Figure 1

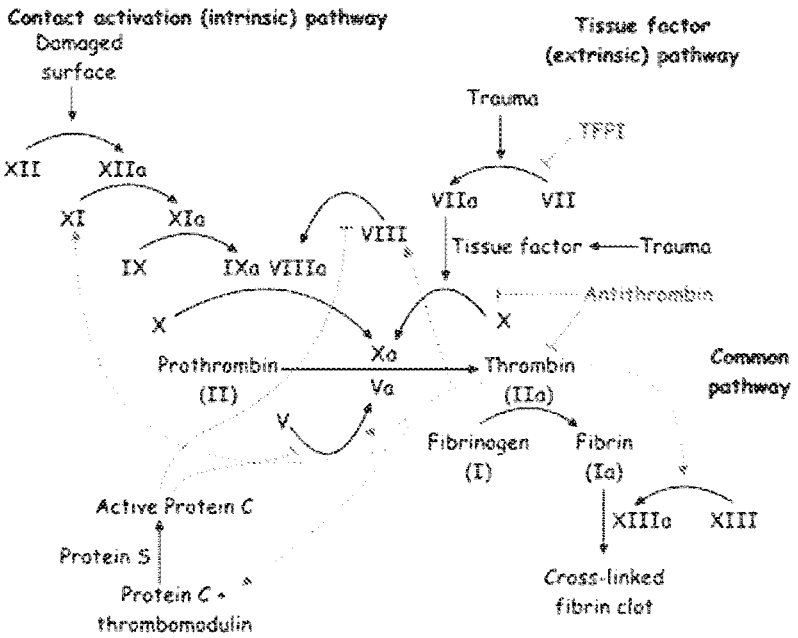


Figure 2

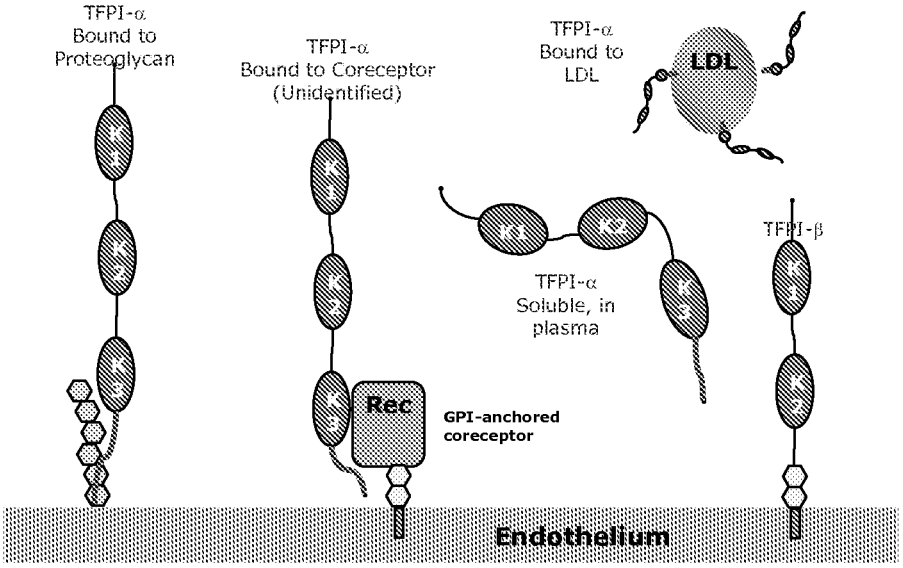
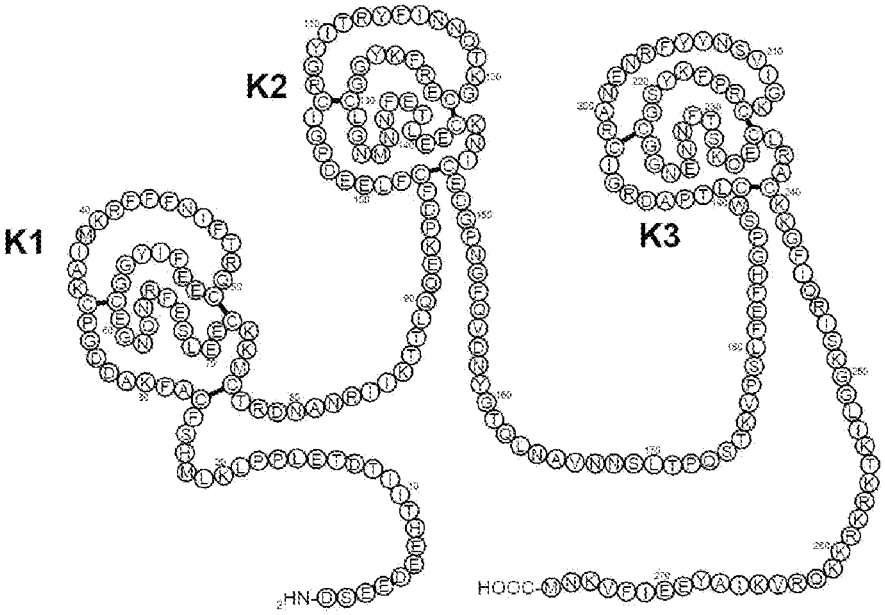


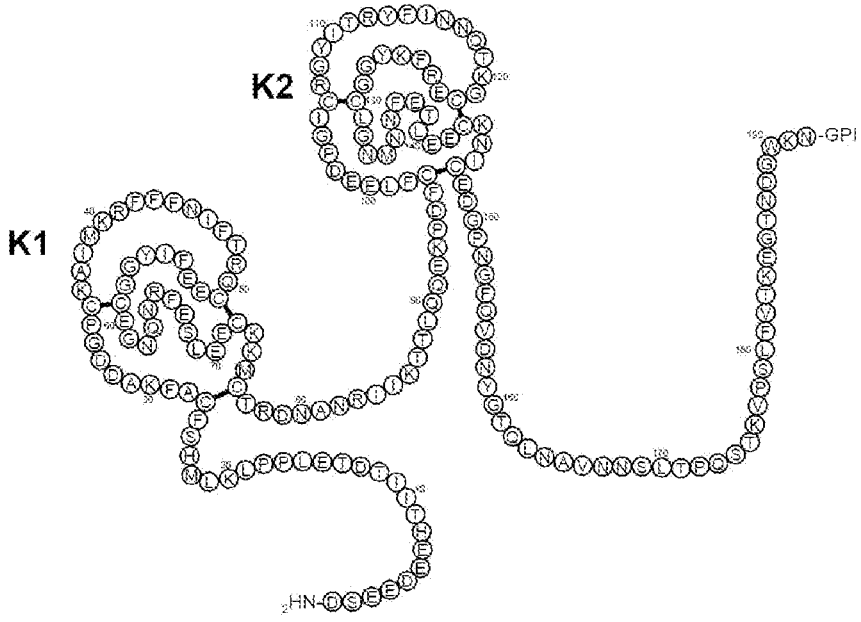
Figure 3

A

SEQ ID NO: 13



B



SEQ ID NO: 14

Figure 4

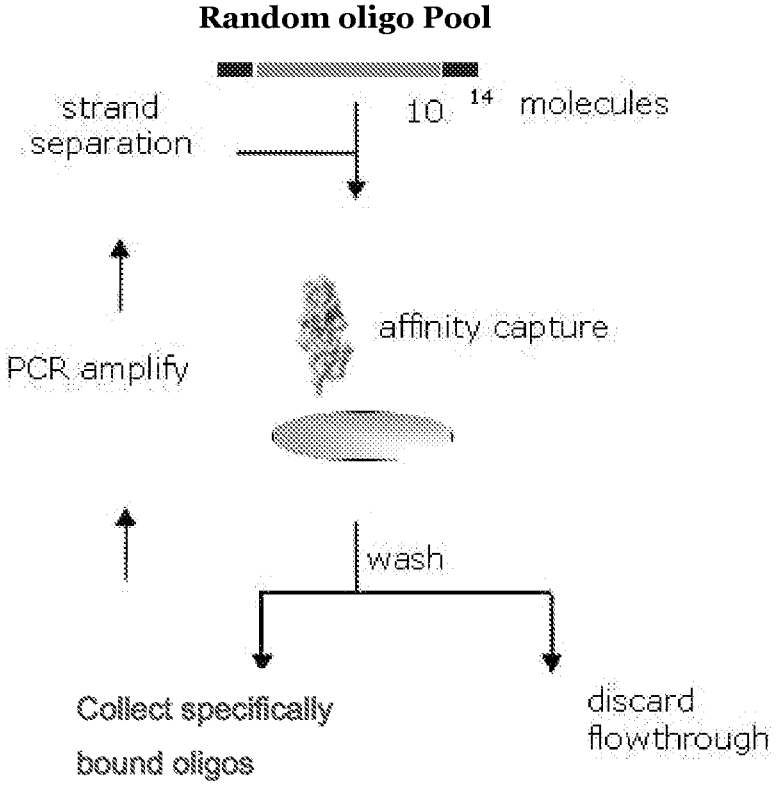


Figure 5

DSEEDEEHTIITDTELPPLKLMHSFCAFKADDGPCKAIMKRFFFNIFTRQCEEFIYGGCEGNQNRFESLEECKK
MCTRDNANRIIKTTLQQEKPDFCFLEEDPGICRGYITRYFYNNQTKQCERFKYGGCLGNMNNFETLEECKNICE
DGPNGFQVDNYGTQLNAVNNSLTPQSTKVPSLFEFHGPSWCLTPADRGLCRANENRFYYNSVIGKCRPFKYSGC
GGNENNFTSKQECLRACKKGFIQRISKGGLIKTKRKRKKQRVKIAYEEIFVKNM (SEQ ID NO: 11)

Figure 6

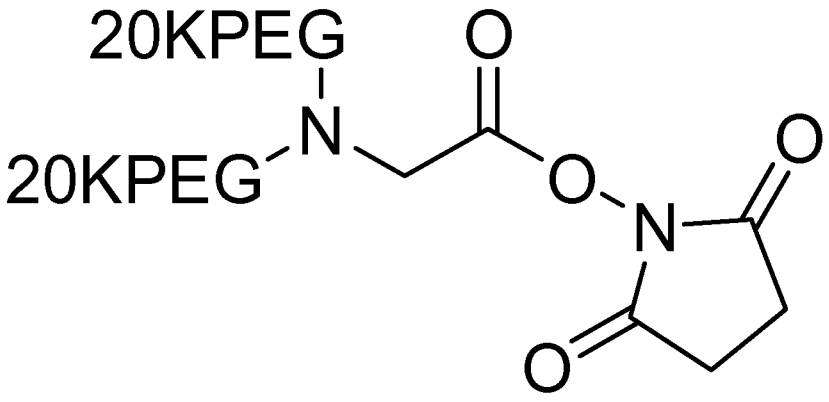


Figure 7

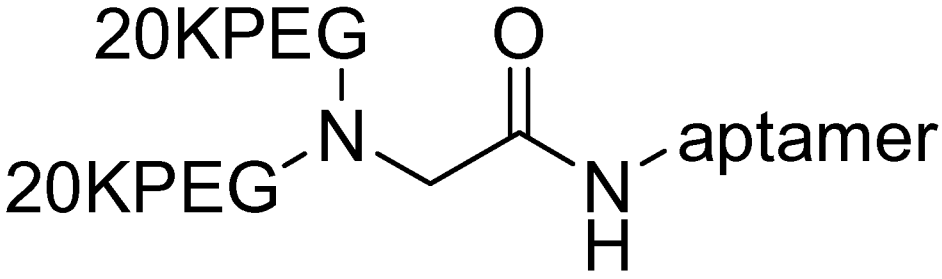


Figure 8

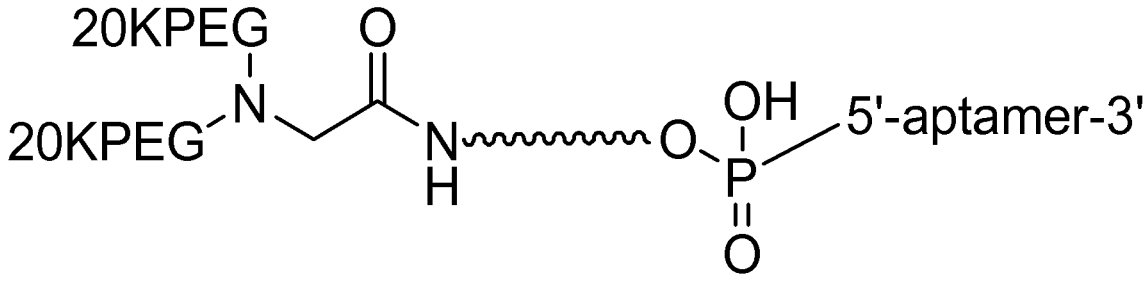


Figure 9A

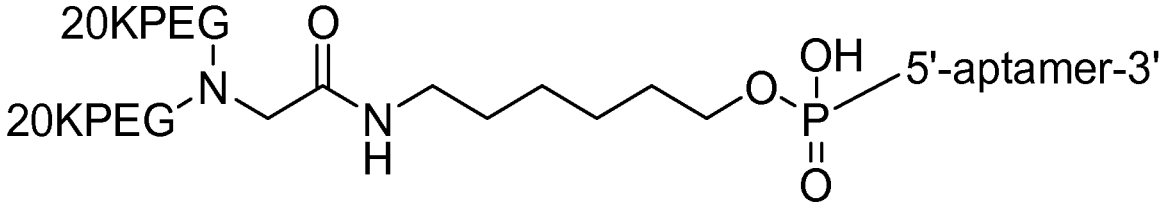


Figure 9B

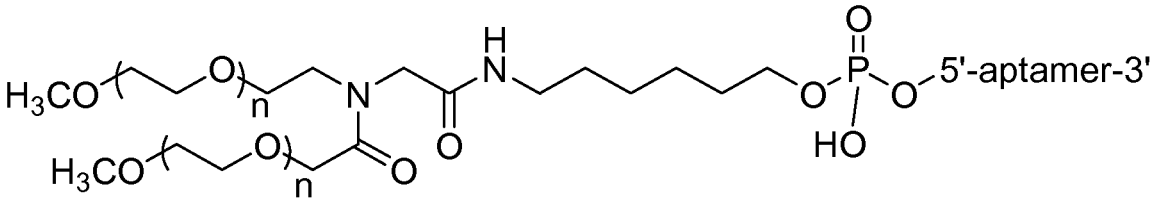
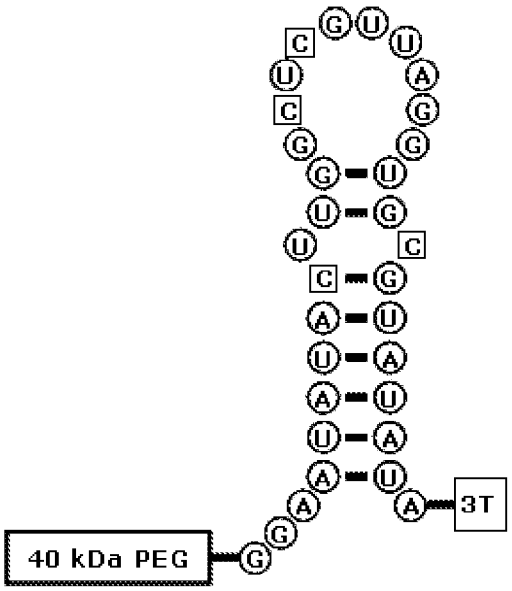
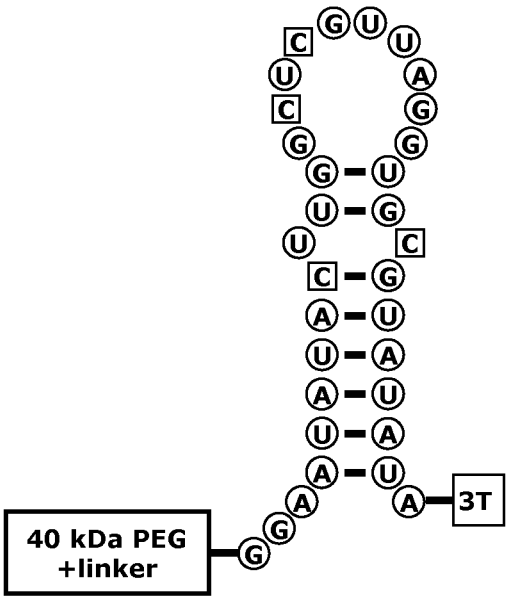


Figure 10A



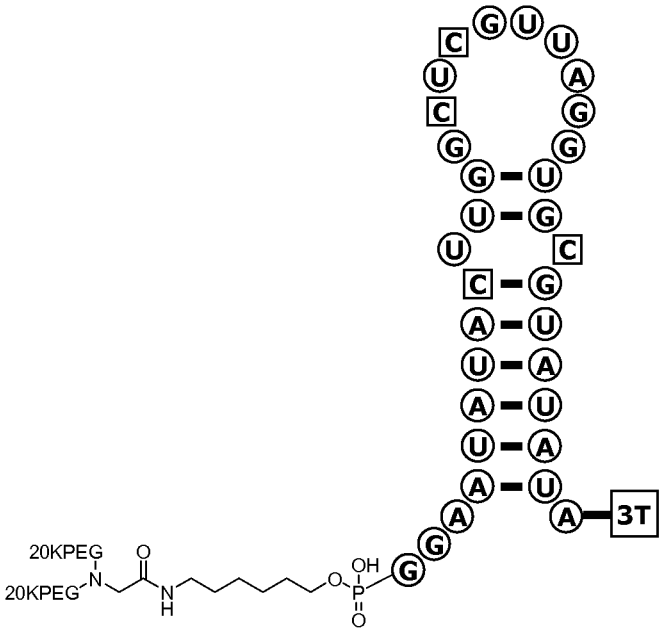
SEQ ID NO: 2 with a 40 kDa PEG moiety

Figure 10B



SEQ ID NO: 2 with a linker and a 40 kDa PEG moiety

Figure 10C



SEQ ID NO: 4

Figure 11

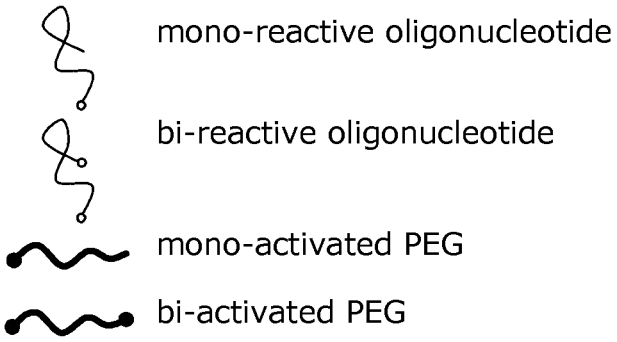

mono-reactive oligonucleotide
bi-reactive oligonucleotide
mono-activated PEG
bi-activated PEG
standard PEGylation
multiple PEGylation
dimerization via PEGylation

Figure 12

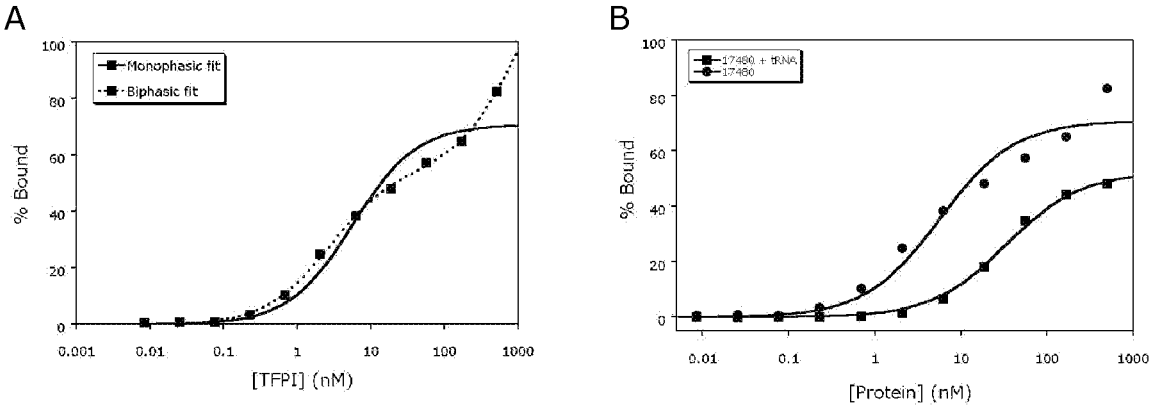


Figure 13

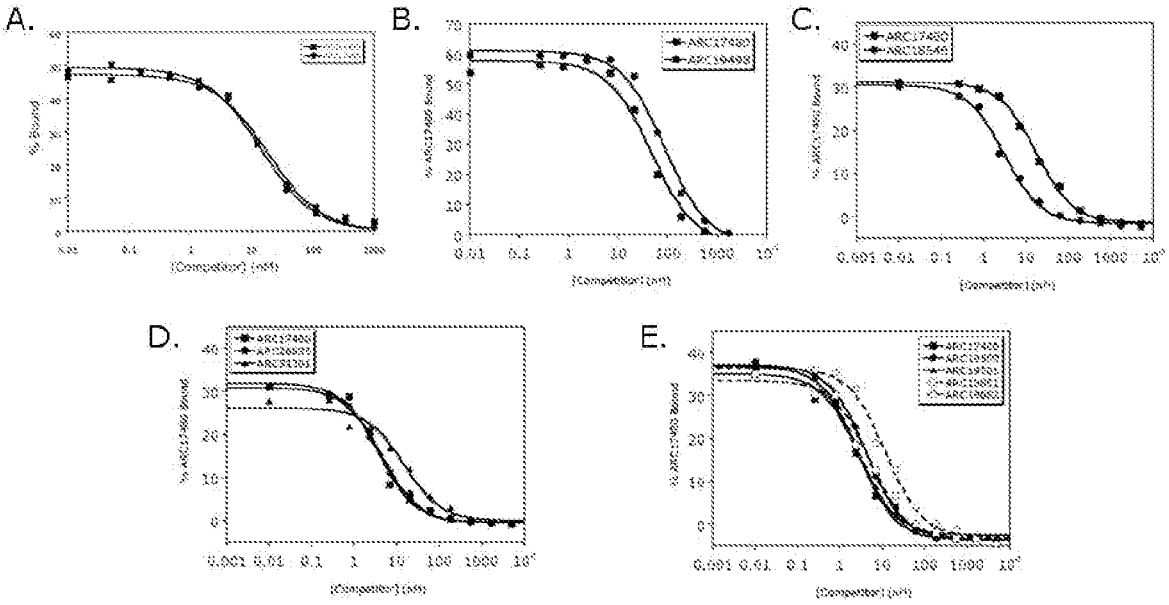


Figure 14

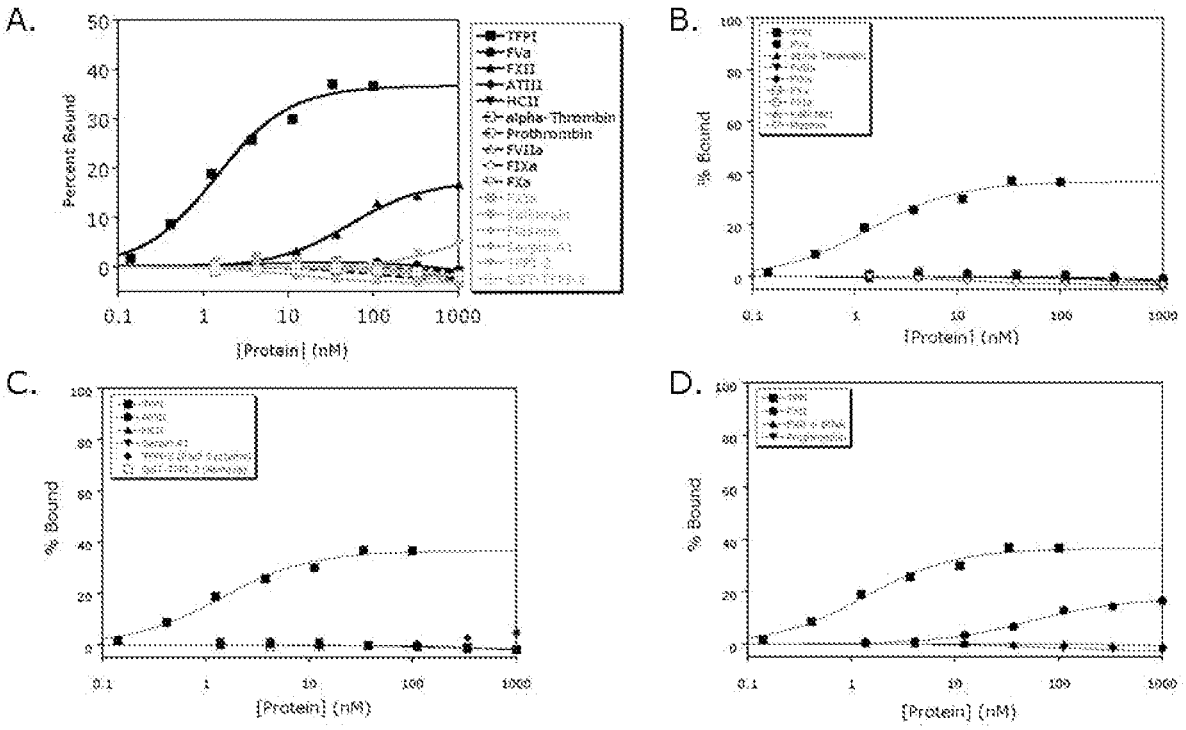

A.
Percent Bound
[Protein] (nM)
TFPI
FVa
FXII
ATIII
HCII
alpha-Thrombin
Prothrombin
FVIIa
FIXa
FXa
B.
% Bound
[Protein] (nM)
C.
% Bound
[Protein] (nM)
D.
% Bound
[Protein] (nM)

