

Established and emerging indications for GLP-1 medicines

Daniel J. Drucker

Lunenfeld-Tanenbaum Research Institute, Mt. Sinai Hospital

University of Toronto

[@DanielJDrucker](#)

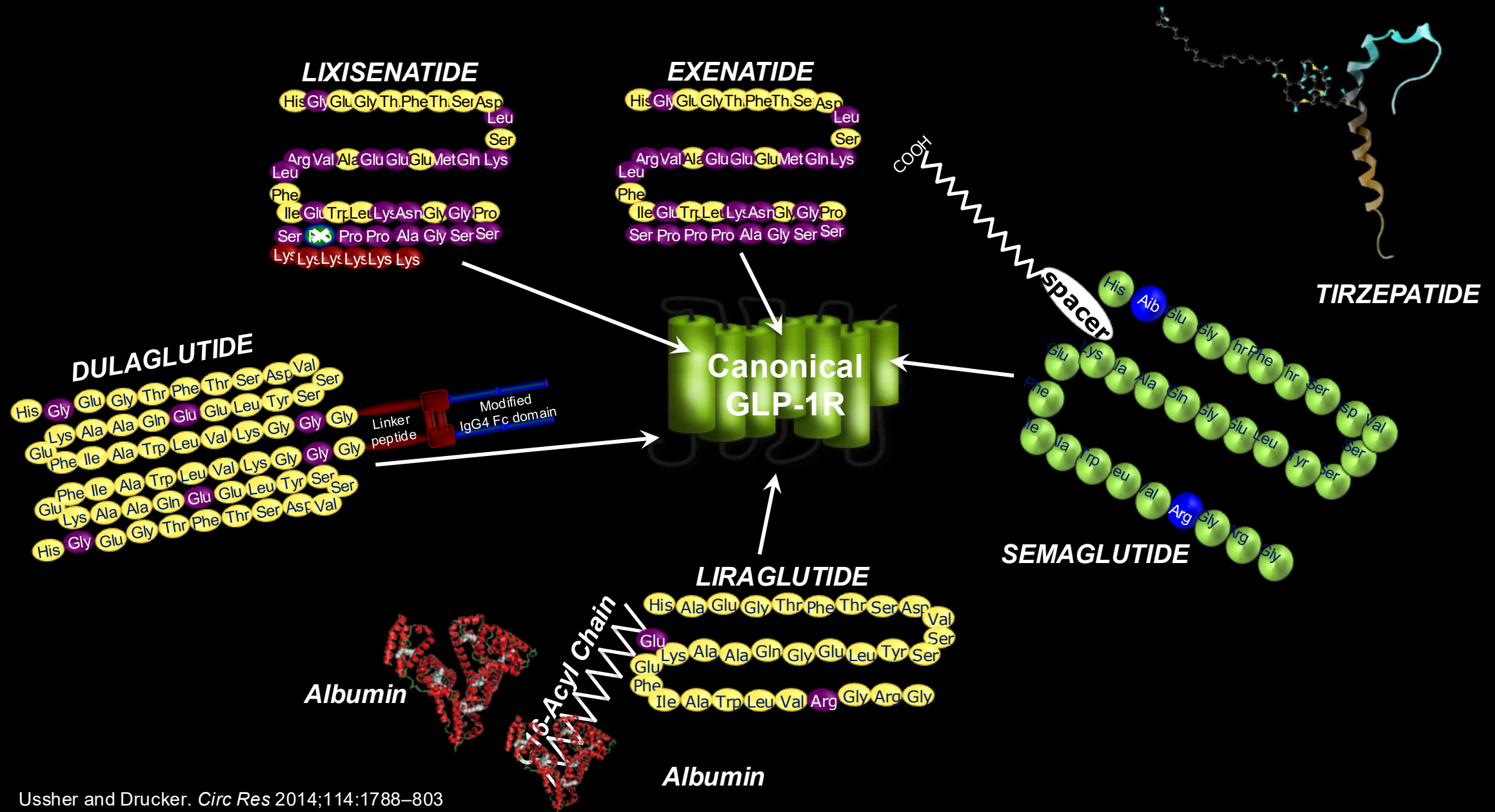
Disclosures

Dr. Drucker has served as an advisor or consultant or speaker within the past 12 months to Altimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Kallyope, Merck Research Laboratories, Novo Nordisk Inc, Pfizer and Zealand Pharma

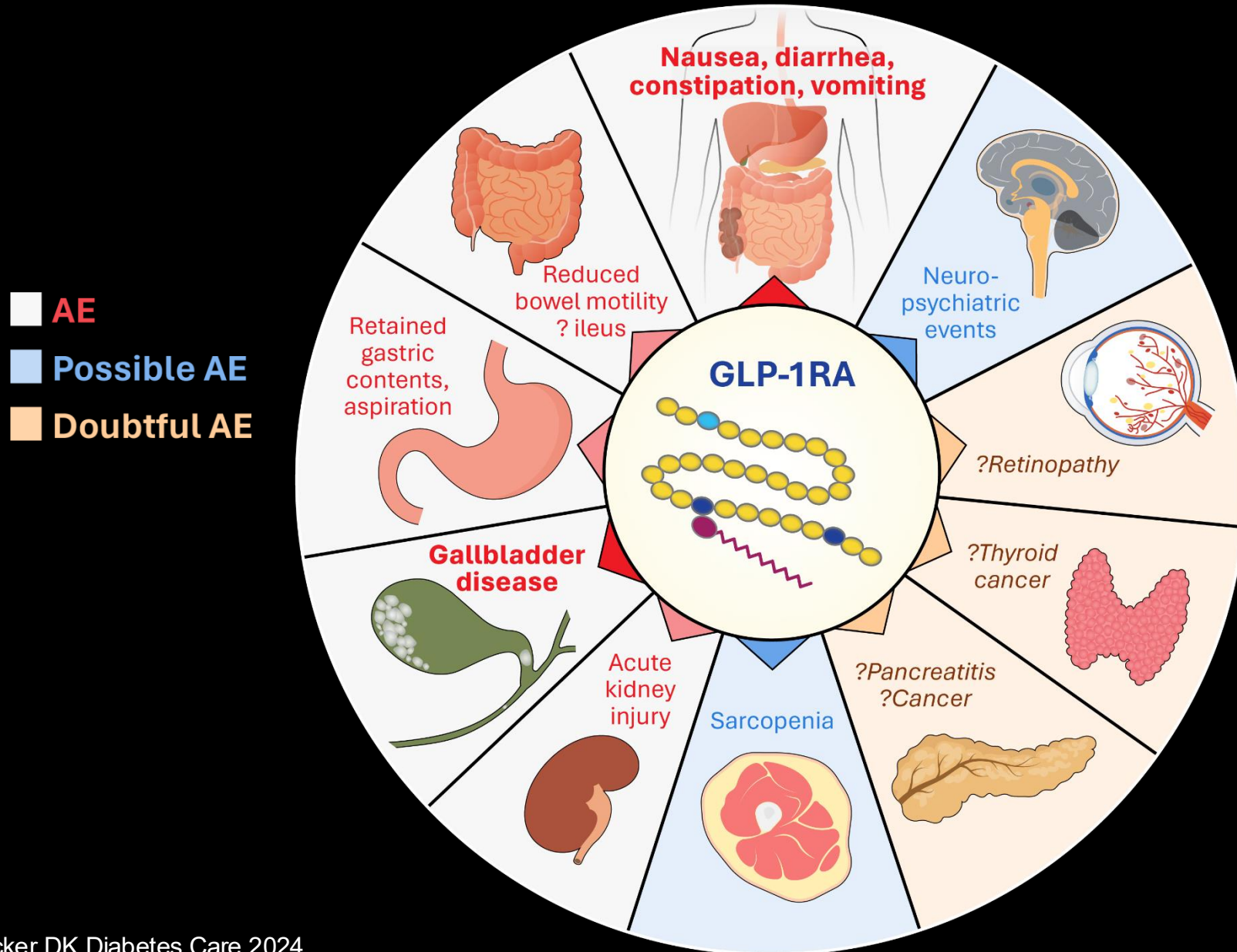
Dr. Drucker receives research support for preclinical studies from Novo Nordisk Inc and Pfizer Inc

Neither Dr. Drucker or his family members hold stock directly or indirectly in any of these companies.

GLP-1-based medicines in 2025

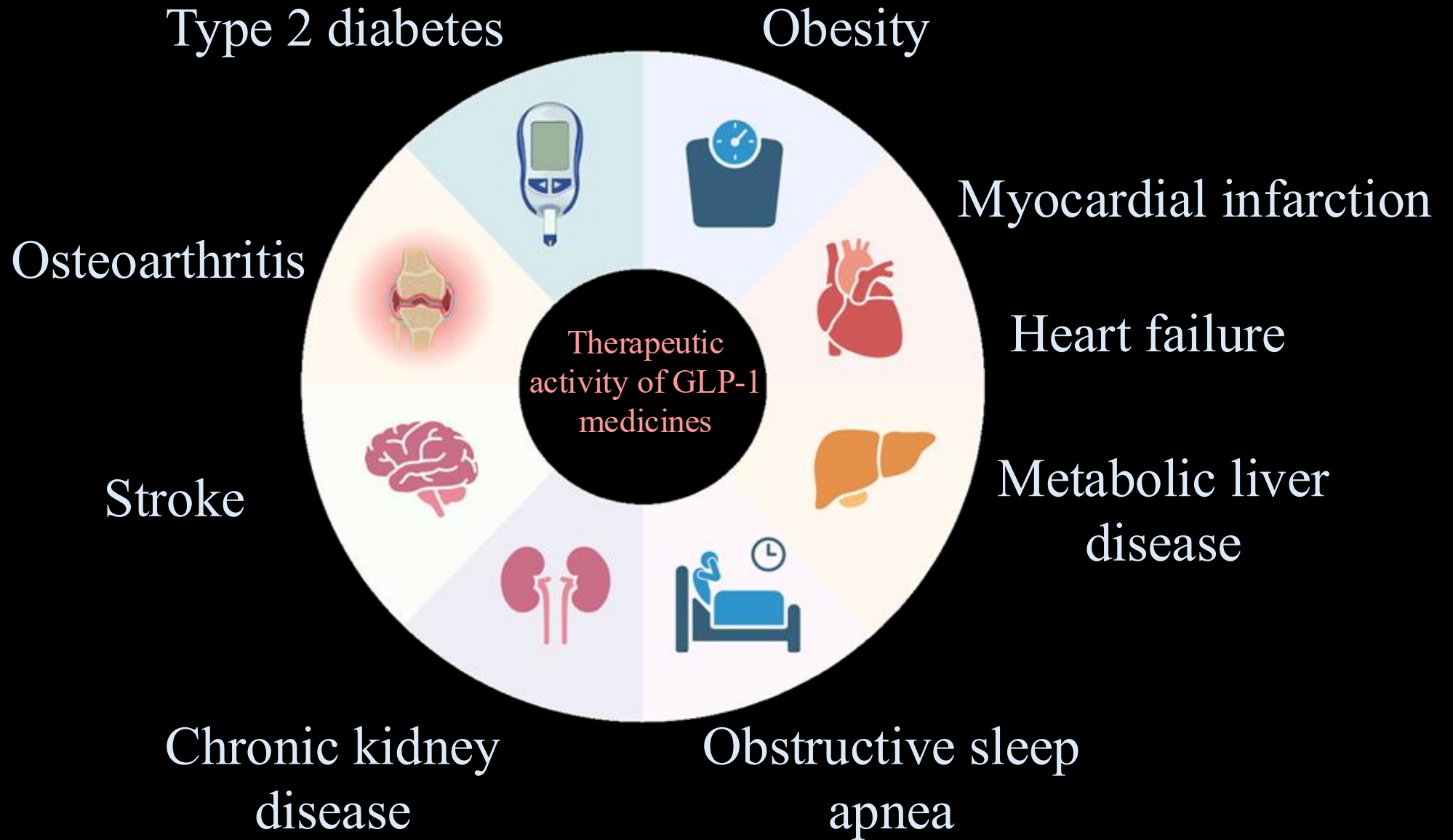


GLP-1 medicines and adverse events



Nausea
Vomiting
Diarrhea
Constipation
Gallbladder events
Acute kidney injury
Small bowel obstruction

