Hemophilia B Gene Therapy in Mice using a Novel Chimeric AAV Capsid Combined with a Potency Enhanced FIX Variant

Gene Therapy for Blood Disorders

March 3rd - 5th 2020

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SVP Translational Research

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Essential Medicines – Superior Outcomes

Late-Stage Asset

SQ Marzeptacog alfa (activated)
MarzAA (FVIIa)

Phase 3 Ready

Hemophilia

SQ MarzAA (FVIIa)

SQ Dalcinonacog alfa – DalcA (FIX)

Factor IX Gene Therapy

Factor Xa

Complement

IVT Anti-C3 Dry AMD
CB 2782-PEG

Biogen

SQ Systemic Complement Inhibitors

Protease Engineering Platform

Presentation outline

New approaches to FIX gene therapy in hemophilia B

+ What patients are looking for in hemophilia treatment
+ The need for improved gene therapy delivery
+ Taking a combined approach to improving FIX gene therapy
+ The origin of the CB 2679d-GT candidate
+ Proof of concept for CB 2679d-GT *vs* Padua: Collaboration with Vrije University, Brussels
+ A novel chimeric capsid combined with CB 2679d-GT: Collaboration with Stanford University
+ Conclusions

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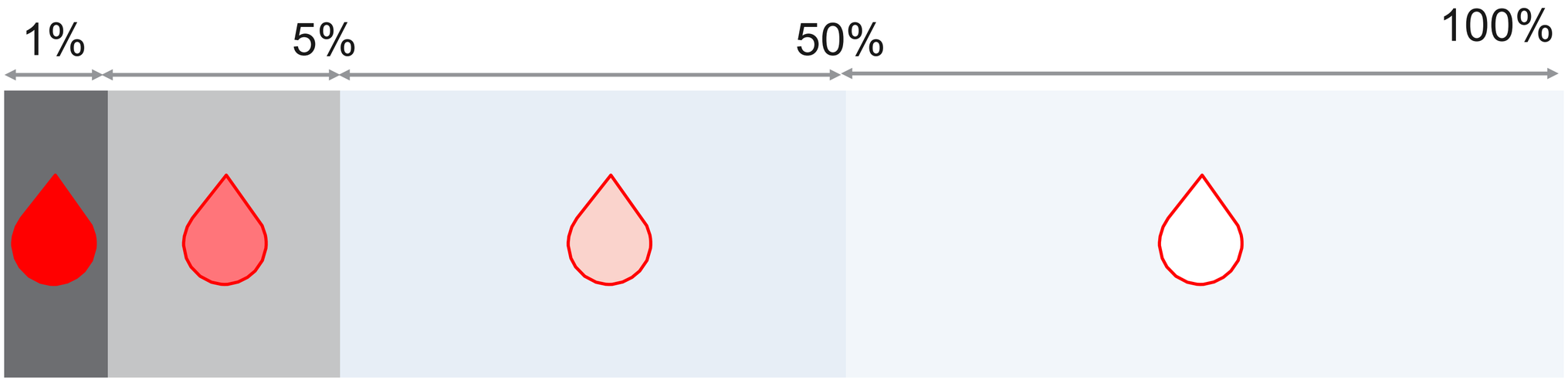
Goal of gene therapying hemophilia: Normal bleeding

Nasdaq: CBIO

Patients are seeking sustained clotting factor activity to normalize phenotype



Severe
~30
Bleeds
annually

Moderate
~15-20
Bleeds
annually

Mild
Protection from spontaneous
hemarthrosis
at >12% Activity

Normal
Clotting Levels

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The next generation of gene therapy in hemophilia B

Nasdaq: CBIO

First generation gene therapies are moving to approval yet there is room for innovation

- Risk of vector dose-limiting toxicity
- Immunogenicity to the vector
- Higher transduction efficiency
- Liver inflammation

Need for more efficient vectors & lower dosing regimen

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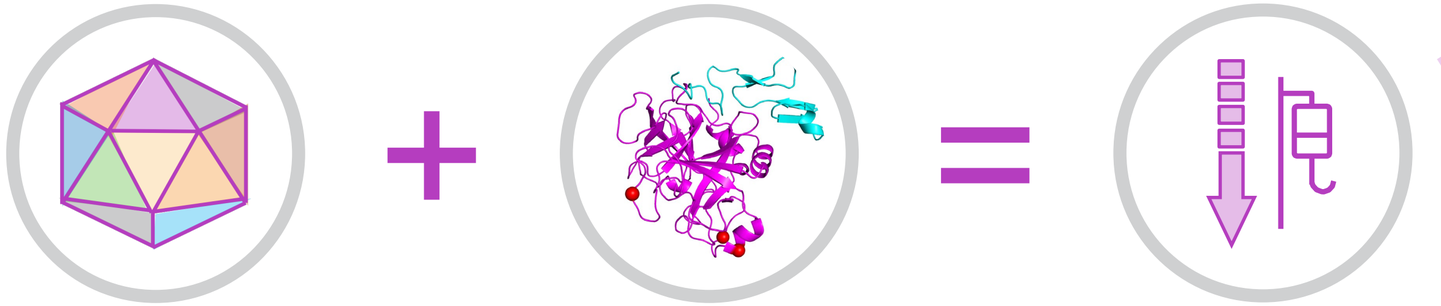
How do we achieve a normal bleeding phenotype?

