ADRENAS THERAPEUTICS

Targeting Classic Congenital Adrenal Hyperplasia at its source

ASGCT Presentation // May 2021

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Intravenous AAV5 Gene Therapy with Human CYP21A2 Corrects Phenotypic Deficiencies of the 21-hydroxylase Knockout Mouse Model and Demonstrates Durability and Safety in Non-Human Primates and Mice.

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Congenital Adrenal Hyperplasia (CAH)

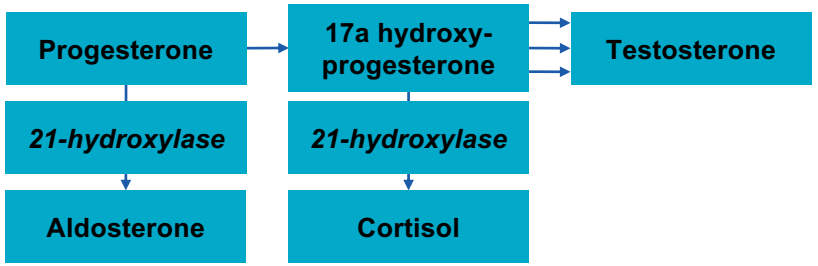
21-hydroxylase deficiency (21OHD) results in hyperandrogenism and reduced cortisol and aldosterone levels

21OHD: Genetic cause and pathophysiology

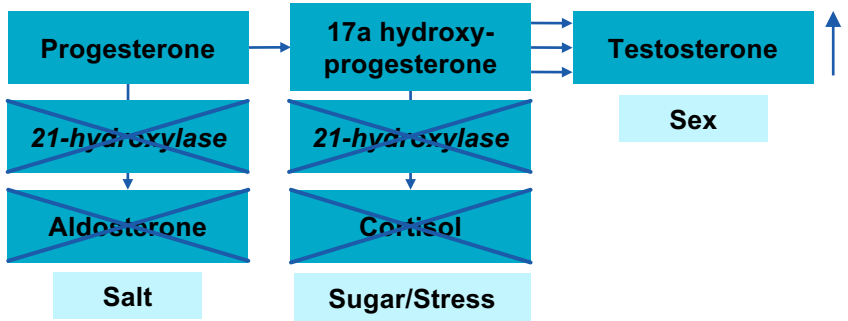
- 21-hydroxylase is a cytochrome P450 enzyme encoded by *CYP21A2* that is responsible for the biosynthesis of aldosterone and cortisol
- In classic 21OHD, mutations in CYP21A2 abrogate the expression of 21-hydroxylase
- Symptoms:
  - No Aldosterone disrupts sodium retention
  - No Cortisol disrupts glucose and stress response
  - Excess androgens causes virilization and infertility in females
- Current standard of care is daily high-dose steroids

- 21OHD is the most common cause of congenital adrenal hyperplasia, accounting for >90% of cases
- We estimate there are more than 75,000 patients in the United States and Europe

Aldosterone and cortisol biosynthetic pathways in healthy humans



Aldosterone and cortisone biosynthetic pathways in 21OHD patients



AAV Gene Therapy as Potential CAH Therapy

21OH gene therapy improves body-weight and biomarkers in Cyp21$^{-/-}$ CAH mouse model

Mouse model

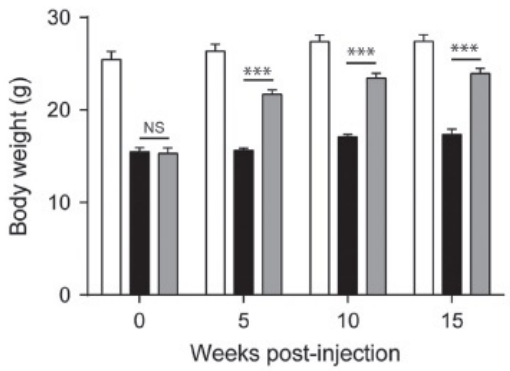
- H-2^{aw18} (CYP21$^{-/-}$) mouse model (3 mth and 7 mth old)
- Deletion is lethal without GC administration; with GC administration, adult mice are still frail
- Increase in biomarkers:
  - Progesterone (21OH substrate) 4x higher
  - Renin 160x higher
  - Aldosterone synthase 40x higher

Vector

- AAVrh10 vector
- Human CYP21A2 cDNA
- Hemagglutinin tag
- CAG promoter

IV injection of 2x10^{13} vector genomes per kg at adulthood

Substantial recovery of mouse body-weight



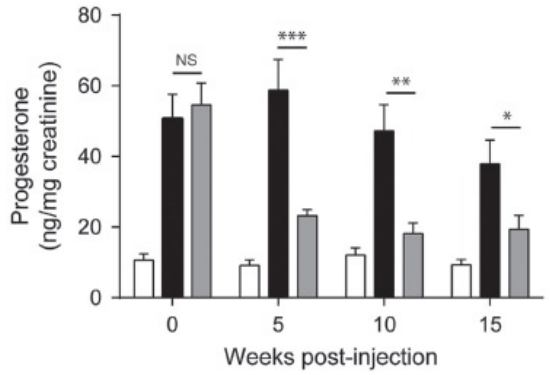
Phenotypic restoration at 15 weeks

Black: Sham vector in model mice

Grey: CYP21 vector in model mice

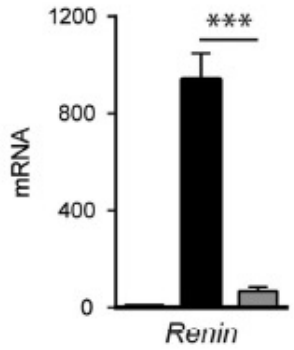
White: Control mice

Partial correction of urinary progesterone



Progesterone is the main substrate of 21OH

Significant improvement in renin mRNA levels

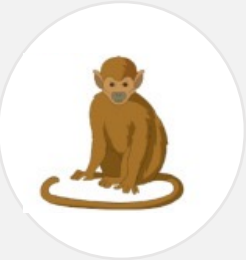


Increased mineralocorticoid levels would allow animals to retain salt

Perdomini M, Dos santos C, Goumeaux C, Blouin V, Bougnères P. An AAVrh10-CAG-CYP21-HA vector allows persistent correction of 21-hydroxylase deficiency in a Cyp21(-/-) mouse model. Gene Ther. 2017;24(5):275-281.