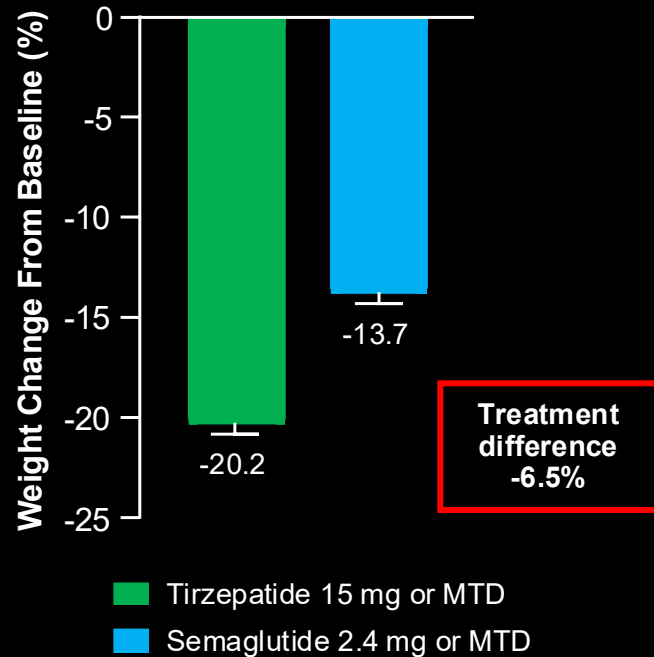
Current disorders with proven benefit for GLP-1 medicines



SURMOUNT-5 Tirzepatide vs. Semaglutide H2H for weight loss

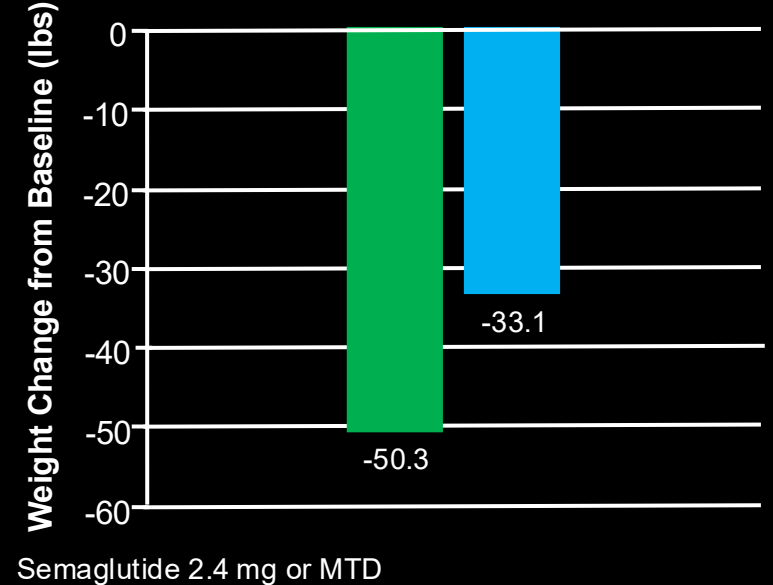
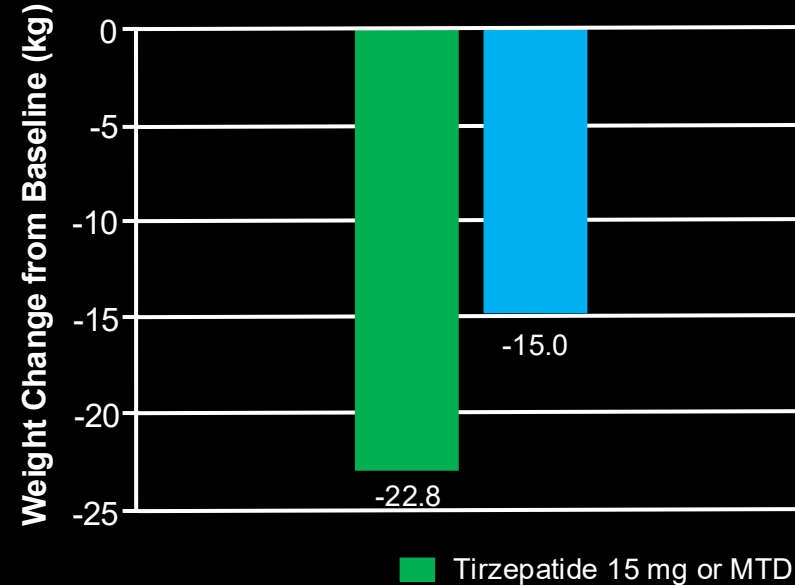
Primary Endpoint: Percentage Change in Body Weight From Baseline to 72 Weeks

Modified Treatment-Regimen Estimand
FAS



Change in Body Weight From Baseline to 72 Weeks
(kg and lb)*

Modified Treatment-Regimen Estimand
FAS

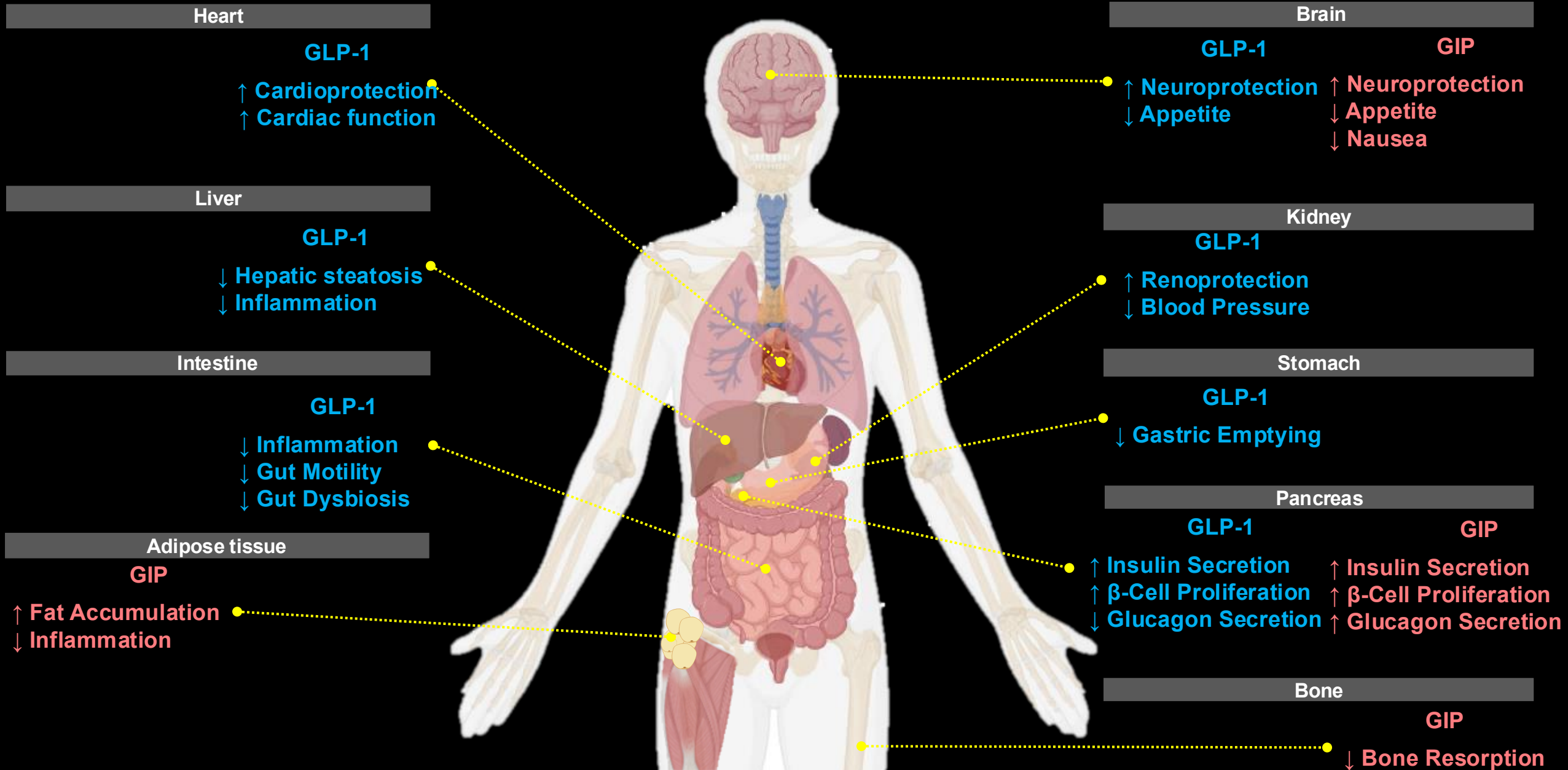


- Tirzepatide shows a 47% greater relative weight loss compared to semaglutide

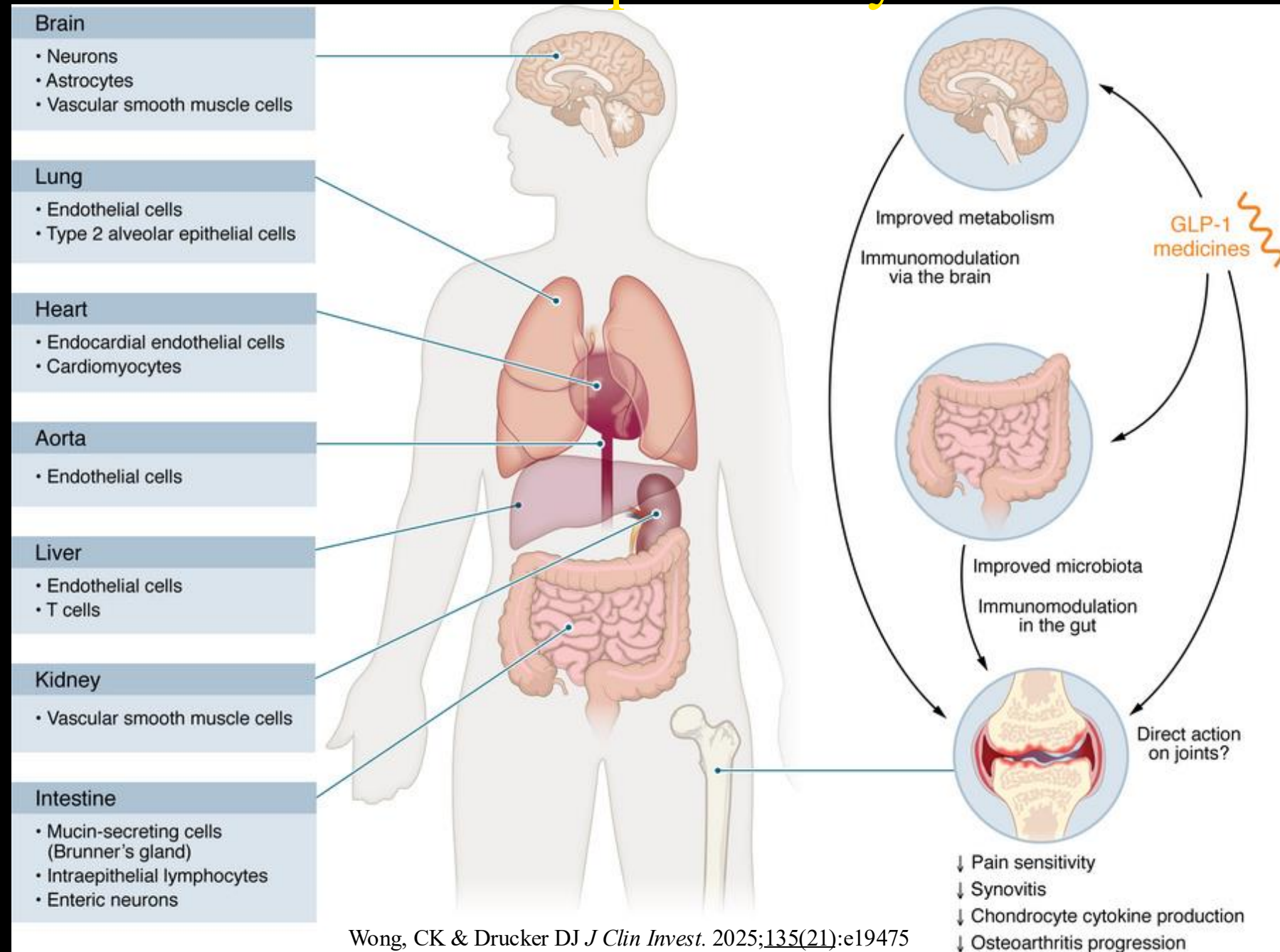
FAS=Full Analysis Set; MTD=Maximum Tolerated Dose.
Eli Lilly and Company. 2024. Available at: <https://investor.lilly.com/news-releases/news-release-details/lillys-zepboundr-tirzepatide-superior-wegovy-semaglutide-head>. Accessed 04 December 2024.

*Not a prespecified endpoint nor controlled for type 1 error
FAS=Full Analysis Set; MTD=Maximum Tolerated Dose.
Eli Lilly and Company. 2024. Available at: <https://investor.lilly.com/news-releases/news-release-details/lillys-zepboundr-tirzepatide-superior-wegovy-semaglutide-head>. Accessed 04 December 2024.

