

# Combination of a Novel Chimeric AAV Capsid and Potency Enhanced FIX Variant for Hemophilia B Gene Therapy

World Federation of Hemophilia

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SVP Translational Research

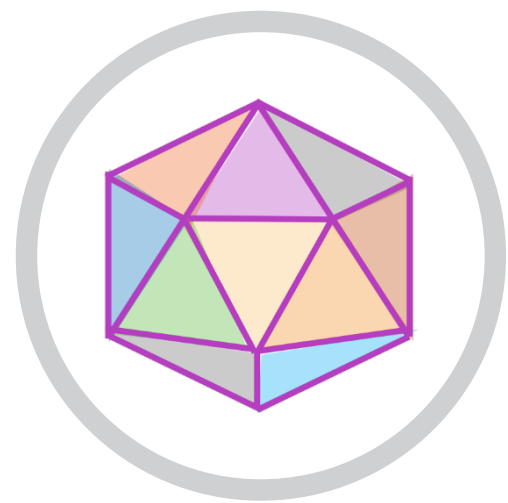


# Disclosures for: Grant E. Blouse, PhD MS

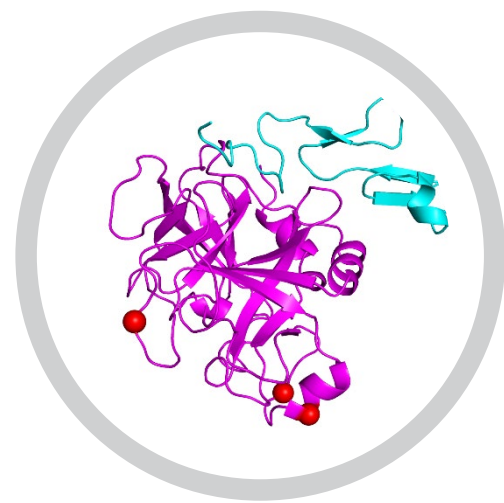
<b>Conflict</b>	<b>Disclosure - if conflict of interest exists</b>
Research Support	none
Director, Officer, Employee	Catalyst Biosciences
Shareholder	Catalyst Biosciences
Honoraria	none
Advisory Committee	none
Consultant	none

# Combining novel capsids & transgenes

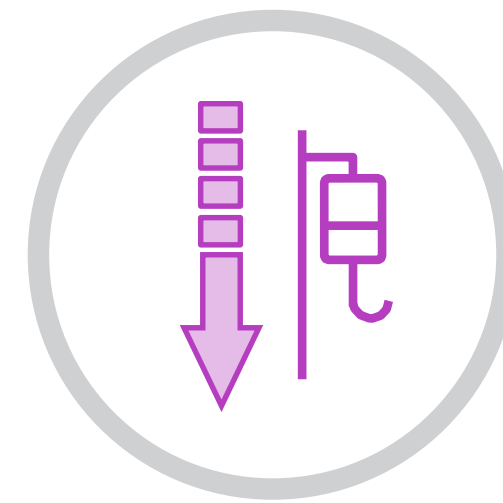
Combining optimized capsid + transgene = improved therapy



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Lower Immunogenicity

Decrease Liver Toxicity

Manufacturing Costs

## Engineered Capsid

- High liver tropism
- Transduction efficiency
- Translatable from preclinical to clinic