Nasdaq: CBIO

Combining optimized capsid + transgene = improved therapy



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

- Lower Immunogenicity
- Decrease Liver Toxicity
- Lower Manufacturing Costs

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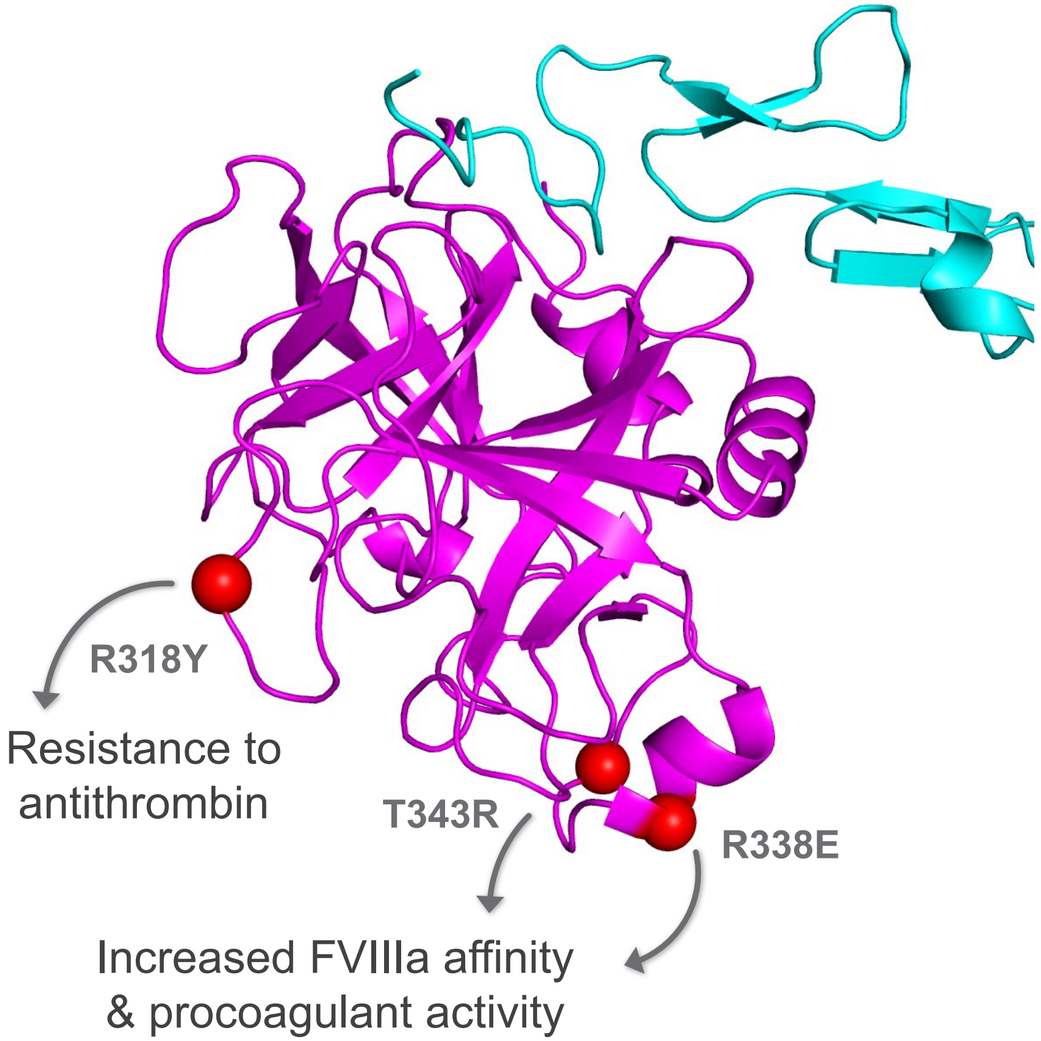
Dalcinonacog alfa: a novel SQ FIX product



Three substitutions within the FIX protein

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

Differentiated from marketed IV FIXs

+ Simple, small volume SQ administration
+ Enhanced pharmacokinetics with prolonged half-life
+ Excellent extravascular distribution
+ Potential to maintain continuous protective levels

Orphan Drug Designation in US & EU

Capitalizing on the gene behind dalcinonacog alfa

Dalcinonacog alfa

- Recombinant FIX
- Subcutaneous delivery
- Currently in Phase 2b
- Sustained factor levels

