen species in the brain leads to cognitive dysfunction.

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



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:

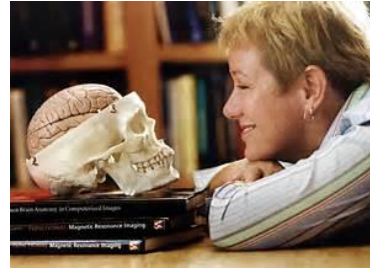
- ✓ Highly expressed in brain and hippocampus
- ✓ Increases endothelial nitric oxide (NO) release = vasodilation and improved blood flow
- ✓ Decreases reactive oxygen (ROS) formation and NOX2 in brain
- ✓ Improves circulating inflammatory profile and pro-neuroregeneration profile
- ✓ Rescues cognitive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

Leveraging Cross-Disciplinary Teams

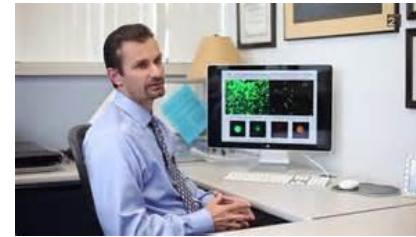
Heart



Brain



Pharmacology

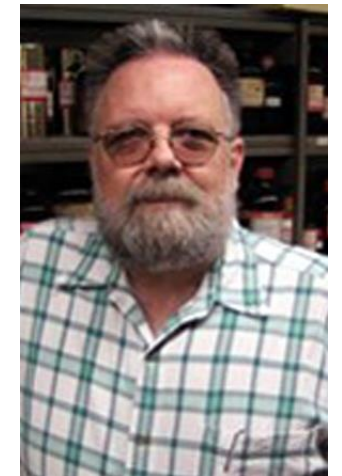
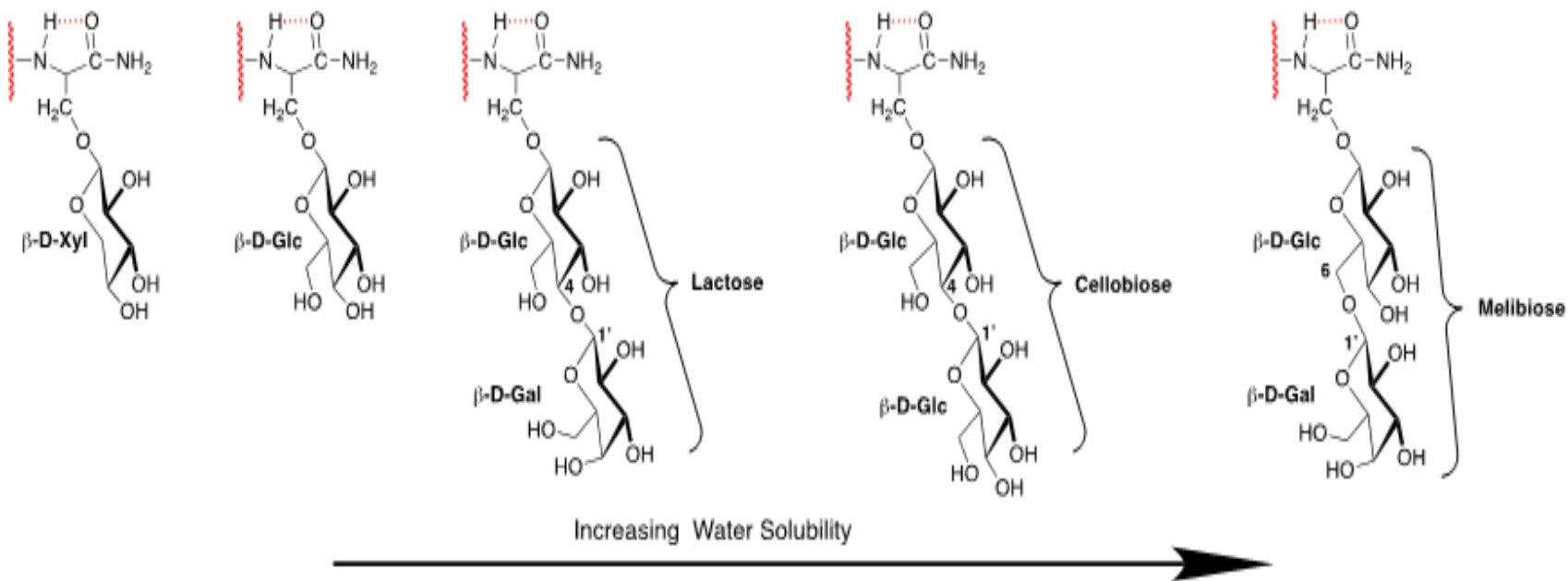


