Pancreatic Intraductal Infusion of Adeno-Associated Virus To Treat Non-Human Primates in a Toxin-Induced Diabetes Model

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Disclosure Slide

- Dr. George Gittes is on the scientific advisory board of Genprex, the industry collaborator for our diabetes program.

Introduction: Diabetes Mellitus (DM)

- Globally, 537 million people have diabetes mellitus (DM)
- 6.7 million individuals die every year because of DM
  - *720 deaths will have occurred by the end of this hour-long oral presentation session*
- Type 1 DM, marked by a loss of beta-cells, leads to insulin deficiency and hyperglycemia
- Type 2 DM is associated with insulin resistance, reduced beta-cell mass, and impaired beta-cell function
- Both populations have insulin deficiency

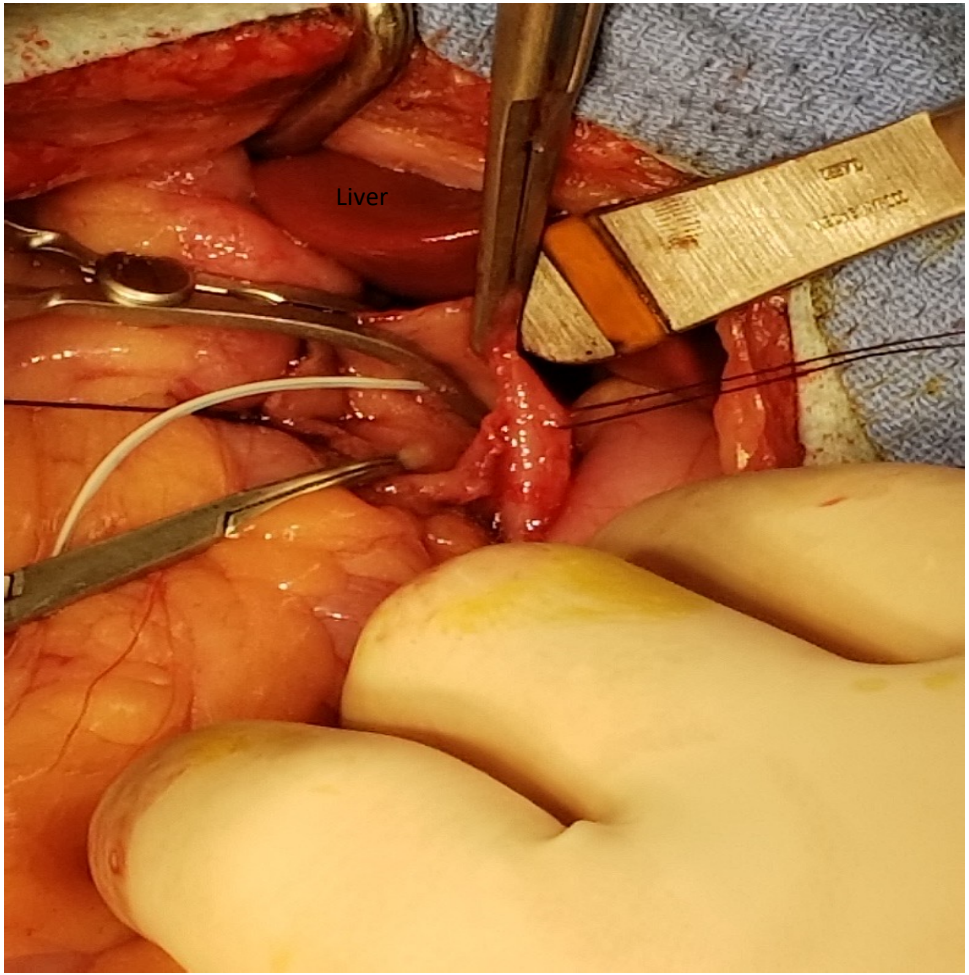
Introduction: Gene therapy as a treatment

