UAB
Universitat Autònoma de Barcelona
Bibliographic Review

GENE THERAPY AS A TREATMENT FOR TYPE 2 DIABETES (T2D) AND OBESITY

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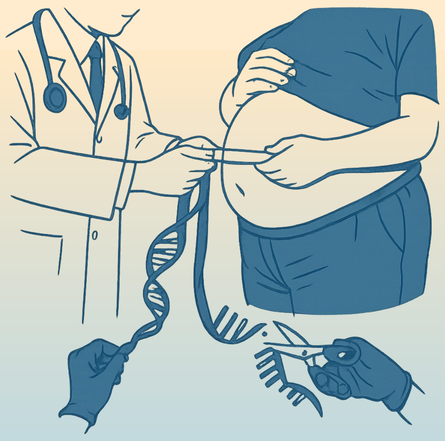
T2D & OBESITY

Type 2 Diabetes and Obesity are closely related metabolic disorders that have risen to epidemic levels causing major health concern. T2D, comprising 95% of diabetes cases, is characterized by *insulin resistance* and persistent *hyperglycemia*. Notably, two-thirds of T2D patients are overweight. Obesity, defined by excessive adipose tissue accumulation due to energy imbalance, triggers chronic inflammation contributing to *insulin resistance* and metabolic dysfunctions.

Given their close connection, clinical studies emphasize the importance of integrated strategies to achieve more effective management of both T2D and Obesity.

WHY GENE THERAPY?



The heritability of these conditions ranges from 45% to 90%, with over 75 loci linked to T2D, highlighting a strong genetic foundation.

Gene Therapy, aims to cure the disease by modifying the patient's genes. Through *Inactivation*, *Replacement* or *Mutation-editing*, it targets the underlying genetic causes, unlike conventional treatments that focus on symptom management.

Therefore, it offers the potential for long-lasting, effective interventions, making it a potentially transformative strategy for treating T2D and Obesity.

OBJECTIVES

- Understand the Genetic and Pathophysiological bases of Type 2 Diabetes (T2D) and Obesity.
- Evaluate the principles of Gene Therapy and their relevance in treating T2D and Obesity.
- Identify the most promising Gene Therapy strategies and their clinical potential for managing both conditions.
- Determine the limitations and challenges of Gene Therapy in addressing these conditions.

METHODOLOGY

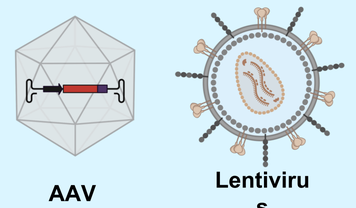
Bibliographic research using *PubMed*, *Europe PMC* and *Google Scholar* to identify recent reviews (<5y) regarding the use of Gene therapy to treat T2D and Obesity.

The most promising approaches from there, were analyzed more in-depth.

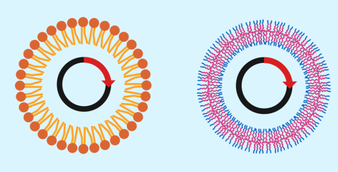
"Gene therapy" ***"Gene editing"*** ***"Type 2 Diabetes"*** ***"CRISPR"*** ***"Obesity"***

Delivery Strategies

Viral



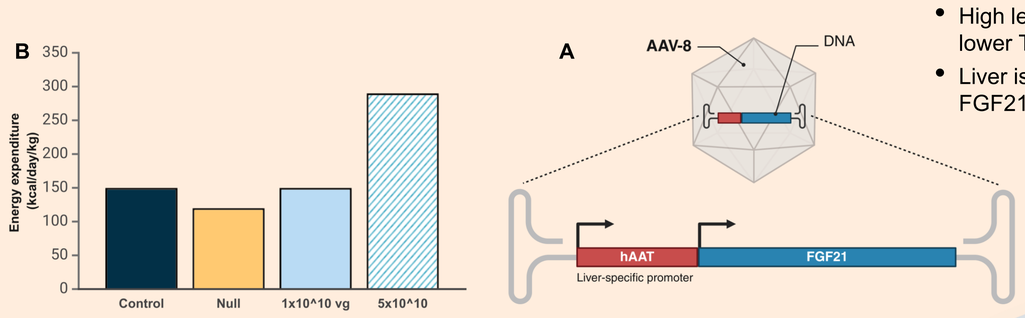
NanoParticles



FGF21

[*AAV8-hAAT-FGF21*]

- Peptide hormone regulating energy balance
- High levels are associated with lower T2D risk
- Liver is the main producer of FGF21



Marked reductions for >1year in:

- Body Weight
- Adipose tissue hypertrophy
- Inflammation
- Hepatic steatosis, inflammation and fibrosis
- Insulin resistance

Fig. 1. FGF21 gene therapy. (A) *Composition of AAV vector.* ***(B)*** *Energy expenditure of mice 2 months after injection.* ***(C)*** *Glucose levels in mice 10w after injection* [1].