Novel Ang-(1-7) Derivatives

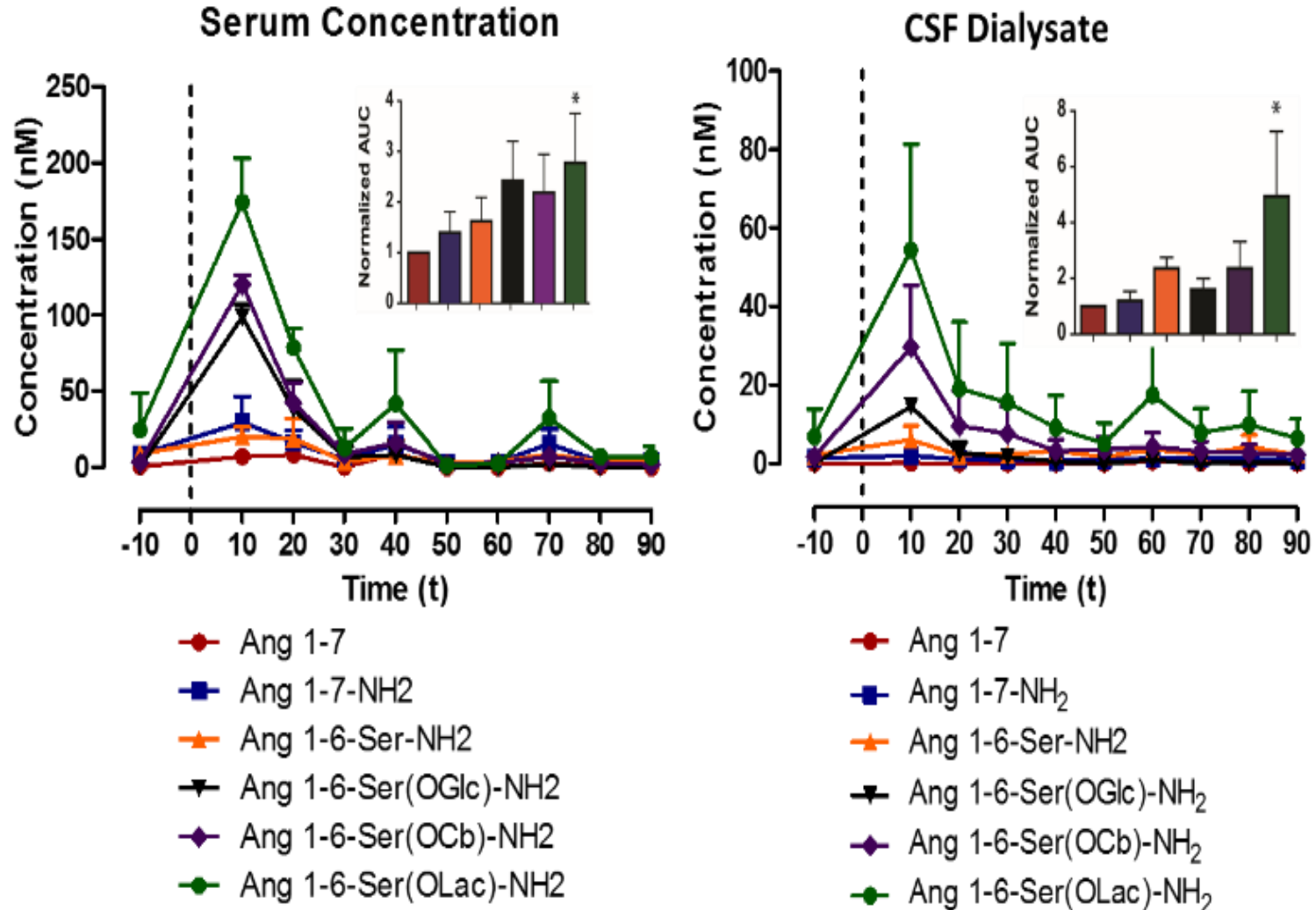
We have developed and patented novel glycopeptide-based Angiotensin-(1-7) derivatives that show:

