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

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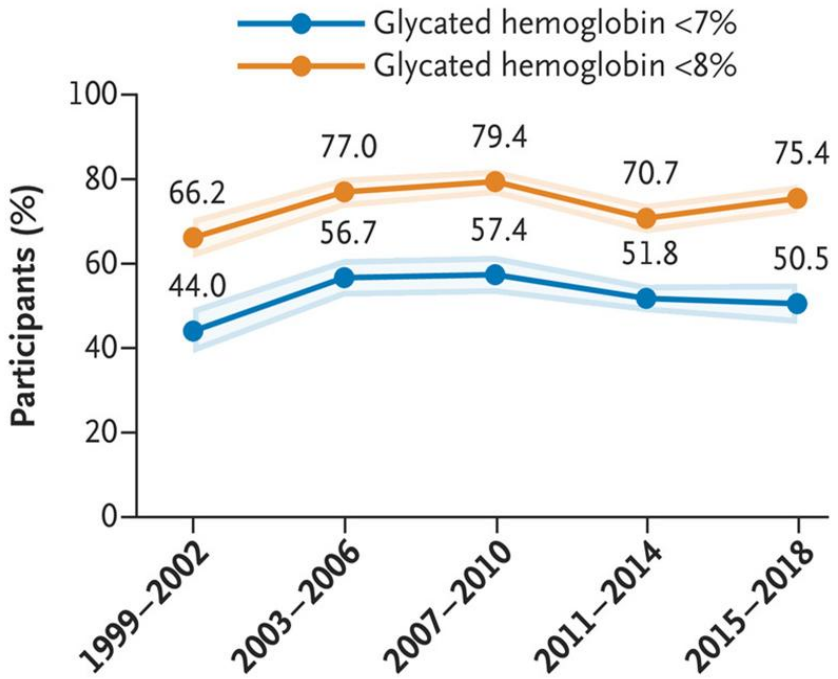
Rejuva is in early development and has not been assessed by any regulatory body for investigational or commercial use

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]

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

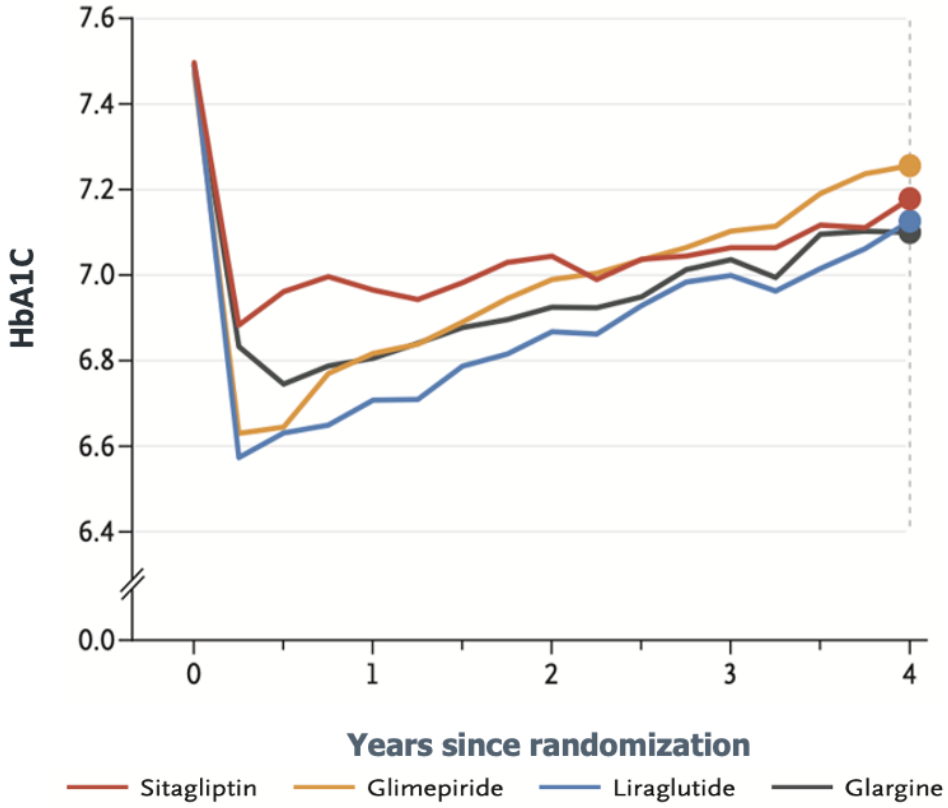


1. https://www.cdc.gov/diabetes/about/about-type-2-diabetes.html 2. Tomic et al. Nat Rev Endocrinol. 2022 Sep;18(9):525-539 3. Julia Hippisley-Cox and Carol Coupland. BMJ. 2016 Mar 30:352:i1450. doi: 10.1136/bmj.i1450 4. Hudish et al. J Clin Invest. 2019 Aug 19;129(10):4001–4008 5. Deborah Hinnen Diabetes 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.

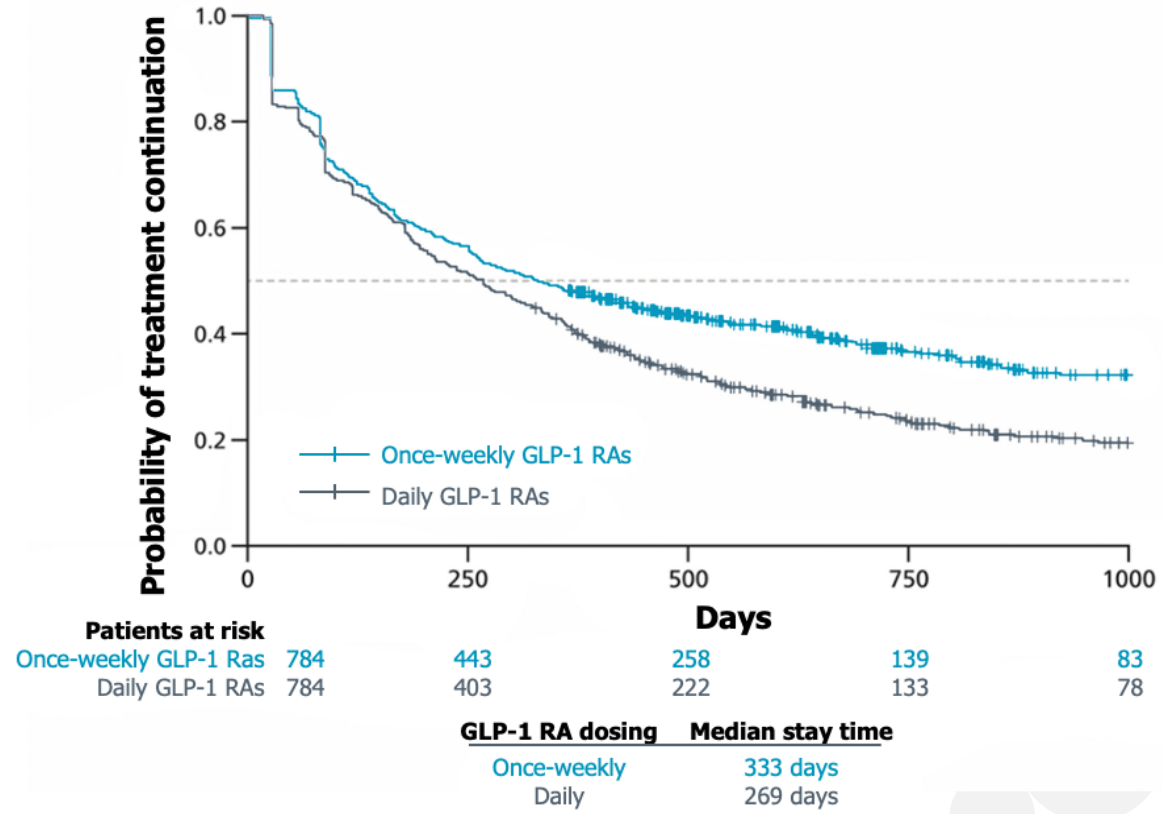
Progression and Poor Persistence Limit Effectiveness

A durable, tolerable, one-time intervention is urgently needed

Progression with current therapies[1]



Real-world persistence for GLP-1RAs in T2D[2]