Figure 15

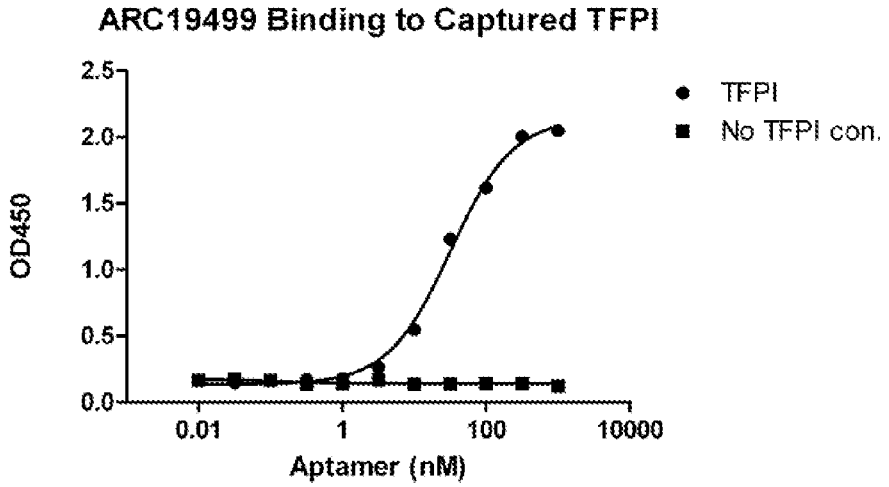


Figure 16

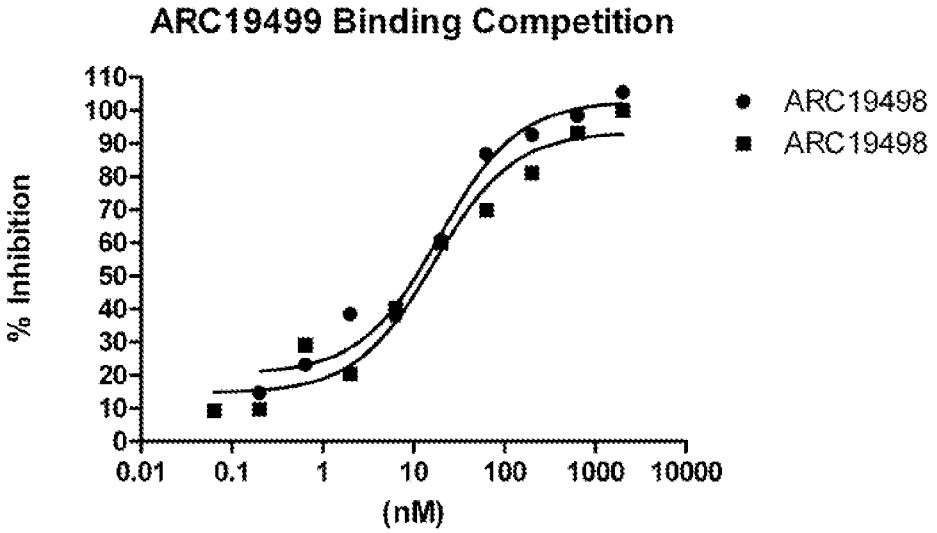


Figure 17

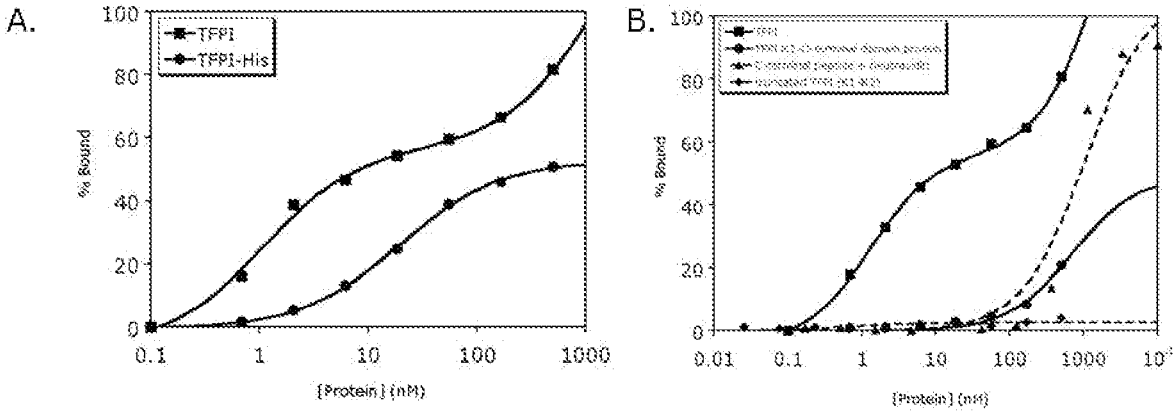


Figure 18

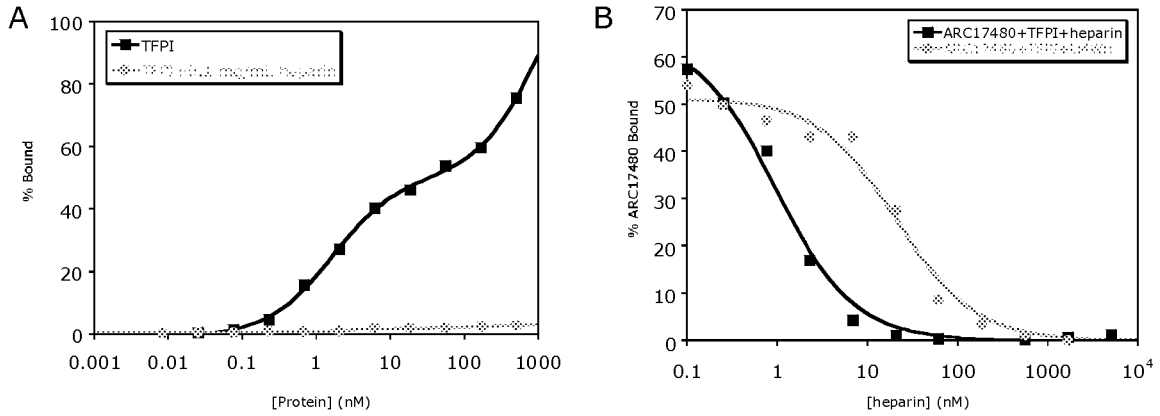


Figure 19

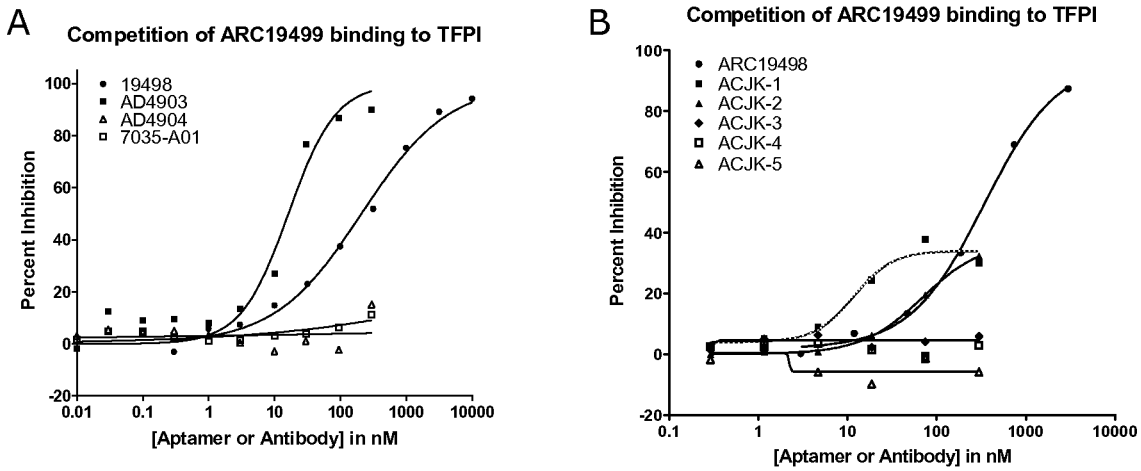


Figure 20

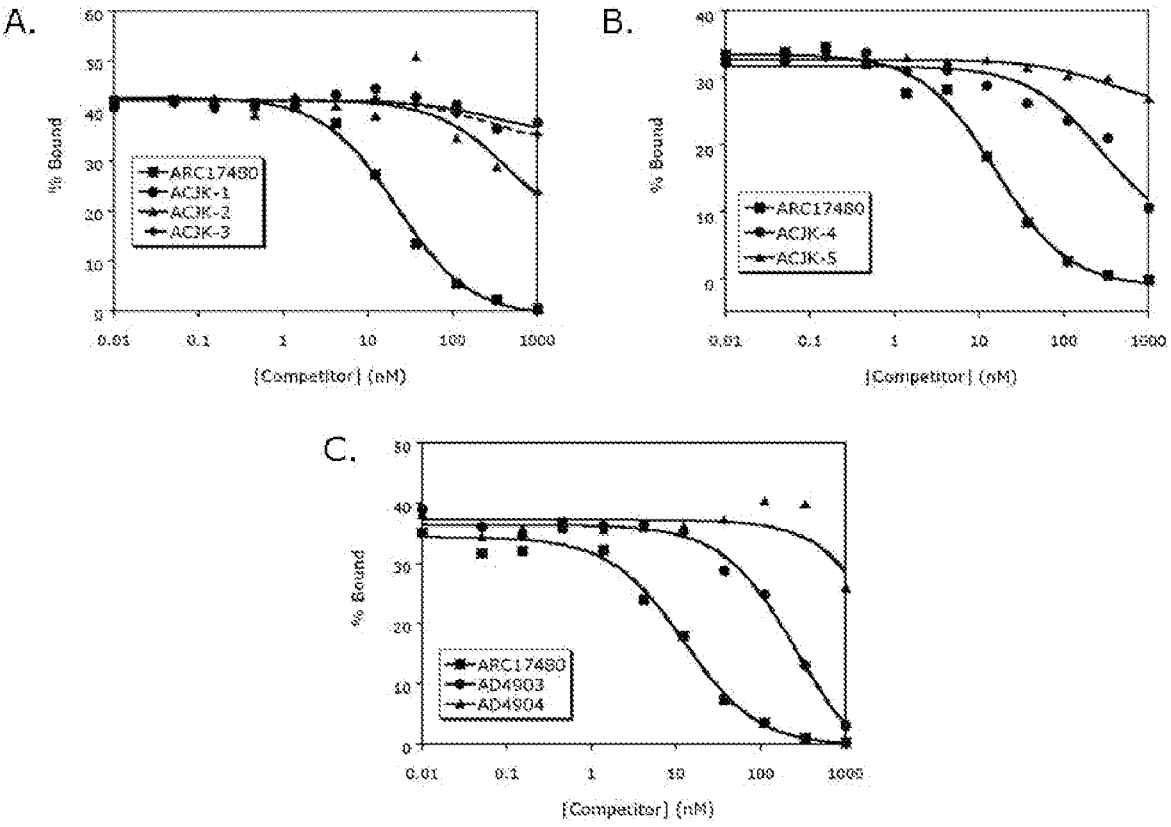


Figure 21

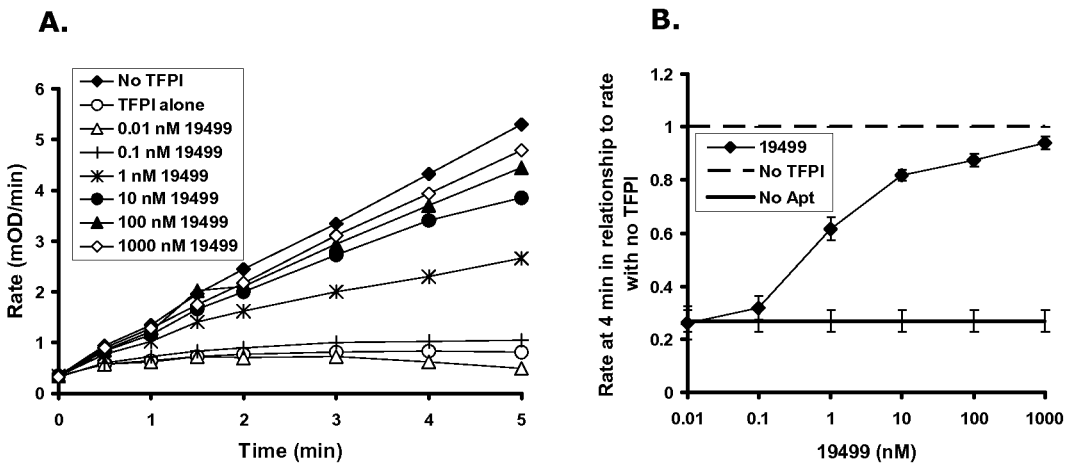


Figure 22

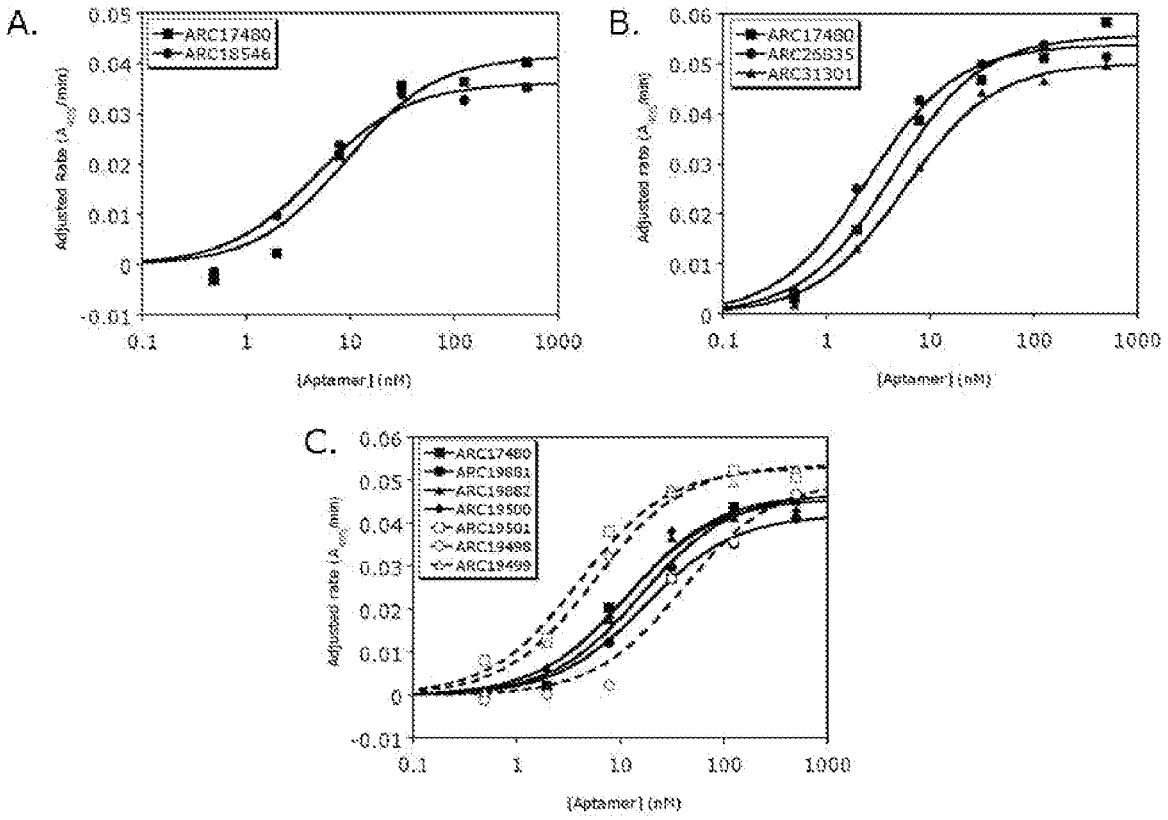


Figure 23

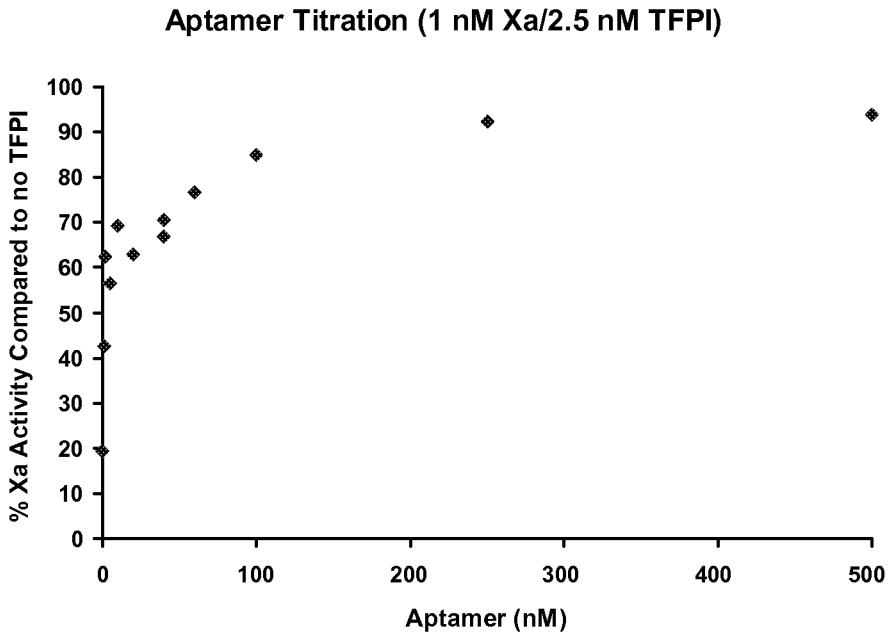


Figure 24

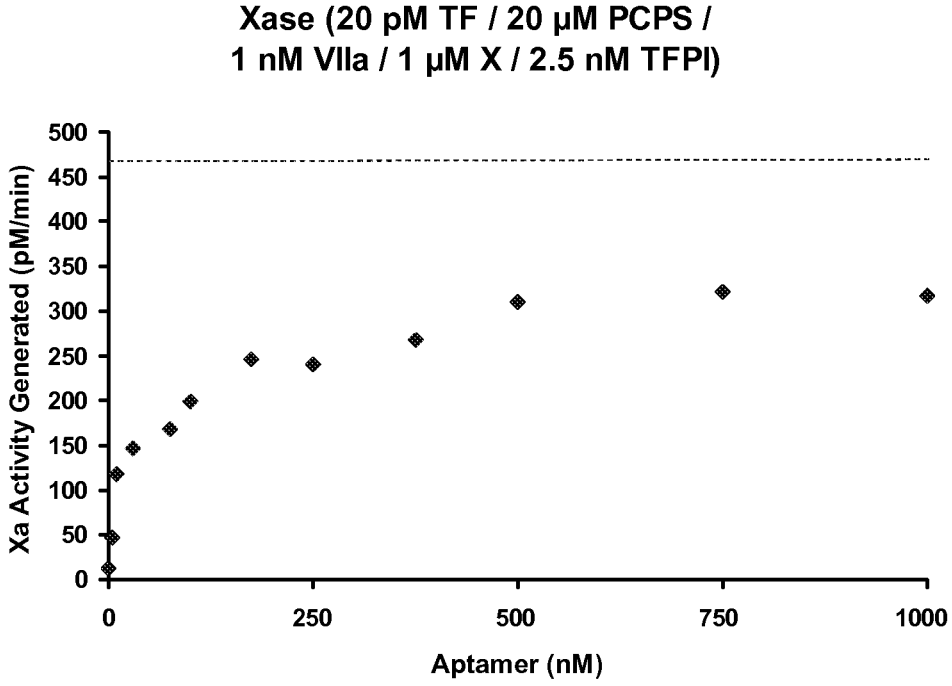


Figure 25

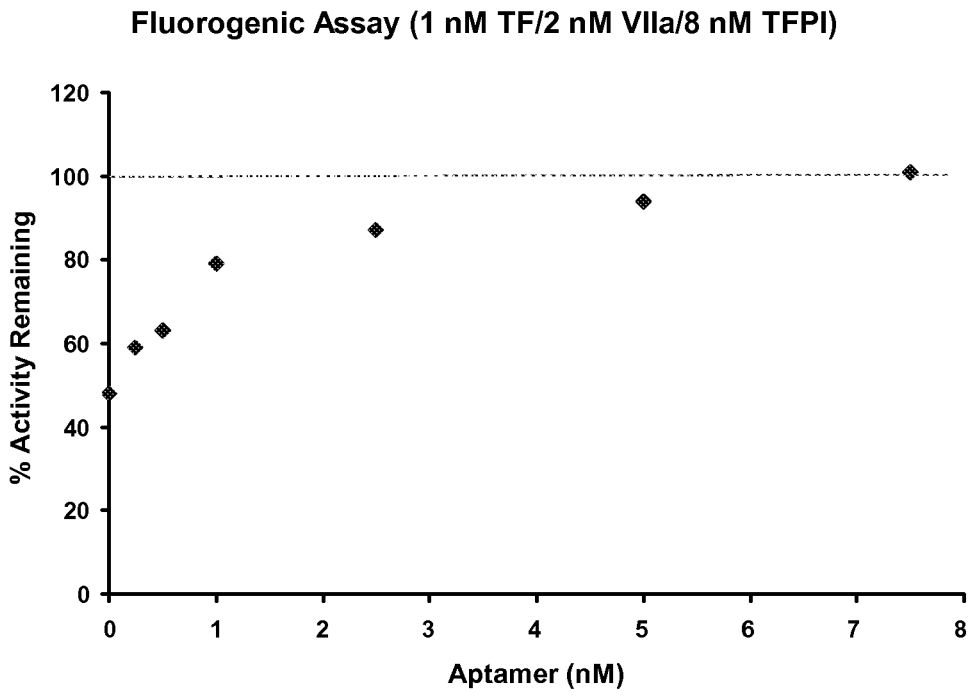


Figure 26

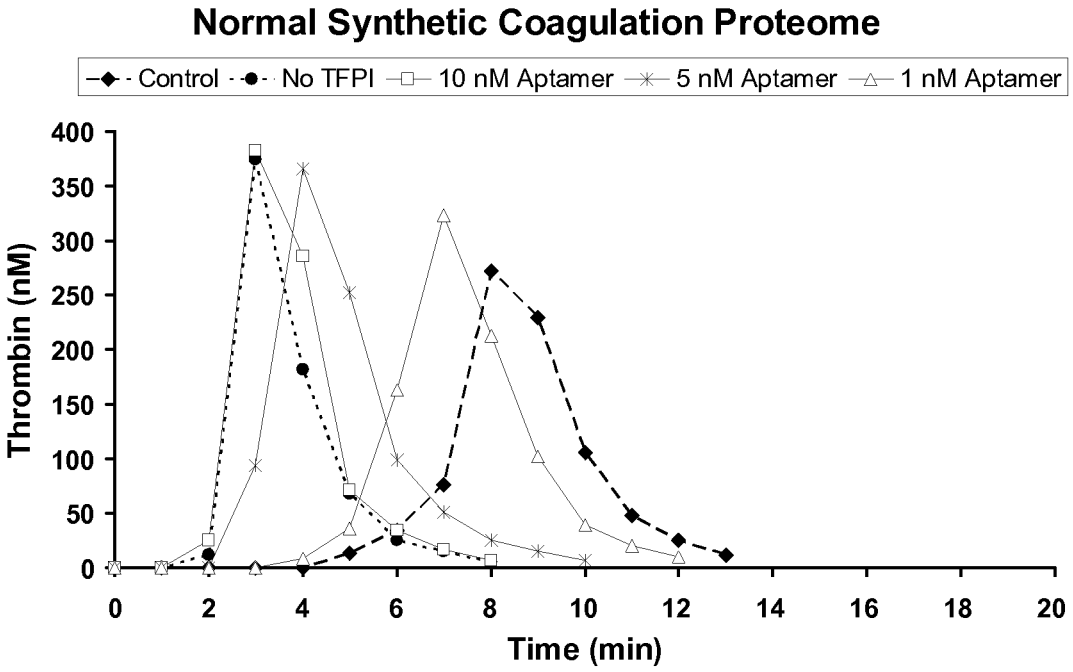


Figure 27

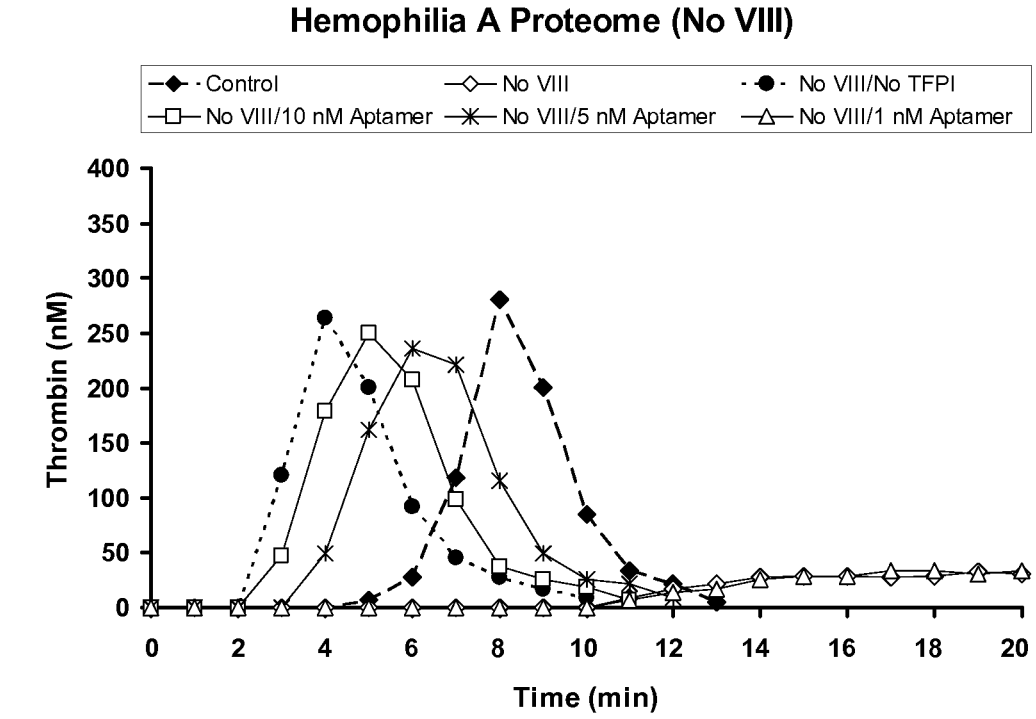


Figure 28

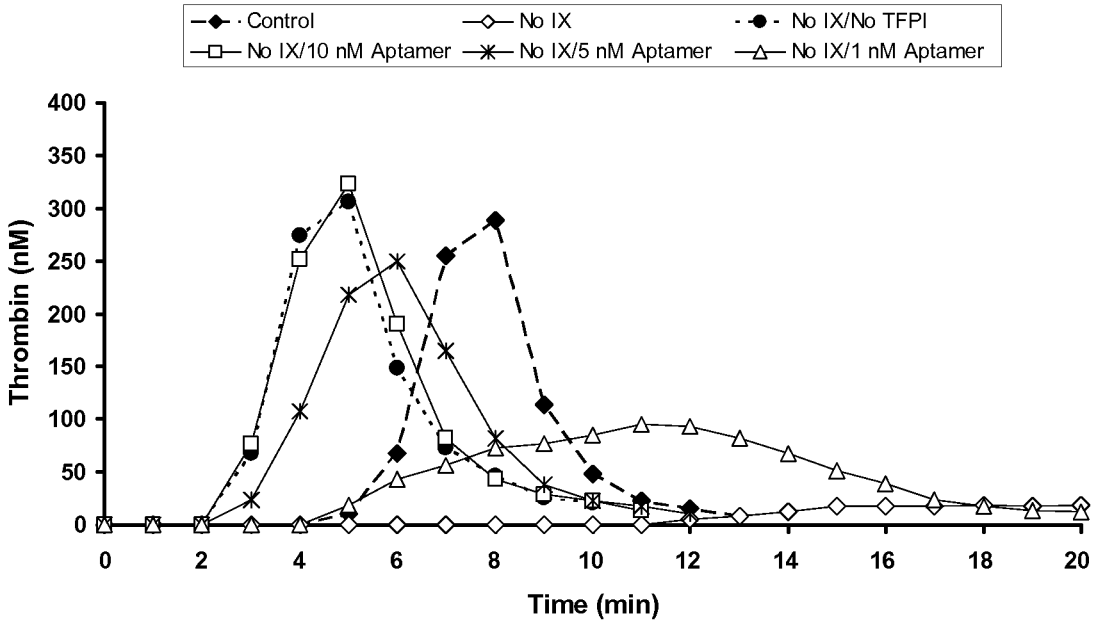


Figure 29

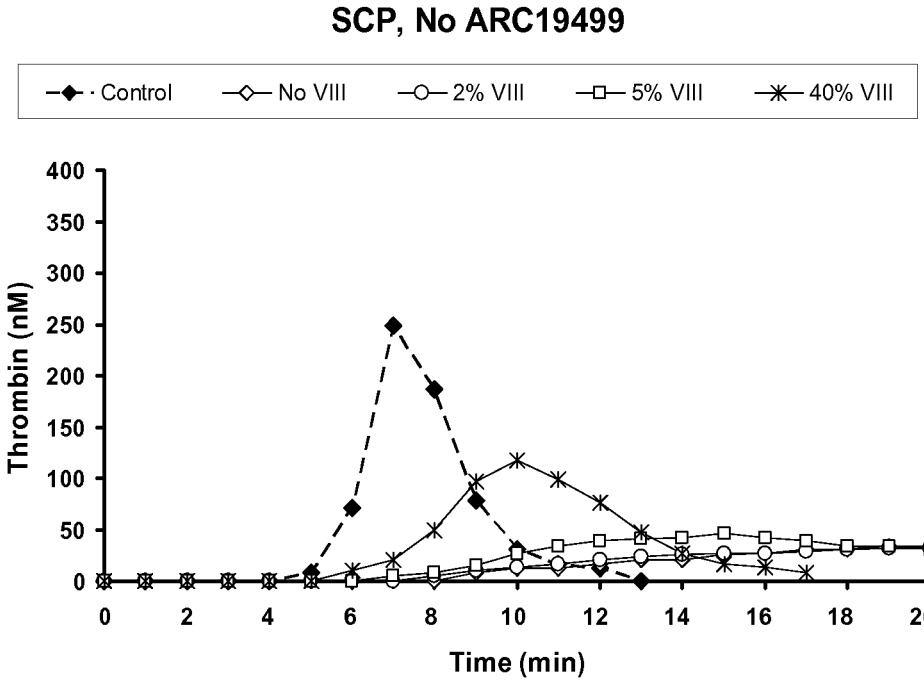


Figure 30

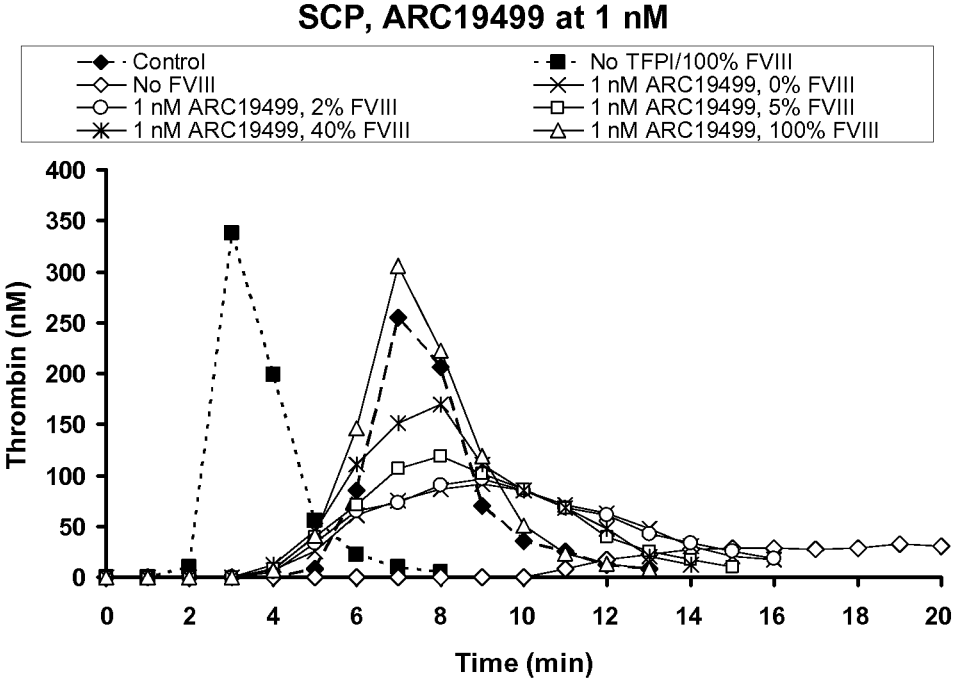


Figure 31

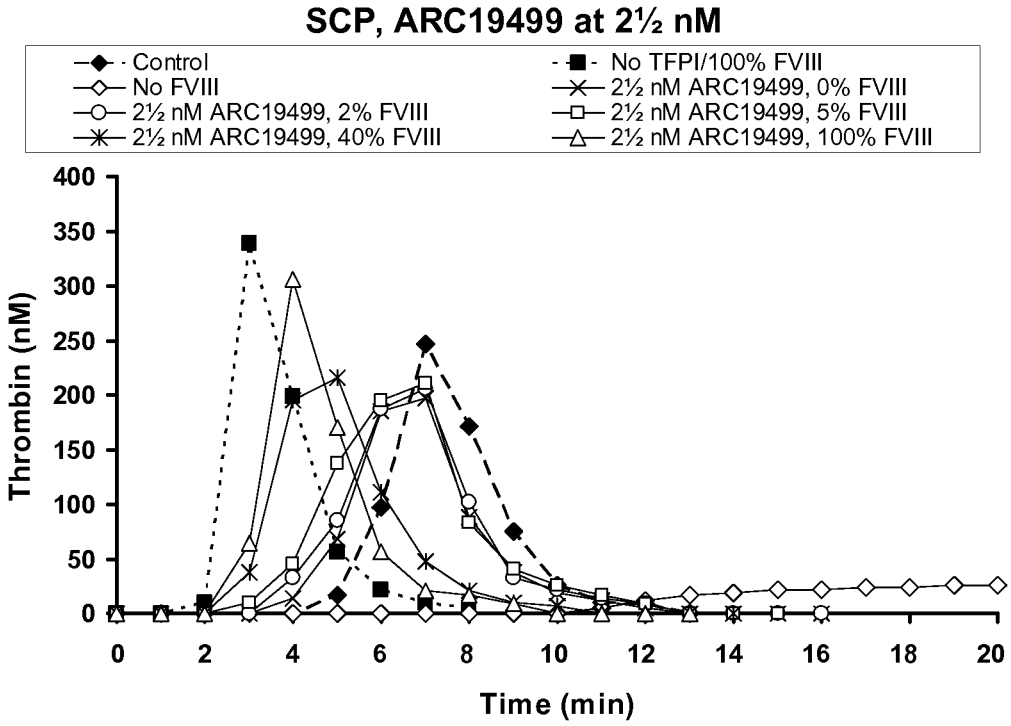


Figure 32

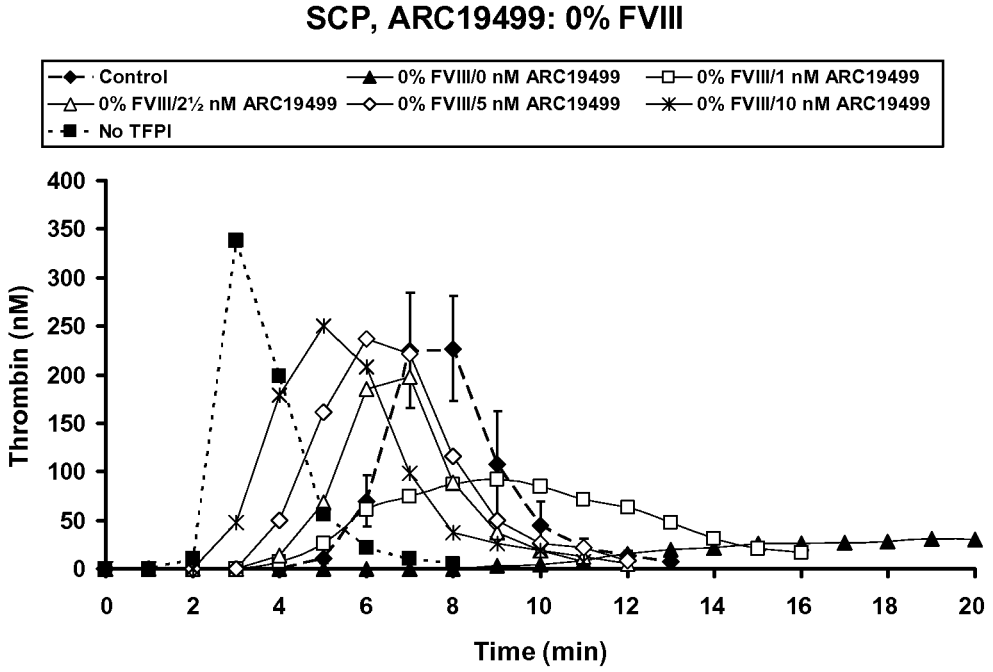


Figure 33

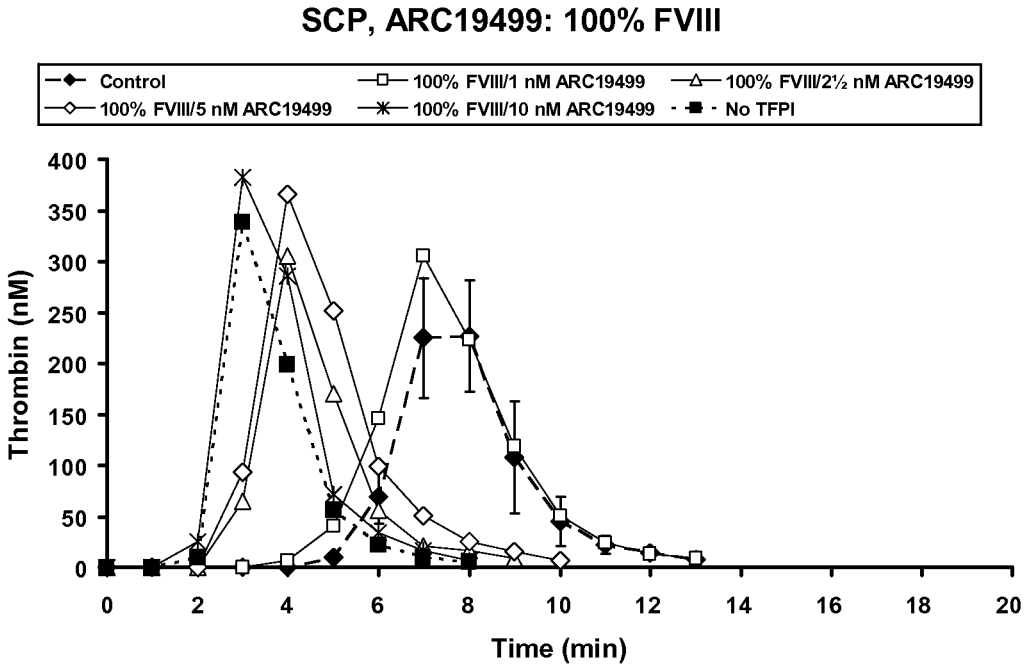


Figure 34

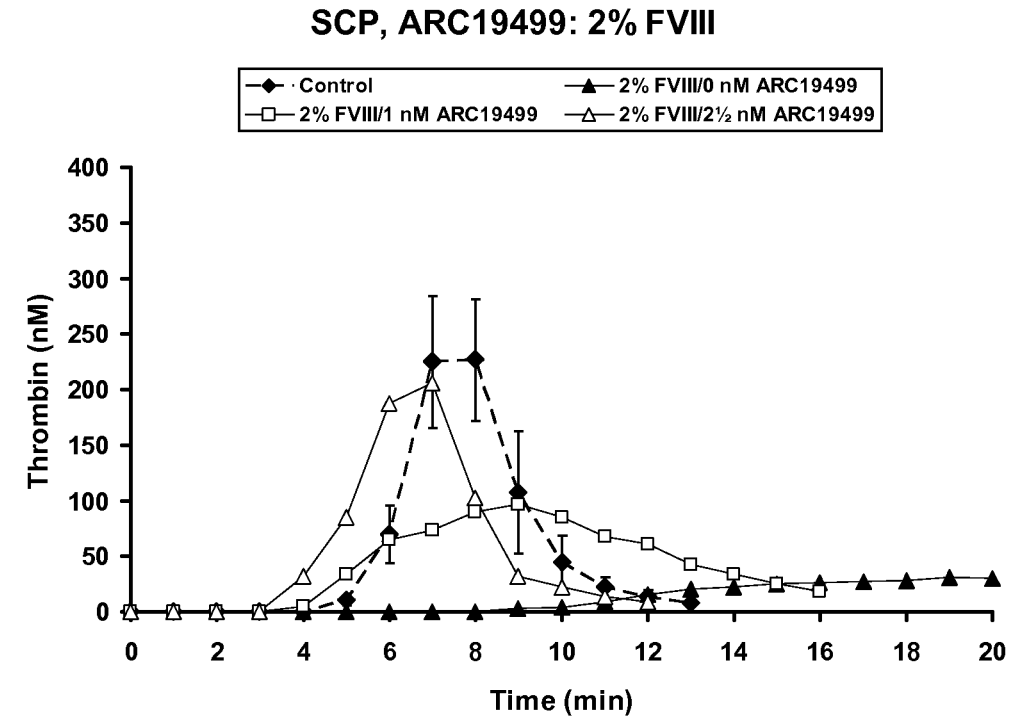


Figure 35

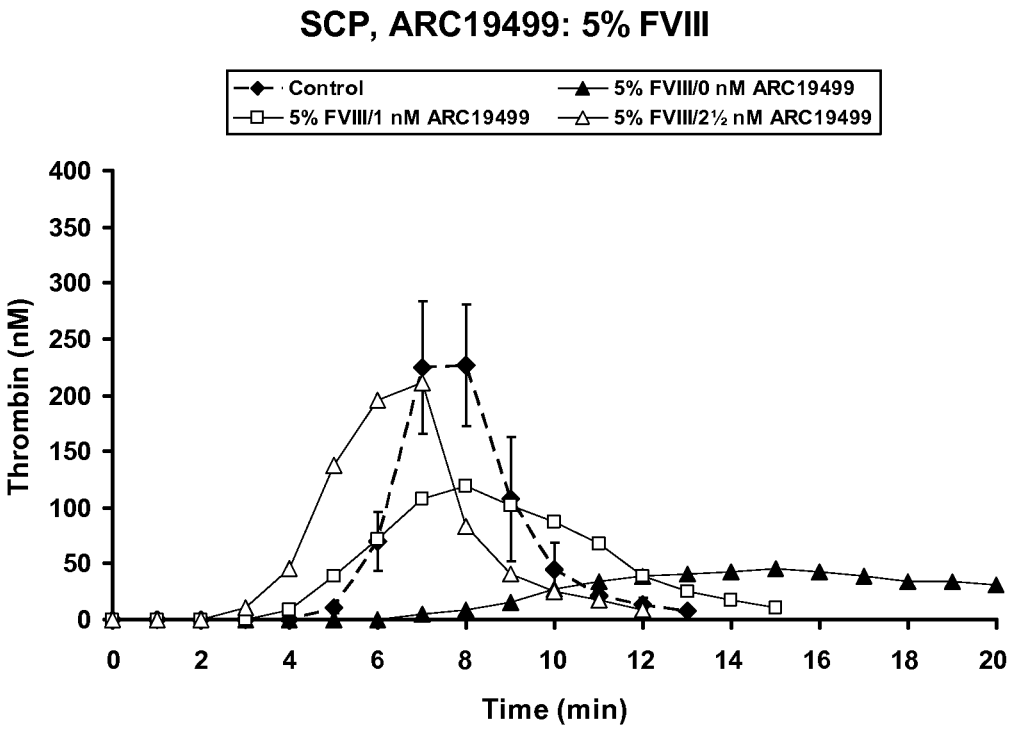


Figure 36

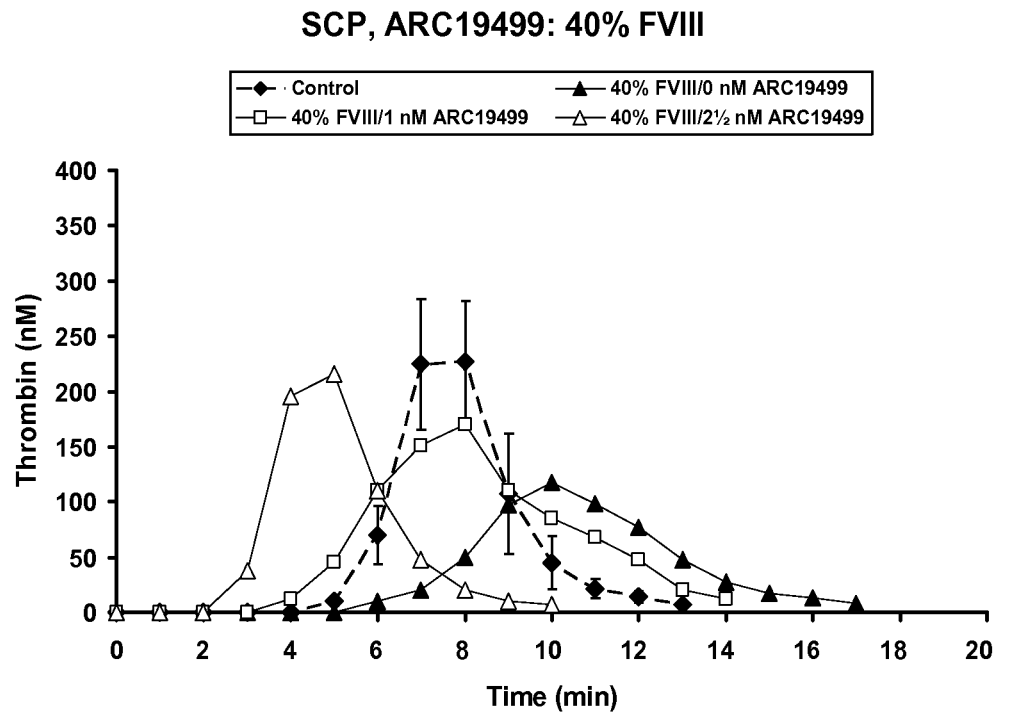


Figure 37

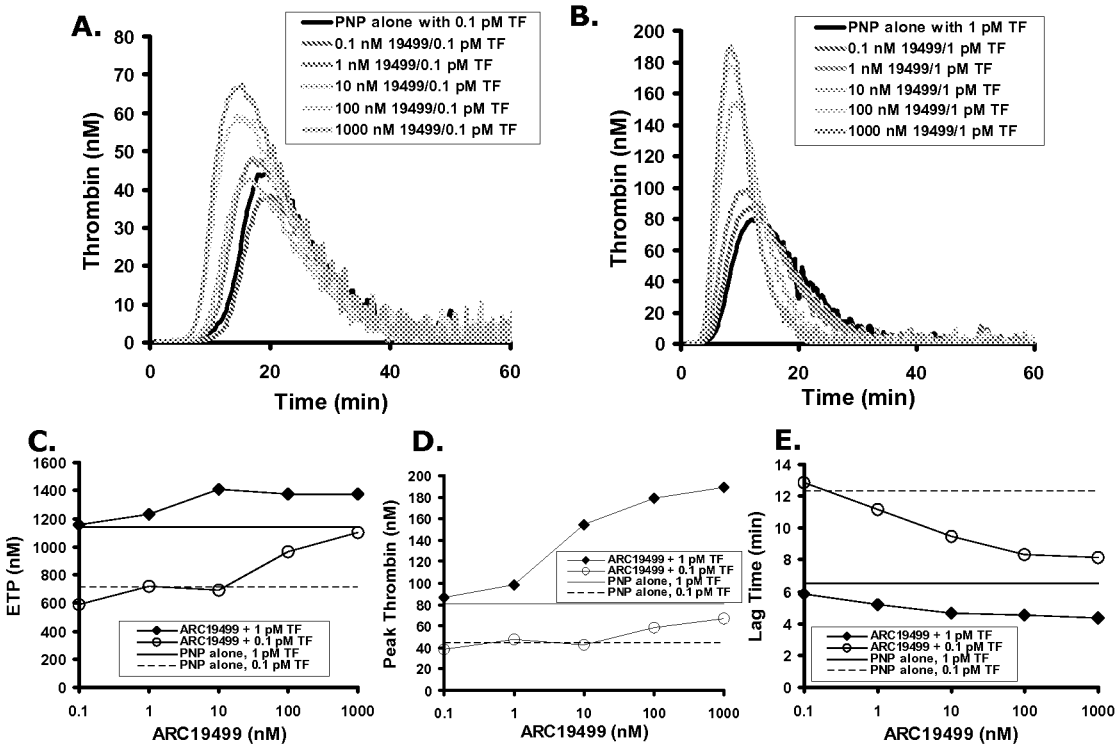

A.
PNP alone with 0.1 pM TF
0.1 nM 19499/0.1 pM TF
1 nM 19499/0.1 pM TF
10 nM 19499/0.1 pM TF
100 nM 19499/0.1 pM TF
1000 nM 19499/0.1 pM TF
Thrombin (nM)
Time (min)
B.
PNP alone with 1 pM TF
0.1 nM 19499/1 pM TF
1 nM 19499/1 pM TF
10 nM 19499/1 pM TF
100 nM 19499/1 pM TF
1000 nM 19499/1 pM TF
Thrombin (nM)
Time (min)
C.
ETP (nM)
ARC19499 + 1 pM TF
ARC19499 + 0.1 pM TF
PNP alone, 1 pM TF
PNP alone, 0.1 pM TF
ARC19499 (nM)
D.
Peak Thrombin (nM)
ARC19499 + 1 pM TF
ARC19499 + 0.1 pM TF
PNP alone, 1 pM TF
PNP alone, 0.1 pM TF
ARC19499 (nM)
E.
Lag Time (min)
ARC19499 + 1 pM TF
ARC19499 + 0.1 pM TF
PNP alone, 1 pM TF
PNP alone, 0.1 pM TF
ARC19499 (nM)

Figure 38

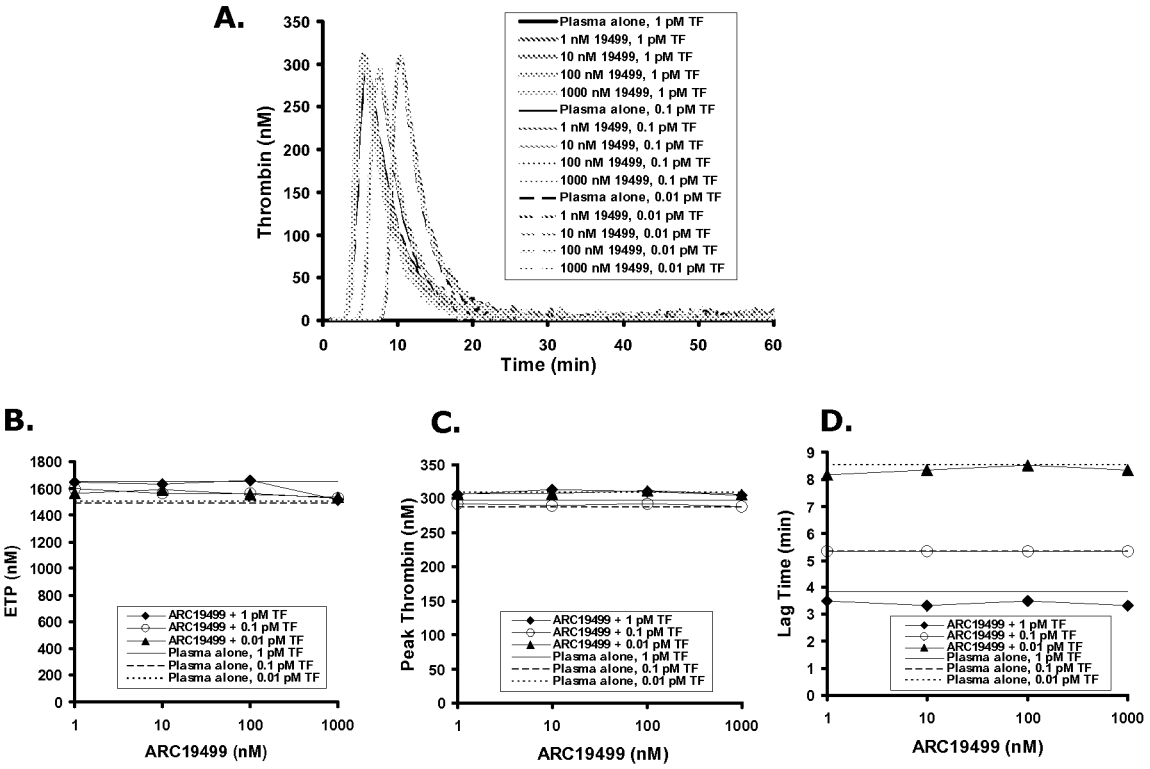

A.
Thrombin (nM)
