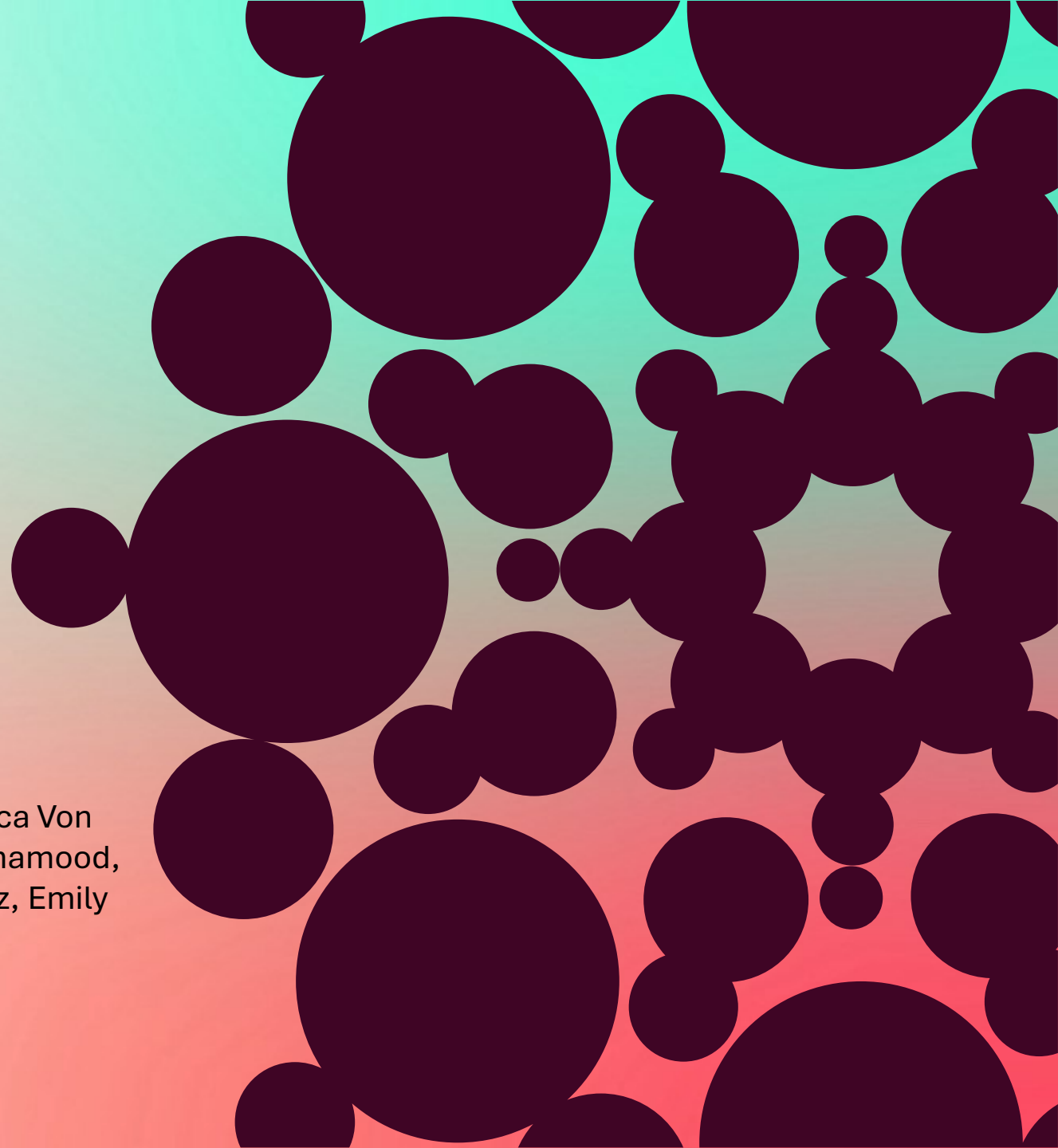




Pancreas-Targeted GLP-1 Gene Therapy Enhances β -Cell Function and Reduces Cellular Stress in Preclinical Type 2 Diabetes Models

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June 6th, 2026



Presenter Disclosure

- Joan Sabadell-Basallote, PhD

Type of Support — Categories

- Employee: Fractyl Health, Inc.
- Stock/Shareholder: Fractyl Health, Inc.
- Research Support: Fractyl Health, Inc. (sponsor of the work presented)

Co-authors: All co-authors are current or former employees / stockholders of Fractyl Health, Inc.

Investigational use disclosure:

RJVA-001 is an investigational preclinical asset which has received Clinical Trial Authorization in the Netherlands.

RJVA-001 is currently under review for clinical research in additional countries in the EU and AUS. RJVA-001 and the Rejuva Device have not been assessed by the FDA.



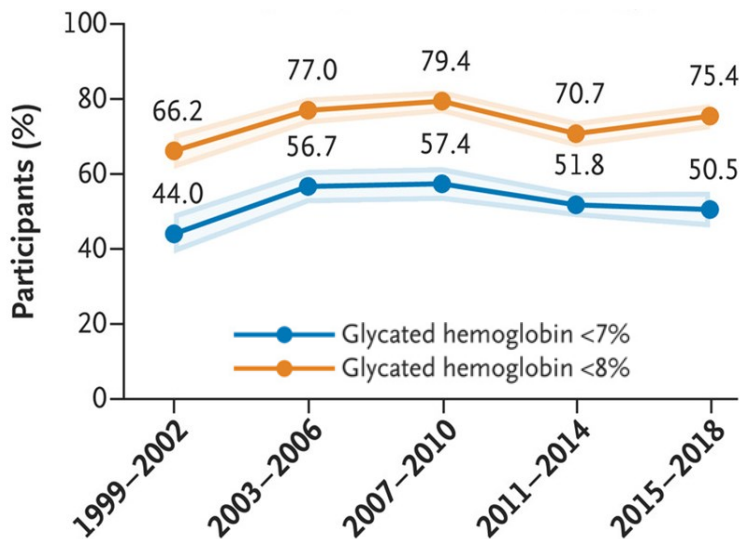
2026
**SCIENTIFIC
SESSIONS**

T2D is a Chronic, Progressive Disease Driven By Beta Cell Failure

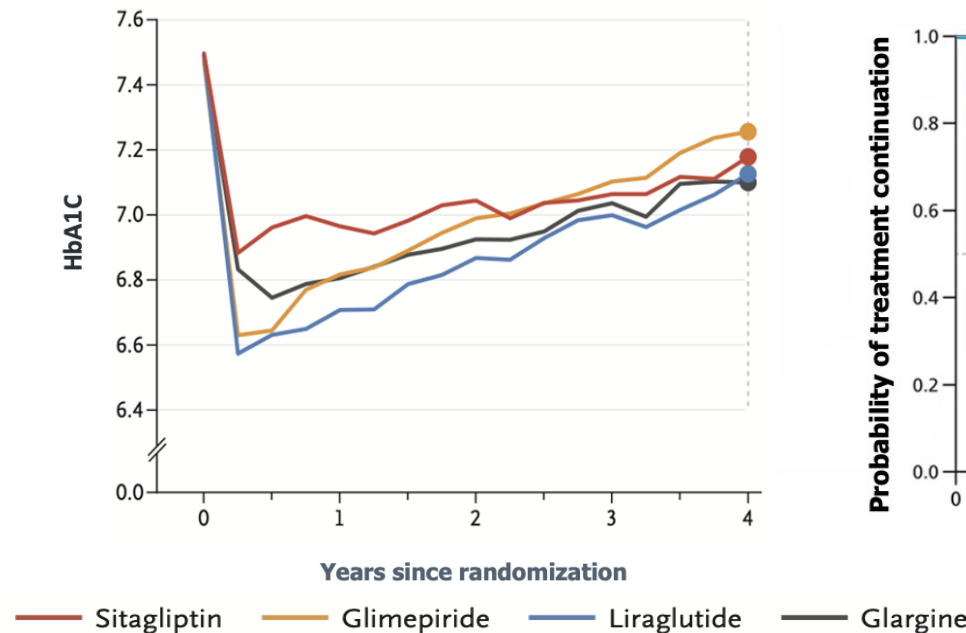
Despite treatment advancements, a clear unmet need remains

