Novel Incretin Therapies for the Treatment of T2DM

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Diabetes Coalition,
Palm Beach County Symposium
The Scripps Research Institute
Jupiter Florida
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Patricia McDonald PhD

Scripps Florida

Drug Discovery & Development

- ***Academic Departments***
  - Infectious Diseases
  - Molecular Medicine
  - Neuroscience
  - Chemistry
  - Structural Biology

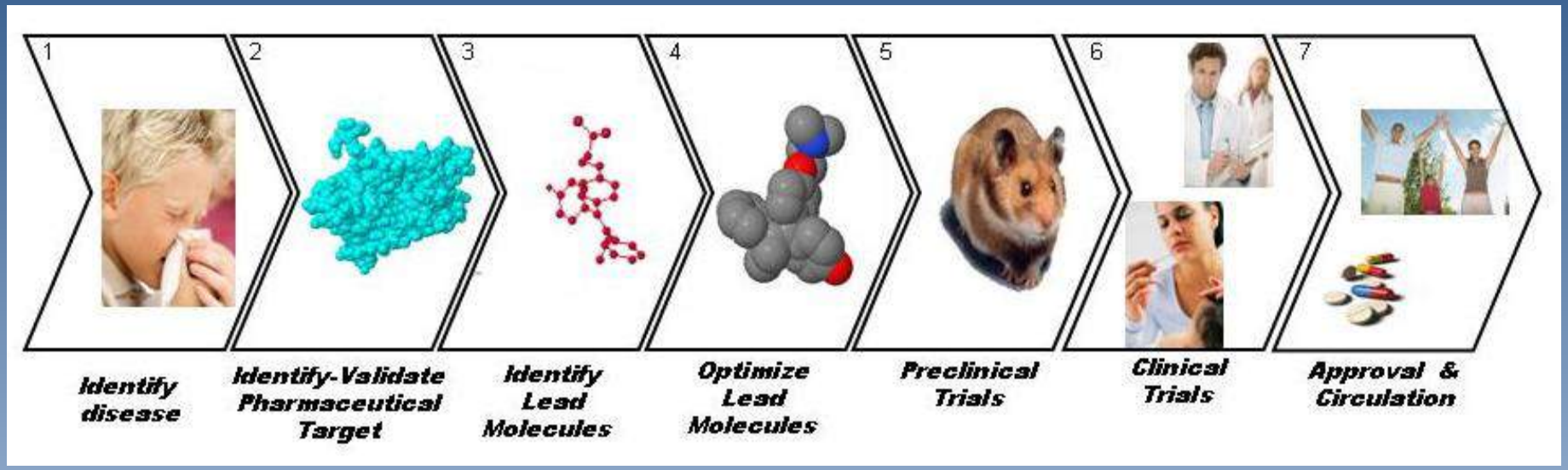
Technology Platforms

- Cell Based Screening
- RNA
- Genomics
- Proteomics
- Informatics

Drug Discovery

- Discovery Biology
- uHTS/Lead ID
- Medicinal Chemistry
- DMPK
- *In vivo* Pharmacology
- Metabolics

Drug Discovery & Development Process



Discovery

Development

3-5 Years

+7 Years

+1.5 Years

‘Bench to Bedside’

Basic Research Done at the Bench

Translational Research Bench -to- Bedside

Clinical Research Done in the Patient

“Don’t worry. All you need is a revolutionary miracle drug that will be the medical discovery of the century. I'll see what I can whip up.”