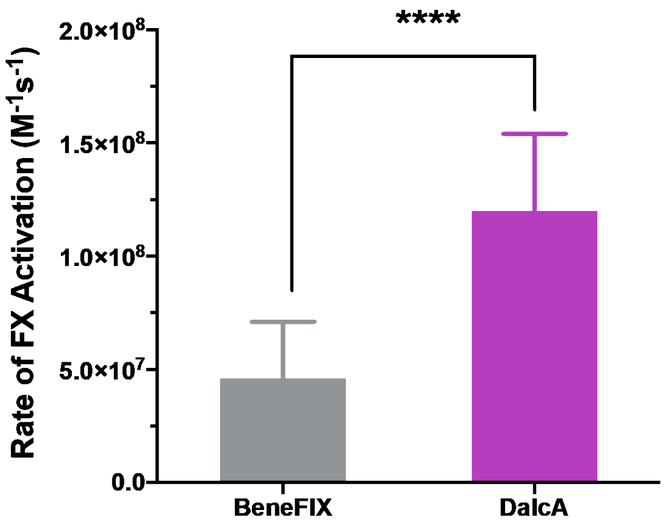
CB 2679d-GT

- Gene therapy
- AAV delivery
- Preclinical

Improved functionality of CB2679d-GT drives high potency

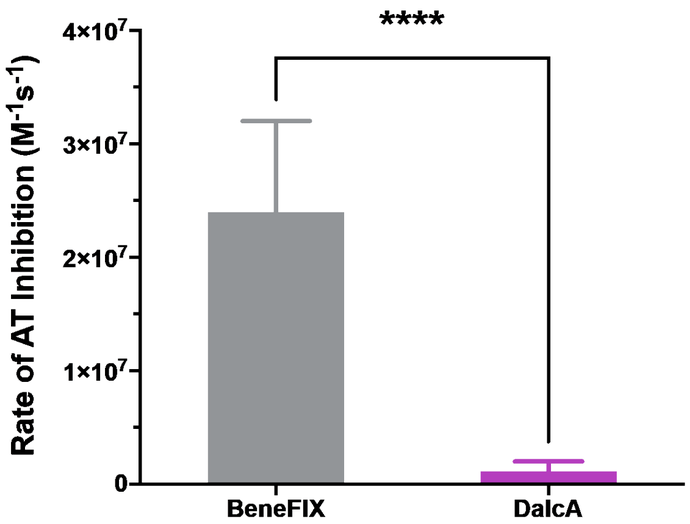
Nasdaq: CBIO

Factor X Activation



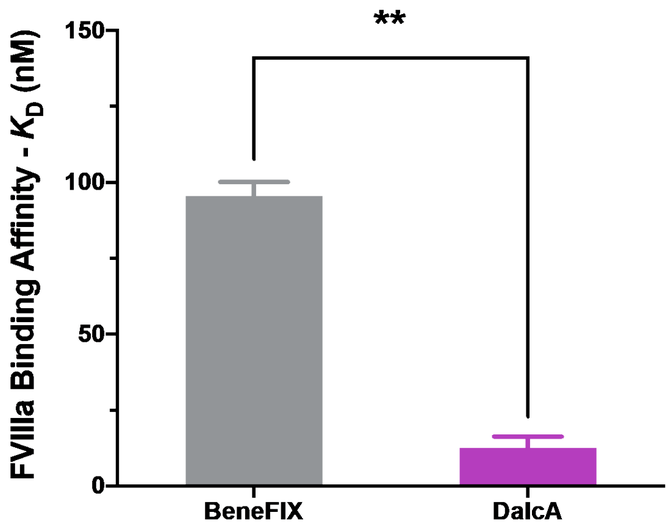
2.5-Fold Increase

Inhibition by Antithrombin



21-Fold Resistance

Enhanced FVIIIa Binding



8-Fold Increase in Affinity

When combined these properties provide a 22-fold enhanced potency in SQ clinical trials

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AAV vector design of CB 2679d-GT in a DJ/8 capsid

Nasdaq: CBIO

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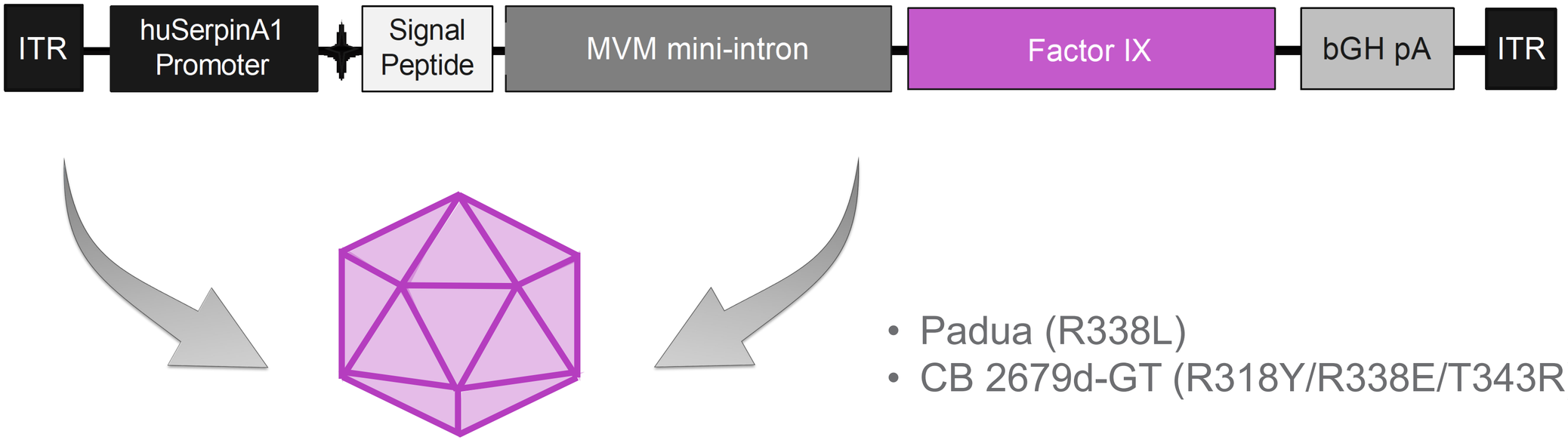

- Padua (R338L)
- CB 2679d-GT (R318Y/R338E/T343R)