- Type 2 diabetes (T2D) and associated co-morbidities affect >30M Americans^{1,2,3}
- Insulin resistance and beta cell dysfunction lead to progressive metabolic failure⁴

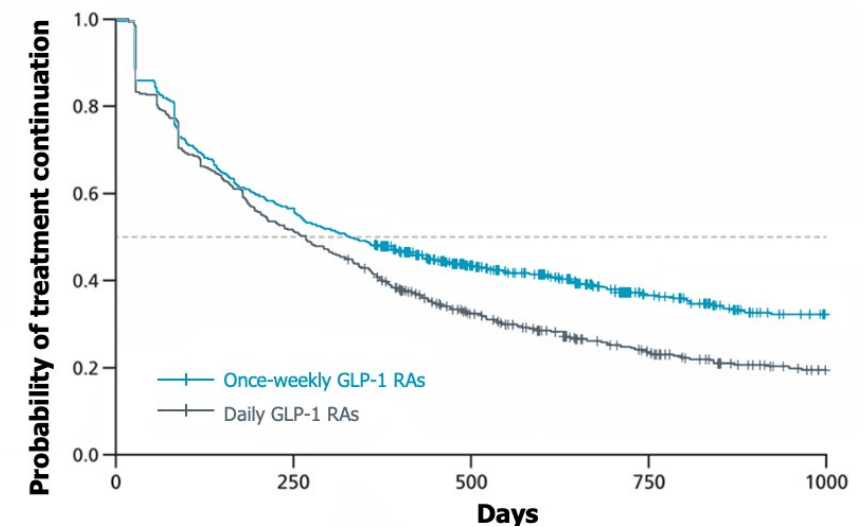
Only 50% of Americans with diabetes achieve recommended glucose target of <7% HbA1c⁵



Maintenance of lowered HbA1c with glucose-lowering agents is challenging⁶



Low persistence and adherence to GLP-1RAs, with majority discontinuing within a year⁷



A durable, tolerable, **one-time intervention** addressing **root-cause metabolic dysfunction** is urgently needed

Rejuva: A "Smart GLP-1™" AAV Gene Therapy Platform for T2D

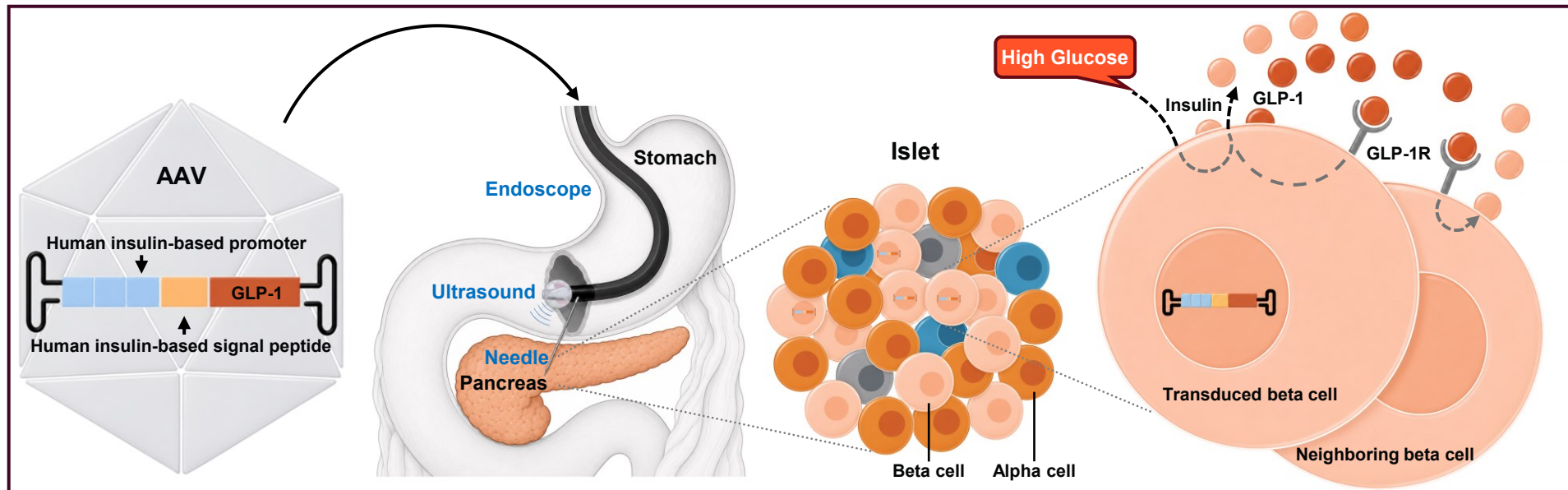
Single treatment → nutrient-responsive, adaptive, and durable effect

Novel ROA

Targeted administration via purpose-built endoscopic ultrasound-guided device

Novel MOA

GLP-1 under insulin-based regulatory and secretory control for beta cell-derived, adaptive expression

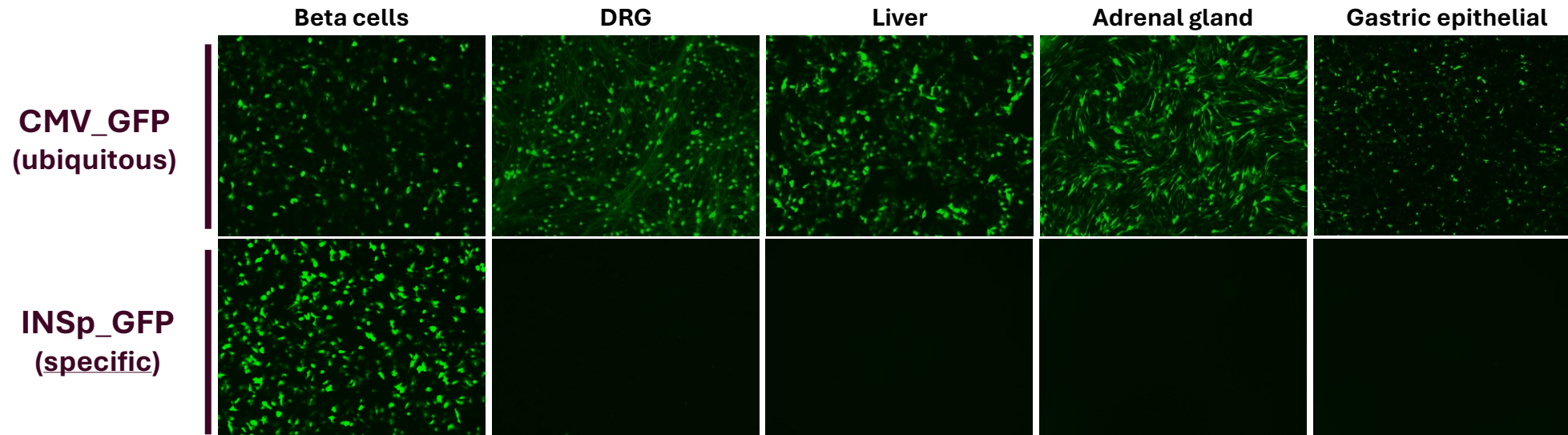


- Targeted AAV delivery
- Low dose
- Restricted biodistribution

- Beta cell-derived expression
- Autocrine, paracrine benefit
- Access to portal circulation