Adrenas Therapeutics is Developing BBP-631, an AAV5 Gene Therapy Designed to Restore 21-Hydroxylase Function

Efficacy Cyp21$^{-/-}$ Mouse Study



Non-Human Primate Study

GLP-Toxicology WT Mouse Study

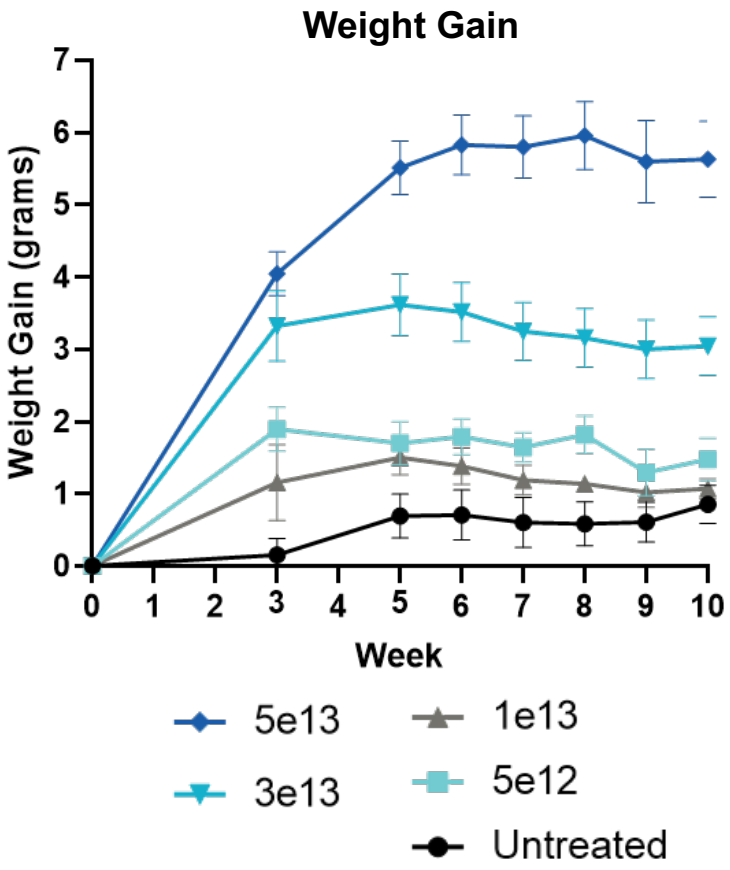
BBP-631 Has Dose-Dependent Biological Activity in Cyp21$^{-/-}$ Mice

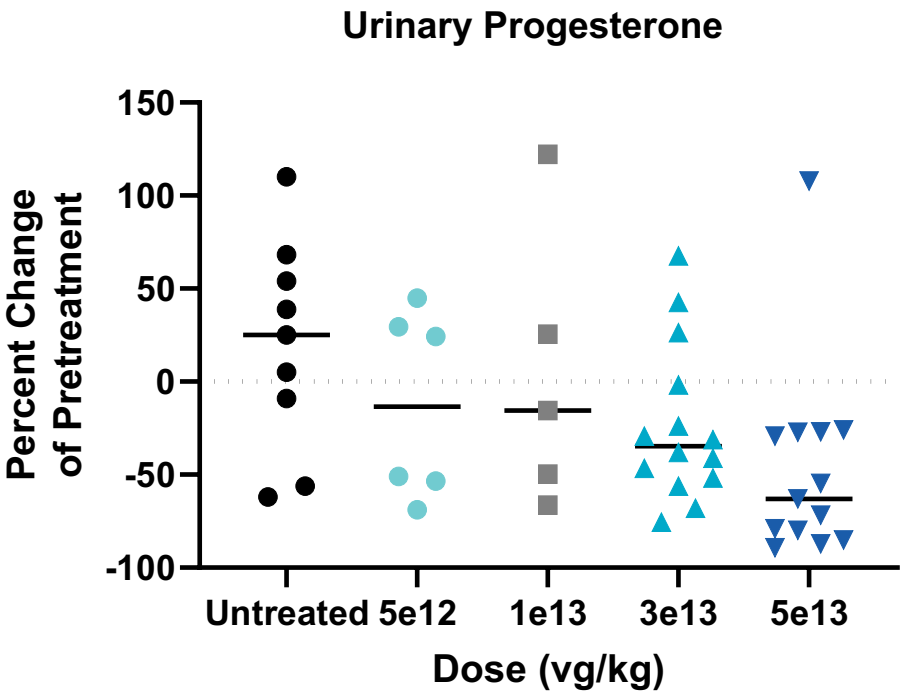
Age >10 Wks Old
Doses: 5E12, 1E13, 3E13, 5E13 vg/kg