- Increased blood-brain barrier penetration,
- Improved serum $\frac{1}{2}$ life
- cognitive protective.

PNA5 and PNA6 are our lead compounds



Glycosylated Ang-(1-7) = Improved Half-life and Brain Penetration



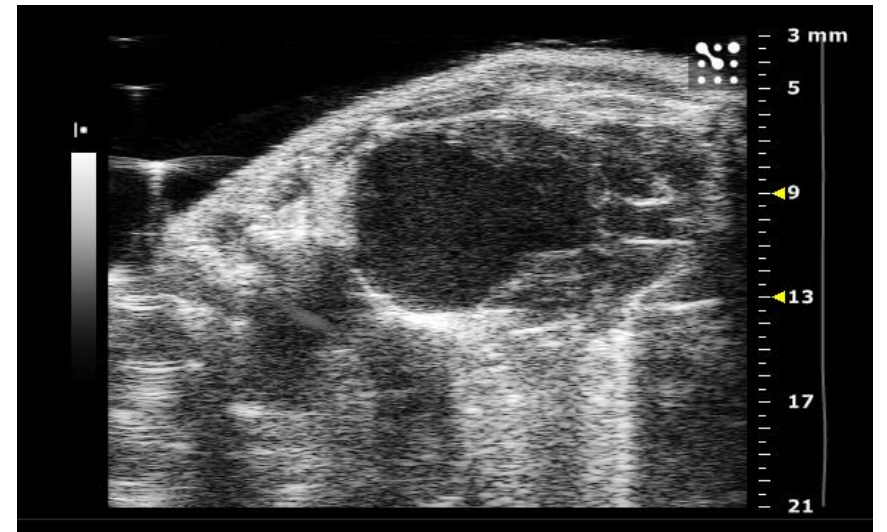
Step 1 Preclinical Phase

- ✓ 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.