Patients at risk

Once-weekly GLP-1 Ras	784	443	258	139	83
Daily GLP-1 RAs	784	403	222	133	78

GLP-1 RA dosing	Median stay time
Once-weekly	333 days
Daily	269 days

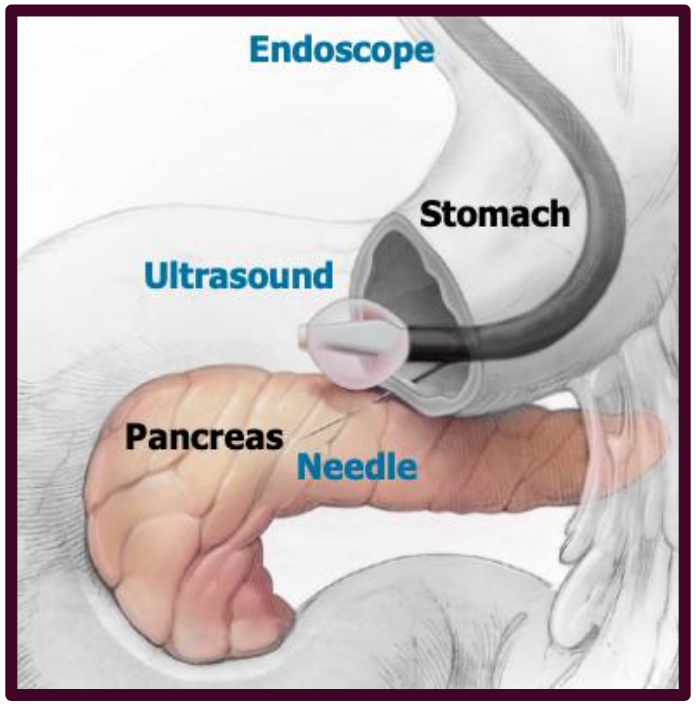
1.GRADE Study 2022 NEJM doi:10.1056/NEJMoa2200433; 2.Polonsky 2022 Diabetes Therapy doi:10.1007/s13300-021-01189-6. GLP-1RA=glucagon-like peptide-1 receptor agonist

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

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

Novel ROA

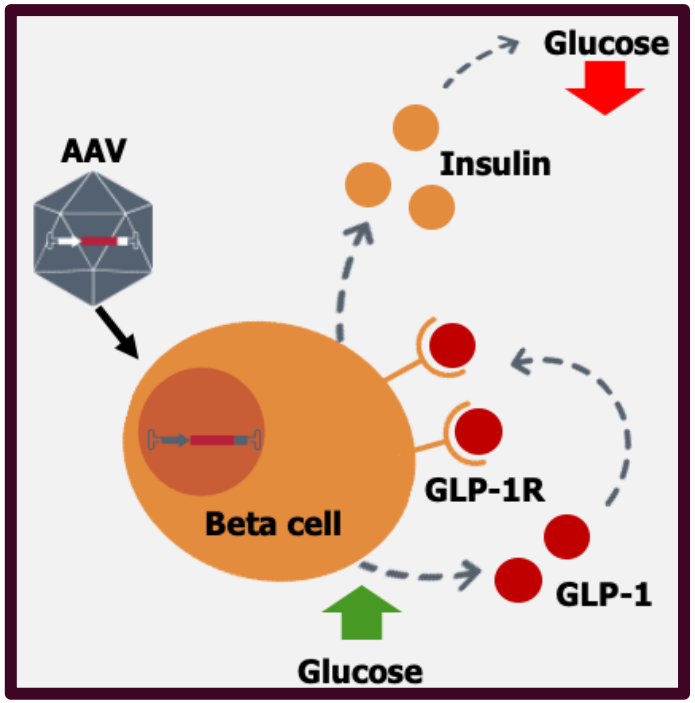
Targeted administration via proprietary endoscopic ultrasound-based needle catheter



- **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=mechanism of action, GLP-1=glucagon-like peptide-1, T2D=type 2 diabetes , AAV=adeno-associated virus

The Rejuva Approach is Differentiated from GLP-1 Drugs

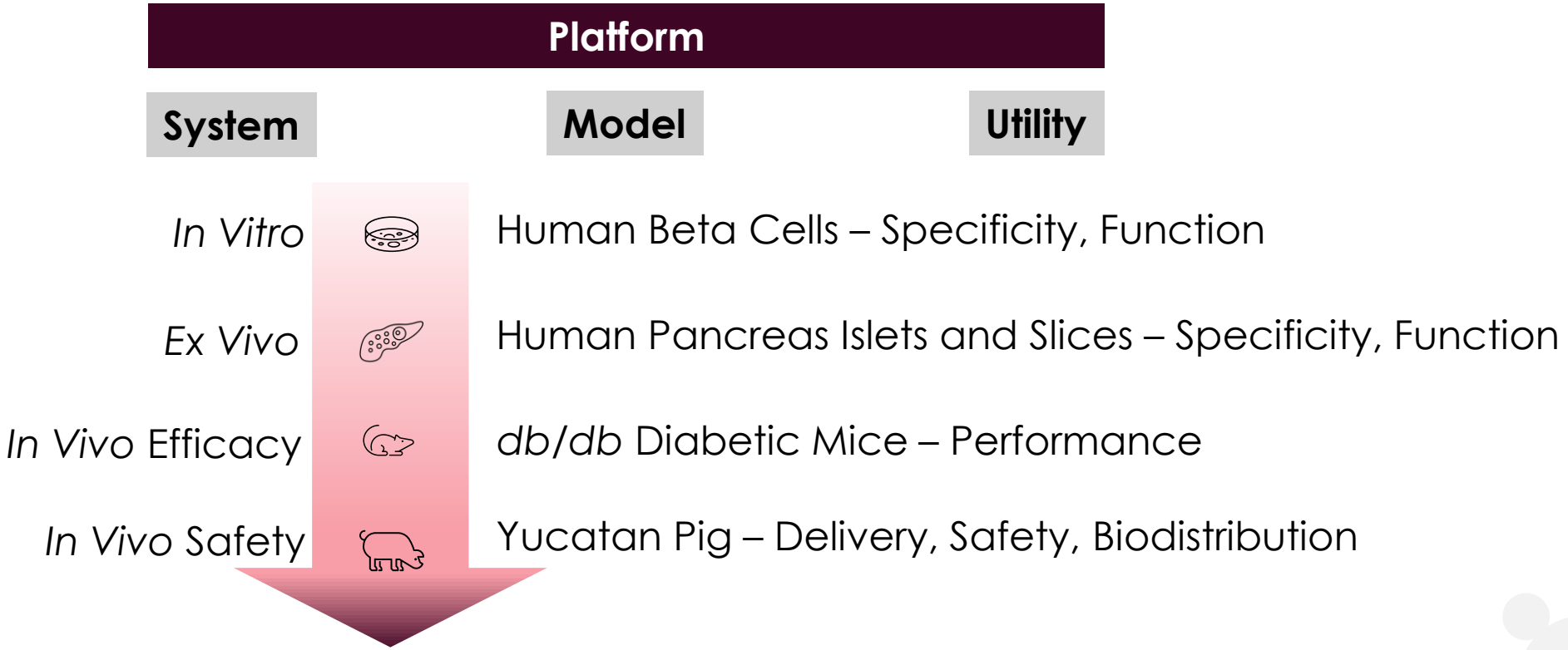
Intrapancreatic, nutrient-responsive: "Smart GLP-1" gene therapy

Feature	Rejuva	GLP-1 Drugs
MOA	Simulates endogenous GLP-1 secretion kinetics ✅	Exogenous, pharmacologic activation of GLP-1R
GLP-1 Biodistribution	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
Durability	Long-term (AAV9) ✅	Short-term (while adherent/persistent)
Potency	Potentially superior to SOC ✅	SOC