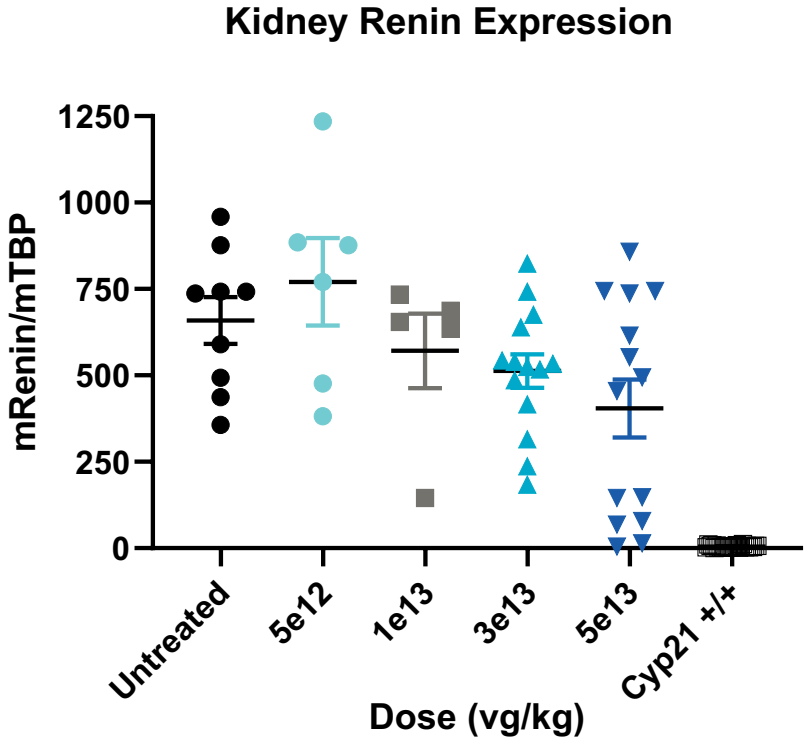
→

10 Wks Necropsy

1. Weight Gain
2. Adrenal Glands: Vector genome, RNA and Protein
3. Urinary Progesterone Analysis
4. Serum Steroids
5. Renin Expression







No Unscheduled Deaths of Treated Mice

BBP-631 Has Dose Dependent Biodistribution in Adrenal Glands of Cyp21$^{-/-}$ Mice

Age >10 Wks Old
Doses: 5E12, 1E13, 3E13, 5E13 vg/kg

→

10 Wks Necropsy

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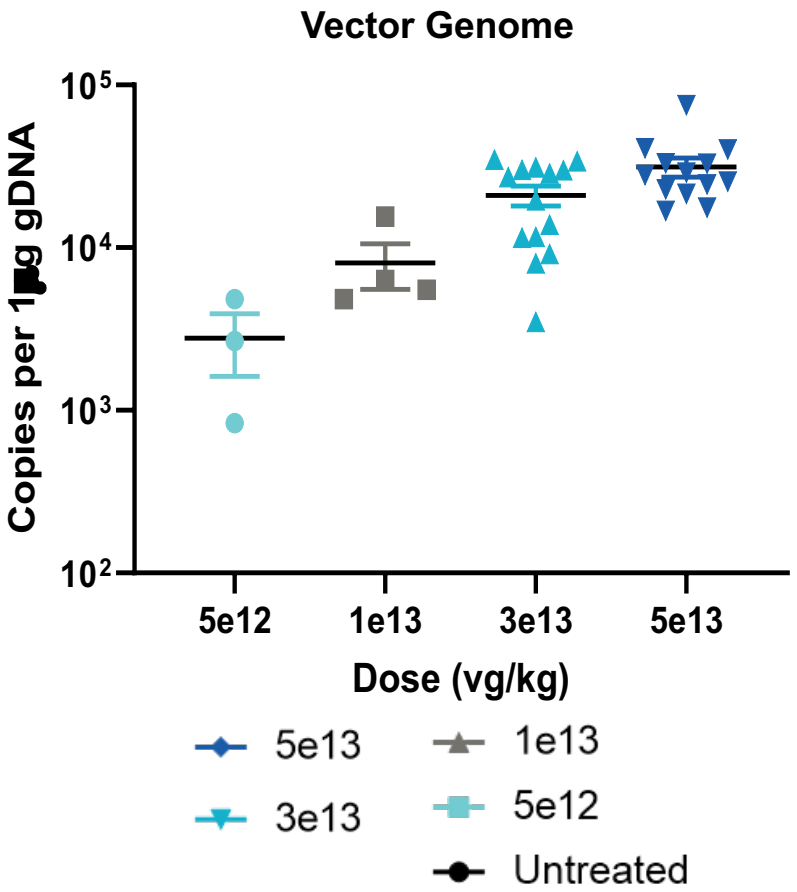
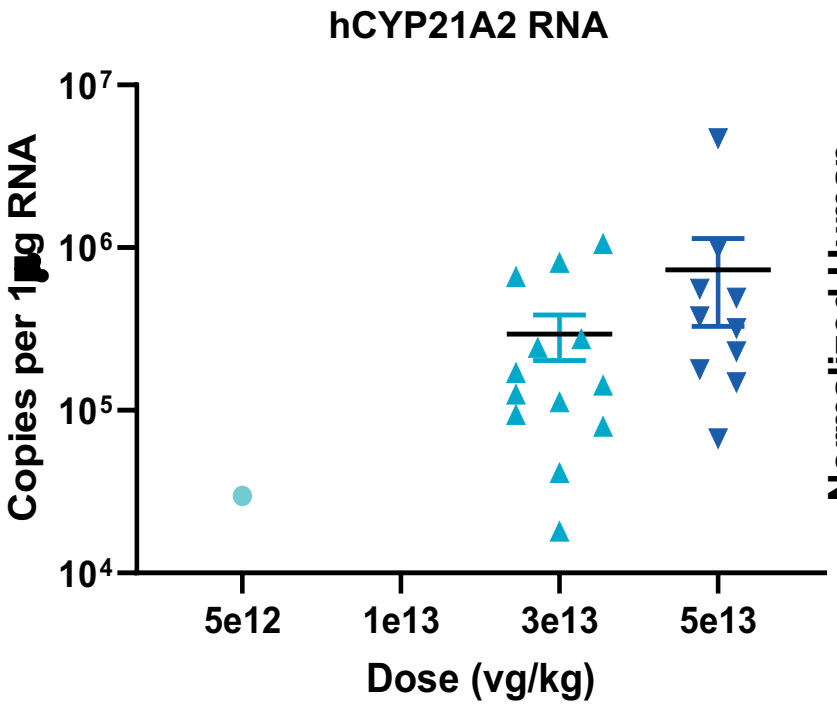
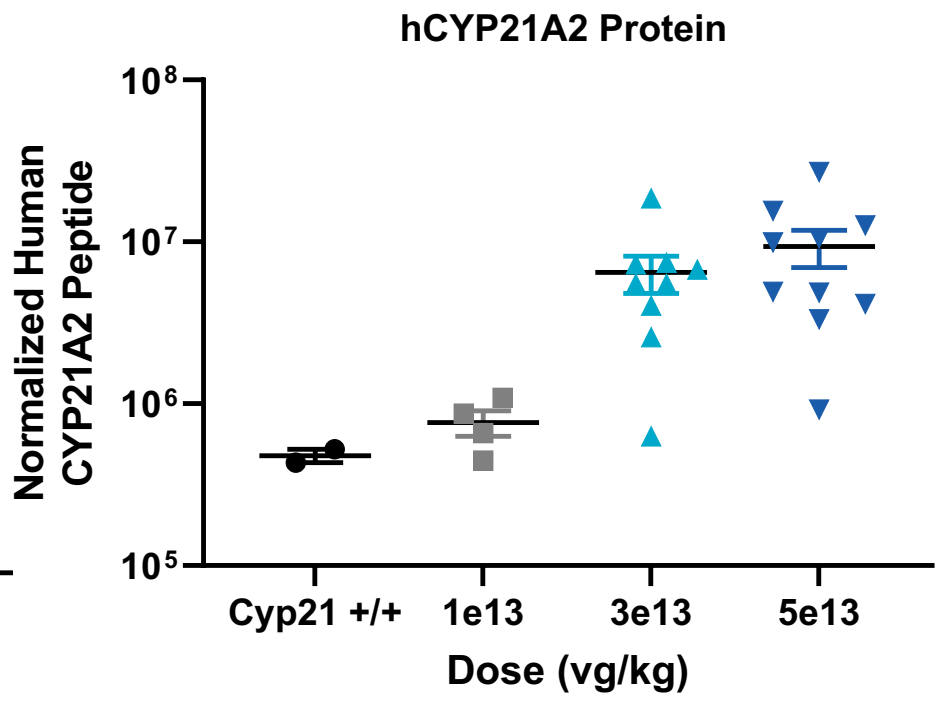