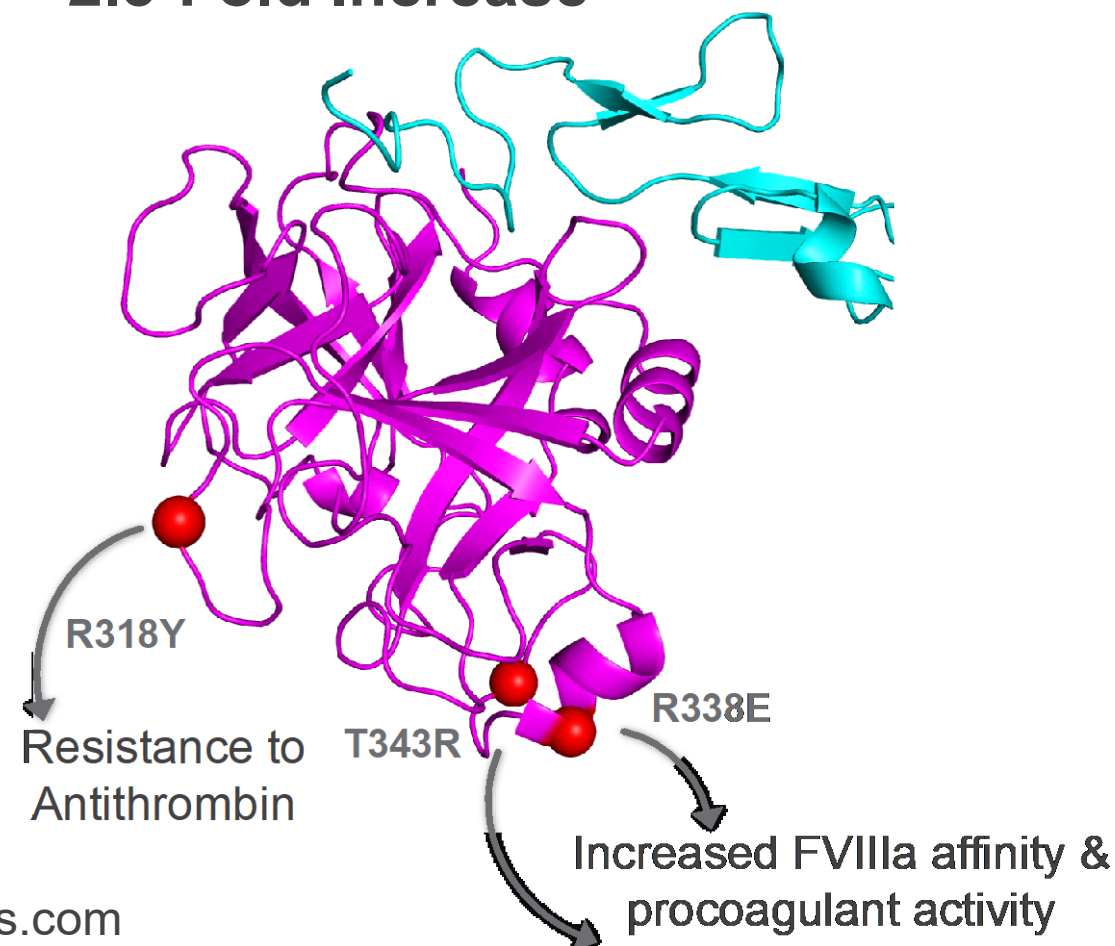
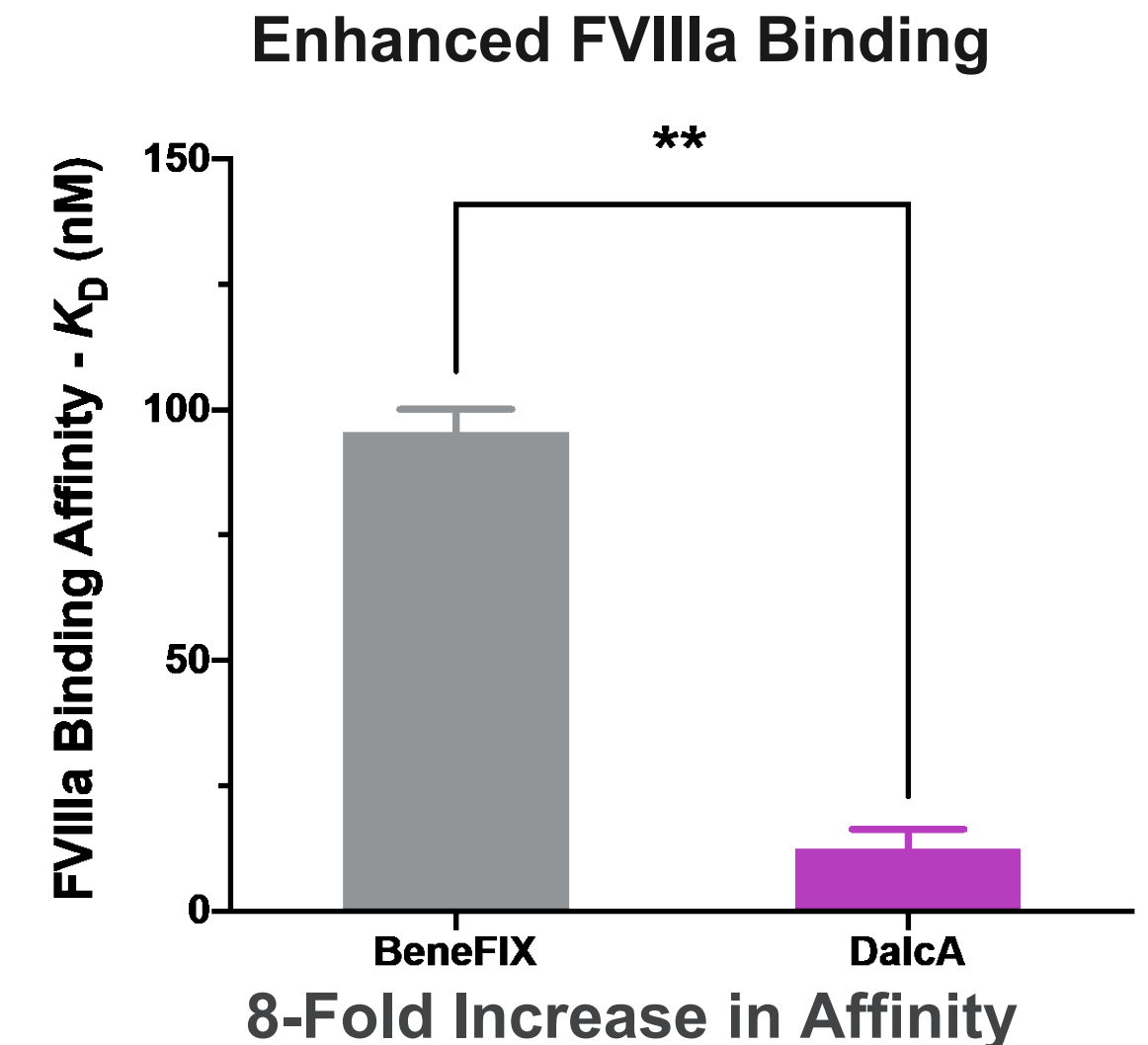
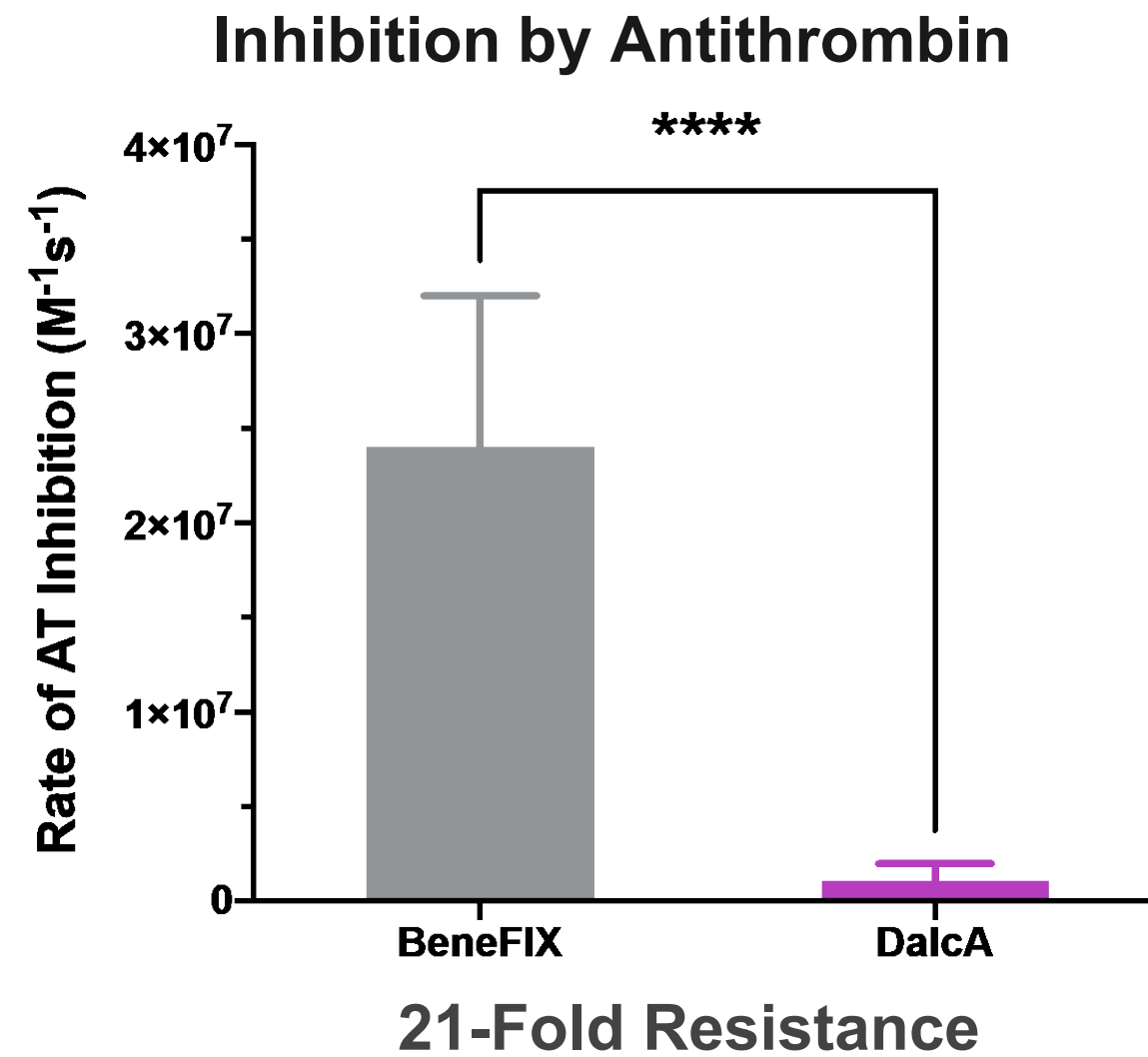
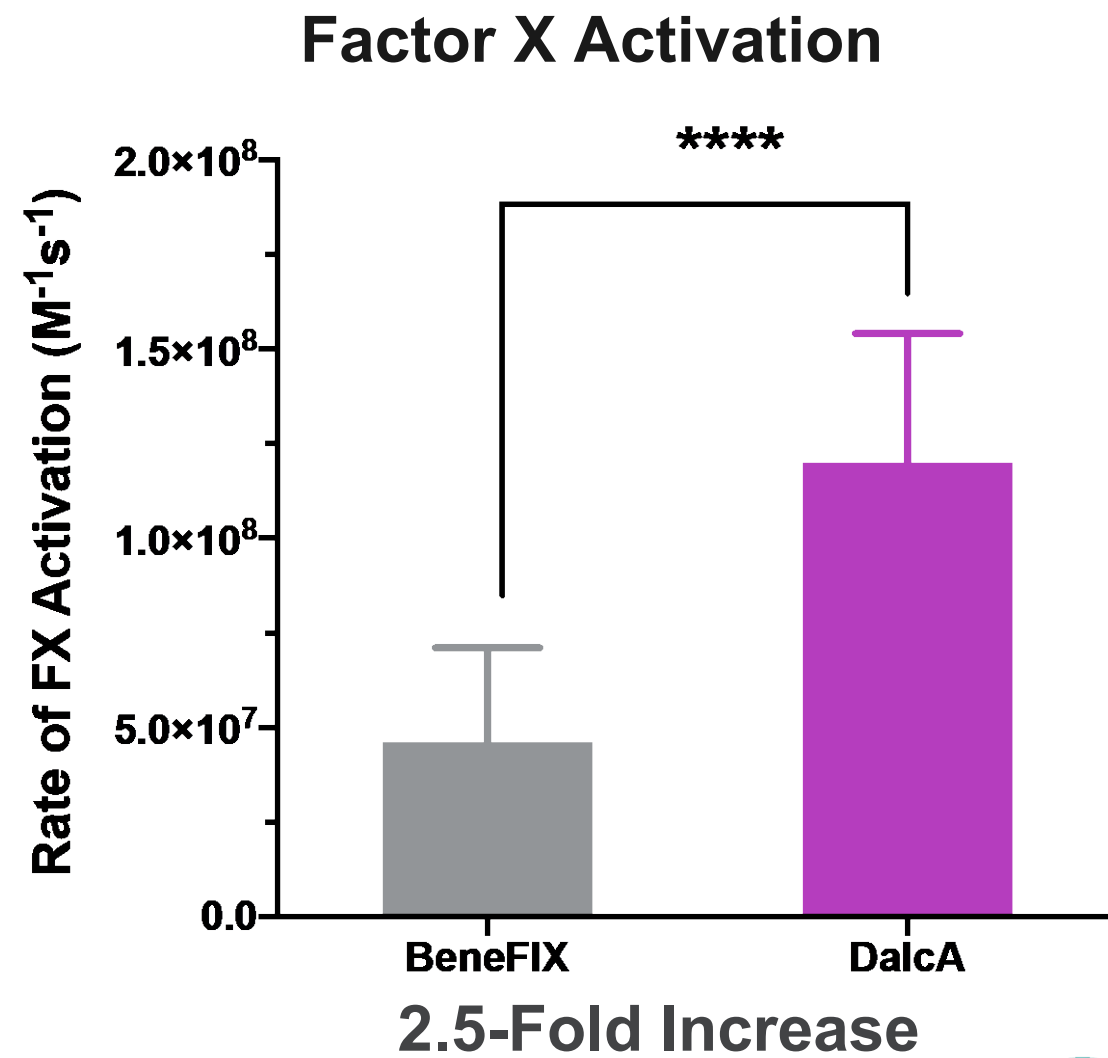
## Novel Transgene

