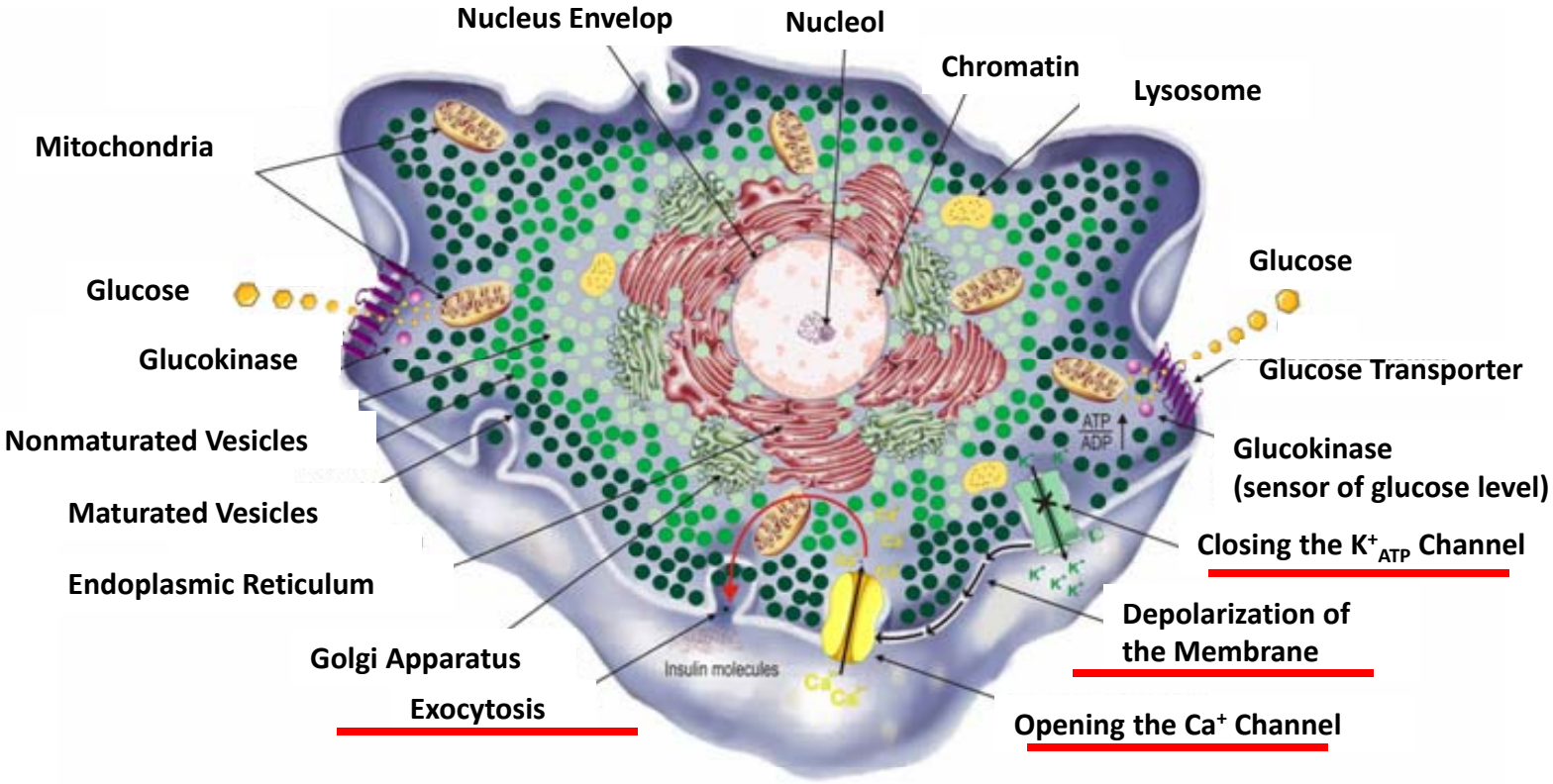
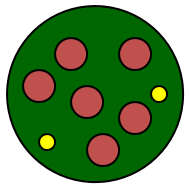
Pancreatic β-Cell

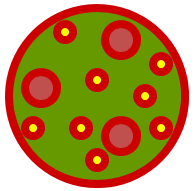


secretory vesicle

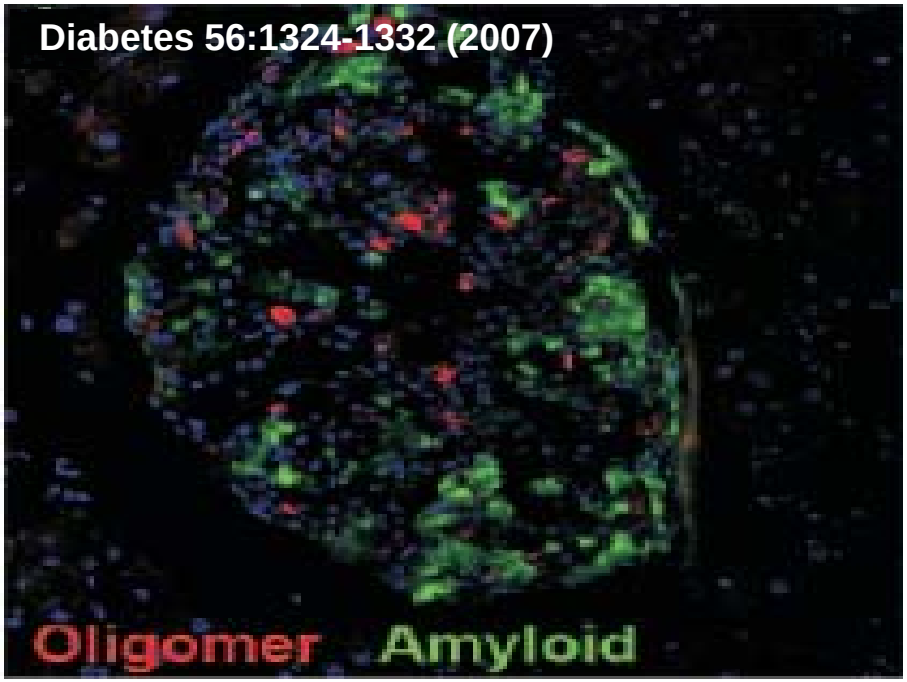
Normal  10^2 ~

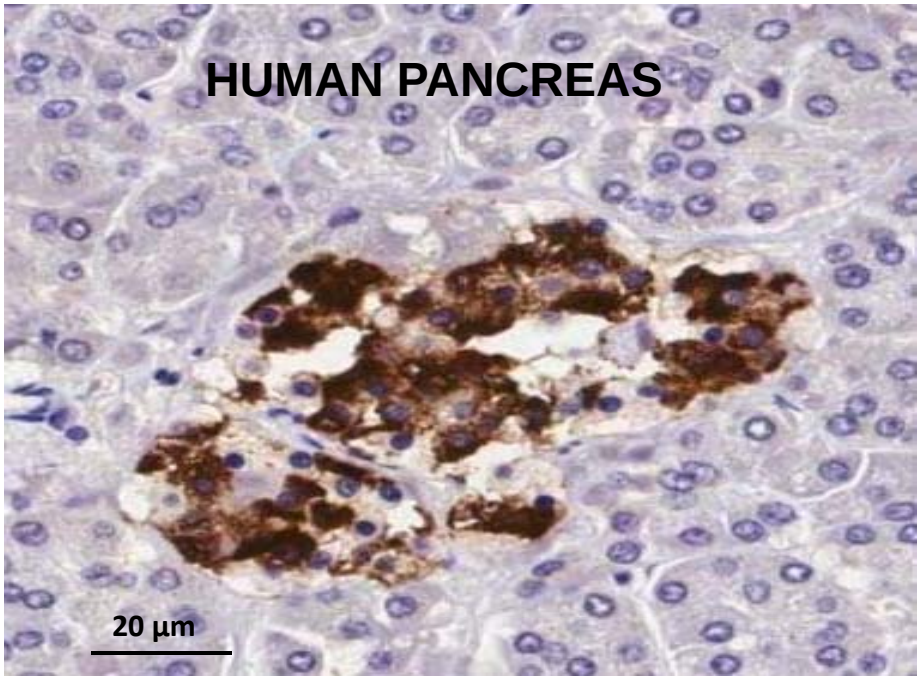
ProInsulin → **Insulin**

ProAmylin → **Amylin**

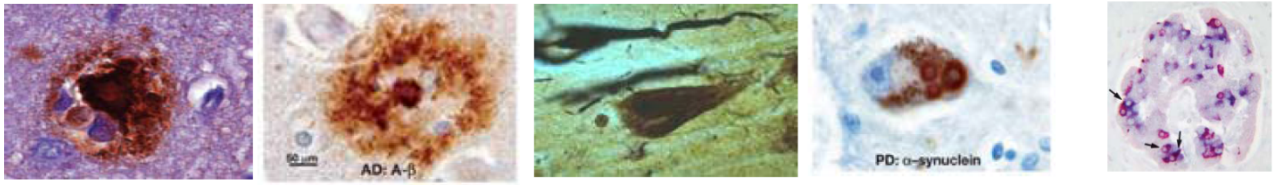
< 10^2 secretory vesicle  **Pro-diabetes**

