generation bio™

Creating a New Class of **Durable Redosable Gene Therapy**

FOR MILLIONS OF PATIENTS LIVING WITH RARE AND PREVALENT DISEASES

NASDAQ: GBIO

MAY 2021

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Non-Viral Gene Delivery of Human FVIII to Hemophilia A Mice and Non-Human Primates

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MAY 2021

Forward-looking statements

Any statements in this presentation about future expectations, plans and prospects for the company, including statements about our strategic plans or objectives, our technology platforms, our research and clinical development plans, and other statements containing the words “believes,” “anticipates,” “plans,” “expects,” and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: uncertainties inherent in the identification and development of product candidates, including the conduct of research activities, the initiation and completion of preclinical studies and clinical trials and clinical development of the company’s product candidates; uncertainties as to the availability and timing of results from preclinical studies and clinical trials; whether results from preclinical studies will be predictive of the results of later preclinical studies and clinical trials; expectations for regulatory approvals to conduct trials or to market products; challenges in the manufacture of genetic medicine products; whether the company’s cash resources are sufficient to fund the company’s operating expenses and capital expenditure requirements for the period anticipated; the impact of the COVID-19 pandemic on the company’s business and operations; as well as the other risks and uncertainties set forth in the “Risk Factors” section of our most recent annual report on Form 10-K, which is on file with the Securities and Exchange Commission, and in subsequent filings the company may make with the Securities and Exchange Commission. In addition, the forward-looking statements included in this presentation represent the company’s views as of the date hereof. The company anticipates that subsequent events and developments will cause the company’s views to change. However, while the company may elect to update these forward-looking statements at some point in the future, the company specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the company’s views as of any date subsequent to the date on which they were made.

Generation Bio has built the foundation to unlock the full potential of gene therapy

PATIENTS

Non-immunogenic

- Patients with existing antibodies to AAV
- Titration to effect for every patient
- Ability to intervene early in life when it matters most

ceDNA
closed-ended DNA

Large cargo capacity

- Genes that are too large for AAV
- More potent constructs
- Addition of regulatory elements

RAPID DEVELOPMENT & SCALING ENGINE

Manufacturing scale & speed

- Rapid cycle from idea to test article (4 weeks)
- Currently comparable scale and cost to biologics
- Move to enzymatic process enables scale more comparable to mRNA

ctLNP
cell-targeted LNP

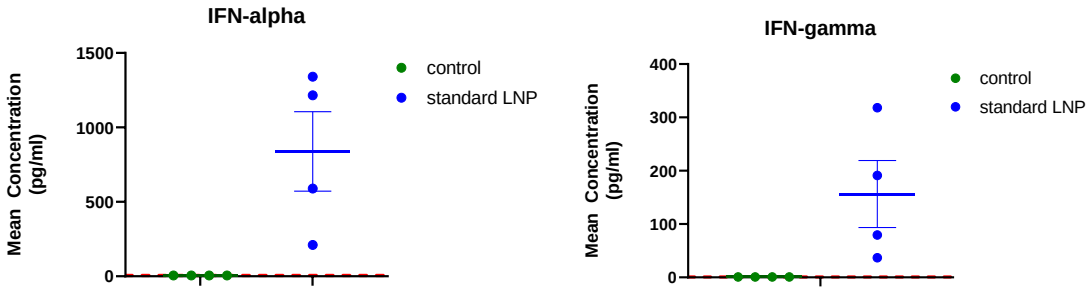
Specific, on-target delivery

- High selectivity for cell type of choice
- Amenable to many tissues/cell types

To unlock this potential, solutions to two independent, decades old challenges are required

Innate Immunity

- Non-viral delivery systems deliver DNA to endosome and cytoplasm of macrophages which are rich in DNA pattern recognition receptors (PRRs)
  - AAV “shields” DNA from innate immune sensors until DNA is in nucleus

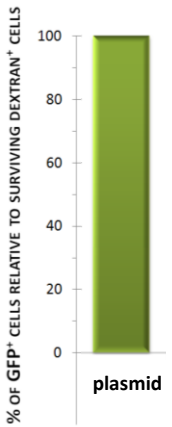


- This response limits doses of traditional LNPs/DNA to 0.5 mg/kg or less – below where these systems can drive therapeutically meaningful expression