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

Key Features of the Rejuva Development Platform

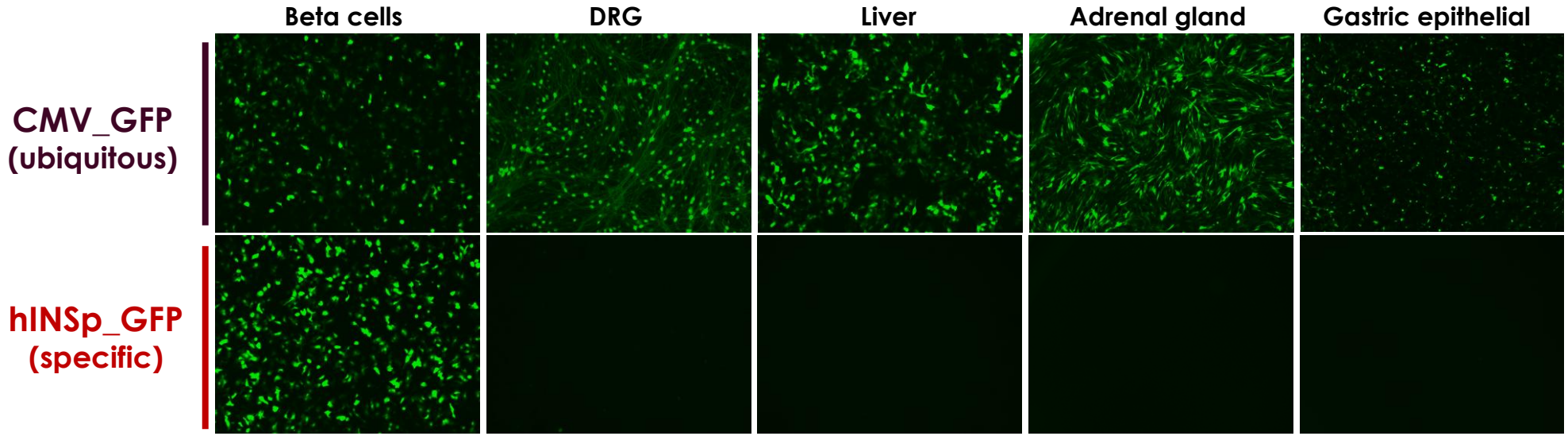
Gradient of systems to screen for “smart” and safe GLP-1 gene therapies



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**

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, CMV= cytomegalovirus, GFP=green fluorescent protein.

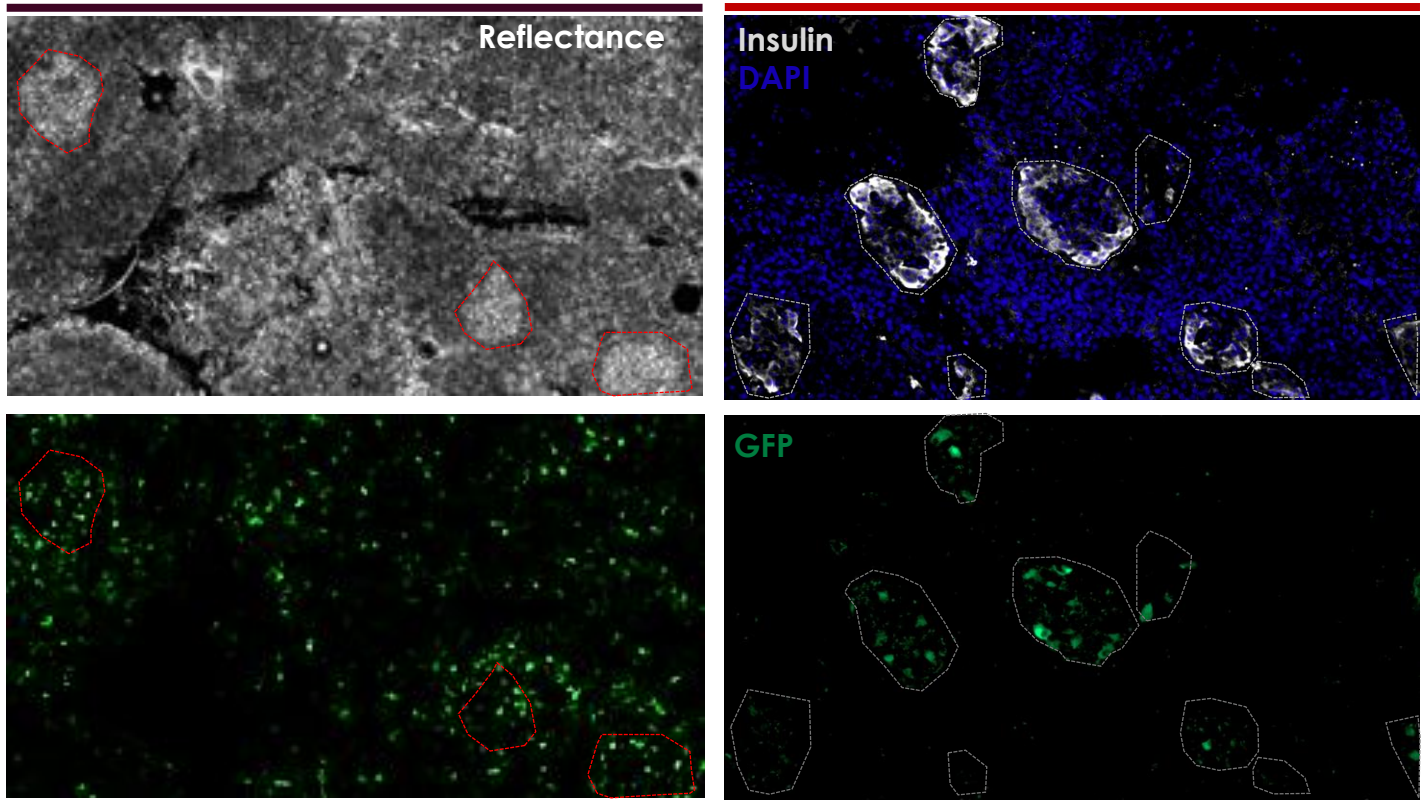
hINSp = engineered human insulin promoter

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

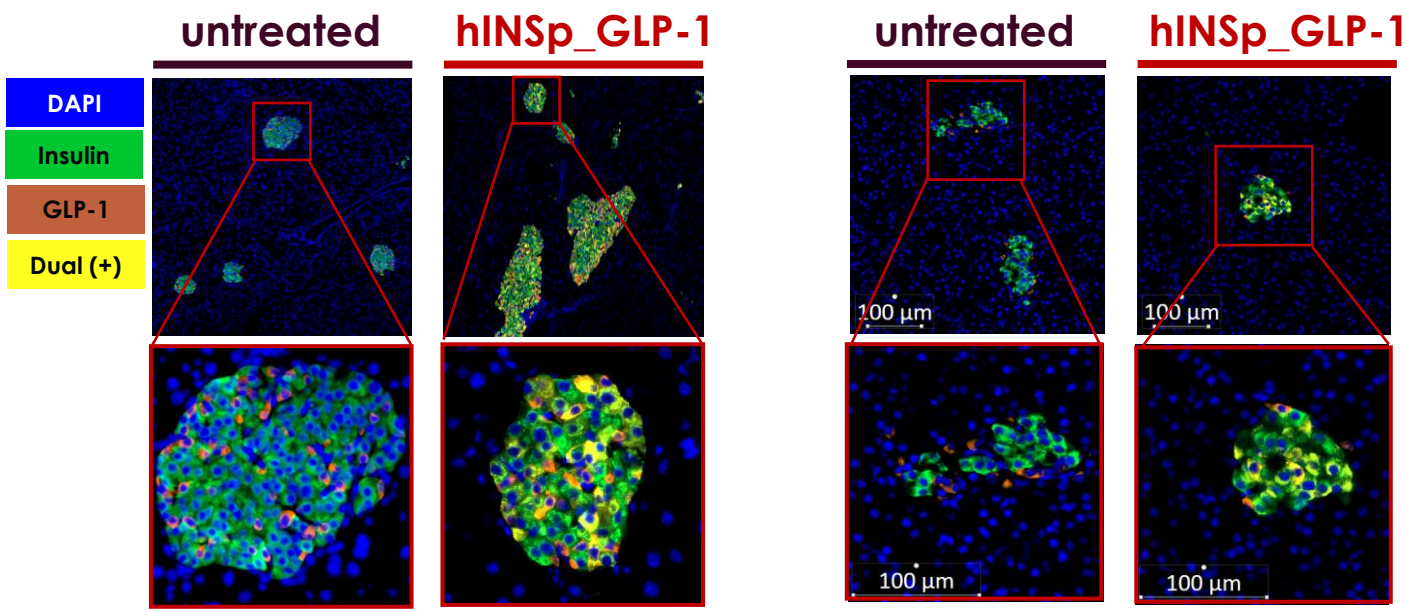
Human pancreas slice analysis performed by Julia Panzer, PhD, City of Hope. CMV= cytomegalovirus, GFP=green fluorescent protein, DAPI=4',6-diamidino-2-phenylindole.