- Creation of new beta-like-cells via forced expression of specific transcription factors:
  - pancreas/duodenum homeobox protein-1 (Pdx1)
  - V-maf musculoaponeurotic fibrosarcoma oncogene homolog A (mafA)
- Adeno-associated Virus (AAV) construct used:
  - AAV-CMV-Pdx1-mafA
- Pancreatic intraductal infusion of the engineered AAV construct
  - Led to new beta-like cells, which sensed hyperglycemia, and in response, secreted insulin, restoring normoglycemia[1]
- Effective in mouse models of DM
  - Toxin-induced model
  - Auto-immune genetic model

[1] Cell Stem Cell 2017;22:78-90

AAV to treat DM in non-human primates (NHP)

- In a toxin-induced diabetes model in NHPs using a similar construct we aimed to replicate the results seen in mice
  - AAV-CMV-Pdx1-mafA
- We hypothesized that an intraductal viral infusion would generate new beta-like cells and reverse the hyperglycemia, alleviating or eliminating the need for exogenous insulin
- Eight NHPs were made diabetic using streptozocin (a drug that results in >98% beta cell death), and after confirmation of diabetes and an appropriate acclimation period (approximately one month), we proceeded with surgery

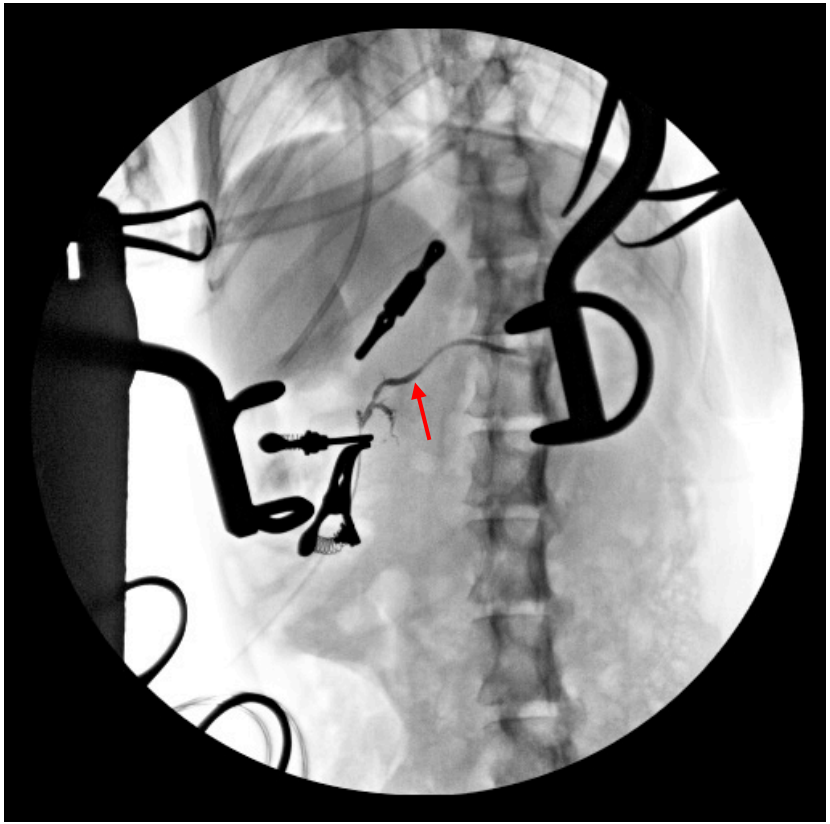


Procedure in NHPs

- Midline incision
- Identify and clamp common bile duct (CBD)
- Duodenal incision
- Advance catheter through major papilla and clamp into place
- Infuse dye to identify spillage
- Pancreatography (next slide) to confirm placement
- Infuse engineered AAV construct
- Close incisions