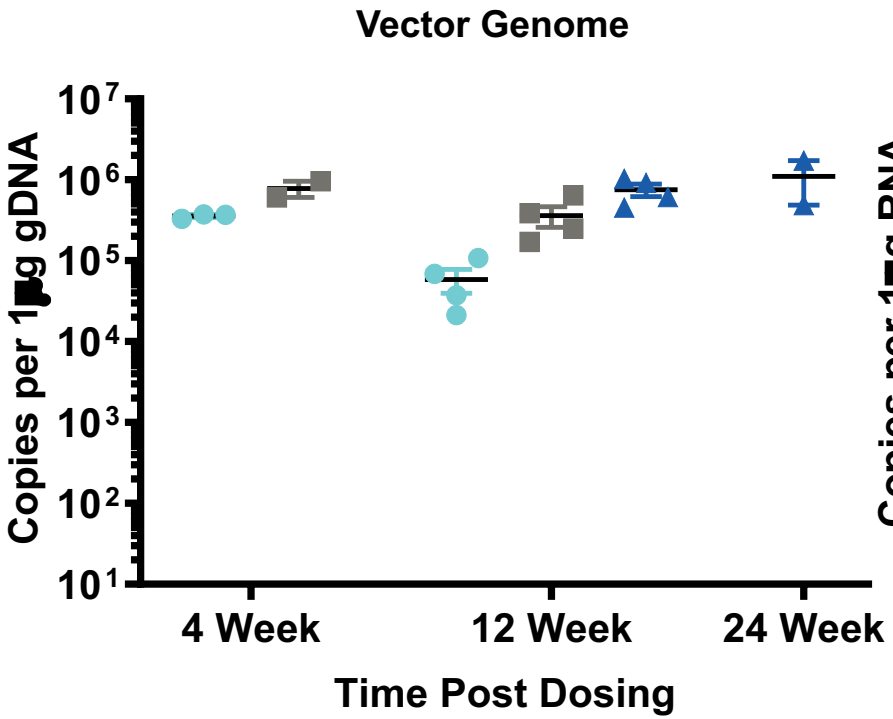


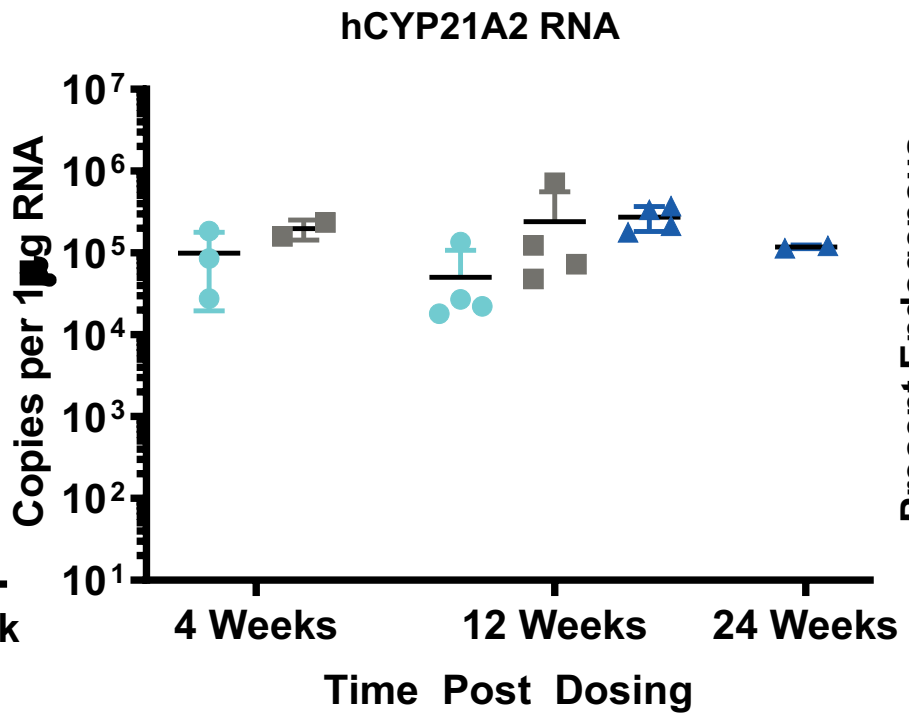
BBP-631 Has Efficient, Persistent and Dose-Dependent Delivery to the Adrenal Gland in Non-Human Primates