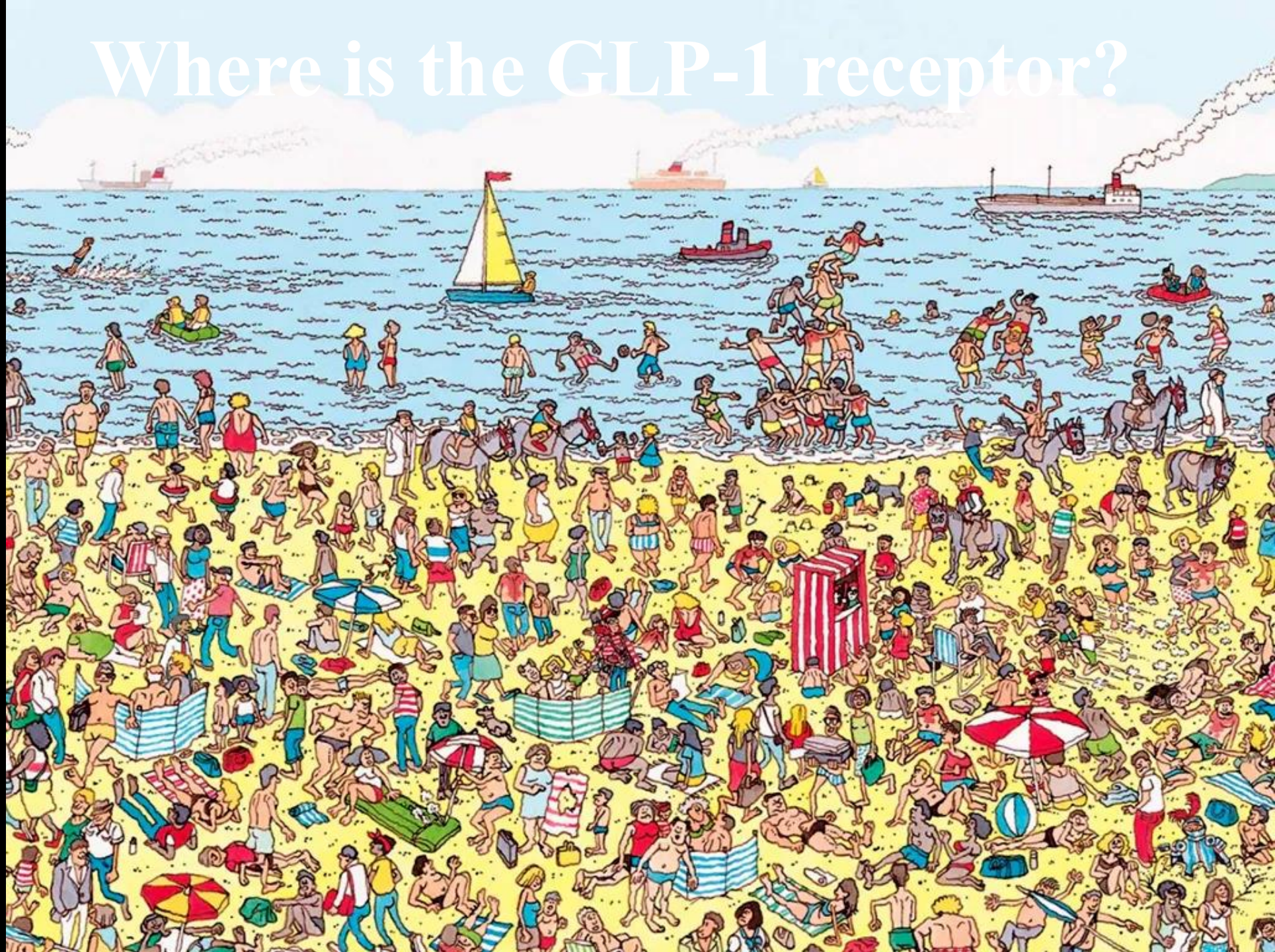
Metabolic actions of GIP and GLP-1-alone vs. together?



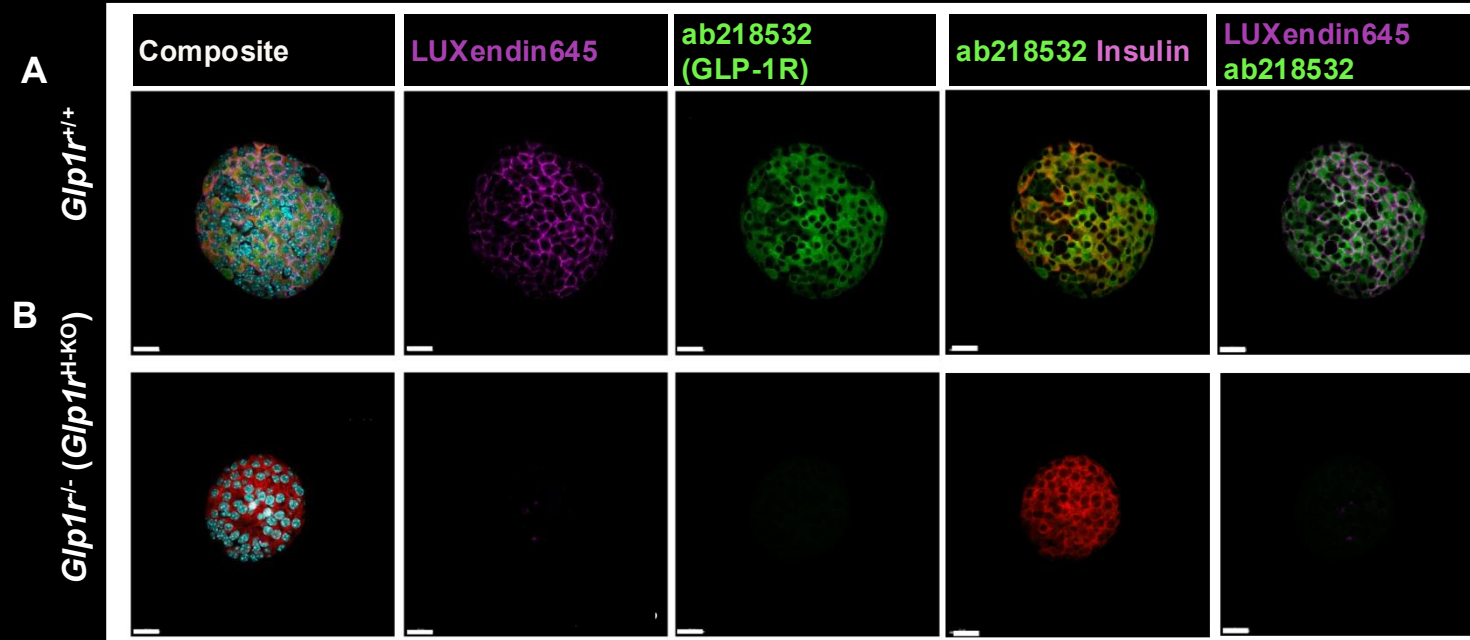
Cellular sites of GLP-1 action potentially linked to inflammation



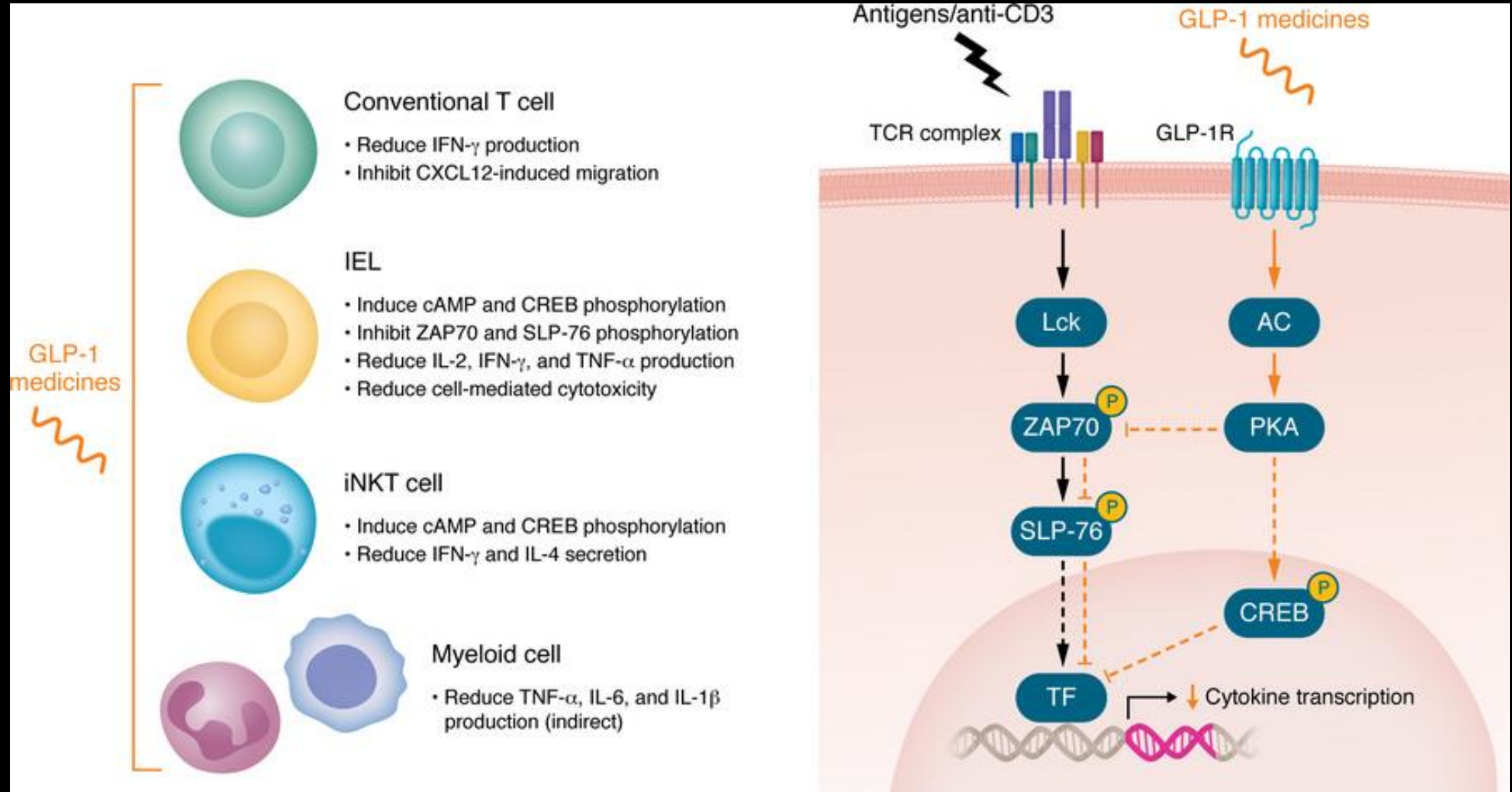
Where is the GLP-1 receptor?