- High potency
- Improved efficacy

## Lower AAV Dose

- Achieve clinically relevant levels
- Reduced viral load

# CB 2679d-GT is the gene behind dalcinonacog alfa

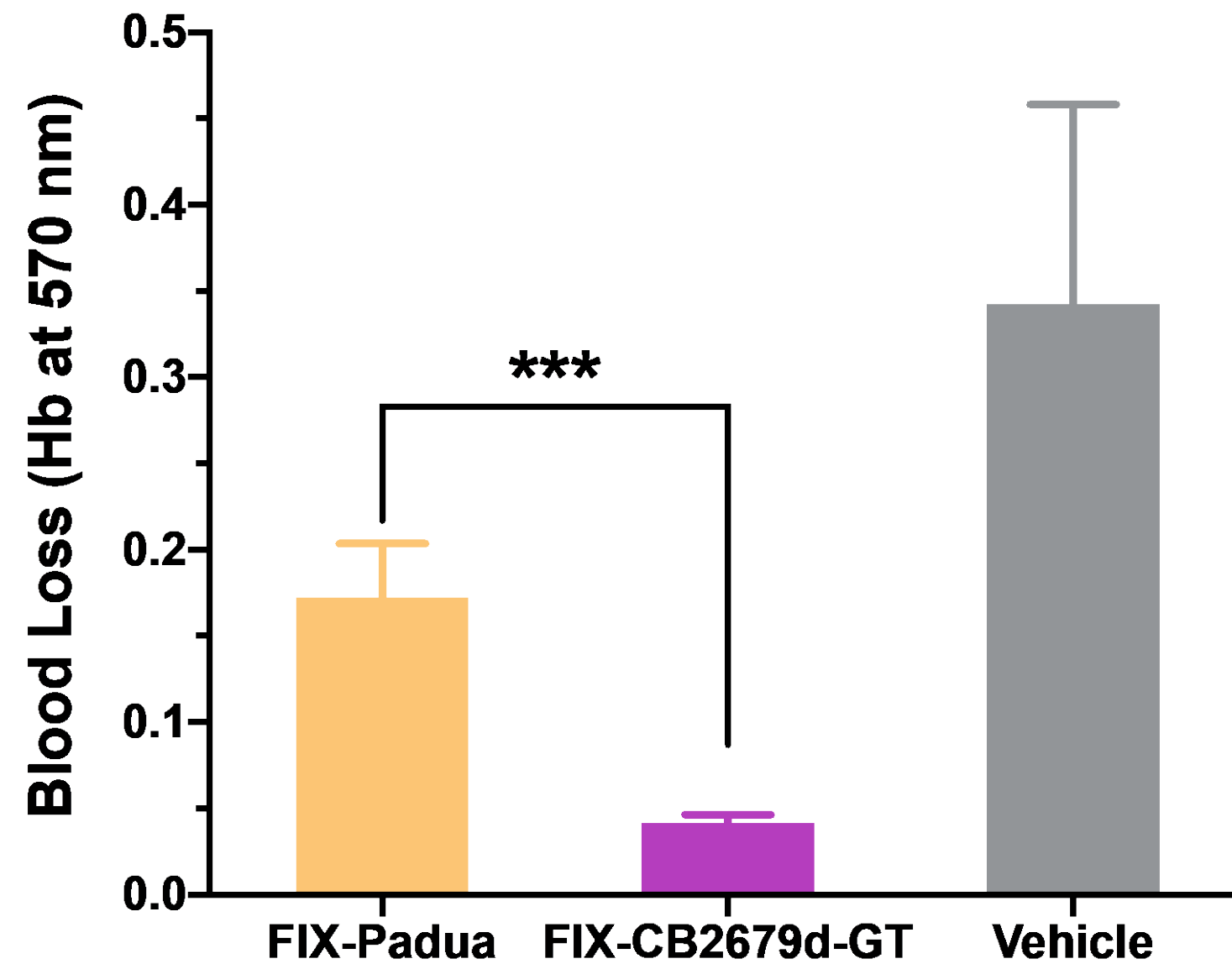


## Three substitutions within the FIX protein

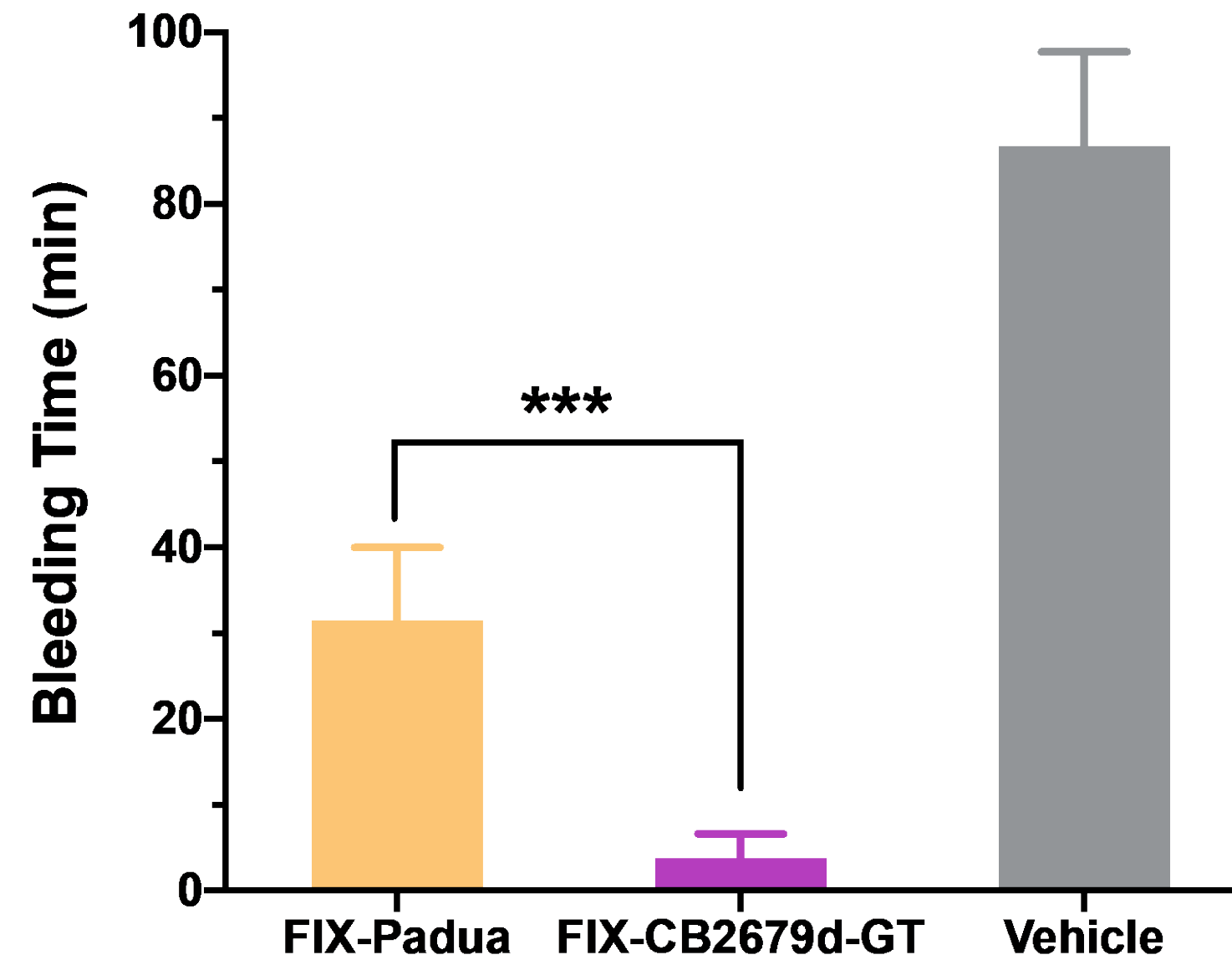
- + Increased catalytic activity
- + Higher affinity for FVIIIa
- + Resistance to antithrombin inhibition
- + 22-fold increased potency over BeneFIX

# CB 2679d-GT is more efficacious than Padua

2.5 x 10<sup>11</sup> vg/kg



2.5 x 10<sup>11</sup> vg/kg

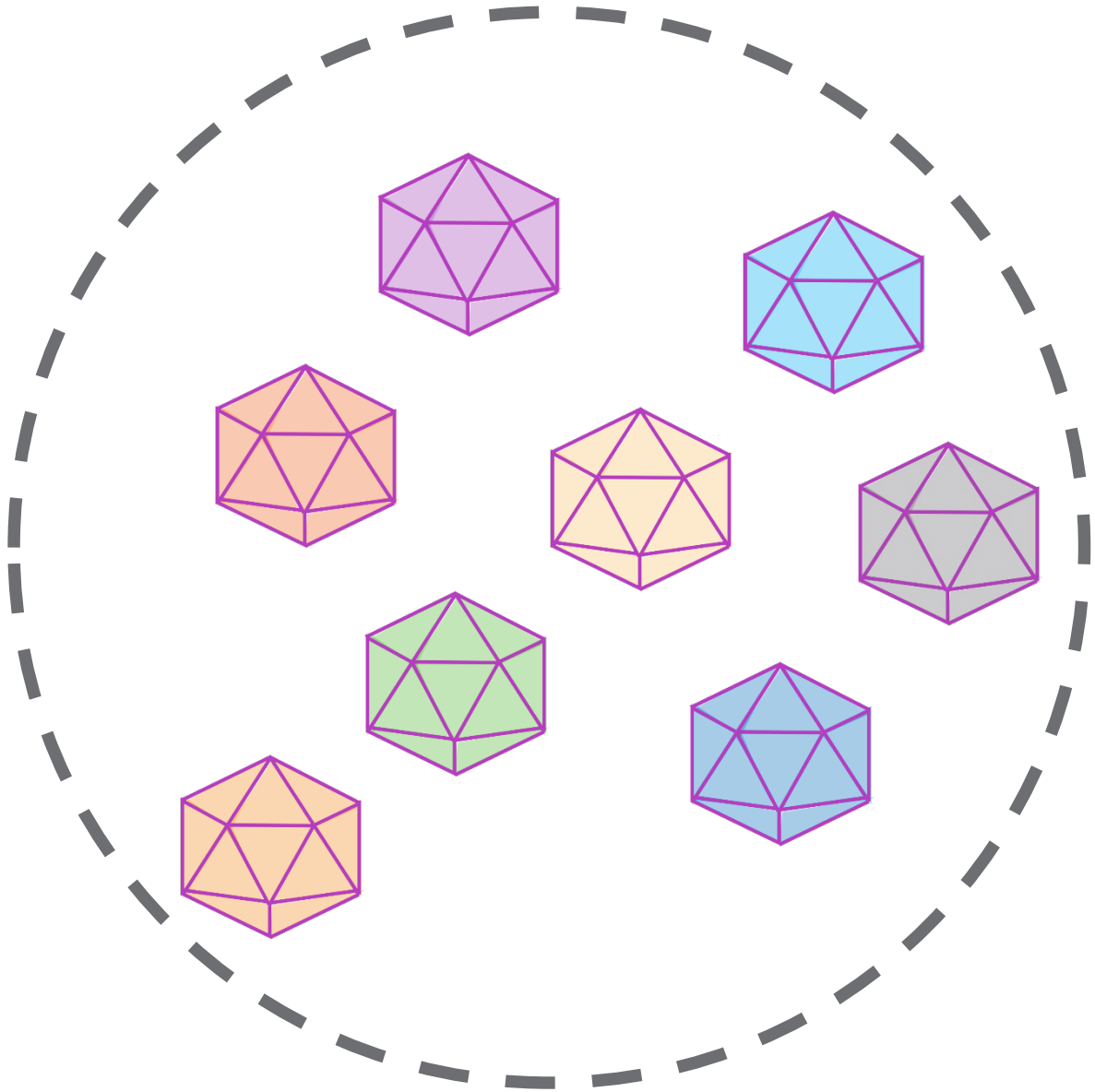


**4-fold reduction in blood loss and 8-fold reduction in bleeding time**

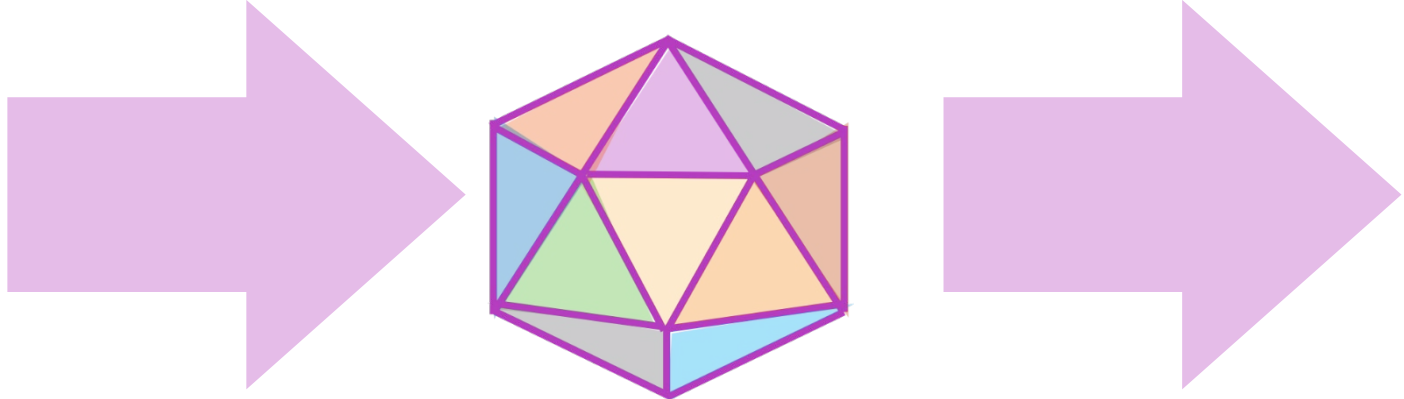
(Student's T-Test: \*\*\* P<0.001, \*\* P<0.01, \* P<0.05 and NS – Not Significant)