GLP-1

Mechanisms of action of Glucagon Like Peptide-1

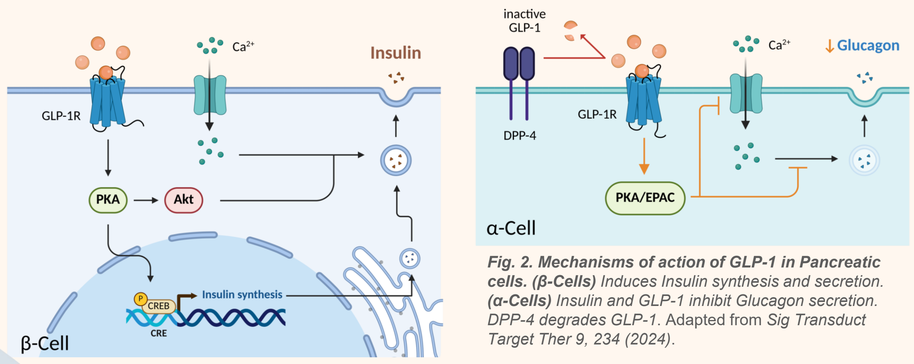
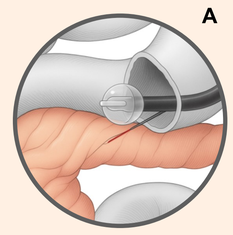


Fig. 2. Mechanisms of action of GLP-1 in Pancreatic cells. (β-Cells) *Induces Insulin synthesis and secretion.* ***(α-Cells)*** *Insulin and GLP-1 inhibit Glucagon secretion. DPP-4 degrades GLP-1.* Adapted from *Sig Transduct Target Ther 9, 234 (2024).*

[*AAV-INS-GLP1*] - Rejuva

- Directly administered to Pancreas via endoscopic delivery
- Specific Insulin Promoter (INS) to target β-Cells
- Nutrient-responsive GLP-1 signaling
- Single-dose Outperformed *Semaglutide* (Ozempic®)