Variable sensitivity and specificity of GLP-1R antisera

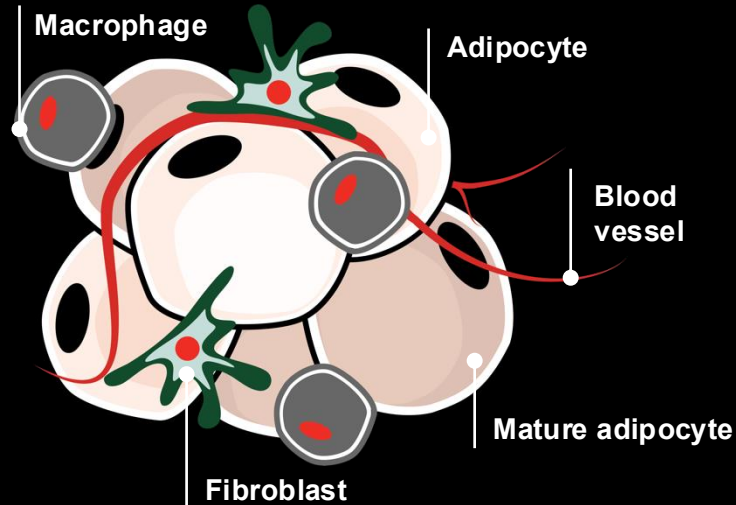


GLP-1 acts directly on immune cells to regulate inflammation



Obesity Impacts the Metabolic and Inflammatory State

Pathological increase of **adipose tissue** and dysfunction induces **qualitative and quantitative changes in adipose tissue signals**¹



Molecules secreted by WAT

Adipokines ↑Leptin², ↓adiponectin², ↑FABP4³, ↑apelin⁴

Lipokines and metabolites ↑ Fatty acids⁵, ↑ceramides⁶, ↑ BCAAs⁷, ↓ FAHFAs^{8,9}

Cytokines ↑IL-6^{10,11}, ↑TNFα¹¹

Molecules secreted by BAT (Batokines)

Lipokines: ↓ diHOMEs¹²

Growth and Metabolites ↓ IGF1¹³⁻¹⁵, ↑FGF21¹⁶, ↓ NRG-4¹⁷, BMPs¹⁸, ↓ GDF-8^{19,20}

Cytokines: ↑IL-6²¹

Factors secreted by WAT and BAT

Others: Exosomes, miRNAs^{1,22,23}

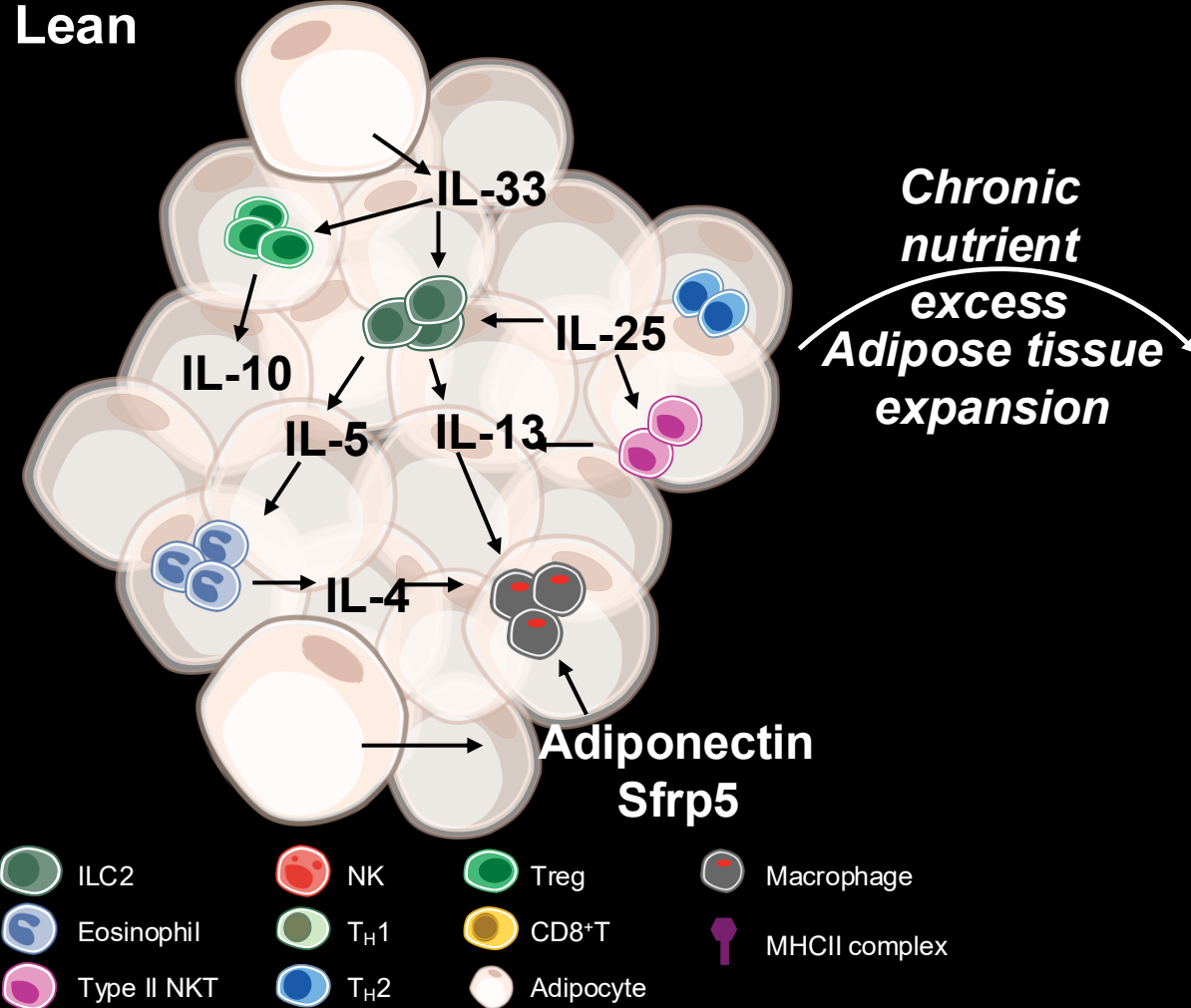
These changes lead to a low-grade chronic systemic inflammation.

BAT=Brown Adipose Tissue; BCAA=Branched-chain Amino Acid; BMP=Bone Morphogenetic Protein; diHOME=Dihydroxy Octadecenoic Acid; FABP4=Fatty Acid-binding Protein 4; FAHFA=Fatty Acid Esters of Hydroxy Fatty Acid; FGF=Fibroblast Growth Factor; GDF=Growth Differentiation Factor; IGF=Insulin-like Growth Factor; IL=Interleukin; miRNA=Micro Ribonucleic Acid; NRG=Neuregulin; TNFα=Tumor Necrosis Factor Alpha; WAT=White Adipose Tissue.

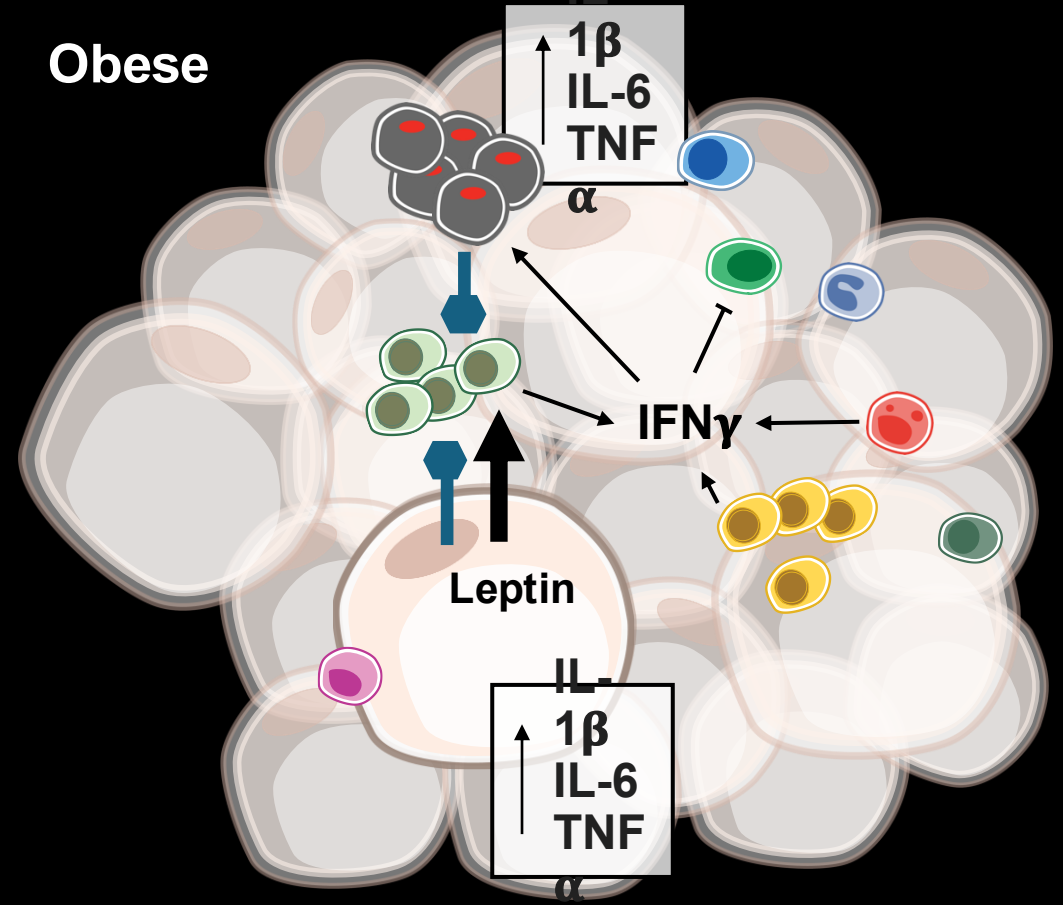
1. Favaretto F, et al. *Rev Endocr Metab Disord*. 2022;23(1):71-85; 2. Zorena K, et al. *Int J Mol Sci*. 2020;21(10):3570; 3. Josephrajan A, et al. *Diabetes*. 2019;68(9):1767-1777; 4. Boucher J, et al. *Endocrinology*. 2005;146(4):1764-1771; 5. Longo M, et al. *Int J Mol Sci*. 2019;20(9):2358; 6. Chavez JA, Summers SA. *Cell Metab*. 2012;15(5):585-594; 7. Abdulkader AM, et al. *J Pharm Pharm Sci*. 2024;27:13040; 8. Brejchova K, et al. *Prog Lipid Res*. 2020;79:101053; 9. Li L, et al. *Obes Rev*. 2024;25(6):e13735; 10. Jonas MI, et al. *Int J Mol Sci*. 2015;16(10):25817-25830; 11. Kern L, et al. *Cancers (Basel)*. 2018;11(1):24; 12. Lynes MD, et al. *Nat Med*. 2017;23(5):631-637. doi:10.1038/nm.4297; 13. Al-Samerria S, Radovick S. *Int J Mol Sci*. 2023;24(11):9556; 14. Gunawardana SC, Piston DW. *Diabetes*. 2012;61(3):674-682; 15. Rao MN, et al. *J Clin Endocrinol Metab*. 2010;95(9):4361-4366; 16. Zhang X, et al. *Diabetes*. 2008;57(5):1246-1253; 17. Blüher M. *Obesity (Silver Spring)*. 2019;27(10):1555-1557; 18. Chen Y, et al. *J Diabetes Res*. 2021;2021:6707464; 19. Sharma A, et al. *PLoS One*. 2014;9(3):e92608; 20. Fournier B, et al. *Mol Cell Biol*. 2012;32(14):2871-2879; 21. Villarroja J, et al. *J Endocrinol*. 2019;243(2):R19-R27. 22. Lee MW, et al. *J Clin Med*. 2019;8(6):854. 23. Mei R, et al. *Front Endocrinol (Lausanne)*. 2022;13:73865.

Pro-Inflammatory Immune Cell Changes Occur in Obesity

Lean



Obese

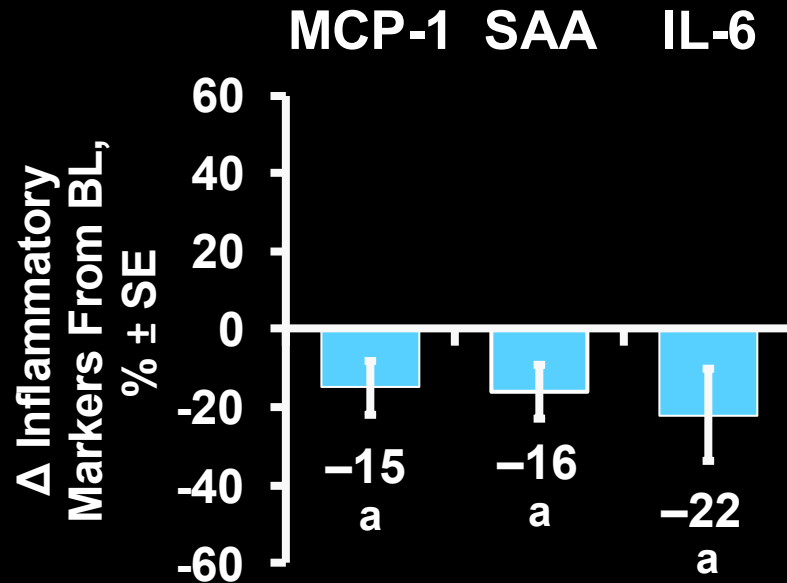


These changes lead to a low-grade chronic systemic inflammation.