Pancreatography

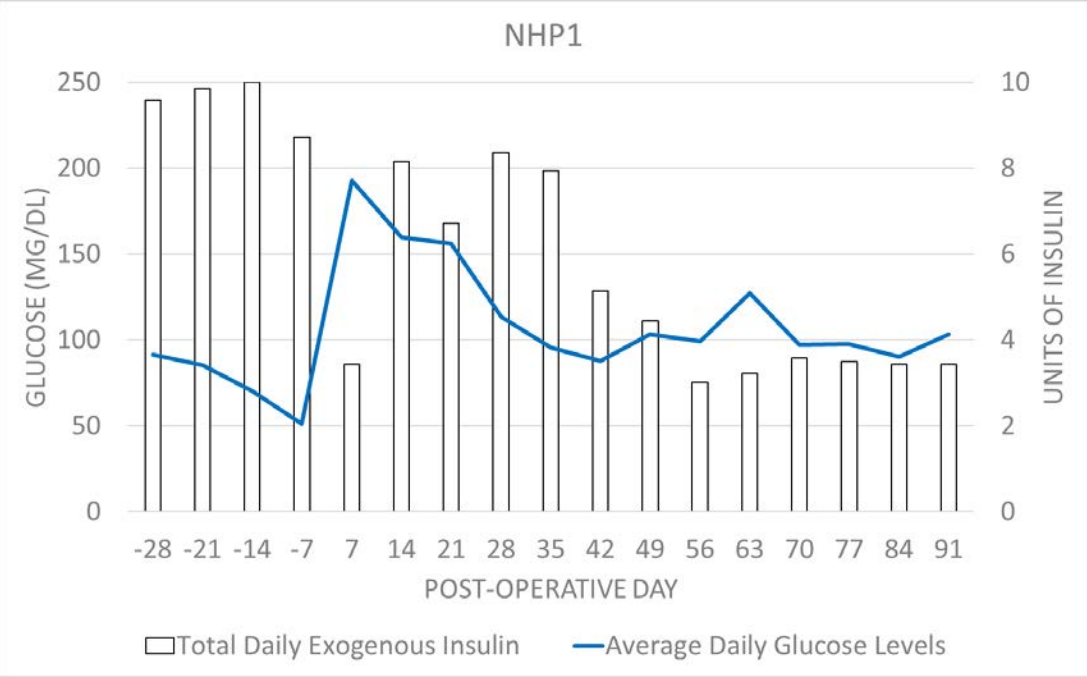
- Normal filling of the pancreatic duct (arrow)