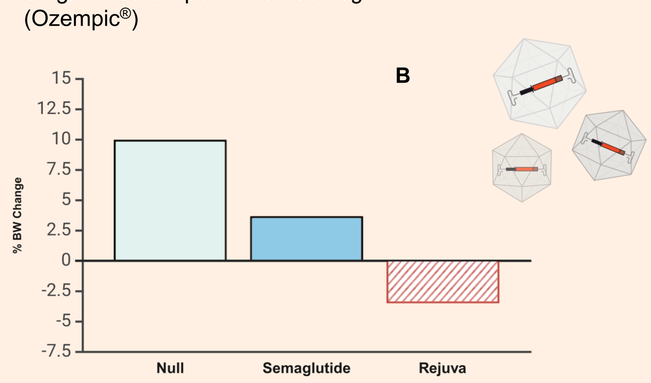
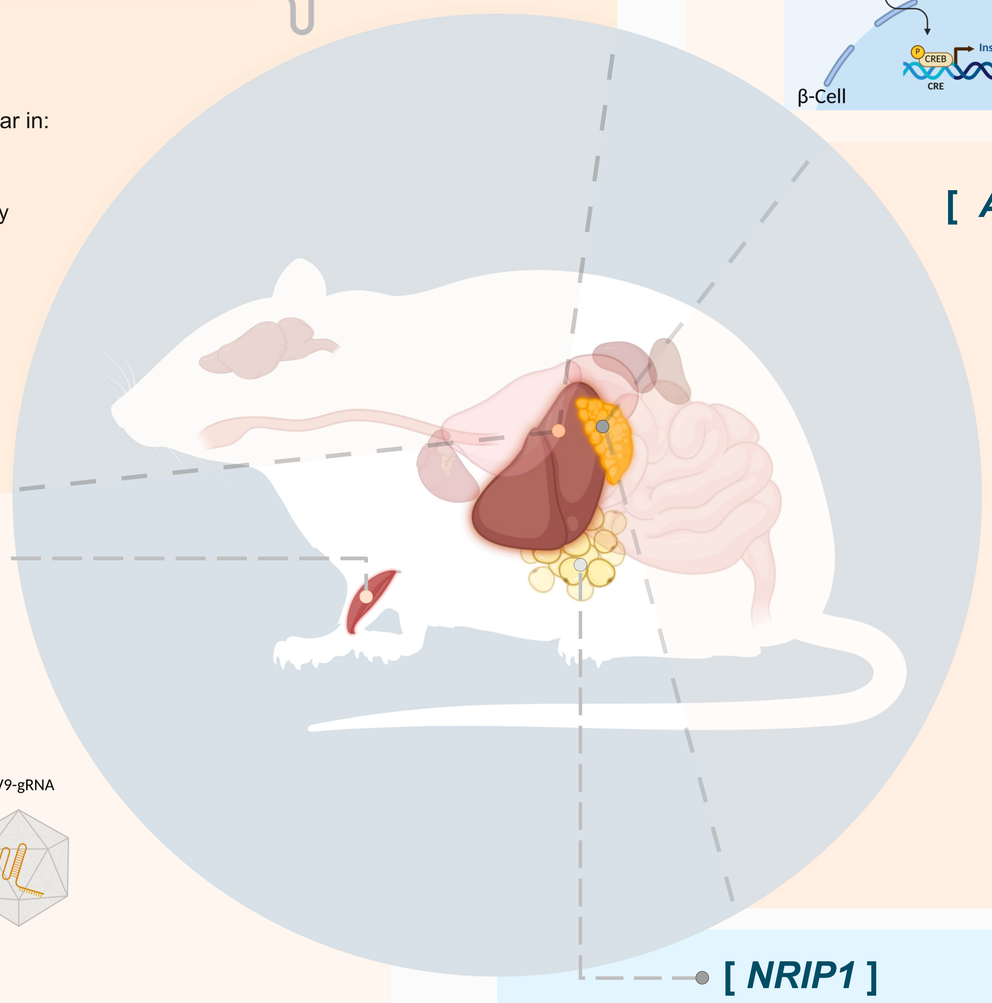


Fig. 3. Fractyl Health Rejuva therapy. (A) *Endoscopic delivery system.* ***(B)*** *percentage of Body Weight change from baseline* [2].



[*CRISPRa*]

- Reduced obesity, lowering body weight and fat mass
- Enhanced Browning and Thermogenesis
- Improved Glucose tolerance and Insulin sensitivity
- Avoidance of DNA editing

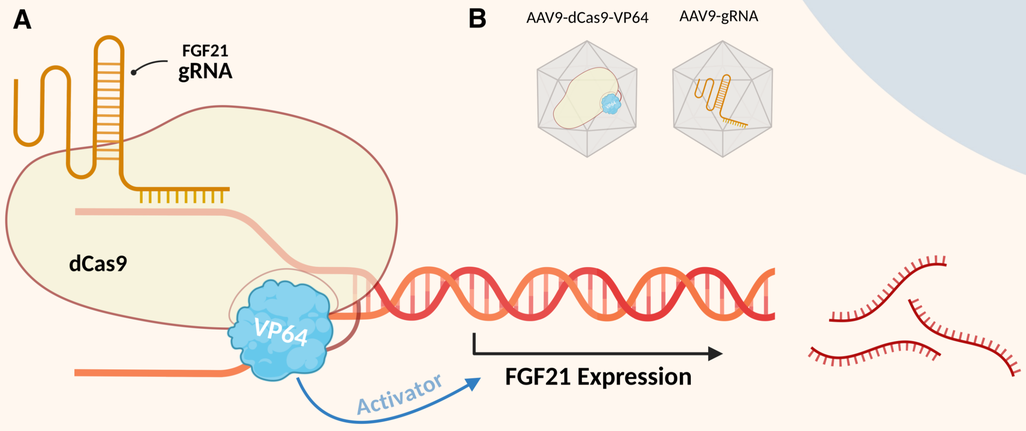


Fig. 5. CRISPRa system employed by Zhang et al (2023). (A) *dead Cas9 gets to the target DNA, directed by FGF21 gRNA. VP64 upregulates FGF21 expression.* ***(B)*** *Two separate AAV9 were used: one to deliver dCas9-VP64 and another for the gRNA* [4].

