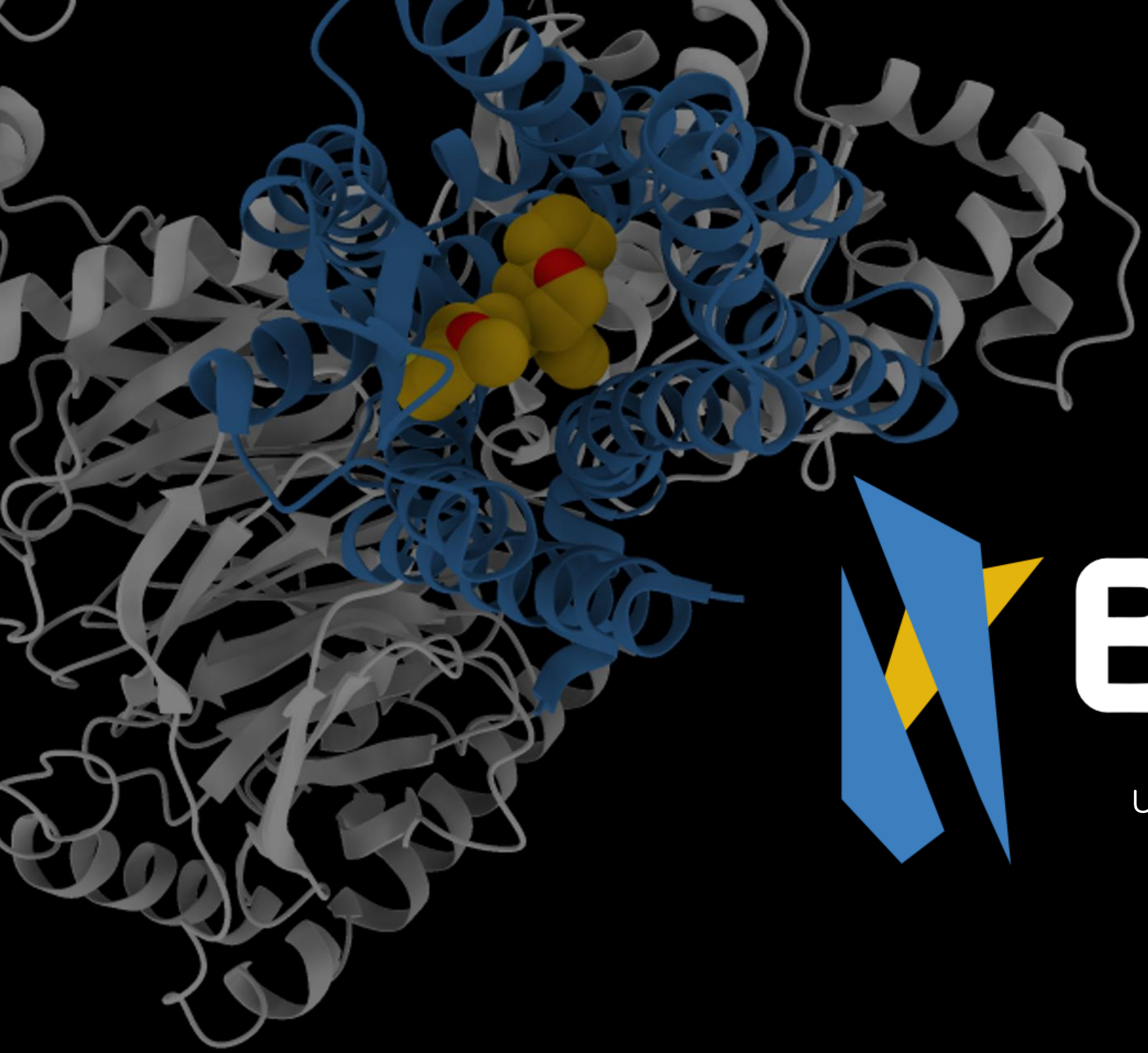


Biagon Inc.

Unlocking the therapeutic potential of the B3AR with biased agonism

Weight medication are well accepted as obesity treatments

Weight regain is an overlooked are of unmet need

Desensitization

Biased GLP-1R agonists (orfoglipron), dual or triple agonists, combinatorial therapies should eliminate this tissue in the coming years.

