
V1.0
5' ITR
TTP
Intron
BDD-FVIIIco6XTEN
WPRE
bGHpA
3' ITR
V2.0
5' ITR
A1MB2
mTTR482
Chimeric Intron
Co-BDD-FVIIIXTEN
WPRE
bGHpA
3' ITR
V3.0
5' ITR
A1AT
Chimeric Intron
Co-BDD-FVIIIXTEN
WPRE
bGHpA
3' ITR

FIG. 1

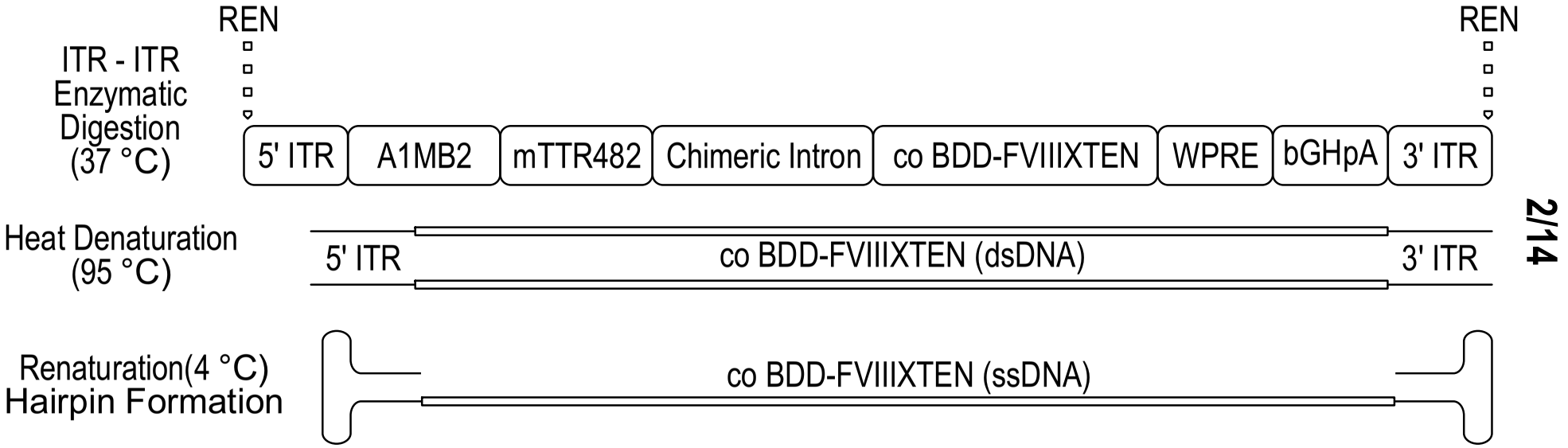

REN
REN
ITR - ITR
Enzymatic
Digestion
(37 °C)
5' ITR
A1MB2
mTTR482
Chimeric Intron
co BDD-FVIIIXTEN
WPRE
bGHpA
3' ITR
Heat Denaturation
(95 °C)
5' ITR
co BDD-FVIIIXTEN (dsDNA)
3' ITR
Renaturation(4 °C)
Hairpin Formation
co BDD-FVIIIXTEN (ssDNA)

