FRACTYL health

Rejuva: Beta Cell-Targeted "Smart GLP-1" AAV Gene Therapy

Endoscopic Ultrasound-Guided Delivery of Human Glucagon-like Peptide-1 Pancreatic Gene Therapy: Safety and Feasibility in a Porcine Model

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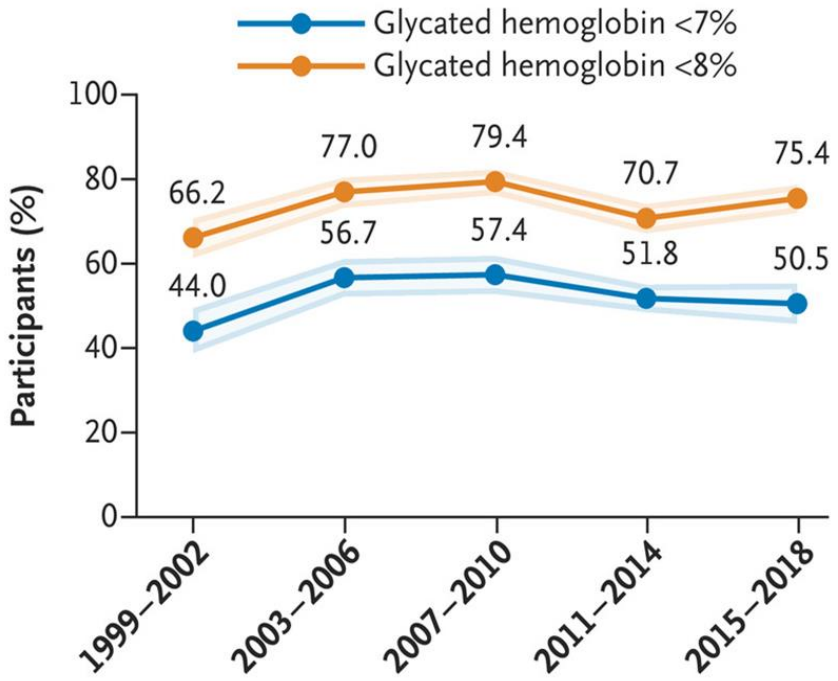
Rejuva is in early development and has not been assessed by any regulatory body for investigational or commercial use

Type 2 Diabetes is a Chronic, Progressive Disease Caused by Pancreatic Beta Cell Failure

- Type 2 diabetes (T2D) affects >30M Americans[1]
- Leading cause of kidney failure, cardiovascular disease, stroke, blindness, amputation[2,3]
- Insulin resistance and beta cell dysfunction lead to progressive metabolic failure[4]
- Patients with T2D have insufficient GLP-1 action; GLP-1 therapies have **validated the GLP-1 axis** but have limitations (e.g., side effects, durability, compliance)[5]
- A durable, tolerable, **one-time intervention** addressing **root-cause metabolic dysfunction** is urgently needed

Only 50% of Americans achieve recommended glucose targets[6] (blue)



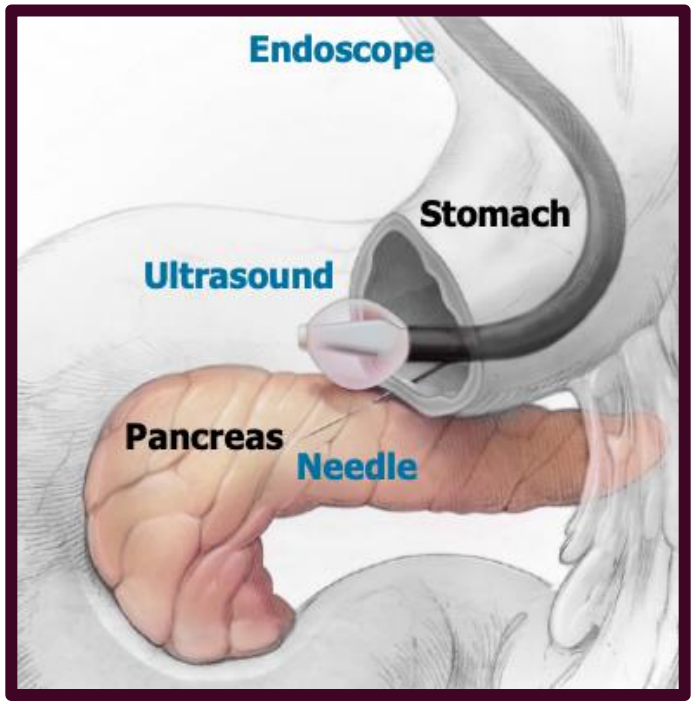
1. https://www.cdc.gov/diabetes/about/about-type-2-diabetes.html 2. Tomic et al. Nat Rev Endocrinol. 2022 Sep;18(9):525-539 3. Julia Hippisley-Cox and Carol Coupland. BMJ. 2016 Mar 30:352:i1450. doi: 10.1136/bmj.i1450 4. Hudish et al. J Clin Invest. 2019 Aug 19;129(10):4001–4008 5. Deborah Hinnen Diabetes Spectr. 2017 Aug;30(3):202–2105. 6. Fang 2021 NEJM doi:10.1056/nejmsa2032271. T2D=type 2 diabetes, GLP-1=glucagon-like peptide-1.

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

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

Novel ROA

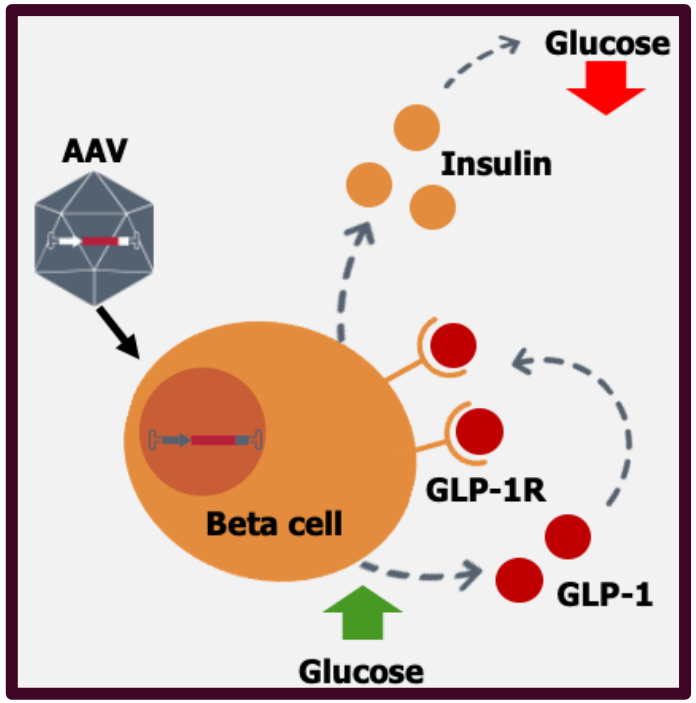
Targeted administration via proprietary endoscopic ultrasound-based needle catheter



- **Local infusion**
- **Low dose**
- **Restricted biodistribution**

Novel MOA

Human GLP-1 and insulin-derived promoter and secretory features for beta cell-specific, adaptive control



- **Beta cell-specific expression**
- **Leverages insulin production pathway**
- **Glucose-responsive GLP-1 secretion**

ROA=route of administrations, MOA=mode of action, GLP-1= GLP-1=glucagon-like peptide-1, T2D=type 2 diabetes , AAV=adeno-associated virus