Weight Regain

Current incretin-based therapies do not provide sustainable weight loss after terminating administration. This massive issue is a major roadblock preventing reimbursement.

Lower manufacturing costs

Oral medications, recombinant protein manufacturing and manufacturing investment will quickly address manufacturing costs passed on to payors.

Orals

Orfoglipron (Eli Lilly), AZD5004 (AstraZeneca), GSBP-1290 (Structure Tx) are current or expected front runners.

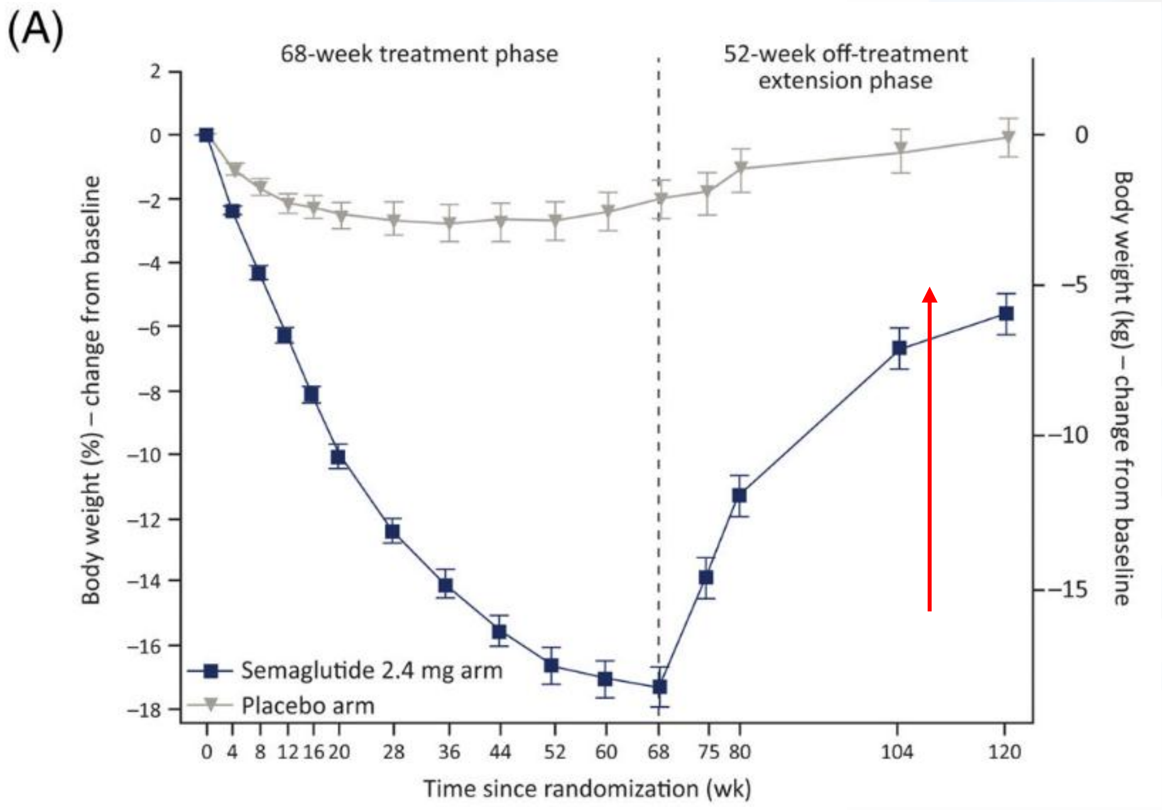
Muscle Preserving Agents

Activin receptor II inhibitors, IFG-2 fusion proteins, myostatin inhibitors, SARMs, testosterone replacement, apelin agonists lead late-stage clinical pipeline.