**FIG. 2**

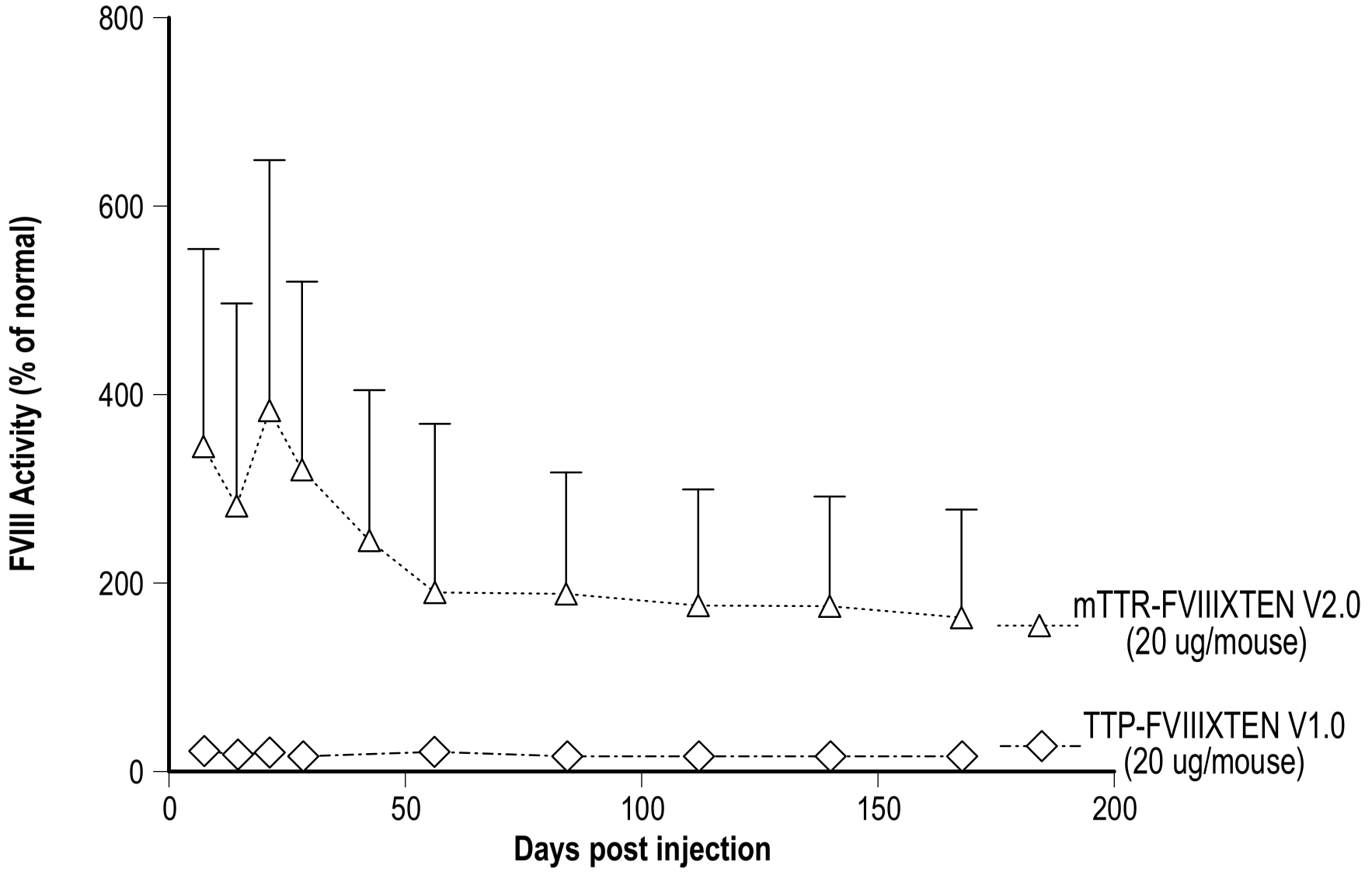

800
600
400
200
0
FVIII Activity (% of normal)
0
50
100
150
200
Days post injection
mTTR-FVIIIXTEN V2.0
(20 ug/mouse)
TTP-FVIIIXTEN V1.0
(20 ug/mouse)

FIG. 3

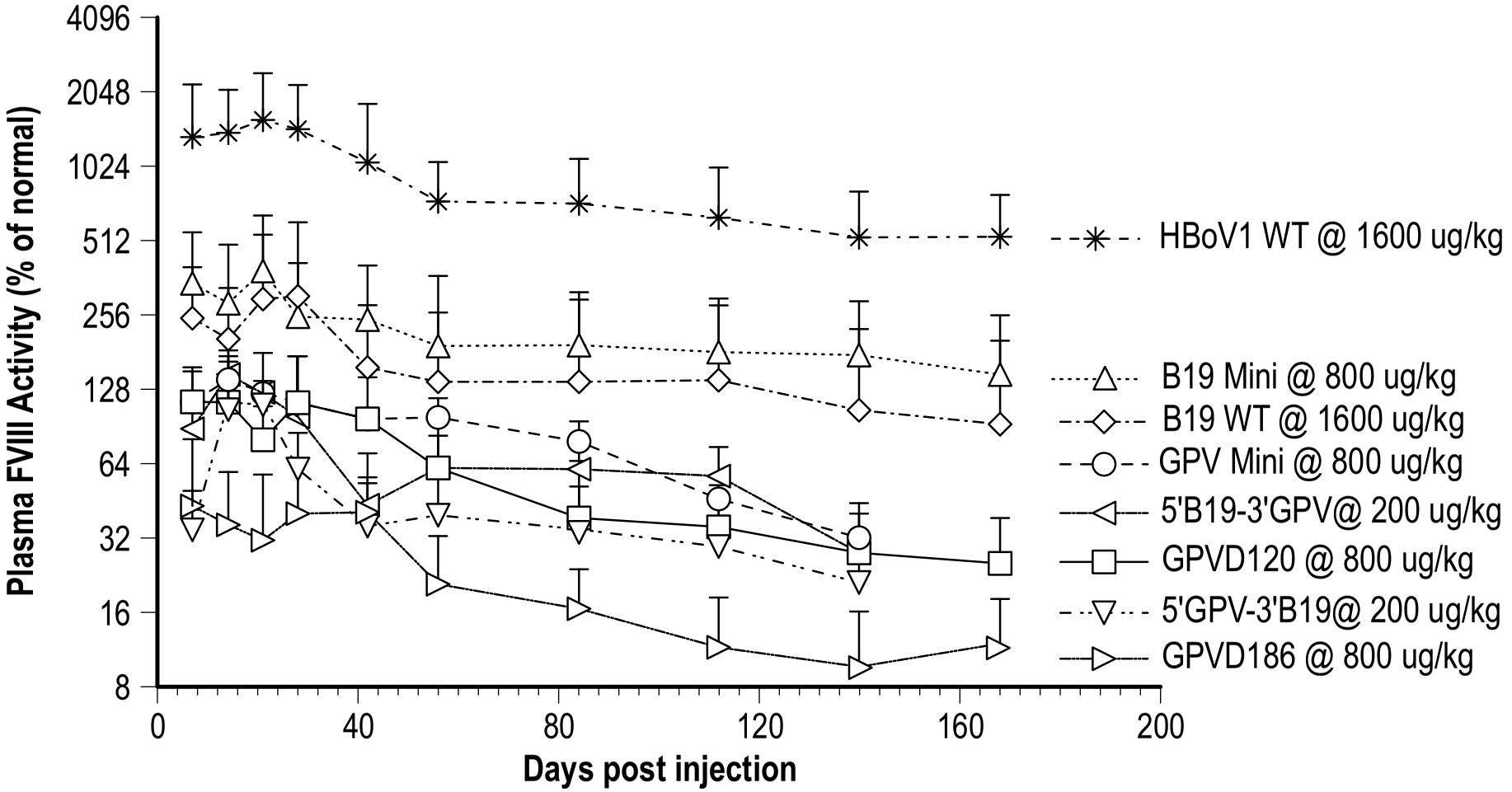

Plasma FVIII Activity (% of normal)
4096
2048
1024
512
256
128
64
32
16
8
0
40
80
120
160
200
Days post injection
HBoV1 WT @ 1600 ug/kg
B19 Mini @ 800 ug/kg
B19 WT @ 1600 ug/kg
GPV Mini @ 800 ug/kg
5'B19-3'GPV@ 200 ug/kg
GPVD120 @ 800 ug/kg
5'GPV-3'B19@ 200 ug/kg
GPVD186 @ 800 ug/kg