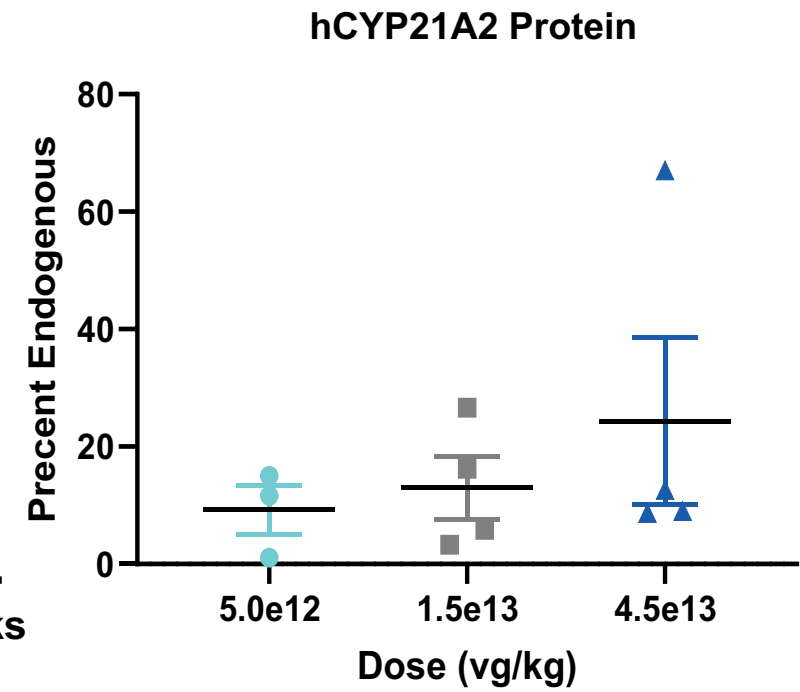
Age 2-3 Yrs Old
Doses: 5E12, 1.5E13, 4.5E13 vg/kg

→ **4 Wks Necropsy** → **12 Wks Necropsy** → **24 Wks Necropsy**

1. Histology, Clinical Chemistry, Hematology, Urinalysis, Immune Response
2. Vector genome, RNA and Protein
3. Serum Steroids







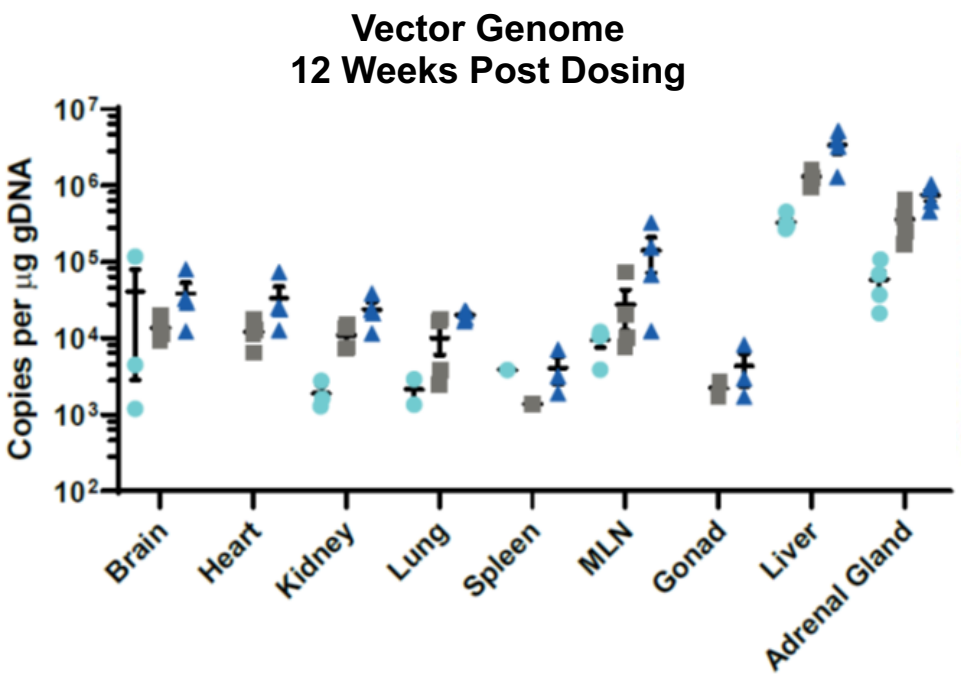
● 5E12 vg/kg ■ 1.5E13 vg/kg ▲ 4.5E13 vg/kg