Time (min)
Plasma alone, 1 pM TF
1 nM 19499, 1 pM TF
10 nM 19499, 1 pM TF
100 nM 19499, 1 pM TF
1000 nM 19499, 1 pM TF
Plasma alone, 0.1 pM TF
1 nM 19499, 0.1 pM TF
10 nM 19499, 0.1 pM TF
100 nM 19499, 0.1 pM TF
1000 nM 19499, 0.1 pM TF
Plasma alone, 0.01 pM TF
1 nM 19499, 0.01 pM TF
10 nM 19499, 0.01 pM TF
100 nM 19499, 0.01 pM TF
1000 nM 19499, 0.01 pM TF
B.
ETP (nM)
ARC19499 (nM)
C.
Peak Thrombin (nM)
ARC19499 (nM)
D.
Lag Time (min)
ARC19499 (nM)
ARC19499 + 1 pM TF
ARC19499 + 0.1 pM TF
ARC19499 + 0.01 pM TF
Plasma alone, 1 pM TF
Plasma alone, 0.1 pM TF
Plasma alone, 0.01 pM TF

Figure 39

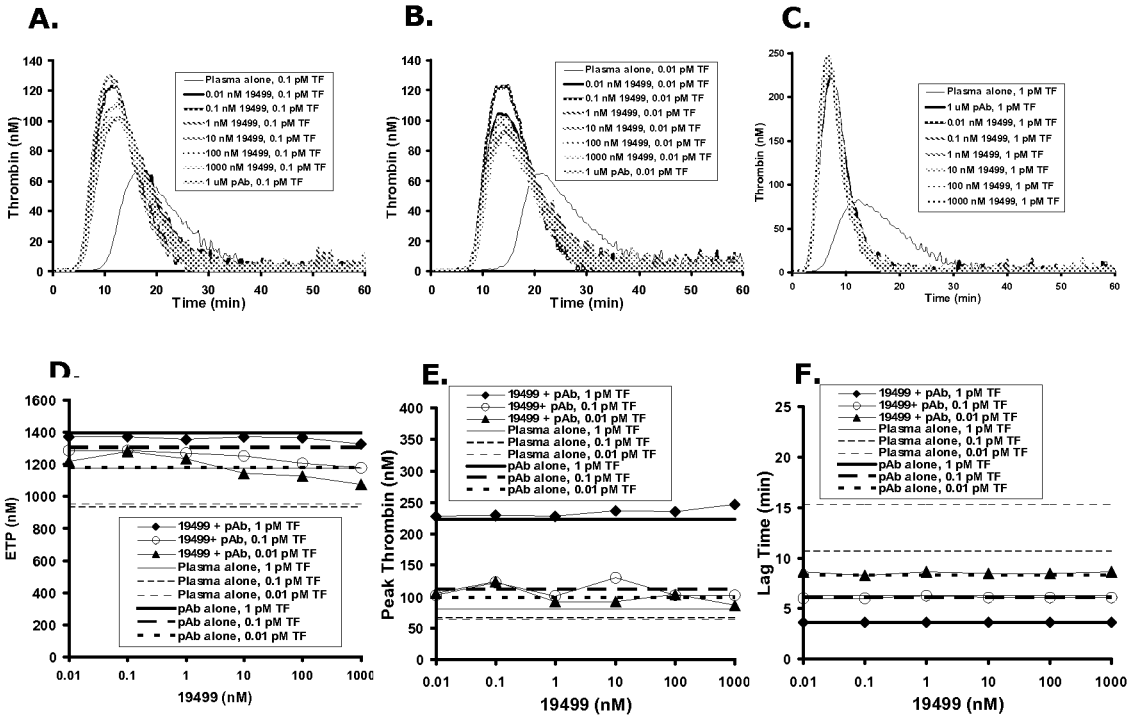

A.
Thrombin (nM)
Time (min)
Plasma alone, 0.1 pM TF
0.01 nM 19499, 0.1 pM TF
0.1 nM 19499, 0.1 pM TF
1 nM 19499, 0.1 pM TF
10 nM 19499, 0.1 pM TF
100 nM 19499, 0.1 pM TF
1000 nM 19499, 0.1 pM TF
1 uM pAb, 0.1 pM TF
B.
Thrombin (nM)
Time (min)
Plasma alone, 0.01 pM TF
0.01 nM 19499, 0.01 pM TF
0.1 nM 19499, 0.01 pM TF
1 nM 19499, 0.01 pM TF
10 nM 19499, 0.01 pM TF
100 nM 19499, 0.01 pM TF
1000 nM 19499, 0.01 pM TF
1 uM pAb, 0.01 pM TF
C.
Thrombin (nM)
Time (min)
Plasma alone, 1 pM TF
1 uM pAb, 1 pM TF
0.01 nM 19499, 1 pM TF
0.1 nM 19499, 1 pM TF
1 nM 19499, 1 pM TF
10 nM 19499, 1 pM TF
100 nM 19499, 1 pM TF
1000 nM 19499, 1 pM TF
D.
ETP (nM)
19499 (nM)
19499 + pAb, 1 pM TF
19499+ pAb, 0.1 pM TF
19499 + pAb, 0.01 pM TF
Plasma alone, 1 pM TF
Plasma alone, 0.1 pM TF
Plasma alone, 0.01 pM TF
pAb alone, 1 pM TF
pAb alone, 0.1 pM TF
pAb alone, 0.01 pM TF
E.
Peak Thrombin (nM)
19499 (nM)
19499 + pAb, 1 pM TF
19499+ pAb, 0.1 pM TF
19499 + pAb, 0.01 pM TF
Plasma alone, 1 pM TF
Plasma alone, 0.1 pM TF
Plasma alone, 0.01 pM TF
pAb alone, 1 pM TF
pAb alone, 0.1 pM TF
pAb alone, 0.01 pM TF
F.
Lag Time (min)
19499 (nM)
19499 + pAb, 1 pM TF
19499+ pAb, 0.1 pM TF
19499 + pAb, 0.01 pM TF
Plasma alone, 1 pM TF
Plasma alone, 0.1 pM TF
Plasma alone, 0.01 pM TF
pAb alone, 1 pM TF
pAb alone, 0.1 pM TF
pAb alone, 0.01 pM TF

