Mechanisms that Impact Cancer Risk with Use of Incretin Mimetics

(R01-Clinical Trial Optional; R21-Clinical Trial not Allowed)

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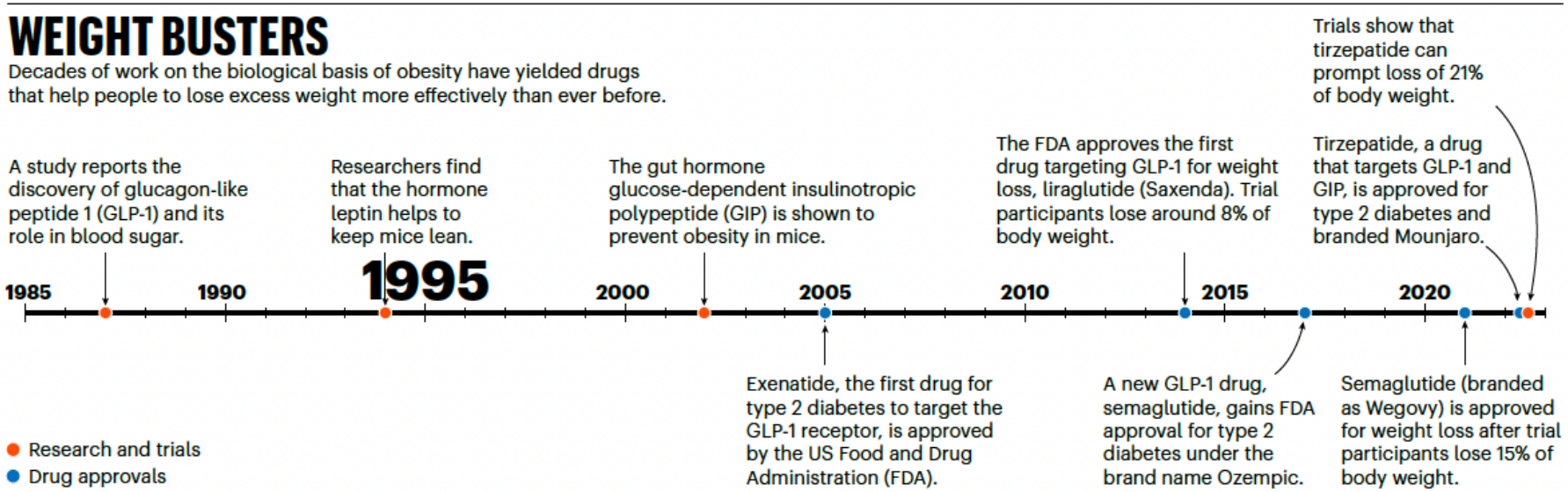
A Bit About Incretins

- Incretins are gut hormones which are secreted in response to a meal
- The two primary incretins are
  - Glucose-dependent insulinotropic polypepide (GIP)-1
  - Glucagon-like peptide (GLP)-1
- The three agent classes currently FDA approved to treat type 2 diabetes (T2DM) to regulate GLP-1 and/or GIP-1 and thereby glucose levels are
  - GLP-1 receptor agonists (RAs), 2 approved to treat obesity w/o T2DM
  - GIP-1 RAs
  - Dipeptidyl peptidase (DPP)-4 inhbitors (DPP-4 degrades GLP-1 and GIP-1)
- Clinical data thus far indicate that GLP-1 and GIP-1 RAs are more effective, with fewer side effects, than DPP-4 inhibitors. For this reason, we will focus on the former agents

GLP-1/GIP-1 Receptor Agonists are Better than Lifestyle Interventions in Obese Subjects

THE SHOWSTOPPER OBESITY DRUGS THAT HAVE STUNNED RESEARCHERS



- The U.S. GLP-1/GIP-1 Receptor Agonist market was valued at $11.3 billion in 2019 and is anticipated to grow annually by of 6.1% from 2023 to 2027.
- Compared to lifestyle interventions, these agonists provide:
  - More weight loss
  - Dramatic improvement in type 2 diabetes mellitus
  - Lower risk of heart disease, stroke and kidney disease
- **Impact on cancer risk is unclear**