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**



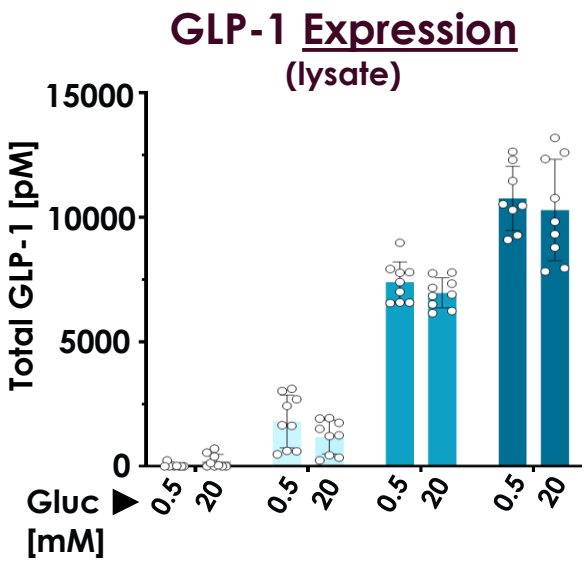
- hINSp drives expression in islets but not exocrine cells when studied *in vivo* in **small and large animal models**

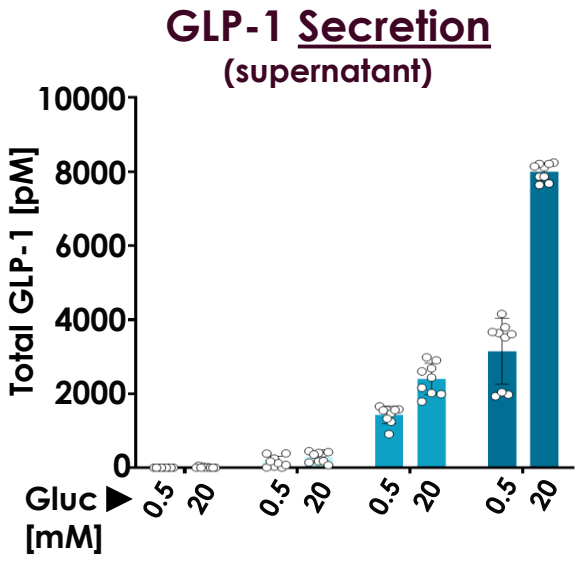
- Rejuva promoter hINSp restricts expression to islets

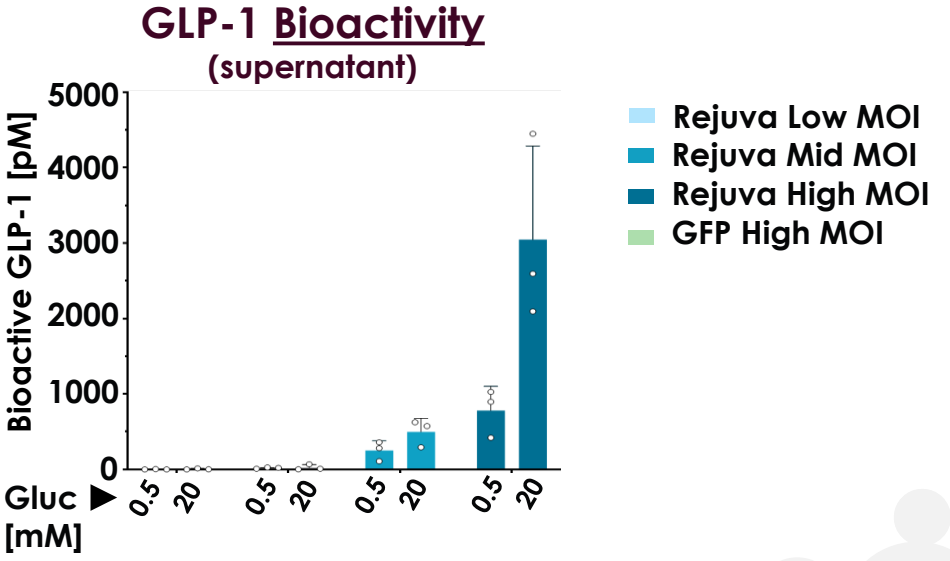
Data are representative of n=3 mice per group and n=5 Rejuva treated pigs and 1 untreated control. Red arrows indicate dual labeling. CMV= cytomegalovirus, GFP=green fluorescent protein, DAPI=4',6-diamidino-2-phenylindole, GLP-1=glucagon-like peptide-1

hINSp = engineered human insulin promoter

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



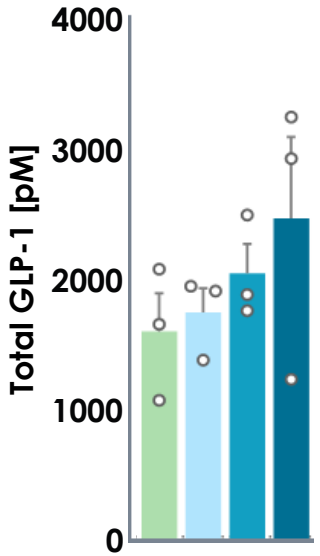




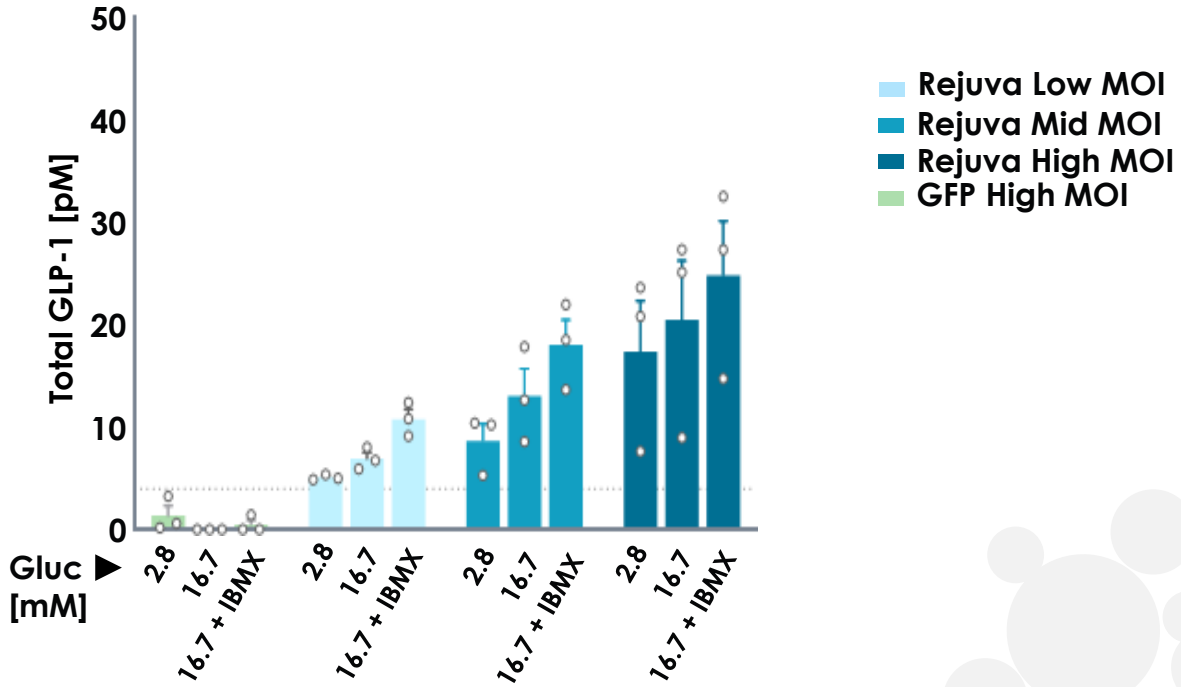
Data are mean ± SD. For GLP-1 expression and secretion, N=3 with 3 technical replicates. For GLP-1 bioactivity, N=1 with 3 technical replicates. GLP-1=glucagon-like peptide 1, Gluc=glucose, GFP=green fluorescent protein, MOI=multiplicity of infection.