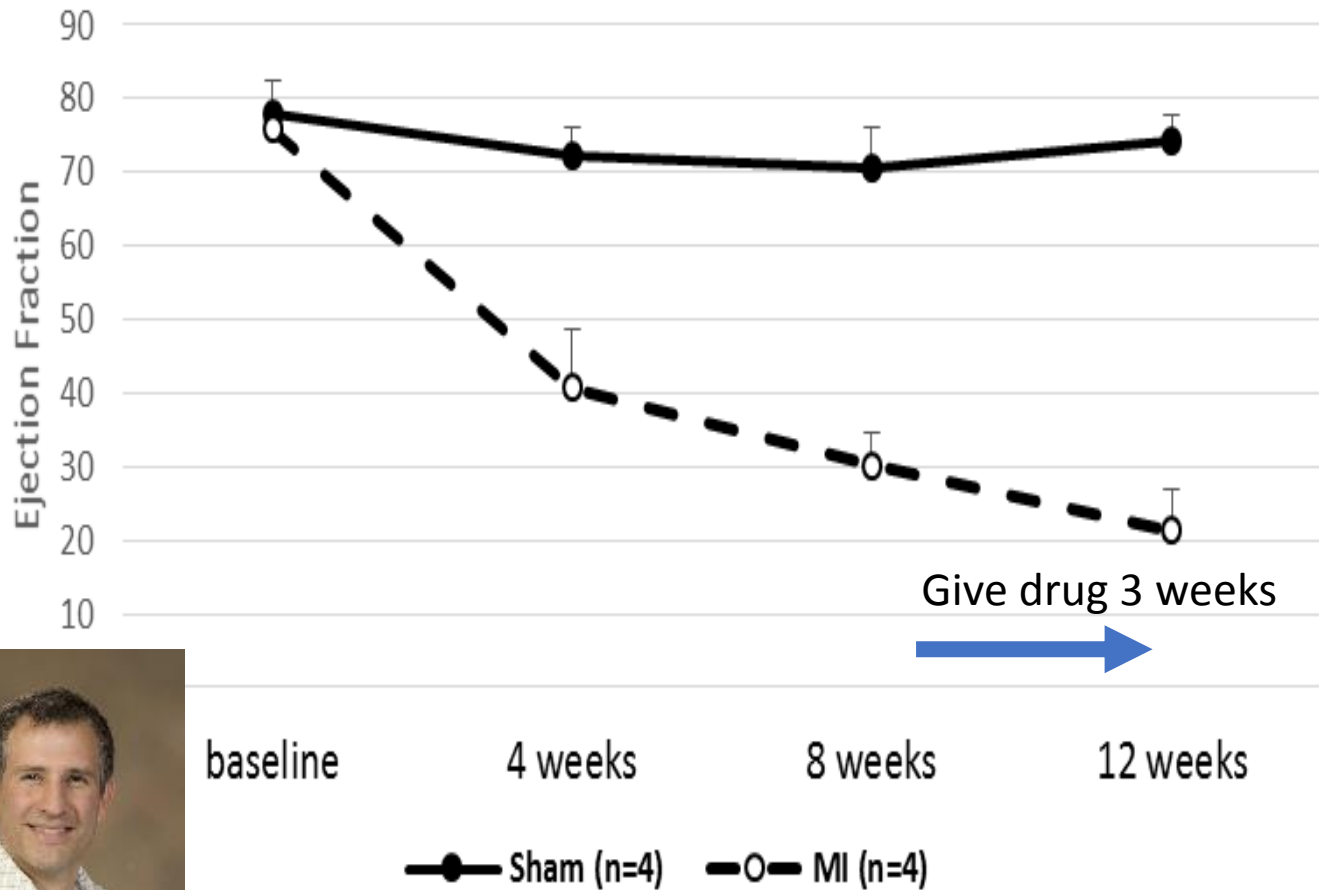
8 Week Sham



8 Week Post MI



Change in Ejection Fraction Post MI



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