The Rejuva Approach is Differentiated from GLP-1 Drugs

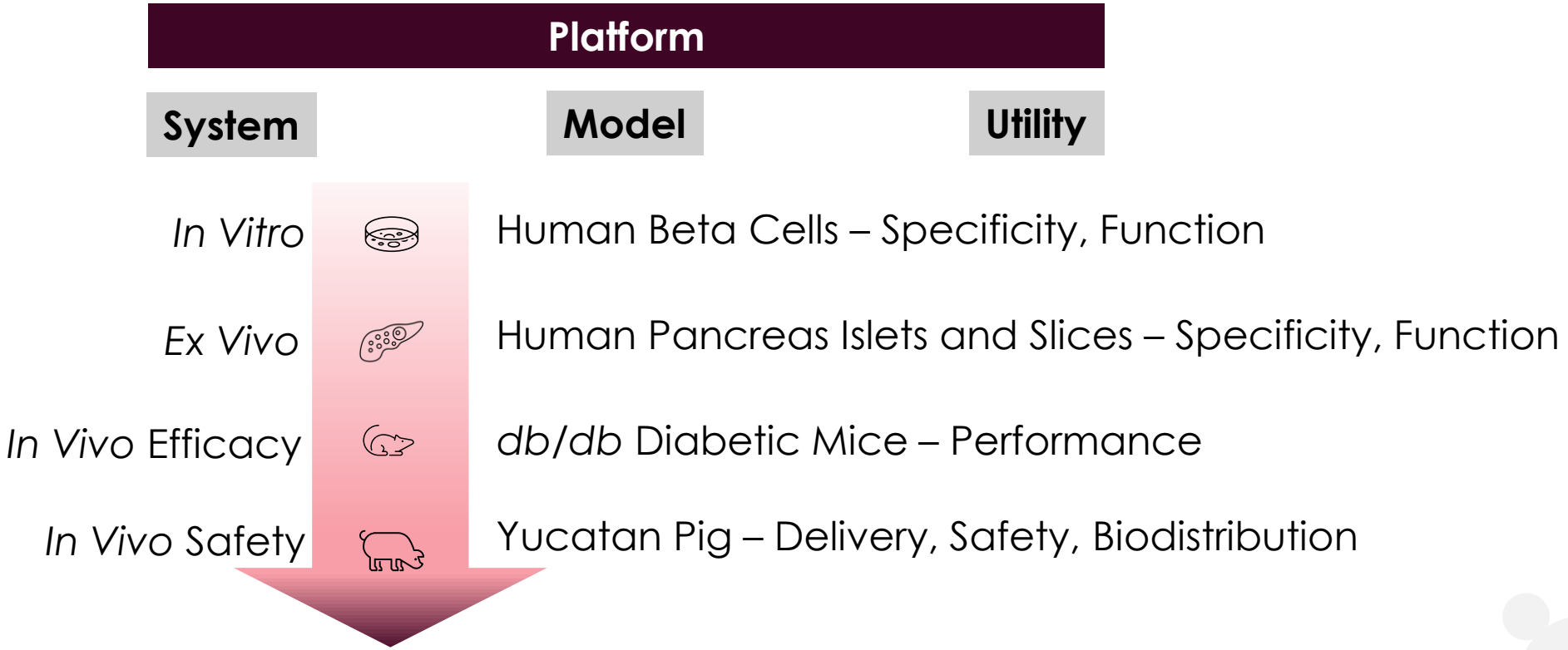
Intrapancreatic, nutrient-responsive: "Smart GLP-1" gene therapy

Feature	Rejuva	GLP-1 Drugs
MOA	Simulates endogenous GLP-1 secretion kinetics ✅	Exogenous, pharmacologic activation of GLP-1R
Tissue Distribution	High pancreas and portal exposure with limited systemic exposure ✅	Systemic, with widespread receptor activation
Safety/Tolerability	Better GI tolerability expected ✅	Broad CNS activation with associated nausea, vomiting risk
Regulation	Nutrient-responsive expression and secretion ✅	Chronic high levels independent of physiologic need
Duration	Long-term (AAV9) ✅	Short-term

GLP-1= GLP-1=glucagon-like peptide-1, GLP-1R=GLP-1 receptor, AAV=adeno-associated virus, GI=gastrointestinal, CNS=central nervous system, MOA=mode of action

Key Features of the Rejuva Platform

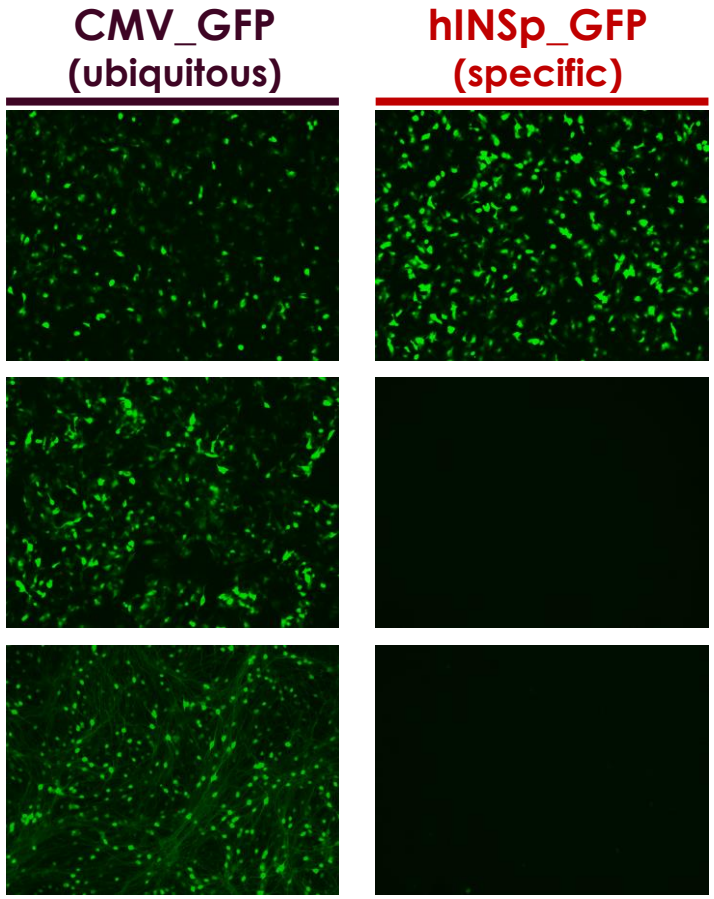
Gradient of systems to screen for “smart” and safe GLP-1 gene therapies



GLP-1= GLP-1=glucagon-like peptide-1

Rejuva Expression is Specific to Beta Cells Via an Engineered Human Insulin Promoter-Derived Sequence

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



- Rejuva utilizes an engineered regulatory sequence derived from human insulin promoter (hINSp)
- hINSp drives expression in human beta cells but not in human liver or DRG cells when studied *in vitro* in **transduced human cell lines**

- Rejuva promoter hINSp restricts expression to beta cells

Data representative of N=3 experiments. GFP expression assessed by fluorescence microscopy 72 hrs post-transduction at 10x magnification. DRG=dorsal root ganglion, MOI=multiplicity of infection, vg=vector genomes, CMV= cytomegalovirus, GFP=green fluorescent protein