Human Insulin-based Promoter (INSp) Drives Expression in Beta Cells

In Vitro: Transduced Human Cell Lines



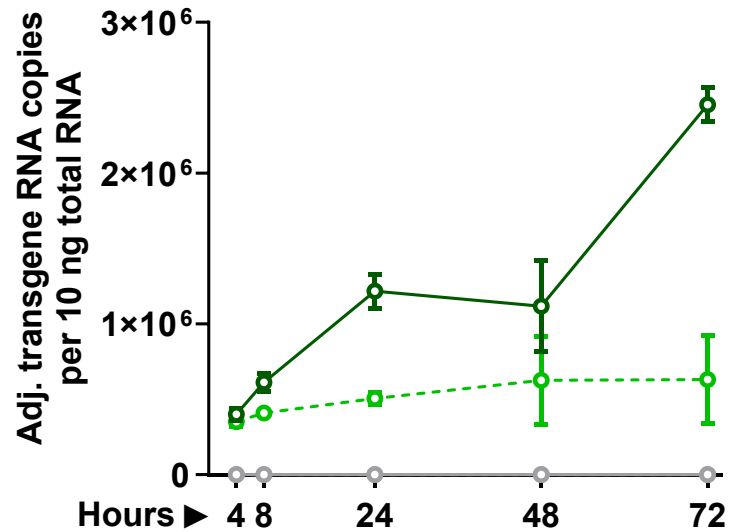
- Cells transduced with a GFP reporter surrogate under the engineered human insulin promoter (**INSp**)
- INSp drives expression in **human beta cells** but not in off-target cells when studied *in vitro*

INSp Drives Nutrient-Responsive Transgene Expression

Chronic high glucose leads to increased transgene expression

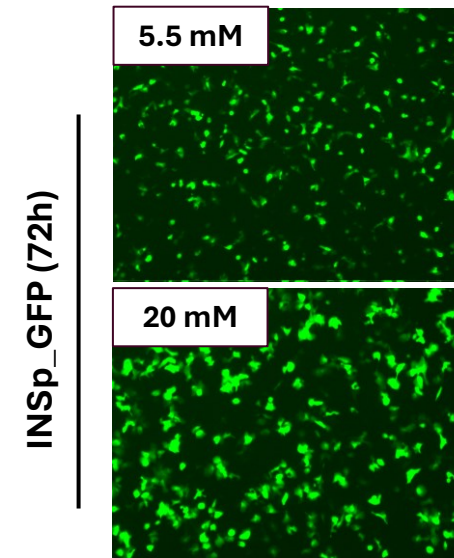
 ***In Vitro***: Transduced Human Beta Cells

Transgene RNA Expression



○ 5.5 mM Gluc.] Untransduced ○ 5.5 mM Gluc.] INSp_GFP
○ 20 mM Gluc.] ○ 20 mM Gluc.]

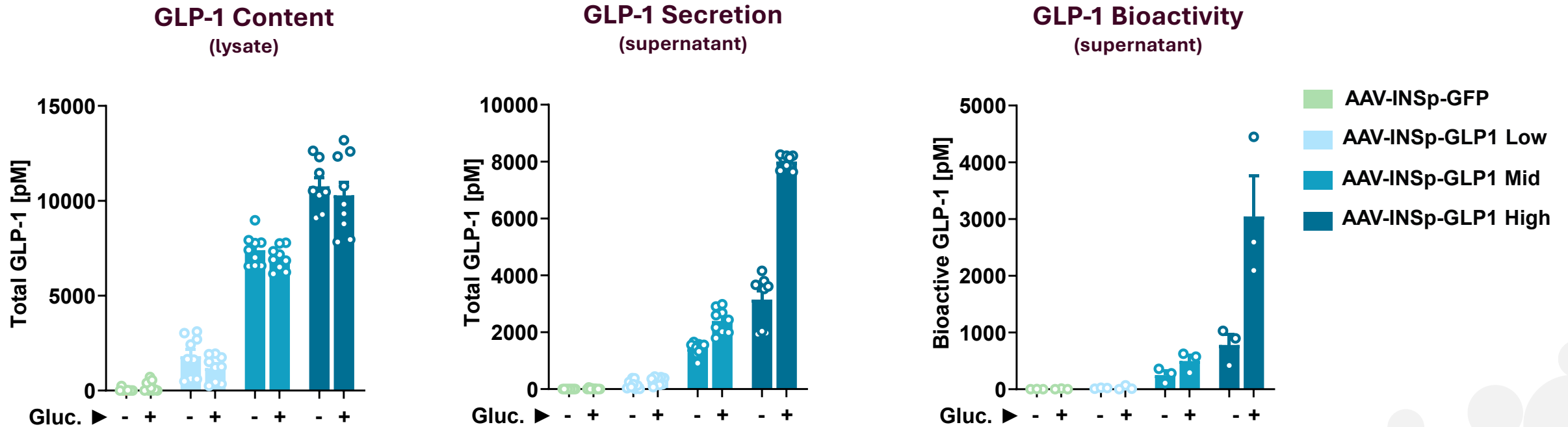
Transgene Protein (GFP)