FIG. 4

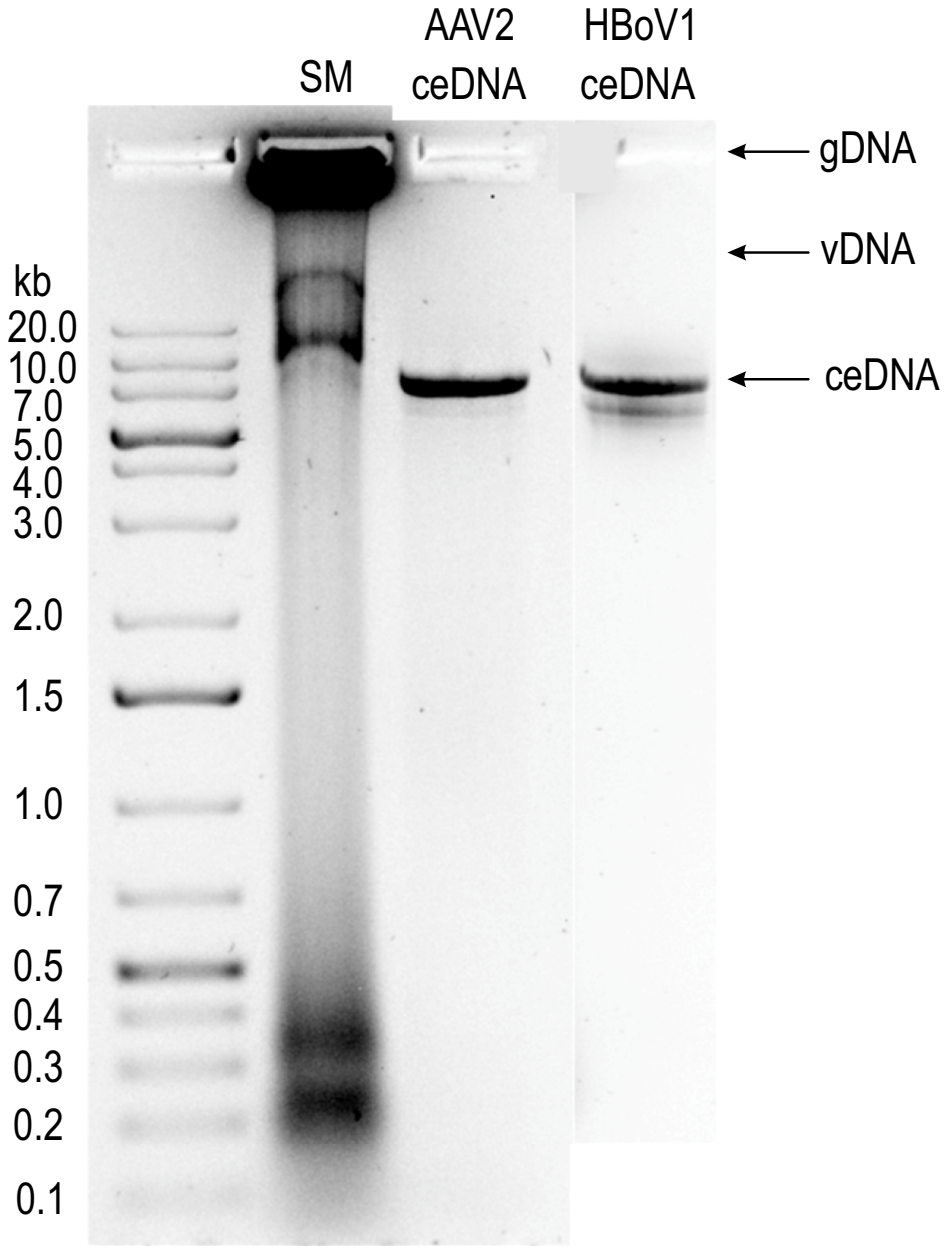

SM
AAV2 ceDNA
HBoV1 ceDNA
gDNA
vDNA
ceDNA
kb
20.0
10.0
7.0
5.0
4.0
3.0
2.0
1.5
1.0
0.7
0.5
0.4
0.3
0.2
0.1