FIX minigene constructs were packaged into a DJ/8 AAV capsid

FIX activity levels remained stable for 20 weeks

Nasdaq: CBIO

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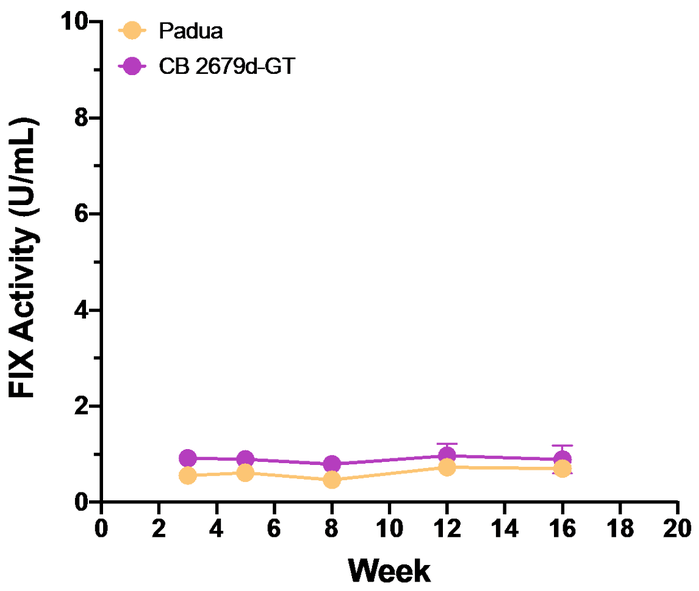
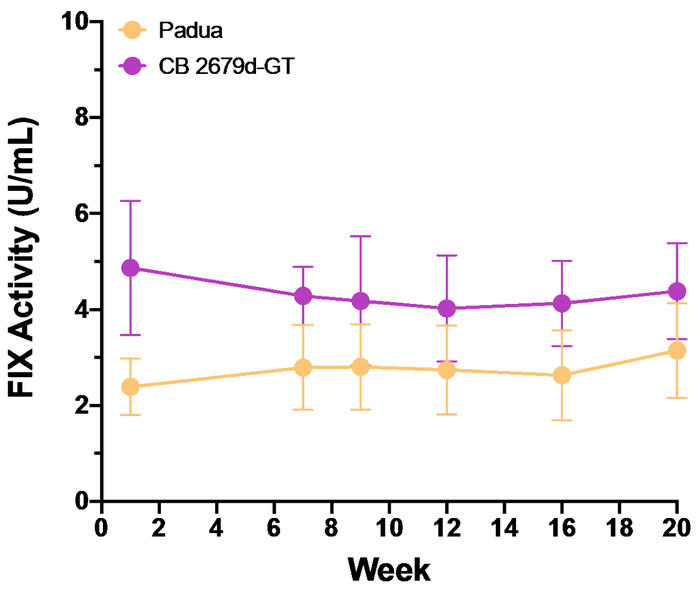
5.0×10^{10} vg/kg



2.5×10^{11} vg/kg



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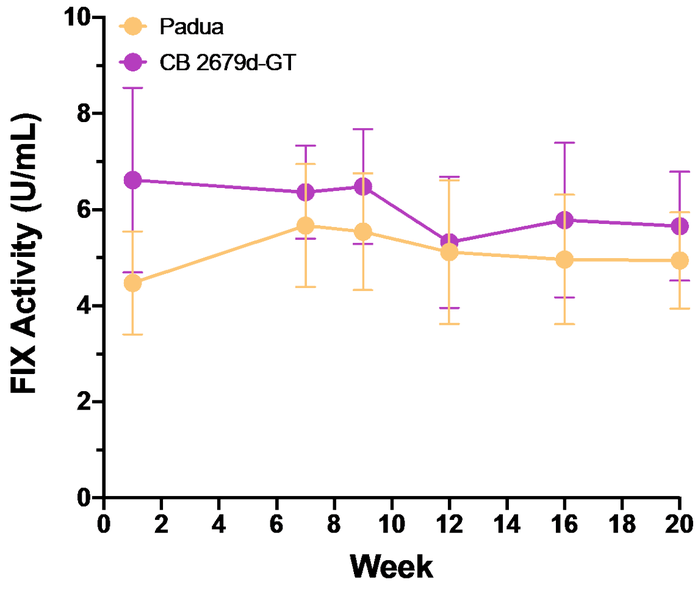


Dose dependent and stable FIX levels observed for 20 weeks

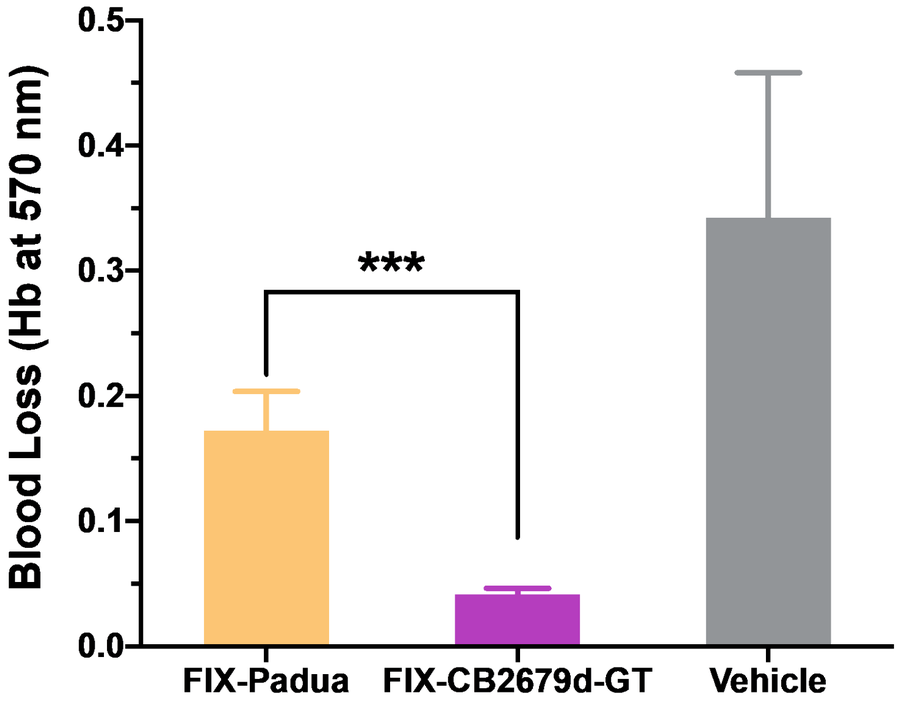
(Activity levels determined by OSA with HemosIL and a WHO standard)