AAV-INSp-GLP1 Drives Nutrient-Responsive Secretion of Bioactive GLP-1

With dose-responsive expression observed

In Vitro: Transduced Human Beta Cells

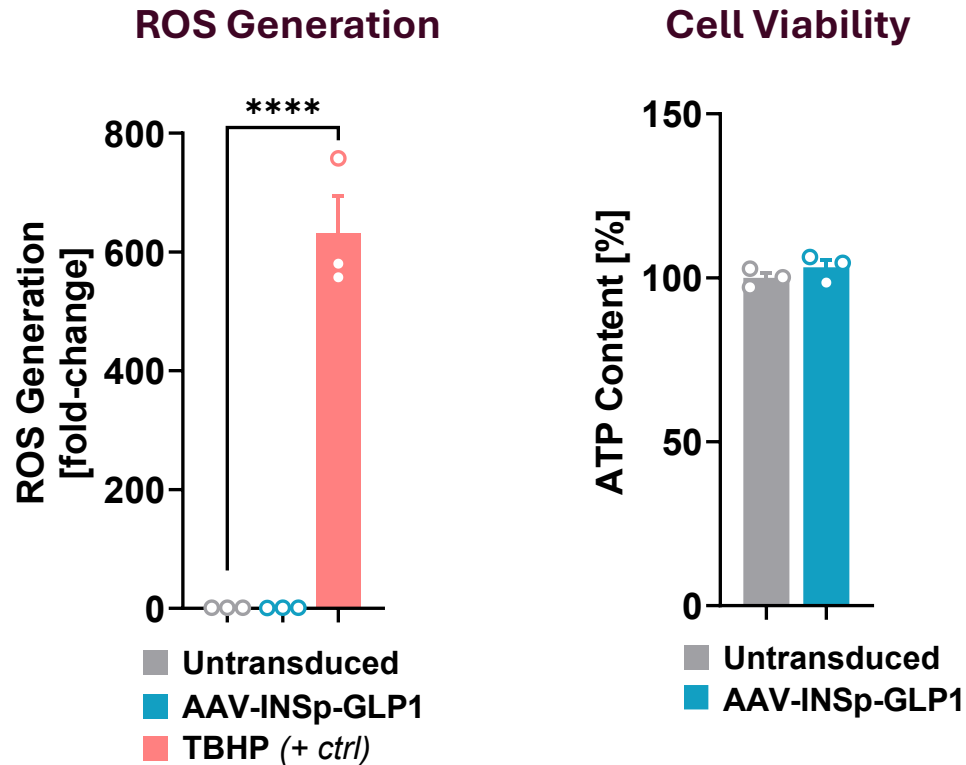


AAV-INSp-GLP1 Preserves and Protects Human Beta Cell Health

Consistent with GLP-1's known beta cell cytoprotective biology

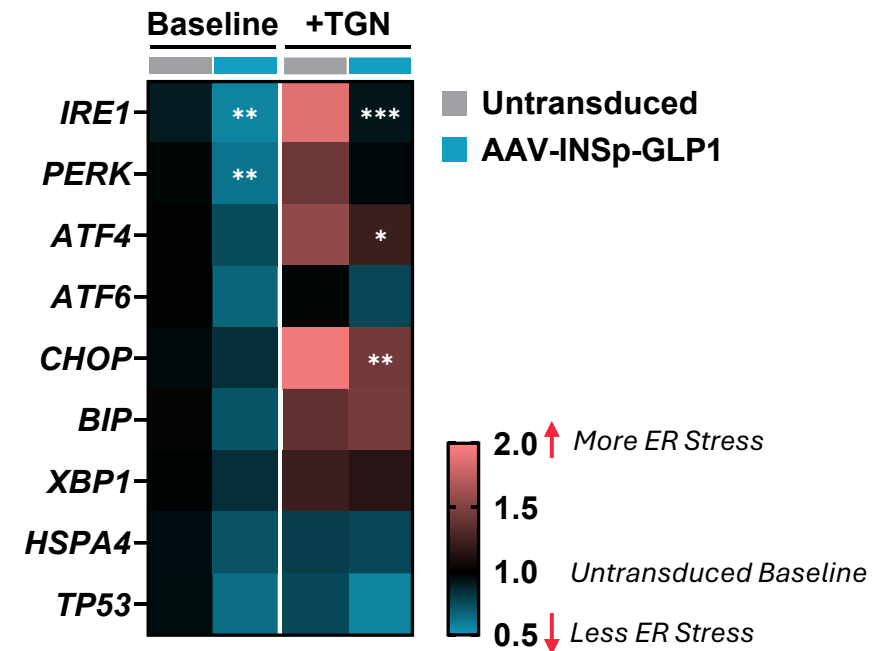
In Vitro: Transduced Human Beta Cells

No ROS Generation or Reduction in Cell Viability



Reduced Baseline AND TGN-induced ER Stress

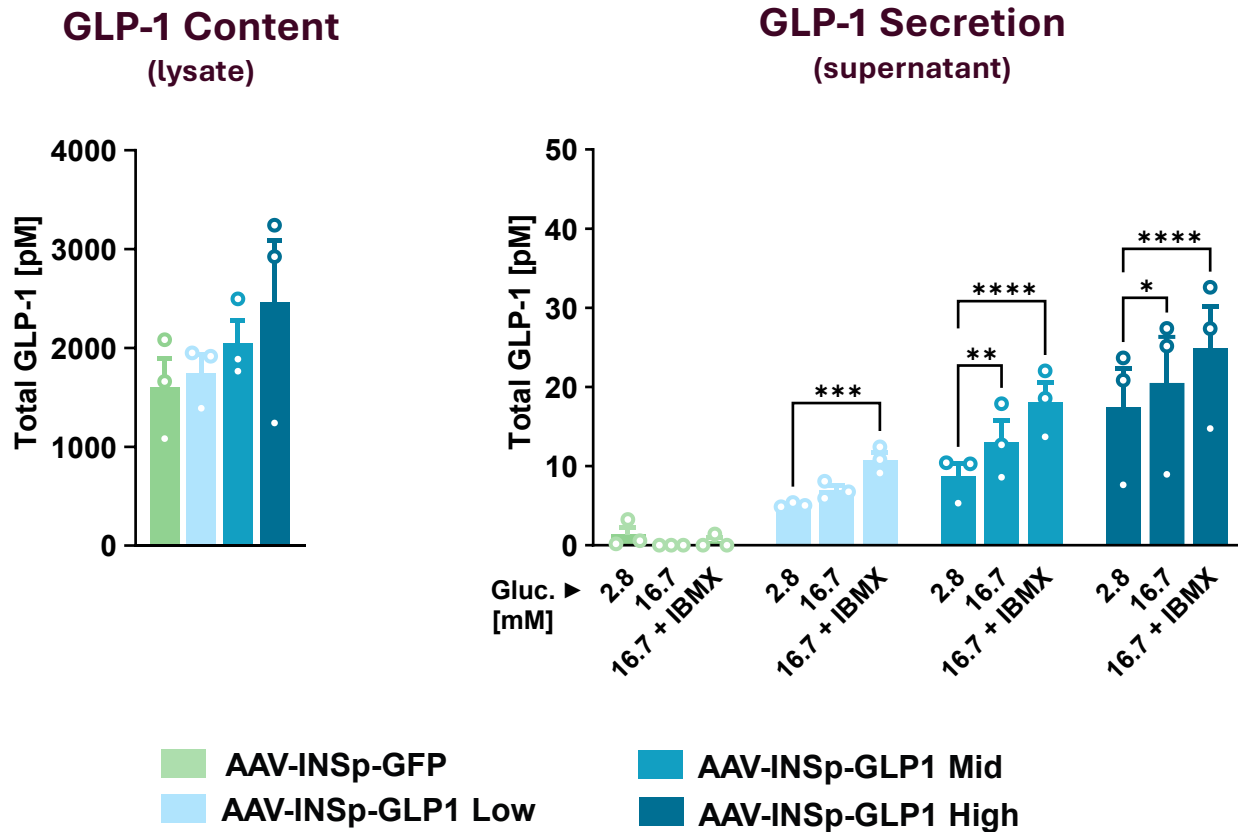
RNA Expression of ER Stress Markers



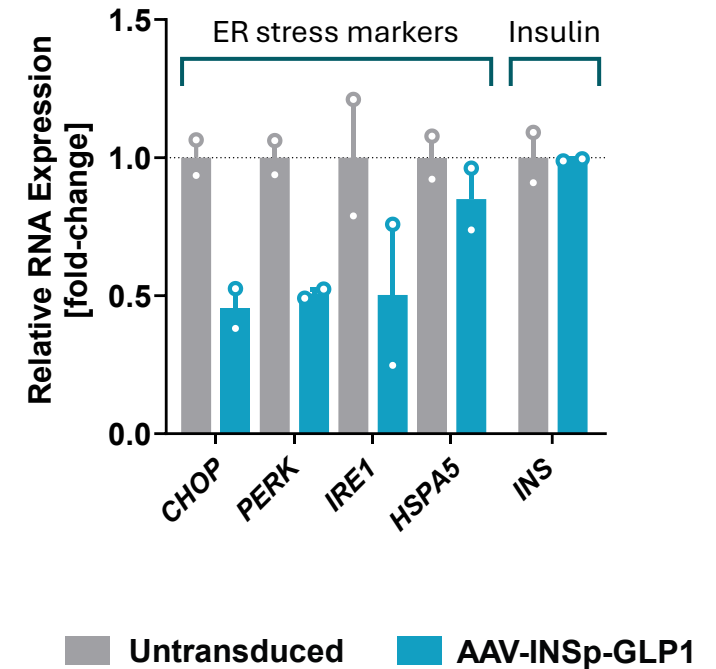
Primary Human Islets Confirm: Enhanced GLP-1 Secretion and Preserved Beta cell Health