Natural Progression of T2DM

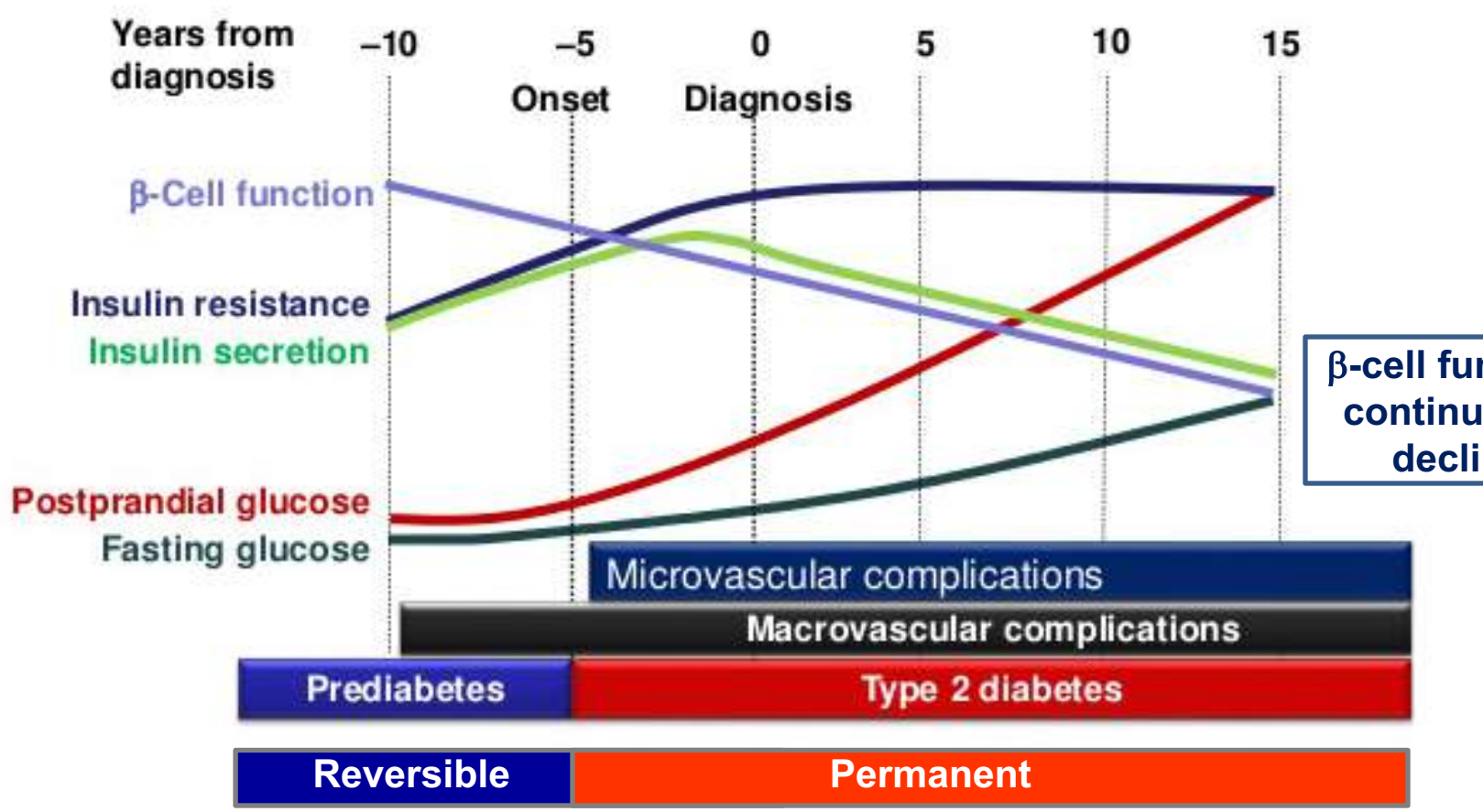
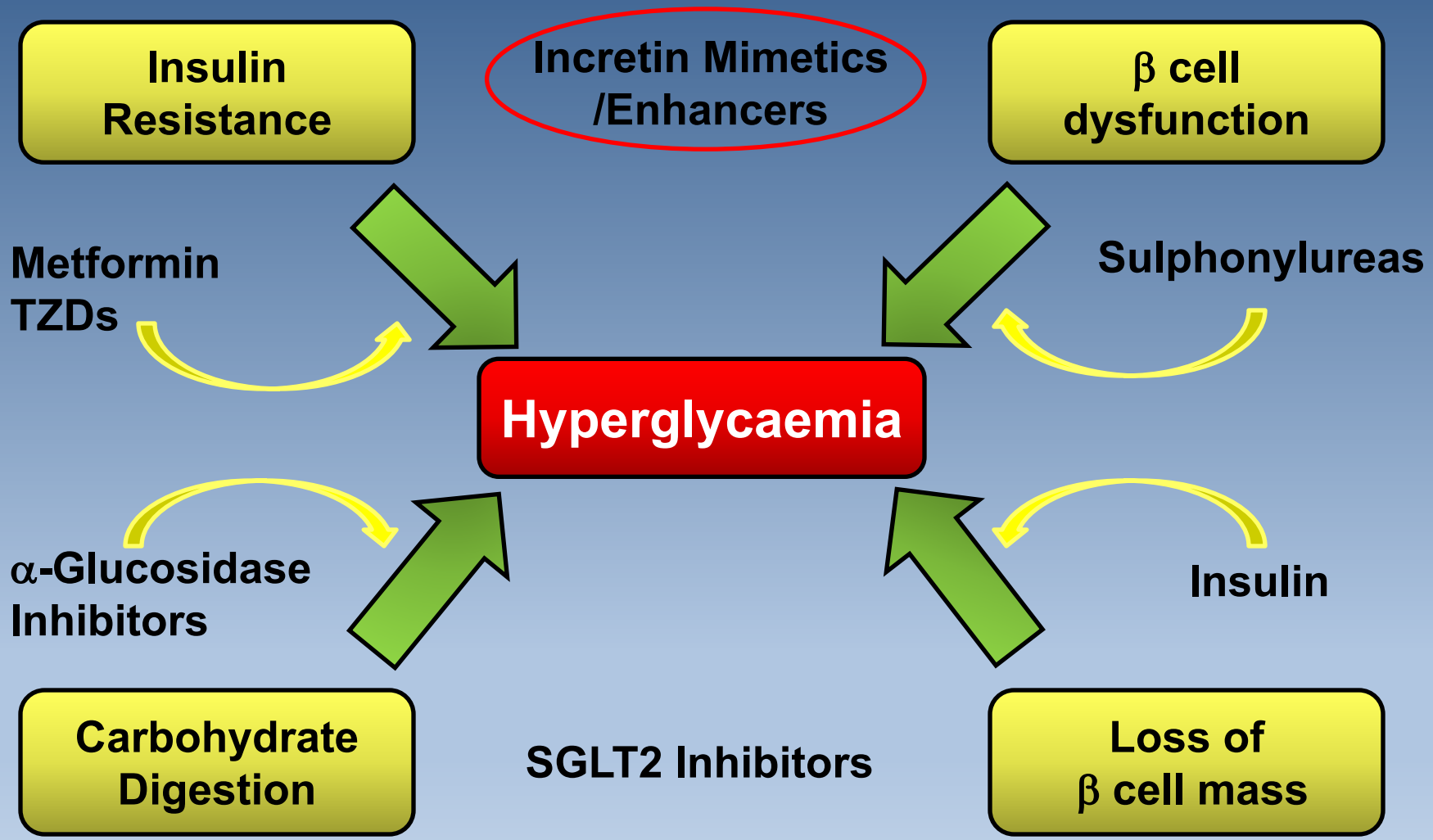


Figure courtesy of the AACE Diabetes Resource Center

β-cell function continues to decline

Need to intervene early with disease modifying therapies!