FIG. 5A

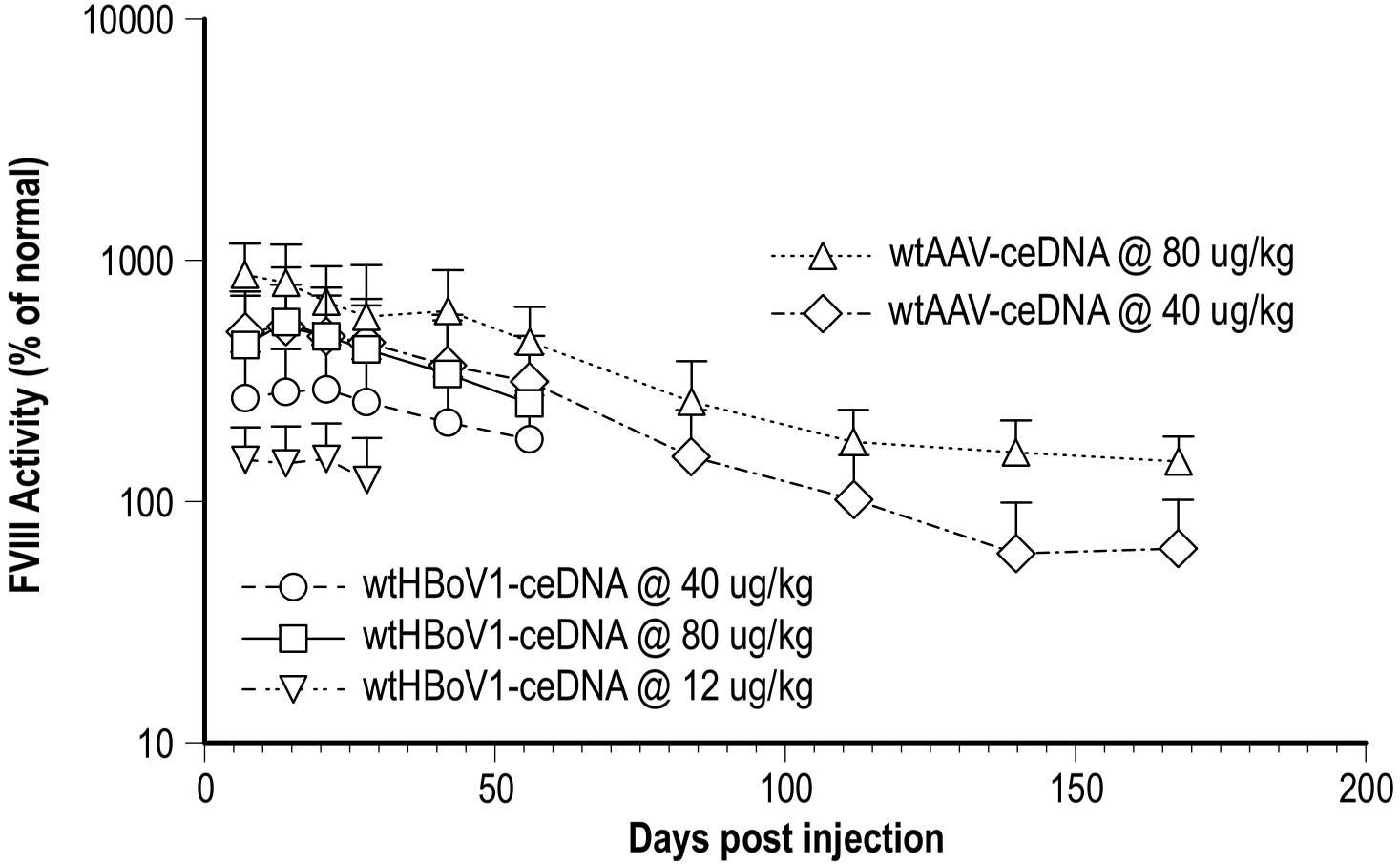

10000
1000
100
10
FVIII Activity (% of normal)
0
50
100
150
200
Days post injection
wtAAV-ceDNA @ 80 ug/kg
wtAAV-ceDNA @ 40 ug/kg
wtHBoV1-ceDNA @ 40 ug/kg
wtHBoV1-ceDNA @ 80 ug/kg
wtHBoV1-ceDNA @ 12 ug/kg

FIG. 5B


ssDNA - mTTR-FVIIIXTEN- HBoV1
HBoV1
A1MB2
mTTR482
Chimeric Intron
BDD-FVIIIXTEN cDNA
WPRE
bGHpA
3' ITR
HBoV1
5' ITR
ssDNA - A1AT-FVIIIXTEN- HBoV1
HBoV1
A1AT
Chimeric Intron
BDD-FVIIIXTEN cDNA
WPRE
bGHpA
3' ITR
HBoV1
5' ITR

FIG. 6A

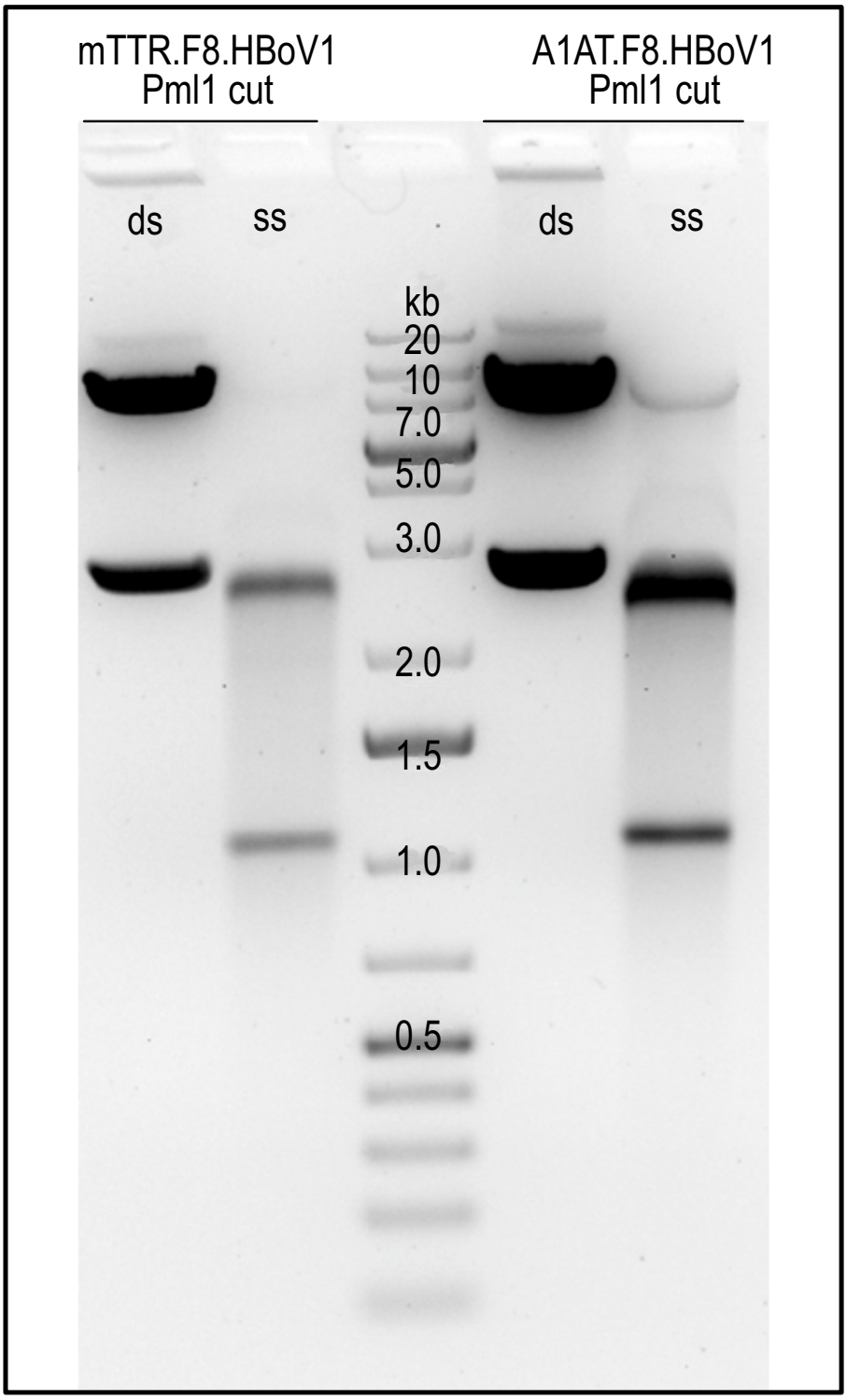

mTTR.F8.HBoV1
Pml1 cut
A1AT.F8.HBoV1
Pml1 cut
ds
ss
ds
ss
kb
20
10
7.0
5.0
3.0
2.0
1.5
1.0
0.5