Access to Nucleus

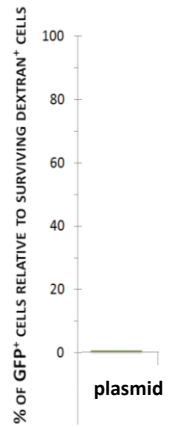
- Non-viral delivery systems such as LNPs only deliver cargo to the cytoplasm of target cells
- For gene therapy applications, independent solutions to nuclear uptake must be implemented

pDNA injected into nucleus:



100% of cells GFP positive

pDNA injected into cytoplasm:



0% of cells GFP positive

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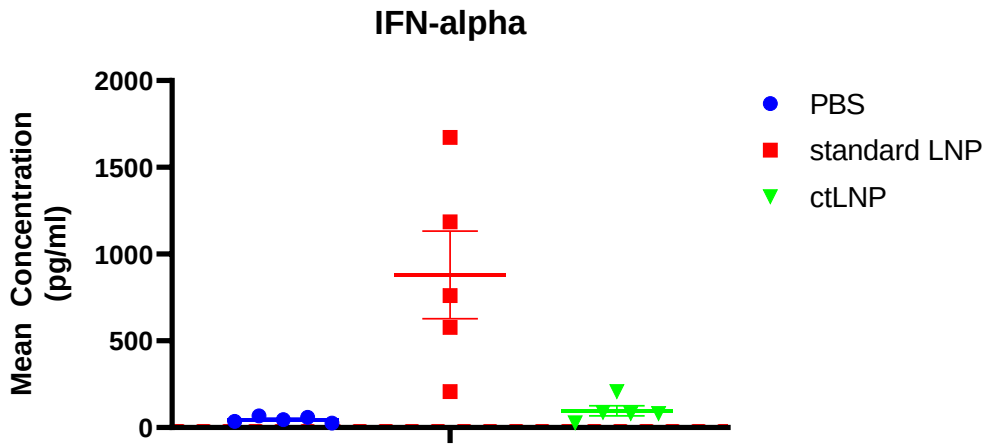
We have developed unique and proprietary solutions to both challenges

Innate Immunity

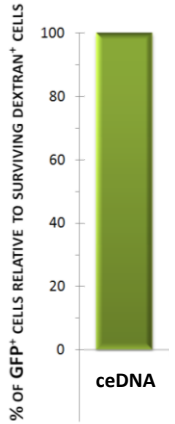
- By engineering our LNPs to “de-target” macrophages and then actively re-targeting them to desired cell types (hepatocytes in liver) we have dramatically opened the therapeutic index for non-viral DNA delivery. We call these cell-targeted LNPs or ctLNP
- 0.5 mg/kg; 6 hours post dose serum IFNα:



Access to Nucleus

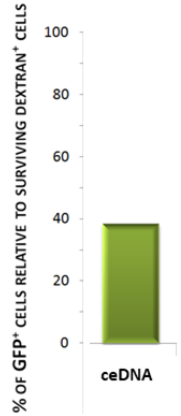
- Unlike pDNA, our closed-ended DNA construct provides GFP positive cell populations after delivery to the cytoplasm of cells

ceDNA injected into nucleus:



100% of cells GFP positive

ceDNA injected into cytoplasm:



40% of cells GFP positive

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More context on ctLNP – our strategy critically relied on the ability to eliminate phagocytosis by macrophages while maintaining endosomal escape

Phagocytosis assay (labeled LNP uptake into human macrophages)

- LNPs are labelled with DiD
- THP1 monocytes are differentiated into macrophages
- Macrophages are incubated with LNPs for a set period of time, cells are then washed and imaged for visualization

pH dependent endosomal escape assay

- LNPs are incubated with serum and followed by mixing with endosome mimicking liposomes for a set period of time at 37°C
- The incubation occurs at controlled pHs
- DNA release from LNPs is measured using PicoGreen assay
- Adapted from Zhang et al., *Journal of Controlled Release* 174 (**2014**) 7–14.