CB 2679d-GT reduces total blood loss more than Padua

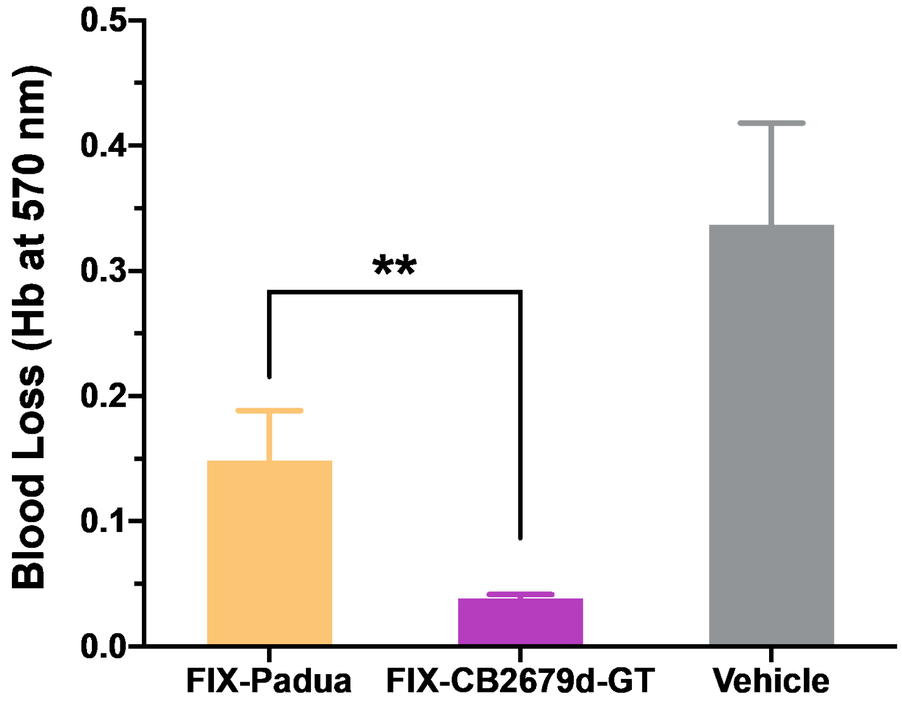
Nasdaq: CBIO

VRIJE UNIVERSITEIT BRUSSEL

2.5 x 10^{11} vg/kg



5.0 x 10^{11} vg/kg



CB 2679d-GT has an ~4-fold reduction in blood loss

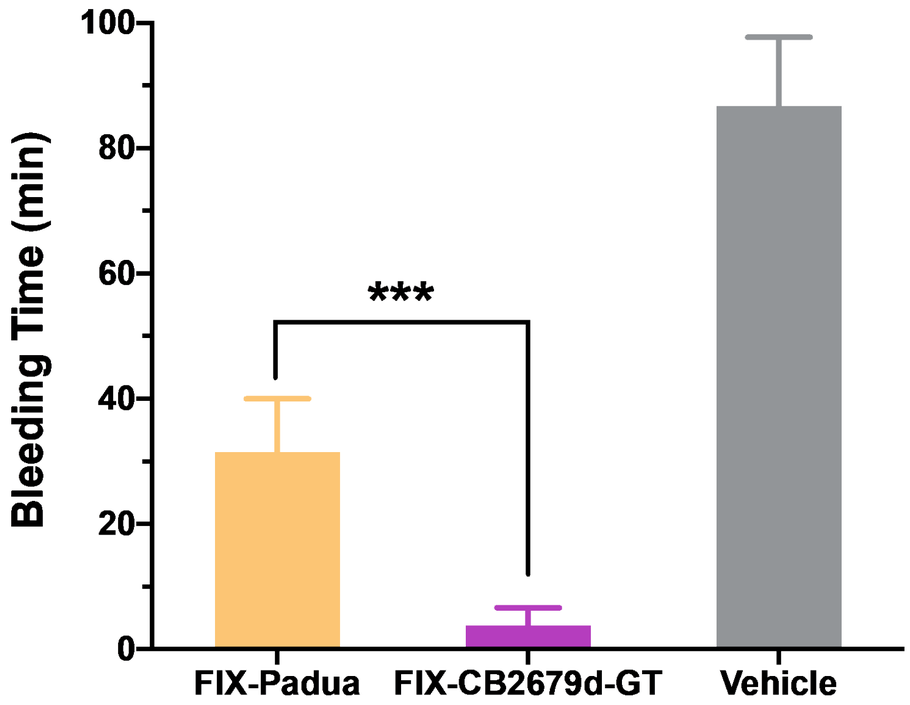
(Student's T-Test: *** P<0.001, ** P<0.01, * P<0.05 and NS – Not Significant)