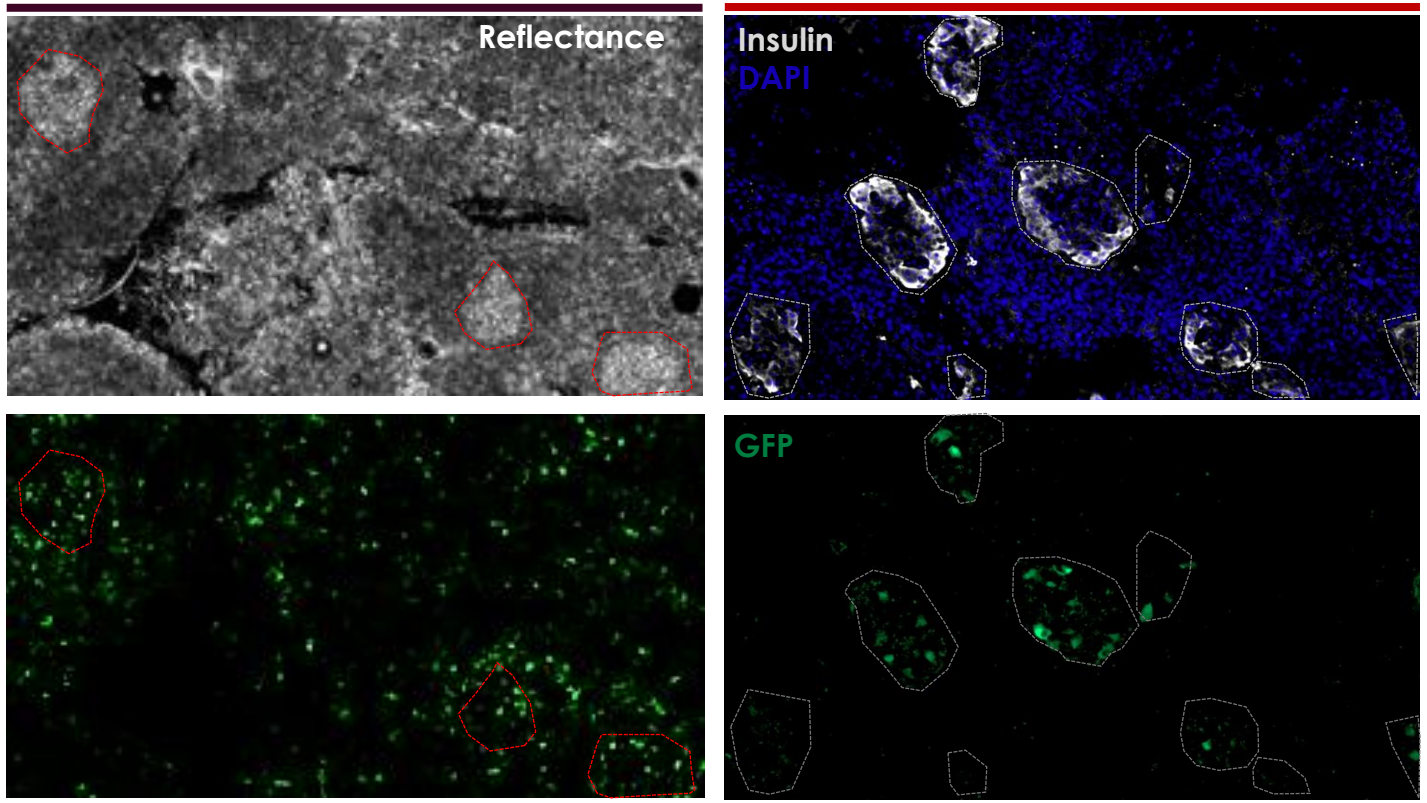
hINSp = engineered human insulin promoter

Rejuva Expression is Specific to Beta Cells Via an Engineered Human Insulin Promoter-Derived Sequence

Ex Vivo: Transduced Human Pancreas Slices

CMV_GFP (ubiquitous)

hINSp_GFP (specific)



- hINSp drives expression in islets but not exocrine cells when studied *ex vivo* in **human pancreas tissue slices**

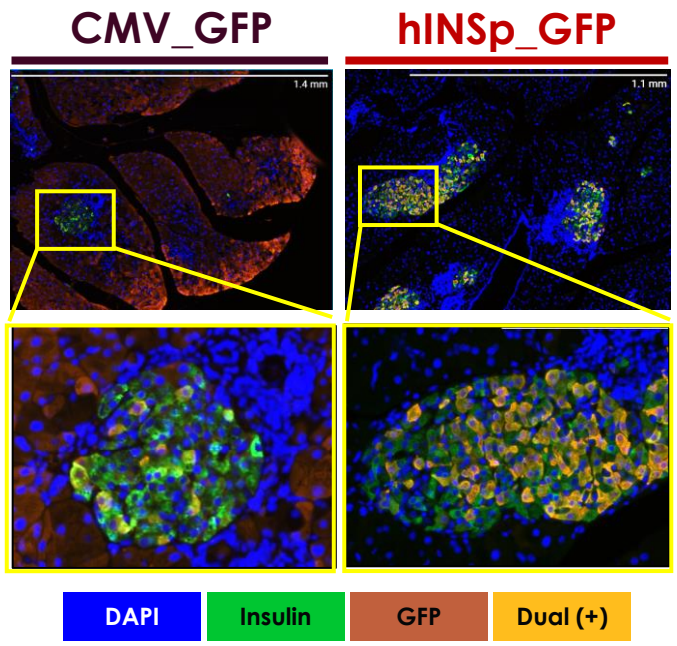
- Rejuva promoter hINSp restricts expression to islets

Human pancreas slice analysis performed by Julia Panzer, PhD, City of Hope. CMV= cytomegalovirus, GFP=green fluorescent protein, DAPI=4',6-diamidino-2-phenylindole

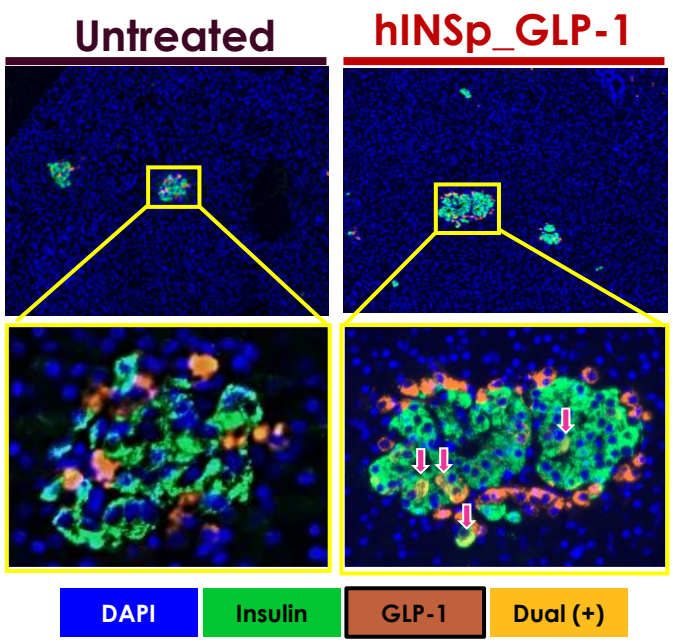
hINSp = engineered human insulin promoter

Rejuva Expression is Specific to Islets in Relevant Animal Models - *db/db* Mice and Yucatan Pigs

***In Vivo*: Transduced Mice**



***In Vivo*: Transduced Pigs**



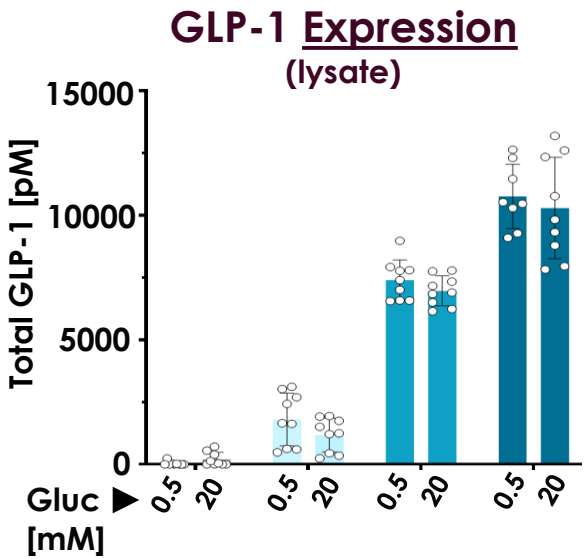
- hINSp drives expression in islets but not exocrine cells when studied *in vivo* in **small and large animal models**

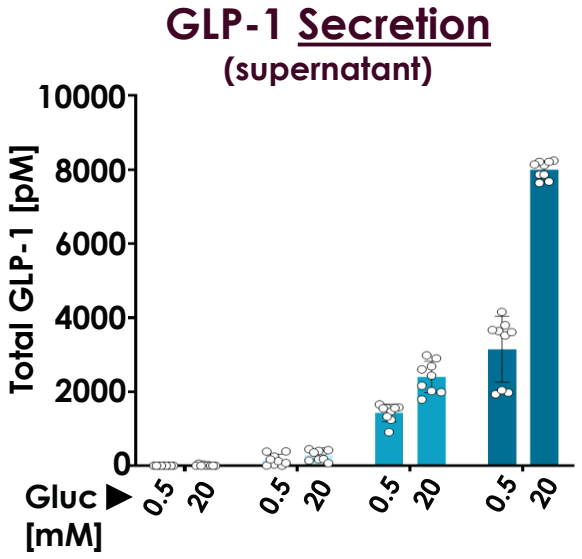
- Rejuva promoter hINSp restricts expression to islets