Figure 40

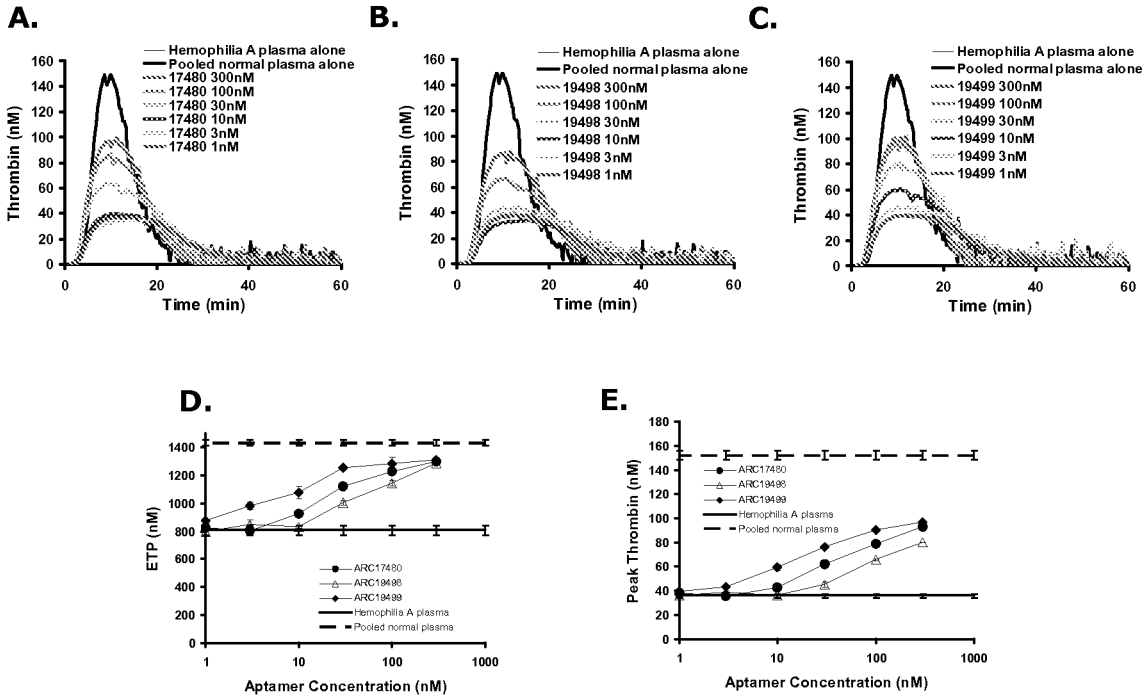


Figure 41

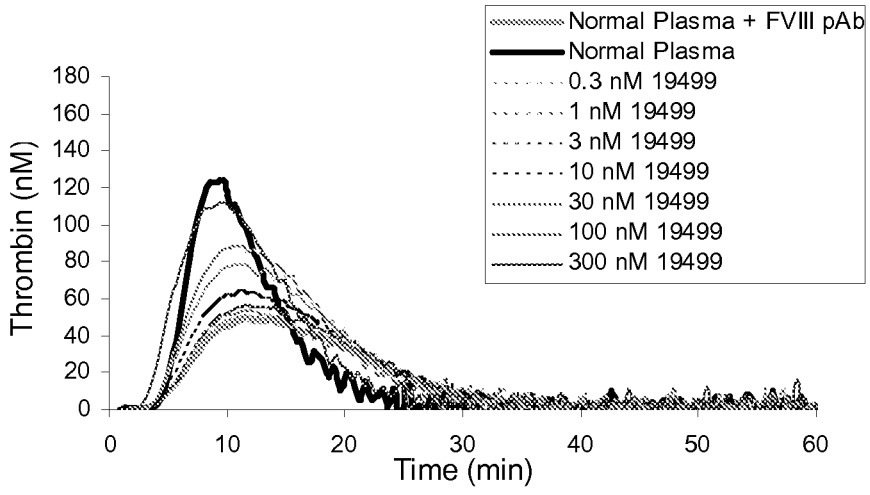


Figure 42

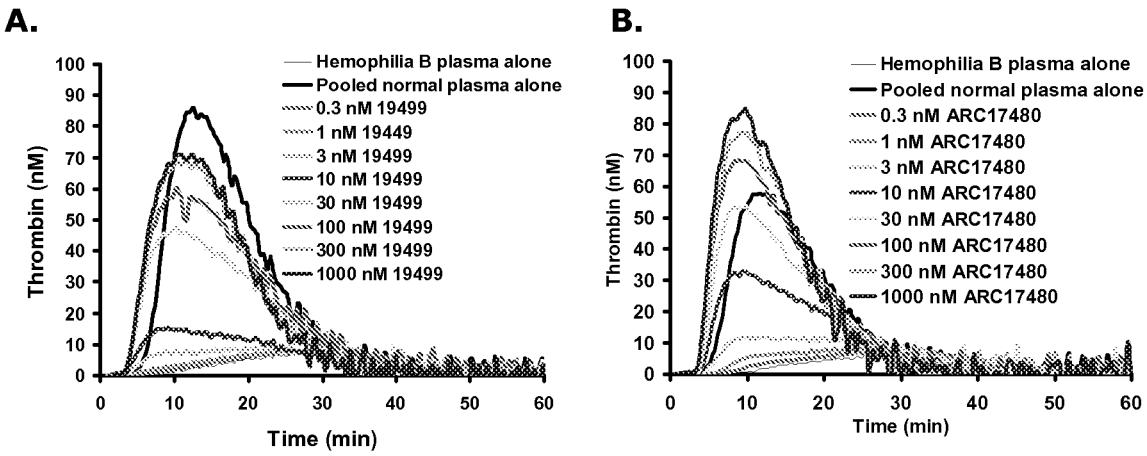

A.
Thrombin (nM)
Time (min)
Hemophilia B plasma alone
Pooled normal plasma alone
0.3 nM 19499
1 nM 19449
3 nM 19499
10 nM 19499
30 nM 19499
100 nM 19499
300 nM 19499
1000 nM 19499
B.
Thrombin (nM)
Time (min)
Hemophilia B plasma alone
Pooled normal plasma alone
0.3 nM ARC17480
1 nM ARC17480
3 nM ARC17480
10 nM ARC17480
30 nM ARC17480
100 nM ARC17480
300 nM ARC17480
1000 nM ARC17480

Figure 43

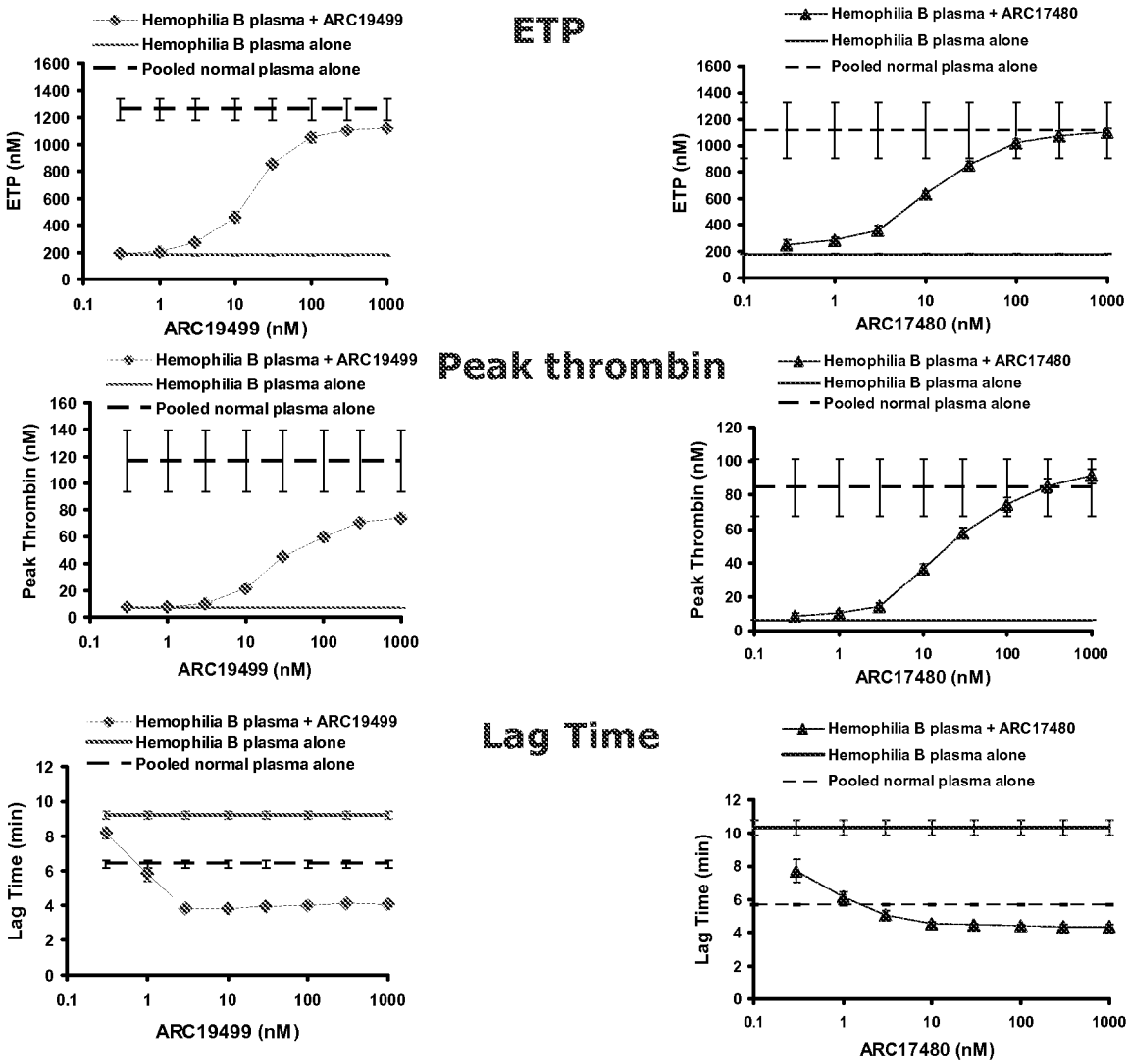

ETP
Hemophilia B plasma + ARC19499
Hemophilia B plasma alone
Pooled normal plasma alone
ETP (nM)
ARC19499 (nM)
Hemophilia B plasma + ARC17480
Hemophilia B plasma alone
Pooled normal plasma alone
ETP (nM)
ARC17480 (nM)
Peak thrombin
Hemophilia B plasma + ARC19499
Hemophilia B plasma alone
Pooled normal plasma alone
Peak Thrombin (nM)
ARC19499 (nM)
Hemophilia B plasma + ARC17480
Hemophilia B plasma alone
Pooled normal plasma alone
Peak Thrombin (nM)
ARC17480 (nM)
Lag Time
Hemophilia B plasma + ARC19499
Hemophilia B plasma alone
Pooled normal plasma alone
Lag Time (min)
ARC19499 (nM)
Hemophilia B plasma + ARC17480
Hemophilia B plasma alone
Pooled normal plasma alone
Lag Time (min)
ARC17480 (nM)

Figure 44

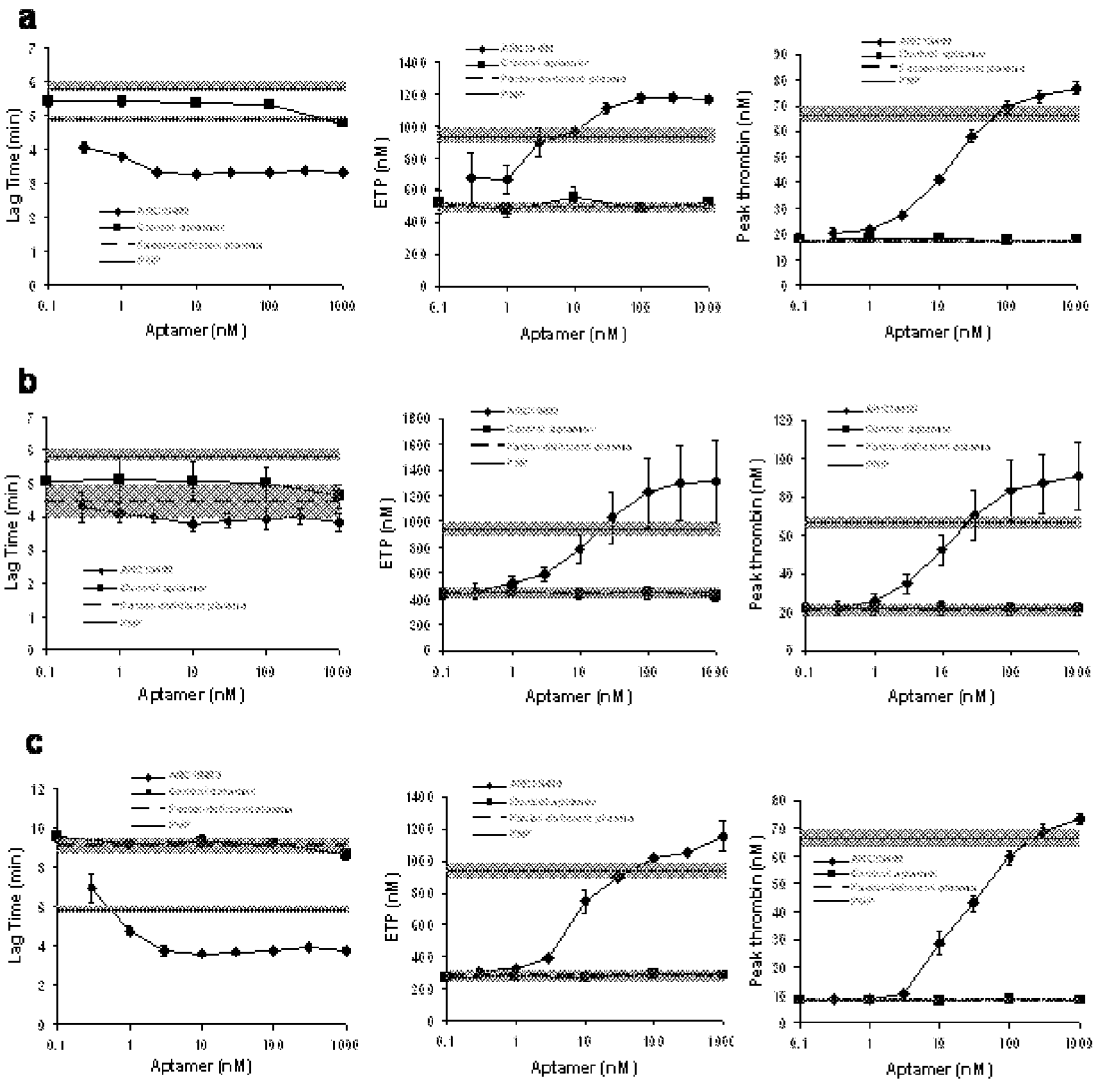


Figure 45

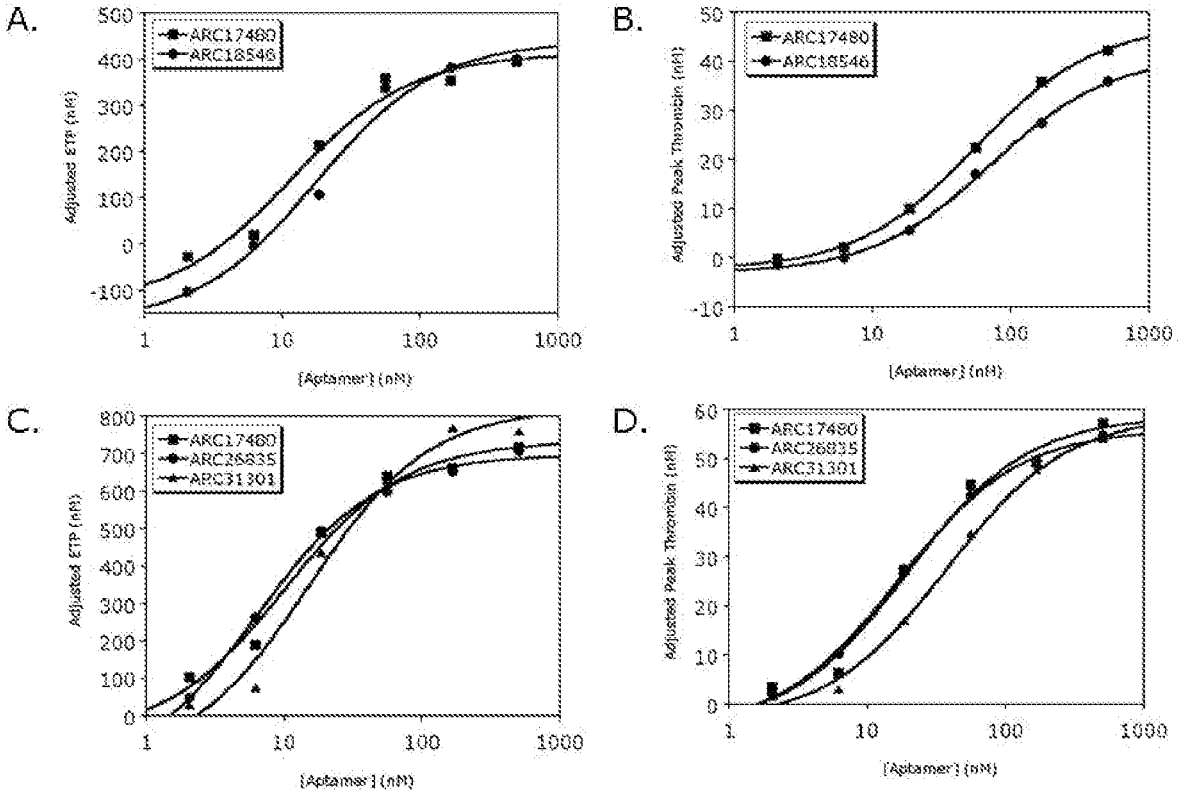


Figure 46

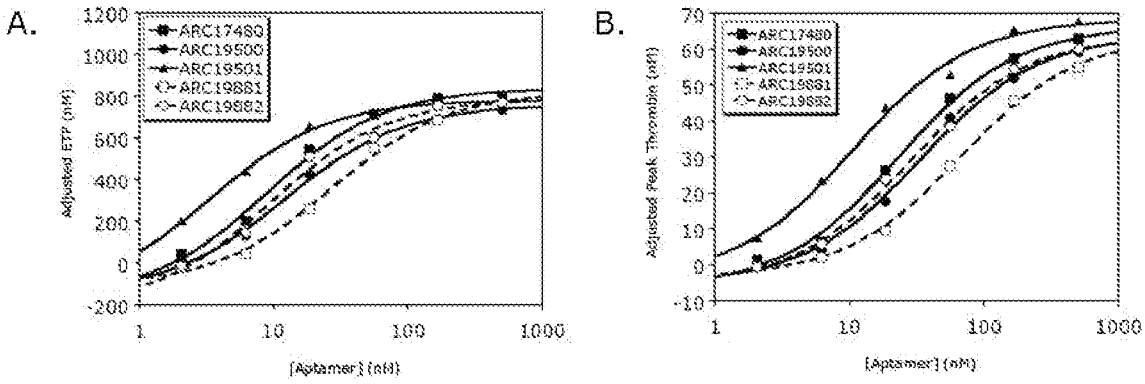


Figure 47

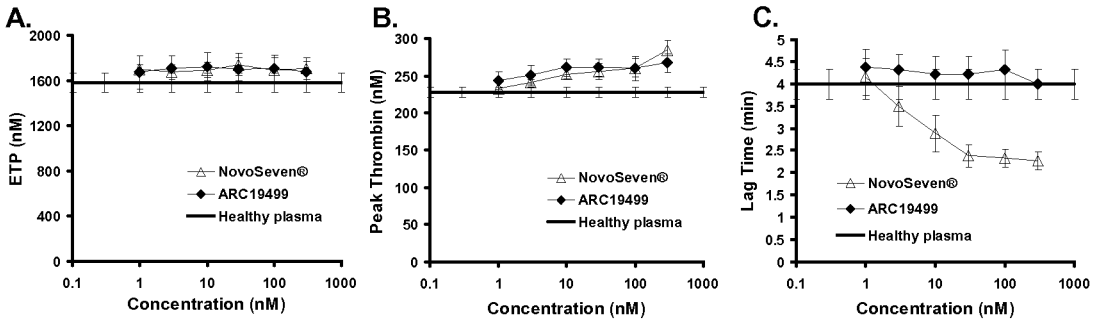


Figure 48

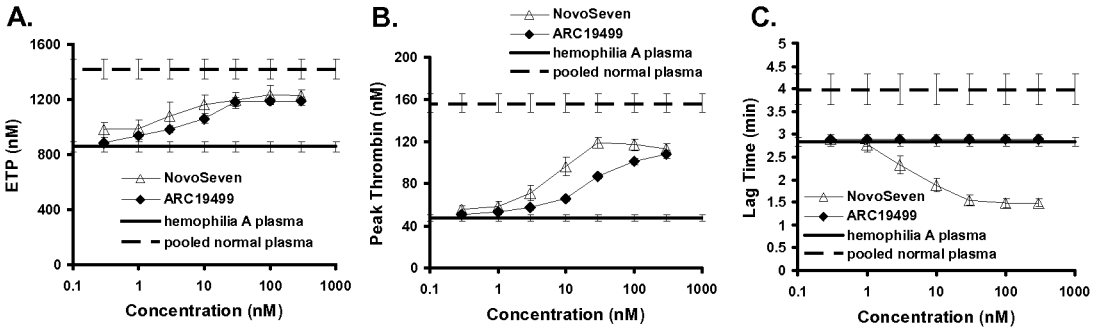


Figure 49

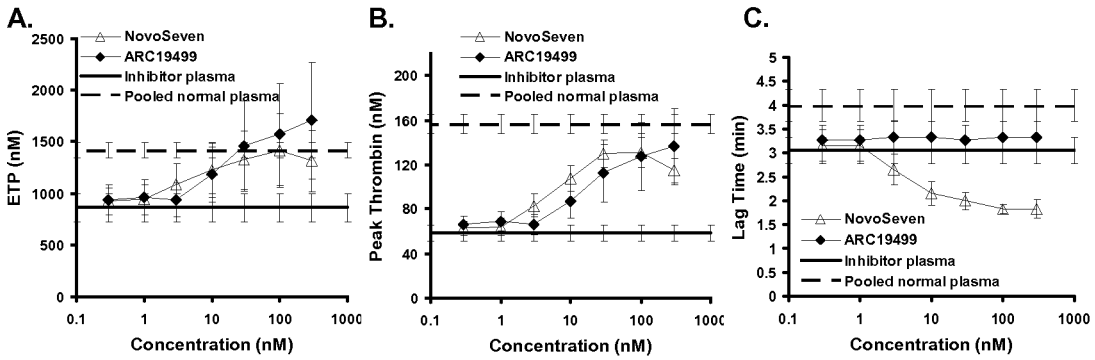


Figure 50

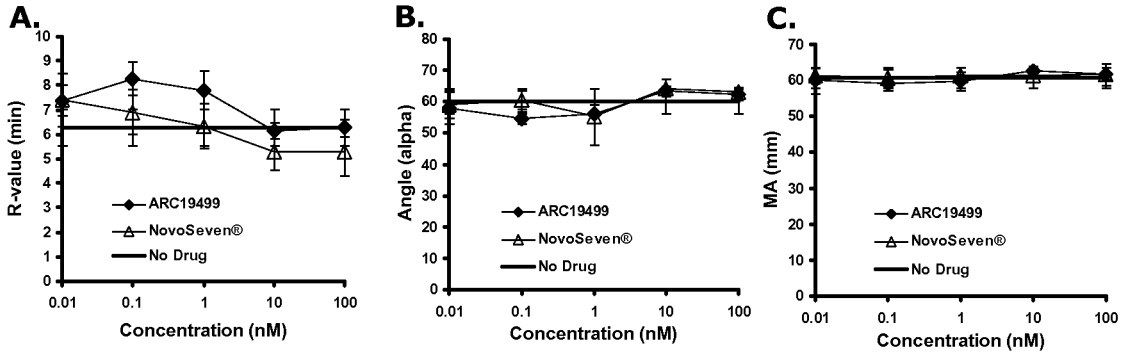


Figure 51

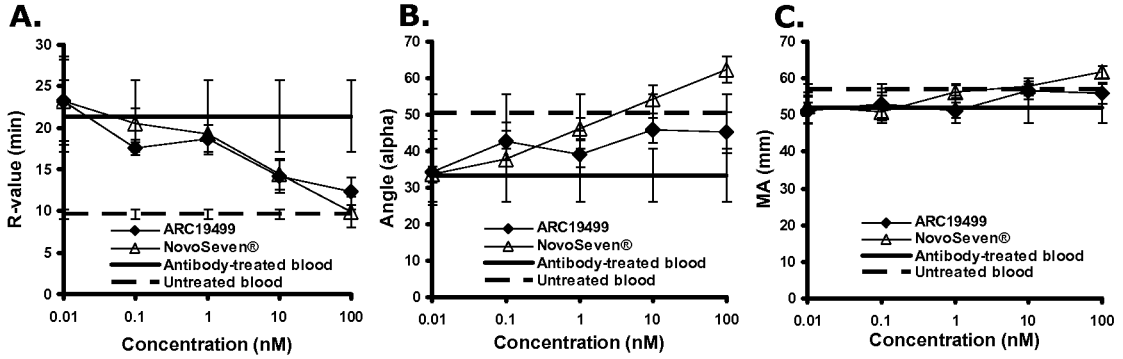


Figure 52

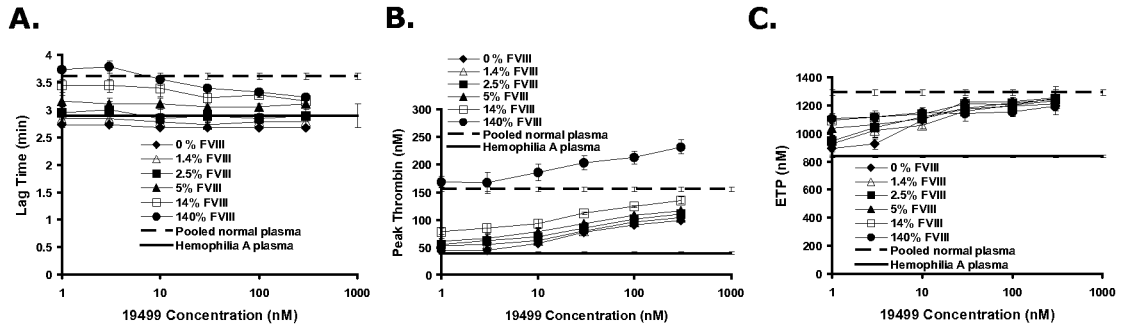
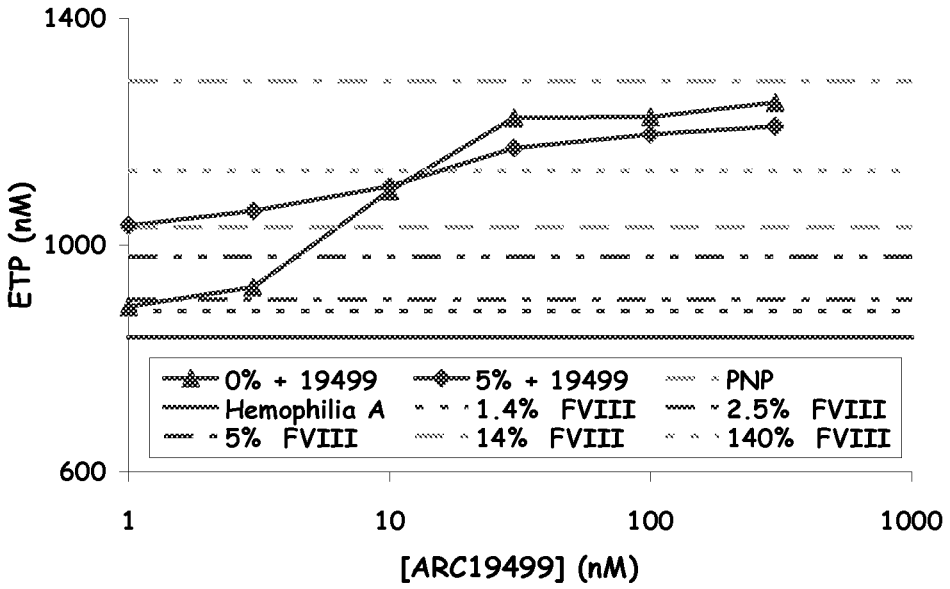


Figure 53

A


1400
1000
600
ETP (nM)
1
10
100
1000
[ARC19499] (nM)
0% + 19499
5% + 19499
PNP
Hemophilia A
1.4% FVIII
2.5% FVIII
5% FVIII
14% FVIII
140% FVIII

B

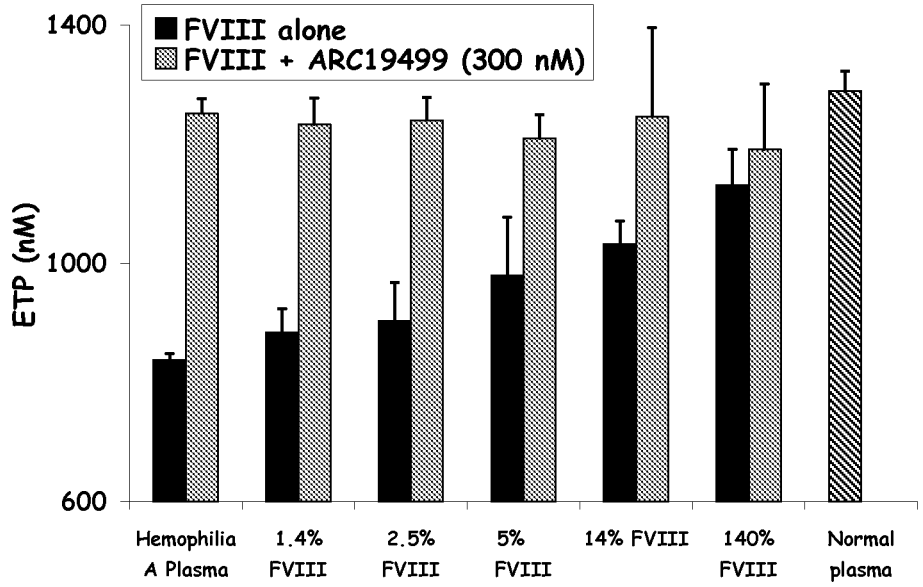
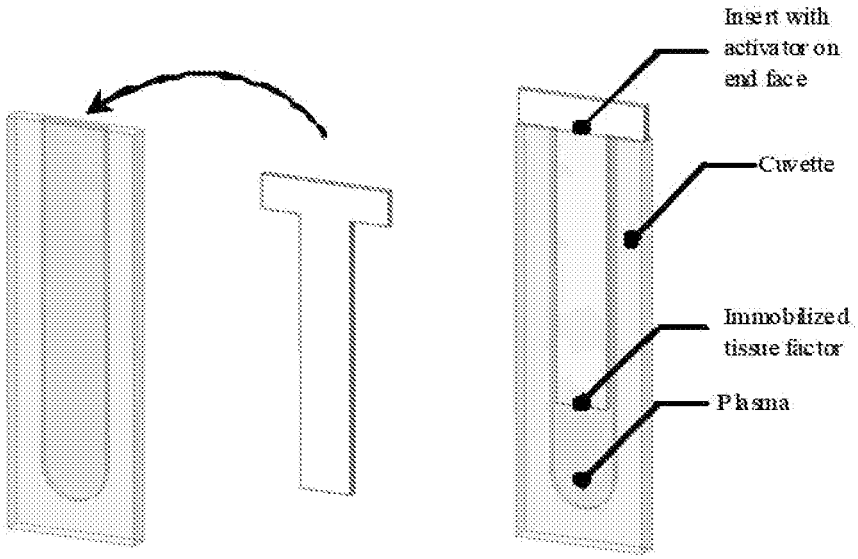