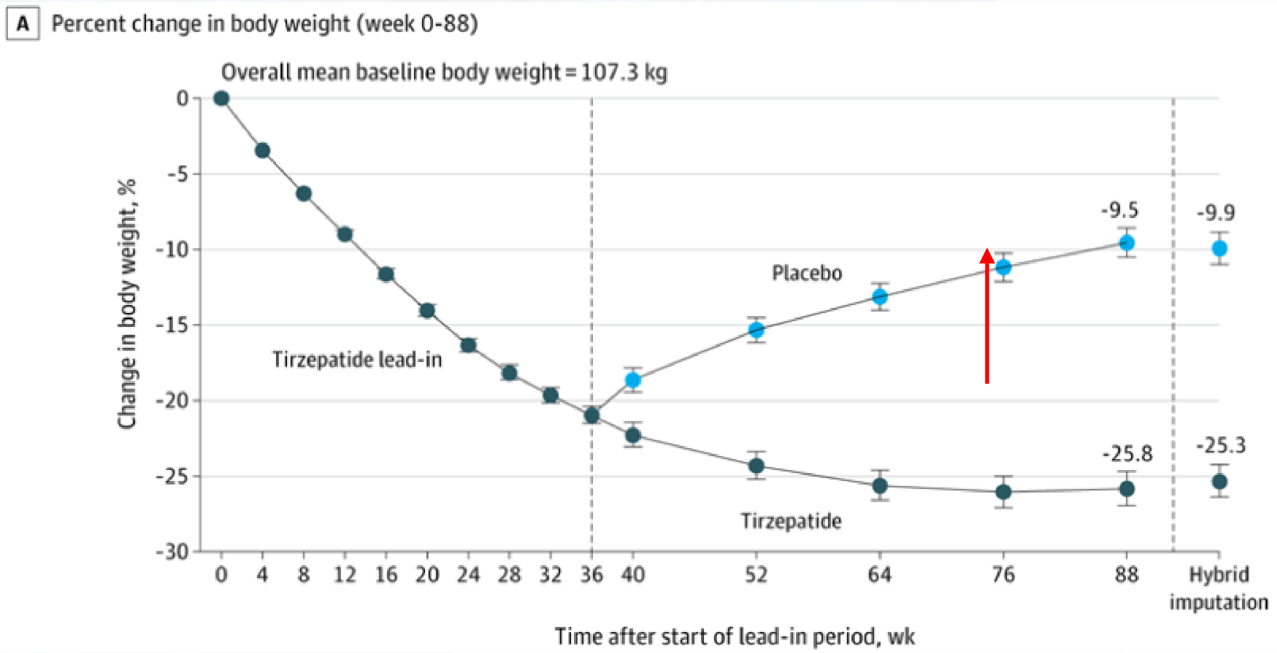
Standard of care does not address weight regain problem

After initial weight loss, there is often a substantial rebound in weight upon cessation of GLP-1 treatment