Addition of GalNAc to target hepatocytes (6 hr qPCR data)

- Perfused tissues were collected at 6 hours and levels of ceDNA were determined by qPCR

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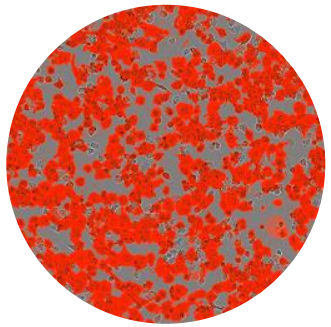
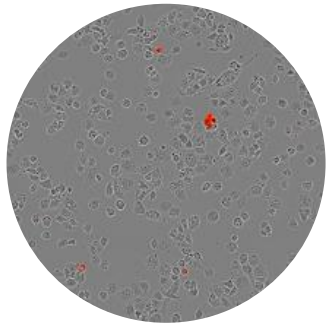
Phagocytosis assay (labeled LNP uptake into human macrophages)

Standard LNPs

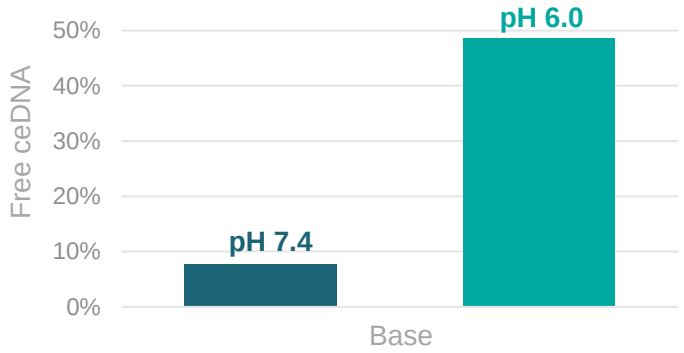


ctLNP

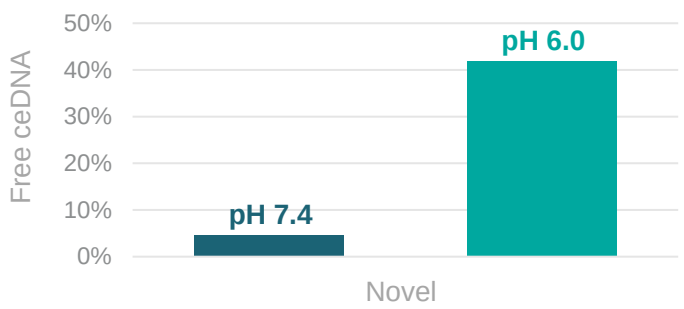


pH dependent endosomal escape assay

Standard LNPs Endosomal Release

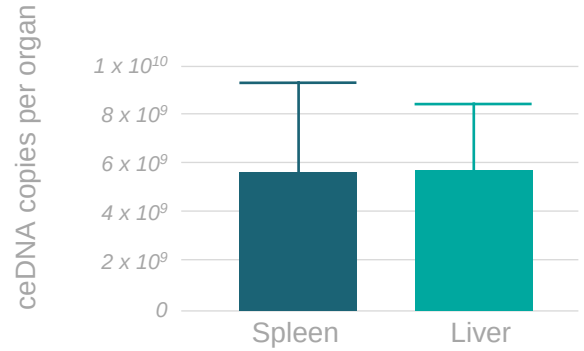


ctLNP Endosomal Release



Addition of GalNAc to target hepatocytes (6 hr qPCR data)

Standard LNPs



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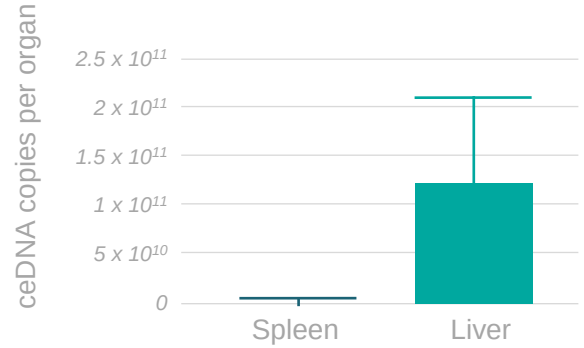