FIG. 6B

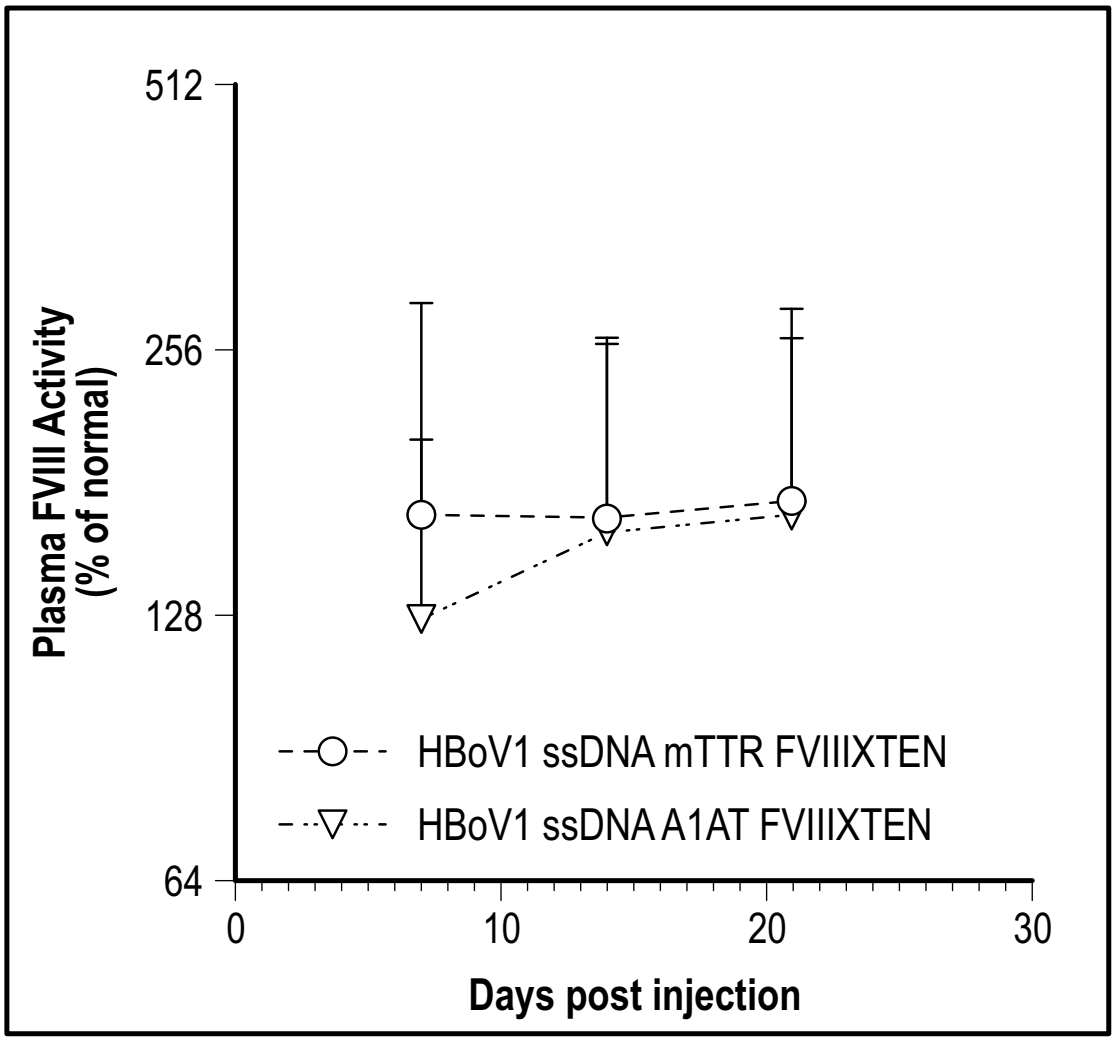

512
256
128
64
Plasma FVIII Activity
(% of normal)
0
10
20
30
Days post injection
HBoV1 ssDNA mTTR FVIIIXTEN
HBoV1 ssDNA A1AT FVIIIXTEN