CB 2679d-GT reduces bleeding time more than Padua

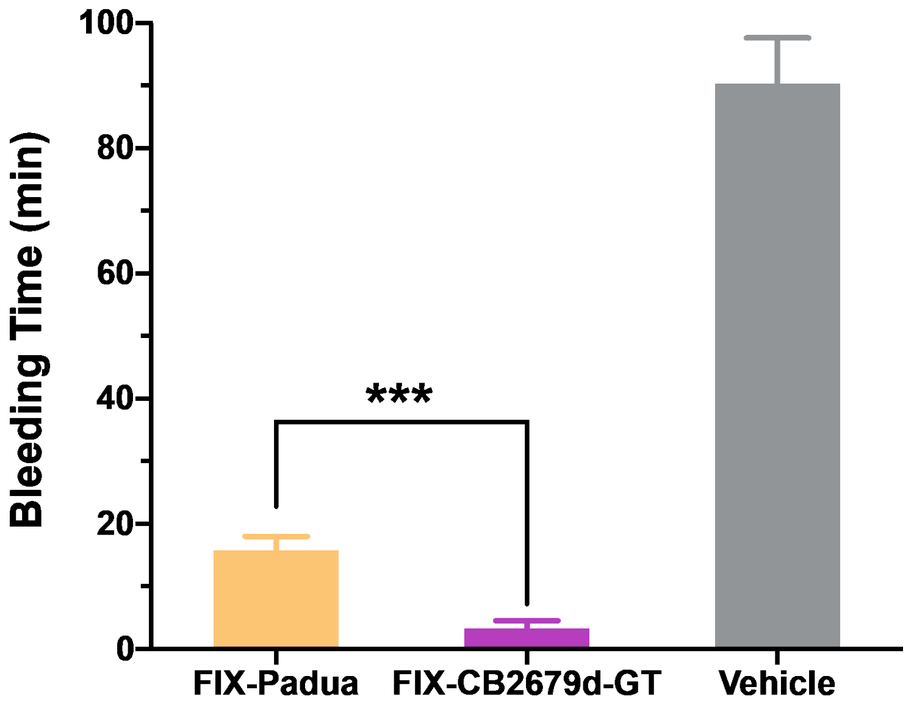
Nasdaq: CBIO

VRIJE UNIVERSITEIT BRUSSEL

2.5 x 10^{11} vg/kg



5.0 x 10^{11} vg/kg



CB 2679d-GT has an ~5 to 8-fold reduction in bleeding time

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

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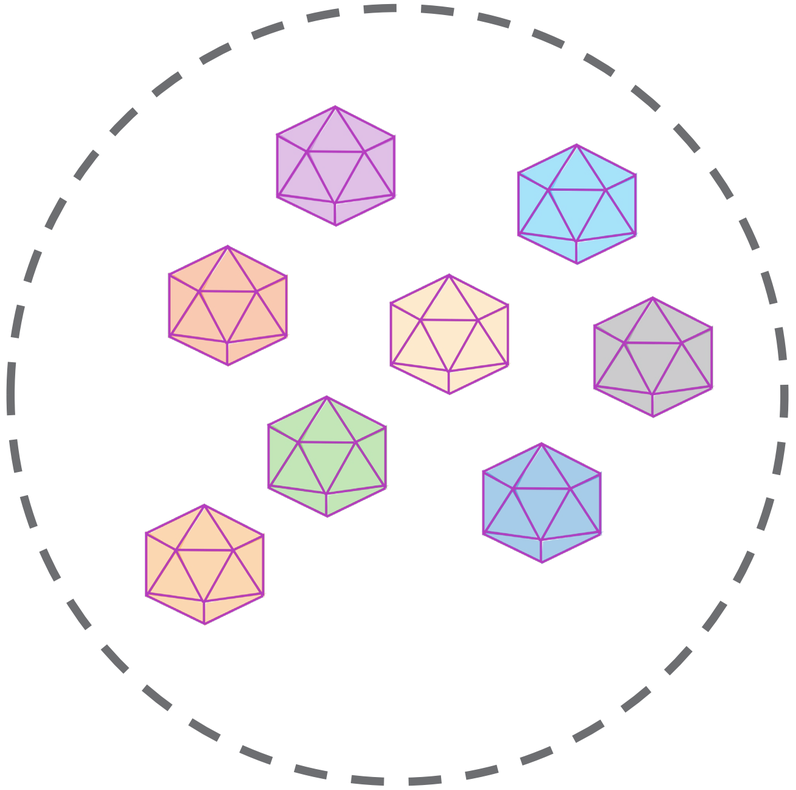
DNA shuffling to create a novel AAV vector