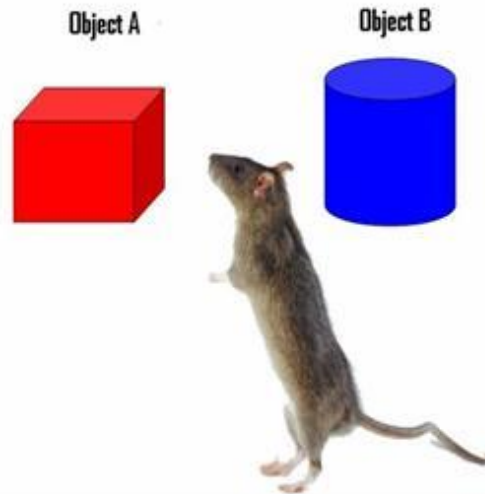
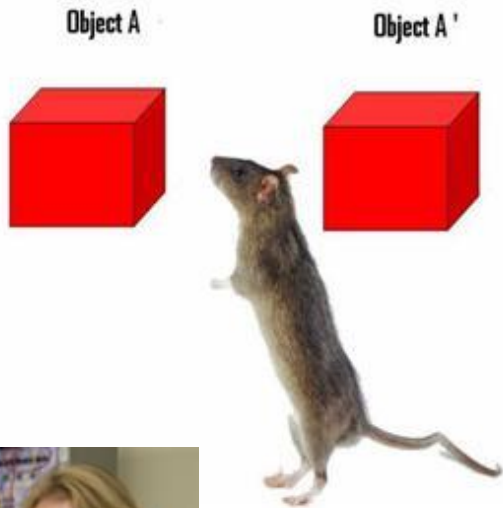
$$\text{DRatio} = (\text{t novel} - \text{t familiar}) / (\text{t novel} + \text{t familiar})$$