Type 2 Diabetes - Standard Therapies



*Standard treatment options are limited to treating symptoms and not underlying cause.

Novel Incretin Therapies for the Treatment of T2DM

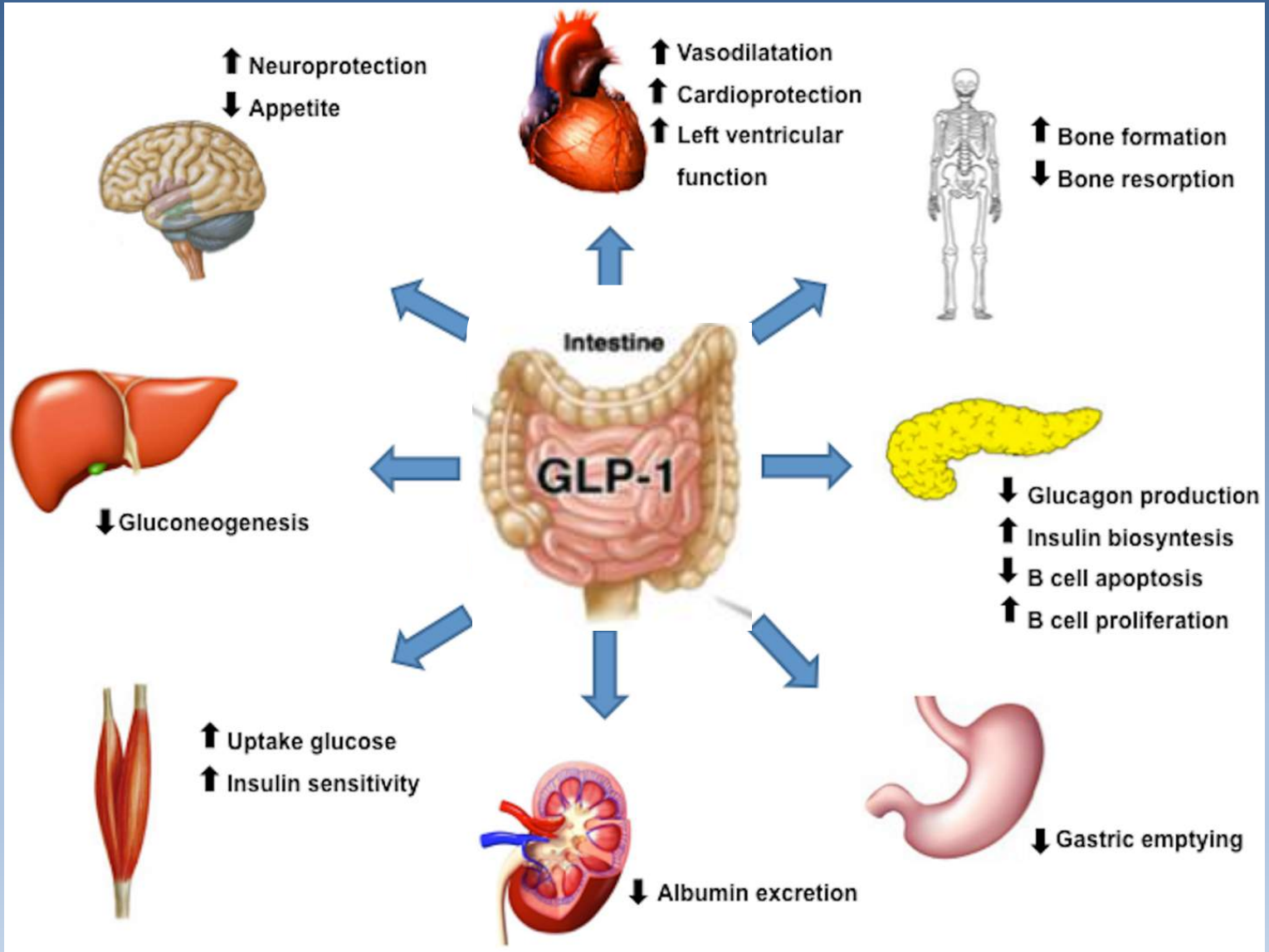
Incretins are a group of gastrointestinal hormones that cause an increase in the amount of insulin released from the beta cells of the islets of Langerhans after eating, even before blood glucose levels become elevated.

In · cret · in

Intestine Secretion Insulin

GLP-1: Glucagon Like Peptide -1

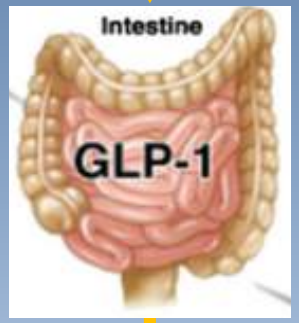
Peripheral and Central Actions of GLP-1



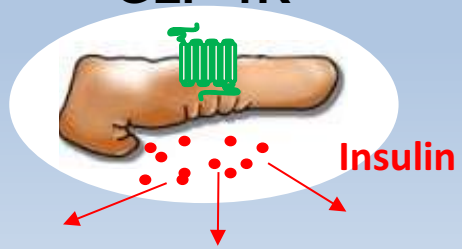
Action of GLP-1 and GLP-1R

GLP-1/GLP-1R Actions that combine to control glycemia

- Enhances glucose-induced insulin secretion
- Reduces circulating glucose levels
- Inhibits glucagon secretion and hepatic glucose production
- Slows gastric emptying
- Promotes satiety



GLP-1R



Additional Actions of GLP-1/GLP-1R (Observed in rodents)

- Restores β cell function
- Increases insulin biosynthesis
- Promotes β-cell mass, β-cell differentiation

Adapted from Deacon et al. *Diabetes*. 1995;44:1126.