FIG. 6C

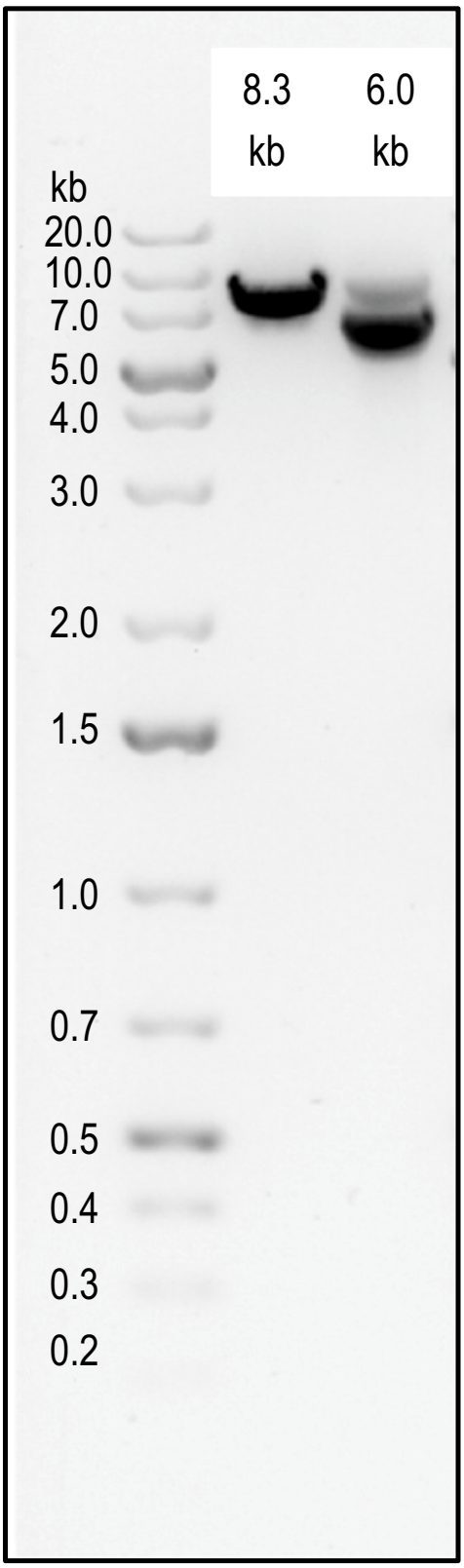
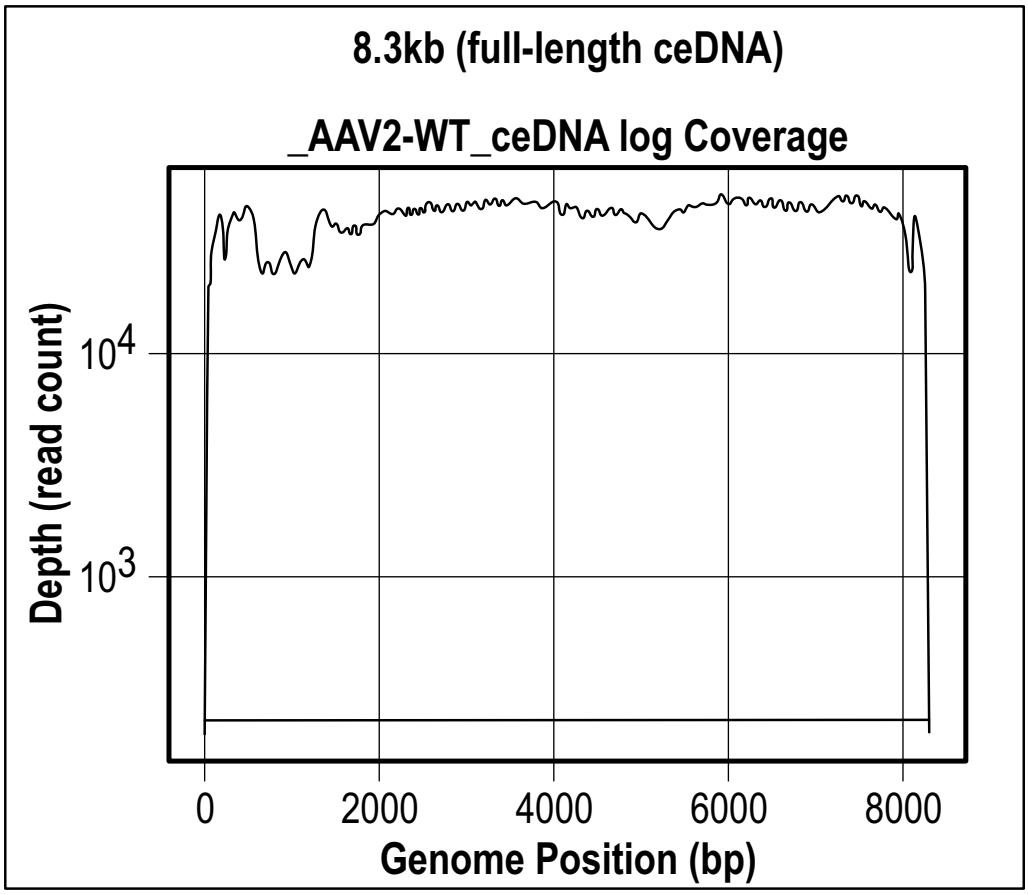



FIG. 7A


8.3kb (full-length ceDNA)
_AAV2-WT_ceDNA log Coverage
Depth (read count)
$10^4$
$10^3$
0
2000
4000
6000
8000
Genome Position (bp)

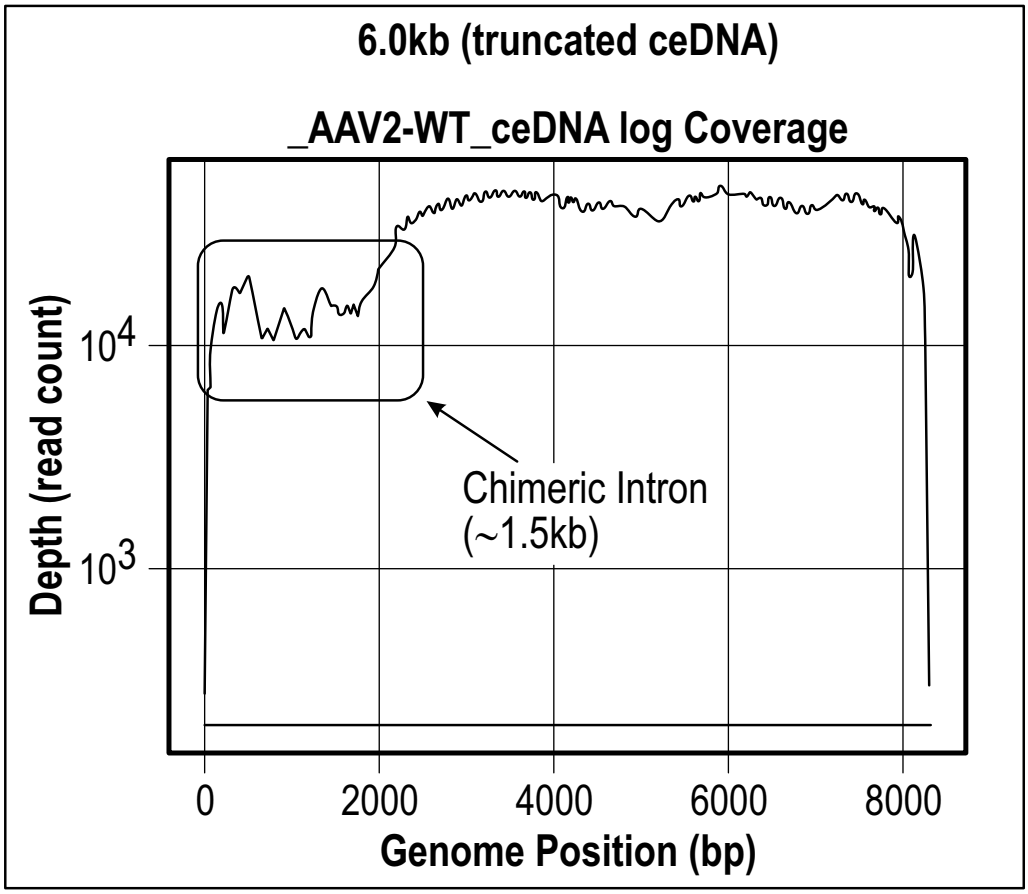

6.0kb (truncated ceDNA)
_AAV2-WT_ceDNA log Coverage
Depth (read count)
$10^4$
$10^3$
Chimeric Intron
(~1.5kb)
0
2000
4000
6000
8000
Genome Position (bp)