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

GLP-1 Content
(lysate)



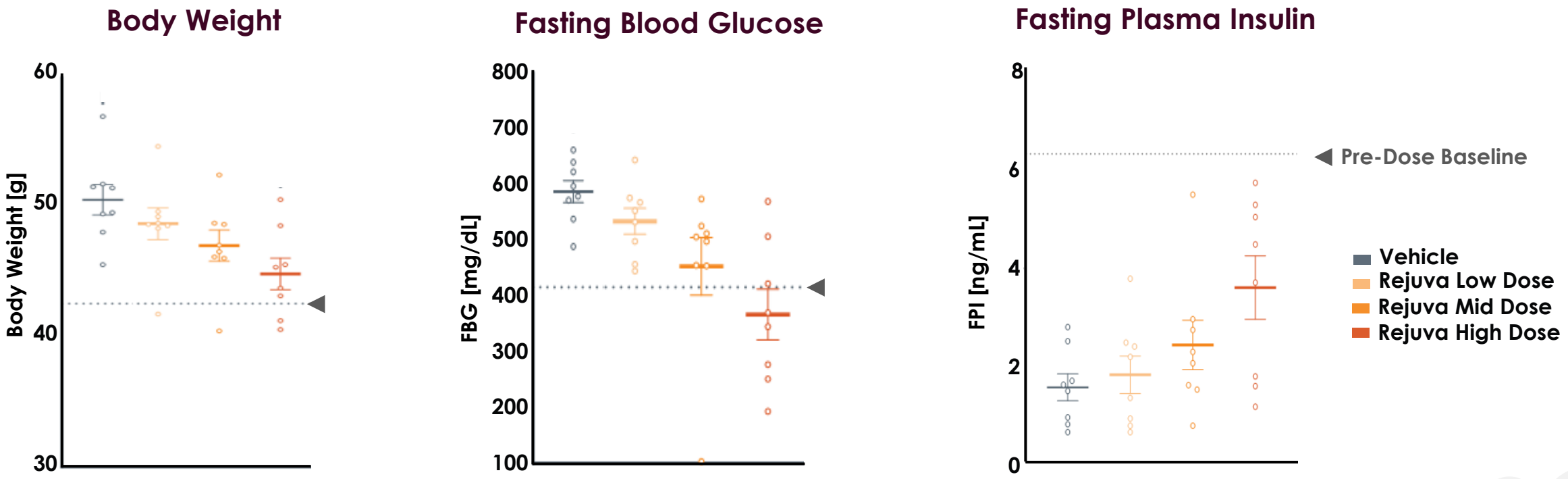
GLP-1 Expression and Secretion
(supernatant)



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

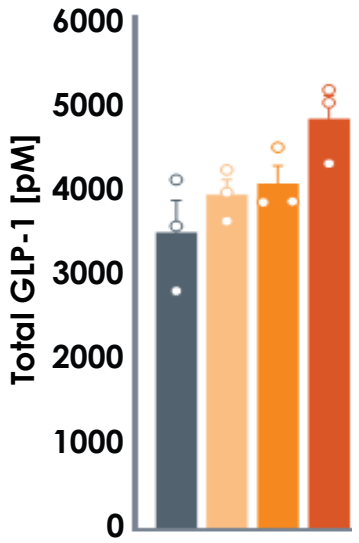


- Rejuva administered in *db/db* mice at 8 weeks of age (advanced T2D model)
- All data from day 46 post-single IP AAV injection (durable, dose-responsive PD effects)

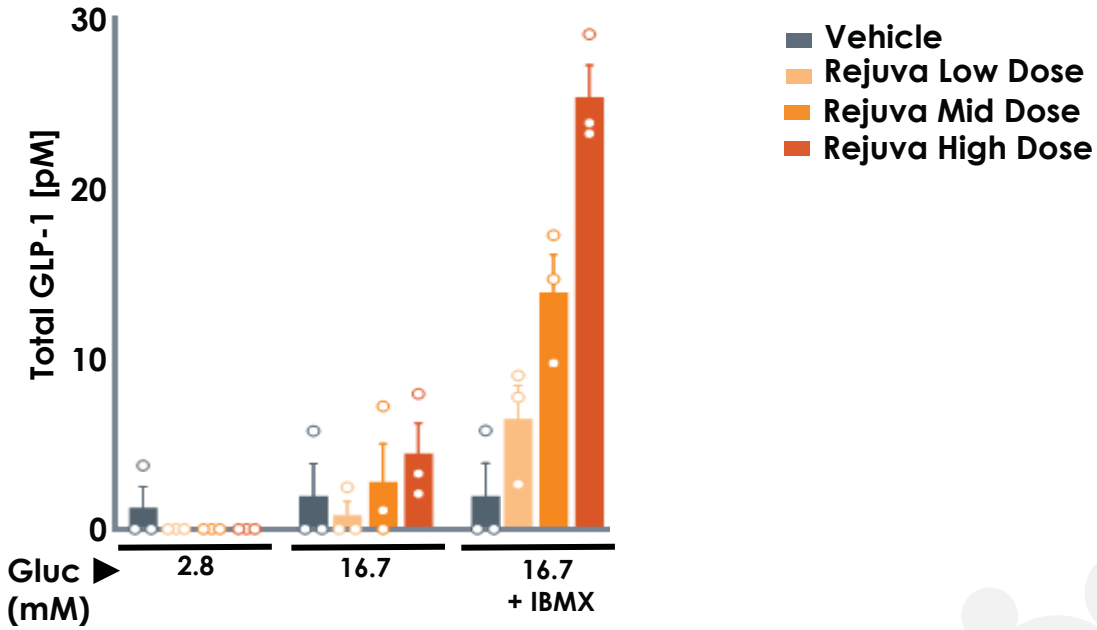
Data mean ± SEM, n=8 per group. FBG=fasting blood glucose, FPI=fasting plasma insulin, GLP-1=glucagon-like peptide 1, T2D=type 2 diabetes, IP=intraperitoneal, PD=pharmacodynamic, AAV=adeno-associated virus.

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)



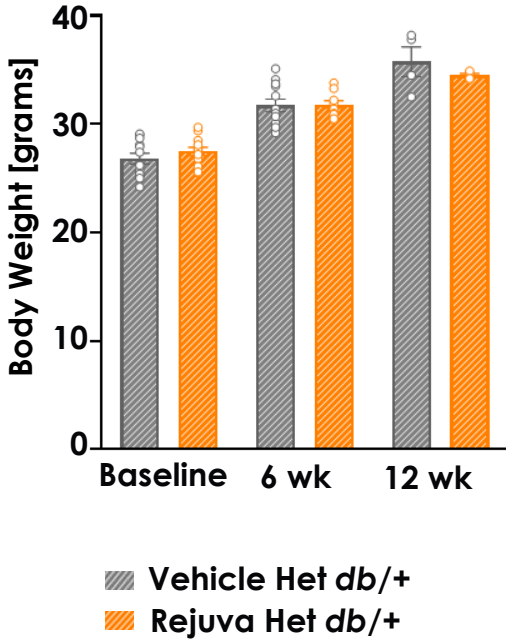
- Islets isolated 49 days post single IP AAV injection

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.