Current GLP-1 Targeted Therapies

Short and Long Acting Injectables

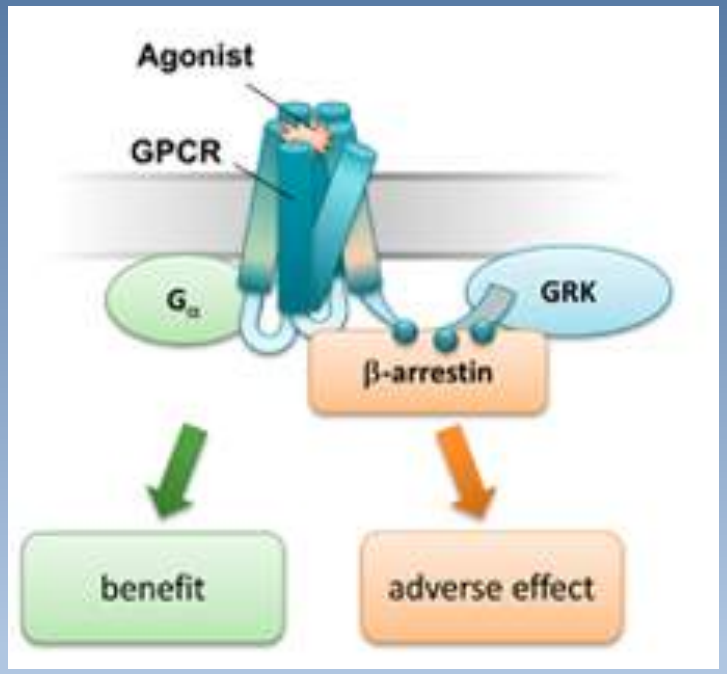
- Compromised β cell function
- Pancreatitis
- Pancreatic cancer
- Thyroid cancer

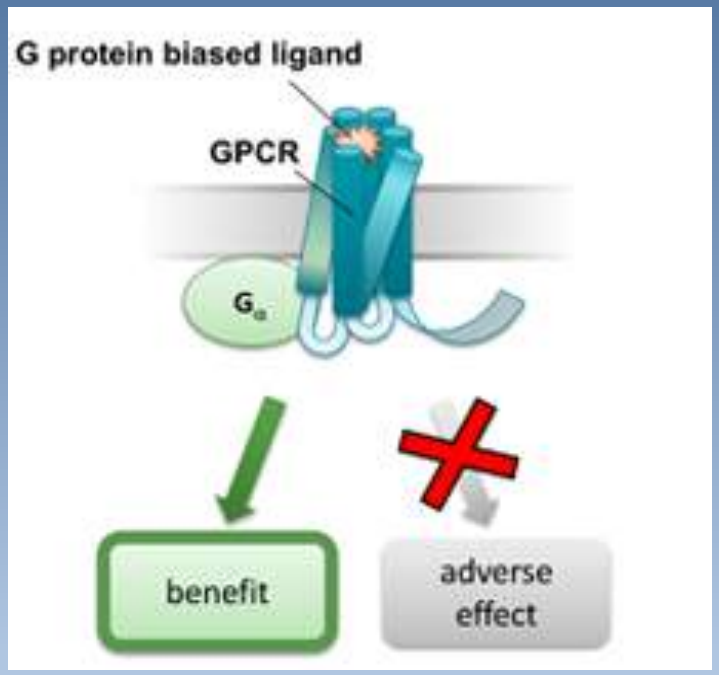
- Enhances glucose-dependent insulin secretion
- Reduces hepatic glucose output
- Regulates gastric emptying
- Promotes satiety
- Increase in β-cell mass?

- Nausea
- Vomiting
- Diarrhea/Constipation
- Abdominal Pain
- Patient Compliance