Amylin Deposition is a Hallmark of Type-2 Diabetes in Humans





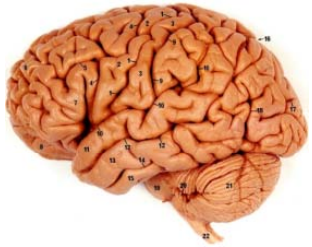
Prion	Aβ	Tau	α-synuclein	Amylin

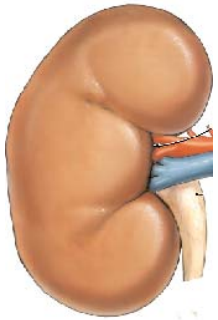


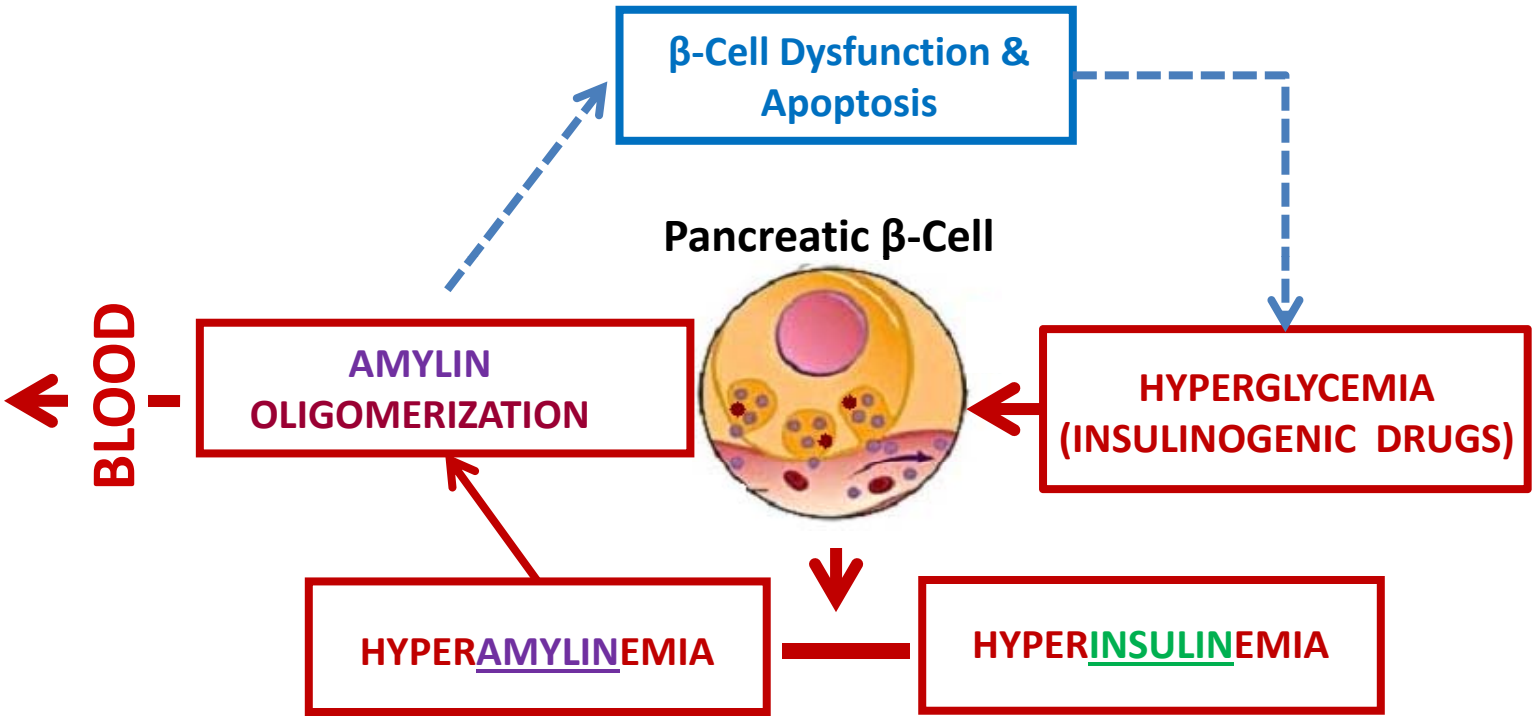
Ross and Poirier, Nature Med (2004); Aguzzi and Haass, Science (2003); Iki and Pour, JHC 2007

Transmissible Spongiform Encephalopathies	Dementia, Alzheimer's Disease	Parkinson's Disease	Type-2 Diabetes

Hyperamylinemia, Amylin Oligomerization, & the Risk of Cardio-Cerebrovascular Diseases







Florin Despa

Department of Pharmacology
University of California, Davis

Relevance to Our Mission

This research project is relevant to understanding, preventing, and, possibly, treating diabetes complications in two ways:

1. It uncovers an early pathogenic mechanism linking age-related metabolic disorders with diabetic brain injury, dementia, and CVD;

2. It identifies hyperamylinemia as a feasible therapeutic target to reduce accumulation of proteinaceous debris in the CV and CN systems, and thus to limit/ delay diabetes complications.

Outline of Research in My Laboratory

1. **Mechanisms of amylin oligomer formation and accumulation:**
   a. understanding the etiology of hyperamylinemia;
   b. testing the circulating amylin oligomer hypothesis.

2. **Amylin oligomer-induced cardiac dysfunction:**
   a. primary structural defect induced by oligomers in myocytes;
   b. hypertrophy, remodeling;
   c. oxidative and inflammatory stress.

3. **Role of oligomeric amylin in diabetic brain damage and dementia:**
   a. interaction & co-localization of amylin with Aβ;
   b. amylin oligomer-mediated inflammatory and oxidative damage.

4. **Curbing amylin deposition to delay/reduce the CVD risk:**
   a. pro-fibrinolytic molecules limit amylin attachment to sarcolemma and reduce ROS production in cardiac myocytes.