Semaglutide: STEP 1 trial extension



Tirzepatide: SURMOUNT-4



Aronne et al., *JAMA* **2023**; Wilding et al., *Diabetes Obes Metab.* **2022**

Why does weight regain happen? Understanding adipocyte obesity memory

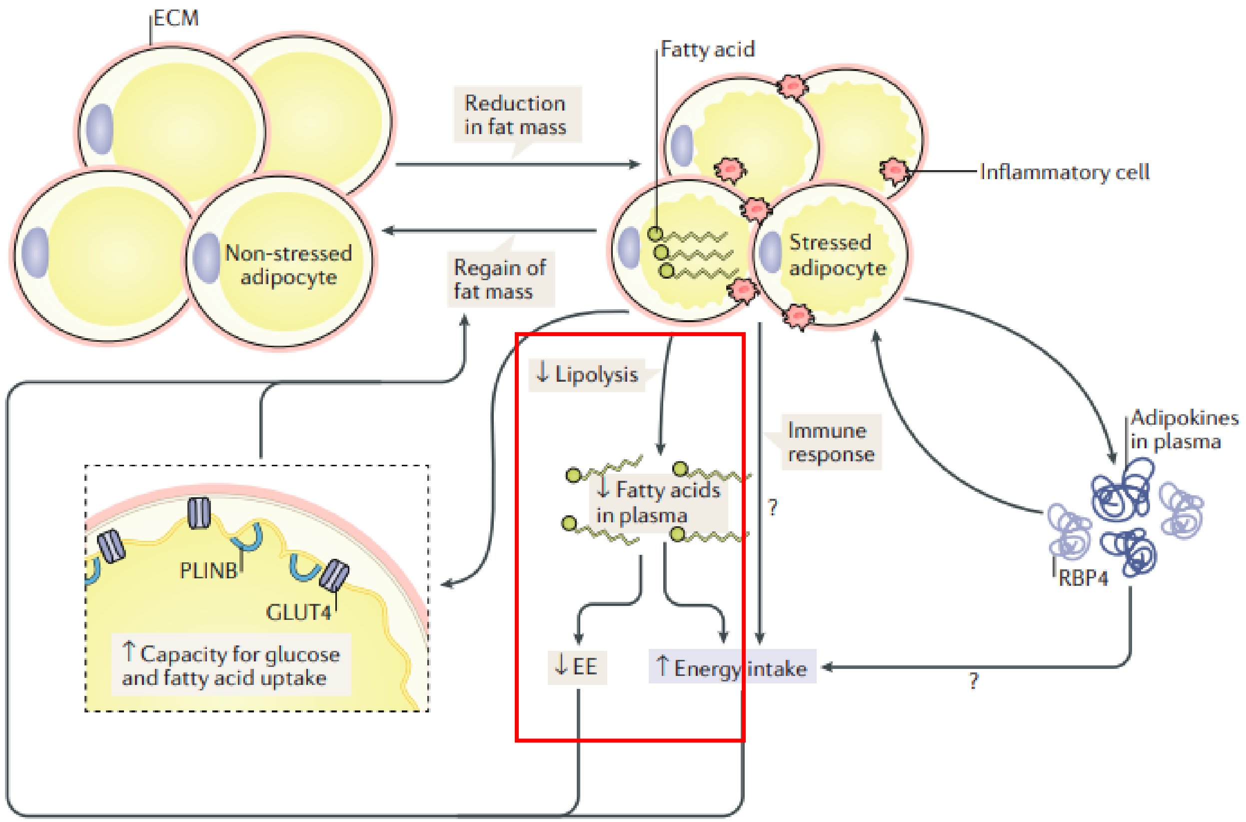


Fig. 5 | **Working model for the role of weight loss-induced changes in adipose tissue in weight regain.** Loss of fat mass induces shrinkage of adipocytes, which is accompanied by cell stress, inflammation, altered adipokine secretion (for example, retinol-binding protein 4 (RBP4)) and reduced lipolysis. These changes may affect energy balance by reducing energy expenditure (EE) and increasing energy intake, thus promoting regain of fat mass and body weight and relieving stress. In addition, the cells express an increased capacity for glucose uptake (glucose transporter type 4 (GLUT4)) and fatty acid uptake (perilipin 1 isoform B (PLINB)), which facilitates renewed fat storage[73]. ECM, extracellular matrix.

Reduction of adipocytes (weight loss) accompanied by:

- Adipokine secretion, which facilitate weight regain after loss by modifying extracellular matrix
- Decreased lipolysis, free fatty acids, lipid oxidation, and energy expenditure (**thermogenesis**)

Permanently changing adipocyte thermogenesis can occur at timescales significantly longer than observed weight loss

After termination of appetite-reducing incretin therapies, a normal diet + decreased thermogenesis puts patients at risk for weight regain

Raising adipocyte thermogenesis has been an attractive therapeutic approach, but thus far, not successfully accomplished

Biagon's approach employs novel adipocyte cellular biology to overcome previous translational barriers of the B3AR

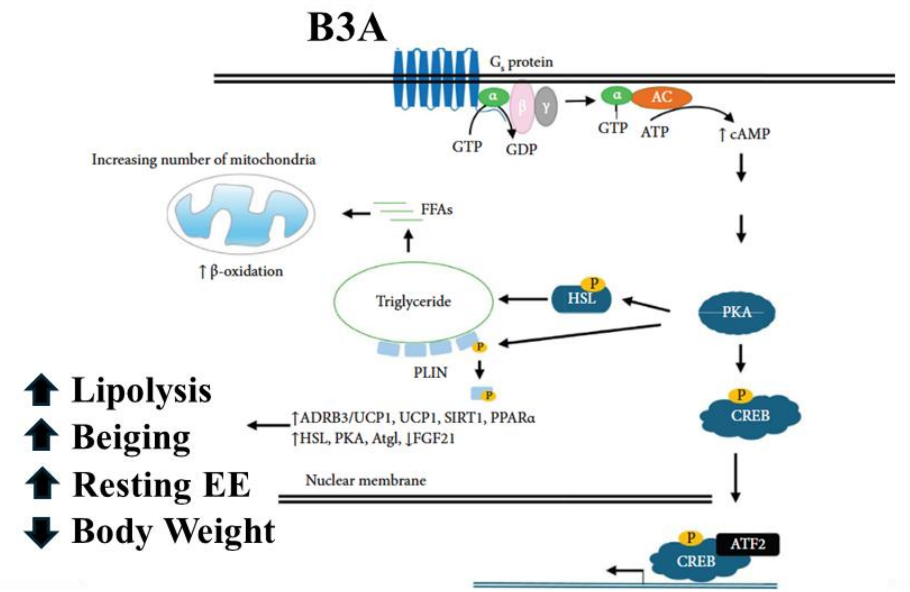
Baak et al., *Nature Reviews Endocrinology* **2023**