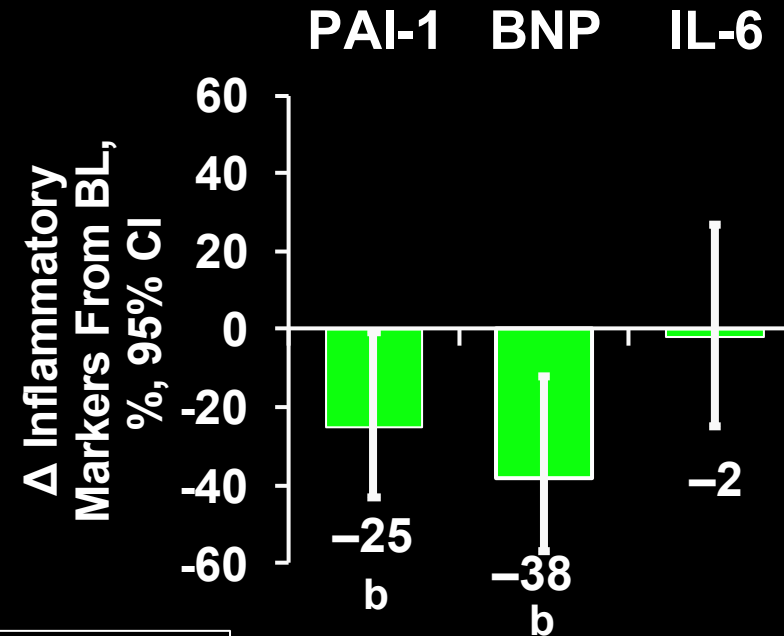
- CD8⁺T=Cytotoxic T Cell; IFN γ =Interferon Gamma; IL=Interleukin; ILC2=Innate Lymphoid Type 2 Cell; MHCII=Class II Major Histocompatibility Complex; NK=Natural Killer; NKT=Natural Killer T; Sfrp5=Secreted Frizzled-Related Protein 5; TH1=T Helper Type 1; TH2=T Helper Type 2; TNF α =Tumor Necrosis Factor Alpha; Treg=Regulatory T cell.
Deng T, et al. *Annu Rev Pathol*. 2016;11:421-449.

Anti-Inflammatory Effects of GLP-1 RAs in People With T2DM

EXN (10 µg BID) vs PBO
12 weeks (N = 24)¹



Liraglutide (1.9 mg QD) vs PBO
14 weeks (N = 165)²



EXN BID also significantly reduced mononuclear cell

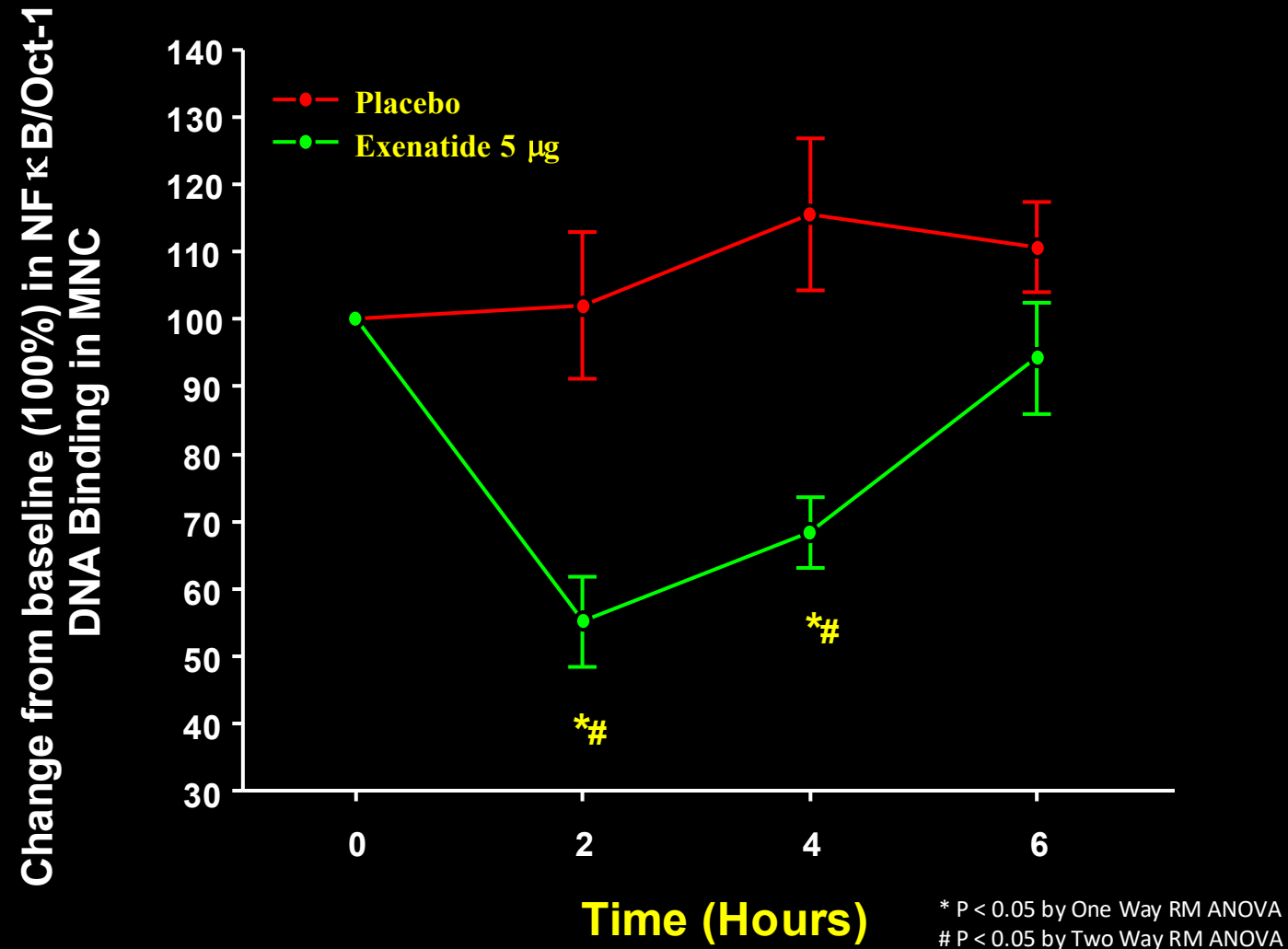
- Production of reactive oxygen species (ROS)
- NFκB activation
- TNF-α and IL-1β expression

^a $P < .05$ vs baseline and control; ^b $P < .05$ vs baseline.

1. Chaudhuri A, et al. *J Clin Endocrinol Metab.* 2012;97:198-207.

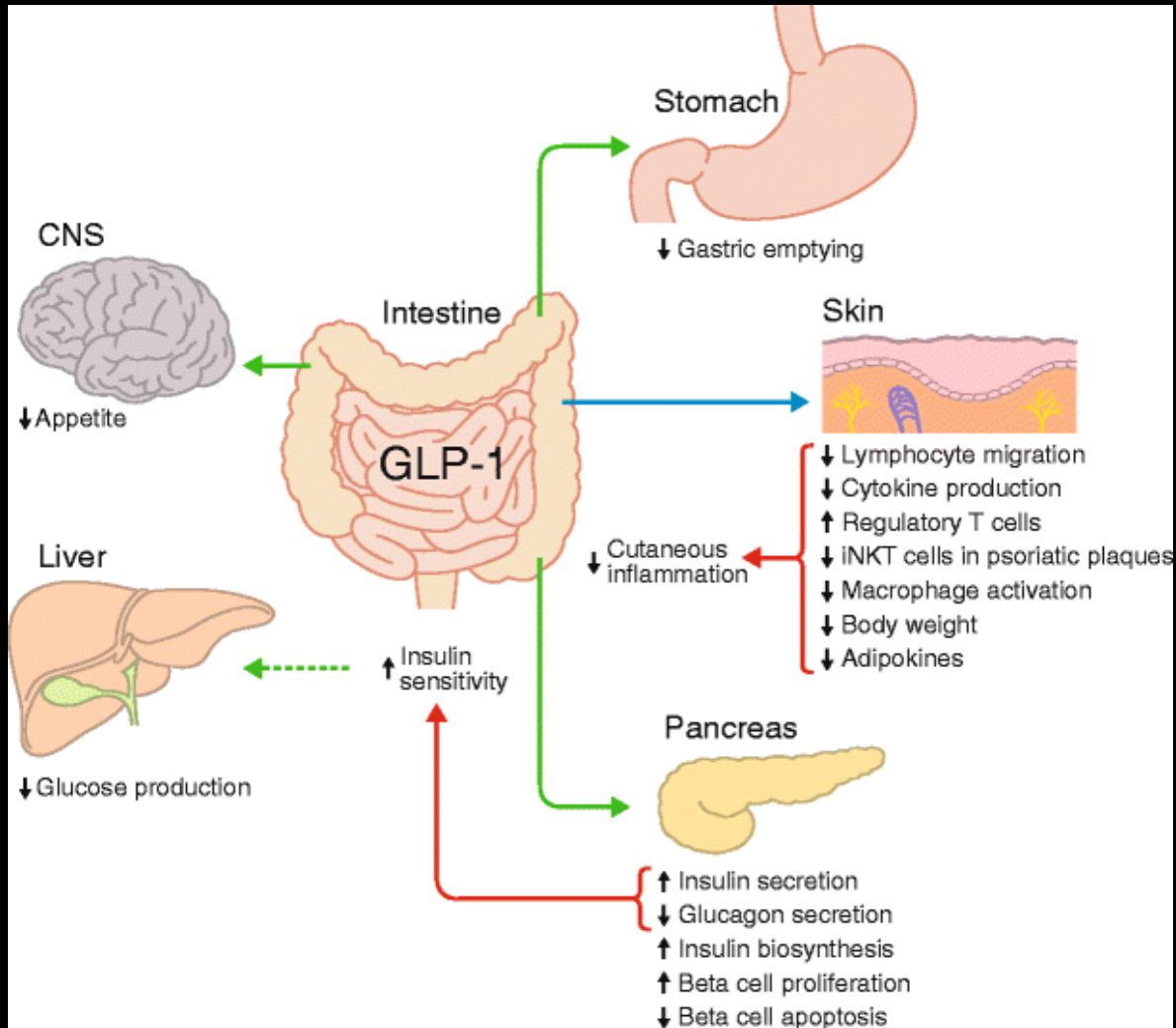
2. Courrèges J, et al. *Diabetic Med.* 2008;25:1125-1131.

Exenatide acutely reduces NFκB Binding activity in nuclear extracts from mononuclear cells in people with Type 2 diabetes



Glucagon-like peptide-1 (GLP-1) receptor agonists, obesity and psoriasis: diabetes meets dermatology

D. J. Drucker • C. F. Rosen



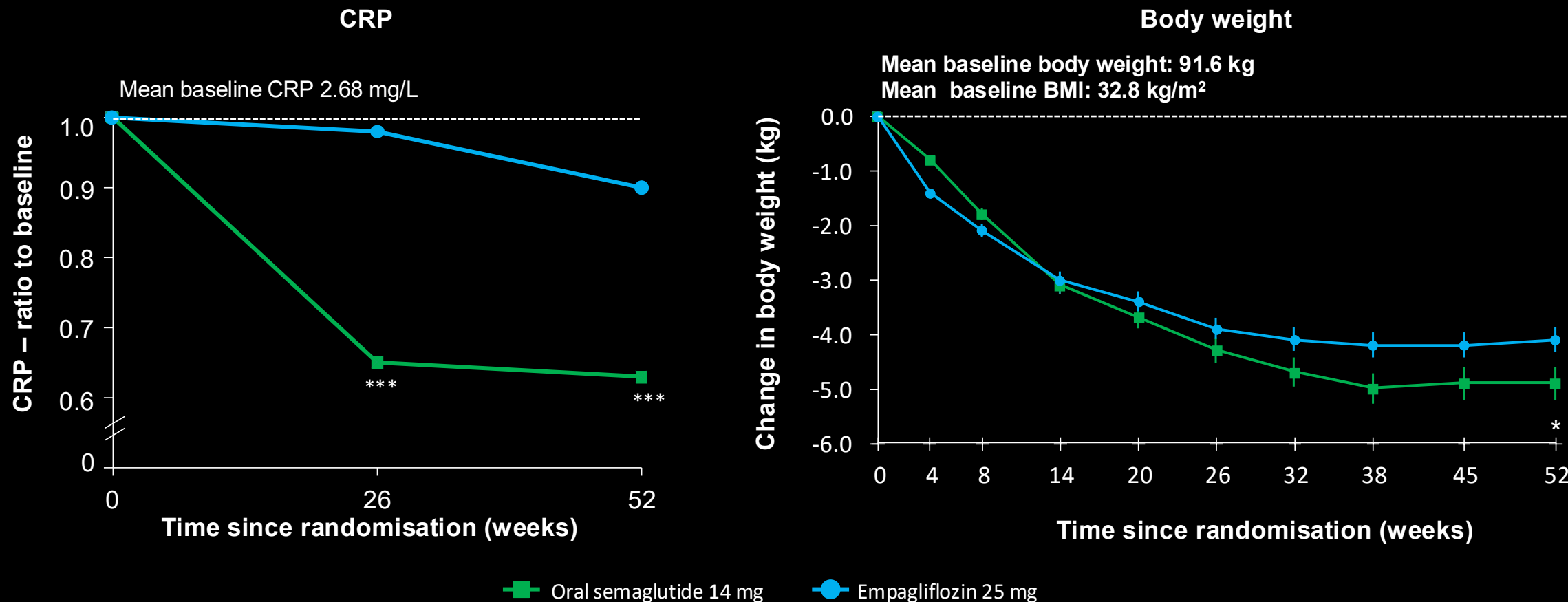
● Enrolling

Ixekizumab Concomitantly Administered With Tirzepatide in Adults With Psoriatic Arthritis and Obesity or Overweight (TOGETHER-PsA)

11F-MC-RHDB - [ClinicalTrials.gov - NCT06588296](https://clinicaltrials.gov/ct2/show/study/NCT06588296)

The main purpose of this study is to demonstrate that when participants with psoriatic arthritis and obesity or overweight receive ixekizumab and tirzepatide concomitantly administered, participants see improvement in their psoriatic arthritis and achieve weight reduction compared to when receiving ixekizumab.