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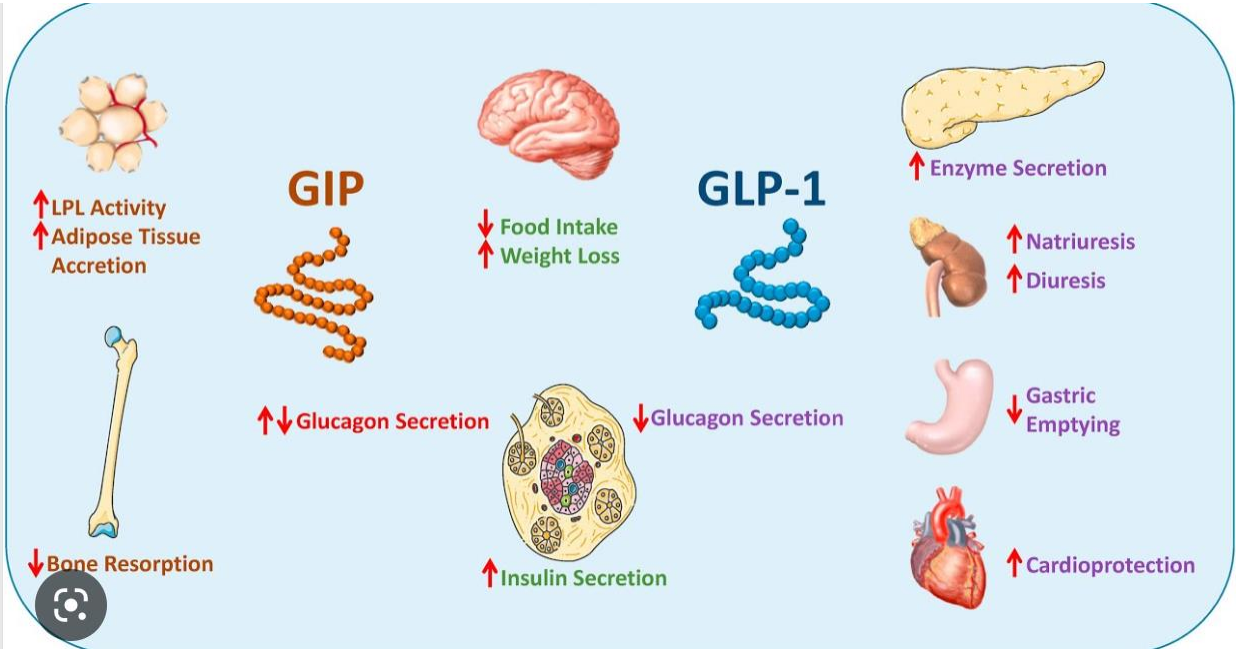
Mechanism of Action: GLP-1 and GIP-1 Receptor Agonist

- GIP-1 and GLP-1 stimulate insulin secretion from pancreatic β cells and decrease glucagon secretion from pancreatic α cells, thereby regulating glucose levels.
- The agents slow GI transit and act in the brain to control appetite.
- GLP-1/GIP-1 receptors are expressed throughout the body, suggesting that off target effects unrelated to hunger suppression are possible.
- While both GIP-1 and GLP-1 RAs stimulate insulin secretion, mice with dysfunctional GIP-1 receptors are resistant to obesity.



Agent approvals and impact on weight loss

Medication	Mechanism	Administration	FDA Approved (Y/N)		Population	Mean weight loss		
			For T2DM	For Obesity		Time on study	1 year	Study end
Exenatide	GLP-1 RA	sq twice daily	Y	N	Obese, no DM	16 wks	na	2.70%
Exenatide ER	GLP-1 RA	sq weekly		N	T2DM	104 wks	4.10%	2.40%
Lixisenatide	GLP-1 RA	sq daily	Y	N	T2DM	76 wks	4.50%	6.30%
Dulaglutide	GLP-1 RA	sq weekly	Y	N	T2DM	40 wks	na	3 kg
Liraglutide	GLP-1 RA	sq daily	Y	Y	Obese, no DM	68 wks	7%	6.40%
Semaglutide	GLP-1 RA	sq weekly	Y	Y	Obese, no DM	68 wks	15.80%	15.80%
Semaglutide	GLP-1 RA	oral daily	Y	N	T2DM	69 wks	3.30%	4.60%
Tirzepatide	GLP-1/GIP-1 dual RA	sq weekly	Y	N	Obese, no DM	72 wks	19.90%	20.90%