Ex Vivo: Transduced Human Primary Islets



Reduced ER Stress Gene Expression



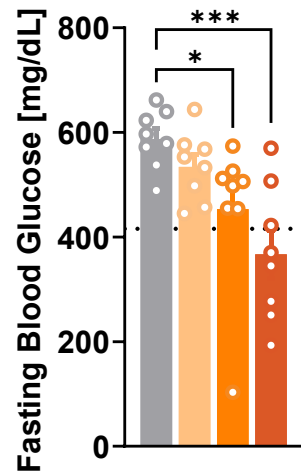
AAV-INSp-GLP1 Improves Metabolic Control in db/db Mice

Dose-responsive improvement in blood glucose, plasma insulin, and body weight

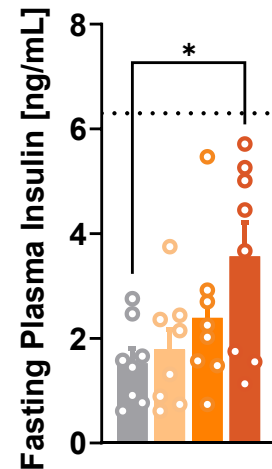


In Vivo: Treated 8-week-old BKS db/db mice, 46 days post single IP AAV injection

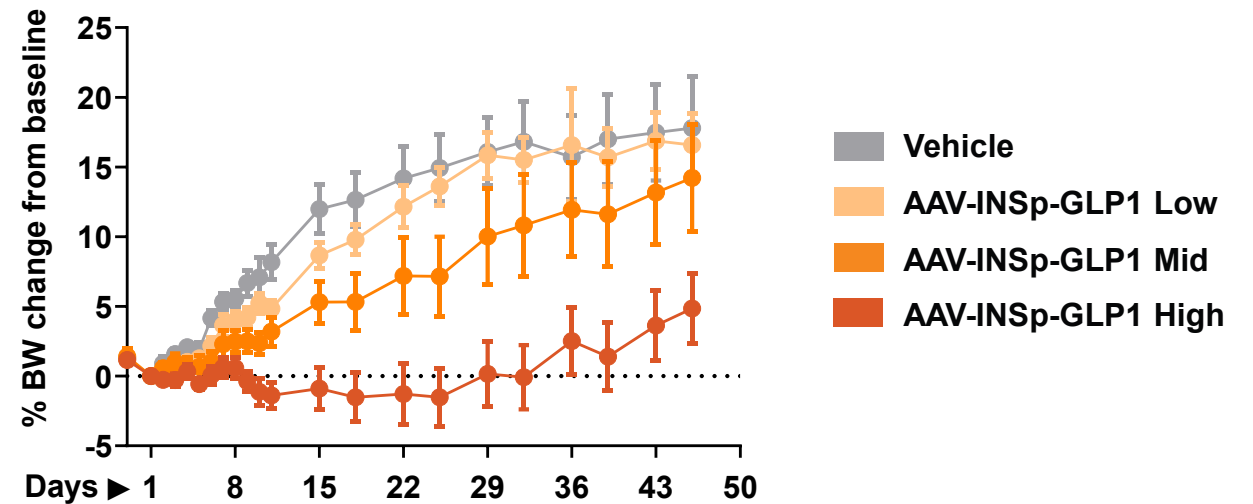
Fasting Blood Glucose



Fasting Plasma Insulin

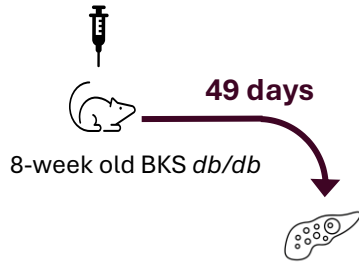


Body Weight

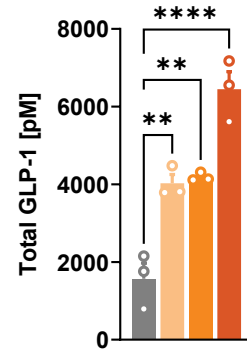


- **Return to normal pancreatic islet architecture** - Histopathological assessment showed decreased incidence and severity of pancreas islet cell hyperplasia in AAV-INSp-GLP1 High dose animals

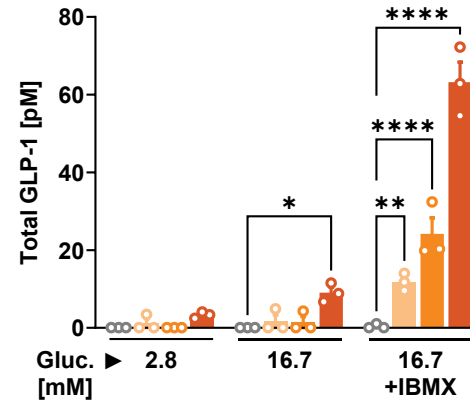
Isolated Islets From Treated *db/db* Mice Confirm: Enhanced GLP-1 and Insulin Content and Co-secretion