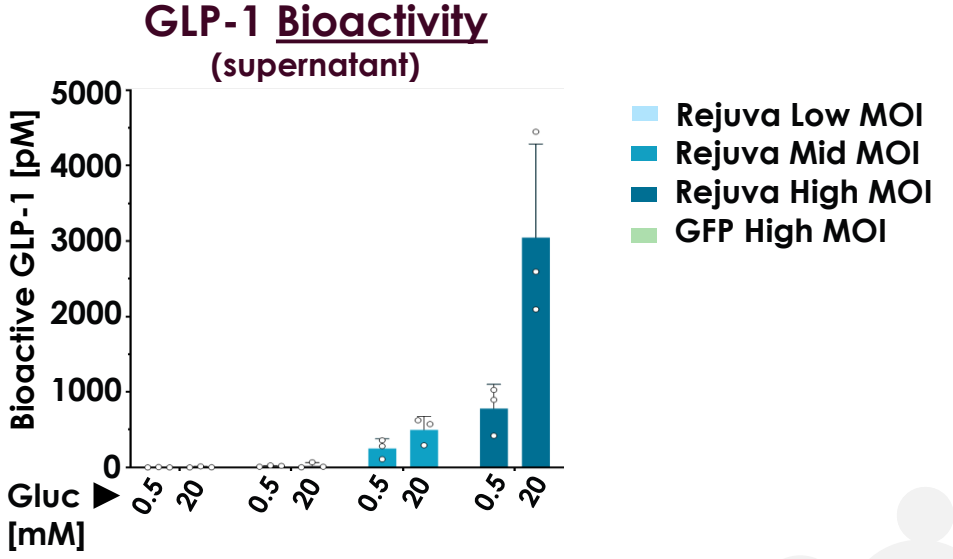
Data are representative of n=3 mice per group and n=5 Rejuva treated pigs and 1 untreated control. Red arrows indicate dual labeling. CMV= cytomegalovirus, GFP=green fluorescent protein, DAPI=4',6-diamidino-2-phenylindole, GLP-1=glucagon-like peptide-1

hINSp = engineered human insulin promoter

Rejuva Shows Nutrient-Responsive, Dose-Responsive GLP-1 Expression and Secretion in Transduced Human Beta Cells

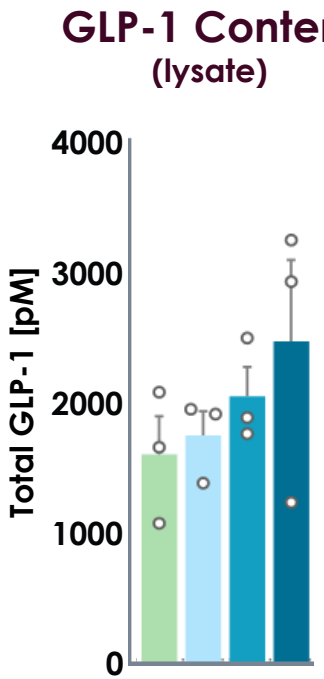


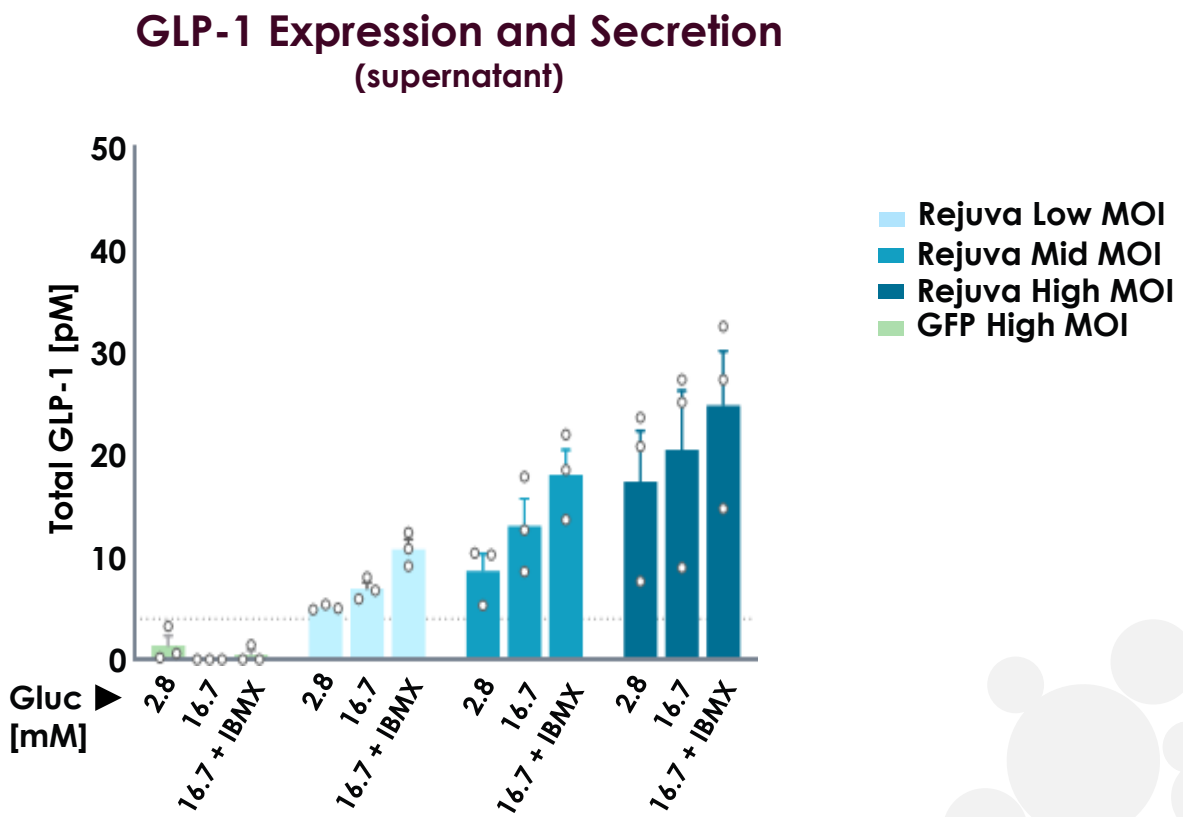




Data are mean ± SD. For GLP-1 expression and secretion, N=3 with 3 technical replicates. For GLP-1 bioactivity, N=1 with 3 technical replicates. GLP-1=glucagon-like peptide 1, Gluc=glucose, GFP=green fluorescent protein, MOI=multiplicity of infection.

Rejuva GLP-1 Shows Nutrient-Responsive, Dose-Responsive Expression and Secretion in Transduced Human Islets