Collaborators

- Kaleena Jackson
- Kathy Guglielmino
- Brian Koch

- Sanda Despa
- Bruce Hammock
- Peter J Havel
- Anne Knowlton
- Donald Bers
- Heinrich Taegtmeyer (UTHS)
- Keneth B. Margulies (U Penn)
- Donald Steiner (U Chicago)
- Simon Xie (Stanford)

- Heike Wulff
- Elva Diaz
- Gustavo Barisone
- Dave Speca

AD Center

- Charles DeCarli
- Lee-way Jin

Funds: AHA, NSF, UCD AD Center, Vision Grant - UC Davis

Cardiotoxicity of Hyperamylinemia (RATIONALE)

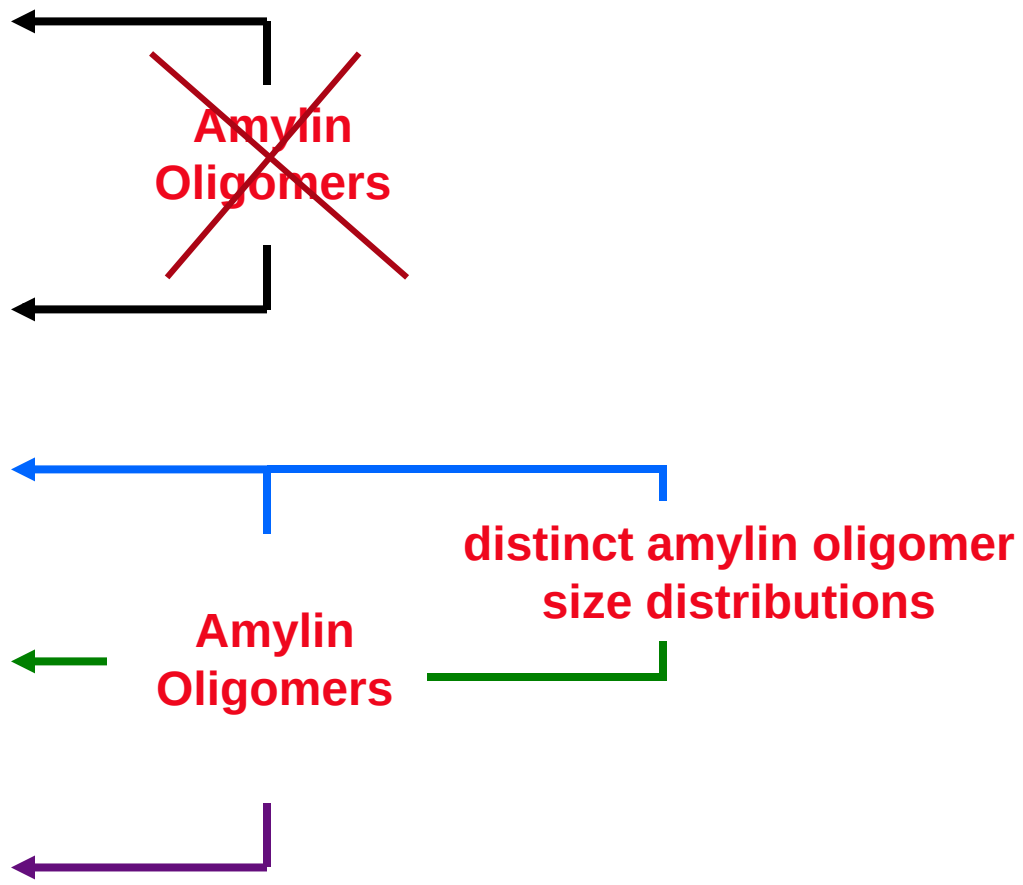
Lean
Non-Failing Hearts

Lean, Non-diabetes
Failing Hearts

Obese/Overweight
Non-Failing Hearts

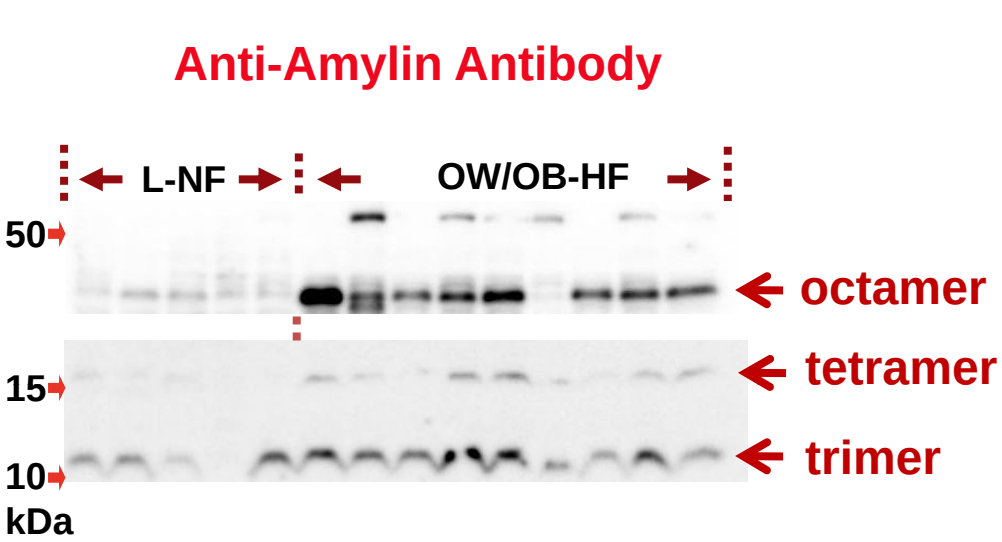
Obese/Overweight
Failing Hearts

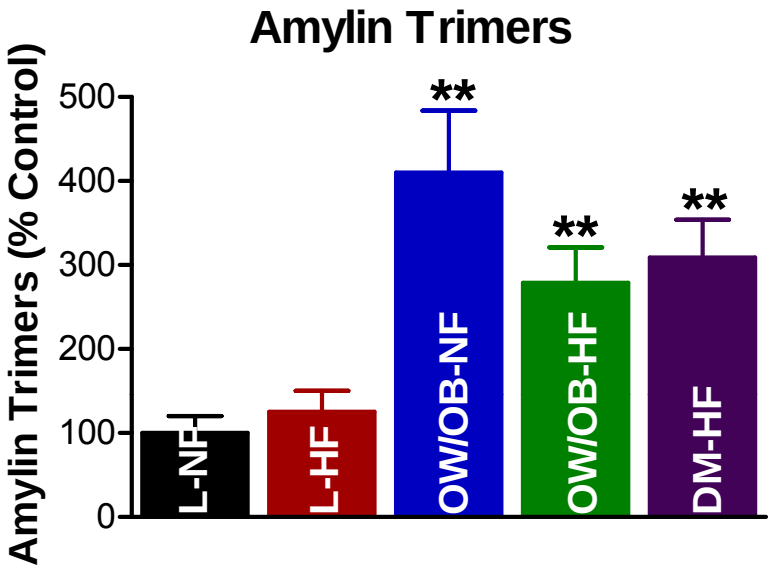