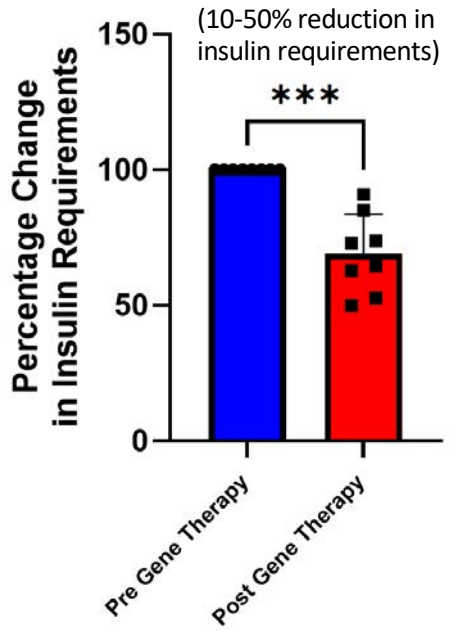


Summary of Results

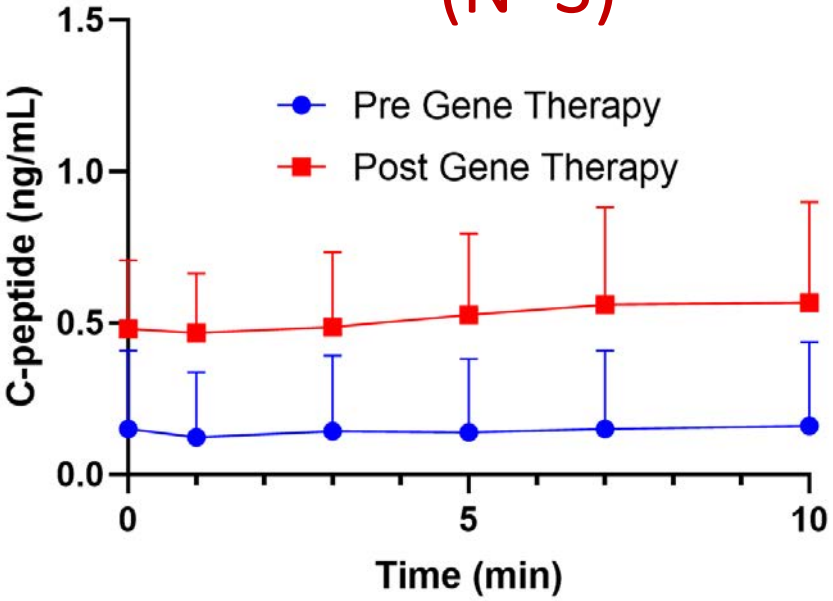
- After the pancreatic intraductal infusion of the AAV engineered construct, the eight non-human primates had:
  - Decreased insulin requirements ($p<0.001$)
  - Increased c-peptide levels ($p<0.05$)
  - Improved glucose tolerance compared to baseline ($p<0.05$)
    - One with normal glucose tolerance three months post gene therapy
  - The presence of more **insulin-positive cells** compared to non-treated diabetic controls based on immunohistochemistry (IHC)

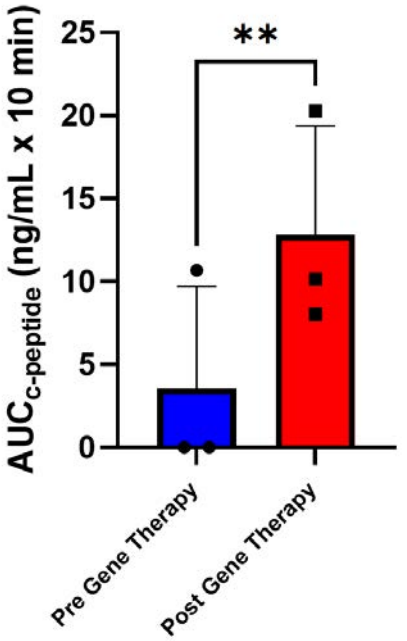
Blood Glucose and Insulin Requirements (N=8)