G_s-biased β-3 adrenergic agonist for sustainable weight loss

*Biagon's β3A biased agonist will **prevent weight regain** by maintaining adipose metabolism when co-administered with an incretin therapy (GLP-1Ra)*

Why β-3 Adrenergic Receptor (B3A)?

- B3A is primarily expressed in the bladder, GI tract, and **adipose tissues**
- B3A Gs signaling **increases lipolysis**, beiging, and raises resting energy expenditure in adipose tissues,
- Directly **combat decreased lipolysis** and resting energy expenditure levels post weight loss
- Orthogonal to standard-of-care incretin therapies

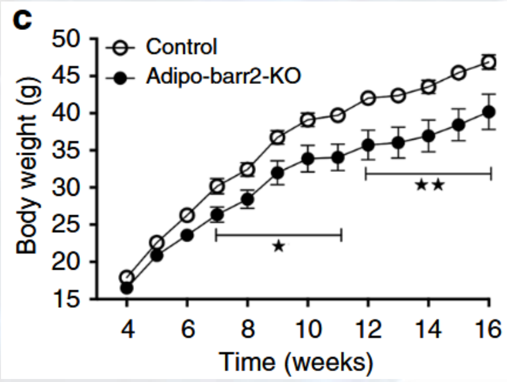


Why a selective B3A agonist?

- Mirabegron, a "selective" B3A agonist shows improved metabolism accompanied with cardiac liabilities via B1A/B2A activation at high doses
- Improved B3A selectivity would reduce cardiac liabilities

Why a Gs biased B3A agonist?

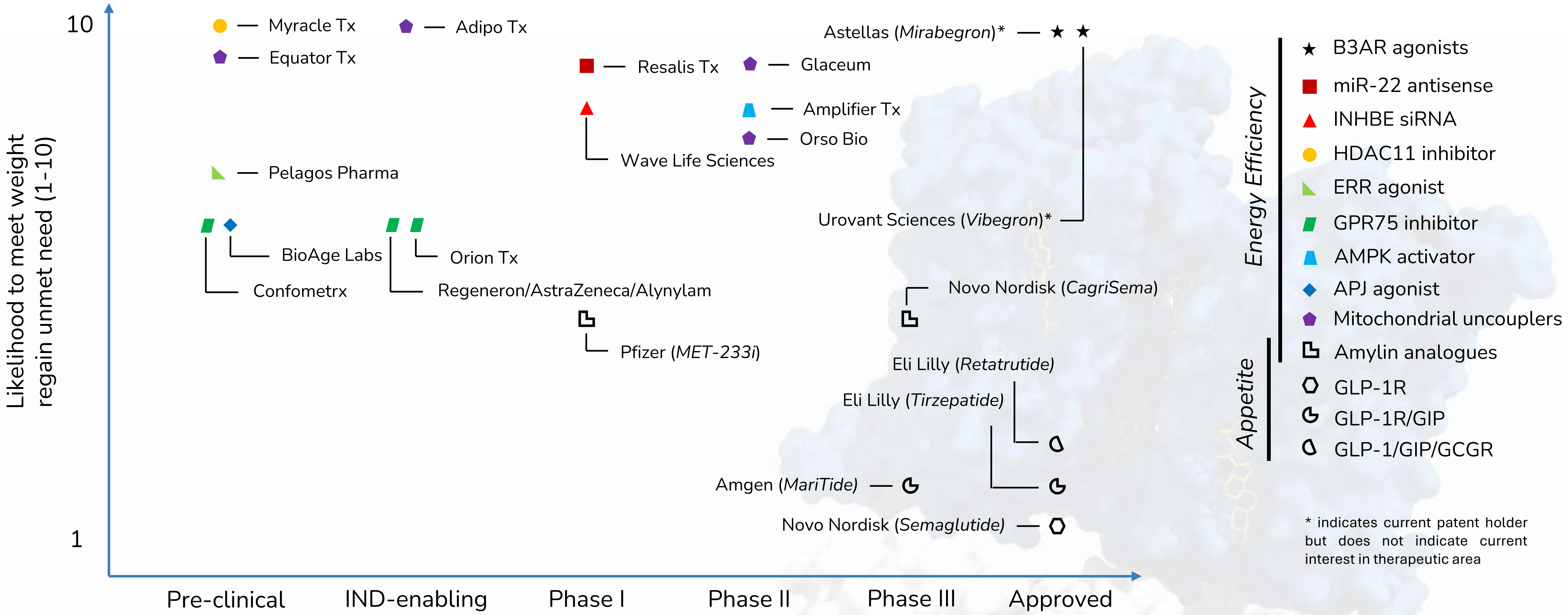
- β-arrestin-2 KO mice show **improved metabolism** in HFD models
- Selectivily activating B3AR/Gs signaling will **improve weight loss and decrease desensitization**