Type-2 Diabetes
Failing Hearts

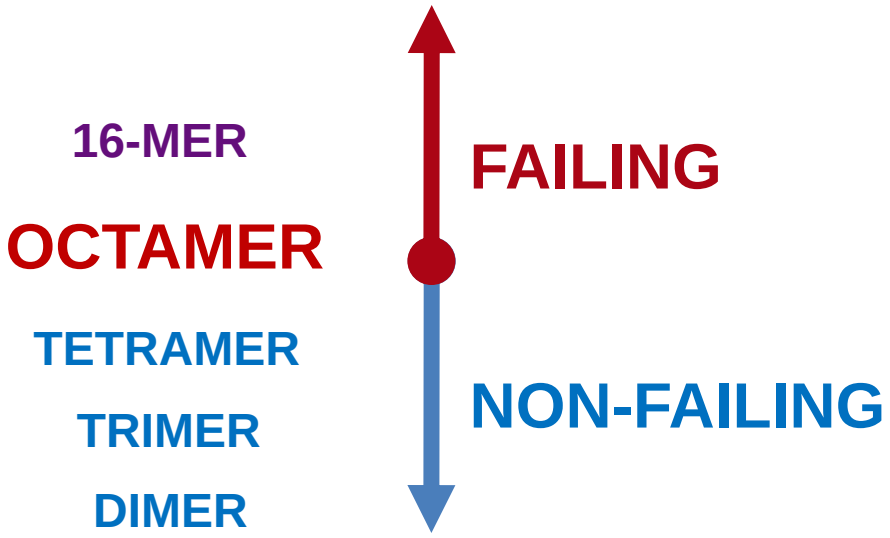


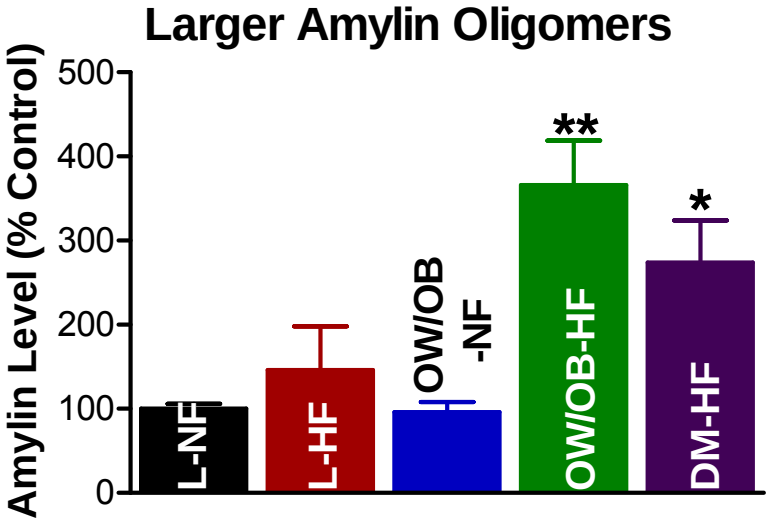
Amylin Oligomers Accumulate in Heart

Failing vs. *Non-failing*



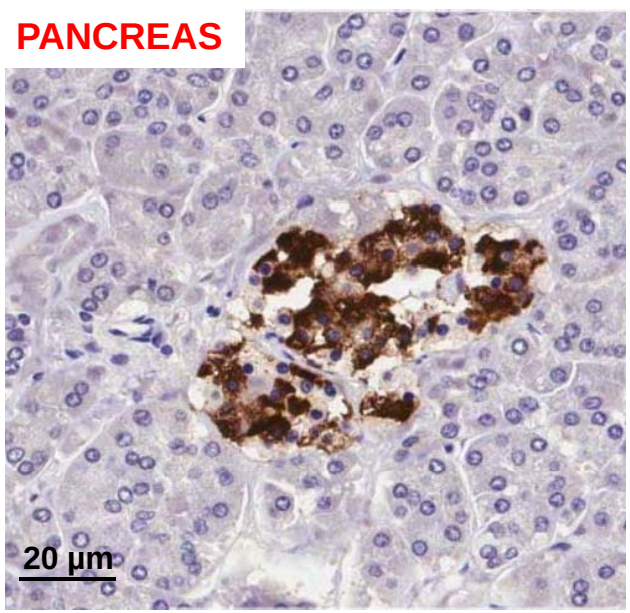


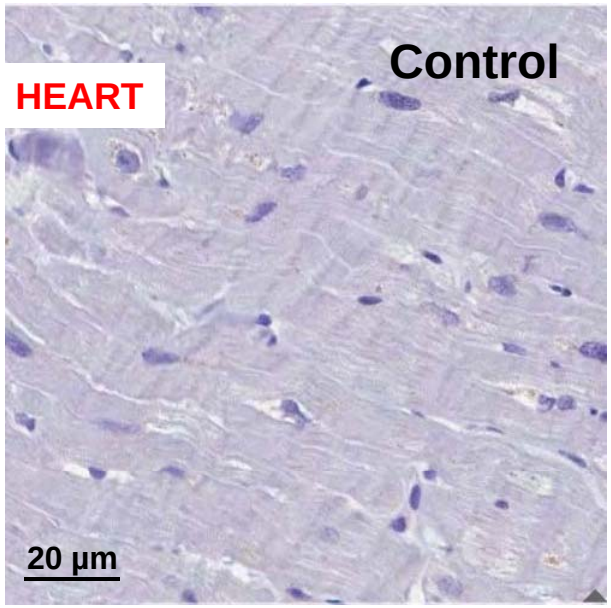




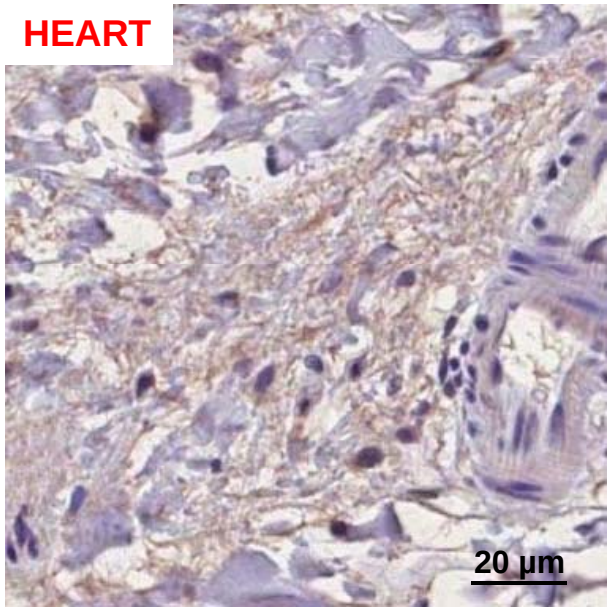
Despa S, …, Despa F. Circ Res. 2012;110:598

Cardiac Amylin Deposition in Humans with Type-2 Diabetes

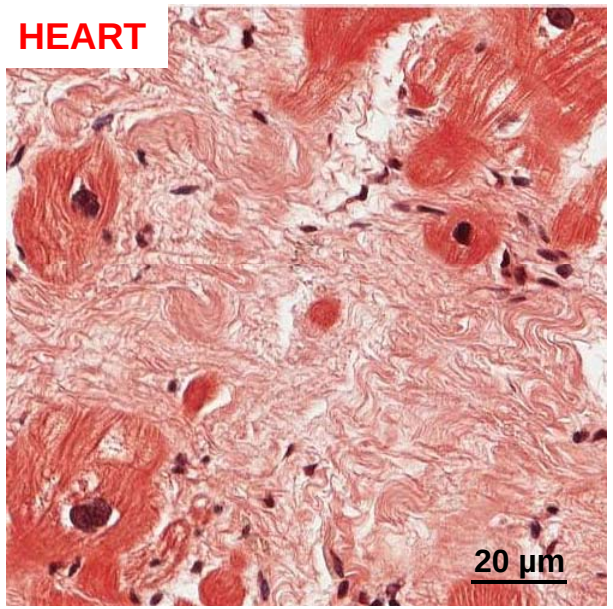




Anti-Amylin Antibody



Congo Red Staining



Despa S, …, Despa F. Circ Res. 2012;110:598

Selection of Human Brain Samples

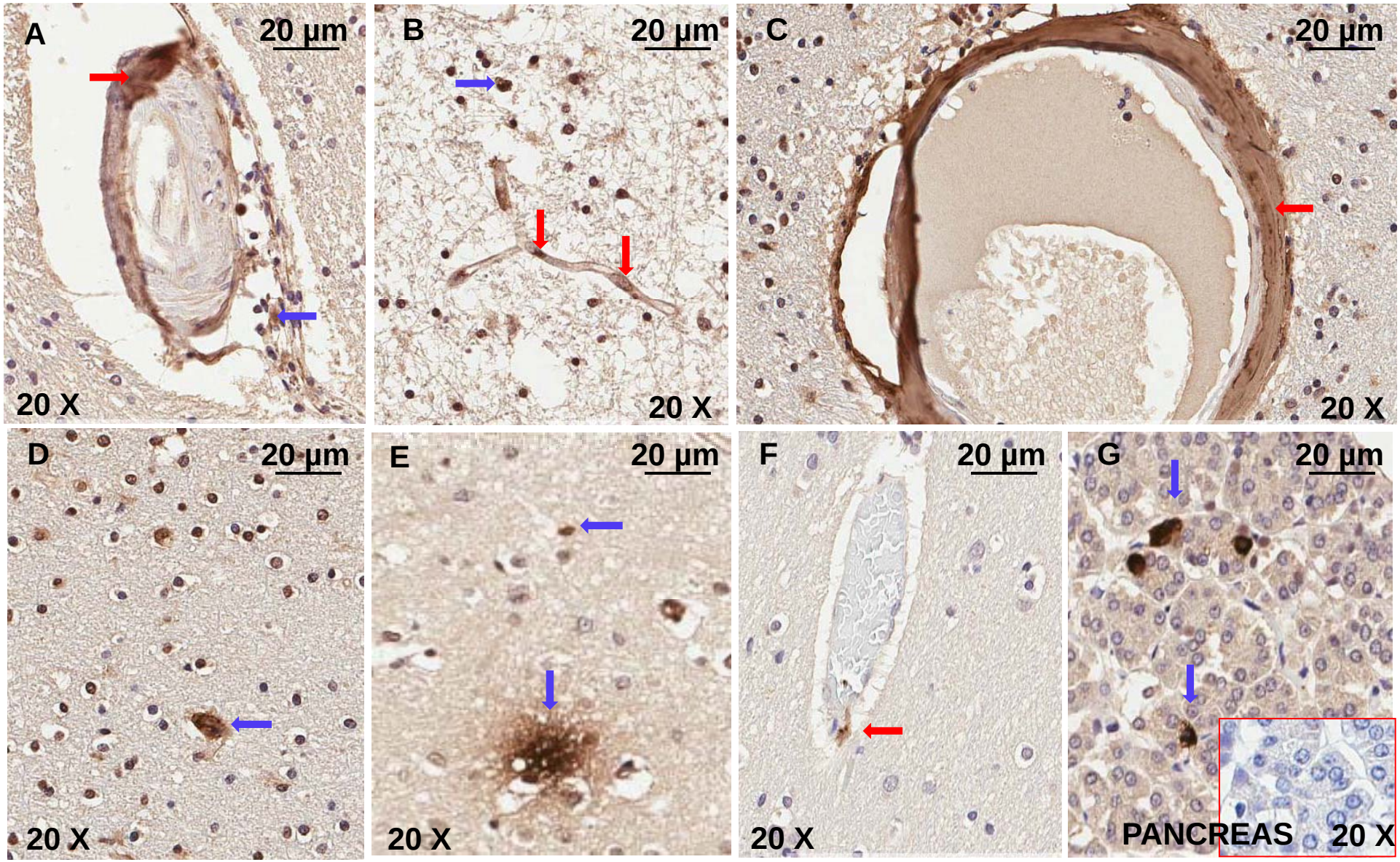
Type-2 Diabetes + CD and/or AD ← **Amylin Accumulation**

