Pancreatic \( \beta \)-Cell

- Nucleus Envelop
- Nucleol
- Chromatin
- Lysosome
- Mitochondria
- Glucose
- Glucokinase
- Glucose Transporter
- Glucokinase (sensor of glucose level)
- Nonmaturated Vesicles
- Maturated Vesicles
- Endoplasmic Reticulum
- Golgi Apparatus
- Exocytosis
- Opening the Ca\(^+\) Channel
- Closing the K\(^+\)\_ATP Channel
- Depolarization of the Membrane

**Secretory Vesicle**

- Normal: \(10^2 \sim\)
- ProInsulin \(\rightarrow\) Insulin < \(10^2\)
- ProAmylin \(\rightarrow\) Amylin

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


HUMAN PANCREAS

Prion | Aβ | Tau | α-synuclein | Amylin

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

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

β-Cell Dysfunction & Apoptosis

Pancreatic β-Cell

Hyperamylinemia

Hyperamylinemia

Hyperinsulinemia

Hyperglycemia (Insulinogenic Drugs)

Amylin Oligomerization

Blood

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

distinct amylin oligomer size distributions
Amylin Oligomers Accumulate in Heart

Failing vs. Non-failing

Anti-Amylin Antibody

Amylin Trimers

L-NF  OW/OB-HF

octamer
tetramer
trimer

Amylin Level (% Control)

L-NF  L-HF  OW/OB-NF  OW/OB-HF  DM-HF

Cardiac Amylin Deposition in Humans with Type-2 Diabetes

Selection of Human Brain Samples

Type-2 Diabetes + CD and/or AD

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
Not All Amylin Species are Amyloidogenic!

Human Amylin (amyloidogenic)

KCNTATCATQRLANFLVHSSNNFGAILSSTNVGSNTY

Rat Amylin (non-amyloidogenic)

KCNTATCATQRLANFLVRSSNNLGPVLPPTNVGSNTY

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

![Image of human amylin in serum](50 \mu M human amylin in serum)

50 nm

![Image of rat amylin in serum](50 \mu M rat amylin in serum)

50 nm

![Image of protein expression in HIP and UCD-T2DM rats](Pancreas)

HIP rats  UCD-T2DM rats

![Image of protein expression in HIP and UCD-T2DM rats](Pancreas)

25 kD  15 kD  10 kD
Animal Models

Human Amylin pancreas

HIP rat

Rat Amylin pancreas

UCD-T2DM rat

Relative mRNA level

- human amylin
- rat amylin

Pre-Diabetes

Blood Glucose (mg/dl)

UCD-T2DM

HIP
**Summary (1)**

Circulating Amylin Oligomers

- Attachment to sarcolemma
  - Ca transients
  - CaMKII/HDAC activation
  - Calcineurin/NFAT activation
  - Hypertrophic signaling
  - SERCA expression
  - Diastolic [Ca]$_i$ increase
  - Slower Ca transient relaxation
  - Diastolic dysfunction
  - Ca transients decrease
  - Systolic dysfunction

- Attachment to endothelial cells
  - ROS increase
  - RAGE increase
  - NF-κB increase
  - TNF-α, IL-6, IL-10 increase
  - Inflammation increase
  - Transition to T2D

**Oligomeric amylin accelerates diabetic HF!**
Cardiac Accumulation of Oligomeric Amylin Induces Contractile Dysfunction in Pre-diabetic HIP Rats

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

attachment to sarcolemma

\( \uparrow \) Ca transients

CaMKII/HDAC activation

Calcineurin/NFAT activation

\( \uparrow \) Hypertrophic signaling

\( \downarrow \) SERCA expression

\( \uparrow \) Diastolic [Ca]\(_i\)

Slower Ca transient relaxation

\( \downarrow \) Ca transients

Diastolic dysfunction

Systolic dysfunction

\( \uparrow \) hypertrophic signaling

Altered glucose/lipid homeostasis; Other factors

mitochondrial dynamics

\( \uparrow \) ROS

\( \uparrow \) EETs

\( \downarrow \) sEH

APAU

Diastolic dysfunction

Systolic dysfunction
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.