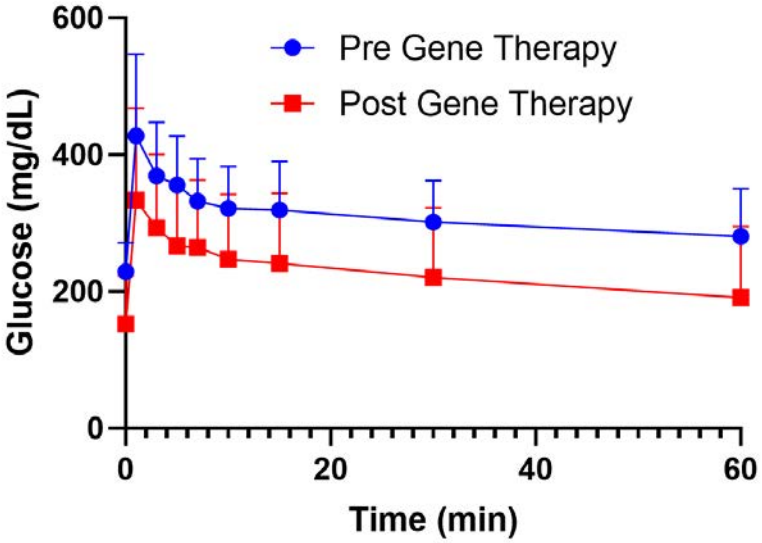


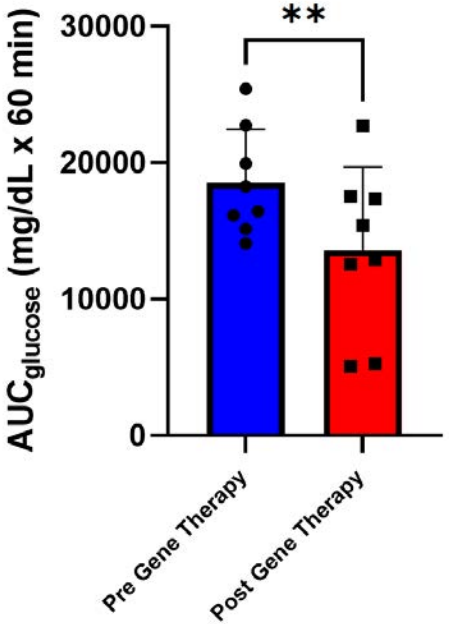
Average Glucose Stimulated Insulin Secretion (C-peptide) Eight Weeks after Gene Therapy (N=3)