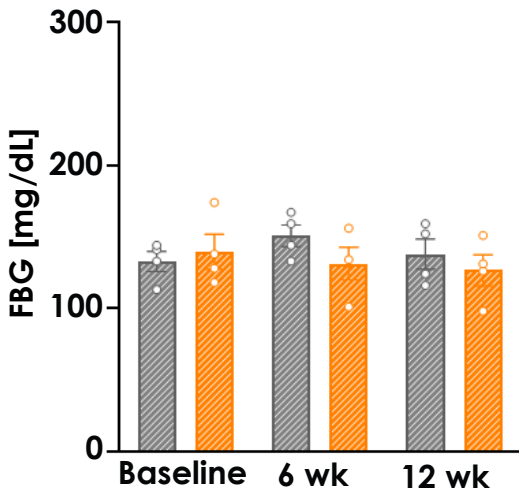
Rejuva Shows Safe and Durable Expression

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

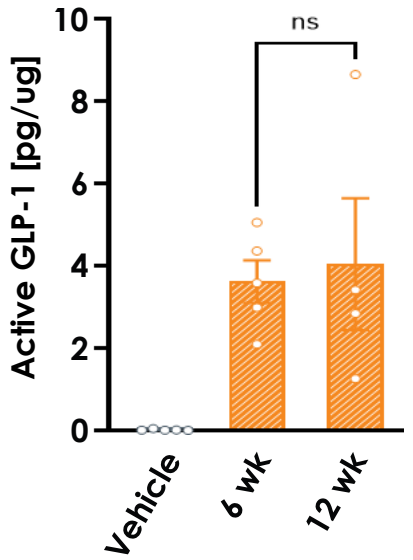
Body Weight



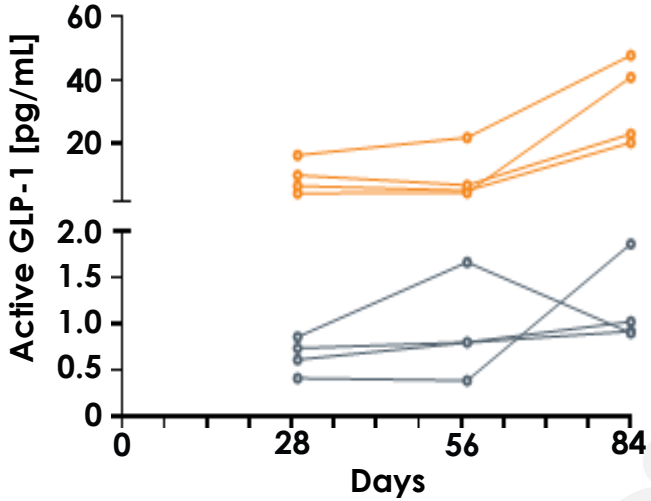
Fasting Blood Glucose



Active GLP-1 (pancreas)



Active GLP-1* (circulating)



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

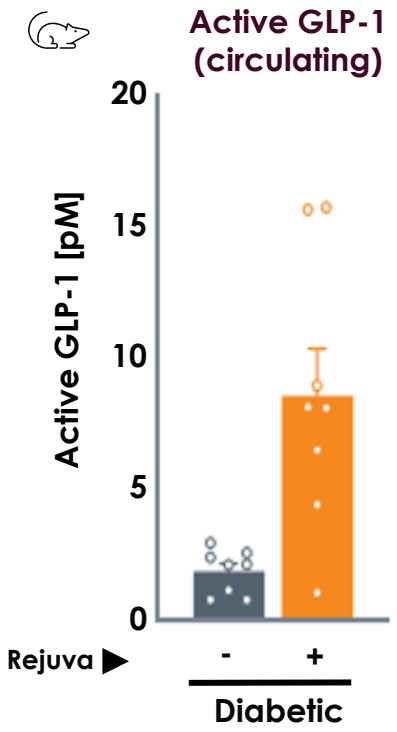
- Rejuva administered to Het *db*/+ (healthy) mice via single IP AAV injection

Data are mean ± SEM, n=4-12 per group. Het=heterozygous, AAV=adeno-associated virus, GLP-1=glucagon-like peptide 1. * Circulating GLP-1 levels in *db*/*db* mice were more than twice those of healthy controls (*db*/+) (data on file).

“Smart” GLP-1 Mimics Endogenous Physiology

Potent efficacy and near physiologic circulating levels

Rejuva



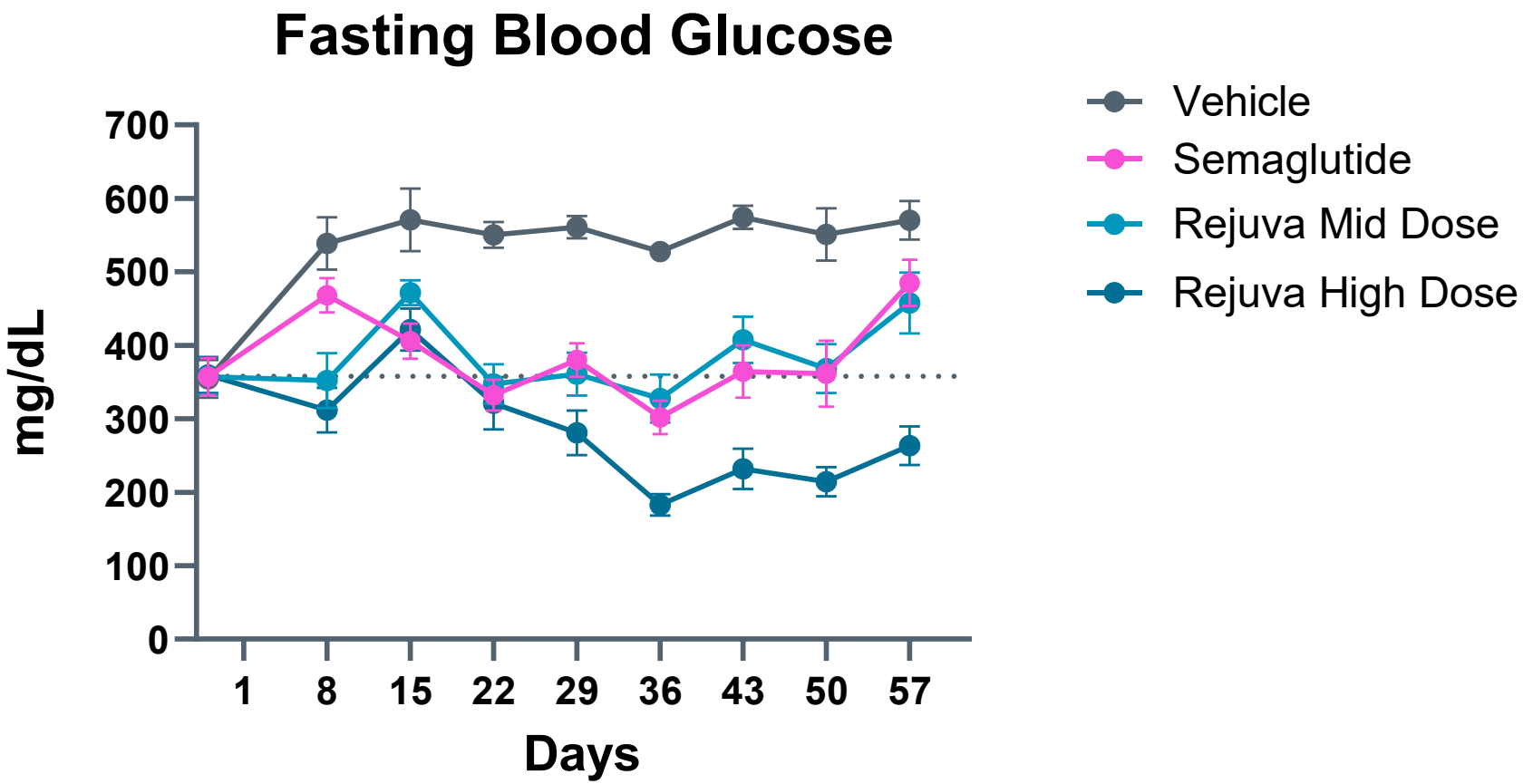
Comparison Chart Active GLP-1 Levels[1]

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. *Levels detected at highest Rejuva dose tested in *db/db* mice. Circulating GLP-1 levels in *db/db* mice were more than twice those of healthy controls (*db/+*) (data on file).