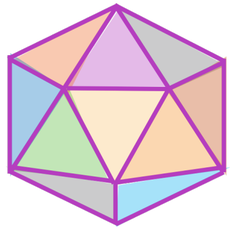
Nasdaq: CBIO

Stanford University

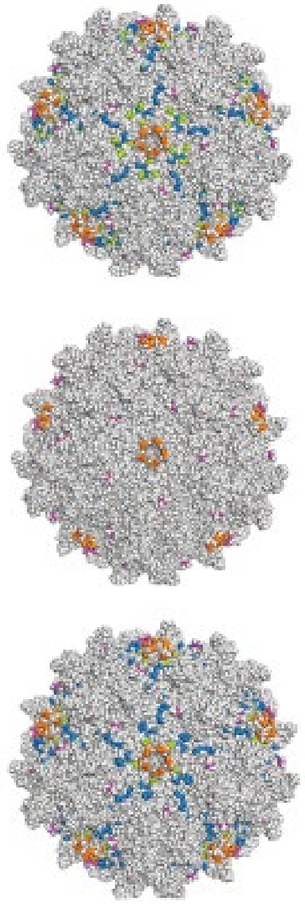
DNA shuffling of 8 serotypes



Select for tropism & increased transduction efficiency



Chimeric Capsids

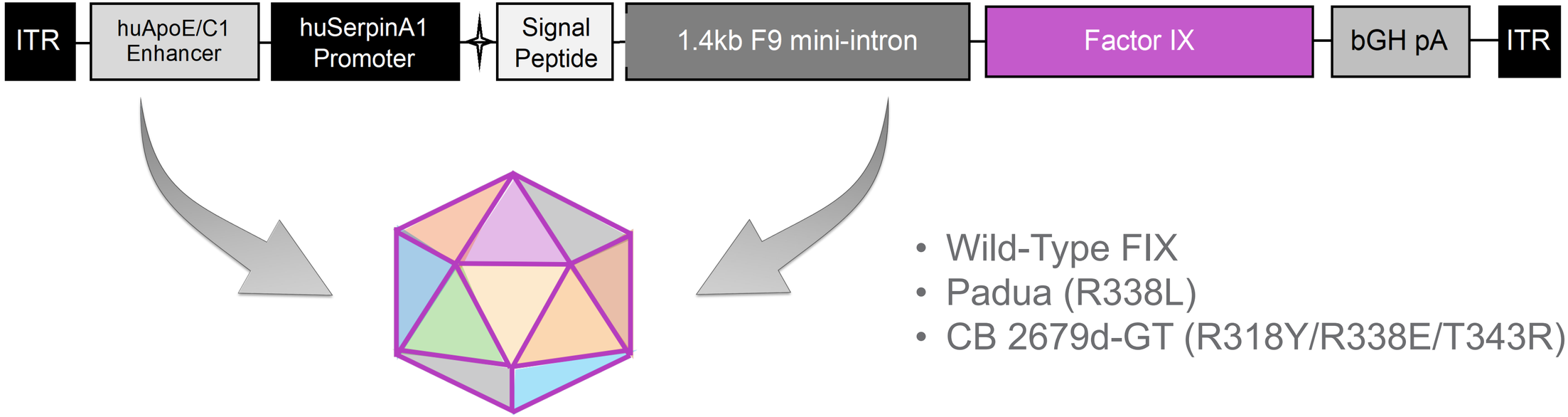


High performing AAV capsid candidates

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

Nasdaq: CBIO

Stanford University



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

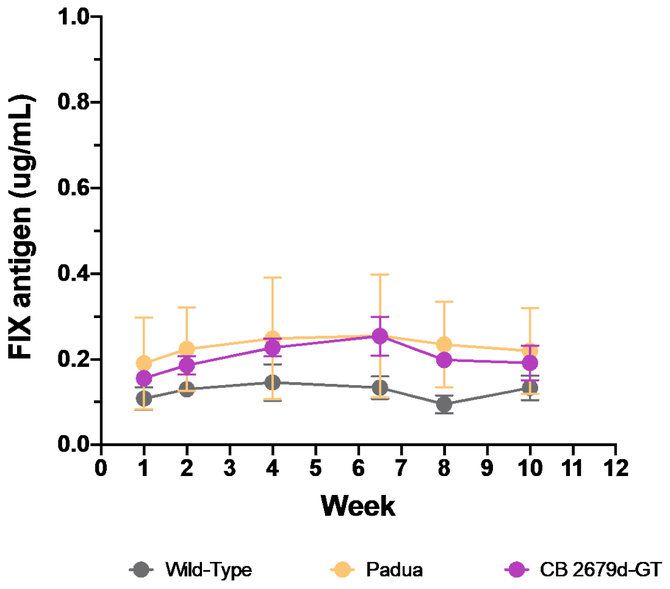
FIX minigene constructs were packaged into a novel AAV capsid designed through DNA shuffling of 8 AAV serotypes and showing a high tropism for liver transduction

FIX antigen levels remained stable

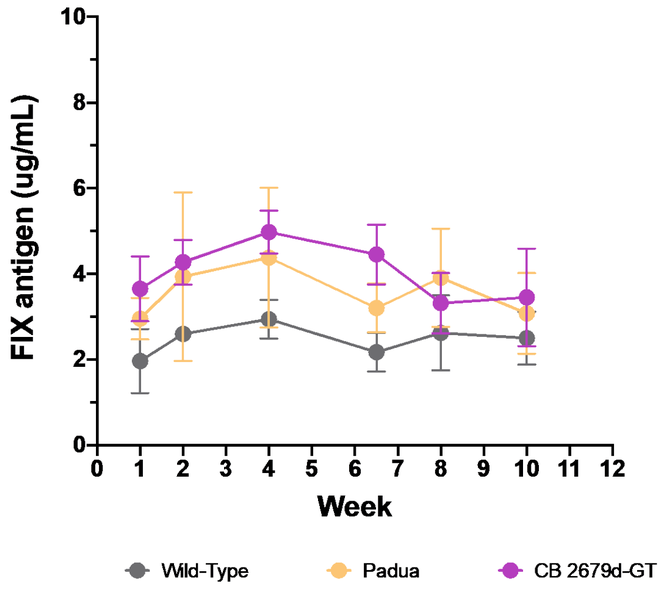
Nasdaq: CBIO

Stanford University

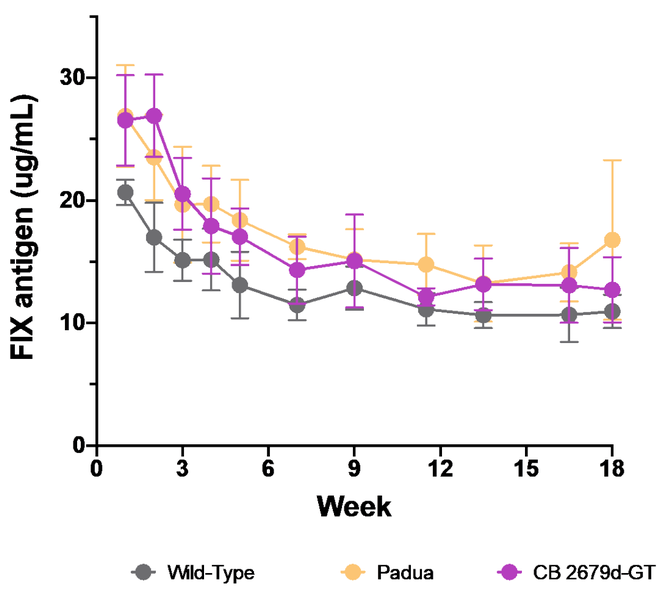
8.0×10^9 vg/kg



8.0×10^{10} vg/kg



8.0×10^{11} vg/kg



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

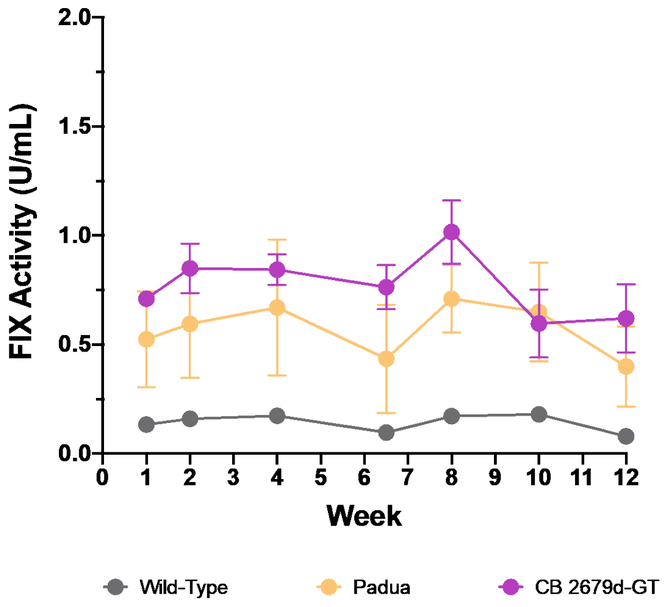
(Activity levels determined by OSA with HemosIL and a WHO standard)