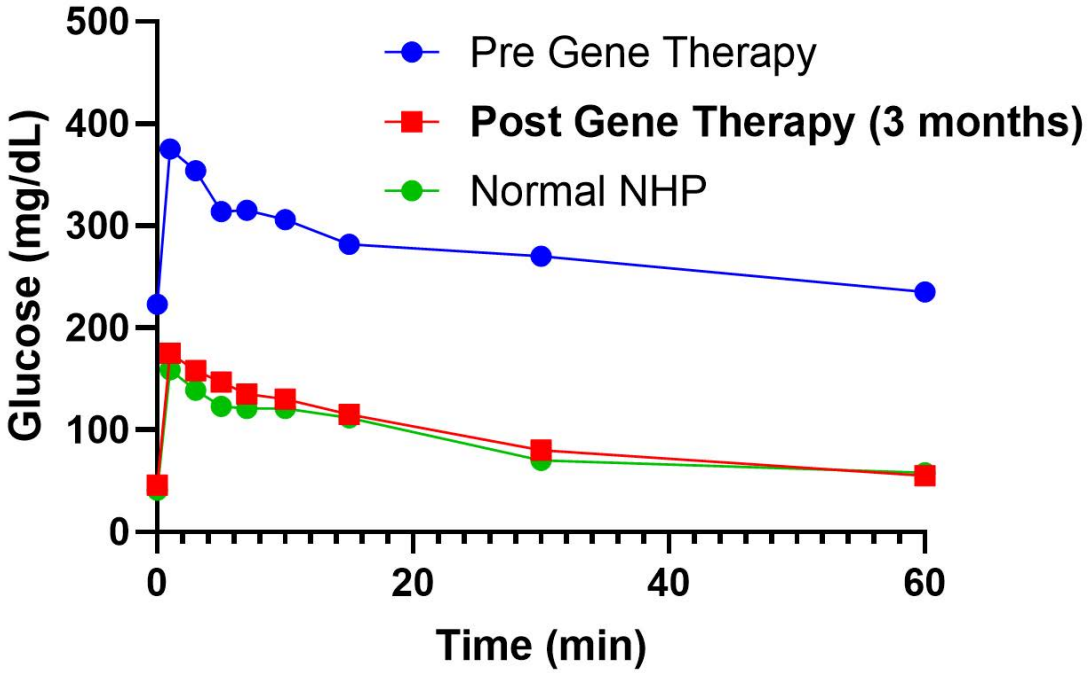


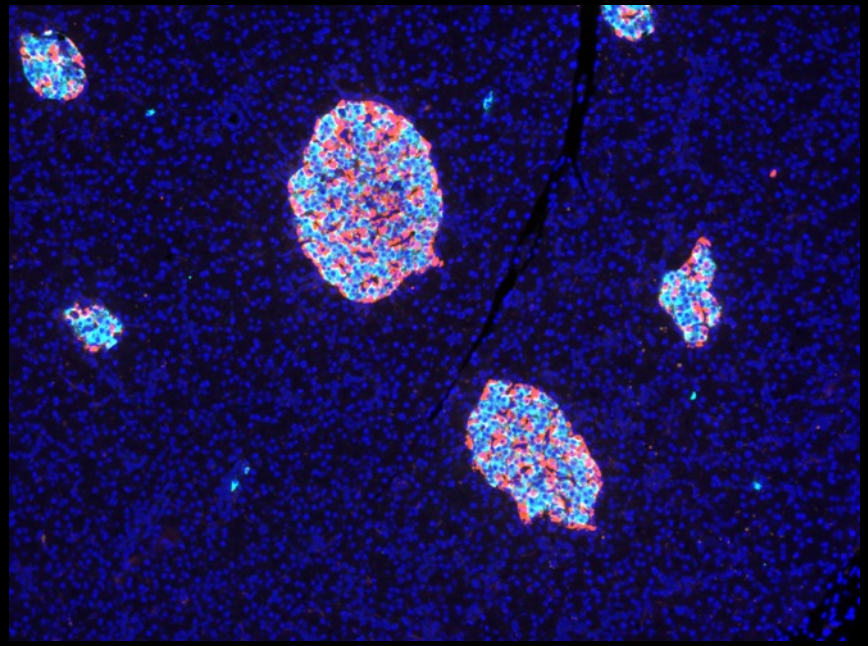
Average Glucose Tolerance Test Eight Weeks after Gene Therapy (N=8)