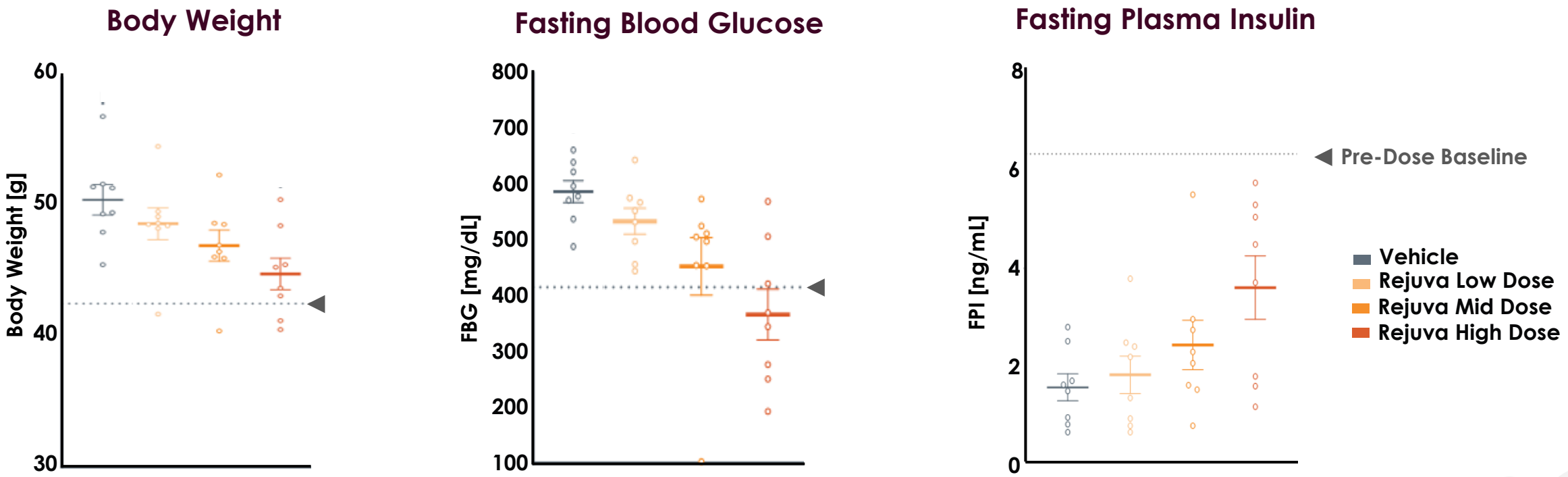




Data are mean± SEM. Data are from a single deceased human donor 7 days post Rejuva transduction. Each data point represents a pool of 40 islets run in triplicate. GLP-1=glucagon-like peptide 1, Gluc=glucose, GFP=green fluorescent protein, MOI=multiplicity of infection, IBMX=3-isobutyl-1-methylxanthine.

Rejuva GLP-1 Improves Metabolic Control in *db/db* Mice

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

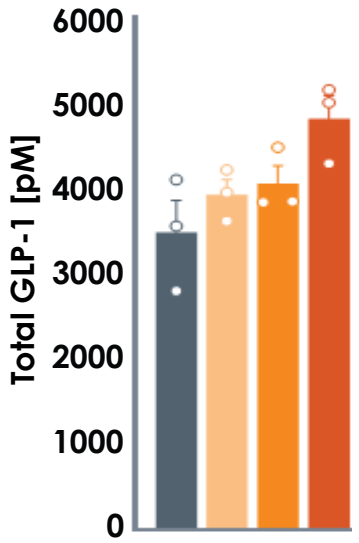


- Rejuva administered in *db/db* mice at 8 weeks of age (advanced T2D model)
- All data from day 46 post-single IP AAV injection (durable, dose-responsive PD effects)

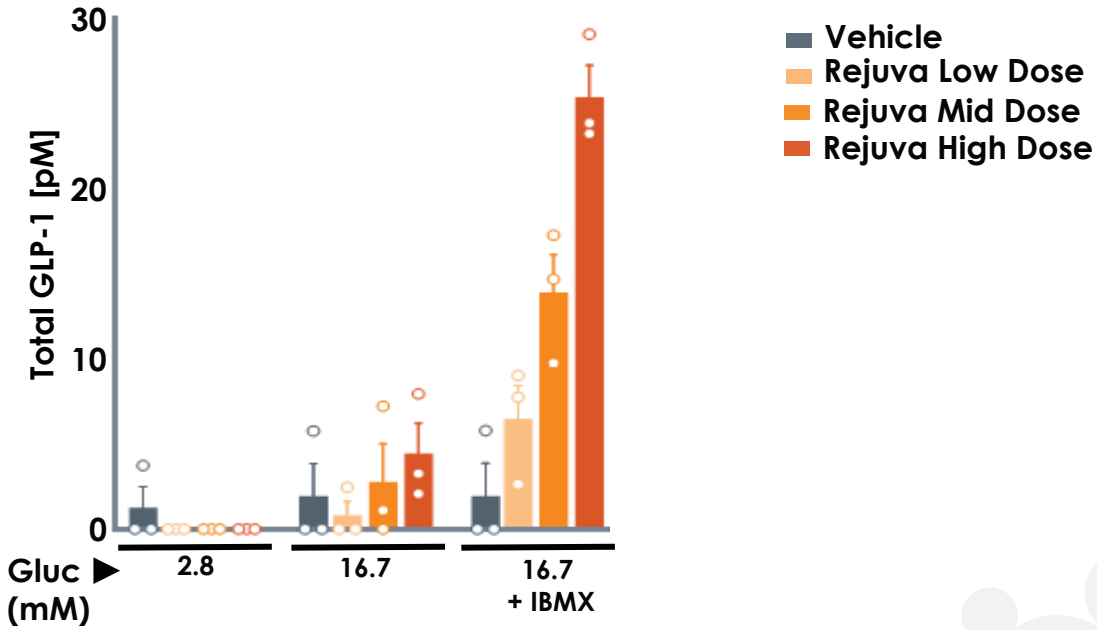
Data mean ± SEM, n=8 per group. FBG=fasting blood glucose, FPI=fasting plasma insulin, GLP-1=glucagon-like peptide 1, T2D=type 2 diabetes, IP=intraperitoneal, PD=pharmacodynamic, AAV=adeno-associated virus.

Rejuva Shows Dose-Responsive, Nutrient-Responsive GLP-1 Expression and Secretion in Islets from Treated *db/db* Mice

GLP-1 Content
(lysate)



GLP-1 Expression and Secretion
(supernatant)

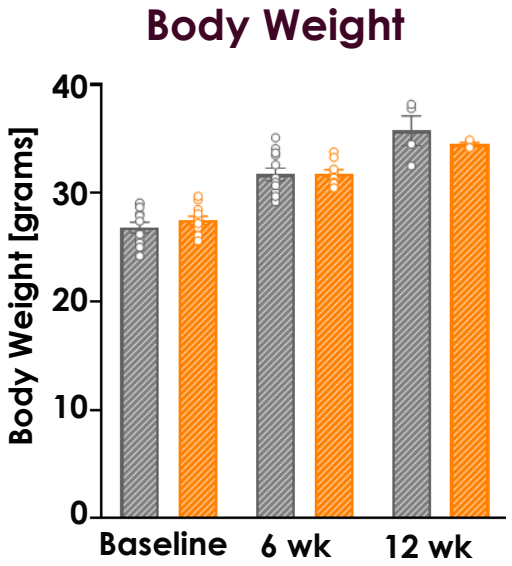


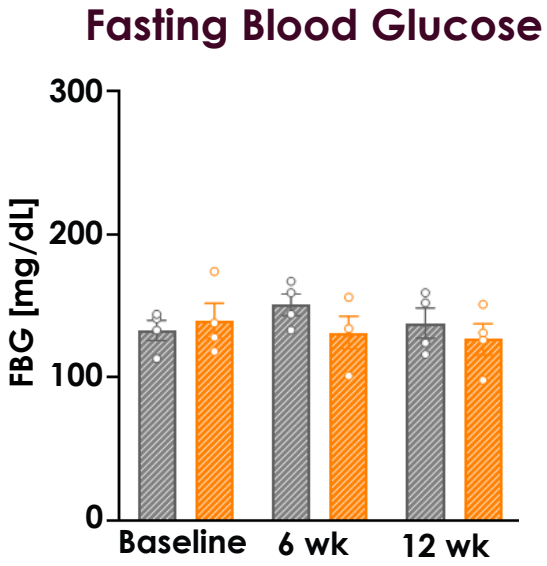
- Islets isolated 49 days post single IP AAV injection

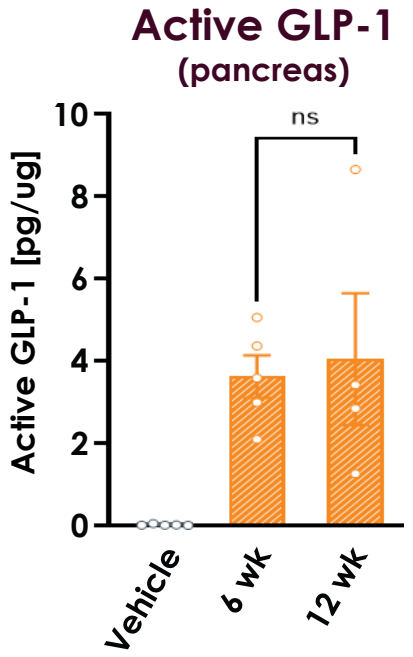
Data are mean ± SEM. Each data point represents a pool of 40 islets run in triplicate. Gluc=glucose, GLP-1=glucagon-like peptide 1, IBMX=3-isobutyl-1-methylxanthine, AAV=adeno-associated virus, IP=intraperitoneal