[*NRIP1*]

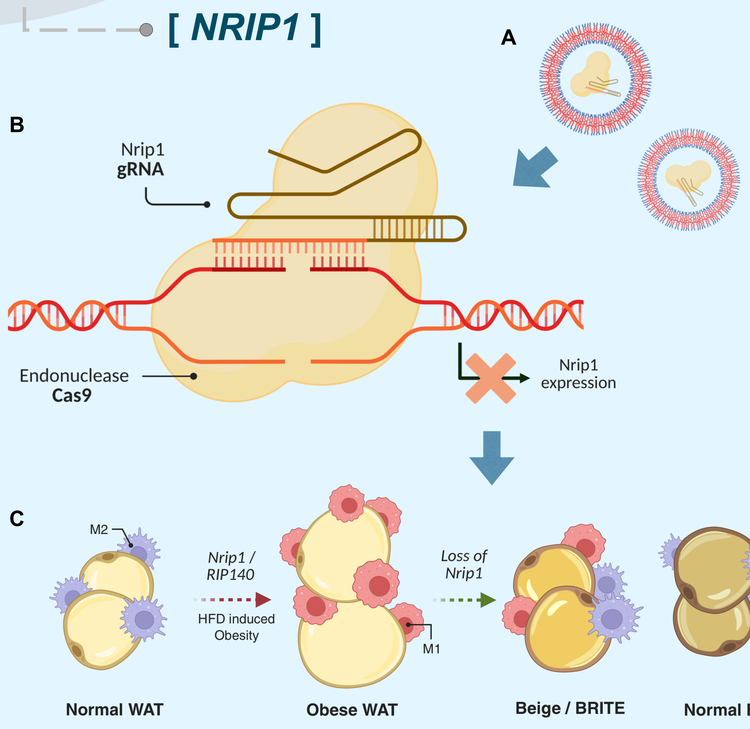


Fig. 4. CRISPR system for Nrip1 KO. (A) *Polymeric Nanoparticles deliver Cas9-gRNA.* ***(B)*** *gRNA directs Cas9 to cut Nrip1 DNA and disrupt its expression* ***(C)*** *Nrip1 and High-Fat Diets promote white fat expansion and inflammation (M1 macrophages), and Nrip1 loss triggers browning into beige fat, enhancing thermogenesis and reducing inflammation (M2 macrophages)* [3].

CRISPR/Cas9

- Gene-editing system to precisely modify DNA

Allows:

- Genetic screening
- Disease modeling in animals
- Study diabetes mechanisms

Ex vivo
Adipose Cells targeting

CONCLUSIONS

- Gene therapy targets core mechanisms of T2D and Obesity, such as glucose regulation, inflammation and metabolism, showing strong preclinical efficacy
- CRISPR/Cas9 enables personalized therapies based on the individual's genetic profile
- Viral vectors offer long-term expression but face immunity and delivery challenges; non-viral methods are safer but less durable.
- Translating results to humans requires long-term safety testing in larger animals and non-human primates
- Gene therapy may improve treatment adherence and outcomes versus standard drugs, but cost and access remain major hurdles.
- Future research must focus on delivery optimization, safety, and scalable solutions to bring gene therapy from lab to clinic.

References

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[2] Rajagopalan H, Fitzpatrick AL, Wang S, Reese R, Picard N, Cozzi E, et al. Single-Dose GLP-1-Based Pancreatic Gene Therapy Durably Maintains Body Composition and Glycemia after Semaglutide Withdrawal in a Murine Model of Obesity. 2024. Presented at *EASD 60th annual meeting.*

[3] Tsagkaraki E, Nicoloro SM, DeSouza T, Solivan-Rivera J, Desai A, Lifshitz LM, et al. CRISPR-enhanced human adipocyte browning as cell therapy for metabolic disease. Nat Commun 2021;12. https://doi.org/10.1038/s41467-021-27190-y

[4] Zhu H, Liu D, Sui M, Zhou M, Wang B, Qi Q, et al. CRISPRa-based activation of Fgf21 and Fndc5 ameliorates obesity by promoting adipocytes browning . Clin Transl Med 2023;13. https://doi.org/10.1002/ctm2.1326