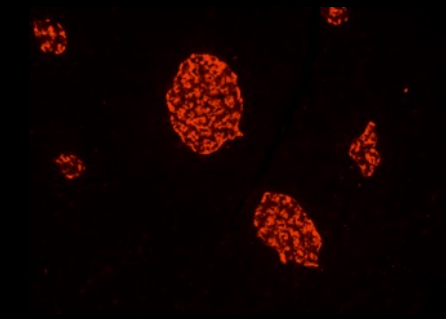


NHP2 Recent Glucose Tolerance Test

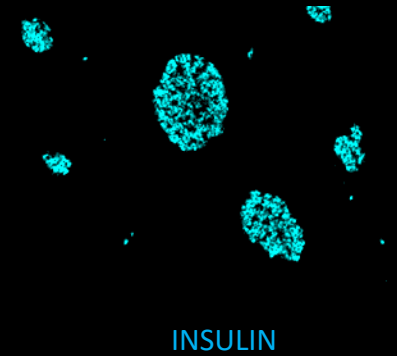




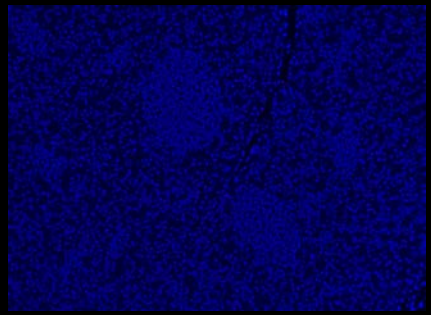
Combined



GLUCAGON



INSULIN



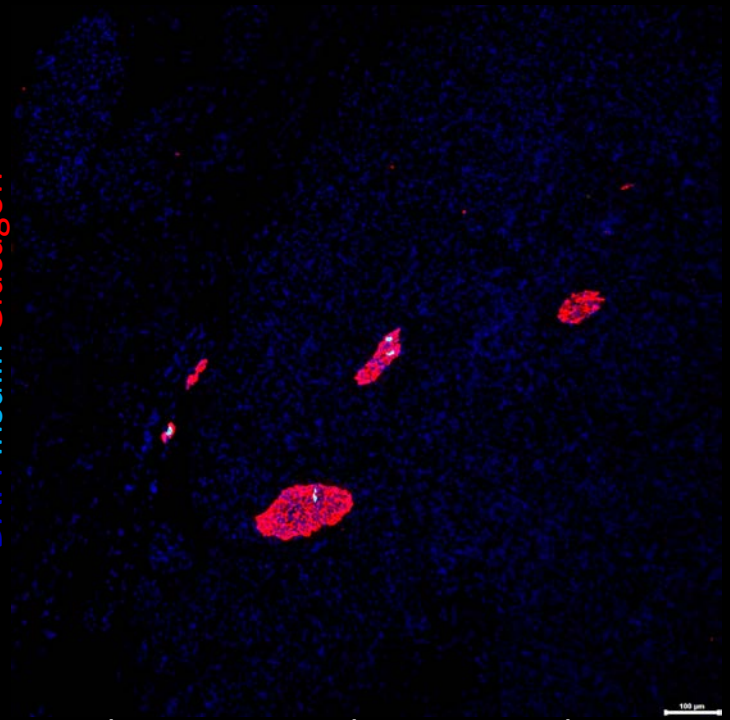
DAPI

IHC in a Normal NHP

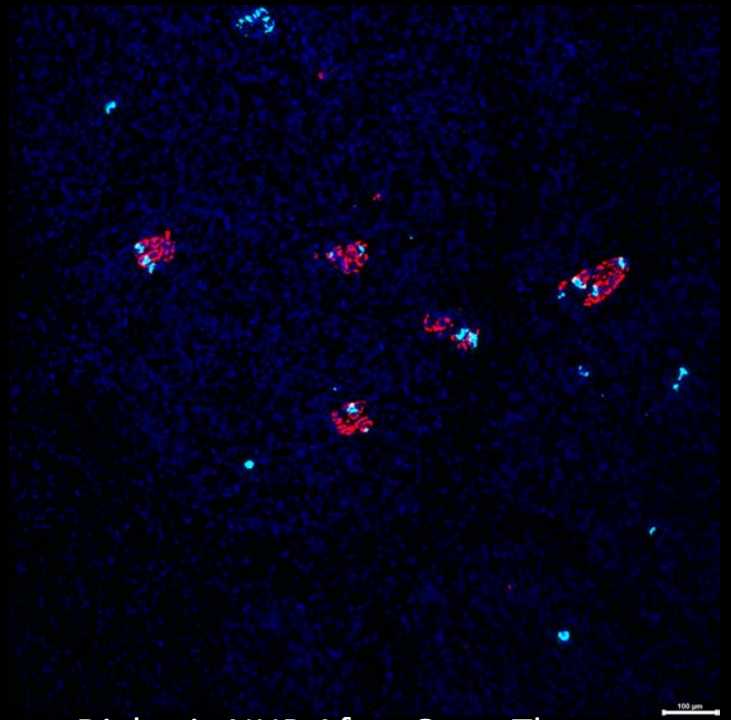
IHC Eight Weeks after Gene Therapy

(Need at least 20% of normal beta cell mass to maintain normoglycemia)