# DNA shuffling to create a novel AAV vector

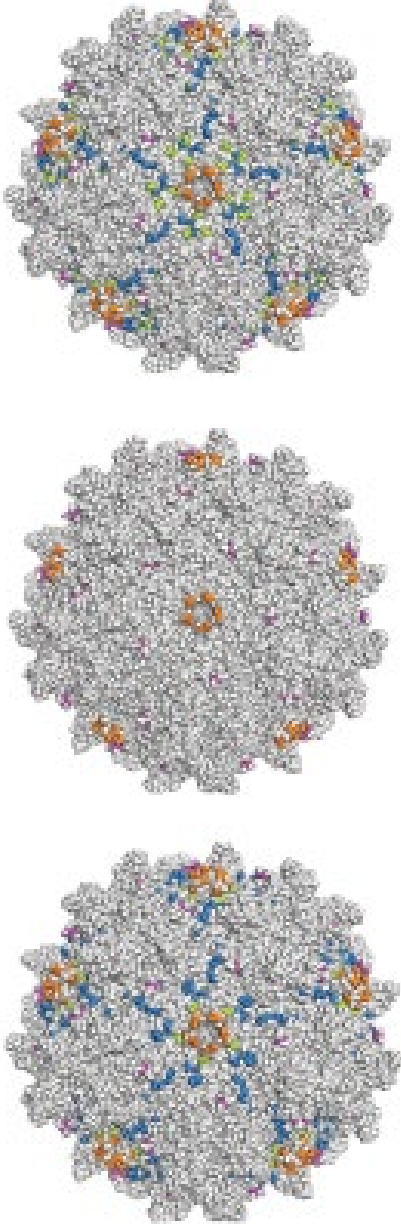
## DNA shuffling of 8 serotypes



Select for tropism & increased transduction efficiency in human



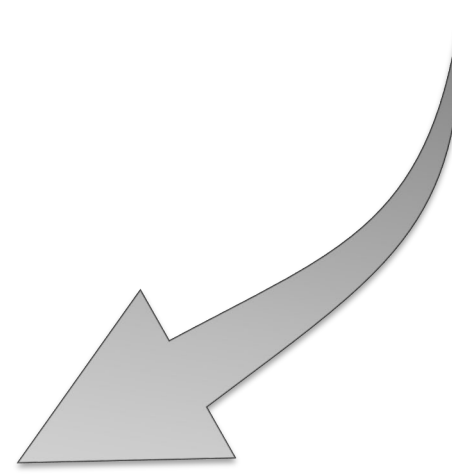
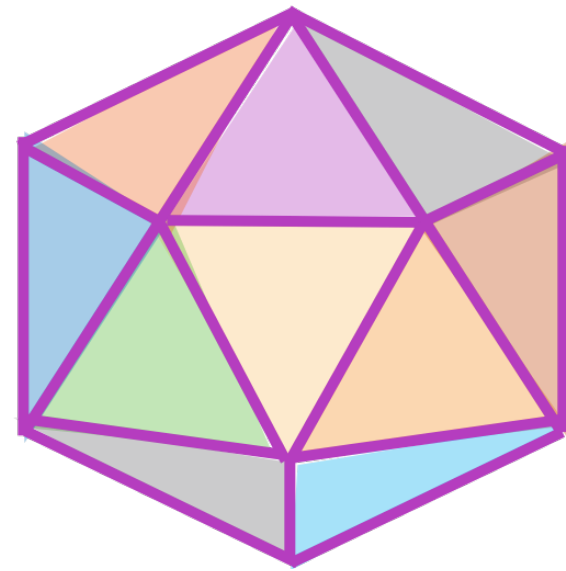
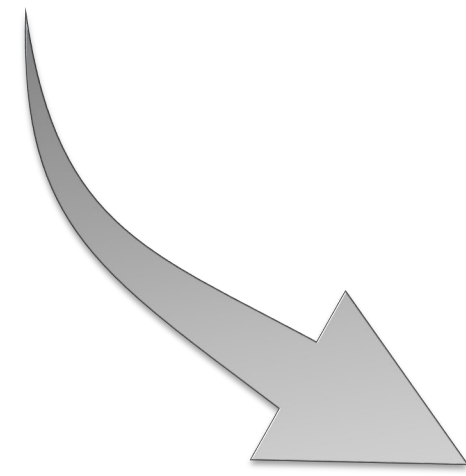
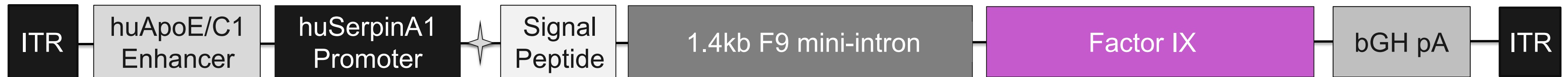
**Chimeric Capsids**