Late-onset AD ***no diabetes***

Age-matched, lean (?), *non-diabetics*, without AD

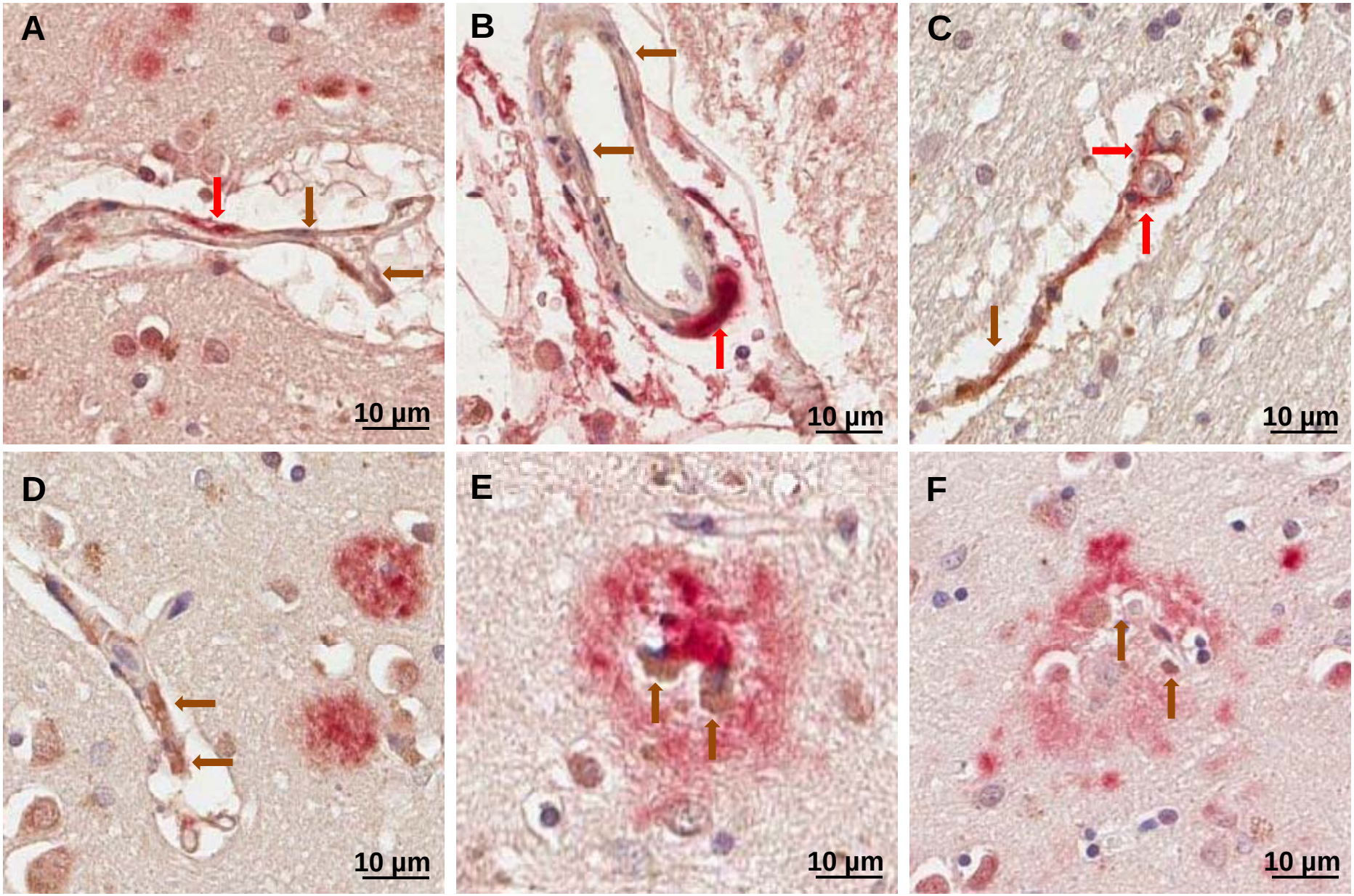
} **Amylin Accumulation ?**

Amylin Deposition in the Brain of Patients with Dementia



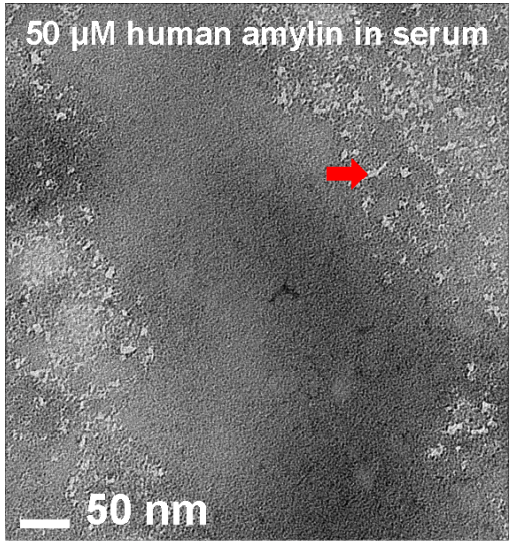
Amylin co-localizes with Aβ

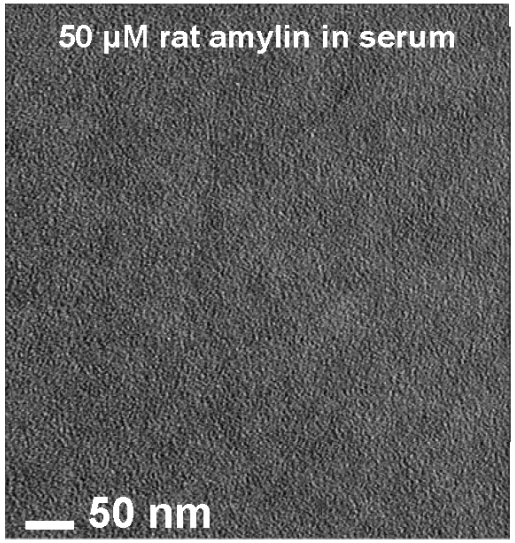
T2D-AD Group



40 X

Not All Amylin Species are Amyloidogenic !