Preclinical Effects of GLP-1/GIP-1 RAs

- RAs downregulate inflammation in adipose tissue (decrease TNFa, IL-1, IL-6 and MCP1)
- Activate macrophages toward a proliferative (M2) phenotype
- Antiproliferative effects (reduced ERK-MAPK signaling and growth in LNCap cells and xenografts)
- Improved lipid metabolism (lowers cholesterol, enhances cholesterol efflux via ABCA1 and ERK1/2 pathways, improves LDL/HDL ratios
- Alters GI microbiome composition (promotes growth of lipid metabolizing microbes (Akkermansia, Lactobacillus, Parabacteroides), lowers the abundance of microbes associated with CRC

Preliminary Clinical Findings

- May increase the overall risk of thyroid cancer. Agents are contraindicated in patients with medullary carcinoma of the thyroid
  - Findings from the FDA Adverse Event Reporting System (FAERS) database: 65% increase in overall thyroid cancer risk
  - French national health insurance database: patients treated vs. not with GLP-1RA for 1-3 years: l thyroid cancer of 58% increase in overall thyroid cancer, 78% increase in medullary thyroid cancer
  - There is a black box warning prohibiting their GLP/GIP-1 RAs use in patients with medullary thyroid cancer
- The agents may reduce the risk of prostate cancer and other obesity associated cancers
  - 4 randomized controlled trials demonstrated a 47% reduction in PCa risk with agent use.
  - UK Clinical Practice Research Datalink cohort study: lower risk of PCa with agent use
  - FAERS database: agent use was associated with decreased risk of colon, lung, and PCa, and benefit increased over time.

Purpose of PAR

Twofold purpose:

- promote studies examining the mechanism(s) through which GLP-1/GIP-1 RAs impact cancer risk
- attract talented scientists who study obesity/weight loss to investigate the dynamic changes induced by RAs that alter cancer risk and outcomes (long term rather than short term outcomes such as weight loss and diabetes)

Program announcements for R21 and R01 applications are suggested:

- three receipt dates per year for three years.
- R21 mechanism will allow for early stage or resource development projects (clinical trial not allowed)
- R01 mechanism will accommodate broader scoped or in-depth mechanistic studies (clinical trial allowed, not required)

What Studies Could be Performed?

- Preclinical studies correlating the effects of GLP-1/GIP-1 RAs on cancer risk reduction with metabolic changes.
- Studies to understand the mechanism of increased risk of thyroid cancer
- Studies with human samples.
- Combine preclinical with human studies.

Mechanistic Questions Include, but not Limited to:

- Is there a role for these agents in cancer risk reduction, and if so, what mechanism(s) is(are) involved?
- Do incretin mimetic-induced changes in the immune system or certain metabolites, hormones, cytokines, or other signaling molecules that alter cancer risk prior to weight loss? If so, in what organ, tissue, or cell type do they originate?
- Which cancers (or cancer subtypes, such as medullary vs. well differentiated thyroid) are impacted by these agents, either favorably or unfavorably, and if so, what are the mechanism(s)?
- Are there certain groups (gender, age, ethnicity or race) that would benefit more or less than others?
- Are there off-target effects that alter cancer risk? Are these off-target effects impacted by dose? If so, what are their mechanisms?
- Does the specific agent within the GLP-1, GIP-1, or dual agent list, influence the cancer promoting or tumor preventative impact? If so, what are the mechanism(s) driving the impact difference?
- Do diet quality and lifestyle behaviors impact the cancer related effects of these agents

Nonresponsive Criteria:

- Applications that focus entirely on in vitro investigations.
- Epidemiologic investigations as the primary focus of the application.
- Animal or human studies that do not evaluate tissue and/or bodily fluid samples collected from animals/participants who have been treated with incretin mimetics.

Discussions with BSA Review Members

- Should epidemiologic studies be included?
  - Currently excluded
  - Many agents have not been on the market long enough, particularly the most effective weight loss agents that are most likely to have an impact on cancer risk.
  - There are ongoing discussions with other Institutes through the NIH Obesity Research Task Force to possibly work jointly on epidemiologic assessment of these agents
- What about combinations with the mimetics including lifestyle and diet quality?
  - The suggestion to add lifestyle and diet quality was appreciated. The FDA indication for use of these agents often includes a statement such as “for use in addition to a reduced calorie diet and increased physical activity,” so understanding the impact of these together is important.
  - Have added a bulletpoint: “Do diet quality and lifestyle behaviors impact the cancer related effects of these agents” based on discussions with BSA reviewers

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