**High performing AAV capsid candidates**



# AAV vector design of CB 2679d-GT in a novel capsid

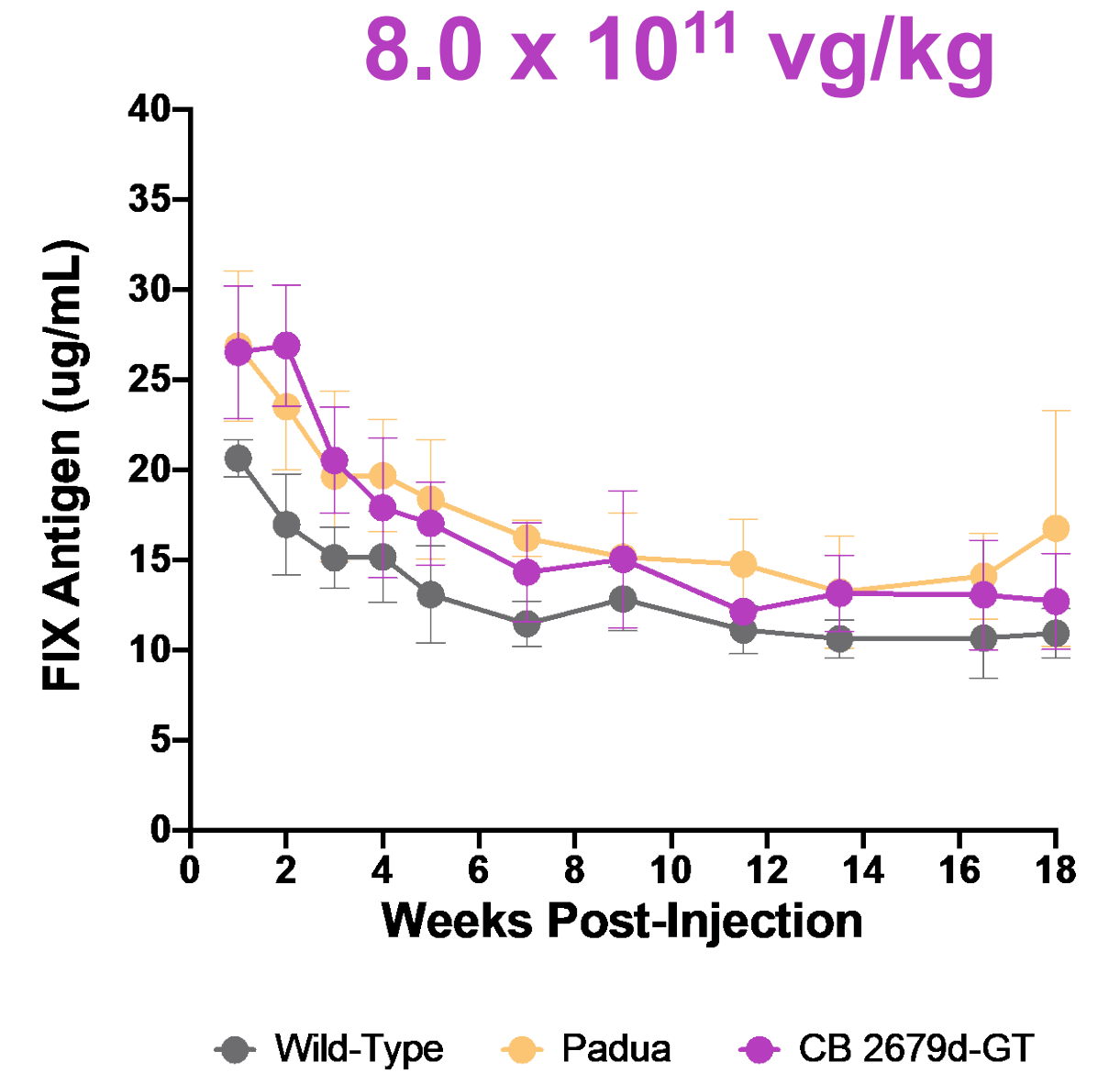
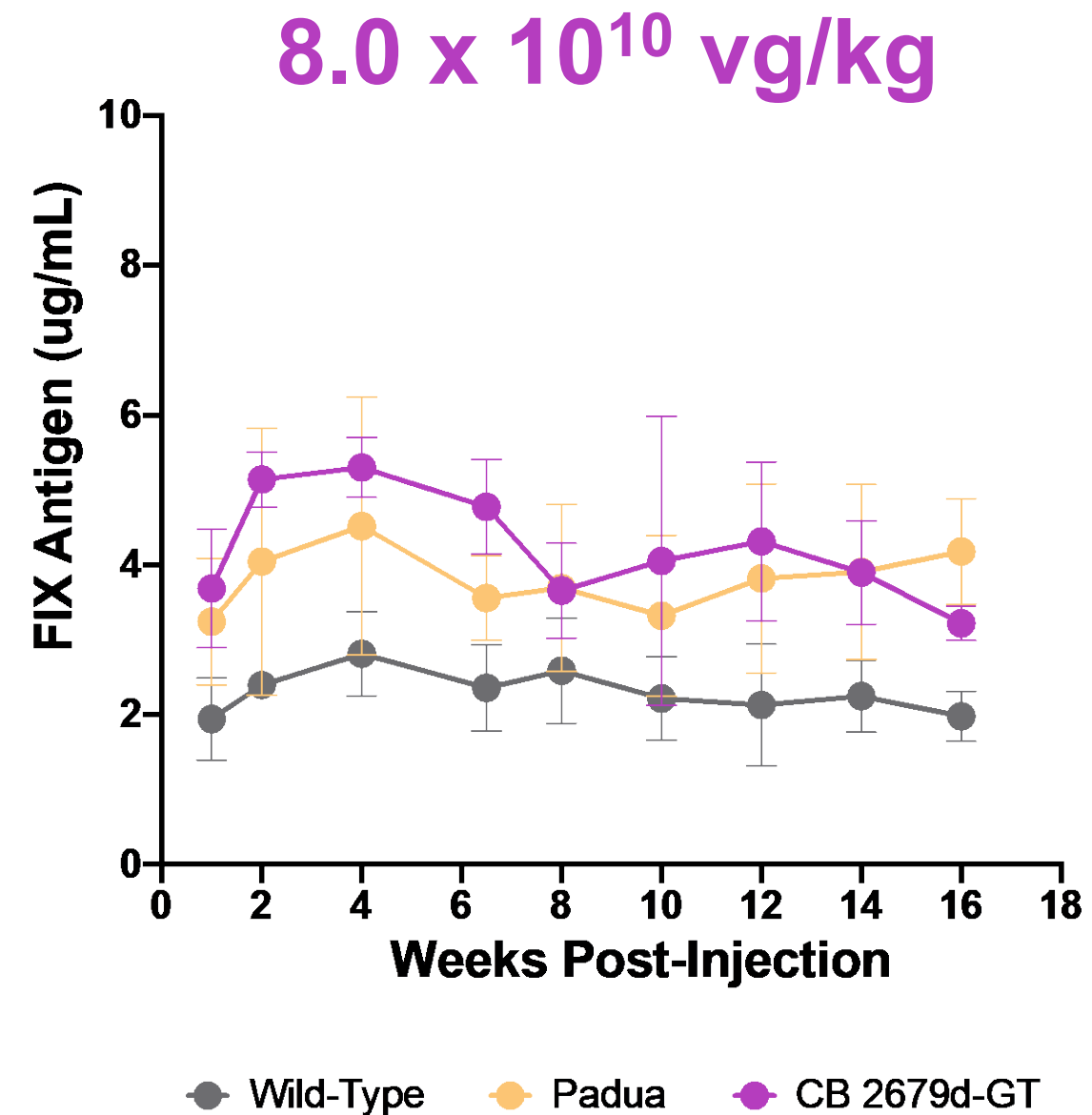
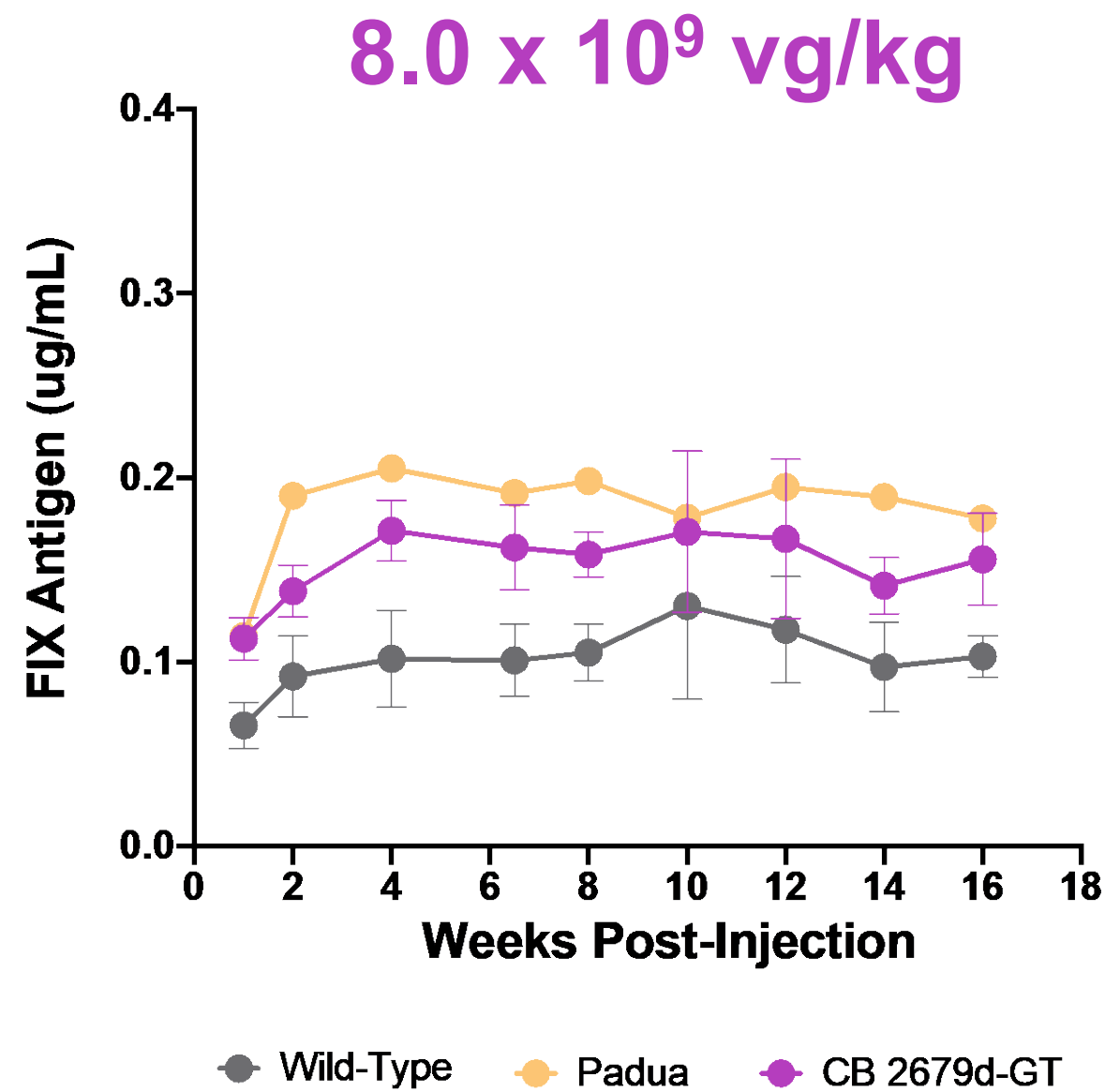


- Wild-Type FIX
- Padua (R338L)
- CB 2679d-GT (R318Y/R338E/T343R)

FIX minigene constructs were packaged into a novel AAV capsid designed through DNA shuffling of 8 AAV serotypes and showing a high tropism for liver transduction

# FIX antigen levels remained stable in hemophilia B mice

## AAV KP1 / CB 2679d-GT study in hemophilia B mice



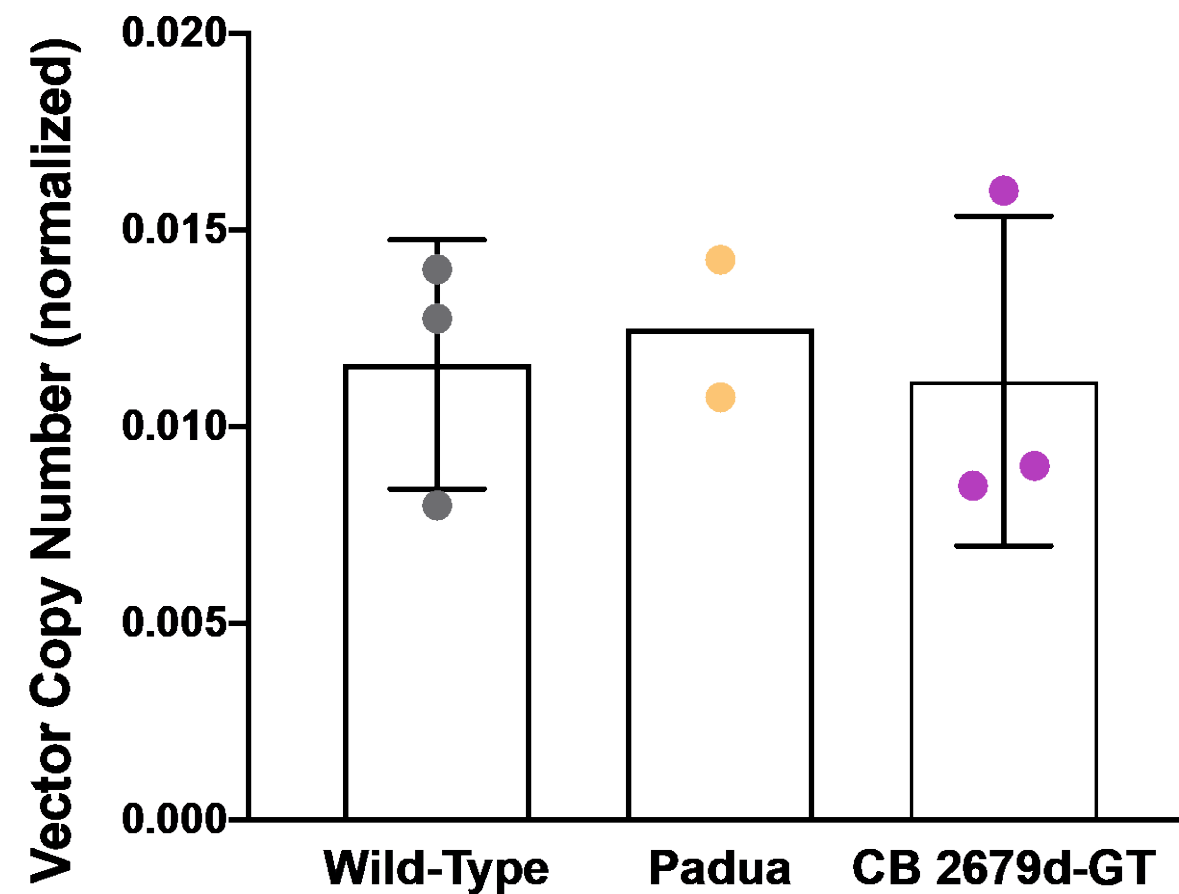
**Dose dependent and stable FIX antigen observed for up to 18 weeks**