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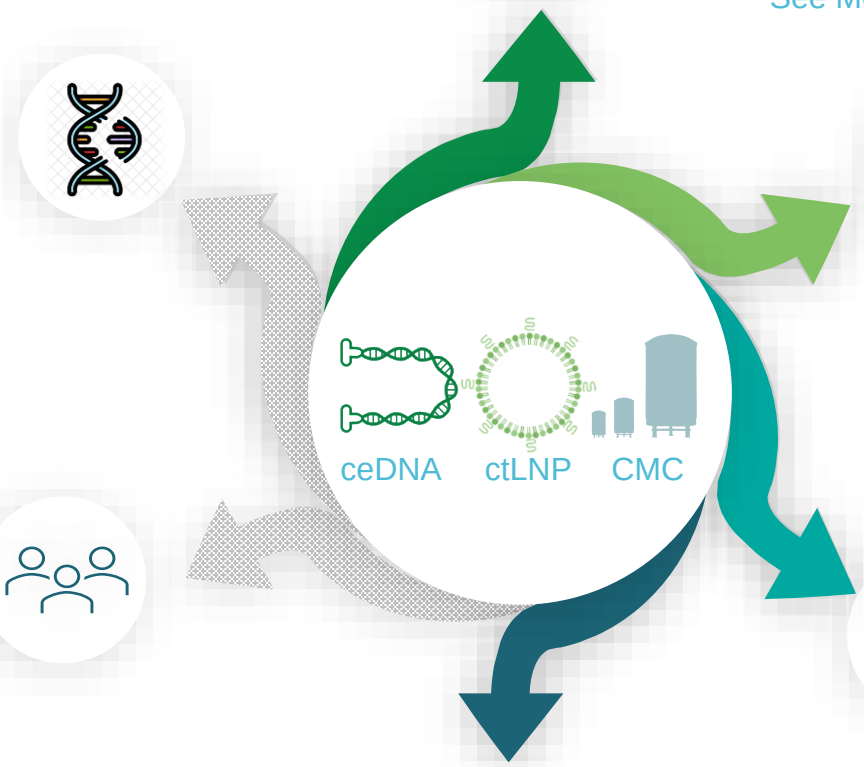
Solutions to innate immunity and/or nuclear uptake open significant new and differentiated opportunities

Rare liver diseases
Lead programs in Hemophilia A and PKU with rapid follow on in Wilson disease, Gaucher and others

See Monds poster

Gene editing in rare liver and retina
Targeted gene insertion for one-time correction



Retinal diseases
Lead programs in LCA10, Stargardt and Wet AMD

Vaccines

Antibody gene transfer
Examples include hepatitis B, HIV and sickle cell disease, Wet AMD, etc.

See Silver poster

Targeted therapy across multiple tissues
Examples include skeletal muscle, CNS and oncology therapies

