Pancreatic β-Cell

- Nucleus Envelope
- Nucleol
- Chromatin
- Lysosome
- Mitochondria
- Glucose
- Glucokinase
- Glucose transporter
- Glucokinase (sensor of glucose level)
- Closing the K⁺ ATP Channel
- Depolarization of the Membrane
- Opening the Ca²⁺ Channel
- Maturated Vesicles
- Nonmaturated Vesicles
- Endoplasmic Reticulum
- Golgi Apparatus
- Exocytosis
- Insulin
- ProInsulin
- ProAmylin
- Amylin

Normal Pro-diabetes

10² ~ ProInsulin → Insulin < 10²

ProAmylin → Amylin

Normal Pro-diabetes

secretory vesicle

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

HUMAN PANCREAS

20 µm

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

BLOOD

AMYLIN OLGOMERIZATION

β-Cell Dysfunction & Apoptosis

Pancreatic β-Cell

HYPERGLYCEMIA (INSULINOGENIC DRUGS)

HYPERAMYLINEMIA

HYPERINSULINEMIA

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 Hyperamylininemia
(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**

- L-NF
- OW/OB-HF

 octamer
tetramer
trimer

**Amylin Trimers**

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

**Larger Amylin Oligomers**

- **L-NF**
- **L-HF**
- **OW/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 Accumulation

?
Amylin Deposition in the Brain of Patients with Dementia
Amylin co-localizes with Aβ

BAC

Amylin co-localizes with Aβ

T2D-AD Group
Not All Amylin Species are Amyloidogenic!

Human Amylin (amyloidogenic)

KCNTATCATQRLANFLVHSSNNFGAILSSTNVGSNTY

Rat Amylin (non-amyloidogenic)

KCNTATCATQRLANFLVRSSNNLGPVLPPTNVGSNTY

Animal Models

- Human Amylin pancreas
  - HIP rat
- Rat Amylin pancreas
  - UCD-T2DM rat

Blood Glucose (mg/dl)
- Pre-Diabetes:
  - UCD-T2DM
  - HIP

Relative mRNA level
- HIP pancreas
- WT pancreas
- Human pancreas
- HIP heart
- WT heart

Comparison of human and rat amylin expression levels in different tissues.
Circulating Amylin Oligomers

attachment to sarcolemma

↑ Ca transients

CaMKII/HDAC activation
Calcineurin/NFAT activation

↑ Hypertrophic signaling
↓ SERCA expression

↑ Diastolic \([Ca]_i\)
Slower Ca transient relaxation

Altered glucose/lipid homeostasis; Other factors

attachment to endothelial cells

↑ ROS

↑ RAGE

↑ NF-κB

↑ TNF-α; ↑ IL-6; ↓ IL-10

inflammation

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

attachment to sarcolemma

↑ Ca transients

CaMKII/HDAC activation

Calcineurin/NFAT activation

↑ Hypertrophic signaling

↓ SERCA expression

↑ Diastolic $[\text{Ca}_{\text{i}}]$ 
Slower Ca transient relaxation

↓ Ca transients

Diastolic dysfunction

↓ Systolic dysfunction

↑ EETs

↓ sEH

APAU

mitochondrial dynamics

↑ ROS

Altered glucose/lipid homeostasis; Other factors
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.