

#### Diva D. De León-Crutchlow, MD, MSCE



**Exendin**-(9-39)

- Derived from exendin-4 Exenatide (Byetta®) approved for type 2DM
- Blocks the effects of the incretin hormone Glucagon-like peptide-1 (GLP-1)
- GLP-1 is secreted in response to ingested nutrients and is a potent stimulator of insulin secretion



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# Role of GLP-1 in the pathophysiology of hyperinsulinism

- Need for exogenous glucose to maintain euglycemia decreases when babies with hyperinsulinism are kept without food for a few hours
  - Suggest an enhanced "incretin" effect in hyperinsulinism



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### **The Incretin Effect**

In - cre - tin Intestine Se<u>cret</u>ion Insulin



N. McIntyre et al. Lancet 2:20-21, 1964

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# **Incretin Hormones**

- Gut-derived peptides that increase glucosestimulated insulin secretion
- Glucose-dependent insulinotropic polypeptide (GIP) first incretin isolated (1970)
- Glucagon-like peptide-1 (GLP-1) more potent and physiologically important incretin
- GIP and GLP-1 account for 90% of incretin response

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### **Glucose lowering effects of GLP-1**

- GLP-1 is secreted in response to ingested nutrients and is a potent stimulator of insulin secretion
- GLP-1 has other glucose lowering effect including: inhibition of glucagon, gastric emptying and appetite
- GLP-1 acts through a receptor in the pancreatic beta cells to stimulate insulin secretion
- Therapies targeting the GLP-1 receptor are now approved for the treatment of type 2 diabetes

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### Exendin-(9-39) *inhibits* amino acidstimulated insulin secretion in HI islets



Calabria, Li, Gallagher, Stanley, De León. Diabetes, 2012

#### **Preclinical proof-of-concept studies with Exendin-(9-39)**



De León, et al. J Biol Chem, 2008

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### **Pilot Clinical Proof-of-Concept Study**

- Pilot study to examine the effect of exendin-(9-39) on fasting blood glucose of subjects with K<sub>ATP</sub> Hyperinsulinism
- > Methods:
  - 9 subjects
  - Randomized, open-label, two-period complete crossover
  - Fasted subjects received an intravenous infusion of exendin-(9-39) (100, 300 and 500 pmol/kg/min) or vehicle for 6 hours in 2 consecutive days (in random order)
  - Primary outcome: Blood glucose levels

www.Clinicaltrials.gov: NCT00571324

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### **Subject Characteristics**

| Subject | Age | Gender | Mutation<br>( <i>ABCC8</i> ) | Pancreatectomy |
|---------|-----|--------|------------------------------|----------------|
| 1       | 29  | F      | delF1388 + 3992-9 G>A        | 85%            |
| 2       | 44  | Μ      | delS1387*                    | None           |
| 3       | 35  | Μ      | S408P*                       | None           |
| 4       | 17  | F      | 3992-9 G>A                   | 95 %           |
| 5       | 15  | F      | 3992-9 G>A                   | 95%            |
| 6       | 18  | Μ      | delS1387*                    | None           |
| 7       | 16  | F      | delS1387*                    | None           |
| 8       | 47  | F      | R1353H*                      | None           |
| 9       | 37  | F      | R521Q*                       | None           |

\*Dominant

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### Exendin-(9-39) increases fasting blood glucose



#### Exendin-(9-39) suppresses plasma insulin



# Exendin-(9-39) *prevents* protein-induced hypoglycemia in K<sub>ATP</sub>HI

|                                | Vehicle (n=8) | Exendin-(9-39) (n=8) | p-value |
|--------------------------------|---------------|----------------------|---------|
| Glucose nadir (mean, SD) mg/dL | 55.1 (2.9)    | 70.4 (5.7)           | 0.02    |
| AUC (mean, SD) mg/dL*min       | 12559 (2097)  | 18675 (4230)         | 0.008   |
| % Subjects < 60 mg/dL (n=8)    | 87.5%         | 37.5%                | 0.046   |
| % Subjects < 50 mg/dL (n=8)    | 37.5%         | 0%                   | 0.083   |

## Safety Profile





- Excellent safety profile in preclinical studies
- Well tolerated
- No significant adverse events in participating children



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### Summary:

- GLP-1 and its receptor may play a role in the pathophysiology of K<sub>ATP</sub>HI
- In mouse and human K<sub>ATP</sub>HI pancreatic islets exendin-(9-39) inhibits insulin secretion
- In adolescents and adults with K<sub>ATP</sub>HI exendin-(9-39) increases fasting plasma glucose
- Exendin-(9-39) prevents protein-induced hypoglycemia in children with K<sub>ATP</sub>HI
- Proof-of-concept single dose escalation study in neonates ongoing

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#### Collaborators

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#### **HI Families**

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