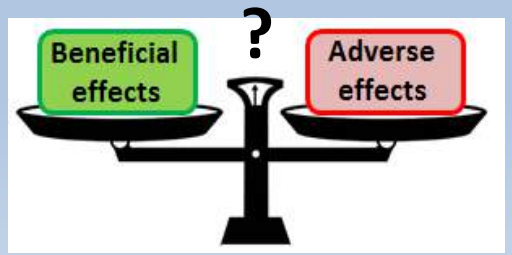
Current Approach: Target Specificity

Novel Approach: Signal Selectivity

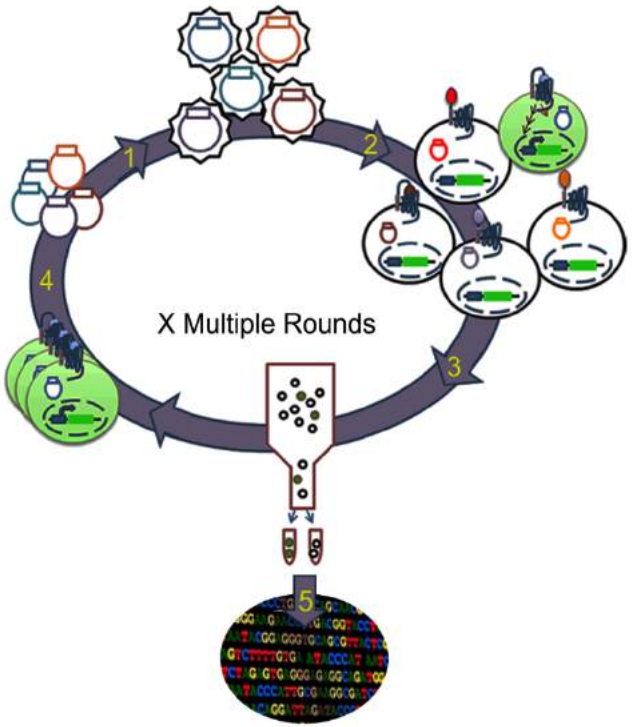


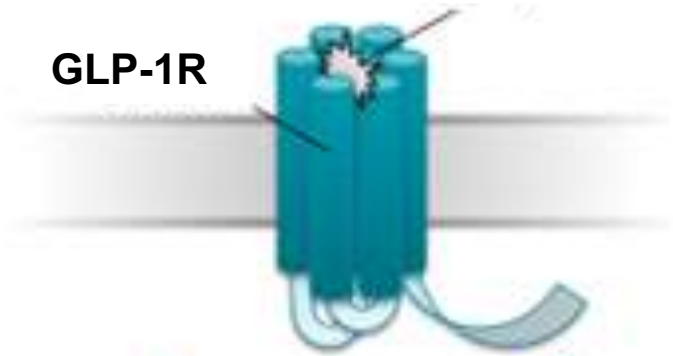


- Byetta (Exendin 4)
- Trulicity (Dulaglutide)
- Victoza (Liraglutide)

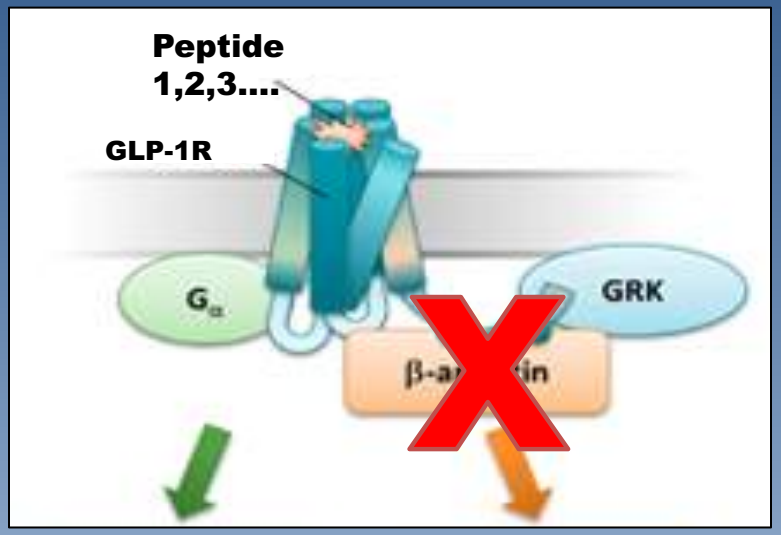


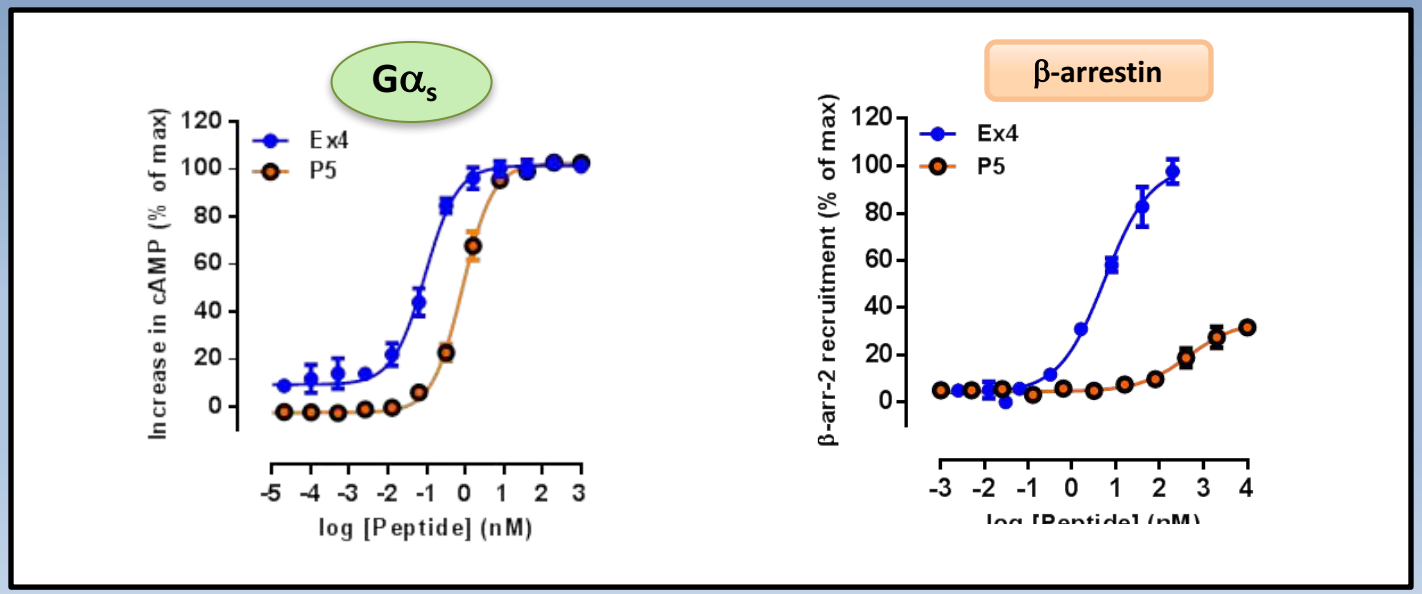
Development of an Autocrine-Based System for Screening Large Combinatorial Peptide Libraries