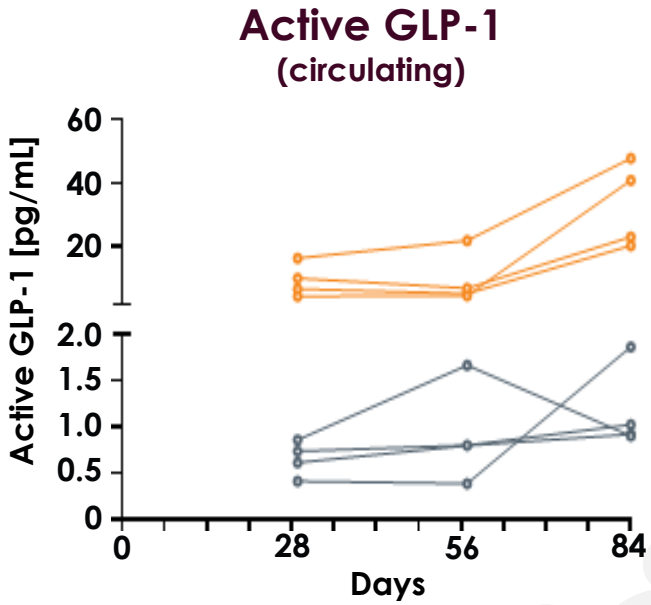
Rejuva Shows Safe and Durable Expression

Normal weight and blood glucose observed **in healthy mice**









Vehicle Het *db*/+
Rejuva Het *db*/+

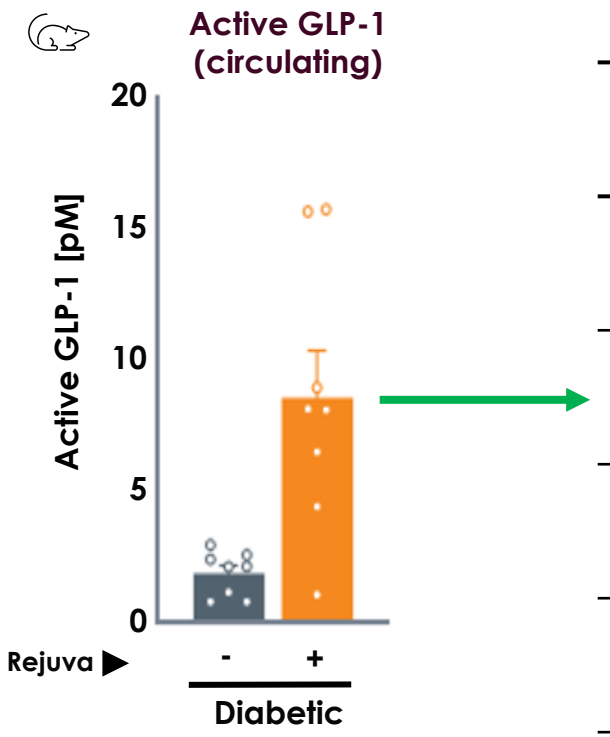
- Rejuva administered to Het *db*/+ (healthy) mice via single IP AAV injection

Data are mean ± SEM, n=4-12 per group. Het=heterozygous, AAV=adeno-associated virus, GLP-1=glucagon-like peptide 1.

“Smart” GLP-1 Mimics Endogenous Physiology

Potent efficacy and near physiologic circulating levels

Rejuva



Comparison Chart Active GLP-1 Levels[1]

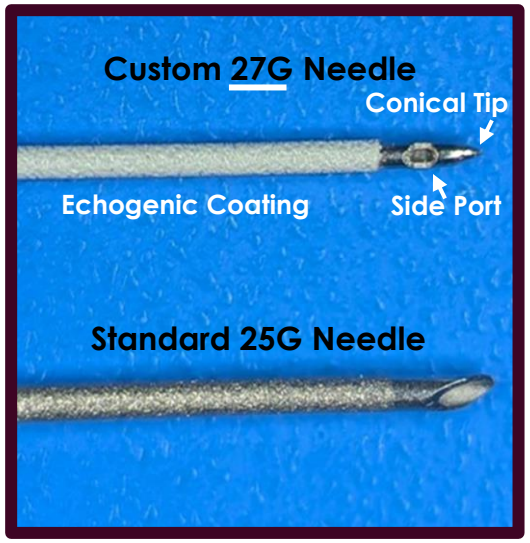
Modality	Levels	Tolerability
Physiological	< 5 pM	✓
DPP4 Inhibition	~ 10 pM	✓
Rejuva GLP-1	**10-20 pM**	✓ **(Expected)**
Roux-en-Y Gastric Bypass	~ 20 pM	✓
GLP-1RA Drugs	50-150 pM	✗

- Rejuva GLP-1 levels are **significantly lower than pharmacologic** GLP-1RA drug levels
- Tolerability believed to tie to circulating levels of active GLP-1
- Implies Rejuva is **less likely to cause tolerability issues** commonly seen with GLP-1 drugs

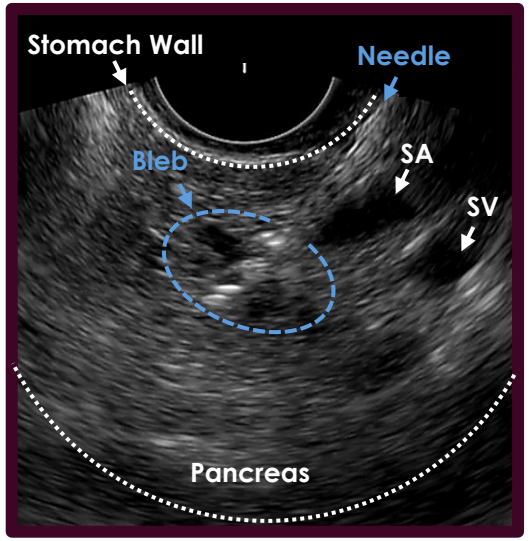
Data are mean ± SEM, n=8 per mice group from day 44 post IP AAV injection 1. Smits and Holst et al. Diabetes Metab Res Rev. 2023 Nov;39(8):e3699. GLP-1=glucagon-like peptide 1, GLP-1RA=GLP-1 receptor agonist, DPP4=dipeptidyl peptidase-4.

Rejuva Device Safely Delivers AAV to Pancreas in Large Animal Safety Model – Yucatan Pig