A **positive score** indicates more time spent with the novel object,

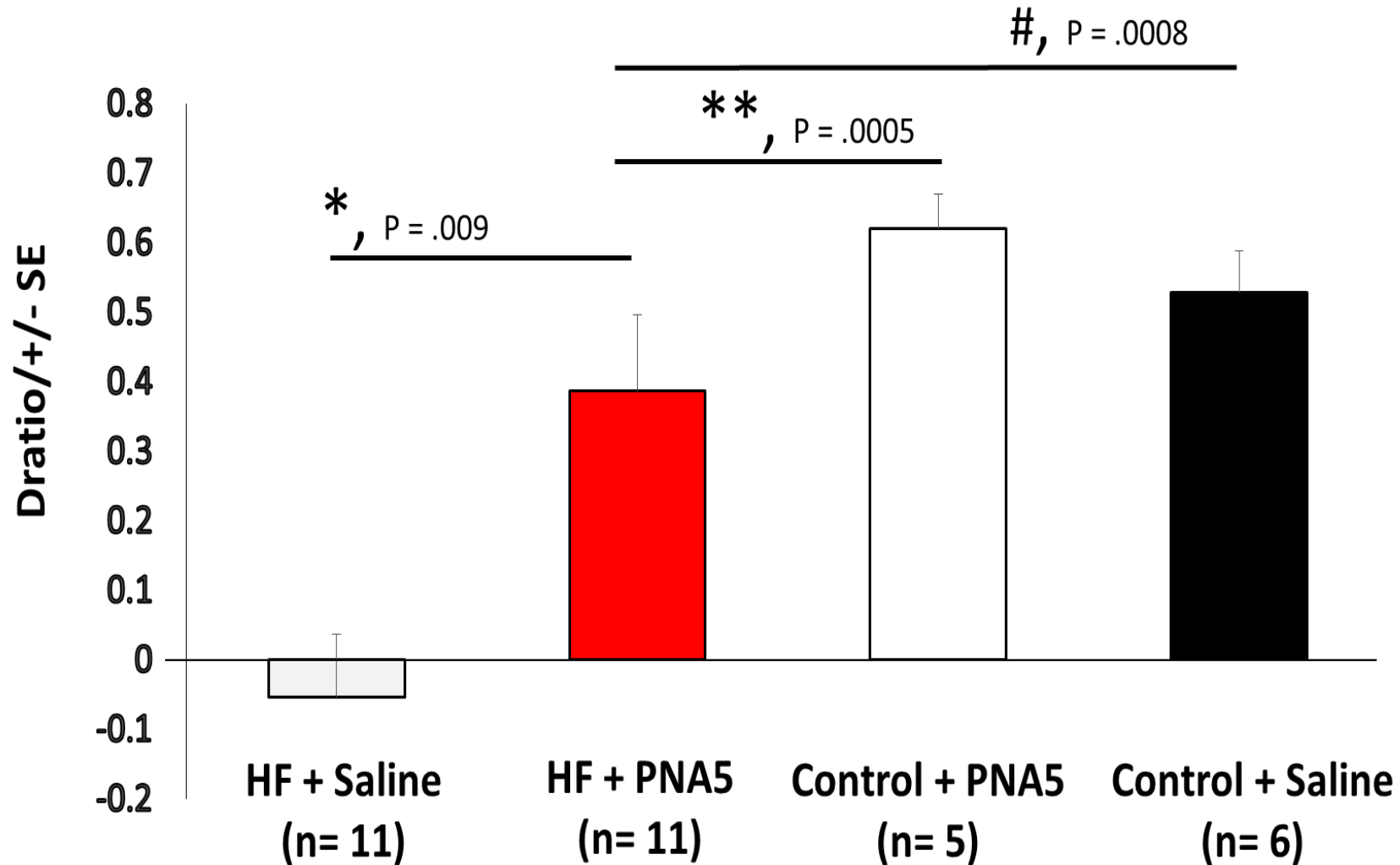
A **negative score** indicates more time spent with the familiar object,