P5: The First Potent, Selective GLP-1R G-protein Biased Agonist

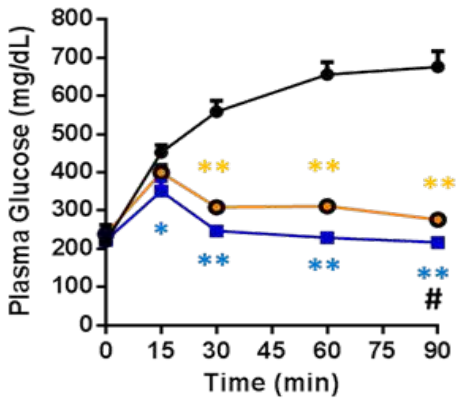


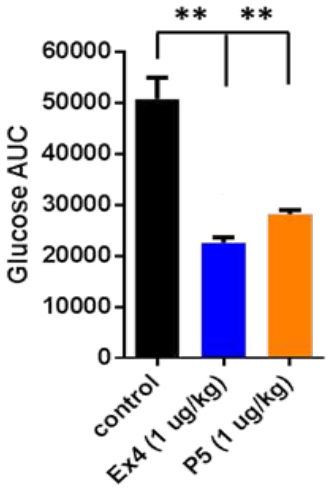


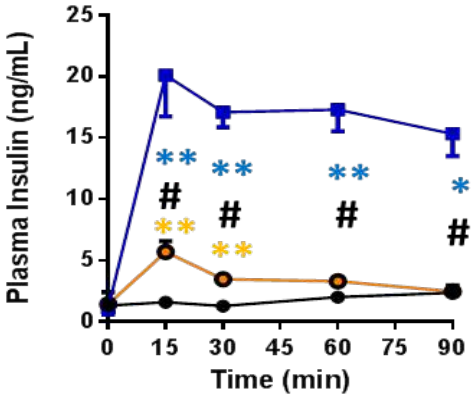
P5 Improves Glucose Tolerance and is Insulin Sparing