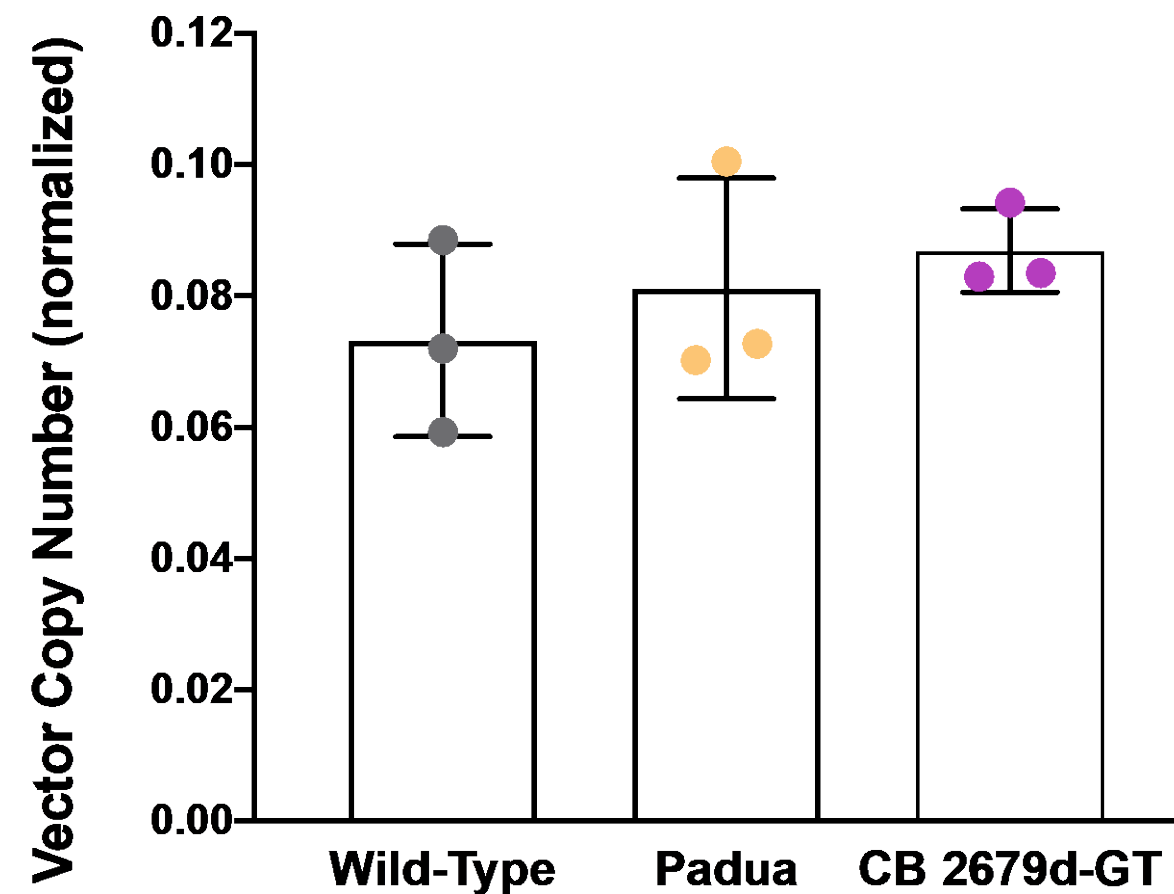
# AAV vector copy numbers were similar for all constructs