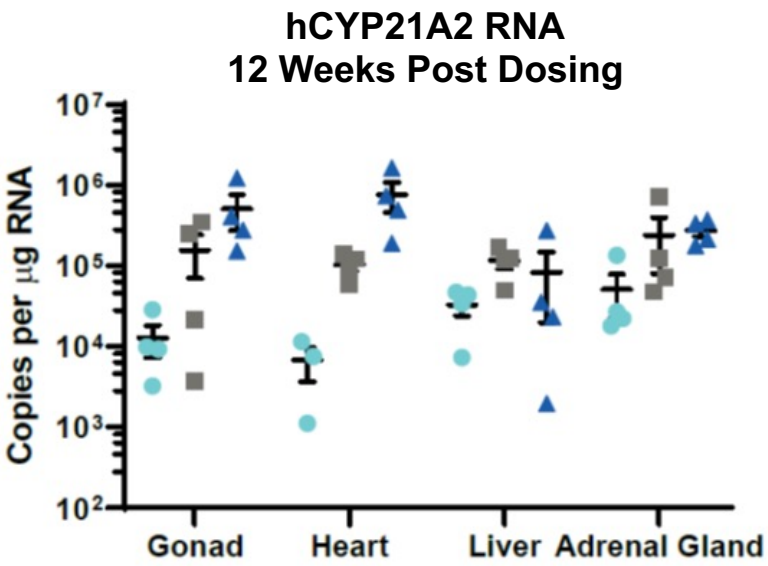
BBP-631 has Minimal DNA and Expression in Other NHP Tissues

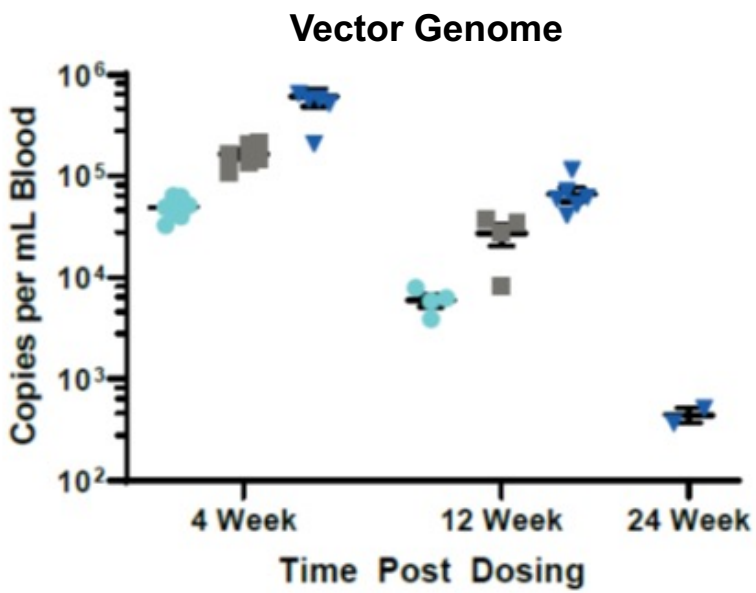
Age 2-3 Yrs Old
Doses: 5E12, 1.5E13, 4.5E13 vg/kg

→ **4 Wks Necropsy** → **12 Wks Necropsy** → **24 Wks Necropsy**

1. Histology, Clinical Chemistry, Hematology, Urinalysis, Immune Response
2. Vector genome, RNA and Protein
3. Serum Steroids





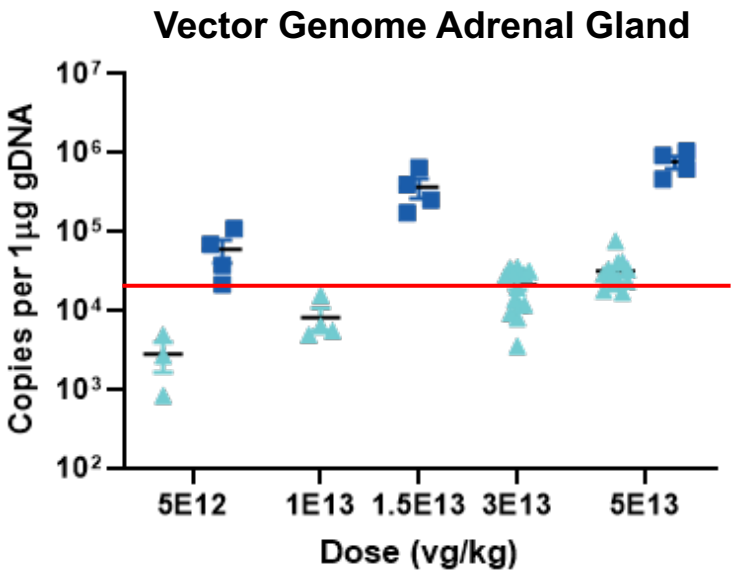


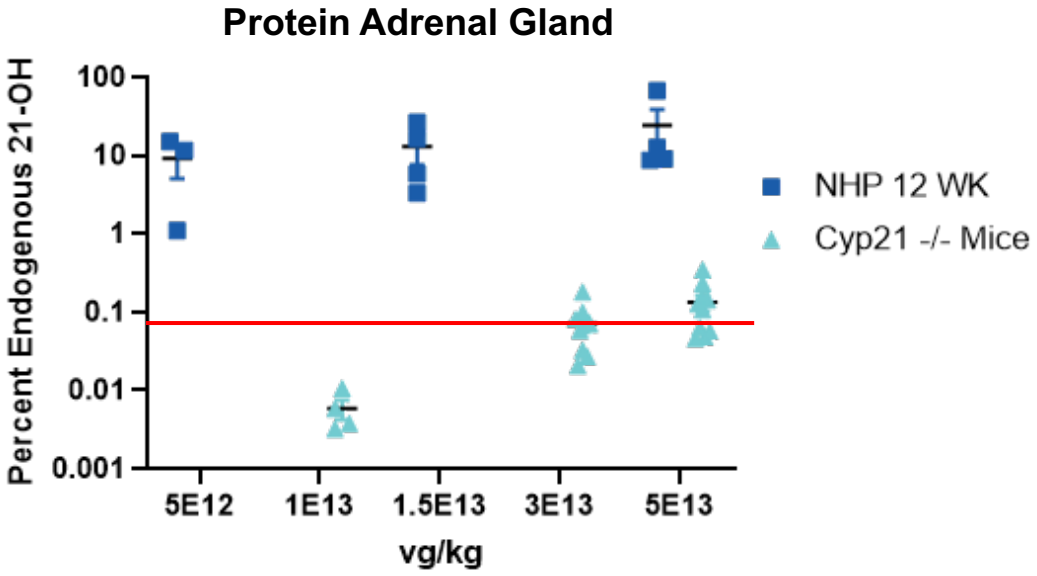
5E12 vg/kg ■ 1.5E13 vg/kg ▲ 4.5E13 vg/kg