1400
1000
600
ETP (nM)
FVIII alone
FVIII + ARC19499 (300 nM)
Hemophilia A Plasma
1.4% FVIII
2.5% FVIII
5% FVIII
14% FVIII
140% FVIII
Normal plasma

Figure 54

A


Insert with activator on end face
Cuvette
Immobilized tissue factor
Plasma

B

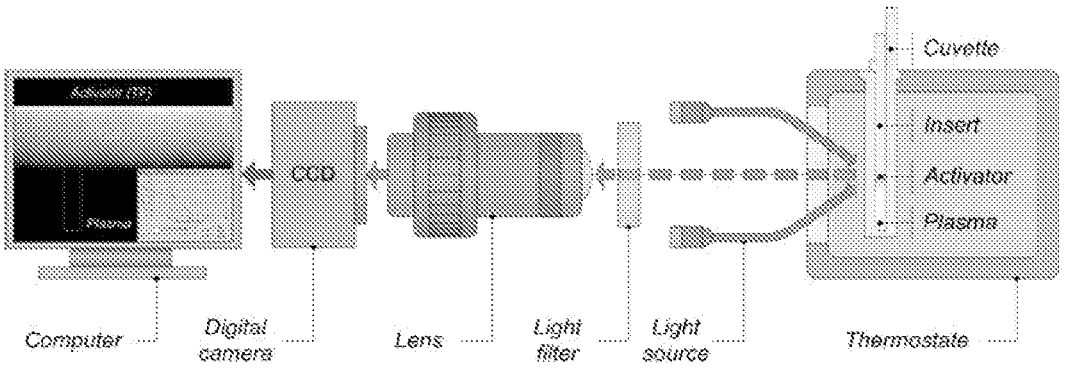

Cuvette
Insert
Activator
Plasma
CCD
Computer
Digital camera
Lens
Light filter
Light source
Thermostate

Figure 55

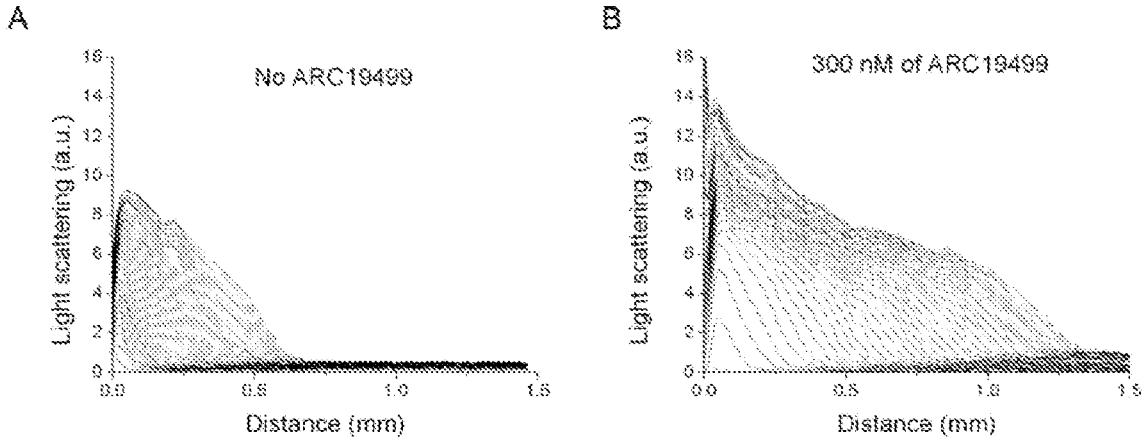


Figure 56

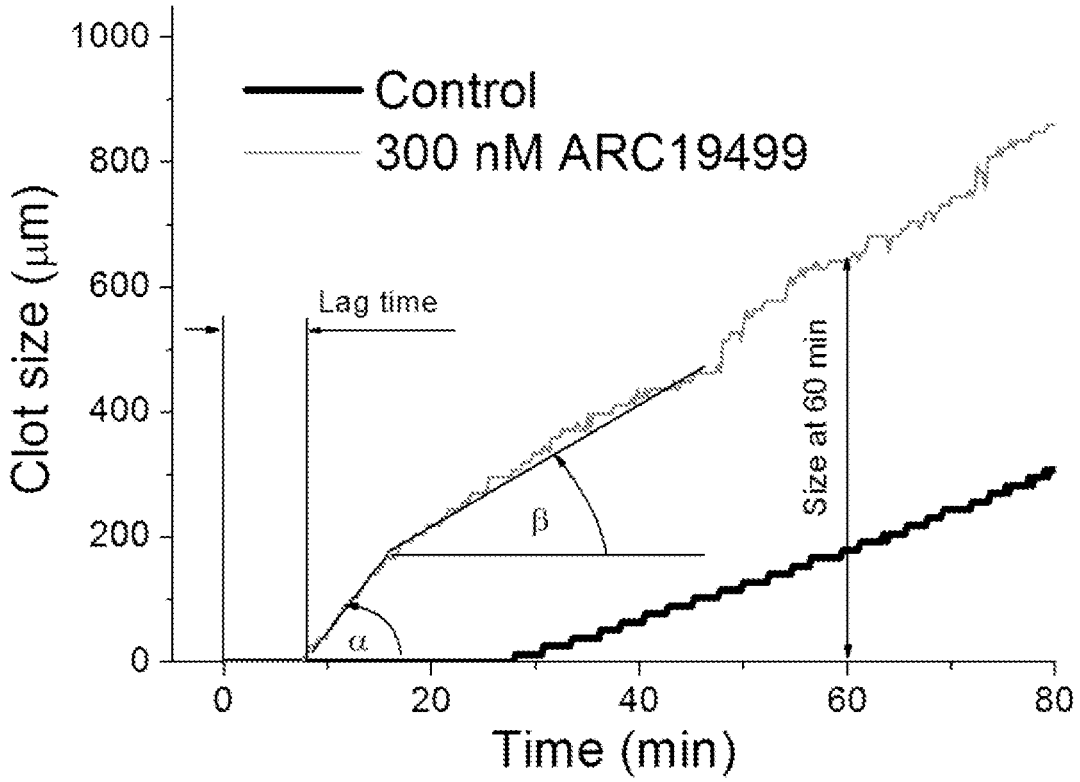


Figure 57

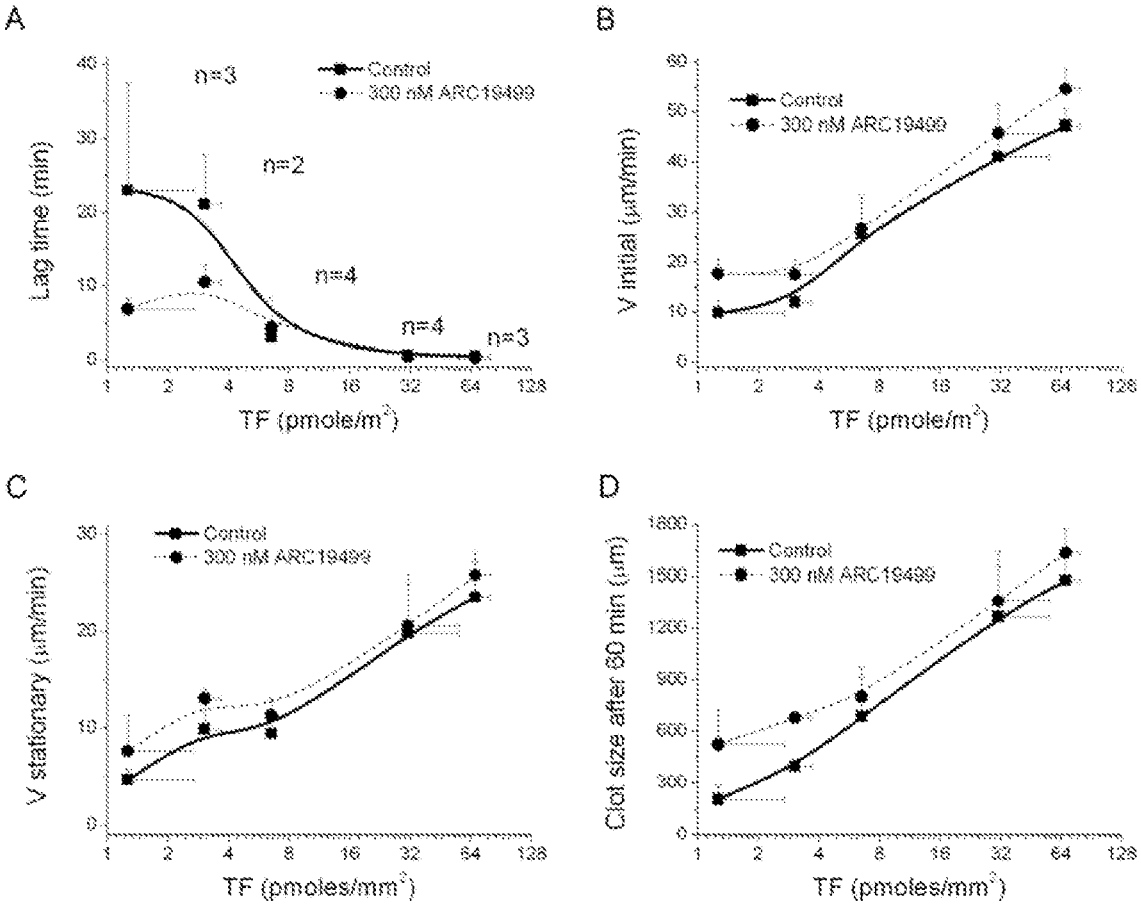

A
Lag time (min)
n=3
n=2
n=4
n=4
n=3
Control
300 nM ARC19499
TF (pmole/m²)
B
V initial (µm/min)
Control
300 nM ARC19499
TF (pmole/m²)
C
V stationary (µm/min)
Control
300 nM ARC19499
TF (pmoles/mm²)
D
Clot size after 60 min (µm)
Control
300 nM ARC19499
TF (pmoles/mm²)

Figure 58

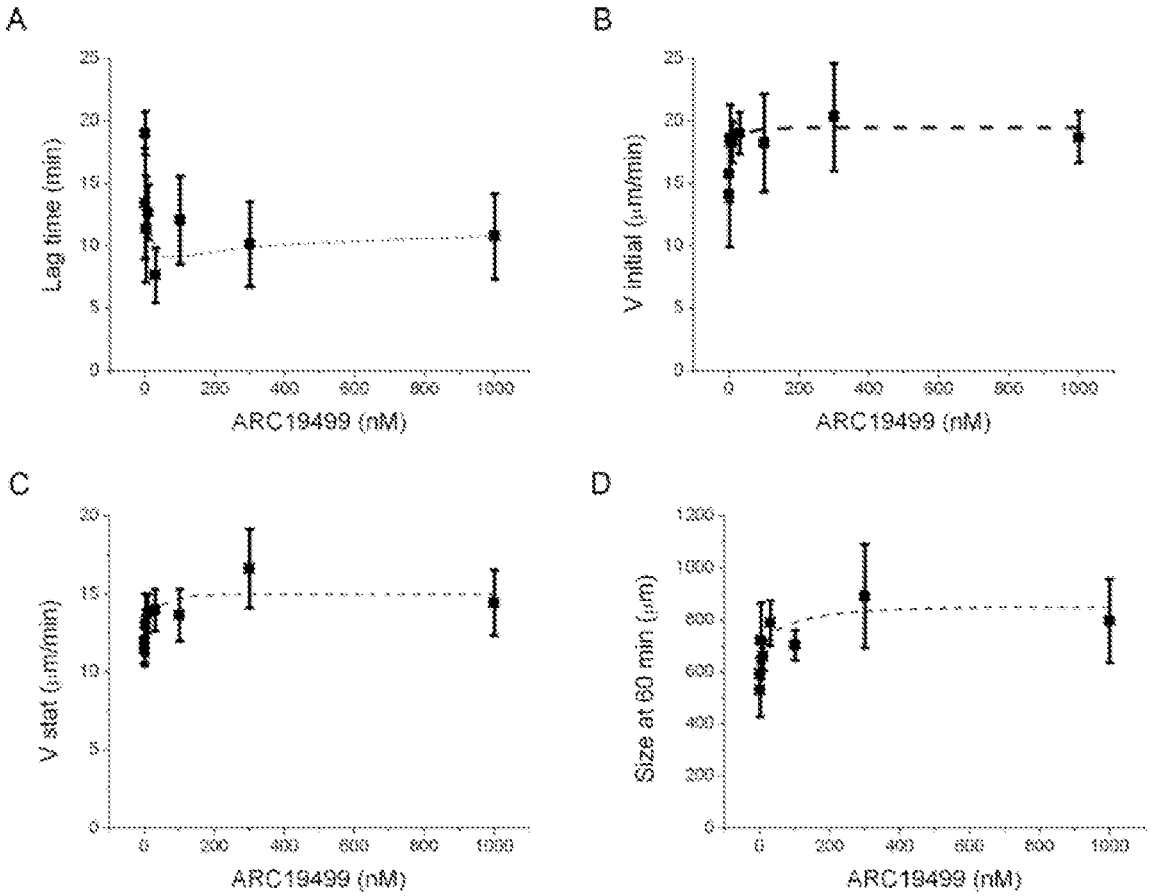

A
Lag time (min)
ARC19499 (nM)
B
V initial (μm/min)
ARC19499 (nM)
C
V stat (μm/min)
ARC19499 (nM)
D
Size at 60 min (μm)
ARC19499 (nM)

Figure 59

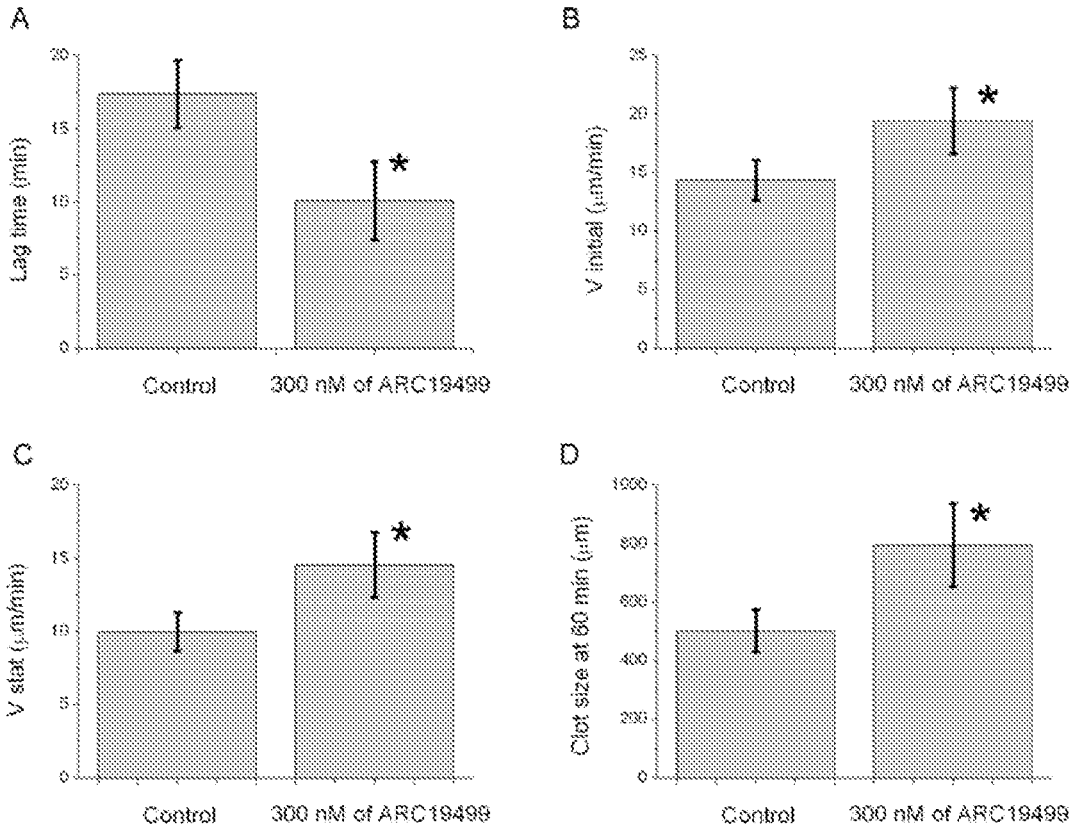

A
Lag time (min)
Control
300 nM of ARC19499
B
V intial (µm/min)
Control
300 nM of ARC19499
C
V stat (µm/min)
Control
300 nM of ARC19499
D
Clot size at 60 min (µm)
Control
300 nM of ARC19499

Figure 60

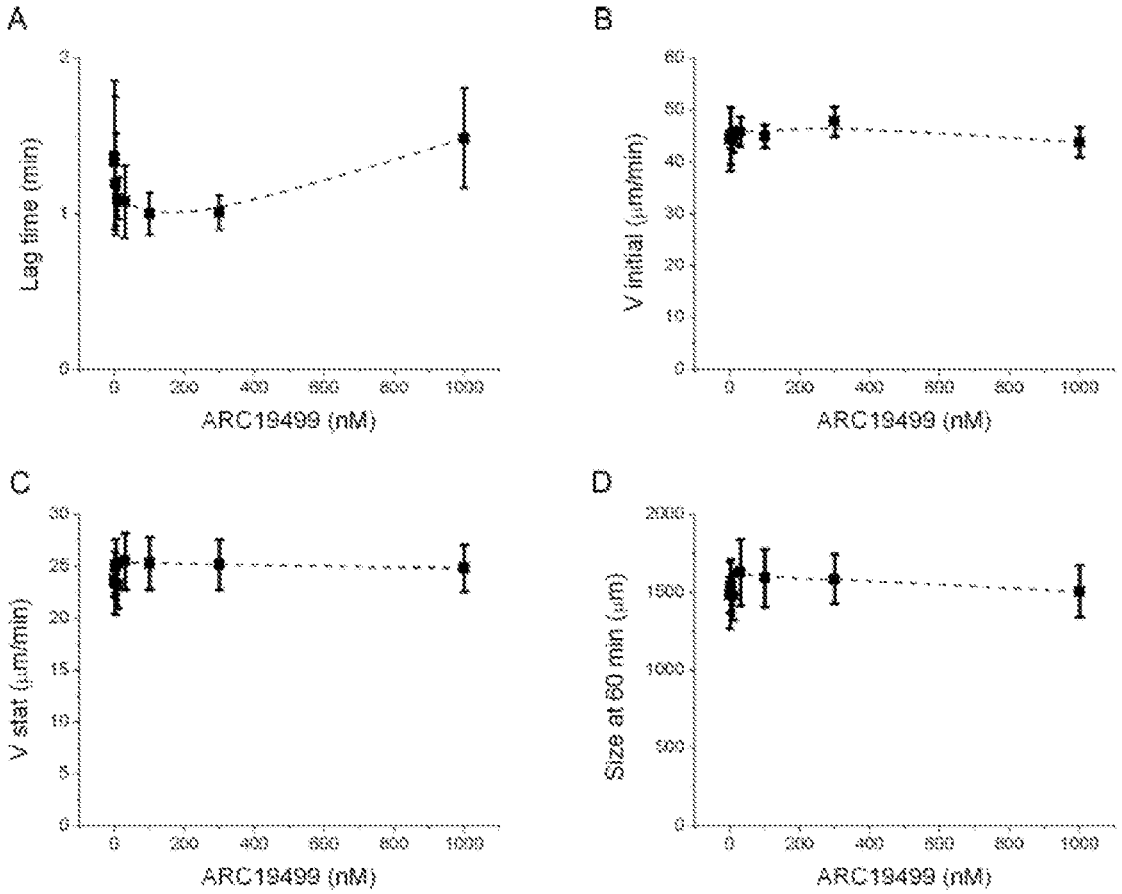

A
Lag time (min)
ARC19499 (nM)
B
V initial (μm/min)
ARC19499 (nM)
C
V stat (μm/min)
ARC19499 (nM)
D
Size at 60 min (μm)
ARC19499 (nM)

Figure 61

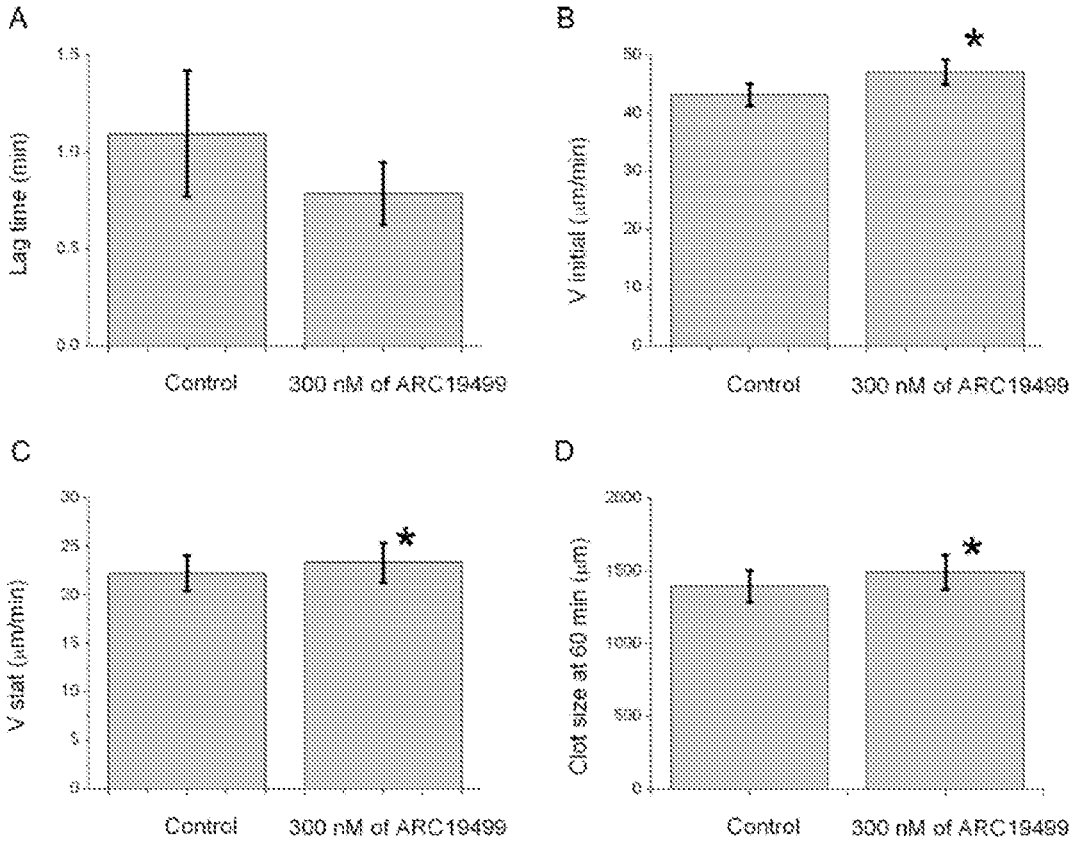

A
Lag time (min)
1.5
1.0
0.5
0.0
Control
300 nM of ARC19499
B
V initial (μm/min)
50
40
30
20
10
0
*
Control
300 nM of ARC19499
C
V stat (μm/min)
30
25
20
15
10
5
0
*
Control
300 nM of ARC19499
D
Clot size at 60 min (μm)
2000
1500
1000
500
0
*
Control
300 nM of ARC19499

Figure 62

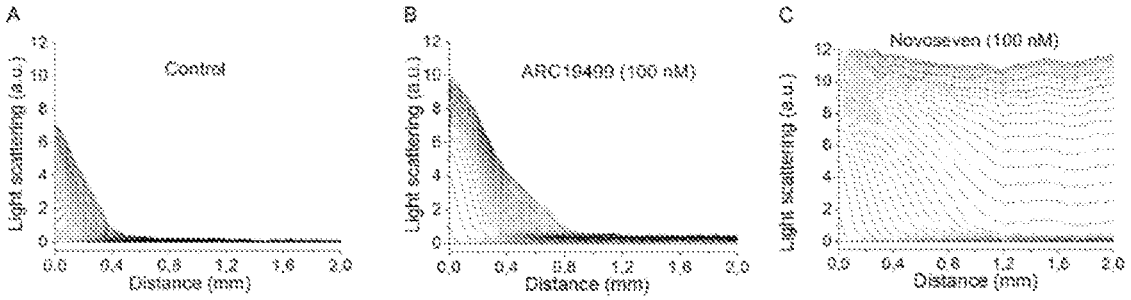


Figure 63

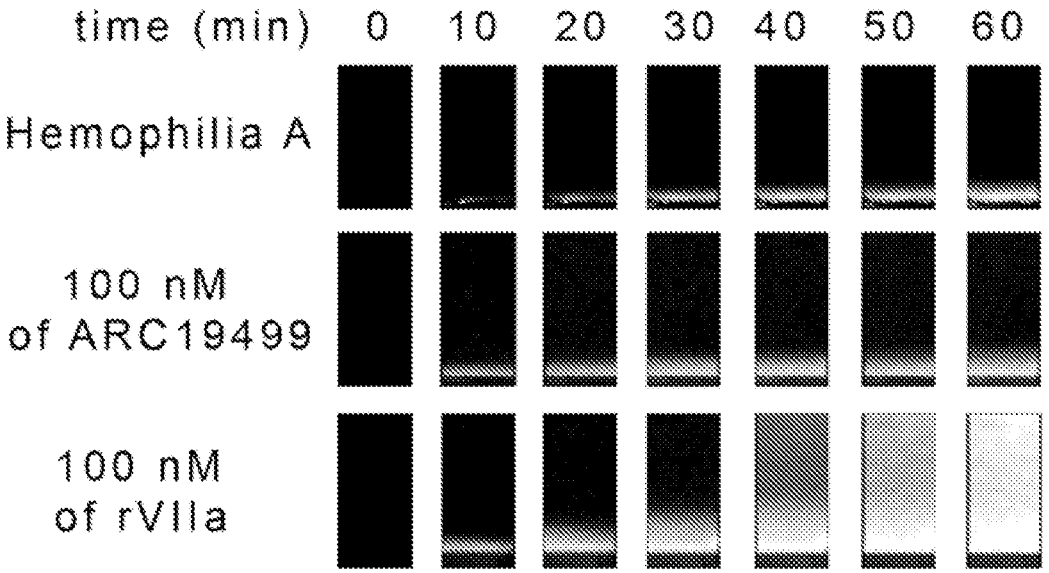


Figure 64

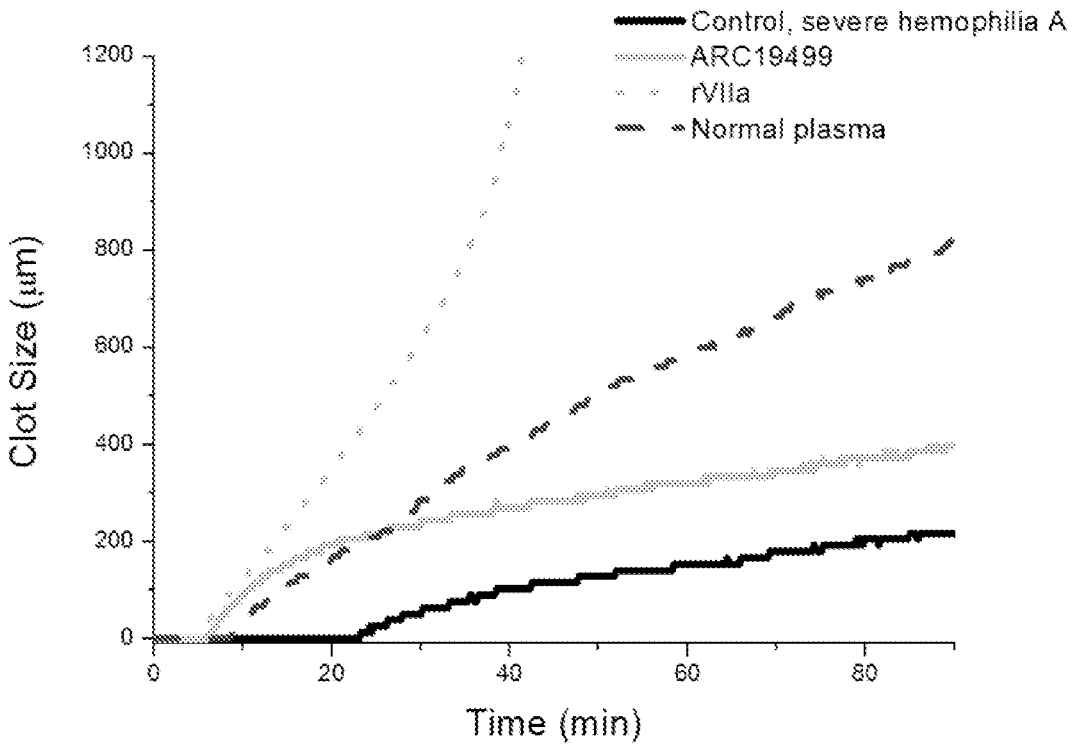


Figure 65

Patient number	Age	Monthly bleeding events	Factor VIII level in the day of experiment, %	APTT, sec
1	21	0-1	<1	103
2	24	1-2	2.1	82
3	43	1-2	1.2	86
4	48	1-2	1.4	80
5	21	1-2	<1	120
6	36	2-3	<1	102
7	19	3-5	2.8	99
8	30	0-1	<1	124