DAPI Insulin Glucagon

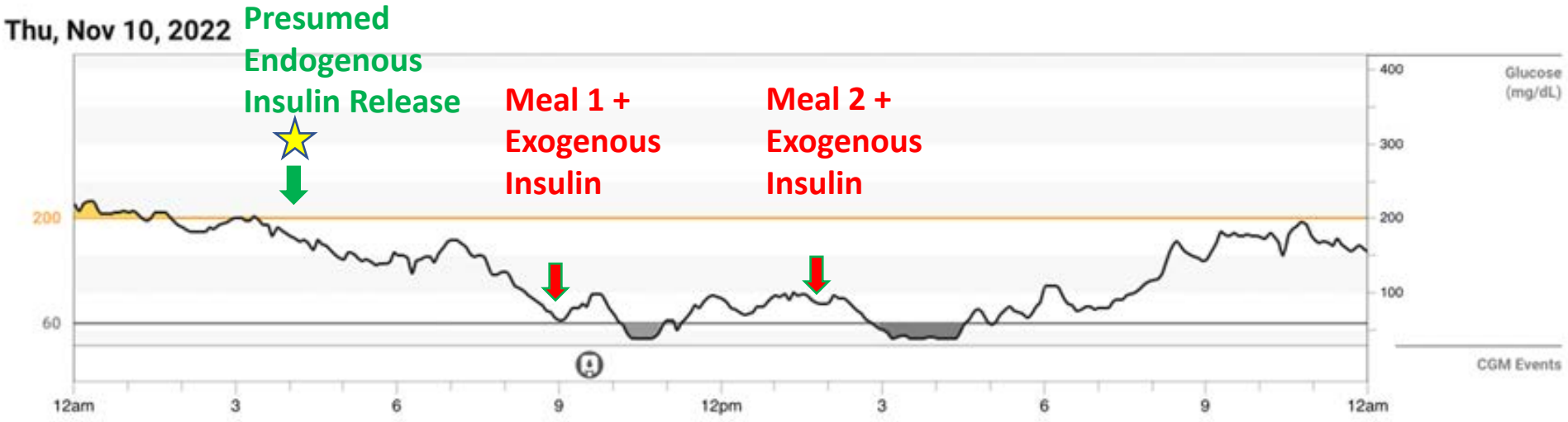


Diabetic NHP Without Gene Therapy



Diabetic NHP After Gene Therapy

Continuous glucose monitor (CGM) after gene therapy (NHP3)

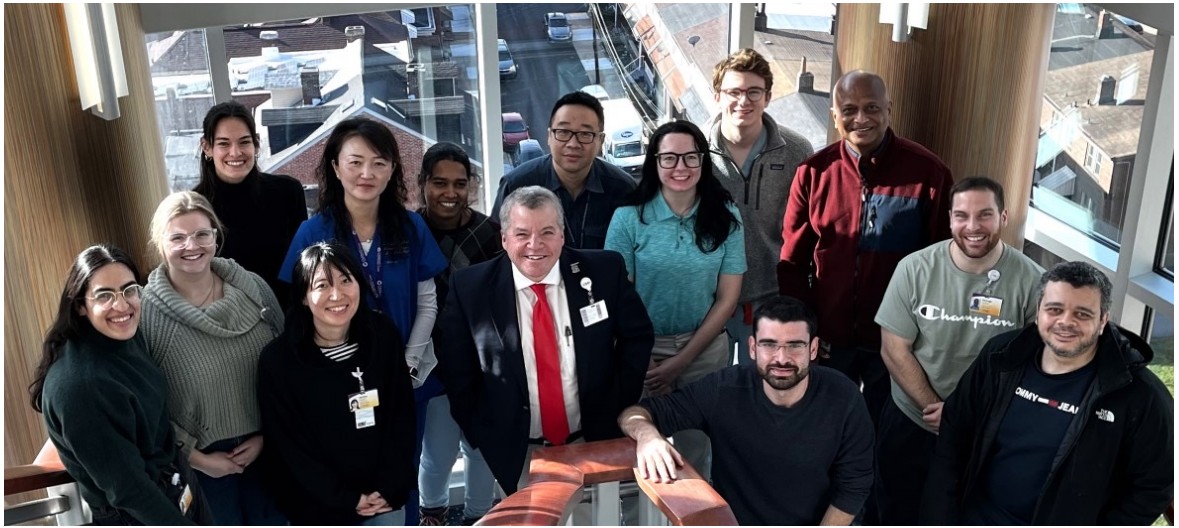


Conclusion

- Building on our previous work in mouse models, we have now utilized similar AAV engineered constructs and shown durable improvements in a model of Type 1 diabetes in NHPs
- In humans this gene therapy could be administered without an operation using routine endoscopic retrograde cholangiopancreatography (ERCP).
- The newly formed beta-like-cells can produce insulin, may avoid the autoimmune attack, and provide long-term replacement of beta-cells
- This potentially disruptive gene therapy could make the administration of exogenous insulin unnecessary, and thus is a promising treatment for both Type 1 and Type 2 diabetes.

Thank you

Mentor: Dr. George Gittes



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