No safety concerns across histology, clinical chemistry, hematology, urinalysis and immune response panels
No notable changes in serum steroids besides slight elevation in ACTH

Improved Biodistribution of BBP-631 in Non-Human Primates Compared to Mouse

Mouse model phenotypic data → Mouse model molecular data → NHP molecular data → Clinical Dose



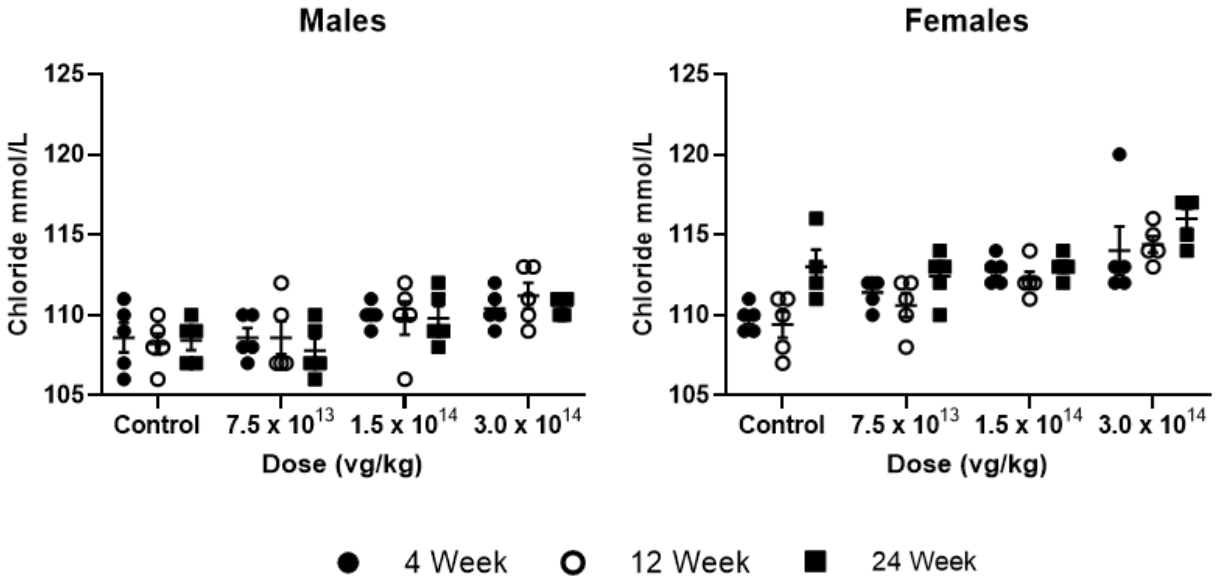


BBP-631 Had No Adverse Hematology or Hepatic Markers of Health Despite Minor Histological Findings in Wild Type Mouse GLP-Tox Study

Age >10 Wks Old
Doses: 7.5E13, 1.5E14, 3E14 vg/kg

→ **4 Wks Necropsy** → **12 Wks Necropsy** → **24 Wks Necropsy**

1. Histology, Clinical Chemistry, Hematology, Urinalysis, Immune Response, Coagulation
2. Vector genome, RNA and Protein, Vector shedding
3. Serum Steroids



- Mild liver inflammation in all groups through Week 24.
- **No systemic effects, no changes in transaminases or other liver function serologies or hematology markers.**
- **There were no changes in any other tissue including brain or spinal cord.**
- **No adverse occurrence of cellular immune response to AAV5 or 21-OH**

BBP-631 Has Dose Dependent Biodistribution with Persistence Through 24 Weeks Wild Type Mouse GLP-Tox Study