FIG. 7B

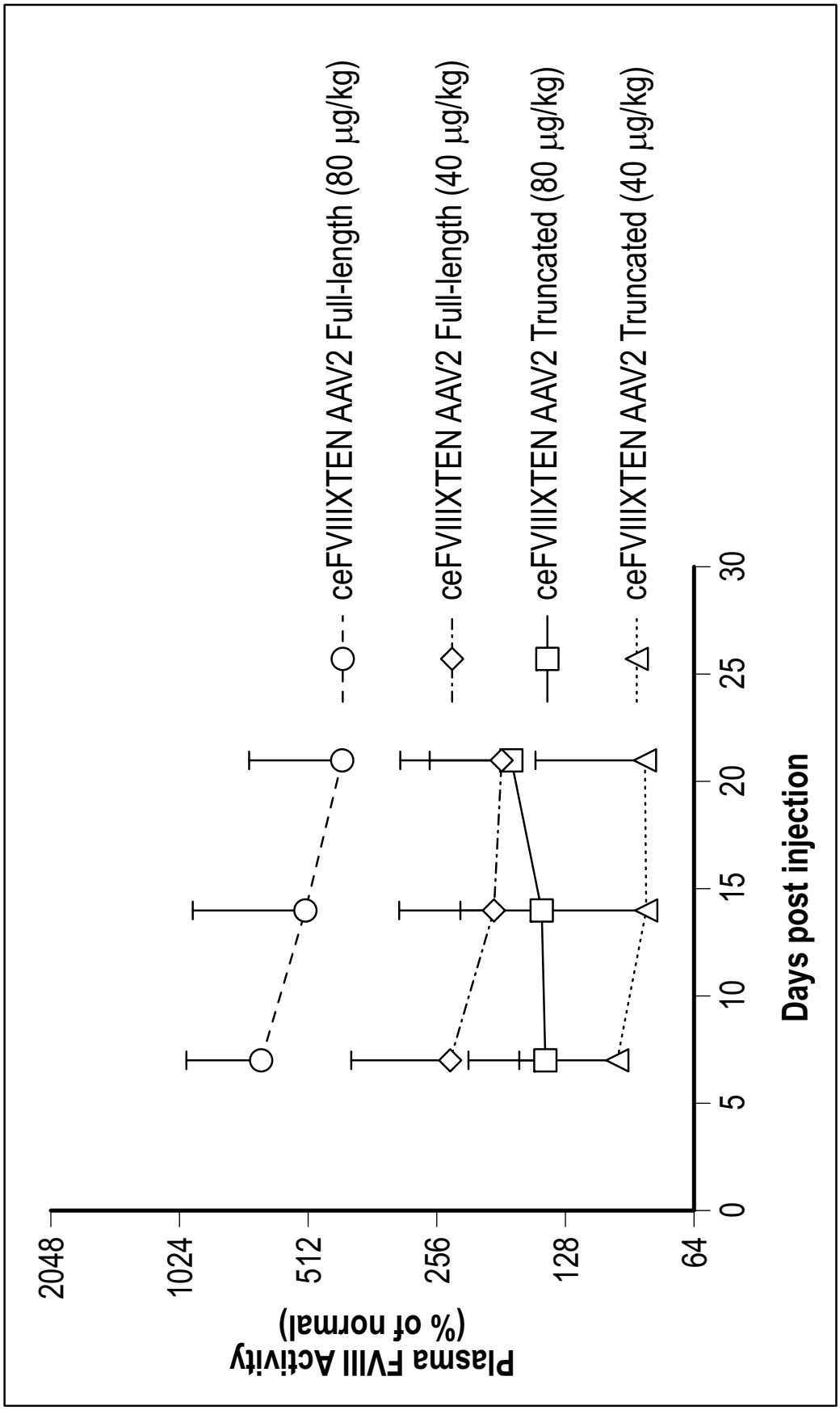

ceFVIIIXTEN AAV2 Full-length (80 µg/kg)
ceFVIIIXTEN AAV2 Full-length (40 µg/kg)
ceFVIIIXTEN AAV2 Truncated (80 µg/kg)
ceFVIIIXTEN AAV2 Truncated (40 µg/kg)
Plasma FVIII Activity (% of normal)
2048
1024
512
256
128
64
0
5
10
15
20
25
30
Days post injection