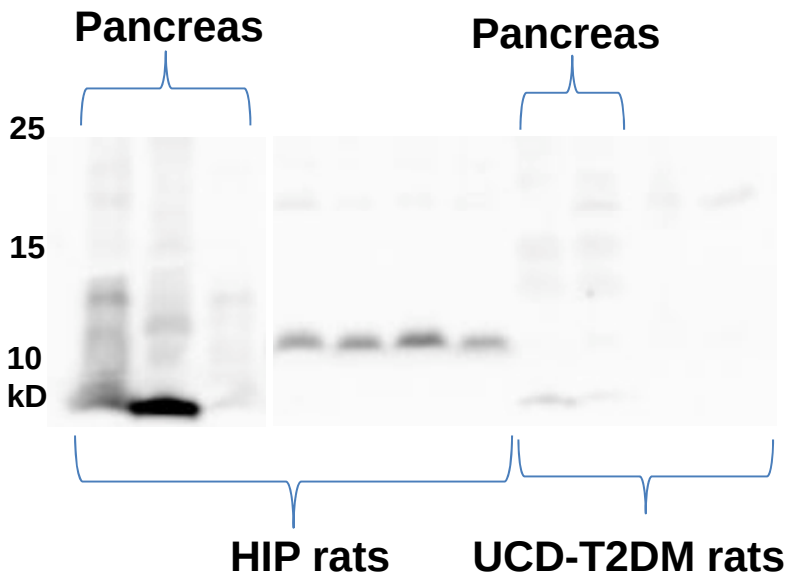
Human Amylin (amyloidogenic)

KCNTATCATQRLANFLVHSSNNFGAILSSTNVGSNTY

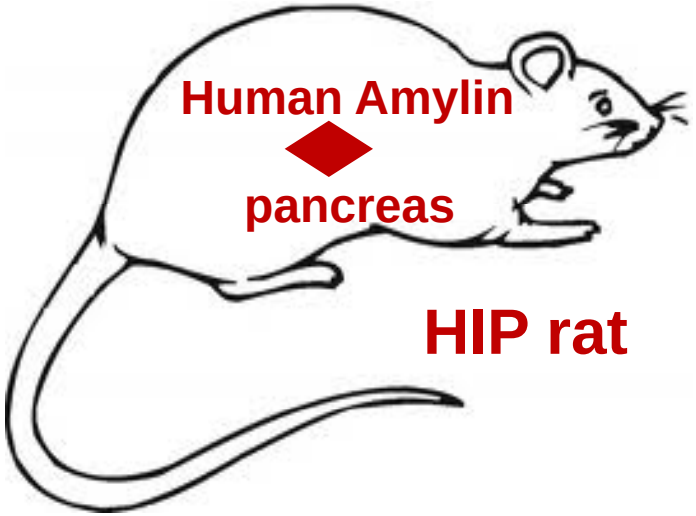
Rat Amylin (non-amyloidogenic)