Rejuva Custom Needle



Live Ultrasound

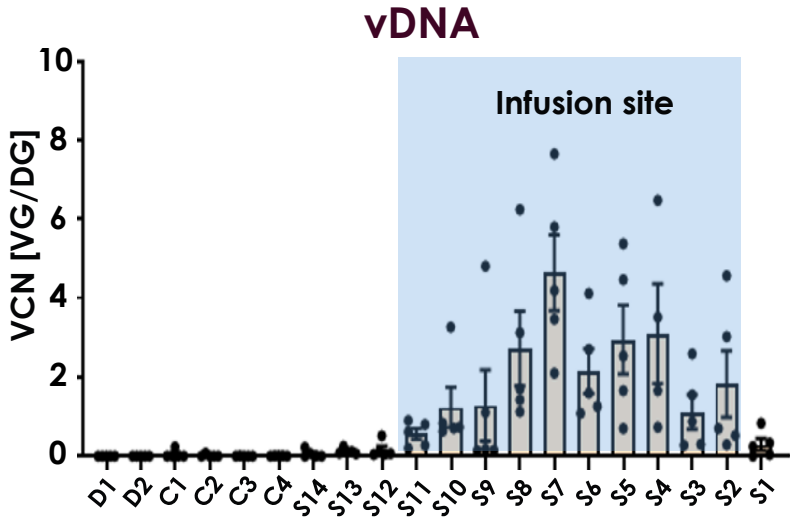


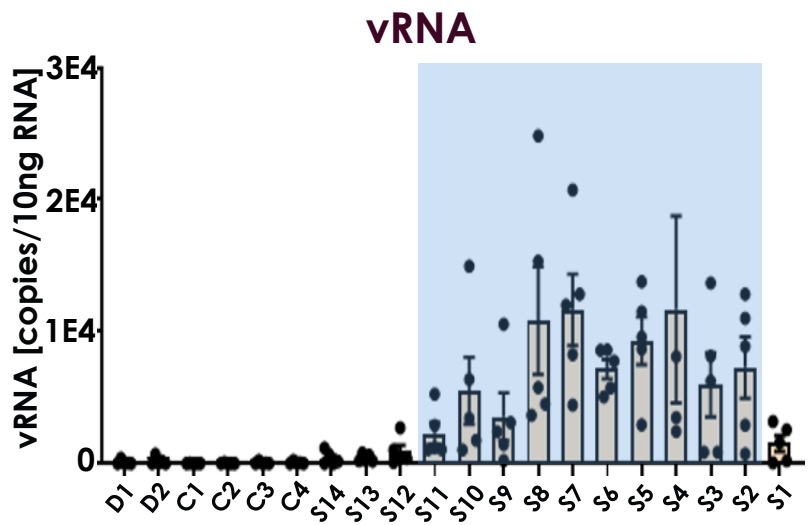
- Rejuva catheter introduced directly to pancreas parenchyma via **standard endoscopic ultrasound techniques** that are already part of standard clinical practice
- Routine upper endoscopic procedure conducted in **~ 20 minutes**

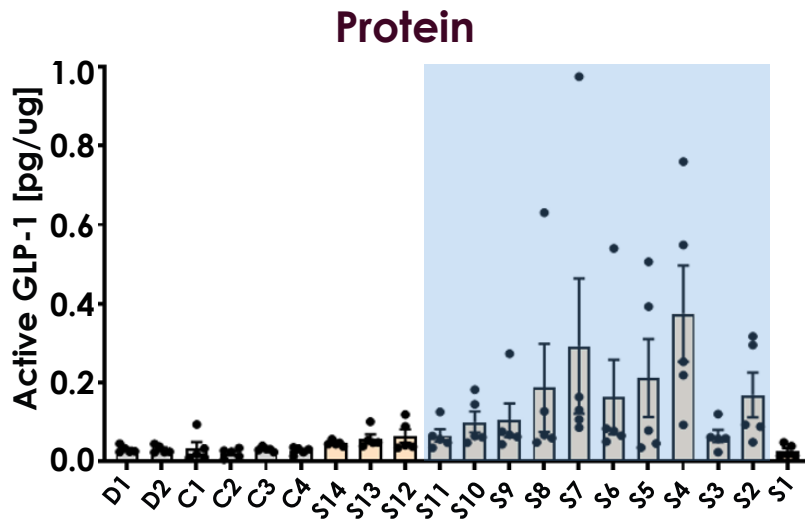
AAV=adeno-associated virus, SA=splenic artery, SV=splenic vein

Rejuva AAV Effectively Delivered to Pancreas Via Targeted ROA

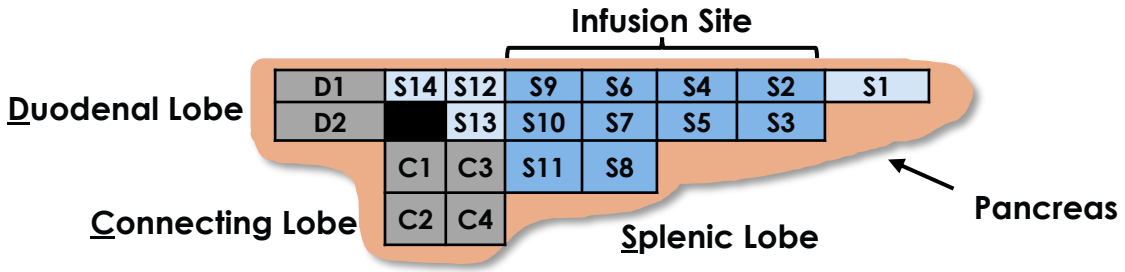
Transgene DNA, RNA, active GLP-1 protein enriched in targeted pancreatic splenic lobe







Pancreas Key

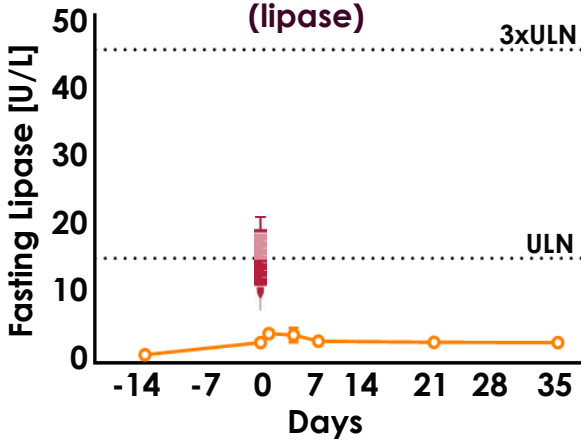


Data are mean ± SEM, n=5 pigs. VCN, RNA, and GLP-1 protein averaged across pancreatic biopsy sections. VCN=vector copy number, GLP-1=glucagon-like peptide 1, VG/DG=vector genome/diploid genome, ROA=route of administration.

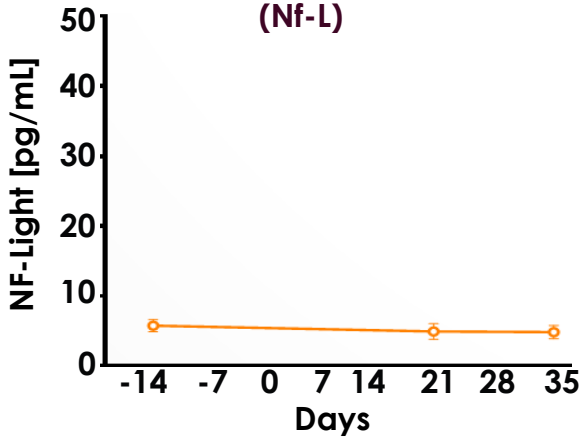
No Toxicity Observed Following Rejuva Treatment

No serum, biodistribution, or histopathologic findings of concern

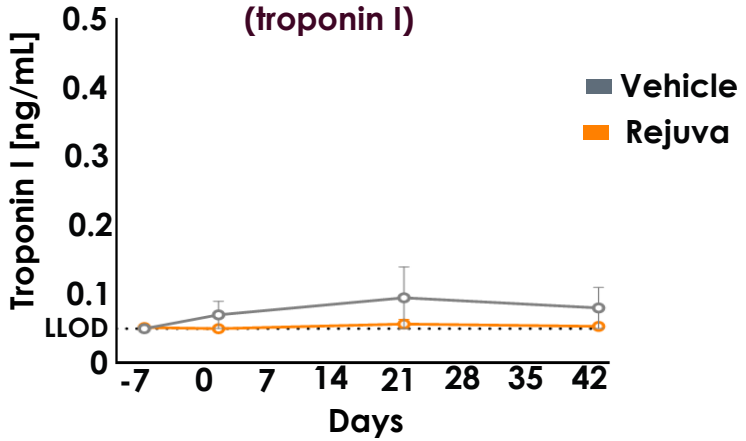
Pancreatitis
(lipase)



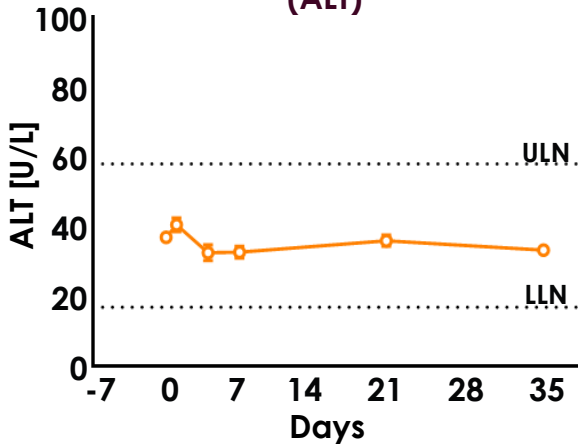
Neurotoxicity
(Nf-L)