Solid arrows = focus areas; spotted gray arrows = conceptual

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Hemophilia A

Redosable childhood intervention; titration to correct level in each patient

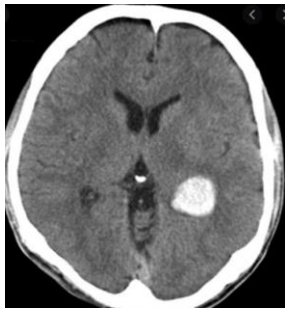
DISEASE

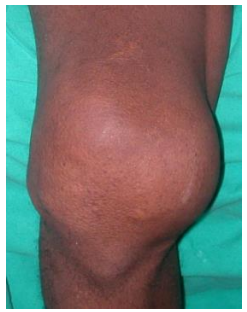
~16,000 patients in US

Diagnosis in early childhood

Bleeding disorder caused by deficiency in clotting factor VIII

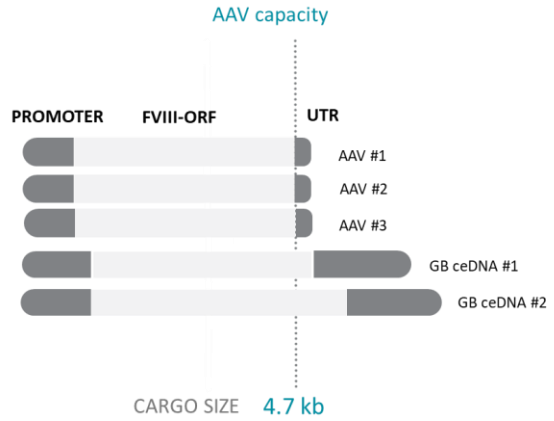
Gene therapy in development limited to adults, efficacy is variable and waning



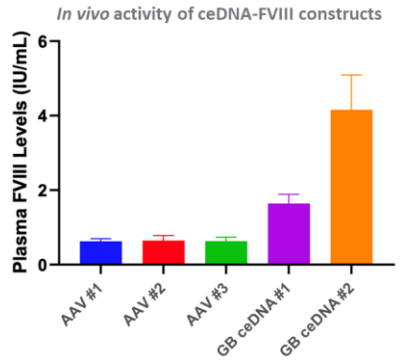


Atalay et al., Ital. J. Med. 9(3): 290-293 (2015)
AAAS EurekAlert! 30 Aug 2018 Univ. Witwatersrand

OUR APPROACH



ceDNA capacity enables optimized Factor VIII constructs



POTENTIAL THERAPEUTIC OPPORTUNITY

- ★ Greater potency based on larger genetic payload
- ★ Titration to target expression level for each patient
- ★ Dosing in childhood before disease progression
- ★ Redosing to extend benefit over a lifetime

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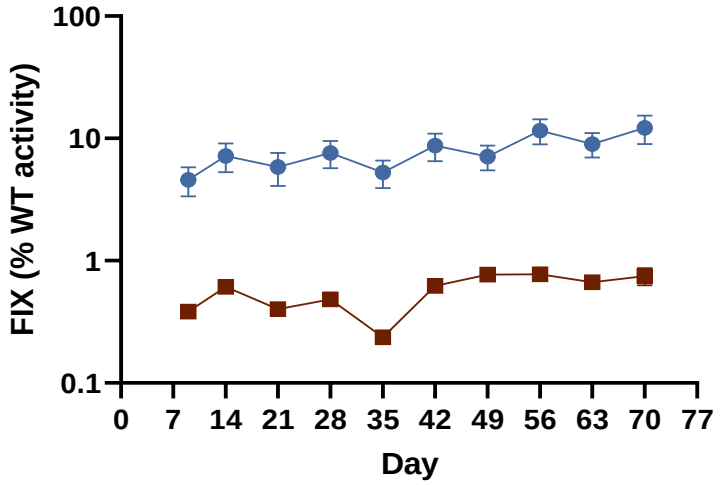
Demonstrated durability and redosing with Factor IX in immune competent mice

No decrease in expression throughout study period, redosing increases expression proportionately

Durability & redosing *in mice*

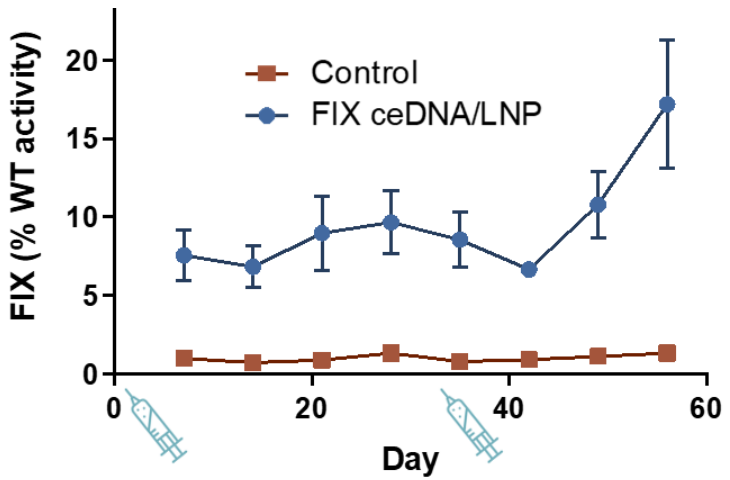
FIX used as surrogate for durability and redosing in wildtype mice because this human protein does not raise neutralizing antibodies in mice, unlike human FVIII