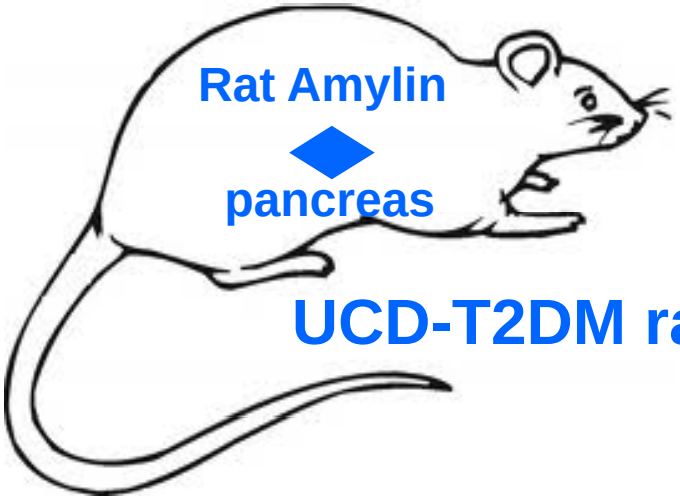
KCNTATCATQRLANFLVRSSNNLGPVLPPTNVGSNTY

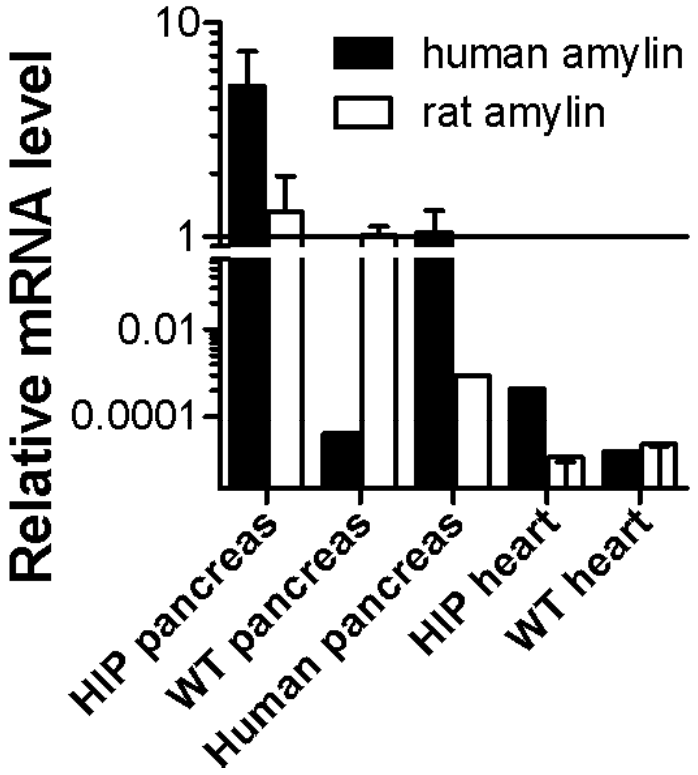
***Despa et al., Biol. Phys.* (2008)**

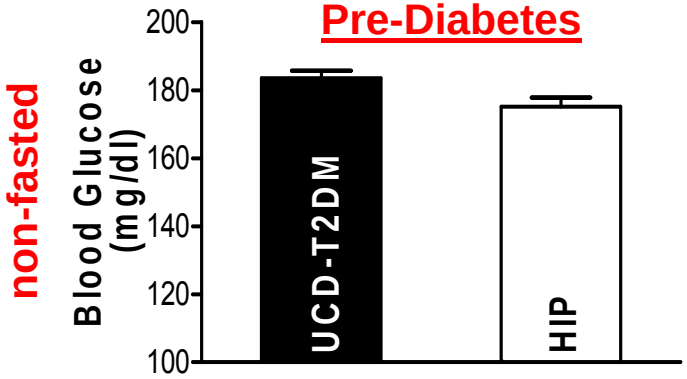


Animal Models

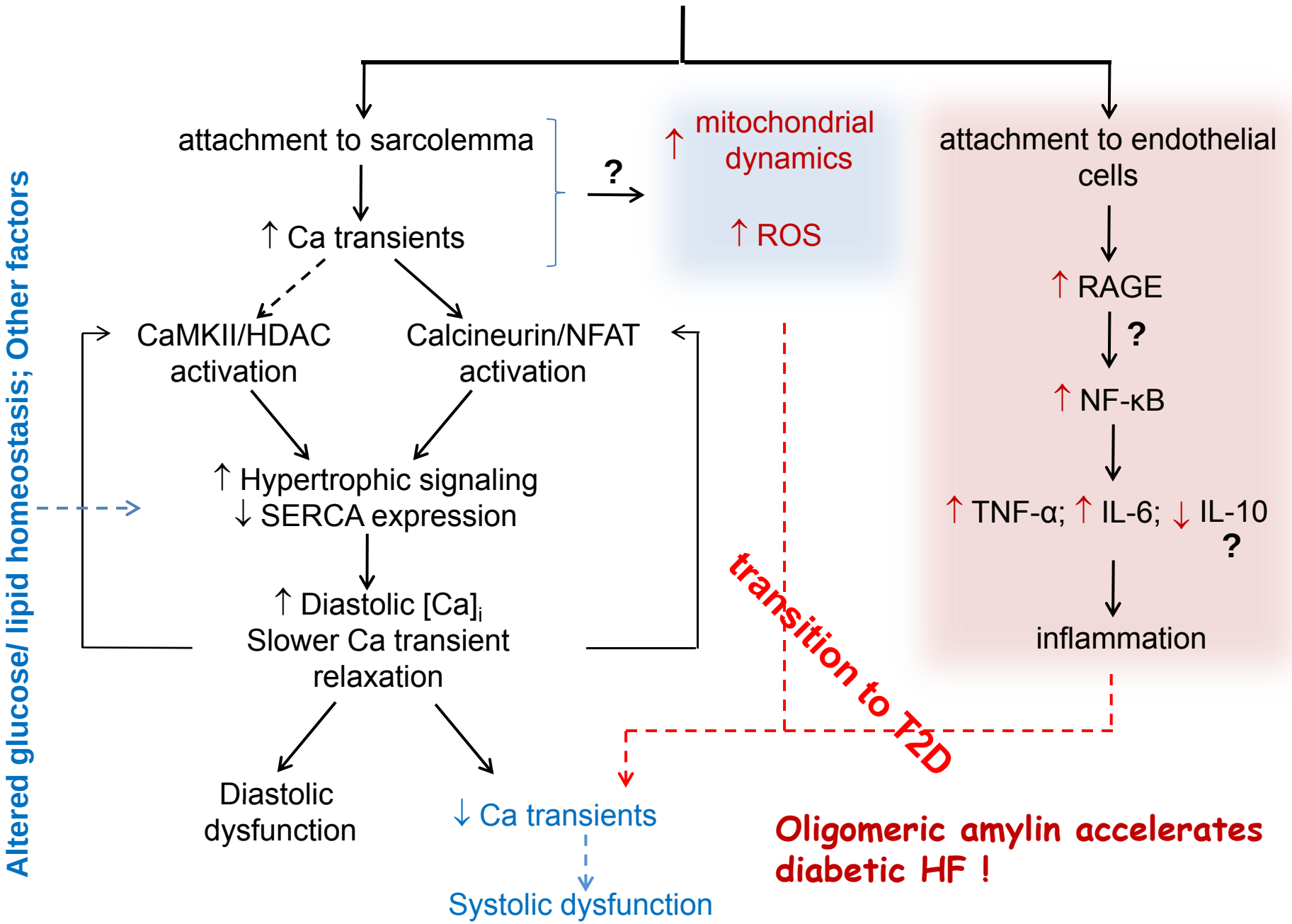




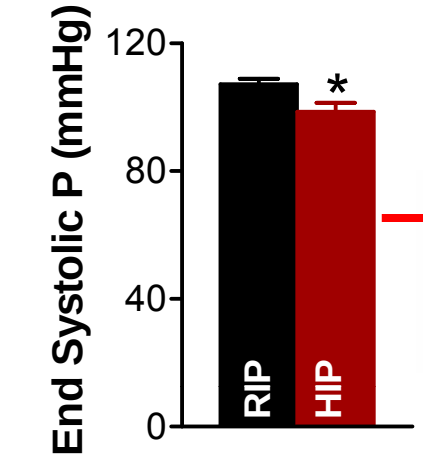




Summary (1)

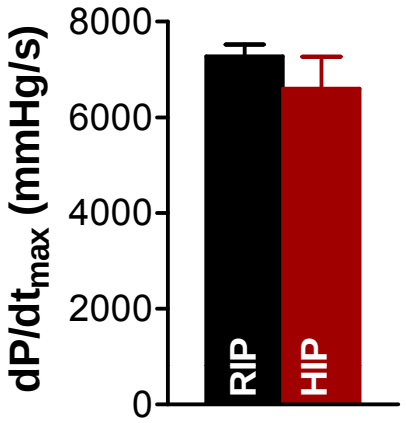

Circulating Amylin Oligomers
attachment to sarcolemma
↑ Ca transients
?
↑ mitochondrial dynamics
↑ ROS
attachment to endothelial cells
↑ RAGE
?
↑ NF-κB
↑ TNF-α; ↑ IL-6; ↓ IL-10
?
inflammation
CaMKII/HDAC activation
Calcineurin/NFAT activation
↑ Hypertrophic signaling
↓ SERCA expression
↑ Diastolic [Ca]i
Slower Ca transient relaxation
Diastolic dysfunction
↓ Ca transients
Systolic dysfunction
Altered glucose/ lipid homeostasis; Other factors
transition to T2D
Oligomeric amylin accelerates diabetic HF !

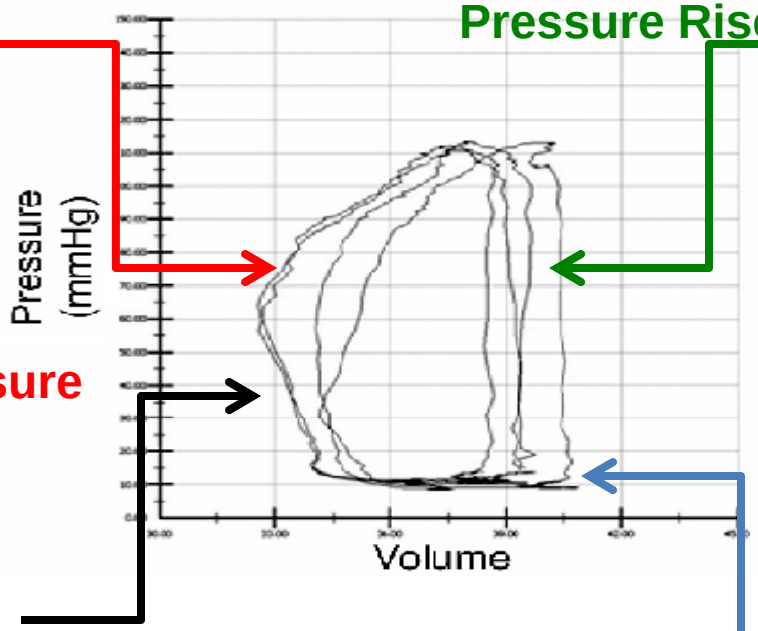
Cardiac Accumulation of Oligomeric Amylin Induces Contractile Dysfunction in Pre-diabetic HIP Rats