Figure 66

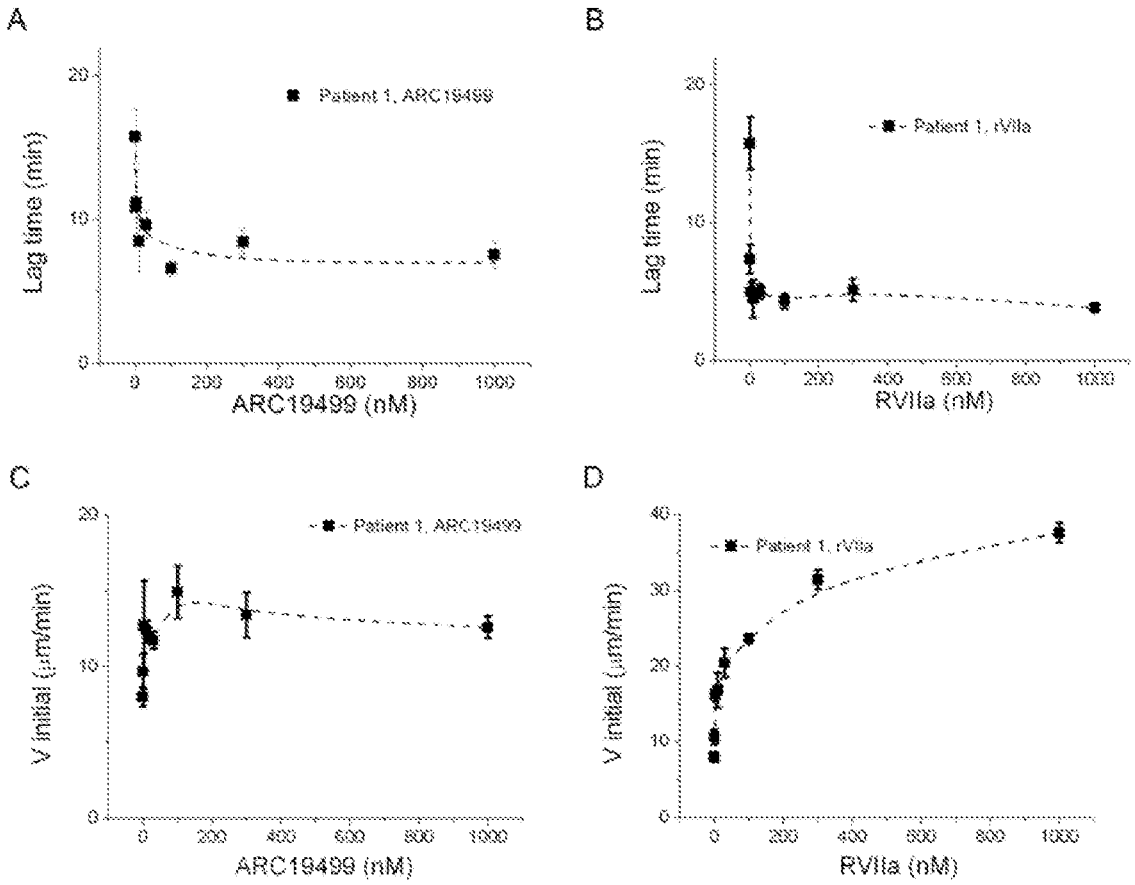

A
Patient 1, ARC19499
Lag time (min)
ARC19499 (nM)
B
Patient 1, rVIIa
Lag time (min)
RVIIa (nM)
C
Patient 1, ARC19499
V initial (um/min)
ARC19499 (nM)
D
Patient 1, rVIIa
V initial (um/min)
RVIIa (nM)

Figure 67

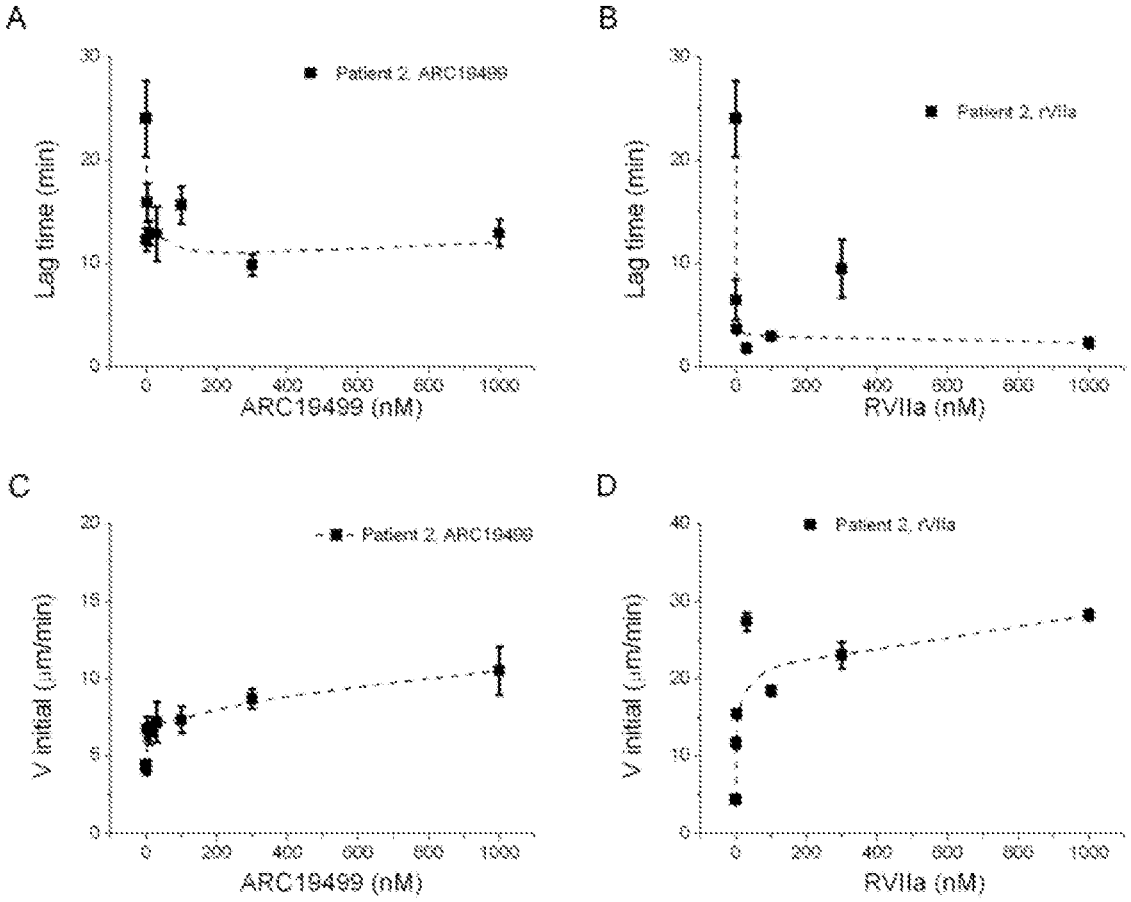

A
Patient 2, ARC19499
Lag time (min)
ARC19499 (nM)
B
Patient 2, rVIIa
Lag time (min)
RVIIa (nM)
C
Patient 2, ARC19499
V initial (μm/min)
ARC19499 (nM)
D
Patient 2, rVIIa
V initial (μm/min)
RVIIa (nM)

Figure 68

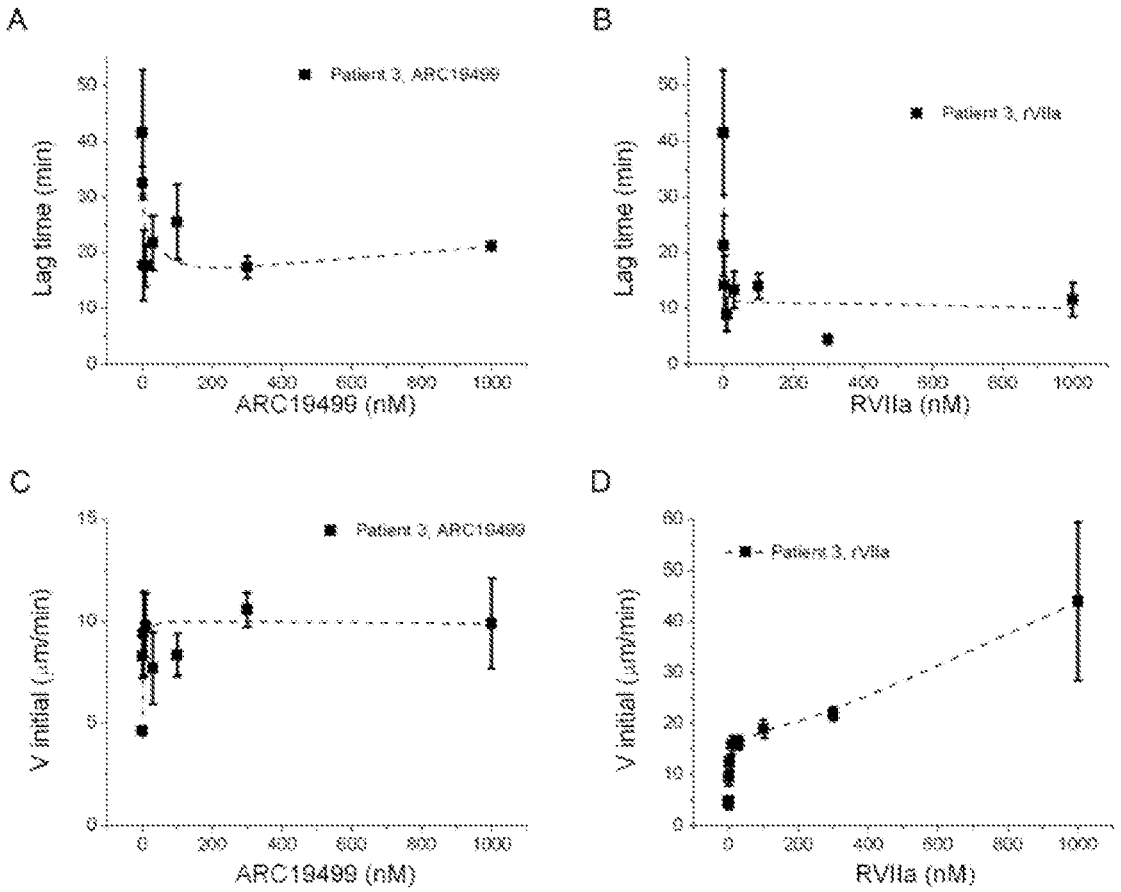

A
Patient 3, ARC19499
Lag time (min)
ARC19499 (nM)
B
Patient 3, rVIIa
Lag time (min)
RVIIa (nM)
C
Patient 3, ARC19499
V initial (μM/min)
ARC19499 (nM)
D
Patient 3, rVIIa
V initial (μM/min)
RVIIa (nM)

Figure 69

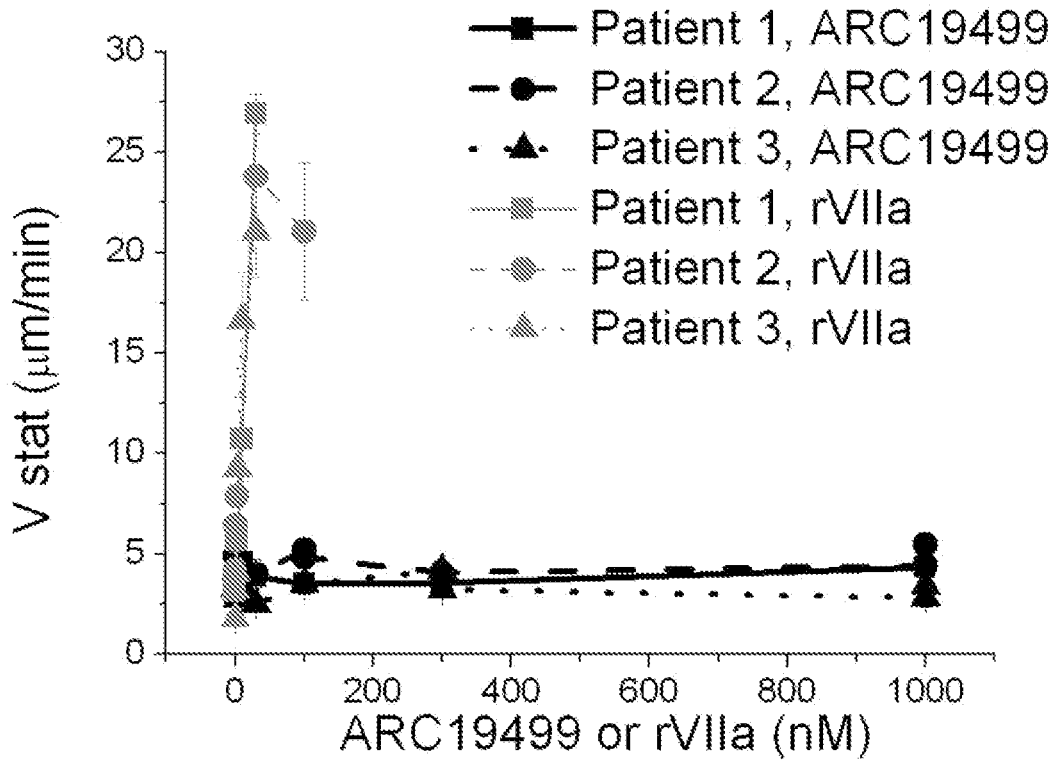


Figure 70

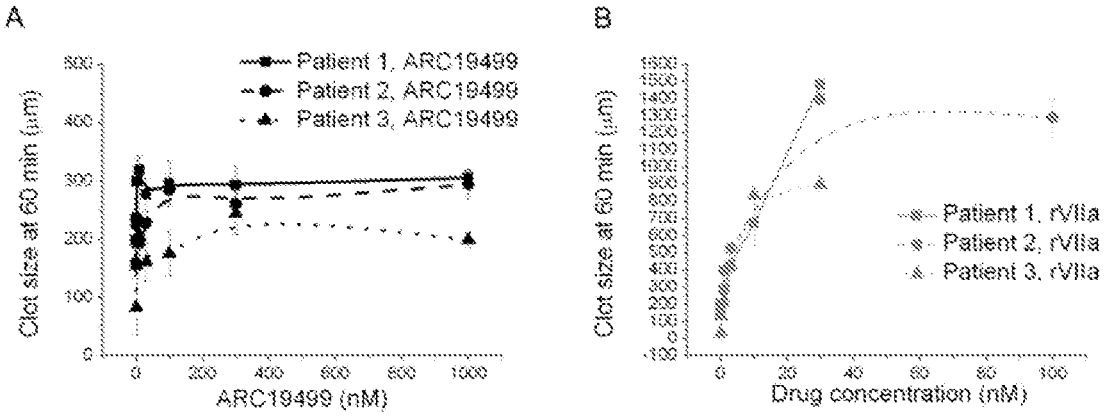


Figure 71

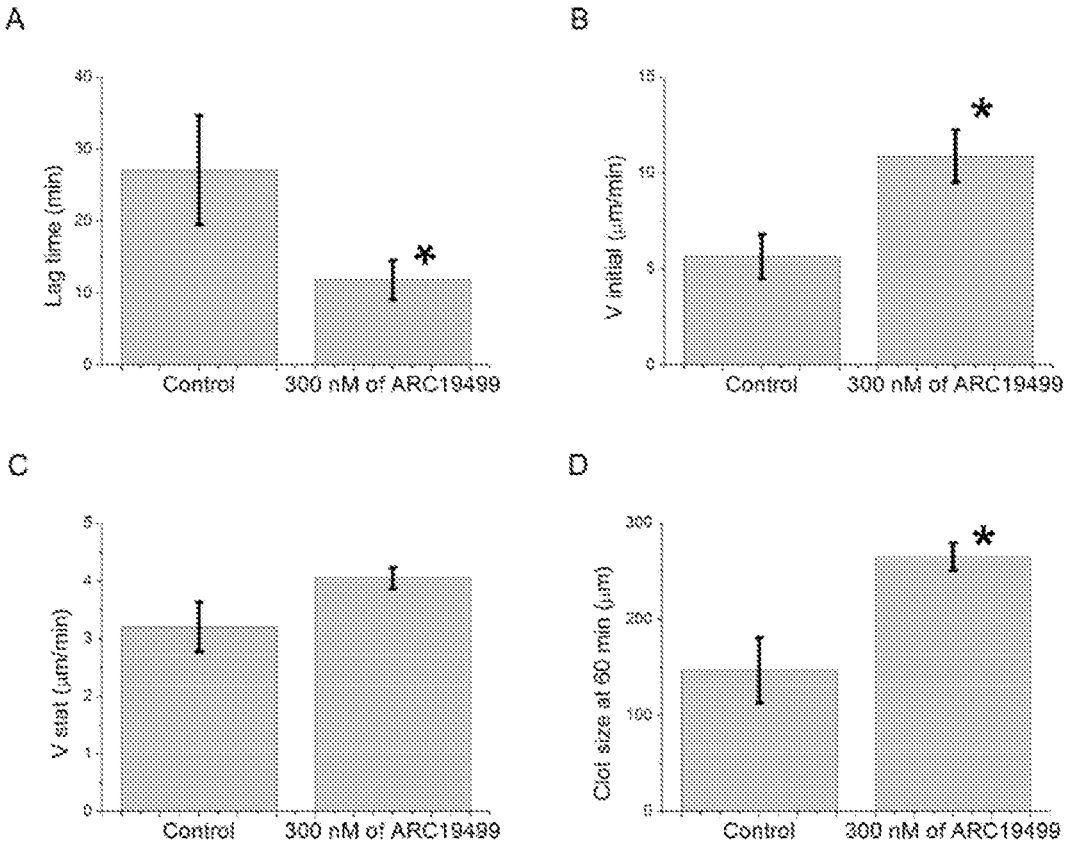

A
Lag time (min)
Control
300 nM of ARC19499
B
V initial (µm/min)
Control
300 nM of ARC19499
C
V stat (µm/min)
Control
300 nM of ARC19499
D
Clot size at 60 min (µm)
Control
300 nM of ARC19499

Figure 72

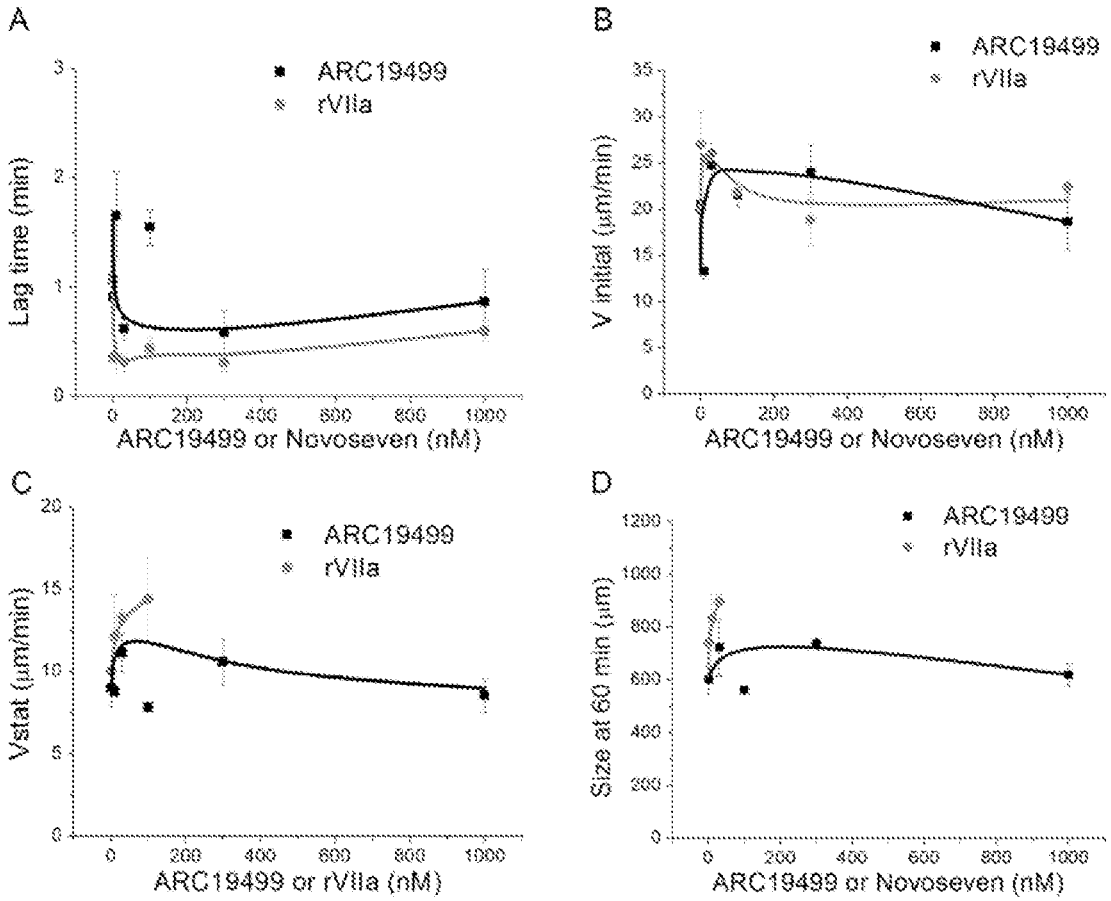

A
Lag time (min)
ARC19499
rVIIa
ARC19499 or Novoseven (nM)
B
V initial (μm/min)
ARC19499
rVIIa
ARC19499 or Novoseven (nM)
C
Vstat (μm/min)
ARC19499
rVIIa
ARC19499 or rVIIa (nM)
D
Size at 60 min (μm)
ARC19499
rVIIa
ARC19499 or Novoseven (nM)

Figure 73

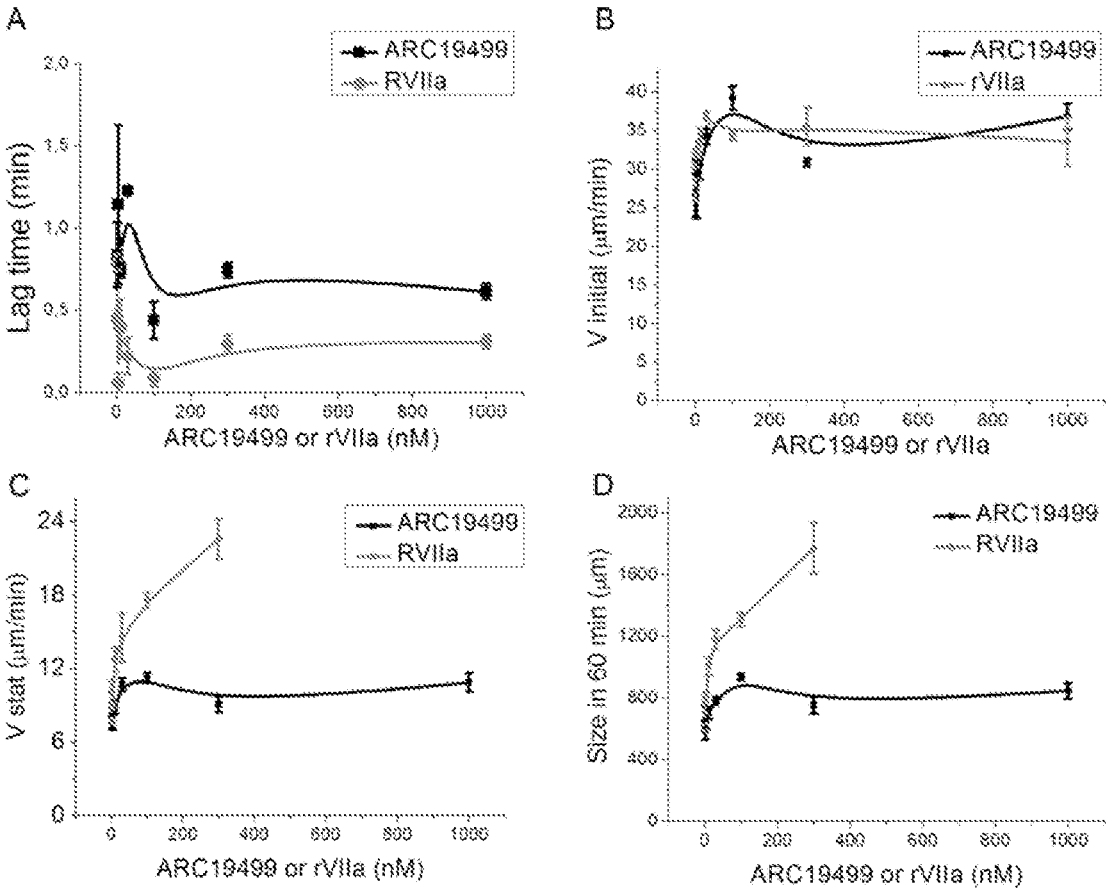

A
ARC19499
RVIIa
Lag time (min)
ARC19499 or rVIIa (nM)
B
ARC19499
rVIIa
V initial (µm/min)
ARC19499 or rVIIa
C
ARC19499
RVIIa
V stat (µm/min)
ARC19499 or rVIIa (nM)
D
ARC19499
RVIIa
Size in 60 min (µm)
ARC19499 or rVIIa (nM)

Figure 74

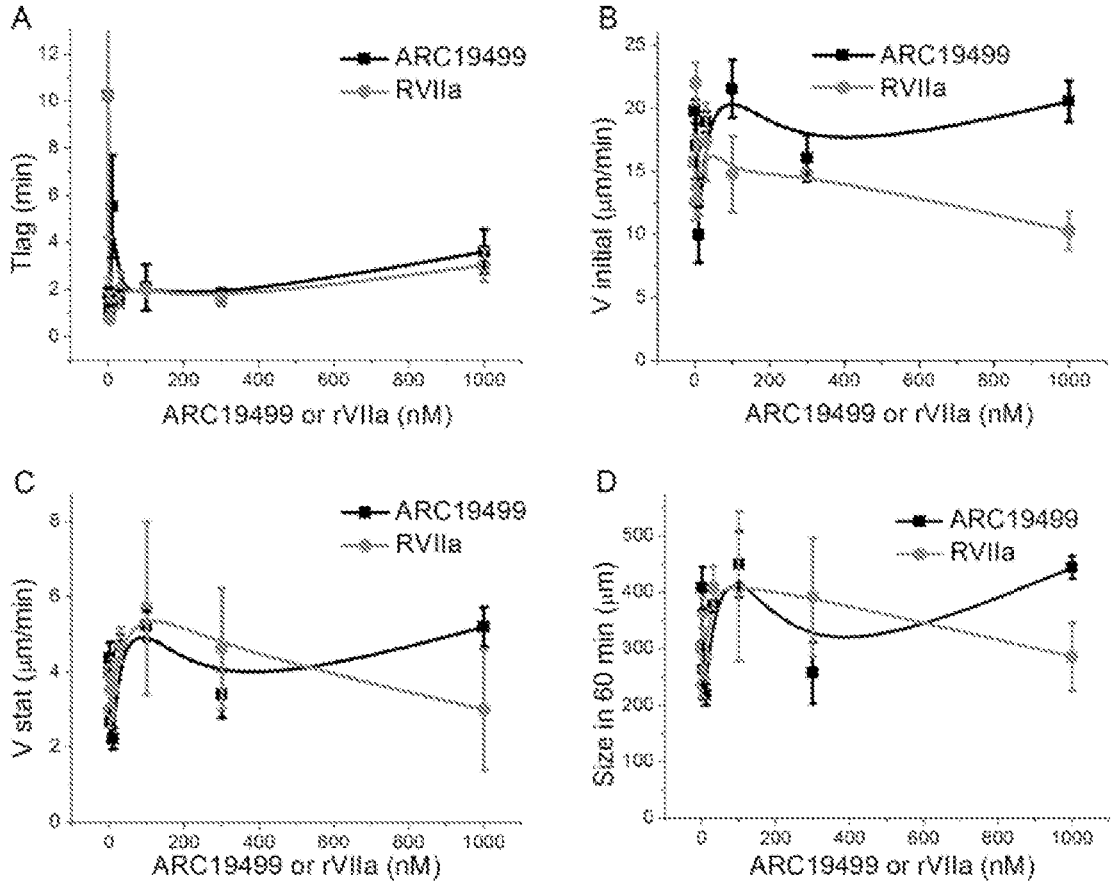

A
ARC19499
RVIIa
Tlag (min)
ARC19499 or rVIIa (nM)
B
ARC19499
RVIIa
V initial (µm/min)
ARC19499 or rVIIa (nM)
C
ARC19499
RVIIa
V stat (µm/min)
ARC19499 or rVIIa (nM)
D
ARC19499
RVIIa
Size in 60 min (µm)
ARC19499 or rVIIa (nM)