A **zero score** indicates a null preference

* = $p < 0.05$, # = $p < 0.05$. ANOVA + posthoc Tukey test

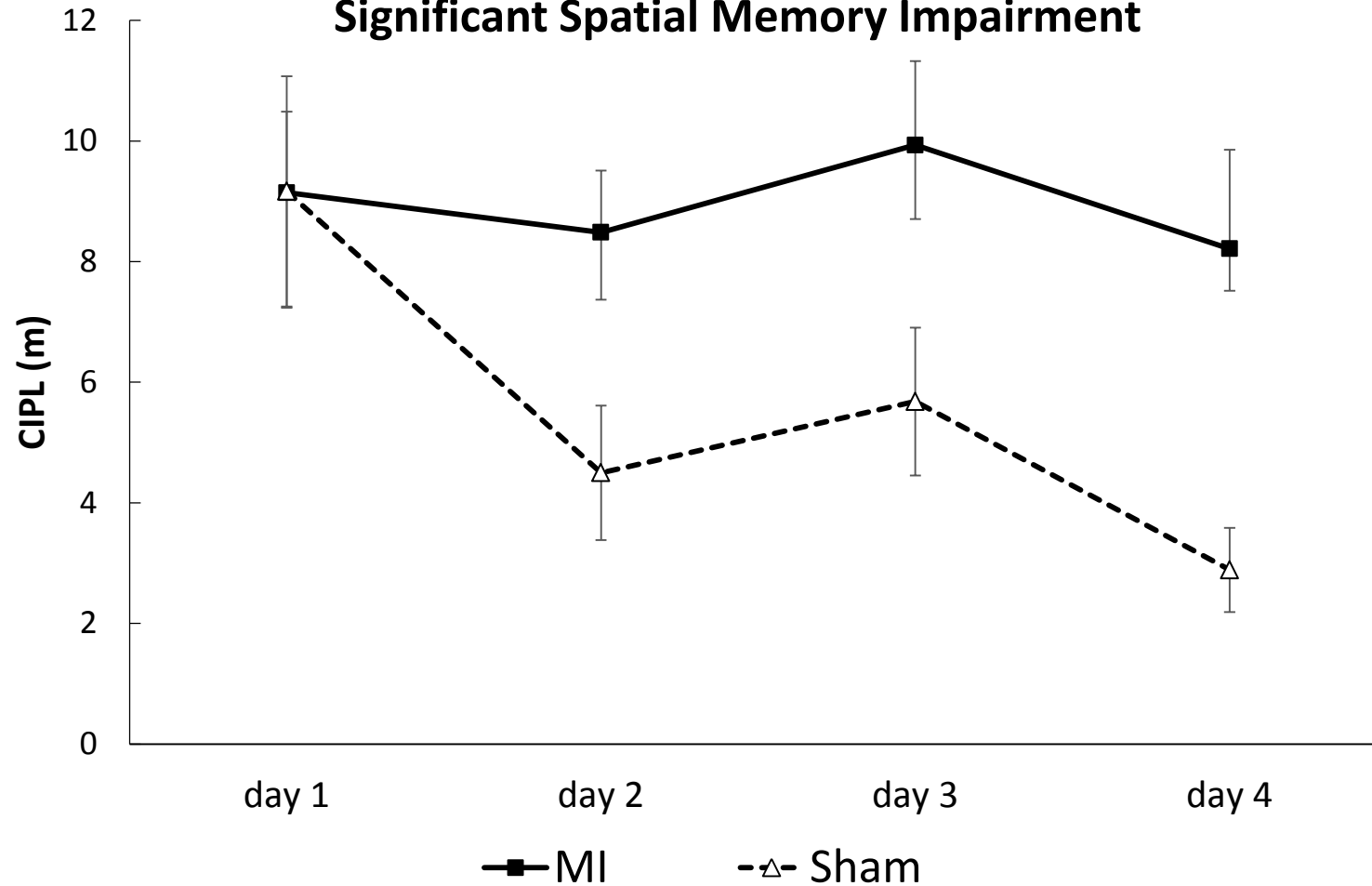


PNA5 – Rescues HF-Induce Cognitive Impairment- Object Memory Test



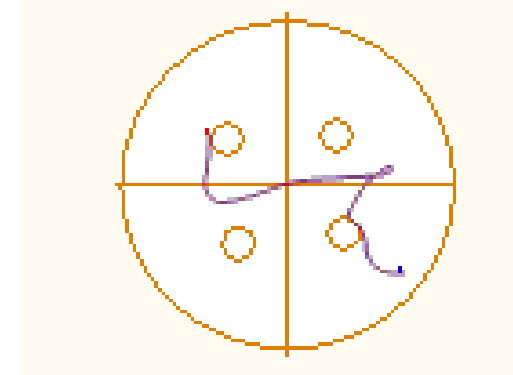
Heart Failure Impairment of Spatial Memory

Week 4 post CHF Induction, Sham (n=4) vs MI (n=10)
Significant Spatial Memory Impairment



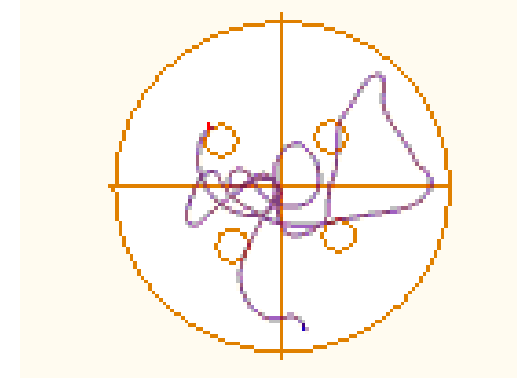
Example Sham Mouse Swim Plot
Day 3 – 4 weeks post sham surgery