## AAV KP1 / CB 2679d-GT study in hemophilia B mice

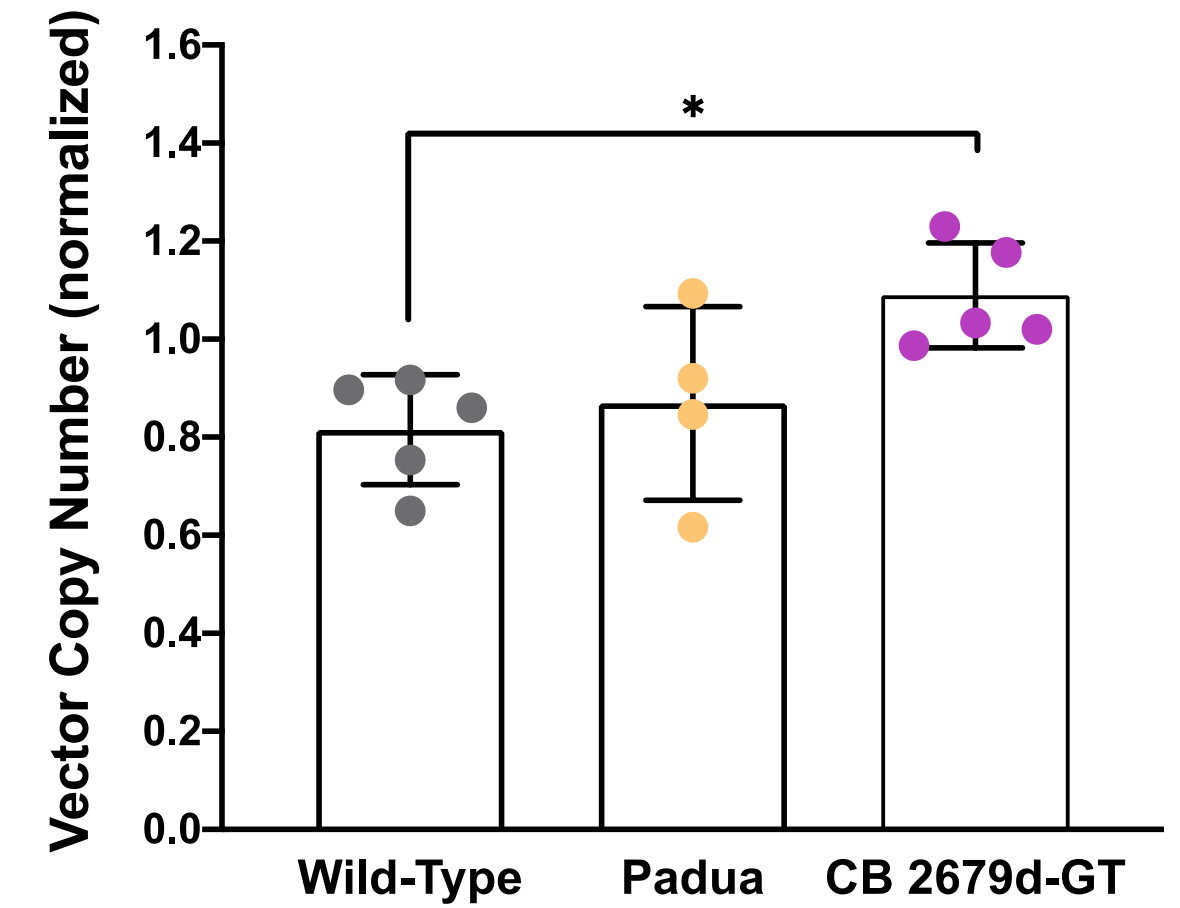
$8.0 \times 10^9$  vg/kg



$8.0 \times 10^{10}$  vg/kg



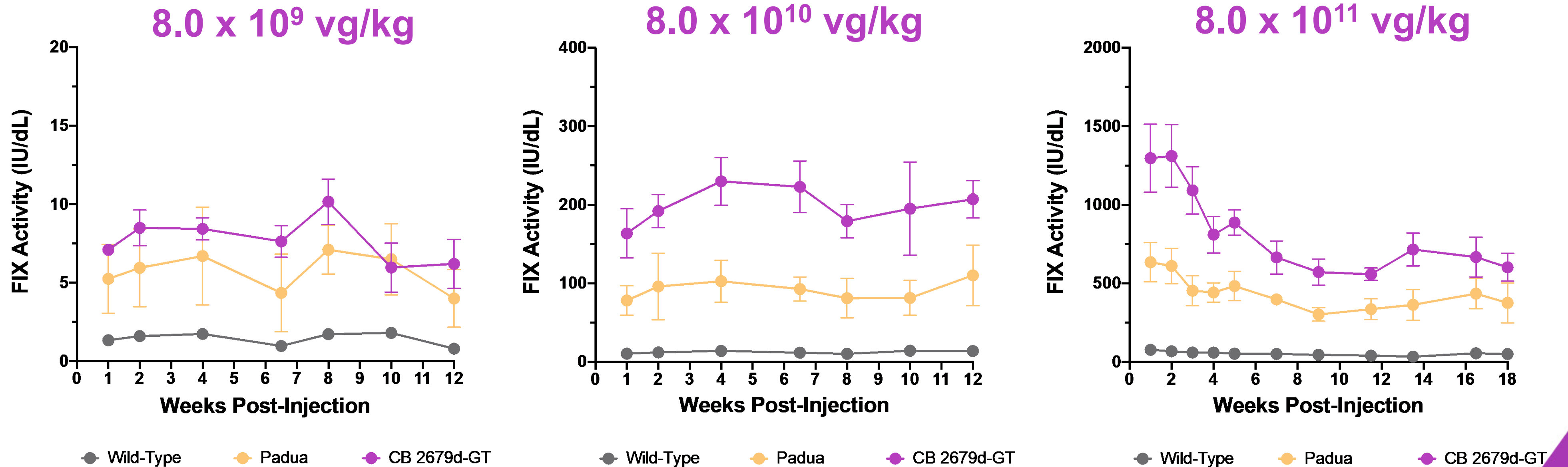
$8.0 \times 10^{11}$  vg/kg



Similar copy numbers were consistent with the comparable antigen levels

# FIX activity levels remained stable in hemophilia B mice

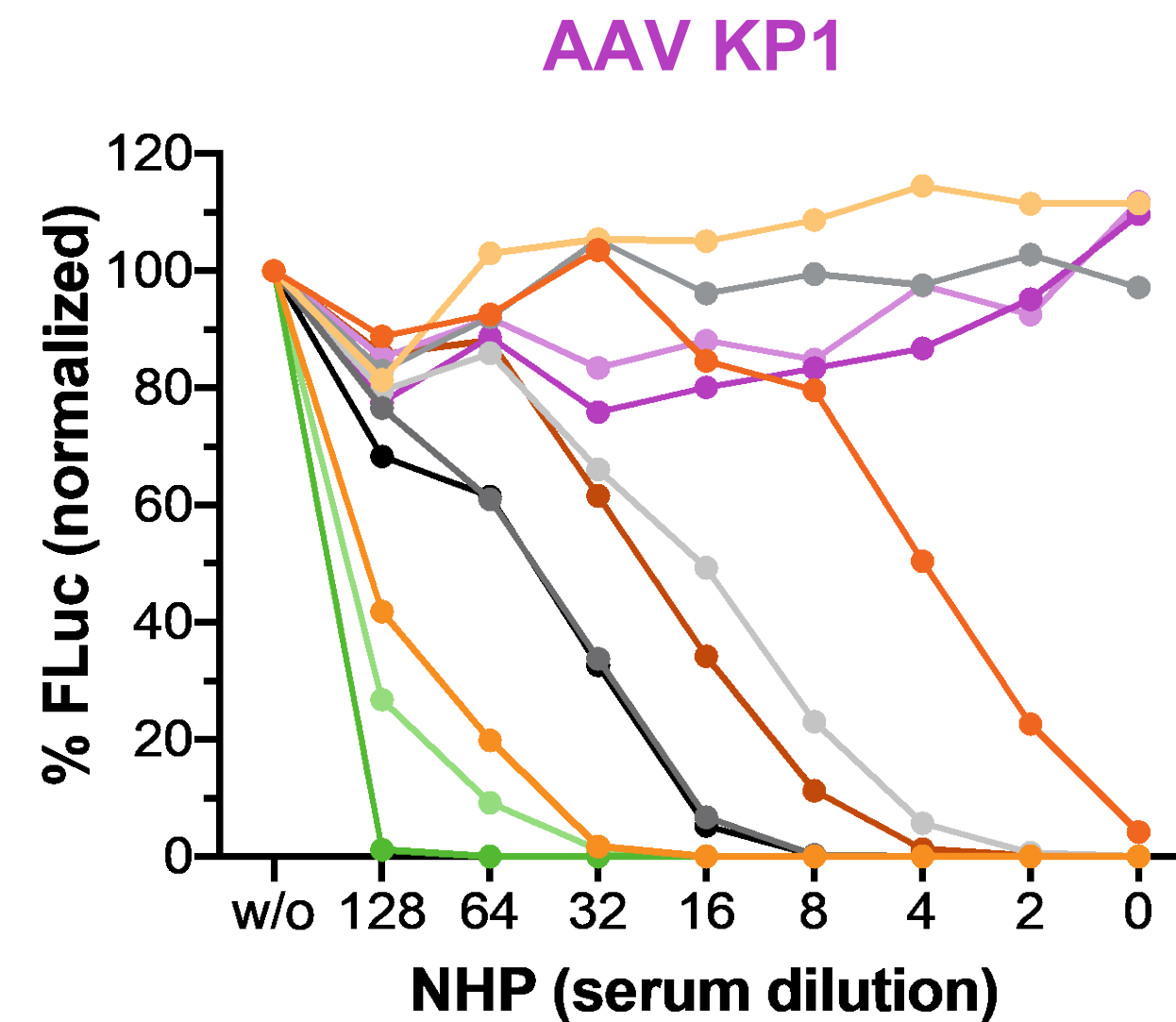
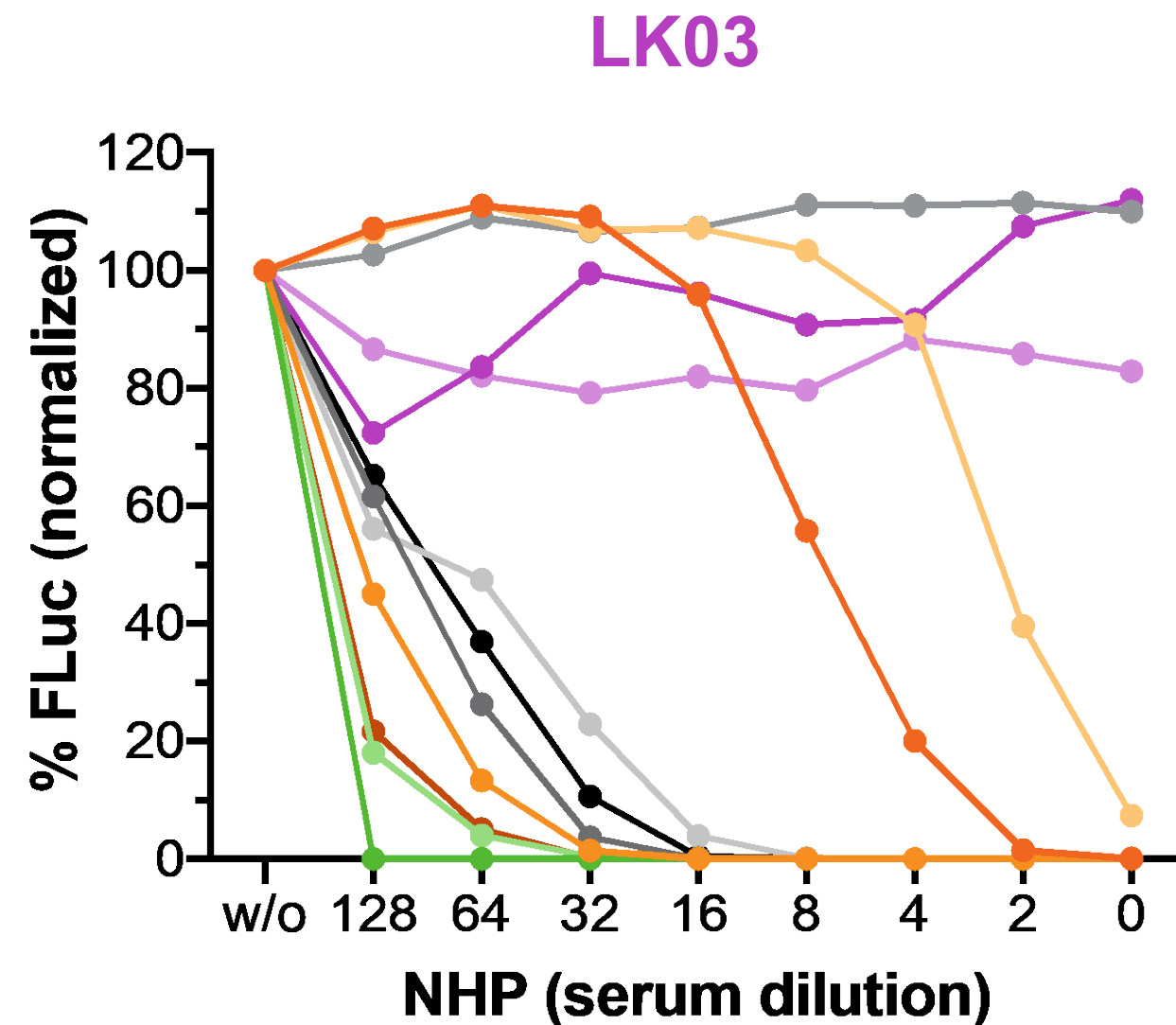
## AAV KP1 / CB 2679d-GT study in hemophilia B mice