Factor IX



- Single IV administration at study day 0
- Factor IX activity calculated from protein ELISA

Factor IX



- Single IV administration at study day 0
- Re-dosed at day 36 at same dose level
- Factor IX activity calculated from protein ELISA

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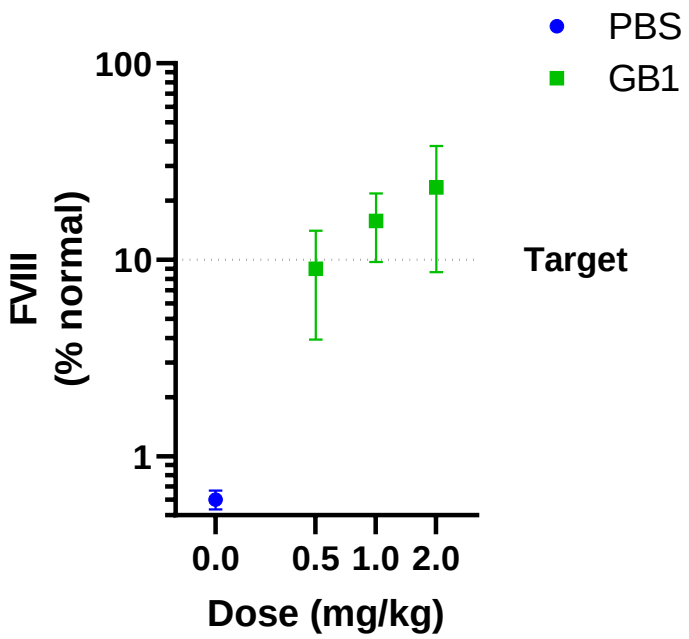
Mouse proof of concept and translation of expression from mouse to NHP

Target levels of factor VIII expression
in Hemophilia A mice

Development Construct: FVIII Expression
Systemic IV administration via ctLNP (Day 10)



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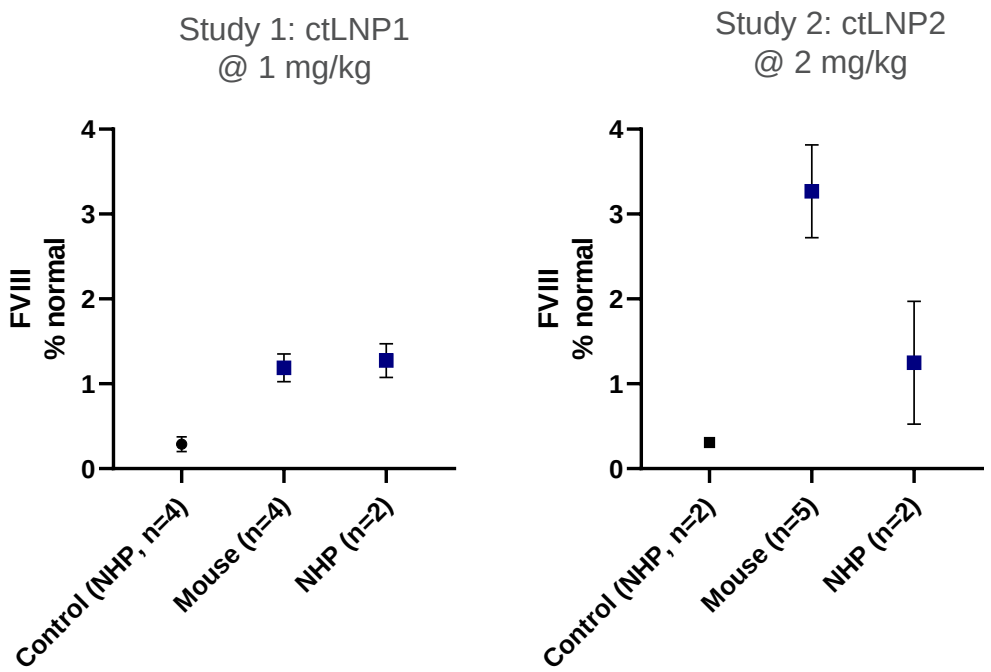
Translation of expression across species
from mouse to NHP