Animal 10 (Test 149) ▶ ||

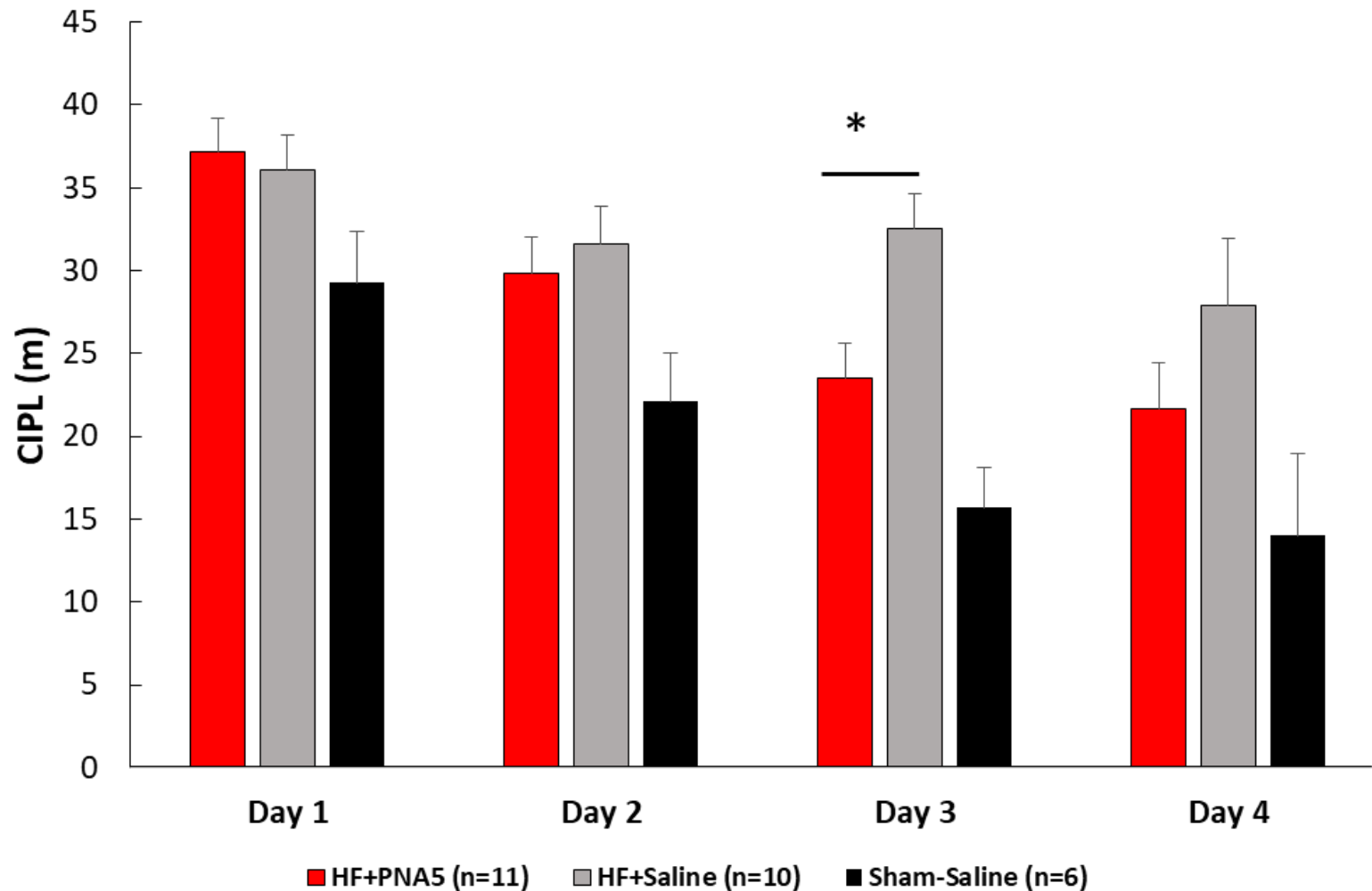


Example MI Mouse Swim Plot
Day 3 – 4 weeks post MI

Animal 3 (Test 134) ▶ ||



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.

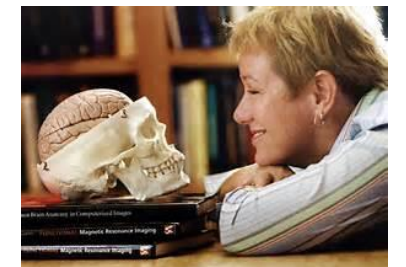
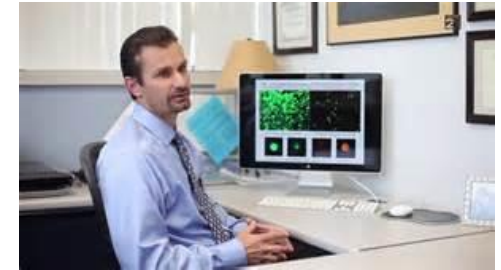
Morris WM test performed 4 weeks post pump implant.

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 IIa 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

Identify Pharma Partner
for Phase 3 Trials,
Marketing and Sales

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

2018

2020

2022

Thank you.

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