FIG. 7C

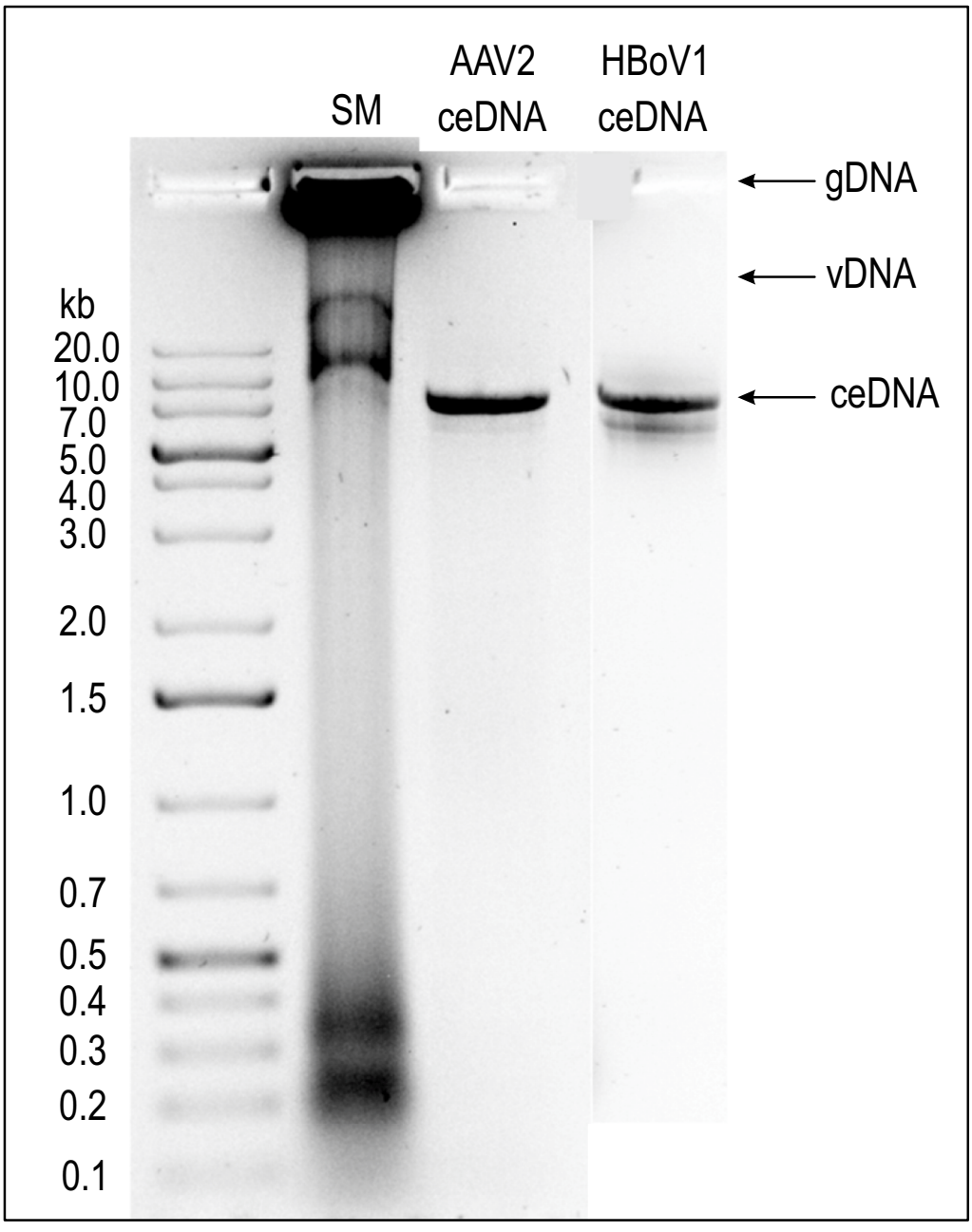

SM
AAV2
ceDNA
HBoV1
ceDNA
gDNA
vDNA
ceDNA
kb
20.0
10.0
7.0
5.0
4.0
3.0
2.0
1.5
1.0
0.7
0.5
0.4
0.3
0.2
0.1

FIG. 8A

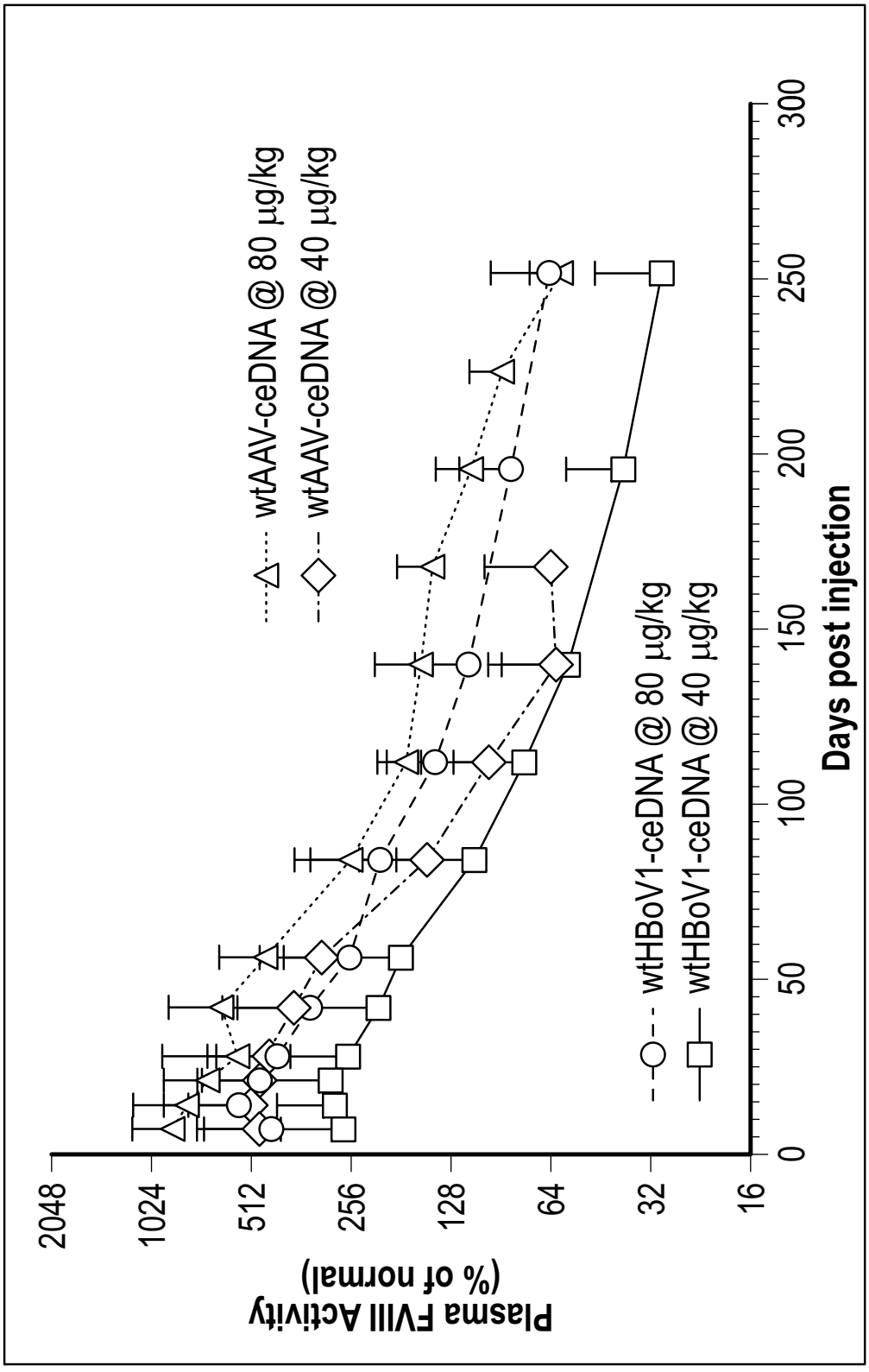

Plasma FVIII Activity
(% of normal)
2048
1024
512
256
128
64
32
16
0
50
100
150
200
250
300
Days post injection
wtAAV-ceDNA @ 80 µg/kg
wtAAV-ceDNA @ 40 µg/kg
wtHBoV1-ceDNA @ 80 µg/kg
wtHBoV1-ceDNA @ 40 µg/kg

FIG. 8B