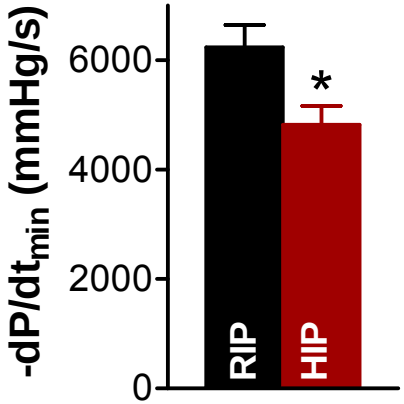
Left-Ventricular End Systolic Pressure

Maximum Rate of Pressure Rise

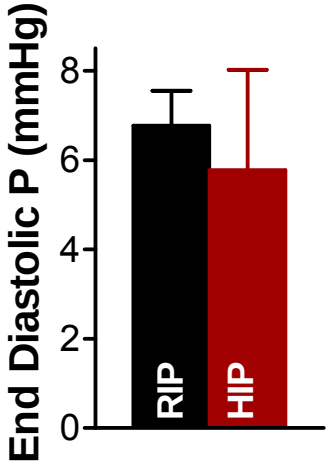




Left-Ventricular End Diastolic Pressure

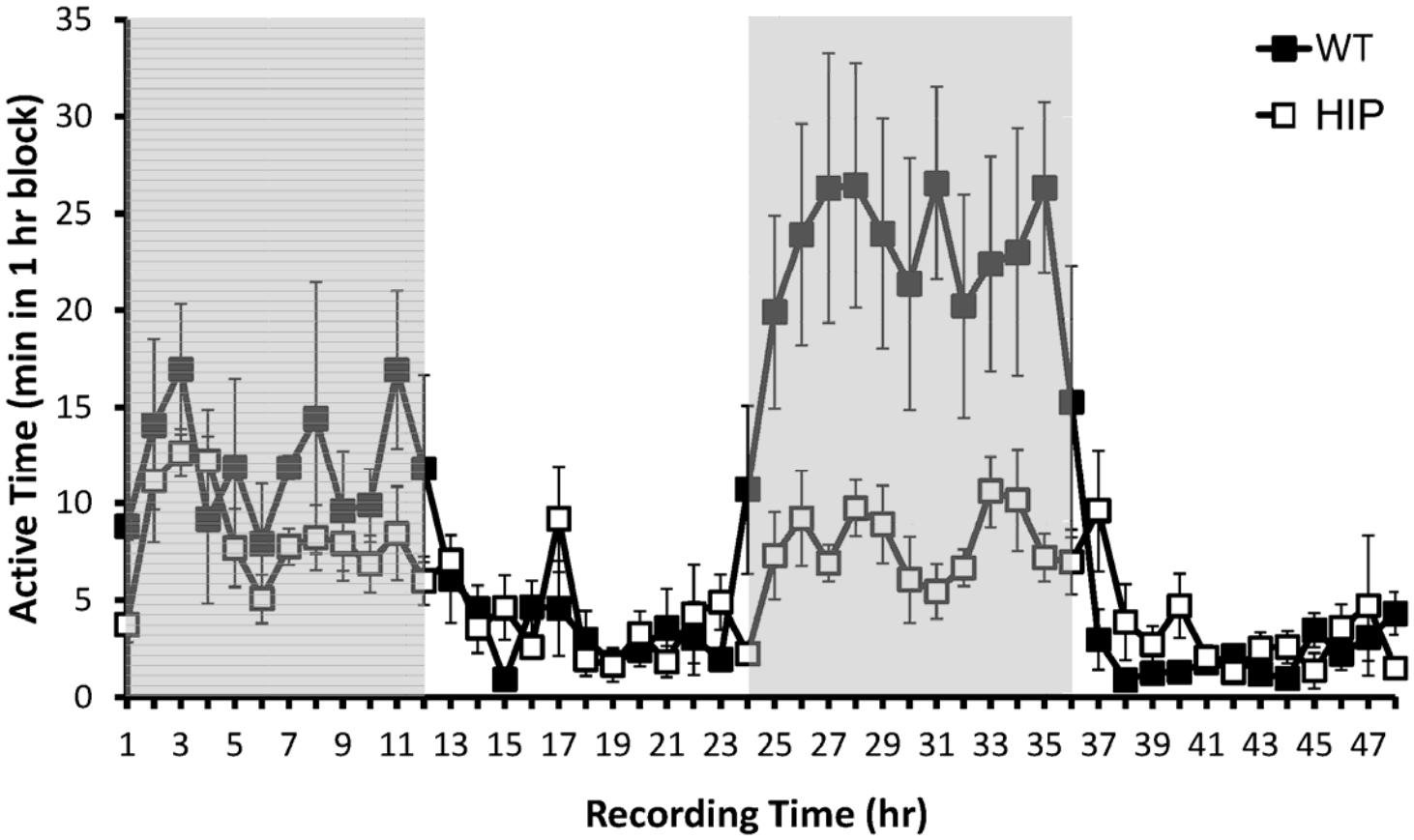


Maximum Rate of Pressure Fall



collab. with A. Knowlton (UC Davis)

Cerebral Accumulation of Oligomeric Amylin Induces Behavioral Changes in HIP Rats

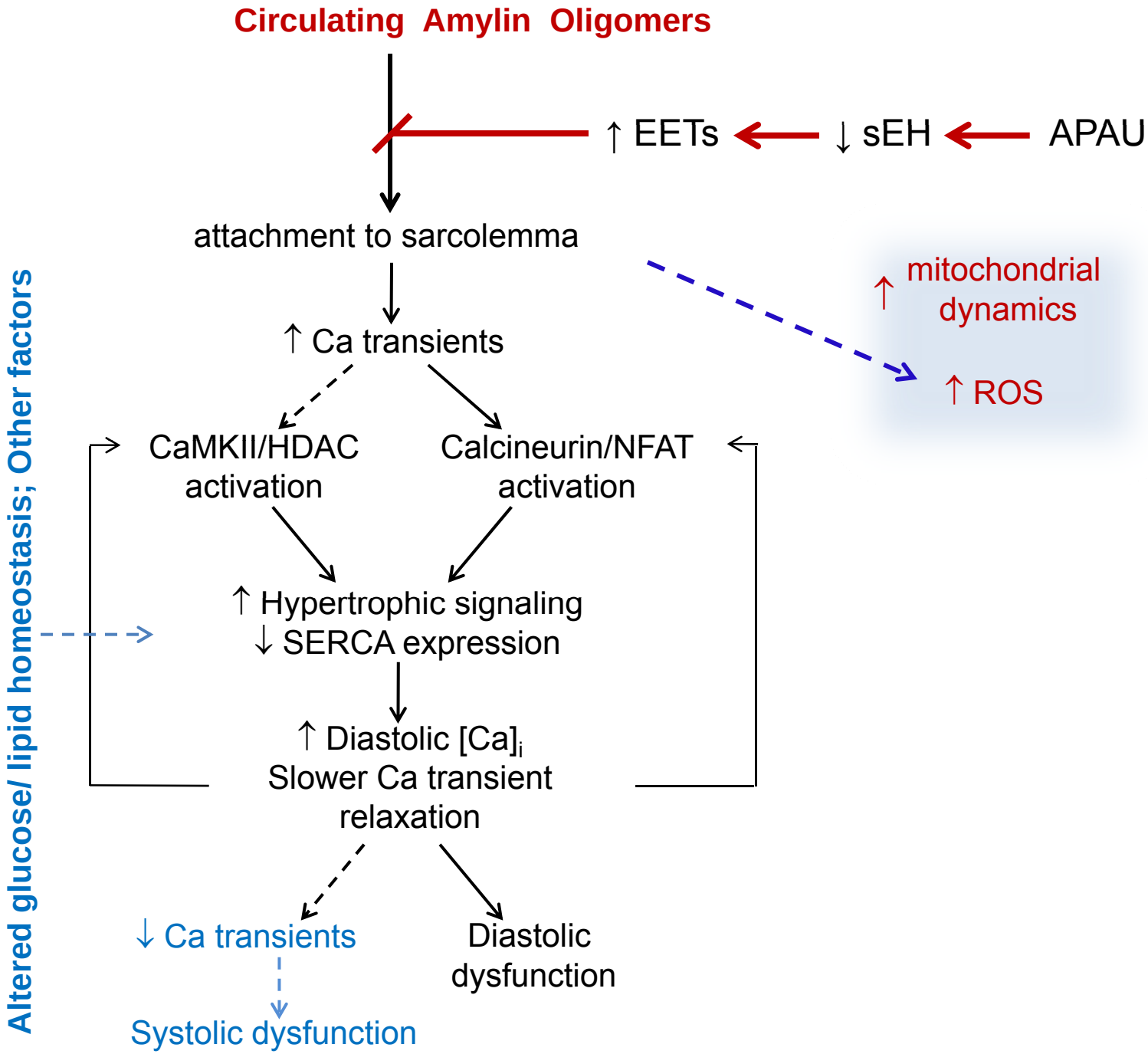


collab. with S. Xie (Stanford)

Therapeutics:

Reversing/Preventing Amylin Oligomer-Induced Injury

Patent US20070031955
"Compositions and Methods for Refolding of Denaturated Proteins"
(sold to Maroon Biotech).


Circulating Amylin Oligomers
↑ EETs
↓ sEH
APAU
attachment to sarcolemma
↑ Ca transients
↑ mitochondrial dynamics
↑ ROS
CaMKII/HDAC activation
Calcineurin/NFAT activation
↑ Hypertrophic signaling
↓ SERCA expression
↑ Diastolic [Ca]i
Slower Ca transient relaxation
↓ Ca transients
Diastolic dysfunction
Systolic dysfunction
Altered glucose/ lipid homeostasis; Other factors

Summary

Hyperamylinemia and consequent amylin oligomerization are an early pathogenic mechanism linking age-related metabolic disorders with diabetic brain injury, dementia, and CVD.

Hyperamylinemia is a feasible therapeutic target to reduce accumulation of proteinaceous debris in the CV and CN systems, and thus to limit/ delay diabetes complications.