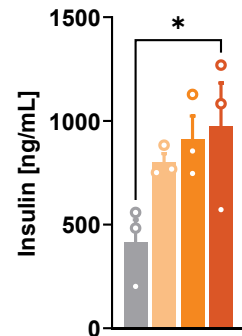
GLP-1 Content



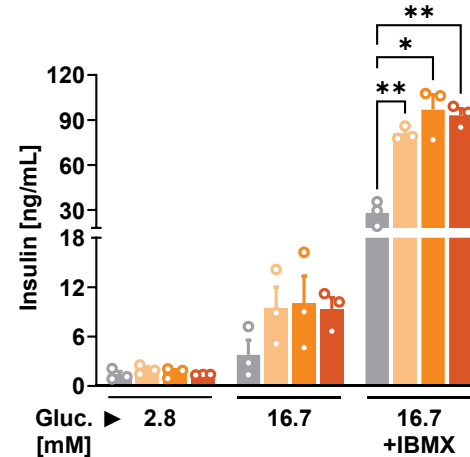
GLP-1 Secretion



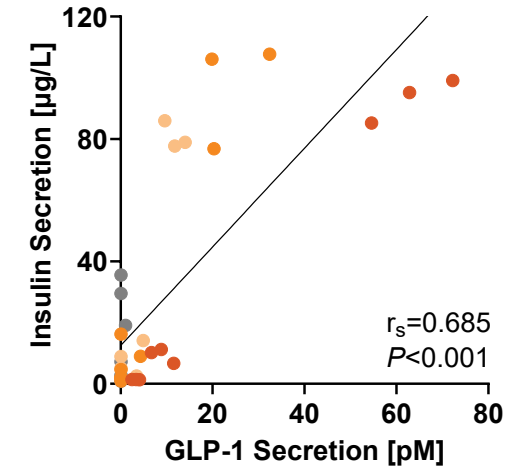
Insulin Content



Insulin Secretion



Strong positive correlation between GLP-1 and insulin secretion



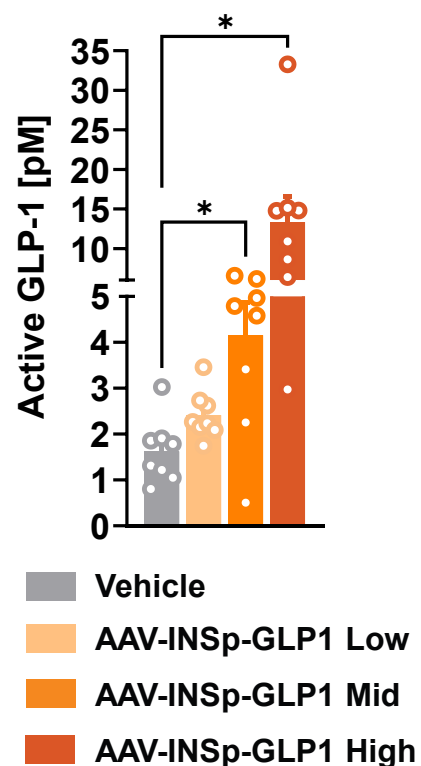
AAV-INSp-GLP1 “Smart GLP-1” Mimics Endogenous Physiology

Potent efficacy with near physiologic circulating levels



BKS *db/db* mice

Circulating GLP-1



Comparison Chart Active GLP-1 Levels¹

Modality	Levels	Tolerability
Physiological	< 5 pM	✓
DPP4 Inhibition	~ 10 pM	✓
AAV-INSp-GLP1 ²	10-20 pM	Expected
Roux-en-Y Gastric Bypass	~ 20 pM	✓
GLP-1RA Drugs	50-150 pM	✗

- “Smart” GLP-1 levels are **significantly lower than pharmacologic GLP-1RA** drug levels
- Therefore, **less likely to cause tolerability issues** commonly seen with GLP-1 drugs

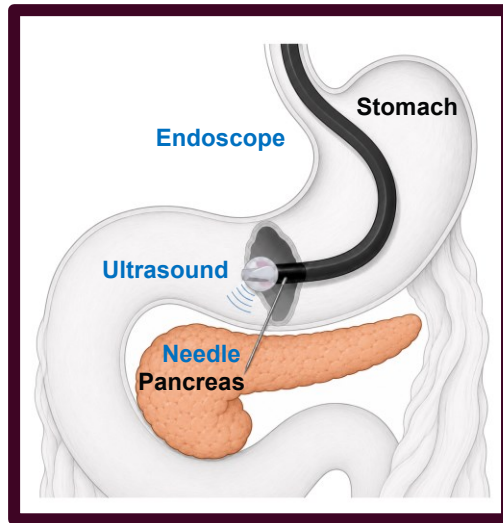
Purpose-built Rejuva Device For Targeted Pancreatic AAV Delivery

Large-animal safety model – Yucatan pig

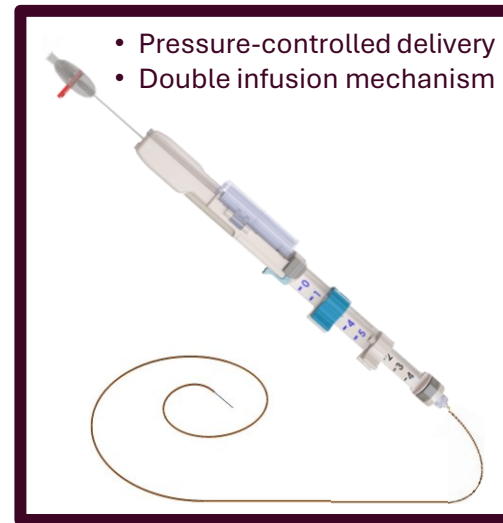


- **Rejuva** catheter introduced directly to pancreas parenchyma via **standard EUS techniques**
- Upper endoscopic procedure conducted in **~ 20 minutes**