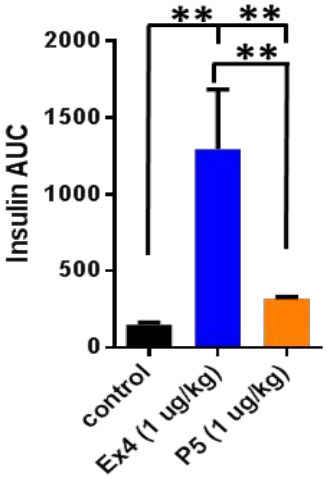
Acute GTT 8 hr Fasting

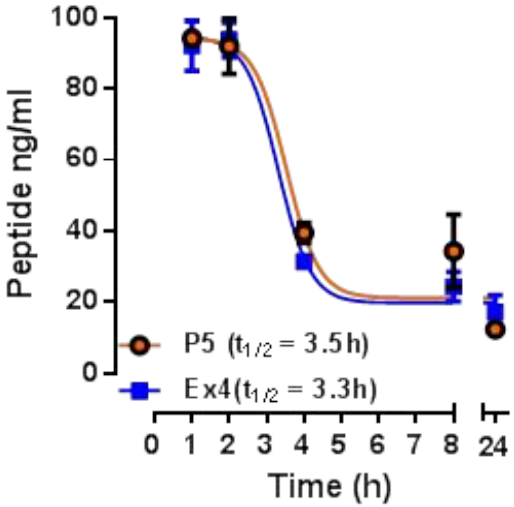
C57BL/6-DIO







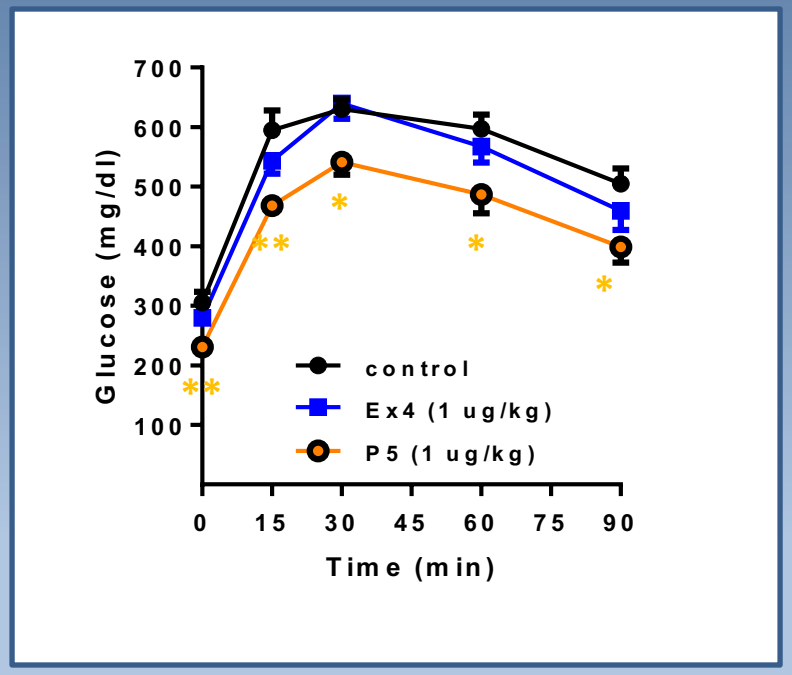




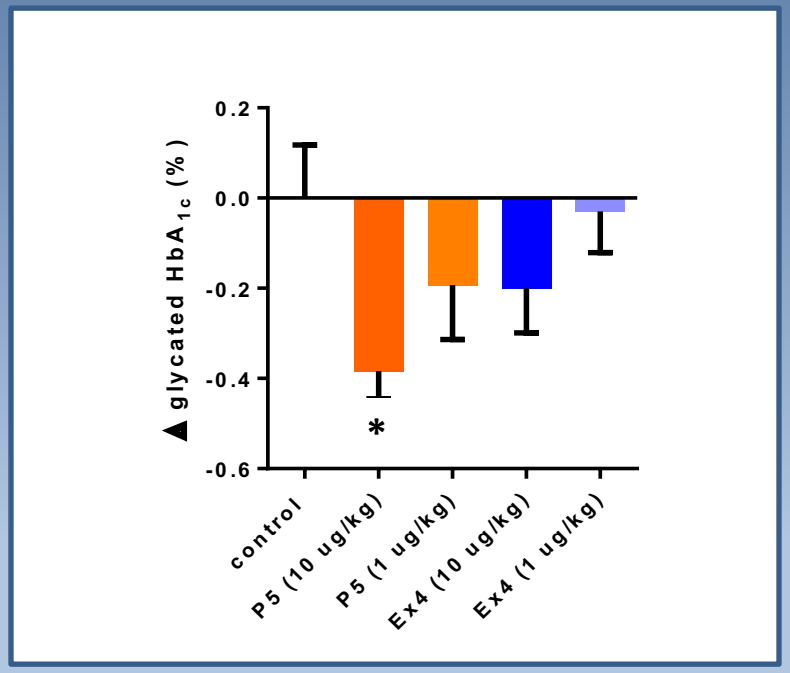
P5 has Superior Antihyperglycaemic Efficacy in DIO Mice

Chronic Study

GTT 8 hr Fasting in following 4wk treatment in DIO

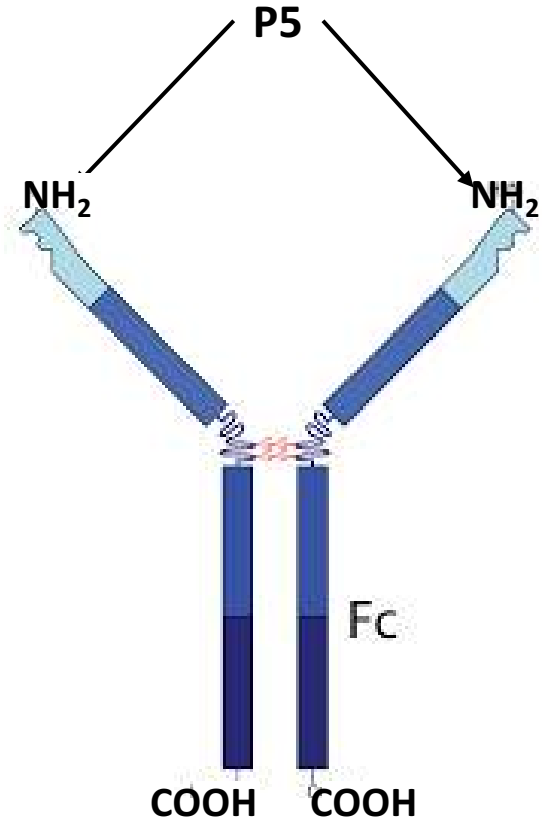


HbA1c



In Vitro Characterization of Long-acting G-protein Biased Agonist P5-Fc

a



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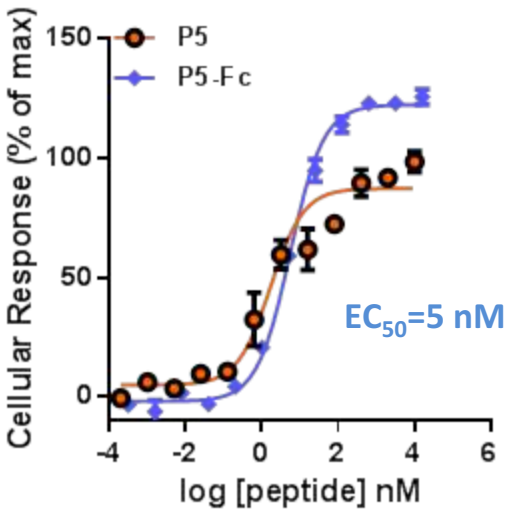
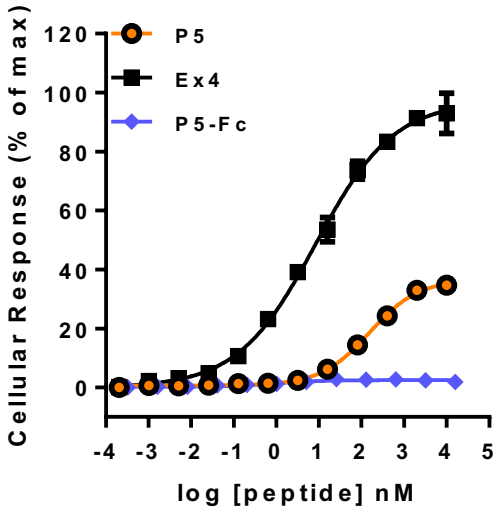
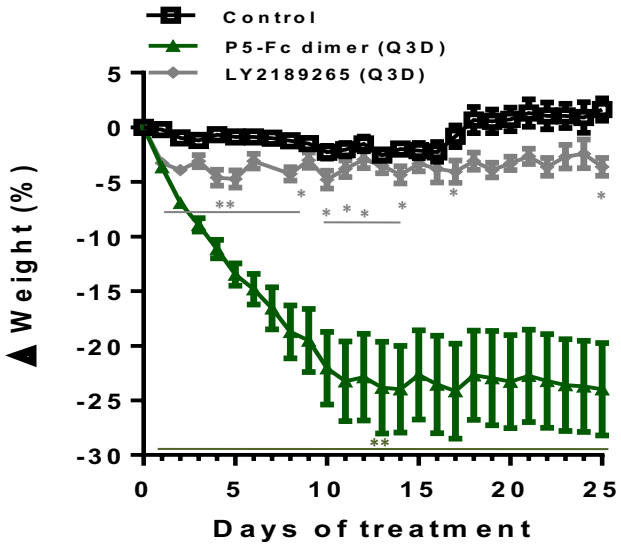
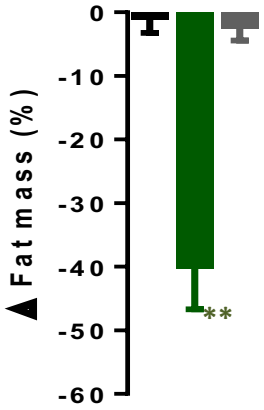