**Dose dependent and stable FIX activity levels observed for up to 18 weeks**

# KP1 has a different response profile to pre-existing nAbs

## AAV KP1 / CB 2679d-GT study in cynomolgus NHP



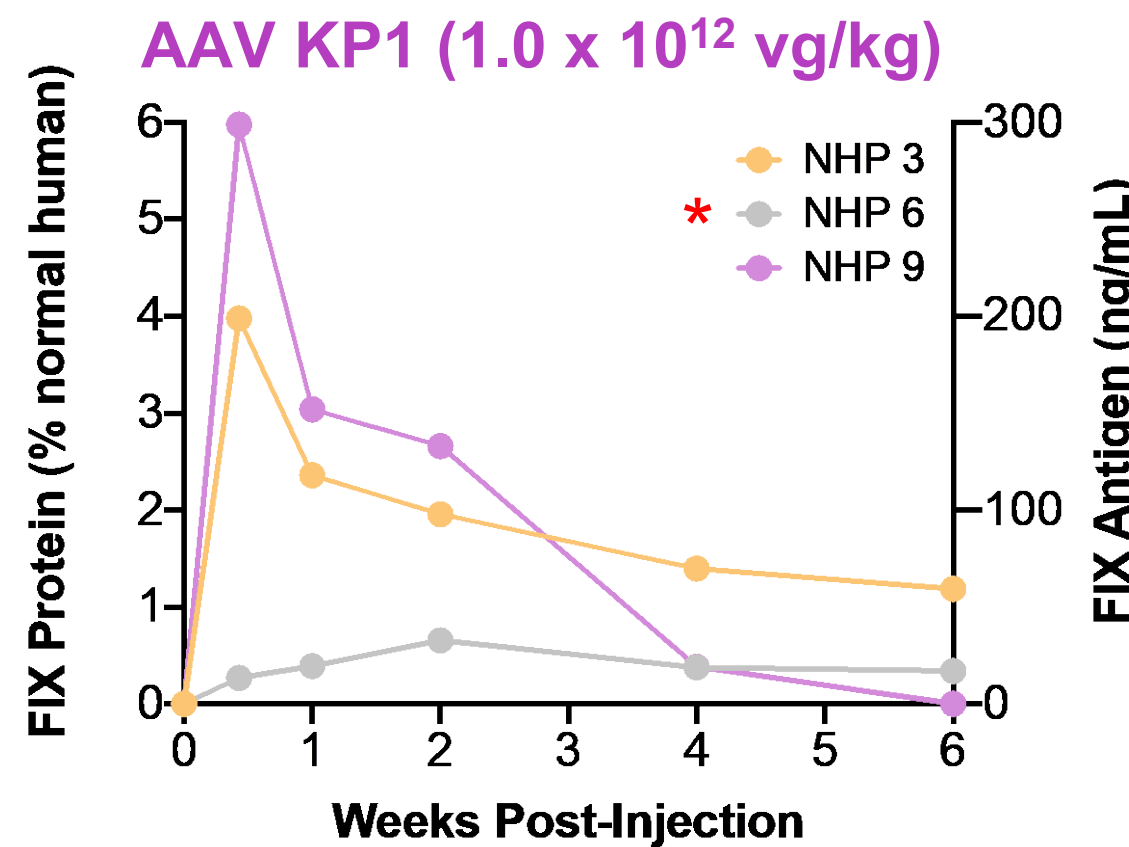
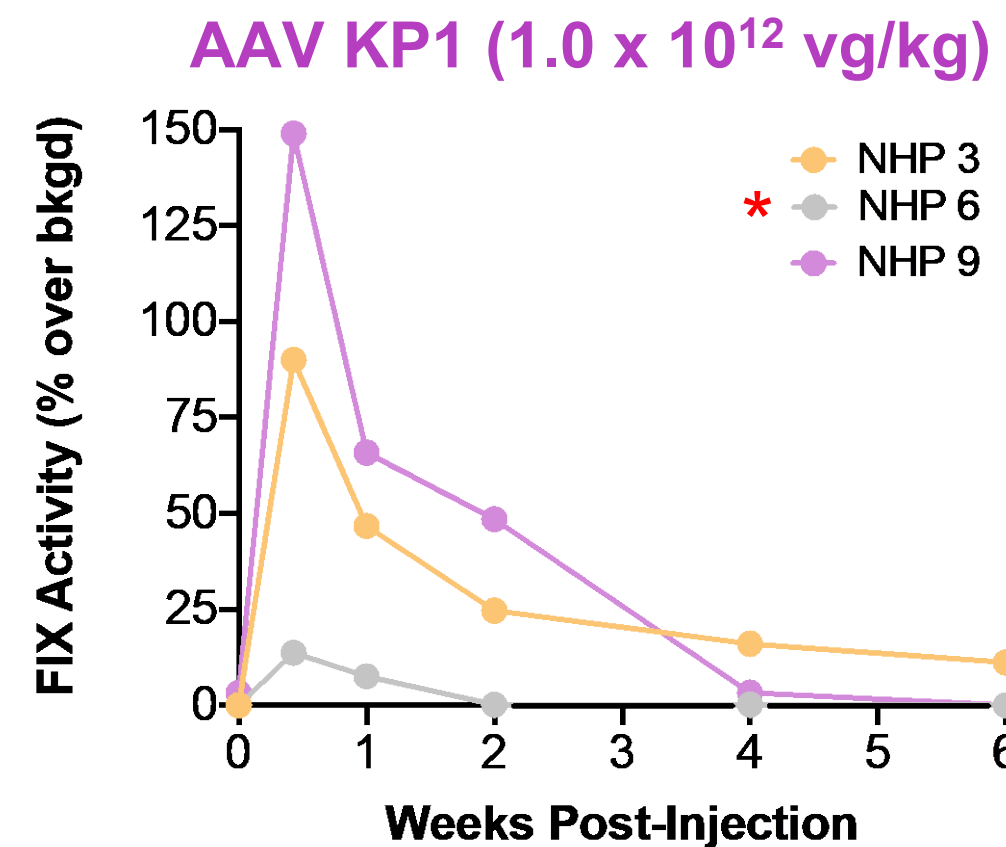
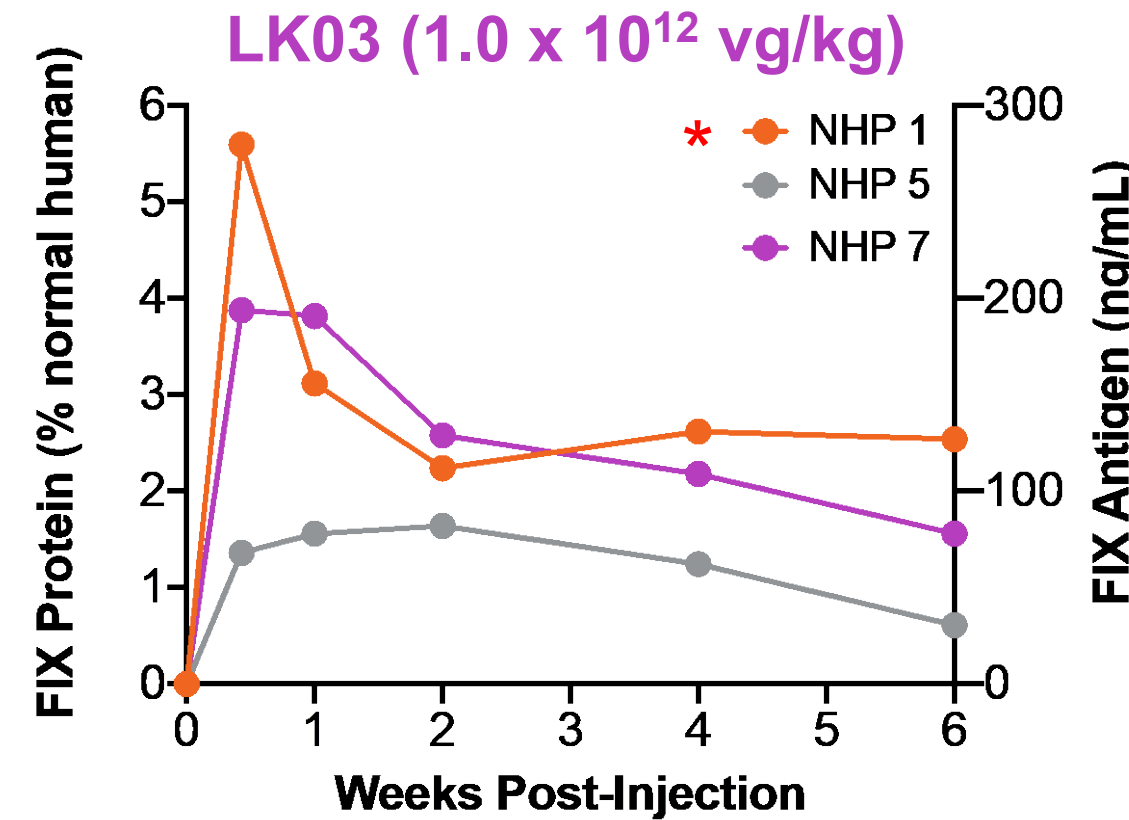
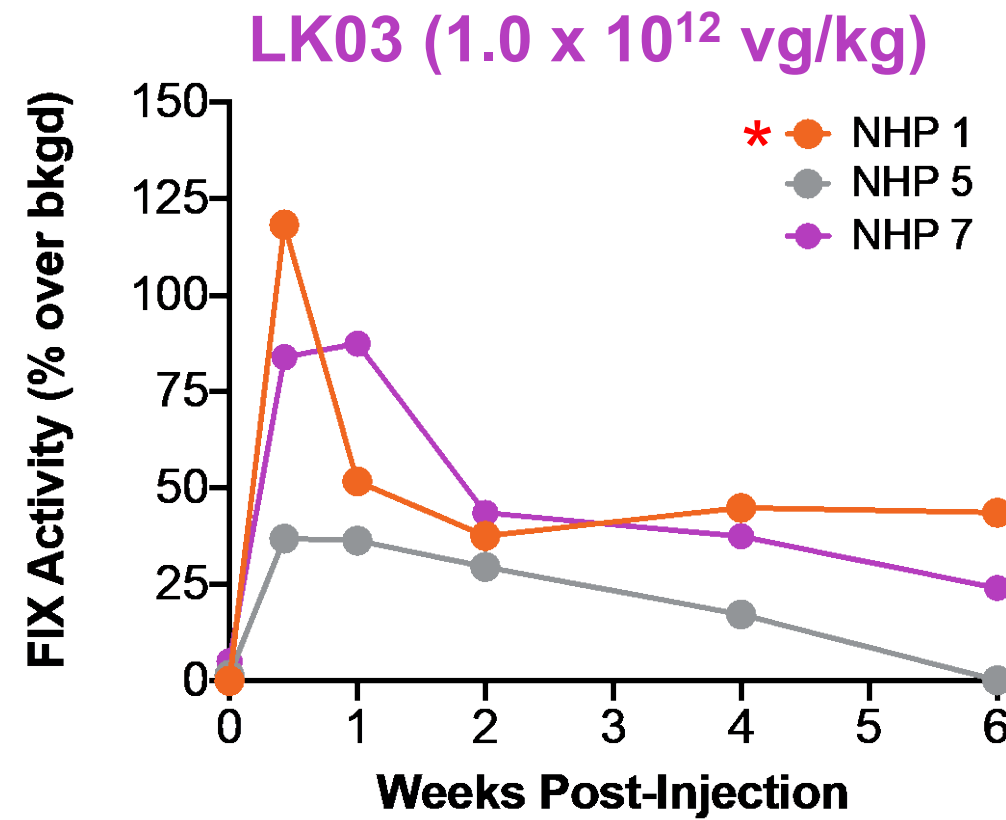
- NHP 1
- NHP 2
- NHP 3
- NHP 4
- NHP 5
- NHP 6
- NHP 7
- NHP 8
- NHP 9
- NHP 10
- NHP 11
- NHP 12

- NHP 1
- NHP 2
- NHP 3
- NHP 4
- NHP 5
- NHP 6
- NHP 7
- NHP 8
- NHP 9
- NHP 10
- NHP 11
- NHP 12

**Less neutralizing effect of pre-existing nAb was observed with KP1**

# Pilot NHP comparison of CB 2679d-GT / AAV KP1 to LK03

## CB 2679d-GT study in cynomolgus NHP (6-week interim data)



- + Achieved **high initial FIX levels**
- + Decreased to a steady plateau
  - 2/3 LK03 & 1/3 AAV KP1 animals
- + Elevated ALT in 1/6 animals consistent with low expression and pre-existing nAb to the capsid
- + Study remains in progress for additional endpoint evaluation
- + **Expression and activity levels comparable to NHP studies of other clinical candidates**
- + **Additional vector optimization & dose ranging studies planned**

# Acknowledgements to our academic collaborators



Mark Kay, MD PhD  
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Nisha Nair, PhD

THANK YOU