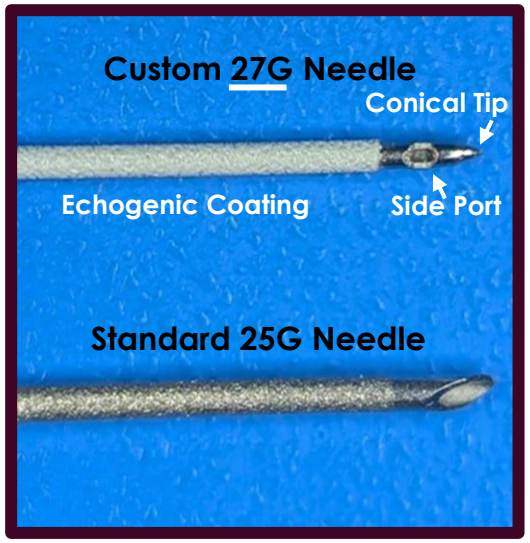
Rejuva Shows Superior Potency Compared to Semaglutide in *db/db* Mice



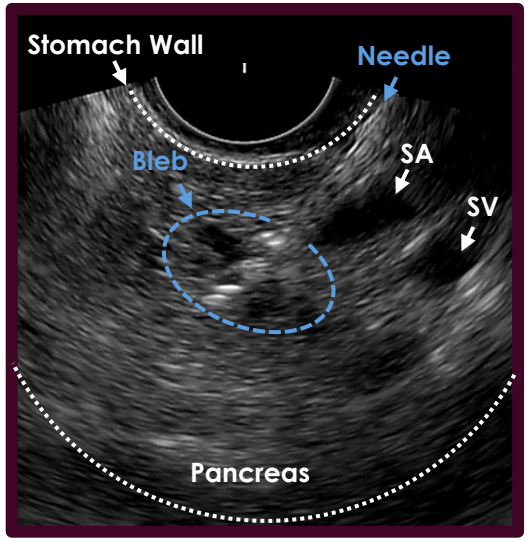
Data are mean ± SEM, n=8 per mice group. Daily s.c. 10nmol/kg semaglutide injection. s.c.=subcutaneous.

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

Rejuva Custom Needle



Live Ultrasound

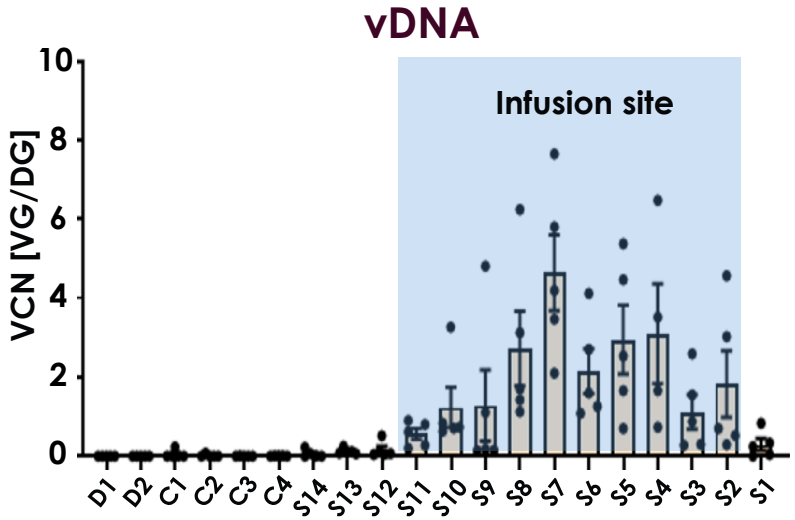


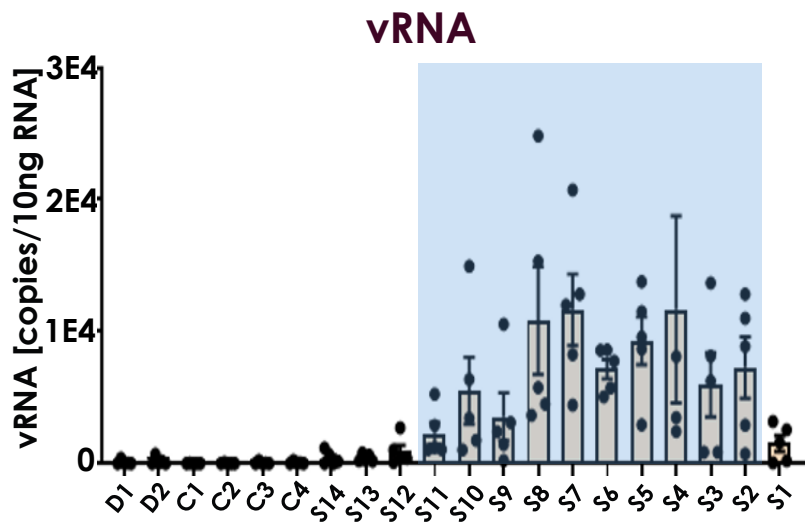
- Rejuva catheter introduced directly to pancreas parenchyma via **standard endoscopic ultrasound techniques** that are already part of standard clinical practice
- Routine upper endoscopic procedure conducted in **~ 20 minutes**

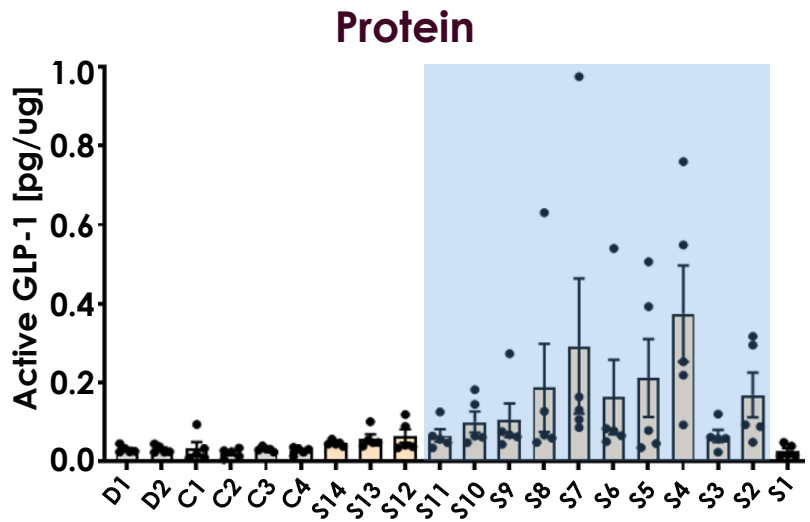
AAV=adeno-associated virus, SA=splenic artery, SV=splenic vein.

Rejuva AAV Effectively Delivered to Pancreas Via Targeted ROA

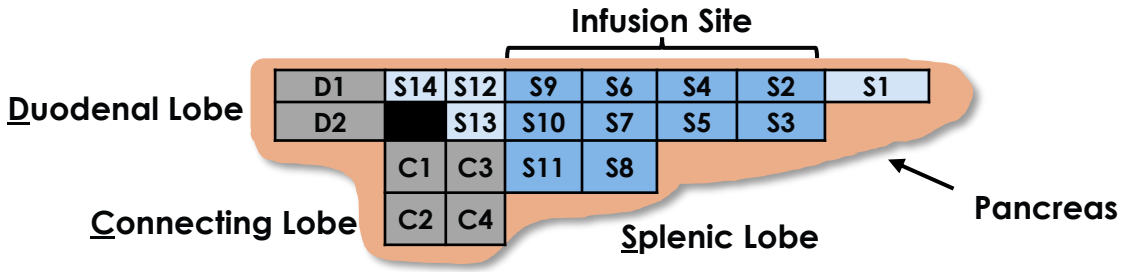
Transgene DNA, RNA, active GLP-1 protein enriched in targeted pancreatic splenic lobe







Pancreas Key

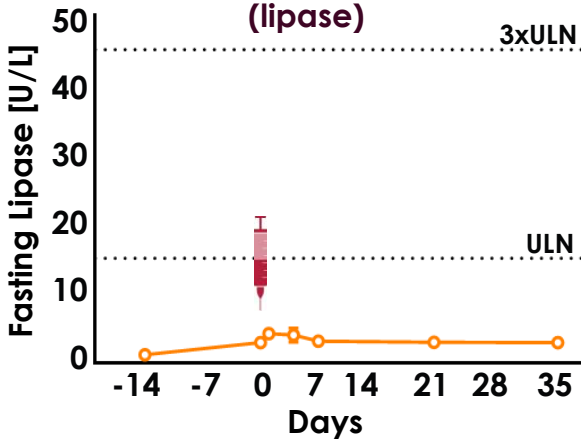


Data are mean ± SEM, n=5 pigs. VCN, RNA, and GLP-1 protein averaged across pancreatic biopsy sections. VCN=vector copy number, GLP-1=glucagon-like peptide 1, VG/DG=vector genome/diploid genome, ROA=route of administration.