FIX activity levels remained stable

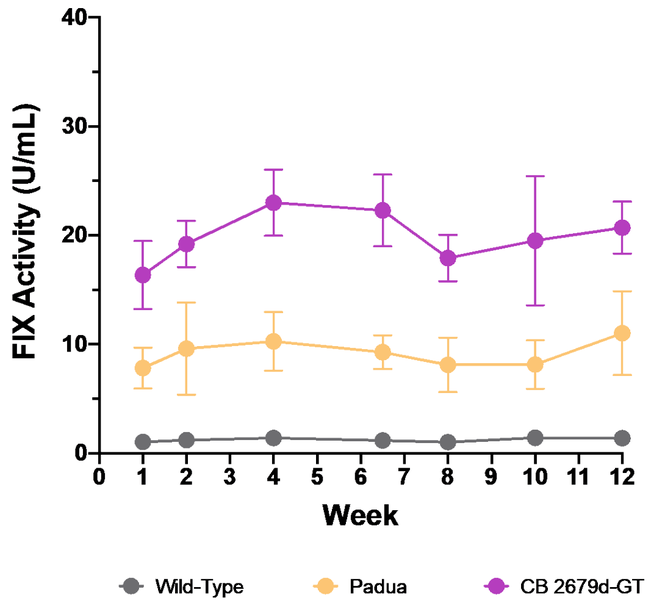
Nasdaq: CBIO

Stanford University

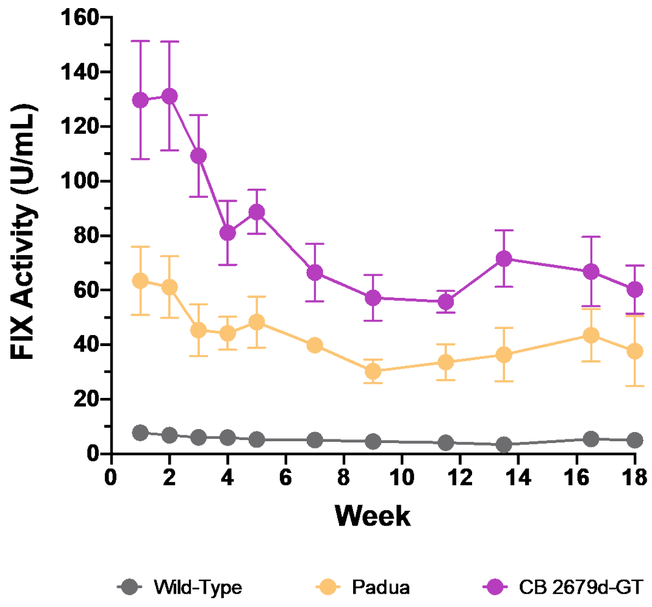
8.0 x 10^9 vg/kg



8.0 x 10^{10} vg/kg



8.0 x 10^{11} vg/kg



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

(Activity levels determined by OSA with HemosIL and a WHO standard)

CB 2679d-GT in combination with a novel chimeric capsid provides a significant improvement in FIX activity levels

Nasdaq: CBIO

Mid-dose data at $8.0x10^{10}$ vg/kg

FIX Transgene	AAV Capsid	Study Dose (vg/kg)	FIX Activity (U/mL)
CB 2679d-GT	Novel Chimeric	$8.0x10^{10}$	20
Padua	TAK-748[2]	$7.4x10^{11}$	20
Padua	TAK-748[2]	$7.4x10^{10}$	1
CB 2679d-GT	DJ/8[1]	$2.0x10^{11}$	4
CB 2679d-GT	DJ/8[1]	$4.0x10^{10}$	1

[1]Blouse GE, Nair N, Vandendriessche T, Chuah MK, Landau, J. (2019) *Haemophilia*, Vol 25, Supplement S1 P124

[2]Weiller M, Wang H, Coulibaly S, Schuster M, Rottensteiner H, Sun K, Chuah MK, Vandendriessche T. (2019) *Blood* Vol. 134, Supplement S1 P4633

Next steps for preclinical development of CB 2679d-GT

CB 2679d-GT Preclinical Development

Mark Kay, M.D. Ph.D. (Stanford)	Peter Lenting, Ph.D. (INSERM)
Development of AAV vectors and evaluation in mouse and monkey models	Functional evaluation of the gene therapy candidates in hemophilia mouse models

What could account for the shortened bleeding time with CB 2679d-GT?

+ Does CB 2679d-GT improve clot structure?
+ Is the clot more stable?
+ Does CB 2679d-GT have a faster time to clot?
+ What functional properties of CB 2679d-GT contribute to the shorter bleeding time?
  - Resistance to antithrombin inhibition?

What is the durability of CB 2679d-GT when delivered in a novel AAV vector?

+ Durability in non-human primates

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AAV CB 2679d-GT is superior to AAV Padua

CB 2679d-GT demonstrates superior preclinical potency *vs* Padua

- CB 2679d-GT differentiated from FIX Padua by further increased FIX activity
- A novel chimeric capsid demonstrates high FIX levels with lower AAV dose
- FIX antigen/activity levels stable and durable for up to 20 weeks in hemophilia B mice
- CB 2679d-GT achieved a more rapid and robust hemostatic correction than Padua
- Program now progressing to non-human primate studies

THANK YOU

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