Figure 75

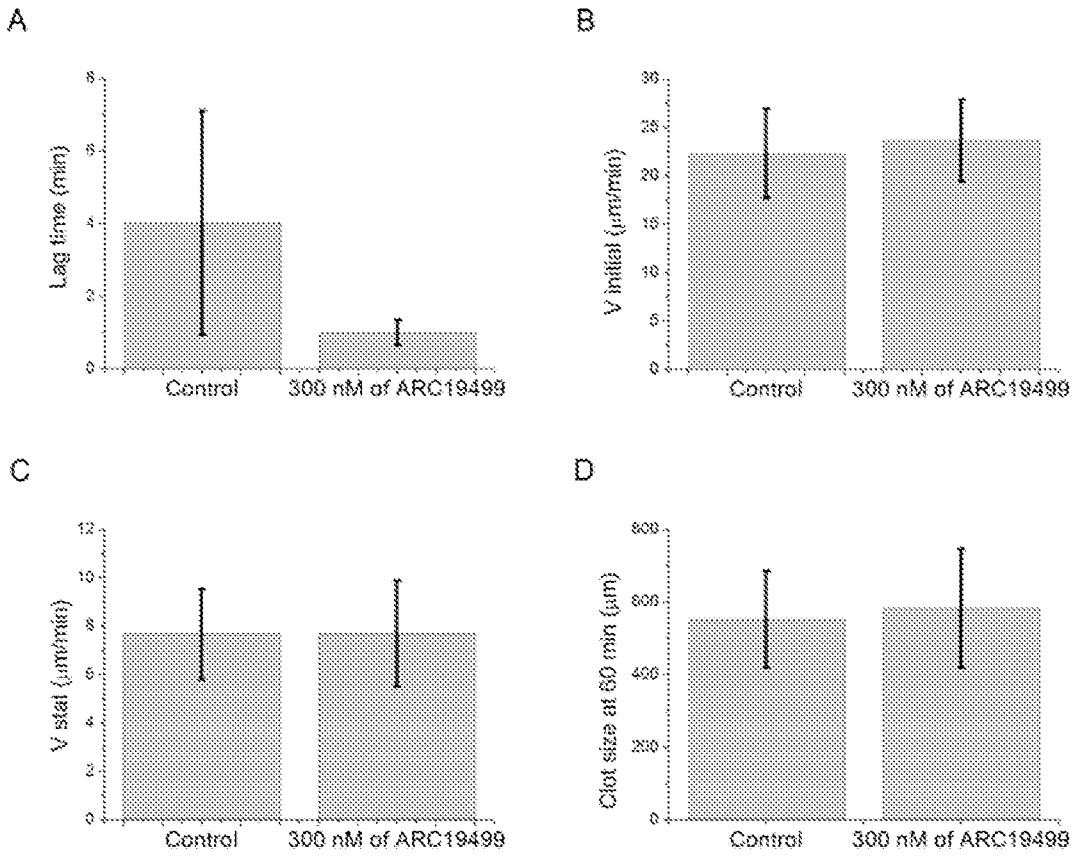

A
Lag time (min)
Control
300 nM of ARC19499
B
V initial (μm/min)
Control
300 nM of ARC19499
C
V stat (μm/min)
Control
300 nM of ARC19499
D
Clot size at 60 min (μm)
Control
300 nM of ARC19499

Figure 76

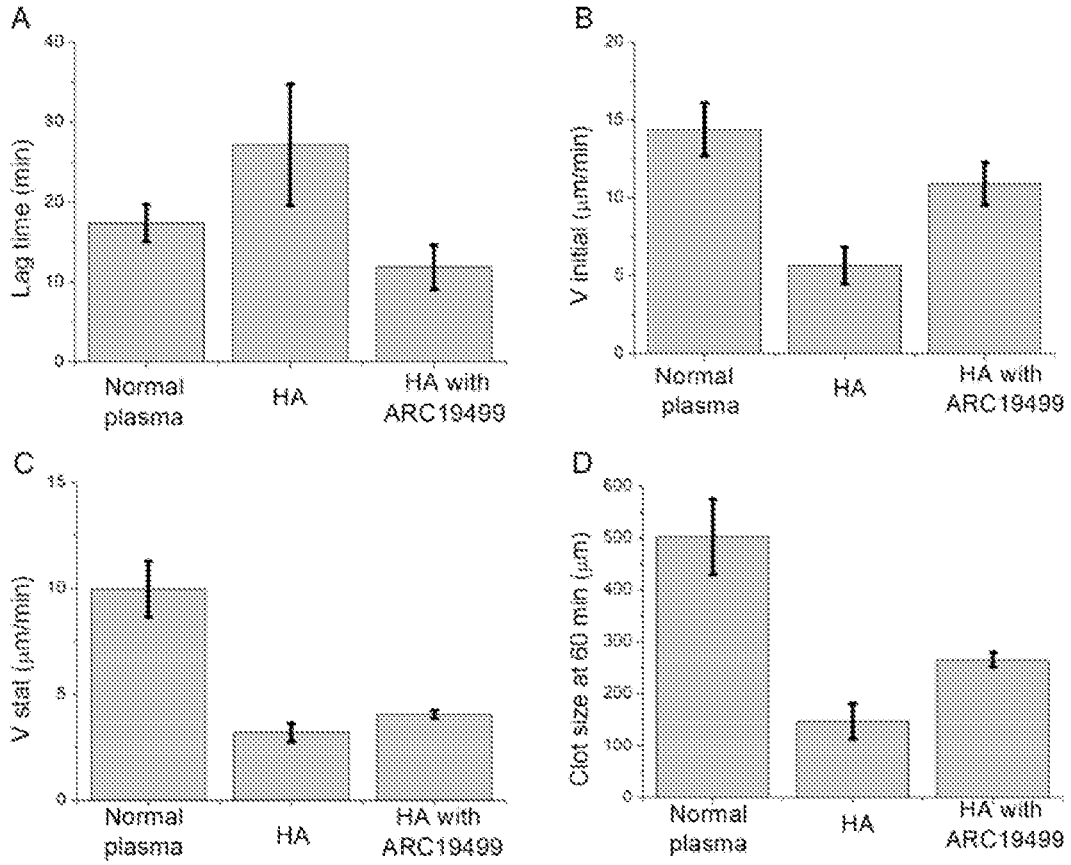

A
Lag time (min)
40
30
20
10
0
Normal plasma
HA
HA with ARC19499
B
V initial (μm/min)
20
15
10
5
0
Normal plasma
HA
HA with ARC19499
C
V stat (μm/min)
15
10
5
0
Normal plasma
HA
HA with ARC19499
D
Clot size at 60 min (μm)
600
500
400
300
200
100
0
Normal plasma
HA
HA with ARC19499

Figure 77

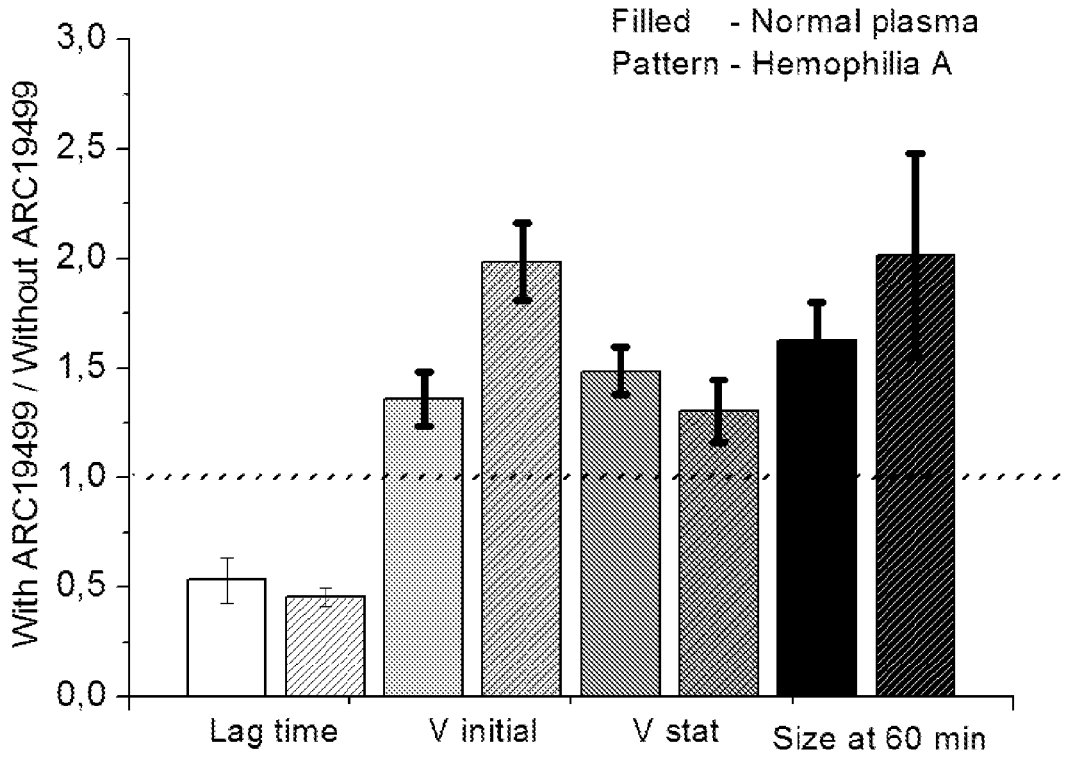
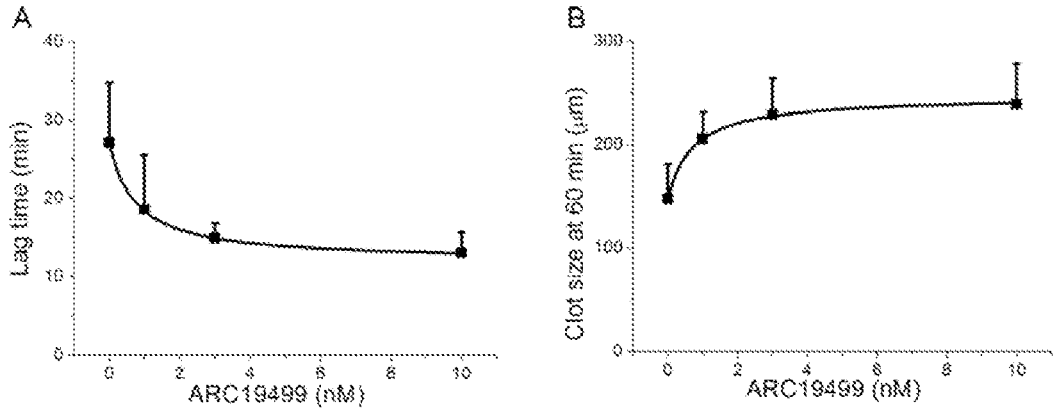


Figure 78



Parameter	IC_{50} (nM)	S.E. (nM)
Lag time	0.7	0.04
Size	0.7	0.06

Figure 79

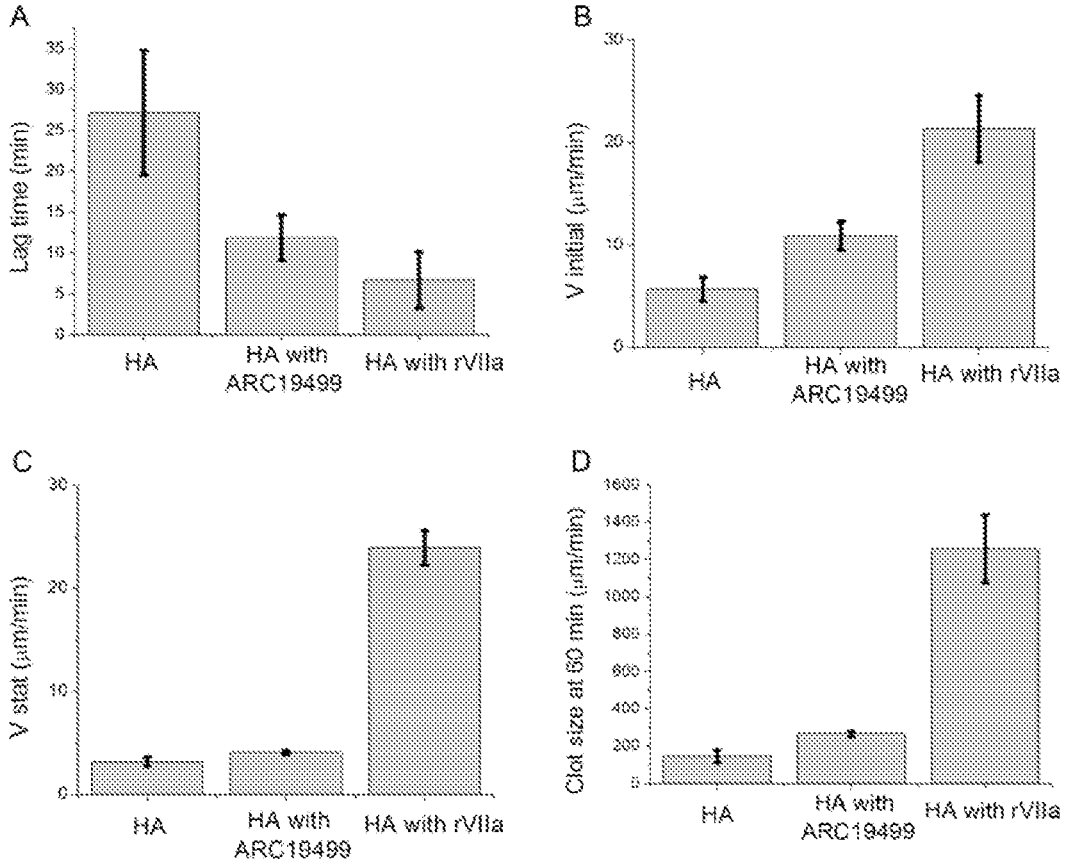


Figure 80

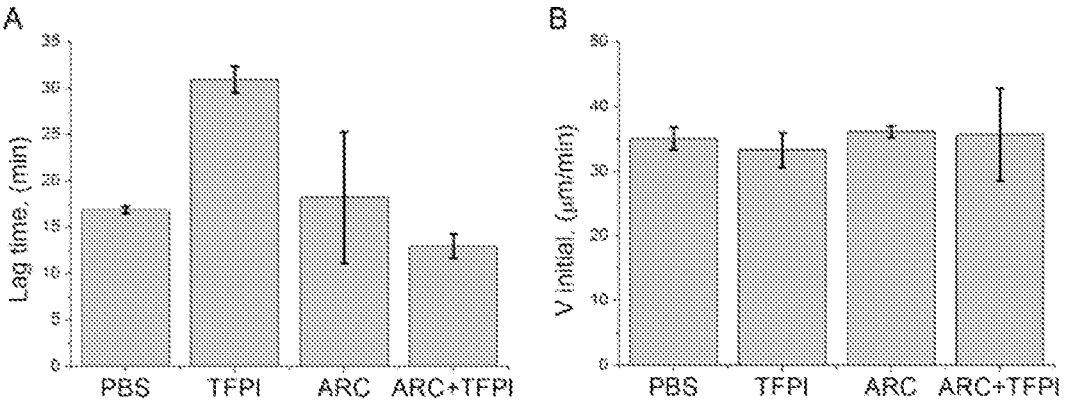


Figure 81

TF-ACT in whole blood from normal subjects			
[ARC19499] (nM)	#2 (N) (seconds)	#6 (N) (seconds)	#7 (N) (seconds)
700		311	
350	317	287	277
175	278	295	293
88	319	305	258
44			267
0	353	342	311

TF-ACT in whole blood from hemophilia B subjects		
[ARC19499] (nM)	#4 (B) (seconds)	#9 (B) (seconds)
350	438	522
175	435	457/510
88	323	420
44	460	510
0	528	580

TF-ACT in whole blood from hemophilia A subjects							
[ARC19499] (nM)	#1 (A) (seconds)	#3 (A) (seconds)	#5 (A) (seconds)	#8 (A) (seconds)	#10 (A) (seconds)	#11 (A) (seconds)	#12 (A) (seconds)
3115	264						
1558	313						
1400						455	299
800	256						
700		551/500	489		416	634	281
350		444	434	483	418	347	295
175		457	392	453	456	491	291
88			468	464		456	306
44					477		
0	578	651	540	642	527	783	328

Figure 82

Dilute PT in plasma from normal subjects

[ARC19499] (nM)	#2 (N) (seconds)	#6 (N) (seconds)	#7 (N) (seconds)
500	179	185	174
125	183	225	168
32	181	242	170
8	191	246	176
2	294	274	265
0	>360	>360	>360

Dilute PT in plasma from hemophilia B subjects

[ARC19499] (nM)	#4 (B) (seconds)	#9 (B) (seconds)
500	215	185
125	227	189
32	225	192
8	241	210
2	>360	>360
0	>360	>360

Dilute PT in plasma from hemophilia A subjects

[ARC19499] (nM)	#1 (A) (seconds)	#3 (A) (seconds)	#5 (A) (seconds)	#8 (A) (seconds)	#10 (A) (seconds)	#11 (A) (seconds)	#12 (A) (seconds)
500	163	162	162	156	154	162	>360
125	167	164	163	157	156	168	>360
32	171	168	164	163	157	171	>360
8	185	193	175	192	163	195	>360
2	>360	>360	>360	>360	169	>360	>360
0	>360	>360	>360	>360	169	>360	>360

Figure 83

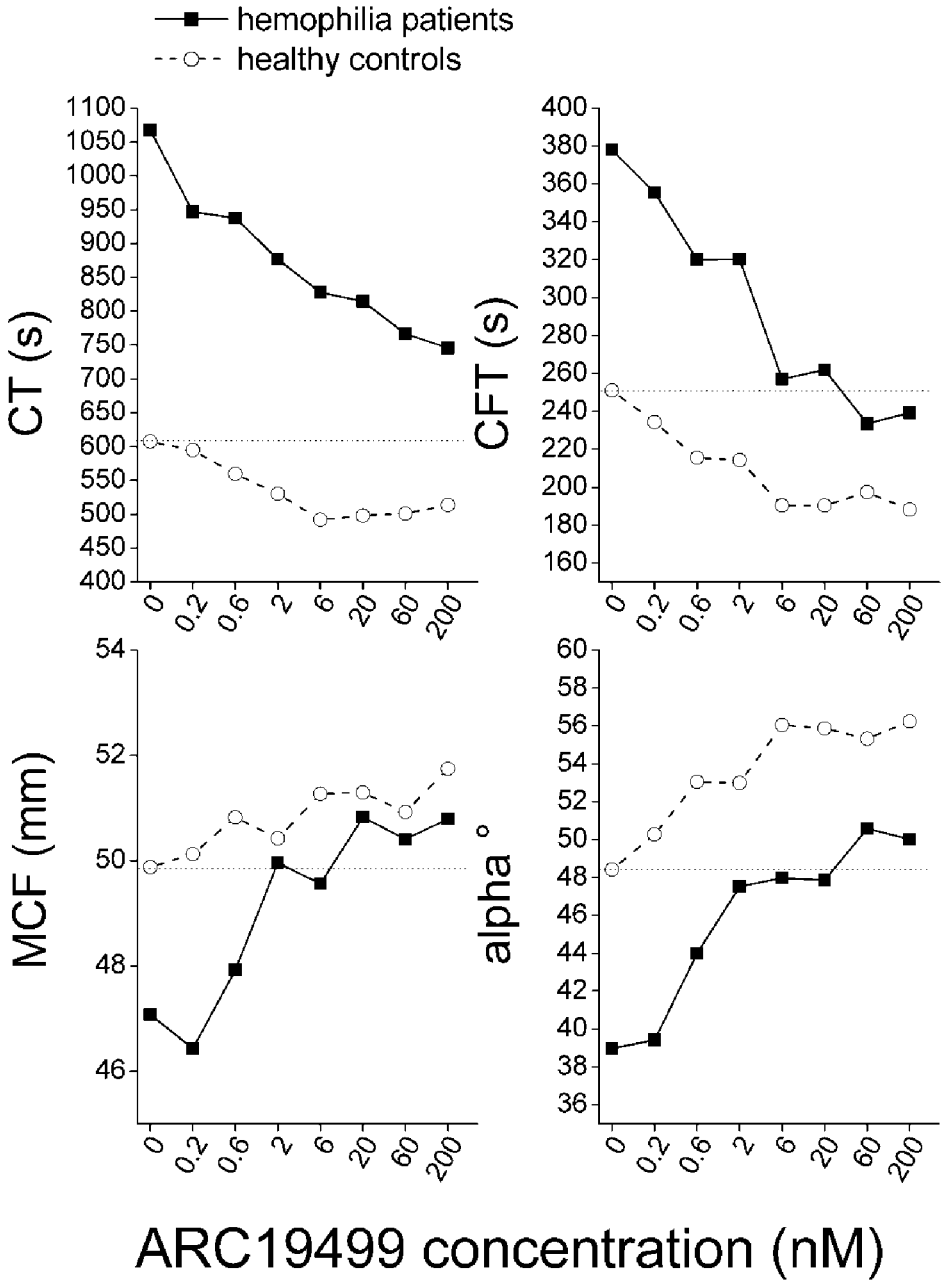

hemophilia patients
healthy controls
CT (s)
CFT (s)
MCF (mm)
alpha °
ARC19499 concentration (nM)

Figure 84

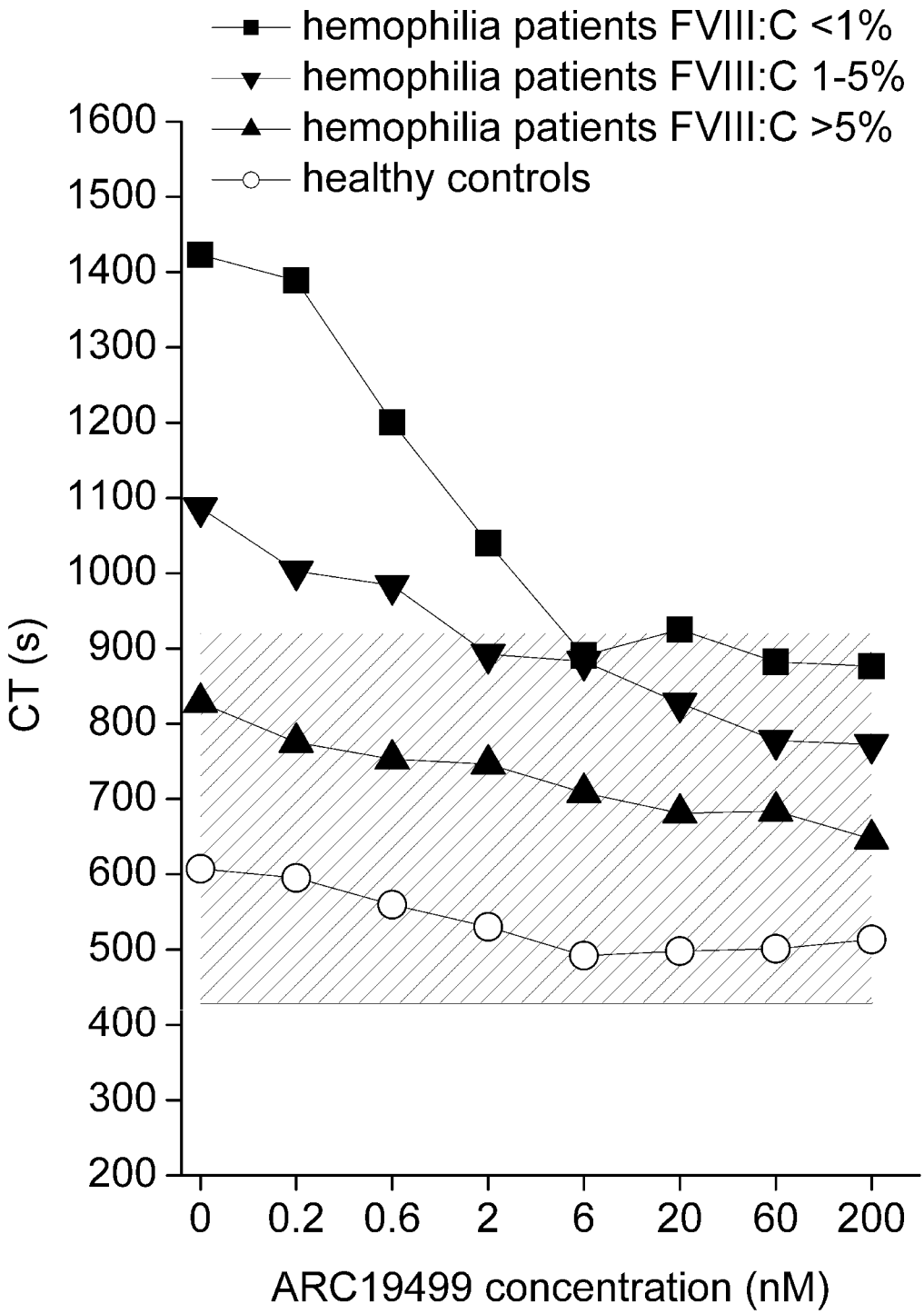

hemophilia patients FVIII:C <1%
hemophilia patients FVIII:C 1-5%
hemophilia patients FVIII:C >5%
healthy controls
CT (s)
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
0
0.2
0.6
2
6
20
60
200
ARC19499 concentration (nM)

Figure 85

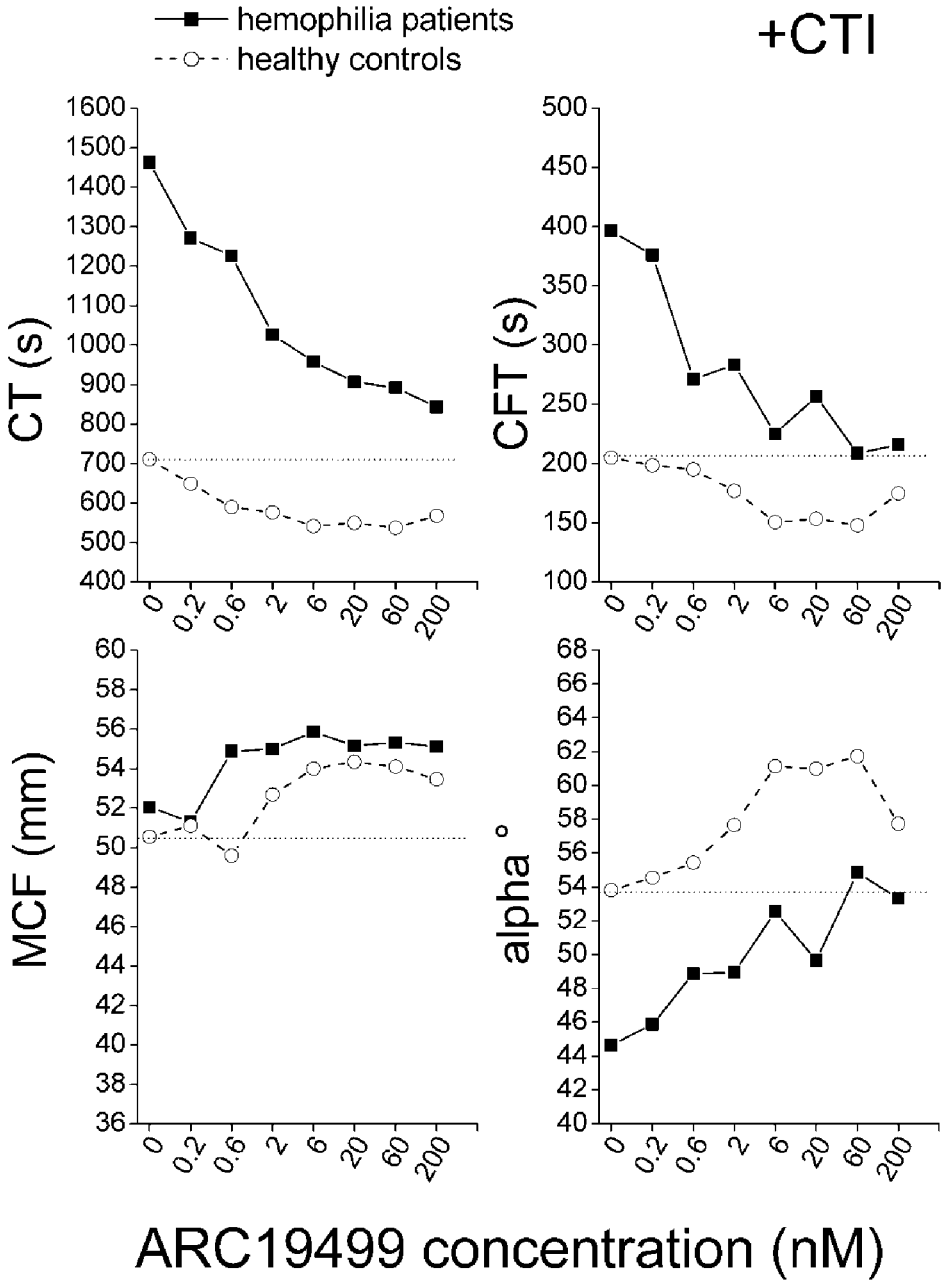

hemophilia patients
healthy controls
+CTI
CT (s)
CFT (s)
MCF (mm)
alpha °
ARC19499 concentration (nM)