Reduction in CRP levels by semaglutide appears to be independent of body weight reduction in the PIONEER 2 trial



***p<0.001 for oral semaglutide vs comparator based on the estimated treatment ratio. Ratio to baseline for estimated geometric means – trial product estimate Line graph for body weight: values are observed means ± standard error of the mean. CRP: ratio to baseline for estimated geometric means *p<0.05 for oral semaglutide vs comparator based on the estimated treatment difference (body weight) or estimated treatment ratio BMI, body mass index; CRP, C-reactive protein; T2D, type 2 diabetes Rodbard HW, et al. Diabetes Care. 2019;42:2272–2281

Gut microbes



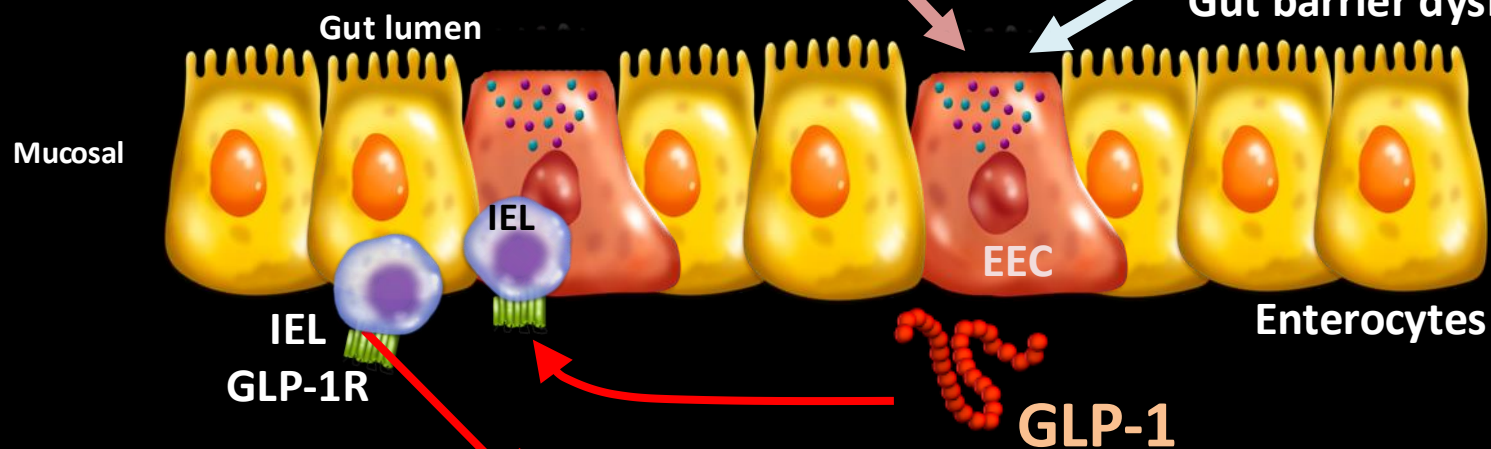
Bacterial proteins
Bile acids
Endotoxins
Ethanalamides
Hydrogen Sulfide
Indole
Lipopolysaccharides
Short & long chain fatty acids
TLR ligands

Pathogen-linked Inflammation

Cell Injury

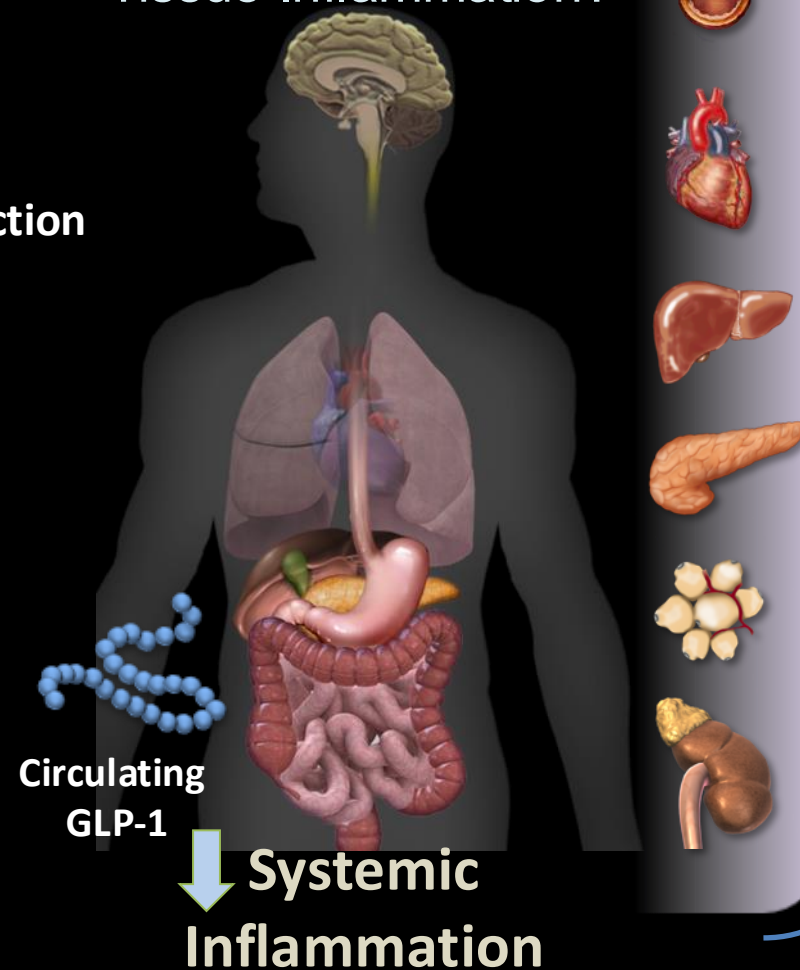
Sterile Inflammation

Ischemic injury
Gut barrier dysfunction

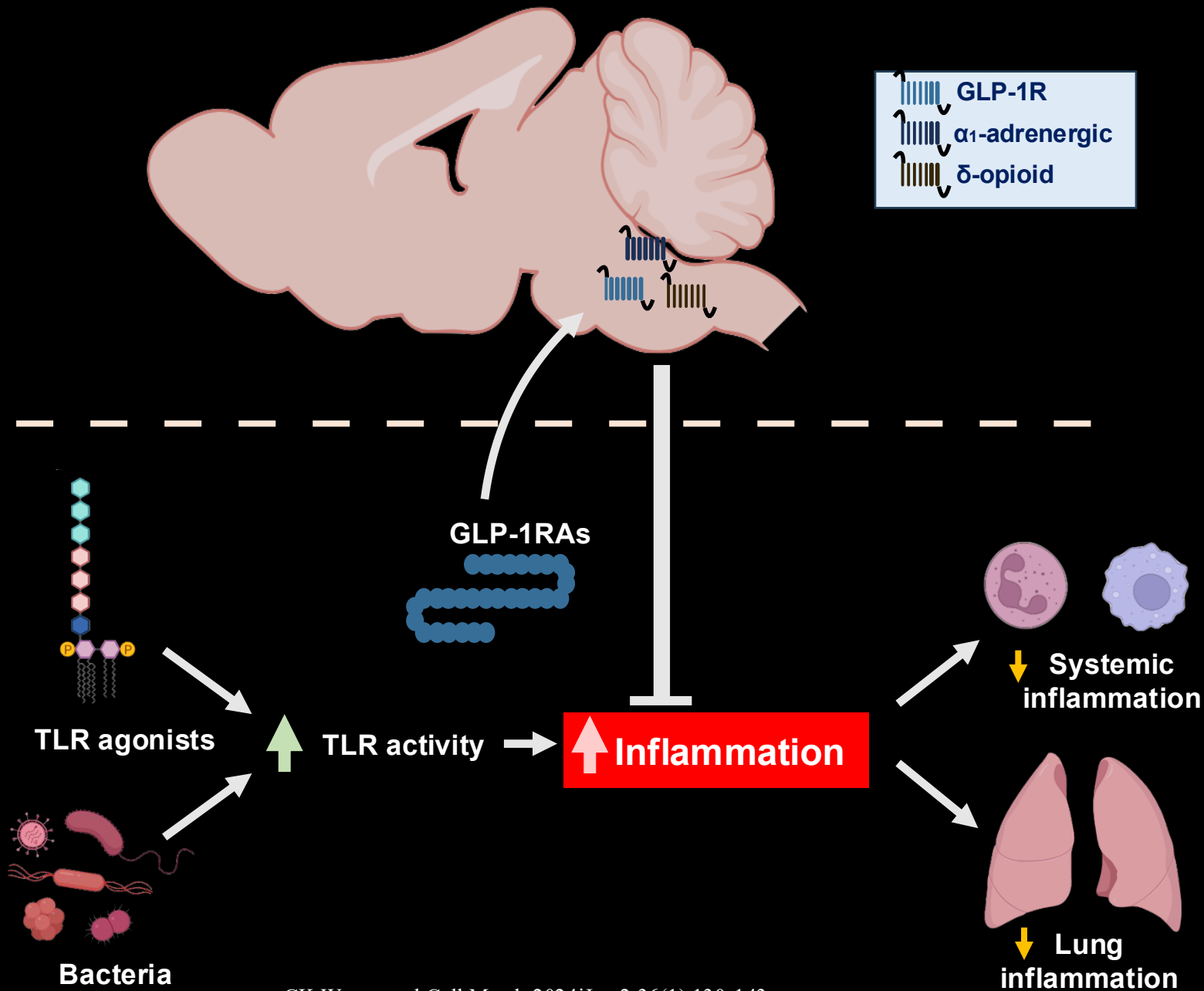


↓
Intestinal
Inflammation

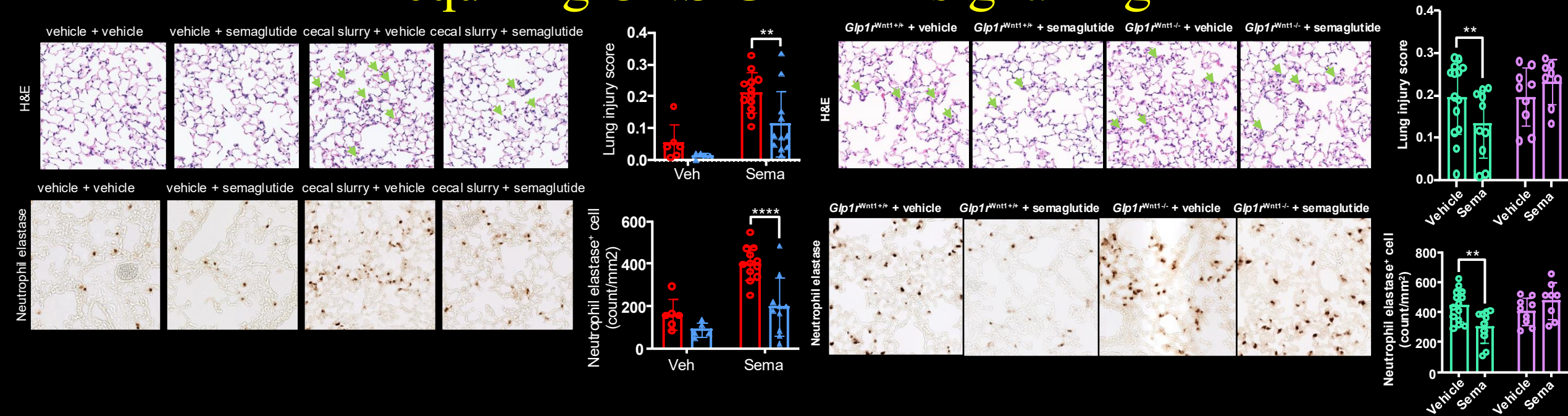
How Does GLP-1 ↓
Tissue Inflammation?