Body weights of control and adipose tissue β-arrestin-2 KO mice consuming a high fat diet (HFD) (n=7-9) . *Pydi et al (2019)*

Bel, J. et al. *Physiol. Rep.* **2021;** Cero, C. et al. *JCI Insi.* **2021;** Cho, Y. et al. *Biomolecules*. **2025;** Dongdem, J. et al. *Adv. Pharmacol.* **2024;** Pydi S. et al. *Nat. Commun.* **2019**

Standard of care and emerging competitors tackling the weight regain problem



* indicates current patent holder but does not indicate current interest in therapeutic area

Biagon's fit into 2035 projected obesity market segmentation

Treatment Phase	Funding Mechanism	Weight Regain High-Risk Population	Metabolic Disease Progression Population	*ARDB3* Trp64Arg Variant Obese Population
Induction	*Direct*	Unlikely to compete with incretin generics.		
	Reimbursement	**Requires clear weight regain prevention differentiation as stand alone or combination therapy without chronic treatment. May require realized reimbursement value$^{\alpha}$.**		**Patient segments with variant-linked co-morbidities realizing reimbursement value$^{\alpha}$. May enhance induction response to incretin generics.**
Maintenance	*Direct*	Unlikely to compete with incretin generics unless tolerability still an issue (unlikely by 2030).		
	Reimbursement	Unlikely to compete with incretin generics and unlikely to convince payors of chronic treatment.	Requires clear need for chronic treatment and clear differentiation to improve insulin resistance in patient segments with reimbursement value$^{\alpha}$. (unlikely to compete with generics or SOC by 2035)	**Patient segments with variant-linked co-morbidities realizing reimbursement value$^{\alpha}$ and/or enabling incretin tapering. <u>Will likely require chronic treatment in high-risk patients.</u>**

$^{\alpha}$Example of reimbursement value are high risk phenotypes, co-morbidities (such as cardiac liabilities, type II diabetes, etc.)
SOC: standard of care

ARDB3 Trp64Arg Variant

- Occurs in 30-40% of obese patients
- Associated with insulin resistance, increased lipid levels, adipokine levels, obesity, hypertension
- Responsible for measurable decrease in adipocyte thermogenesis

Daghestani, M, et al. *Lipids Health Dis.* **2018**; Luo, Z. et al. *Lipids Health Dis.* **2020;** Potocka, N., et al. *Genes* **2023;** Wang, H.-D., et al. Front. Endocrinol. **2021;** Yamada, Y., et al. *PLOS ONE* **2021**. Zhan, S., et al. *Obes. Res.* **2005**

Expected market fit guides program milestones

In vivo weight regain prevention

Demonstrates weight loss and prevention of weight regain after termination of combination or stand-alone administration. Consider studies with Trp64Arg *ARDB3* variant compared to wild type.

Good pharmacokinetics

Promising pharmacokinetic properties for oral and/or subcutaneous administration.

Improved thermogenesis

Improved thermogenesis phenotypes in human adipocyte cells compared to traditional B3AR agonists. No indication of tolerance build up over time.

Lead identification

Lead molecule identified characterized as a selective, biased B3A agonist.