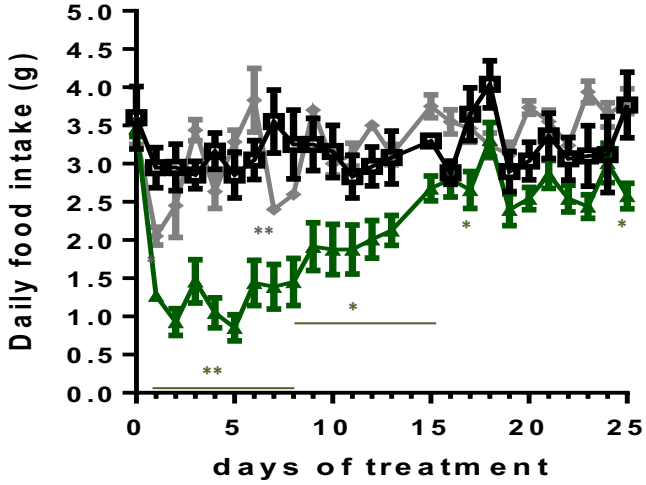
c

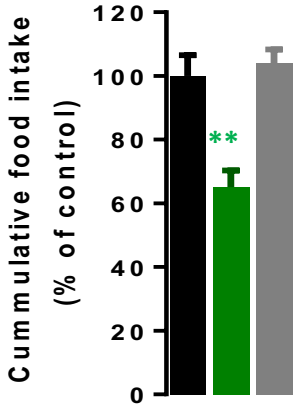


P5-Fc Promotes Weight Loss



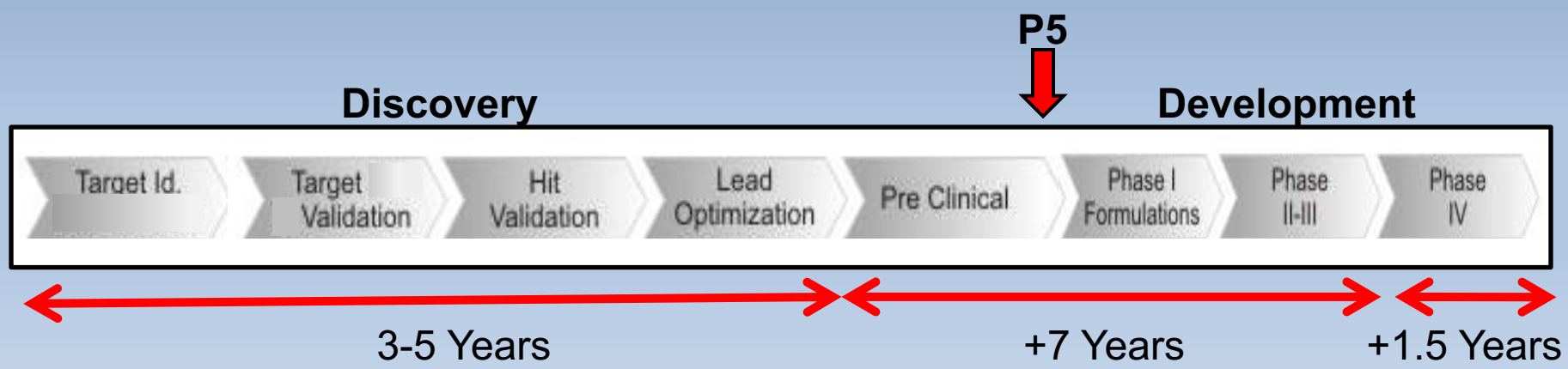






P5 and P5-Fc show Improved Outcomes

		Short acting (QD)		Long acting (QW)	
		P5	Ex4	P5-Fc	Dulaglutide
Efficacy	Secretagogue activity	√	√√√	√√√	nd
	Decrease gastic emptying	√	√	√	√
	Lower blood glucose level	√	√	√√√	√√√
	Decrease HbA1c	√	√	√√√	nd
	Decrease food intake	x	√	√√√	x
	Weight loss	x	√	√√√	x
	Decrease steatosis	√	√	√	nd
Safety	Malaise	x	√	x	nd



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