GLP-1 attenuates systemic inflammation through CNS GLP-1Rs



Semaglutide reduces lung inflammation through pathways requiring CNS GLP-1R signalling

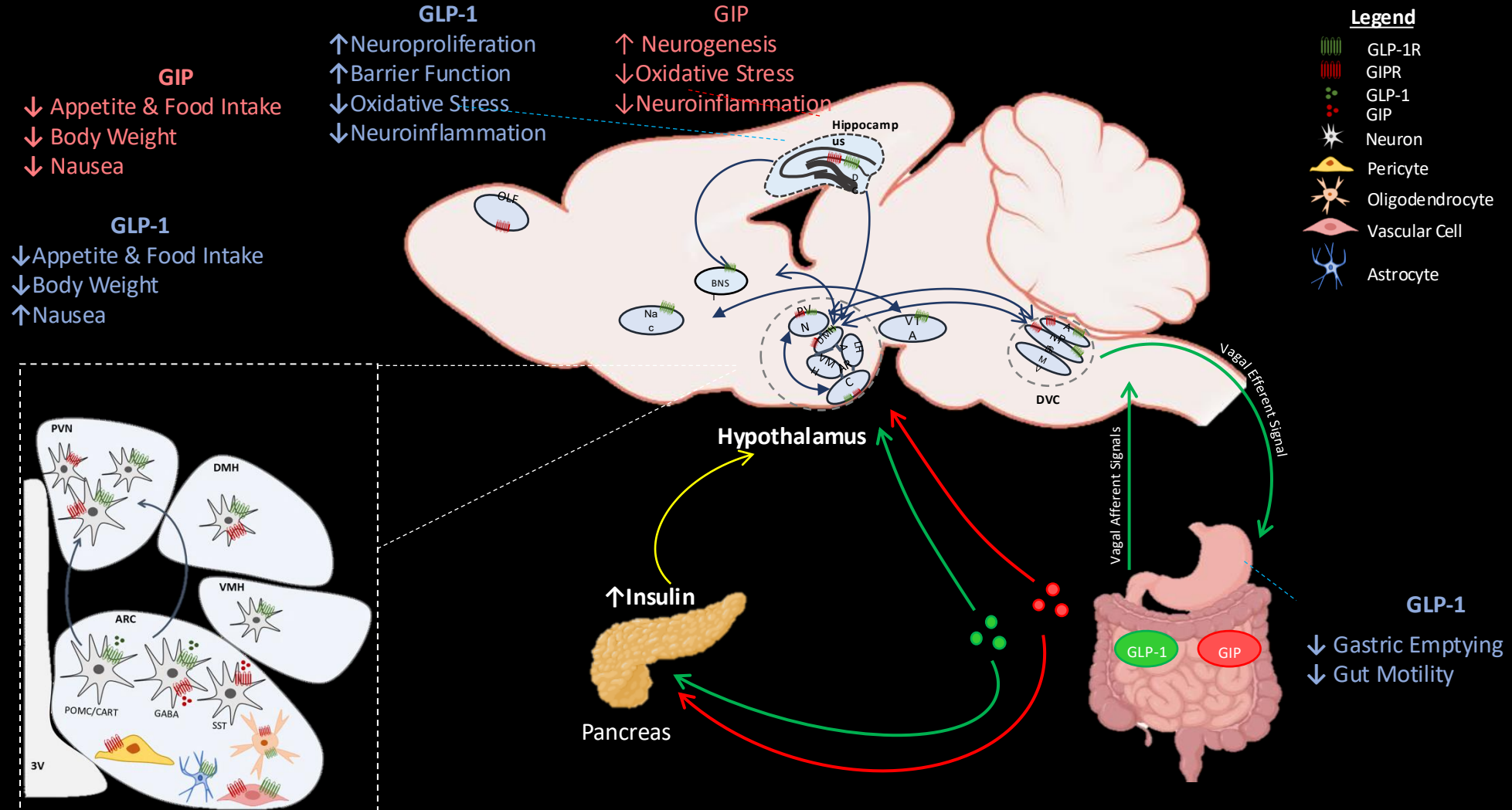


The relationship between the use of GLP-1 receptor agonists and the incidence of respiratory illness: a meta-analysis of randomized controlled trials

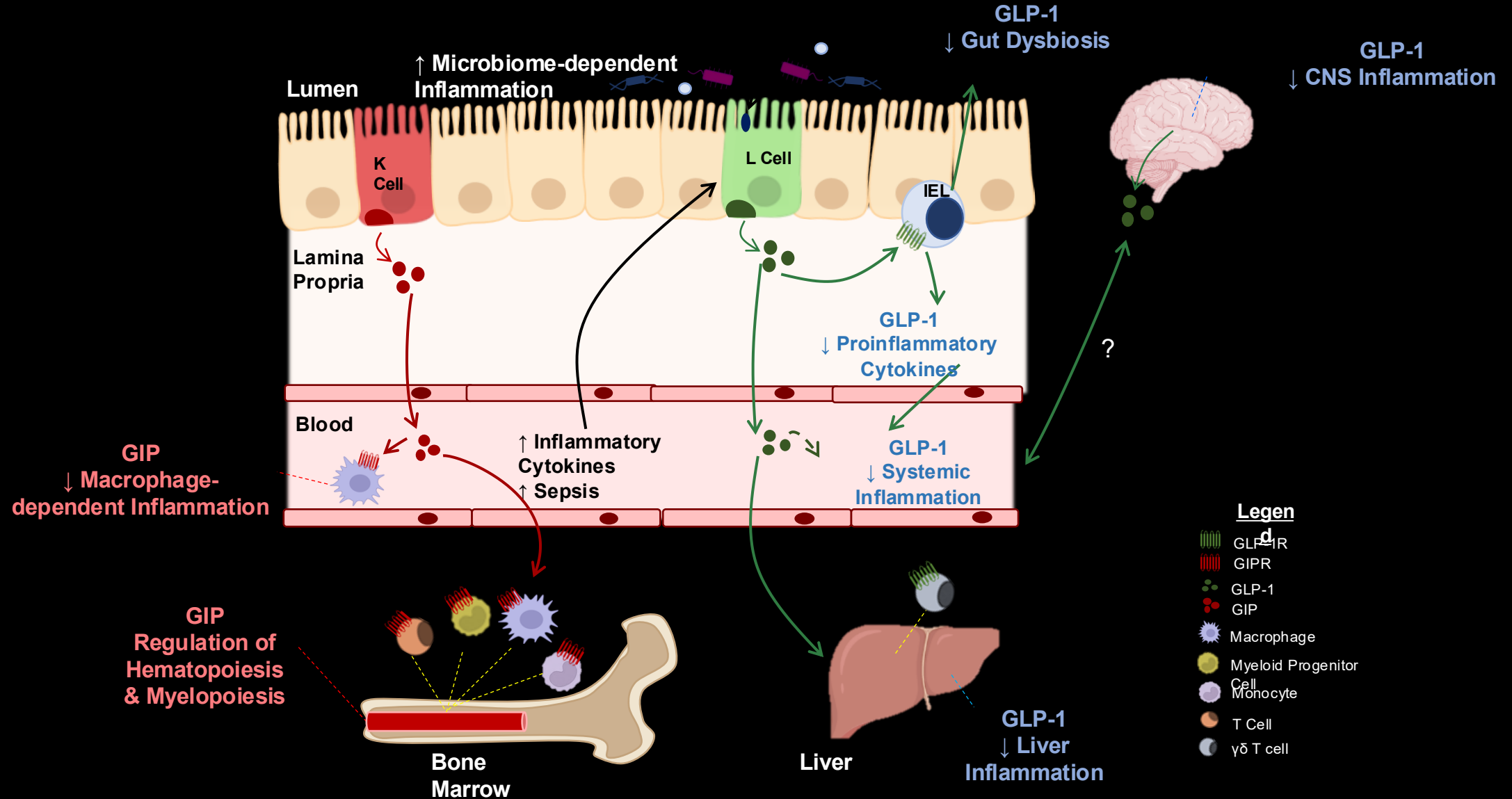
<https://dmsjournal.biomedcentral.com/articles/10.1186/s13098-023-01118-6>

GLP-1RAs were linked to a lower risk of overall respiratory diseases, especially Pulmonary edema and Bronchitis

GIP and GLP-1 act directly in the brain to control appetite and neuroinflammation



How Important are the Actions of GIP vs. GLP-1 on the Hematopoietic and Immune System?



GIPR receptor signaling alleviates gut inflammation in mice

GIPR Agonism



GIPR agonist or GLP-1R/GIPR co-agonist injections

+

Injection of a Cytotoxin (5-FU)



Gut Inflammation

GIPR Loss of Function



Whole Body *Gipr* KO

+

Injection of a Cytotoxin (5-FU)



Gut Inflammation

Bone Marrow *Gipr* deletion



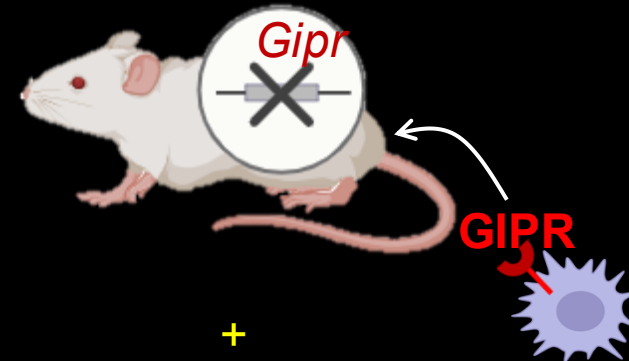
+

Injection of a Cytotoxin (5-FU)