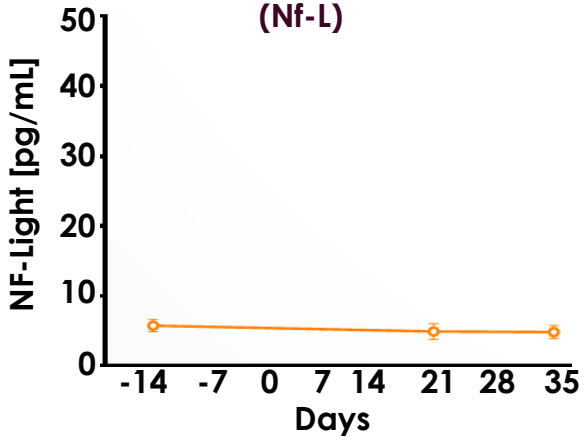
No Toxicity Observed Following Rejuva Treatment

No serum, biodistribution, or histopathologic findings of concern

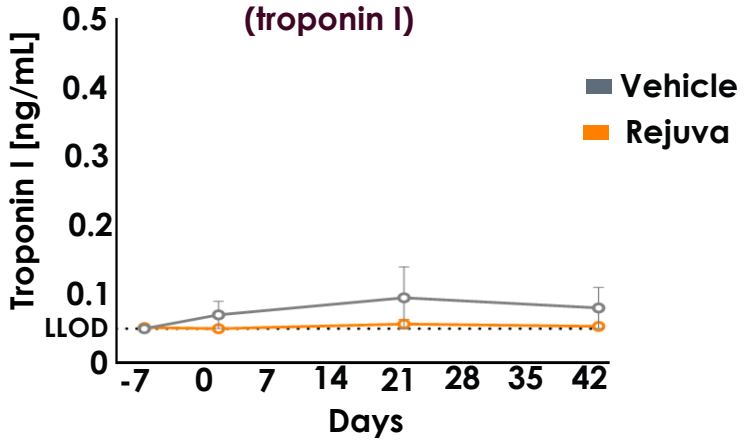
Pancreatitis
(lipase)



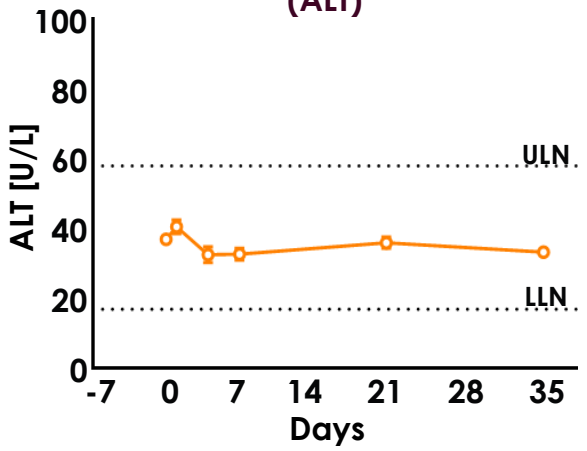
Neurotoxicity
(Nf-L)



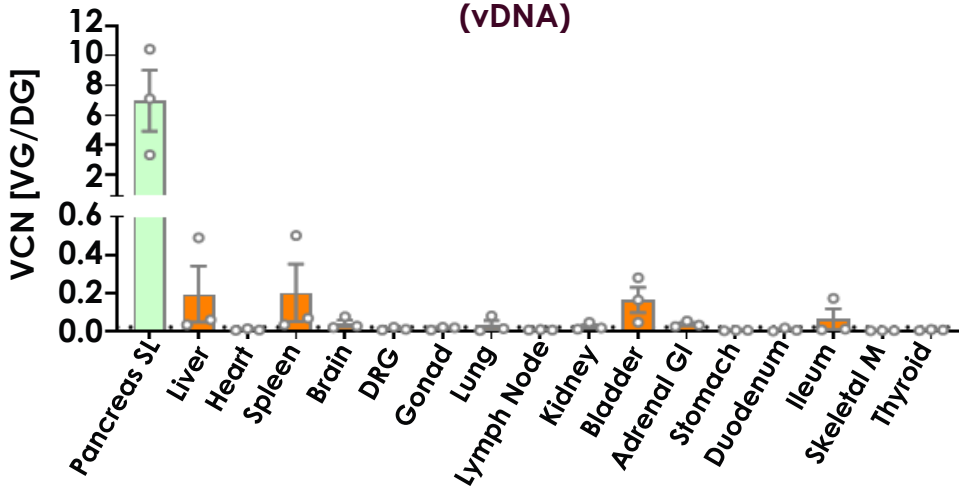
Cardiotoxicity
(troponin I)



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

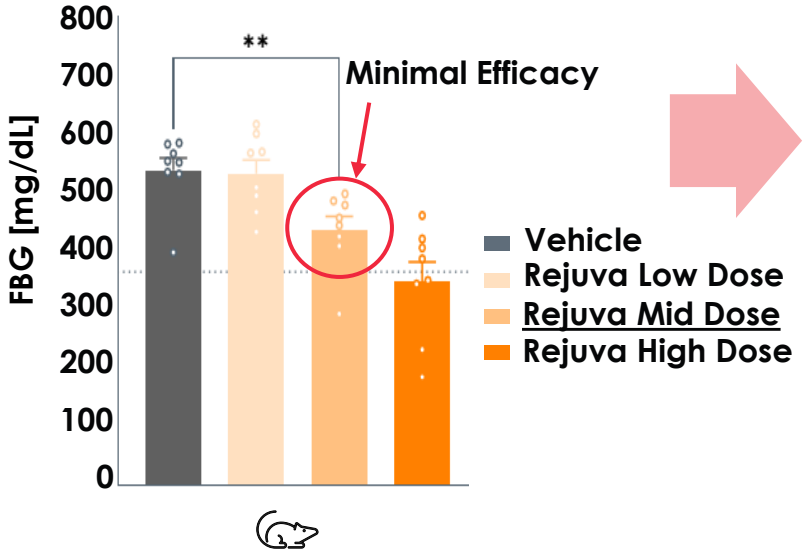
Identify minimally efficacious dose and measure GLP-1 levels

Safety

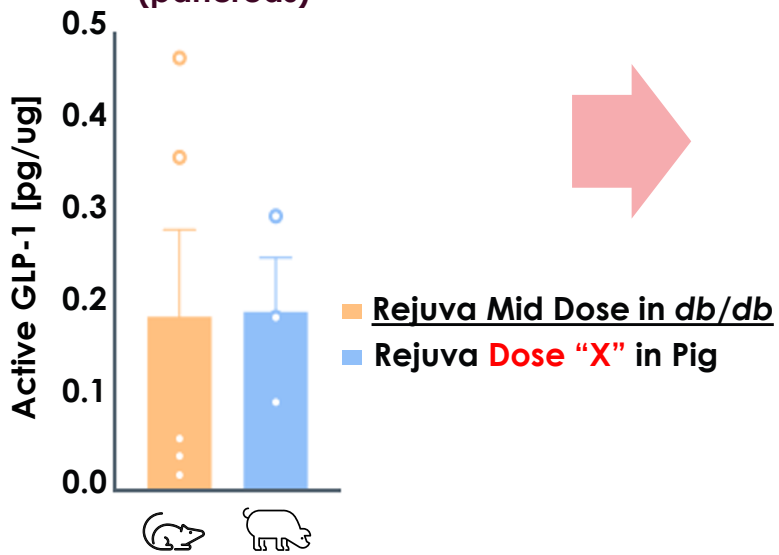
Identify safe dose in pigs with similar GLP-1 levels

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]
- **First patient dosing: 2026**
- **Preliminary data: 2026**

Phase 1 open-label, dose escalation

1. These forward-looking statements are based on management's current estimates and expectations. Refer to the latest disclosures filed with the SEC for a discussion regarding Risk Factors to these and other estimates and expectations. 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.

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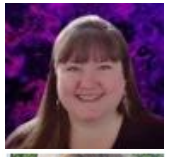

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