Age >10 Wks Old
Doses: 7.5E13, 1.5E14, 3E14 vg/kg

→ **4 Wks Necropsy** → **12 Wks Necropsy** → **24 Wks Necropsy**

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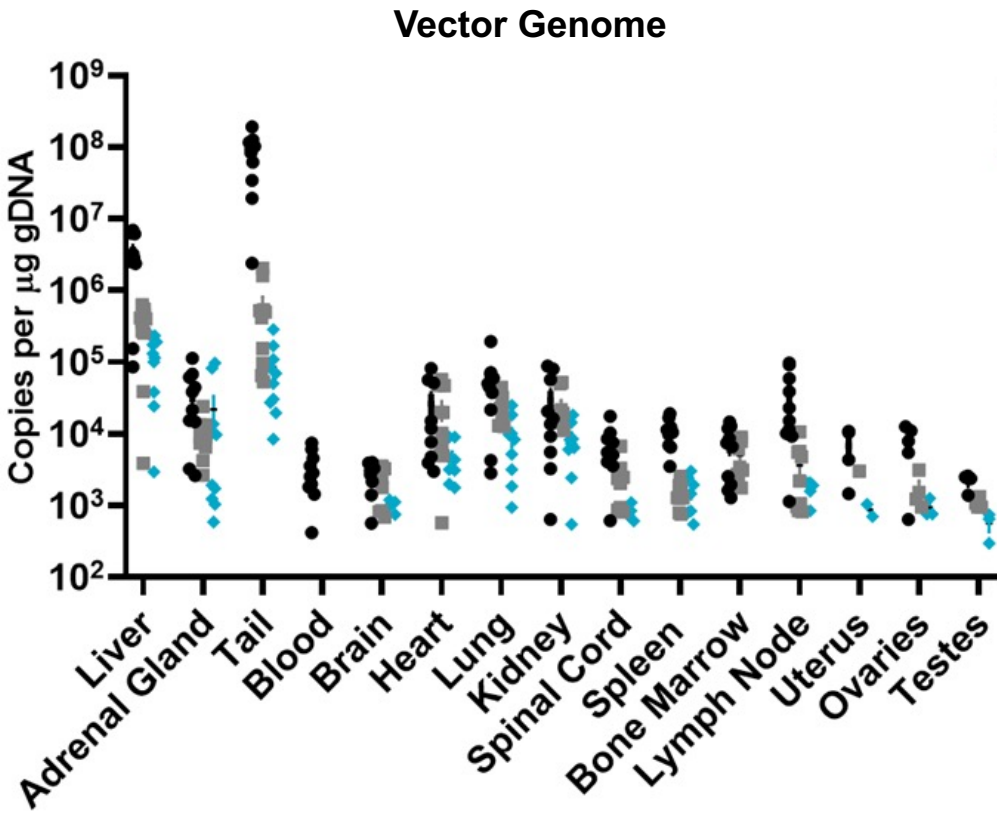
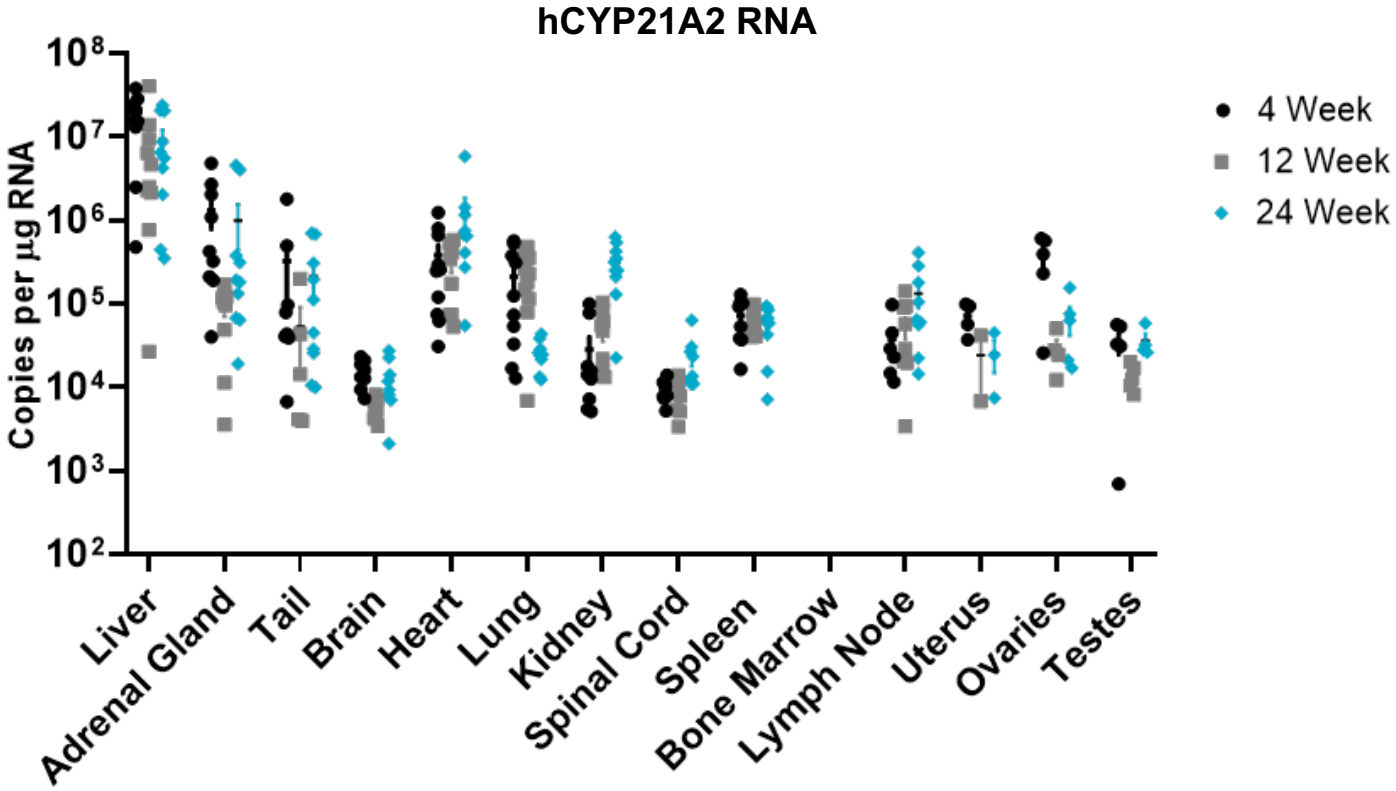
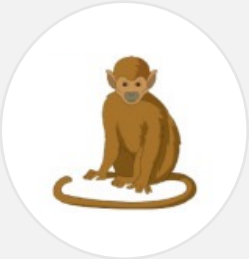




BBP-631: Gene Therapy for Congenital Adrenal Hyperplasia

Efficacy Cyp21$^{-/-}$ Mouse Study

Biologically Active in Cyp21$^{-/-}$ mice



Non-Human Primate Study

Efficient and Persistent Adrenal gland Delivery

No Safety Concerns

GLP-Toxicology WT Mouse Study

NOAEL of 3.0E14 vg/kg

Cleared to Proceed to a Ph. 1/2 Trial

Plan to initiate first-in-human trials by mid 2021

www.CAHGeneTherapy.com

Thank you!

Intravenous AAV5 Gene Therapy with Human CYP21A2 Corrects Phenotypic Deficiencies of the 21-hydroxylase Knockout Mouse Model and Demonstrates Durability and Safety in Non-Human Primates and Mice.

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