Research Construct: Species Translation
Systemic IV administration via ctLNP (day 5 or 7)



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Summary

- Non-viral delivery of DNA represents enormous opportunity to expand reach of genetic medicines (gene transfer and gain of function gene editing)
- Two decades-old hurdles have been uniquely overcome at Generation Bio – ctLNP to dampen innate immune stimulation and ceDNA to gain access to target cell nuclei
- Durable expression of non-immunogenic protein demonstrated in wildtype mice
- Redosing of non-immunogenic protein demonstrated in wildtype mice
- Expression of FVIII for hemophilia A at therapeutically meaningful levels has been achieved in mice
- A roughly 2:1 species translation of expression between mouse and non-human primates has been achieved with tolerability in NHP up to 2 mg/kg

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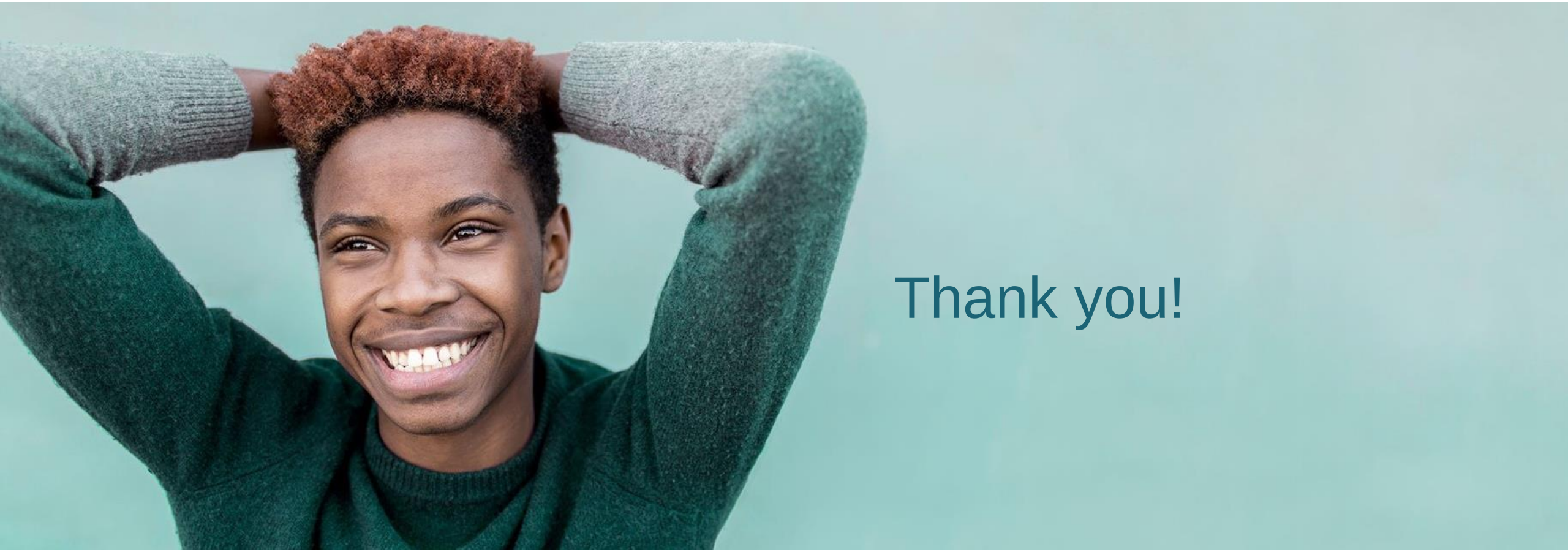

Thank you!