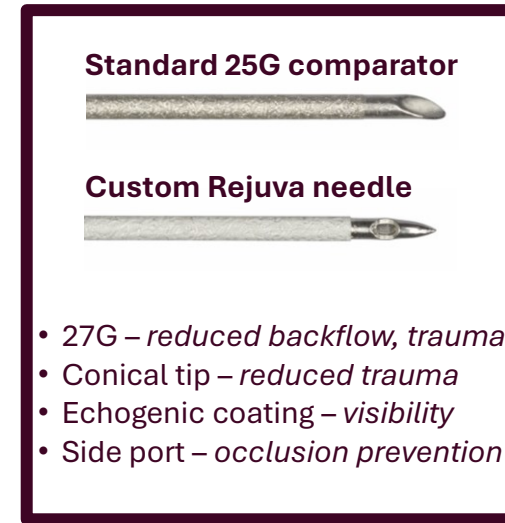
Novel ROA for AAV Delivery



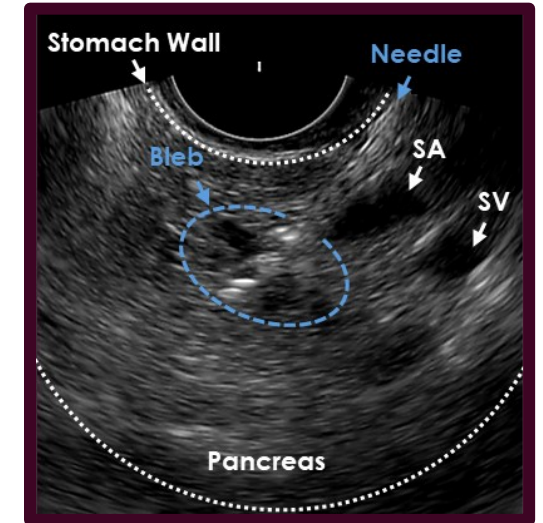
Rejuva Device



Rejuva Needle



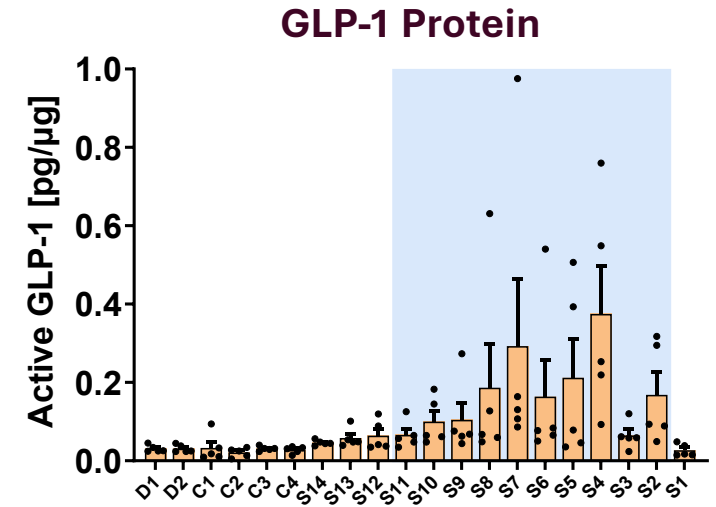
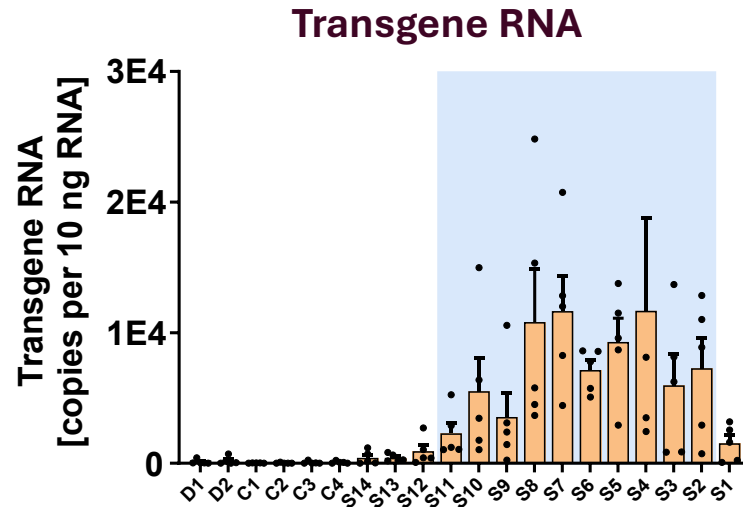
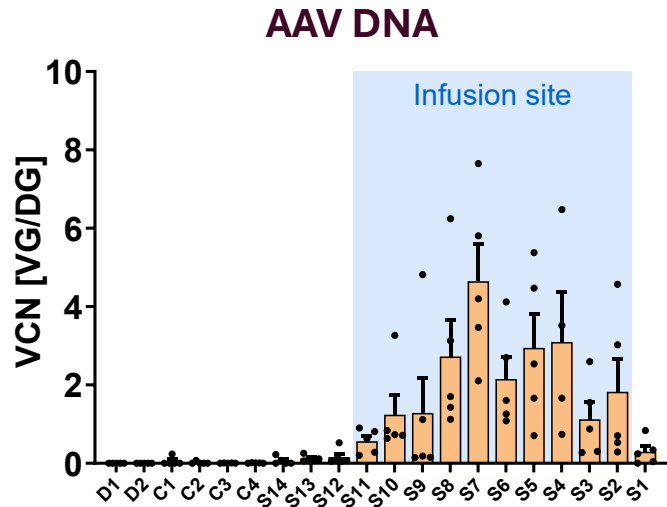
Live Ultrasound



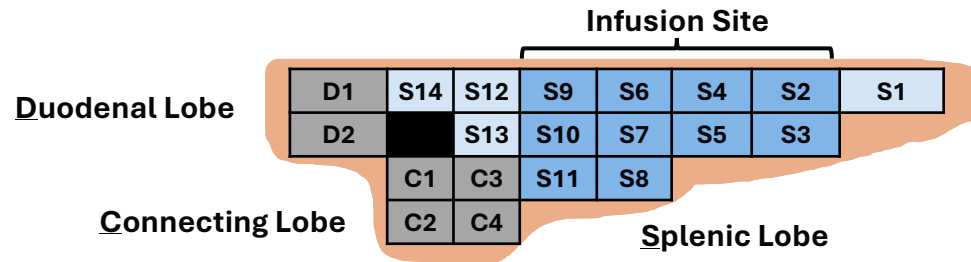
Effective and Precise Delivery to Pancreas in Yucatan Pigs

AAV DNA, transgene RNA, and active GLP-1 protein all enriched at the targeted infusion site

In Vivo: Treated Yucatan Pigs



Pancreas Biopsy Key



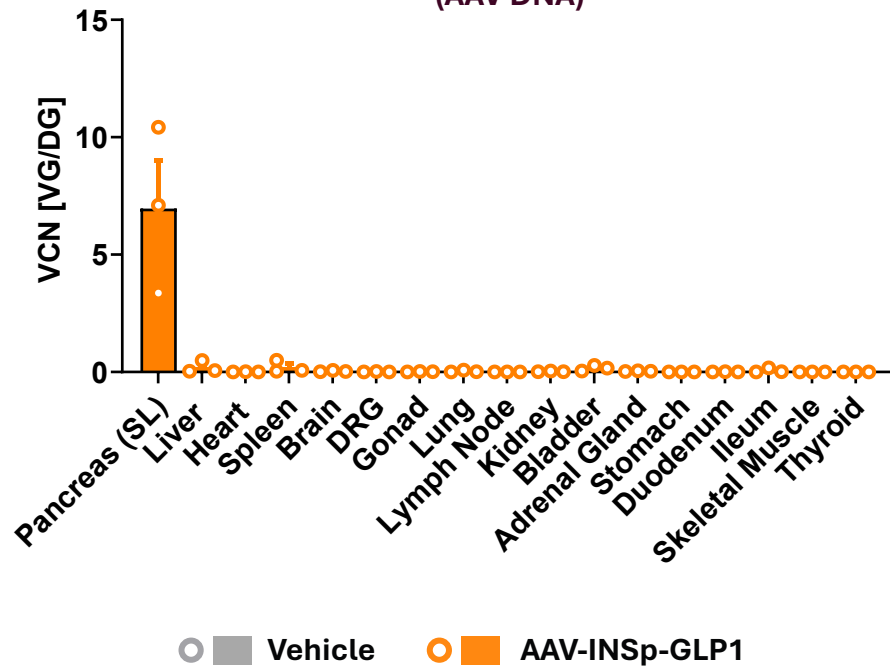
EUS-Guided AAV Delivery is Safe and Well-Tolerated in Yucatan Pigs

Constrained biodistribution and no procedural or vector-related safety signals

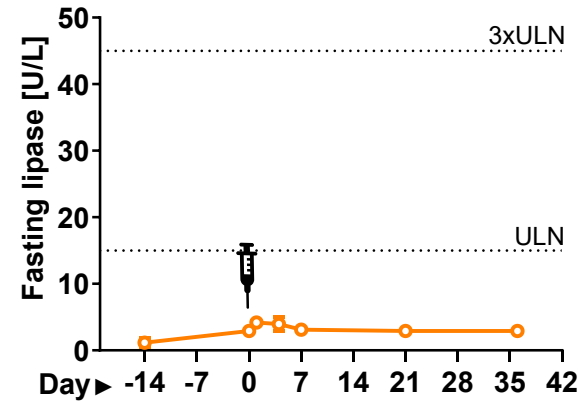


In Vivo: Treated Yucatan Pigs

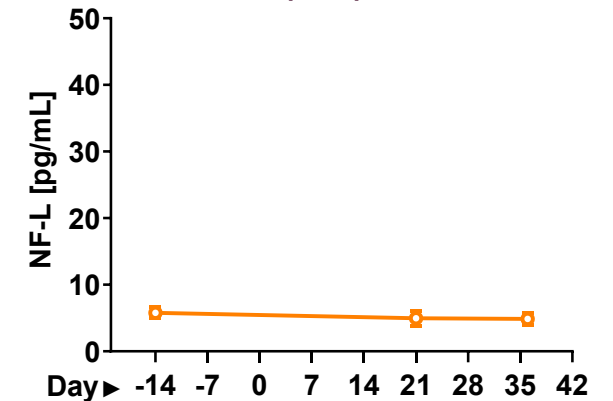
Biodistribution (AAV DNA)