No Effect on Gut Inflammation

GIPR+ BM cells transplanted into a Whole Body *Gipr* KO Mouse



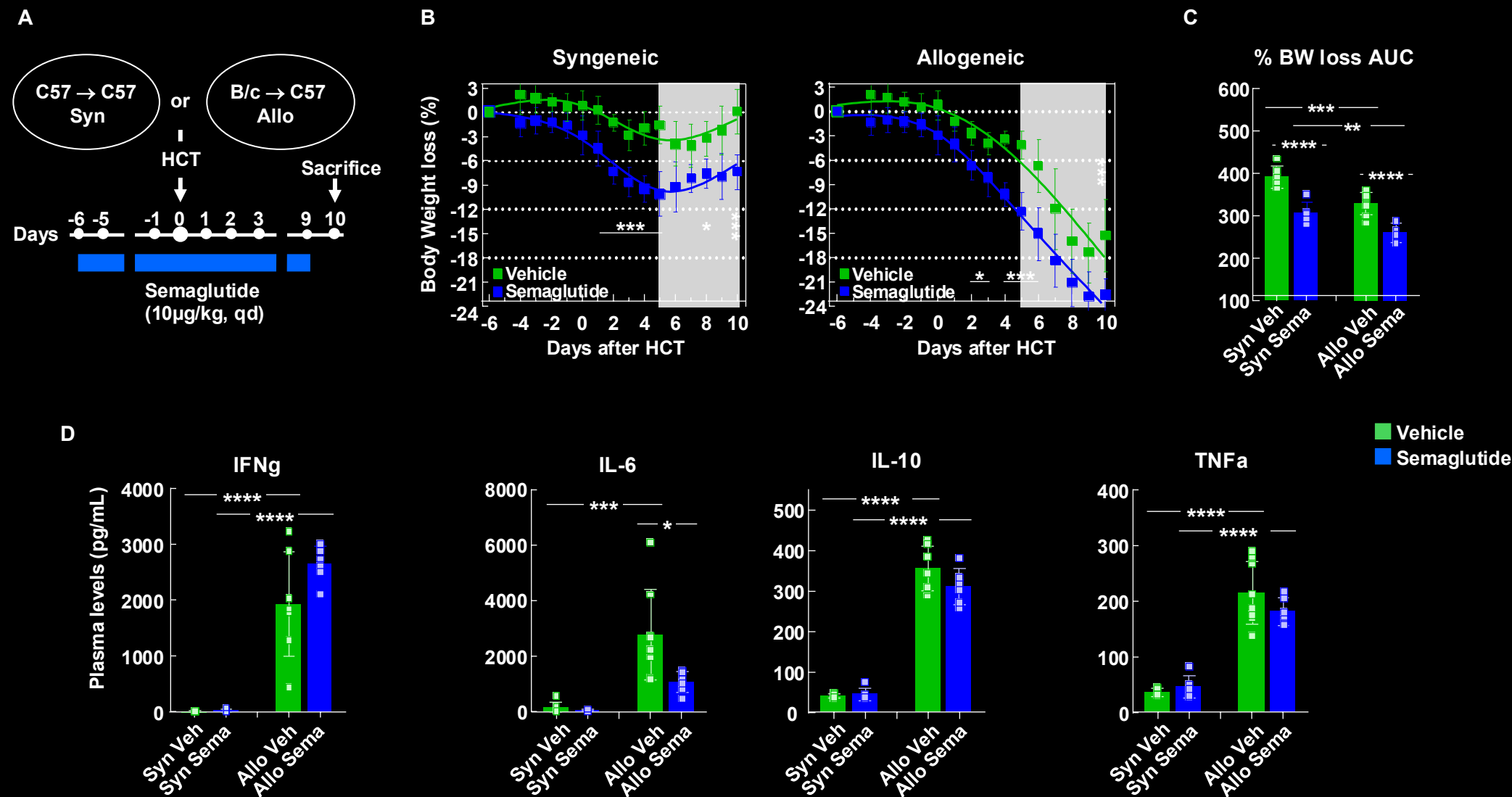
+

Injection of a Cytotoxin (5-FU) BM-derived Cells



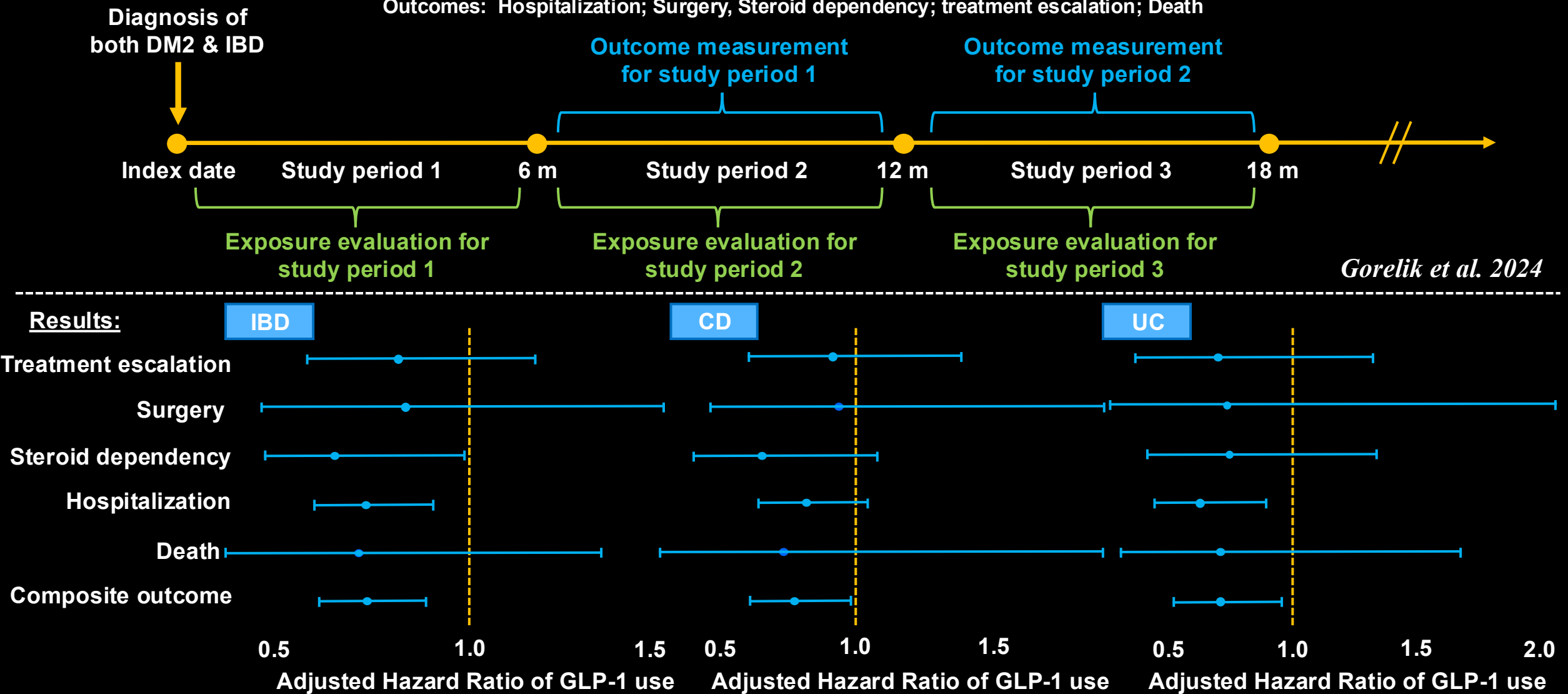
Gut Inflammation

Semaglutide does not modify the severity of intestinal GVHD in mice with allogeneic BMT



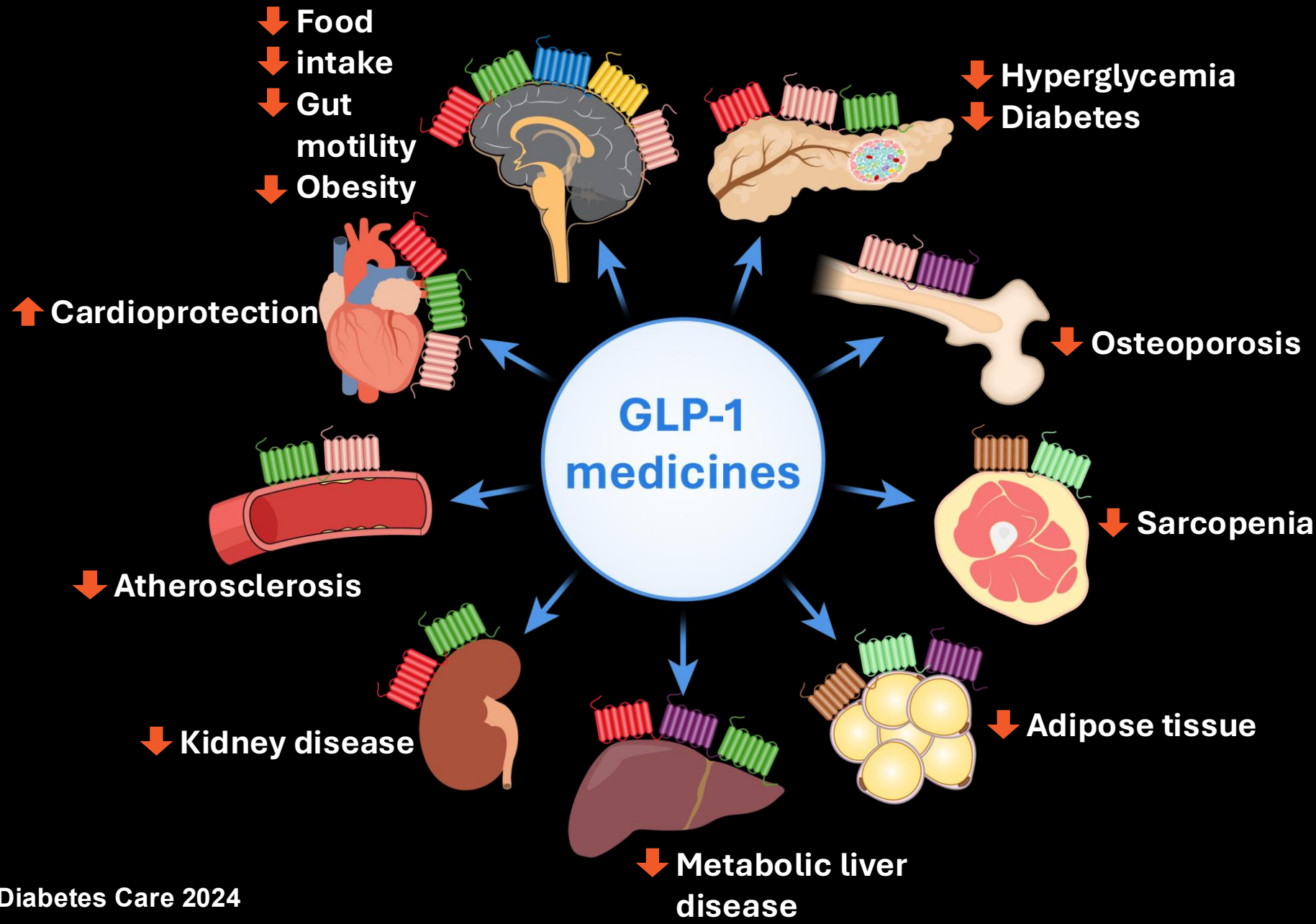
GLP-1 analog use is associated with improved disease course in inflammatory bowel dise

Population: 3,737 IBD and type 2 diabetes mellitus patients in Israel
Follow up: 24,338 patient-years
Exposure: GLP-1 analog use
Covariates: demographics, BMI, IBD features, medications, laboratory data
Outcomes: Hospitalization; Surgery, Steroid dependency; treatment escalation; Death



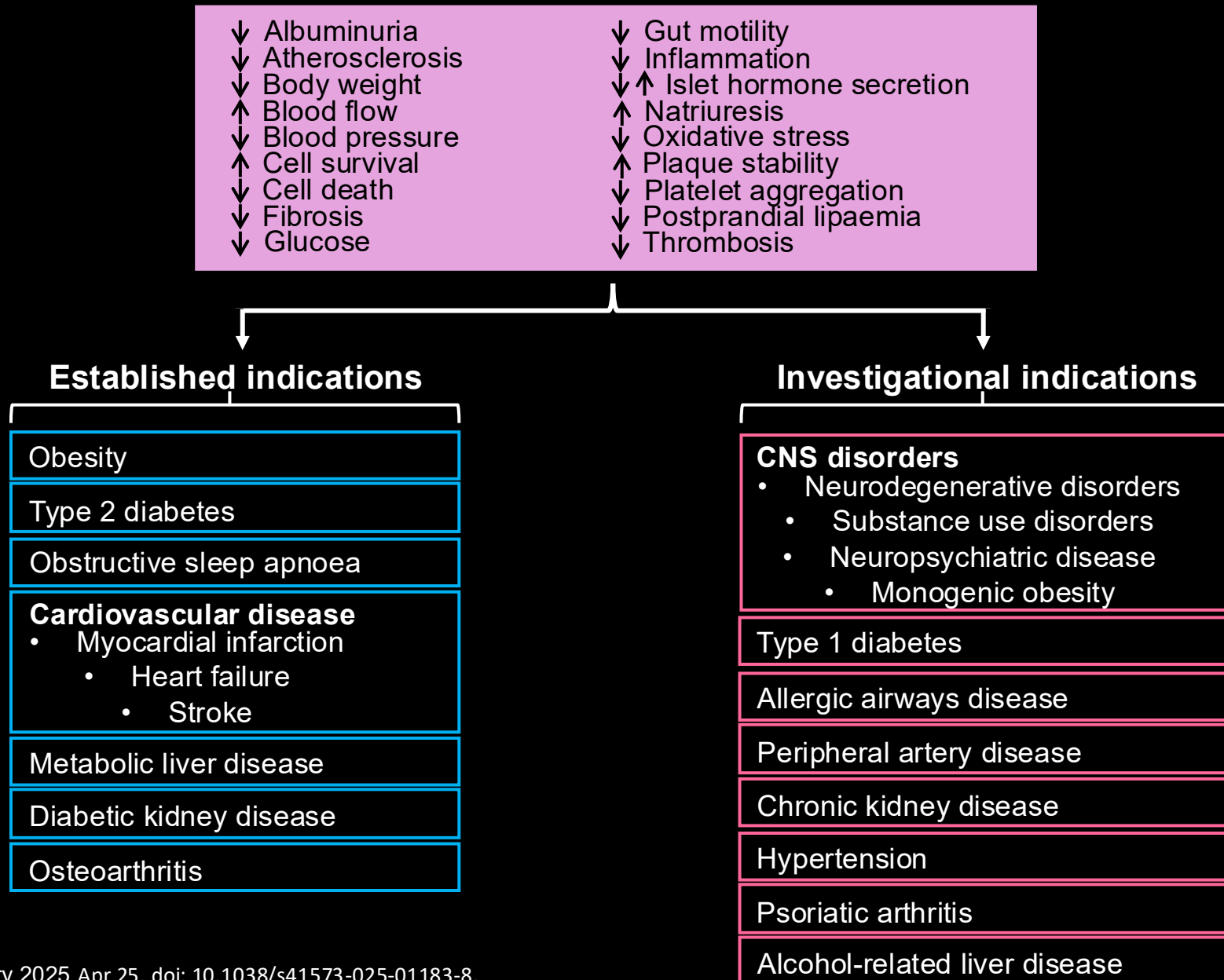
Gorelik et al. 2024

GLP-1 medicines-combinations to enhance efficacy



APLNR	
AMLNR	
GLP2R	
GLP1R	
ACVR2	
NPY2R	
GIPR	
GCGR	

GLP-1 medicines-Actions and Indications



Drucker Lab



Xiemin Cao

Fiona Cui

Susanna Fang

Maria Gonzalez Rellan

Rola Hammoud

Jackie Koehler

Dianne Matthews

Kyle Medak

Wenran Ren

Rui Shang

Bernardo Yusta

CK Wong