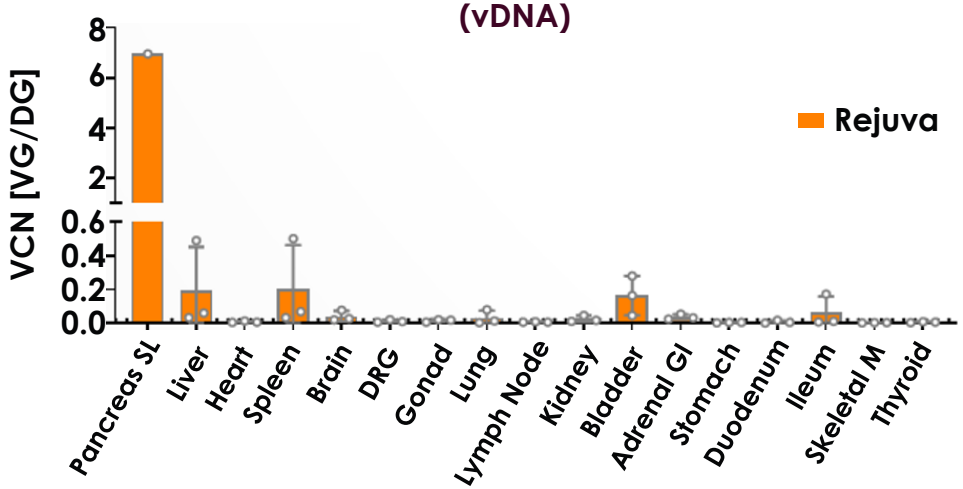
Cardiotoxicity
(troponin I)



Hepatotoxicity
(ALT)



Biodistribution
(vDNA)



Data are mean ± SEM, n=2-6 pigs per group. ALT=alanine transaminase, NF-L=neurofilament light chain, ULN=upper limit of normal, LLN=lower limit of normal, VCN=vector copy number, VG/DG=vector genome/diploid genome

Dose-Bridging Strategy for First-In-Human Dose Selection

Efficacy

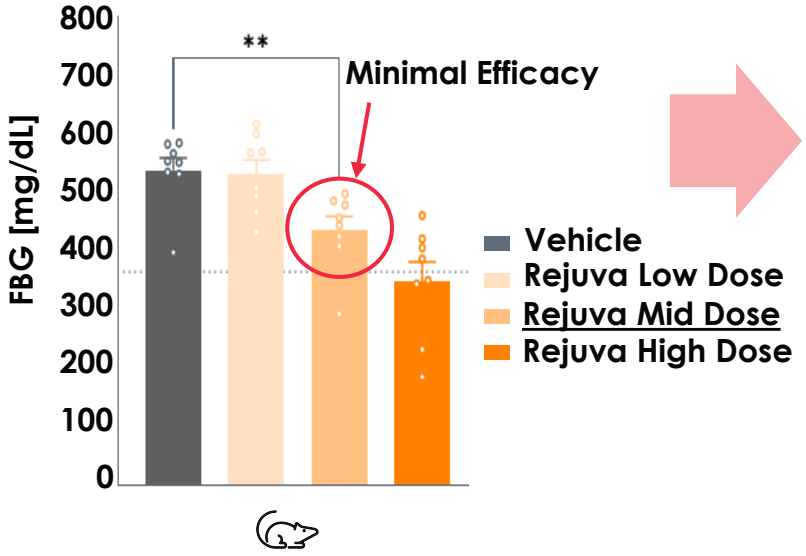
Identify minimally efficacious dose and measure GLP-1 levels

Safety

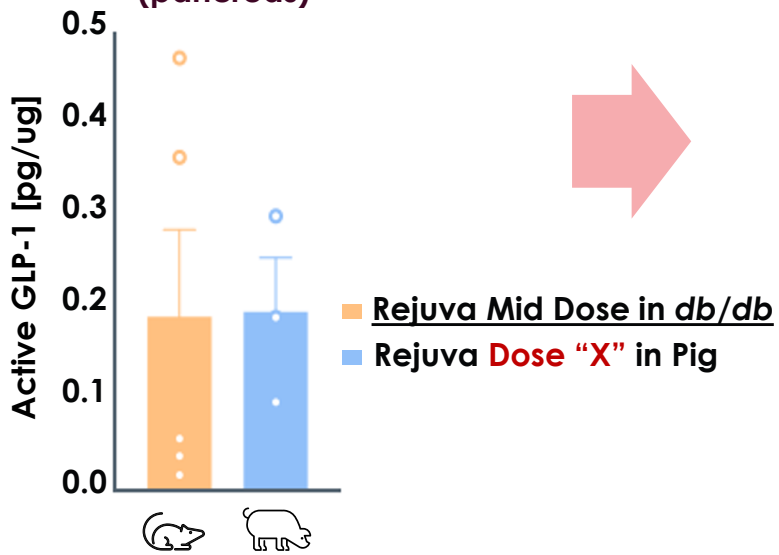
Identify safe dose in pigs with similar GLP-1 levels

Define human starting dose

Fasting Blood Glucose



Active GLP-1 (pancreas)



- **Dose "X"** allometrically scales based on similar ROA and pancreas size

FBG=fasting blood glucose, GLP-1=glucagon-like peptide 1.

Developed a Large-Scale cGMP Manufacturing Process to Support the Projected Patient Population

- Large-scale AAV production in a suspension HEK293 culture (transient transfection) in 500L bioreactors
- Downstream process includes enrichment for filled AAV particles and minimization of product- and process-related impurities
- Working with Forge Biologics to support the Rejuva platform
- Developed a robust set of analytical methods for product release/characterization (e.g., product-specific cell-based potency assay)
- Opportunities to **substantially lower COGS** using increased scale and FUEL™ platform

AAV=adeno-associated virus, cGMP=current good manufacturing practice, COGS=cost of goods

RJVA-001 FIH Dose Escalation Study Design

Aligned with regulators to assess safety, tolerability, PK, preliminary PD

Patient population

- Adults with T2D and obesity and preserved pancreatic function on GLP-1RA therapy
- HbA1c 7-10%; BMI 30-40 kg/m^2
- Not yet on insulin therapy
- No prior AAV9 exposure

Endpoints

- Primary: Safety and tolerability across dose levels
- Secondary: PK profiling, exploratory PD biomarkers (blood glucose, metabolic markers)

Study design

- GLP-1 drug therapy washout prior to therapy
- Sequential dose cohorts receiving escalating single doses of RJVA-001

Anticipated timing[1]

- Submit first CTA module: H1 2025
- Preliminary data: 2026, assuming CTA is authorized

Phase 1 open-label, dose escalation

FIH=first-in-human, PK=pharmacokinetics, PD=pharmacodynamics, GLP-1=glucagon-like peptide 1, AAV-adeno-associated virus, T2D=type 2 diabetes, CTA=clinical trial application

Rejuva: Status and Conclusions

- ✅ Compelling Scientific Rationale
- ✅ Encouraging Preclinical Results
- ✅ Favorable Safety Profile in CTA-Enabling Studies
- ✅ Scalable Manufacturing Enabled
- ✅ FIH Clinical Development Risk-Mitigated via Regulator Alignment on Design and Population

FIH=first-in-human, CTA=clinical trial application

Acknowledgements

Shimyn Slomovic, PhD
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Eric Horowitz, PhD
Exec. Director, Head of Tech Ops

Bill Monahan, BS
Assoc. Director, Lab Ops

Device Engineering

Mike Biasella, BS
Sr. Engineer Manager

Jacob Wainer, BS
Sr. Mechanical Engineer

Doug Garrity, BS
Pr. Mechanical Engineer

in vitro Discovery

Lin Quek, PhD
Assoc. Director

JungHun Lee, PhD
Sr. Scientist

Suya Wang, PhD
Sr. Scientist

Keiko Ishida, BS
Sr. Assoc. Scientist

Abdul Alhamood, MS
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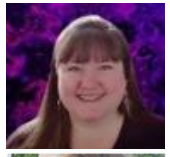

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