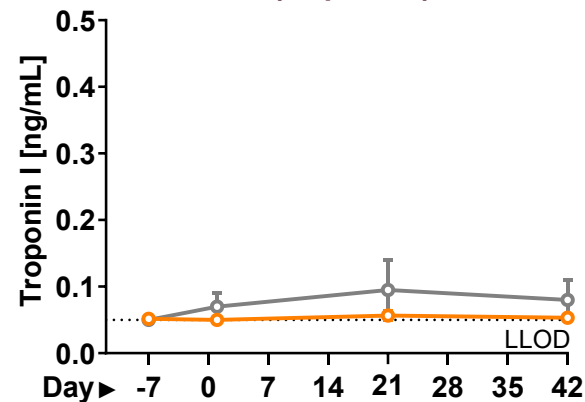
Pancreatitis (lipase)



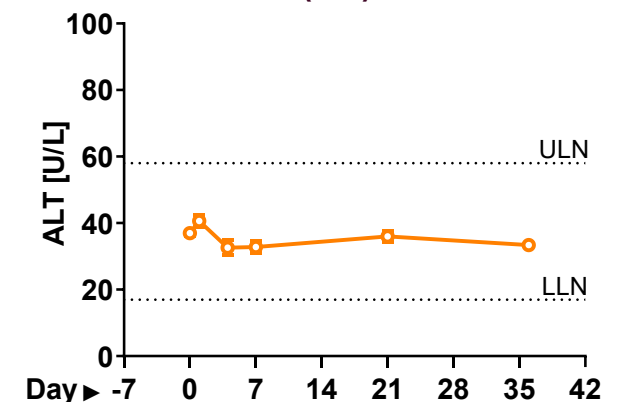
Neurotoxicity (Nf-L)



Cardiotoxicity (troponin I)



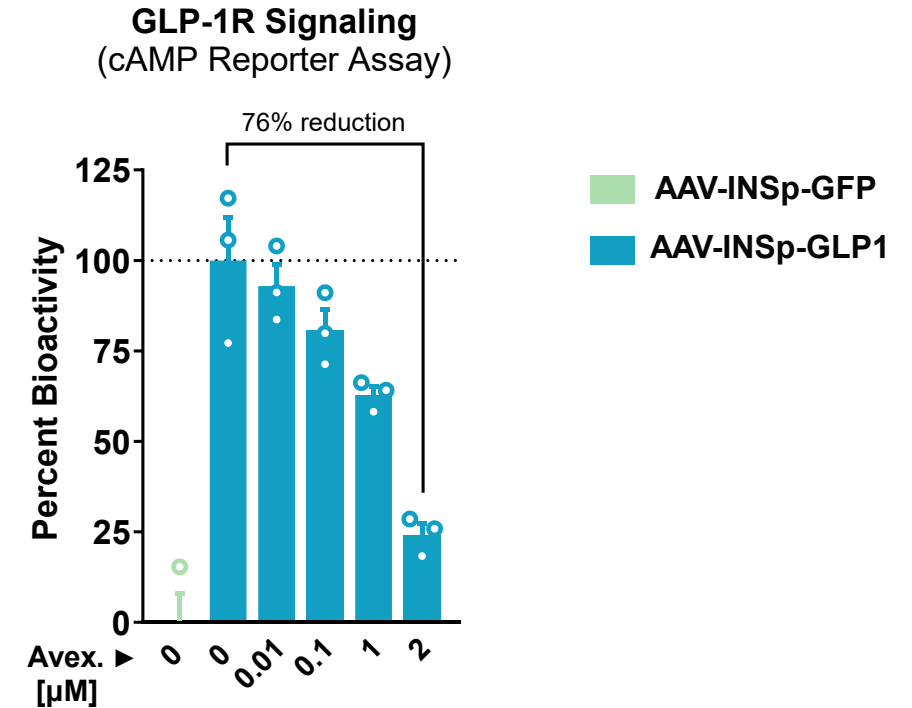
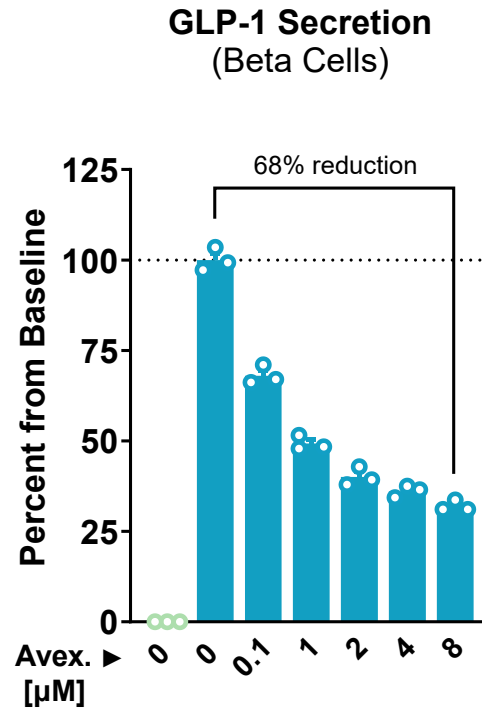
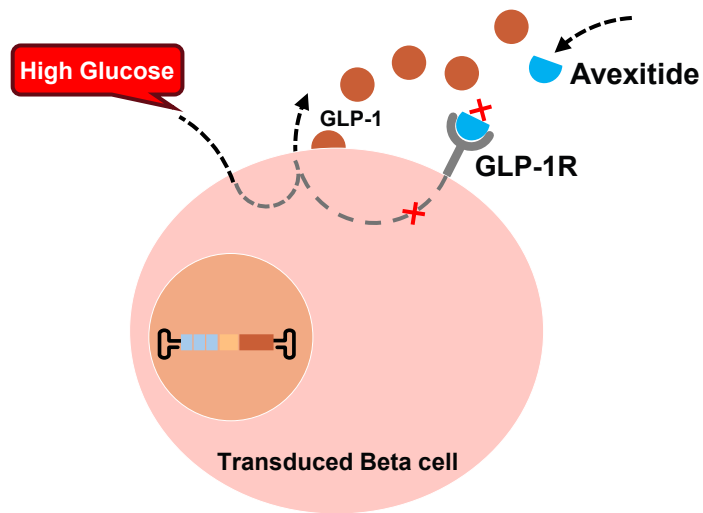
Hepatotoxicity (ALT)



GLP-1R Antagonism Provides Reversible Pharmacological Inhibition

Blocks GLP-1 secretion and GLP-1R signaling

 ***In Vitro*: Transduced Human Beta Cells + Avexitide**



Rejuva: A First-in-Class “Smart GLP-1” AAV Gene Therapy for T2D

Preclinical foundation complete, clinical translation underway


KEY TAKEAWAYS

- **Insulin promoter and regulatory features** drive beta cell-specific, nutrient-regulated GLP-1 expression and secretion
- **Restoration of beta cell function** in diabetic *db/db* mouse islets, with improved glycemic control
- **Beta cell health is protected** — no induction of reactive oxygen species; with ER stress attenuation under cellular stress challenge
- **EUS-guided pancreatic delivery is clinically translatable** — high local but restricted systemic biodistribution, no safety signals in large animal model

CTA approved in Europe.

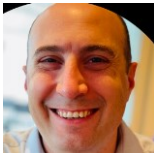
First-in-human dosing and preliminary FIH data anticipated in H2 2026.

Acknowledgements




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Exec. Director, Head of R&D

Tech Ops and Research Ops



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Bill Monahan, BS
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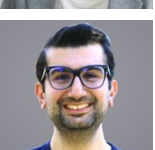
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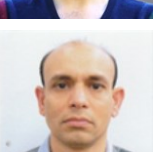
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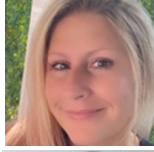
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