Figure 86

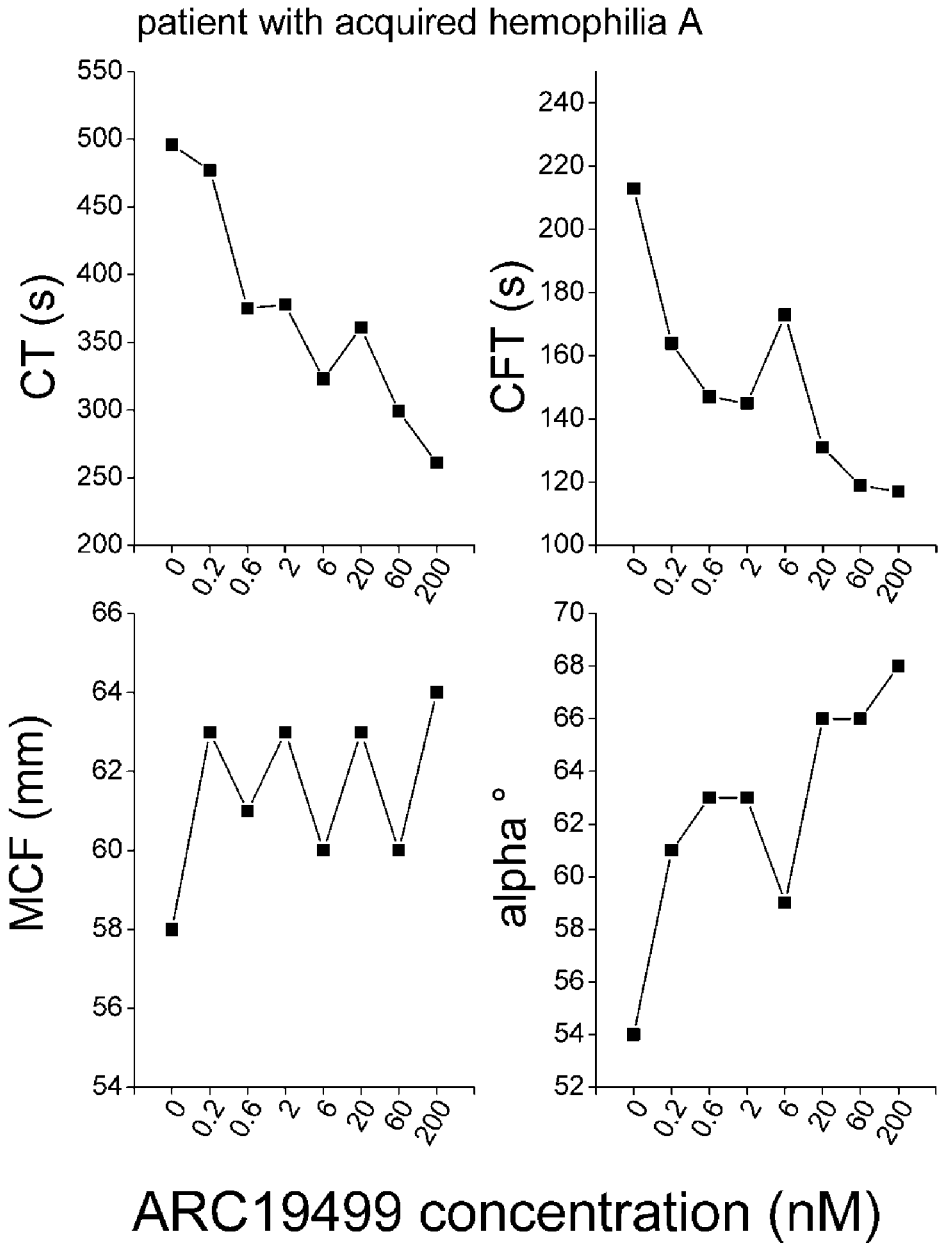

patient with acquired hemophilia A
CT (s)
CFT (s)
MCF (mm)
alpha °
ARC19499 concentration (nM)

Figure 87

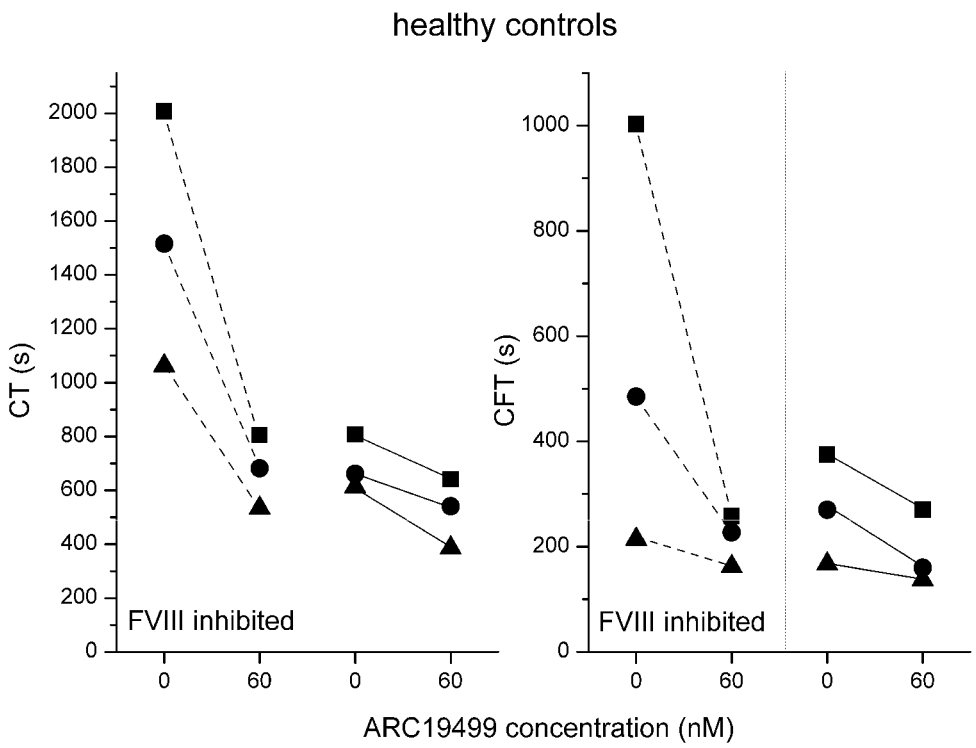

healthy controls
CT (s)
CFT (s)
FVIII inhibited
FVIII inhibited
ARC19499 concentration (nM)
0
60
0
60
0
60
0
60

Figure 88

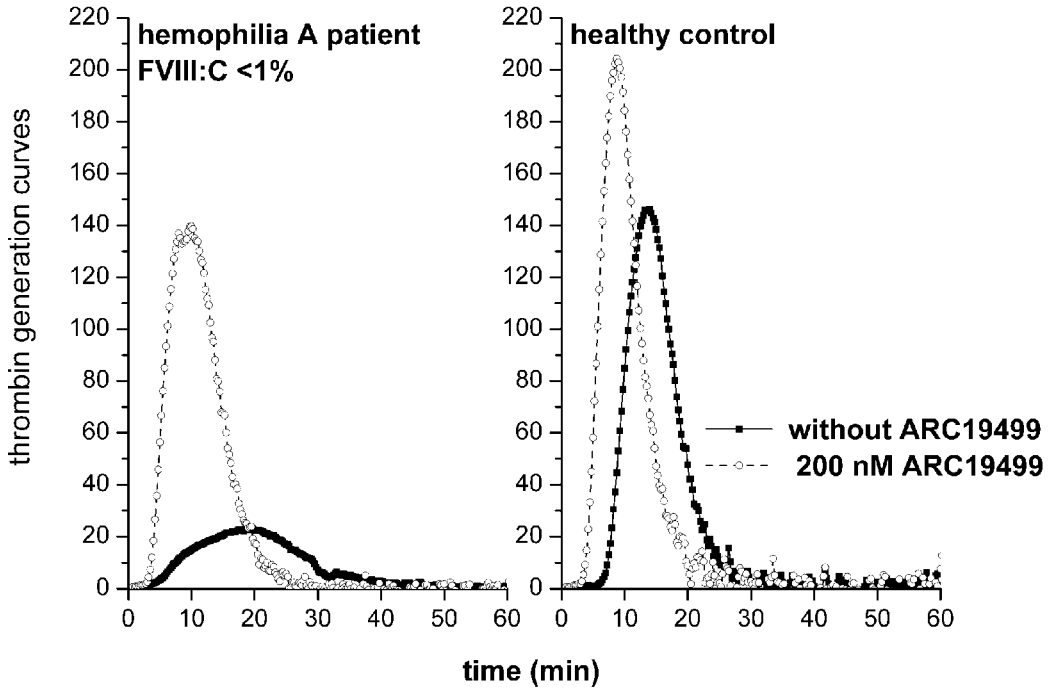

hemophilia A patient
FVIII:C <1%
healthy control
thrombin generation curves
time (min)
without ARC19499
200 nM ARC19499
0
20
40
60
80
100
120
140
160
180
200
220
0
10
20
30
40
50
60

Figure 89

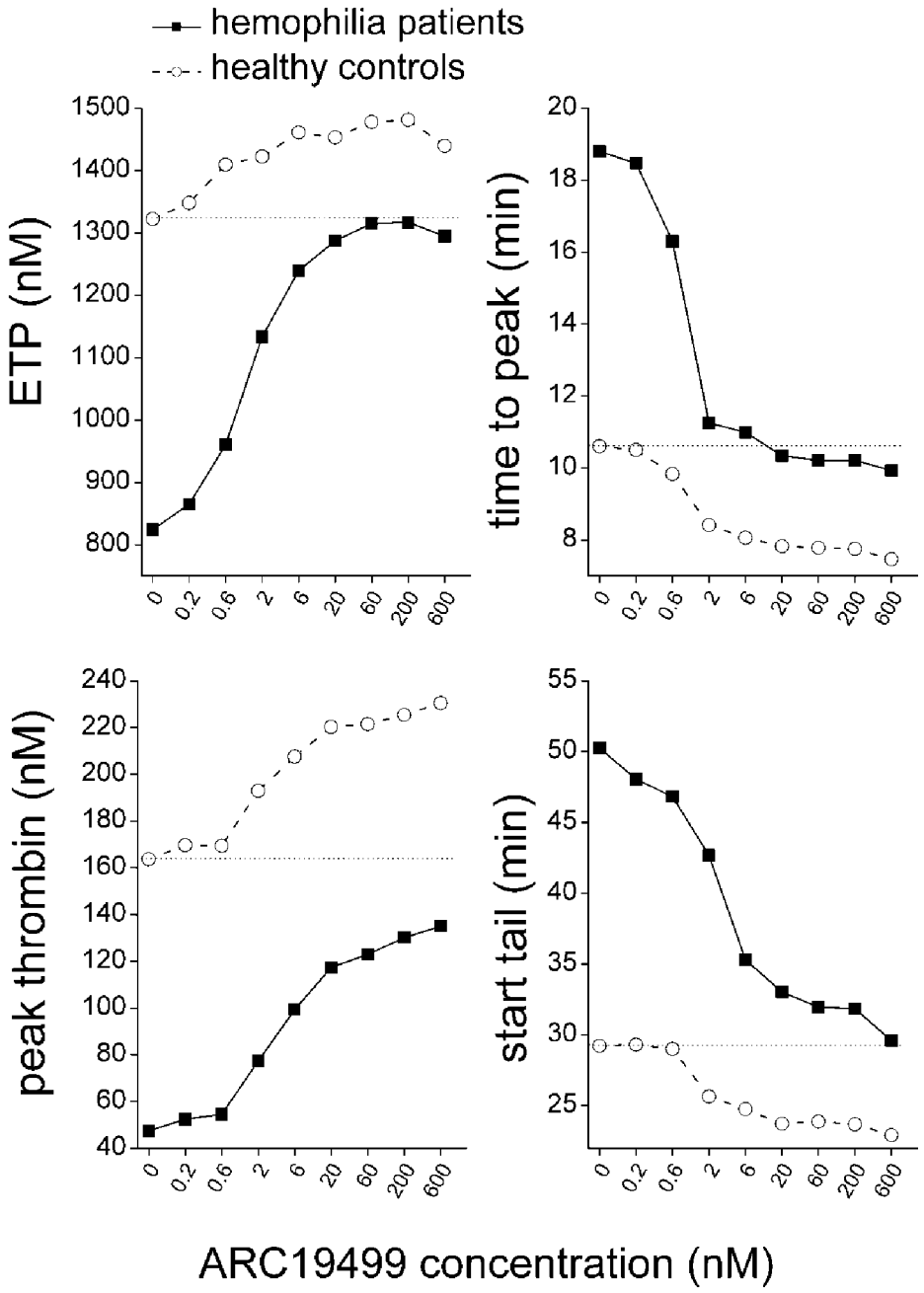

hemophilia patients
healthy controls
ETP (nM)
time to peak (min)
peak thrombin (nM)
start tail (min)
ARC19499 concentration (nM)
0
0.2
0.6
2
6
20
60
200
600

Figure 90

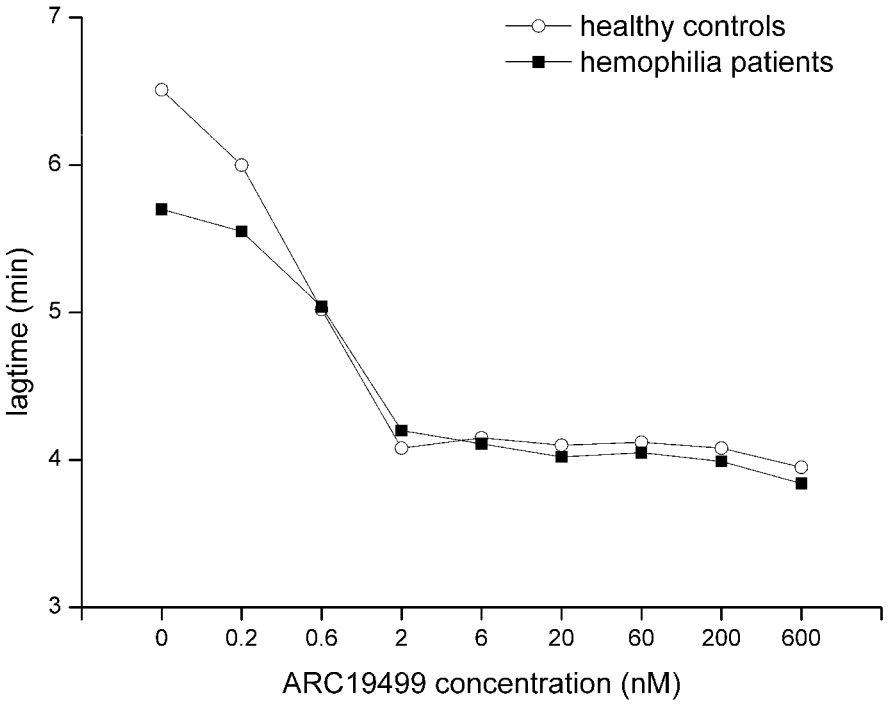

healthy controls
hemophilia patients
lagtime (min)
7
6
5
4
3
0
0.2
0.6
2
6
20
60
200
600
ARC19499 concentration (nM)

Figure 91

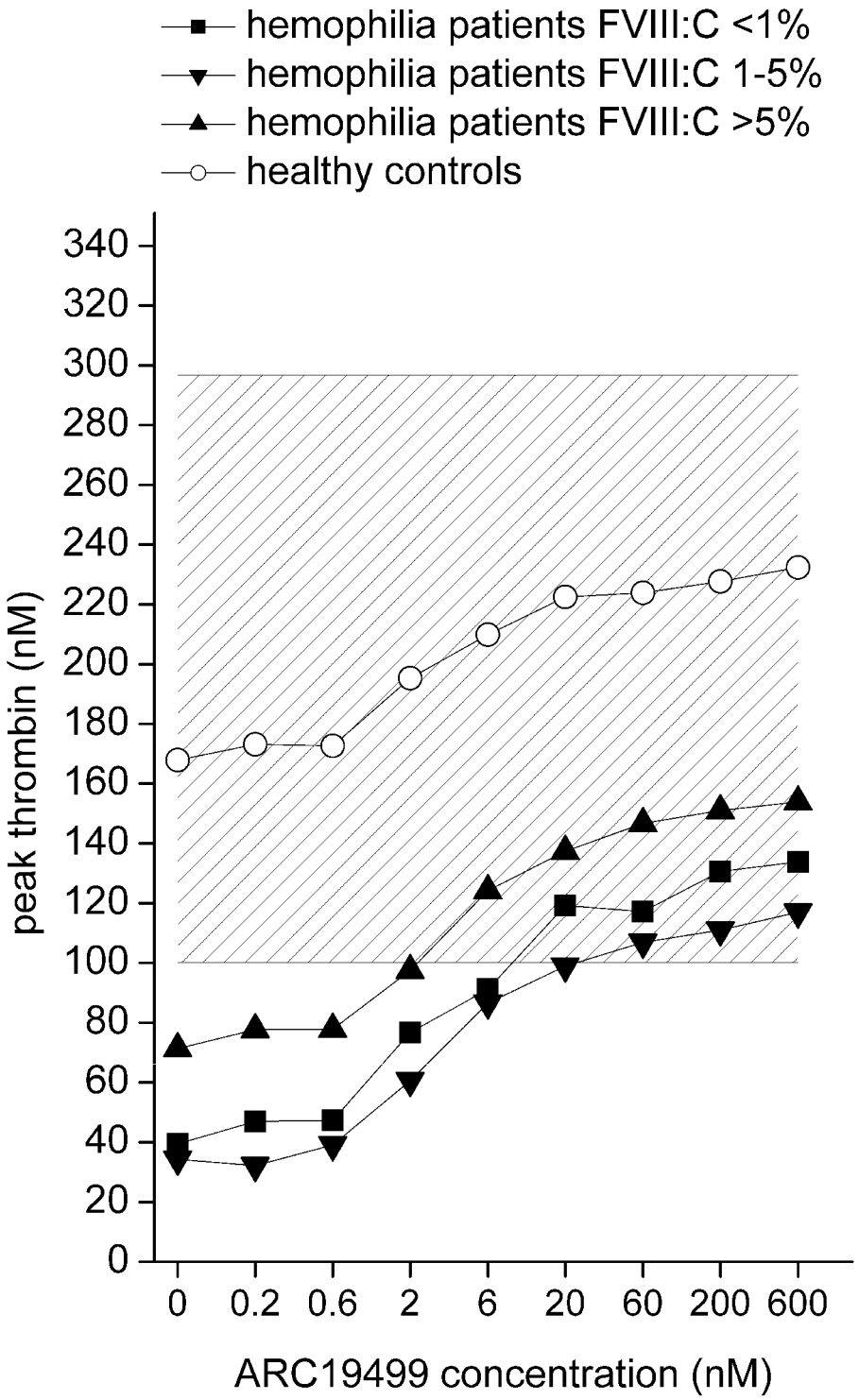

hemophilia patients FVIII:C <1%
hemophilia patients FVIII:C 1-5%
hemophilia patients FVIII:C >5%
healthy controls
peak thrombin (nM)
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
0
0.2
0.6
2
6
20
60
200
600
ARC19499 concentration (nM)

Figure 92

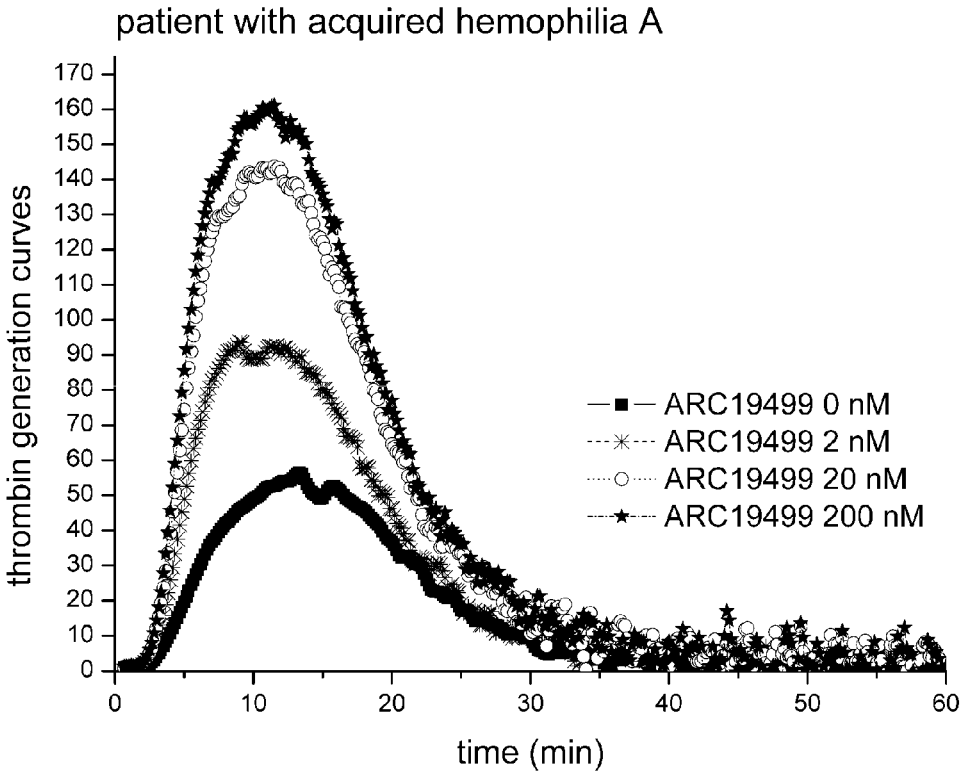

patient with acquired hemophilia A
thrombin generation curves
time (min)
ARC19499 0 nM
ARC19499 2 nM
ARC19499 20 nM
ARC19499 200 nM
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

Figure 93

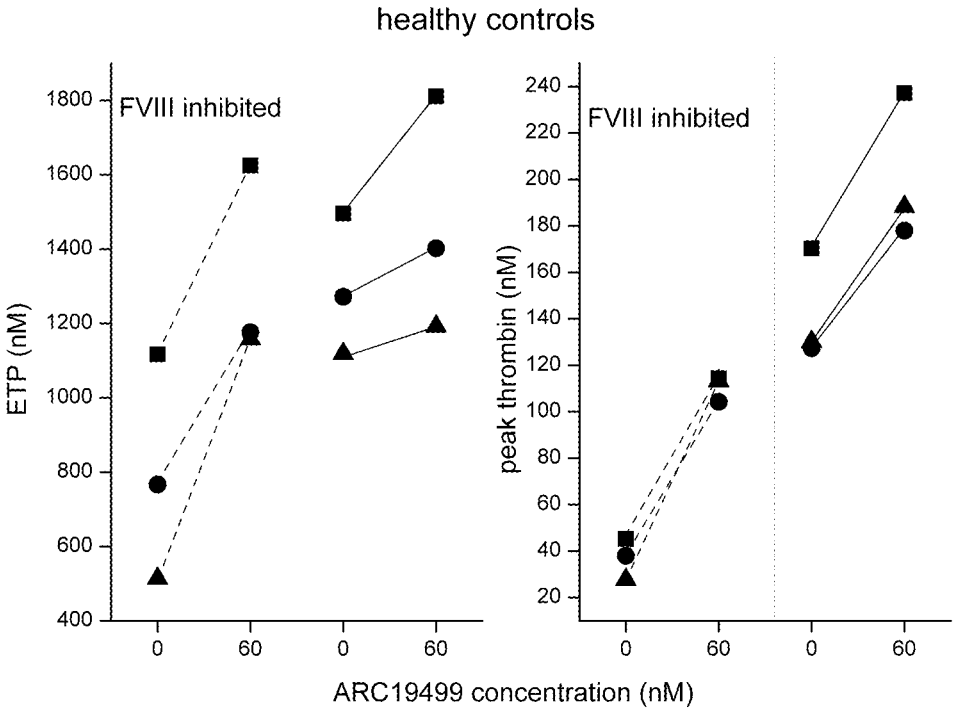
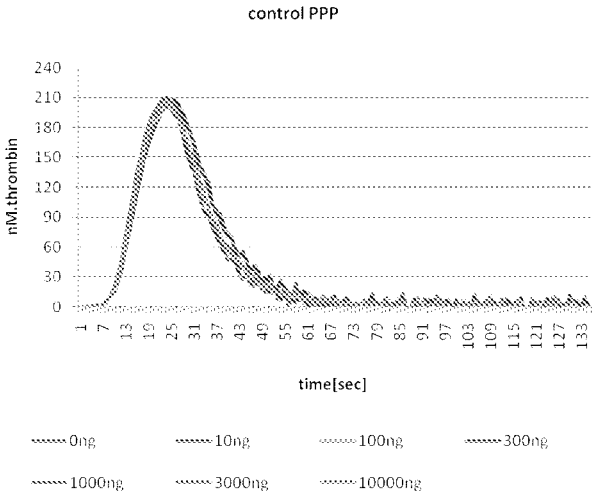
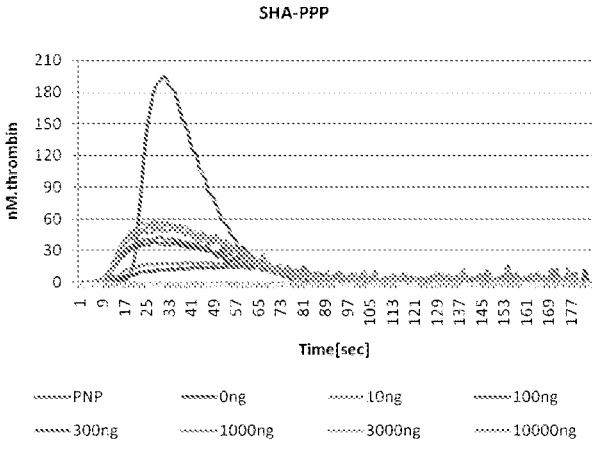

healthy controls
FVIII inhibited
FVIII inhibited
ETP (nM)
peak thrombin (nM)
1800
1600
1400
1200
1000
800
600
400
240
220
200
180
160
140
120
100
80
60
40
20
0
60
0
60
0
60
0
60
ARC19499 concentration (nM)

Figure 94



human conc ng/ml	ETP(nM thrombin.min) (1.41-2174	Peak(nM thrombin) 178-256
	1607.5	193.50
10000	1500.5	202.10
3000	1537.5	206.02
1000	1521.5	208.69
300	1448.5	203.53
100	1497.5	207.64
10	1640.0	208.28
0	1601.5	203.57

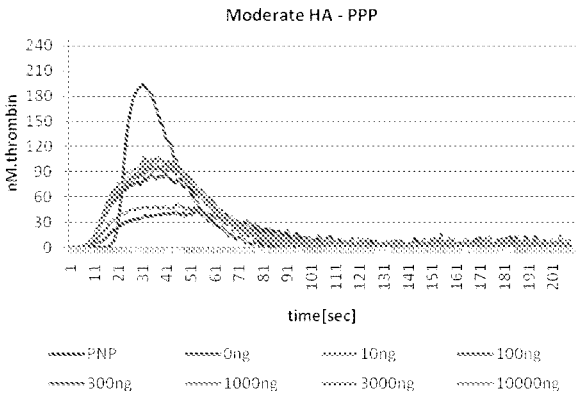
Figure 95



FVIII C 10.3 n/dl

human conc ng/ml	ETP(nM thrombin.min) (1.41-2174	Peak(nM thrombin) 178-256
	1607.5	193.50
10000	818.5	56.60
3000	815.0	53.69
1000	799.0	49.46
300	631.0	41.08
100	570.0	36.33
10	356.5	17.94
0	300.5	14.25

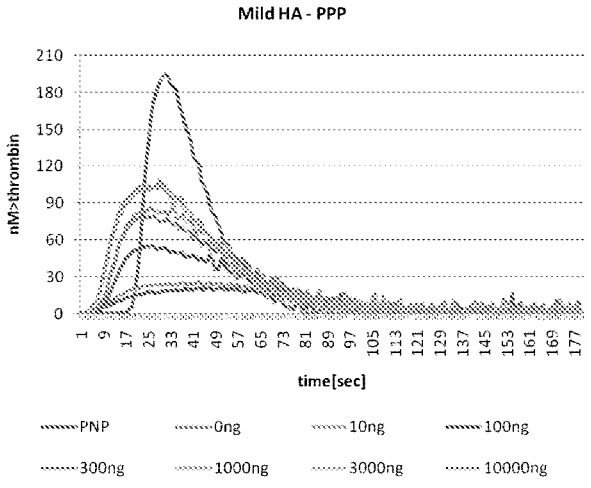
Figure 96



FVIII conc ng/ml	ETP(nM thrombin.min) 1541-2173	Peak(nM thrombin) 170-288
	1607.5	193.50
10000	1531.0	105.60
3000	1520.0	103.29
1000	1495.0	96.64
300	1492.5	94.66
100	1369.5	85.21
10	1013.5	48.64
0	954.0	40.62

FVIII:C – 2.9 iu/dL

Figure 97



FVIII conc ng/mL	ETP(nM thrombin.min) 1541-2173	Peak(nM th rombin) 170-288
	1607.5	193.50
10000	1648.0	84.02
3000	1427.0	81.26
1000	1396.0	73.46
300	1136.0	66.43
100	1052.0	49.53
10	692.8	30.04
0	457.5	19.22

FVIII: C – 16.4 iu/dL

Figure 98

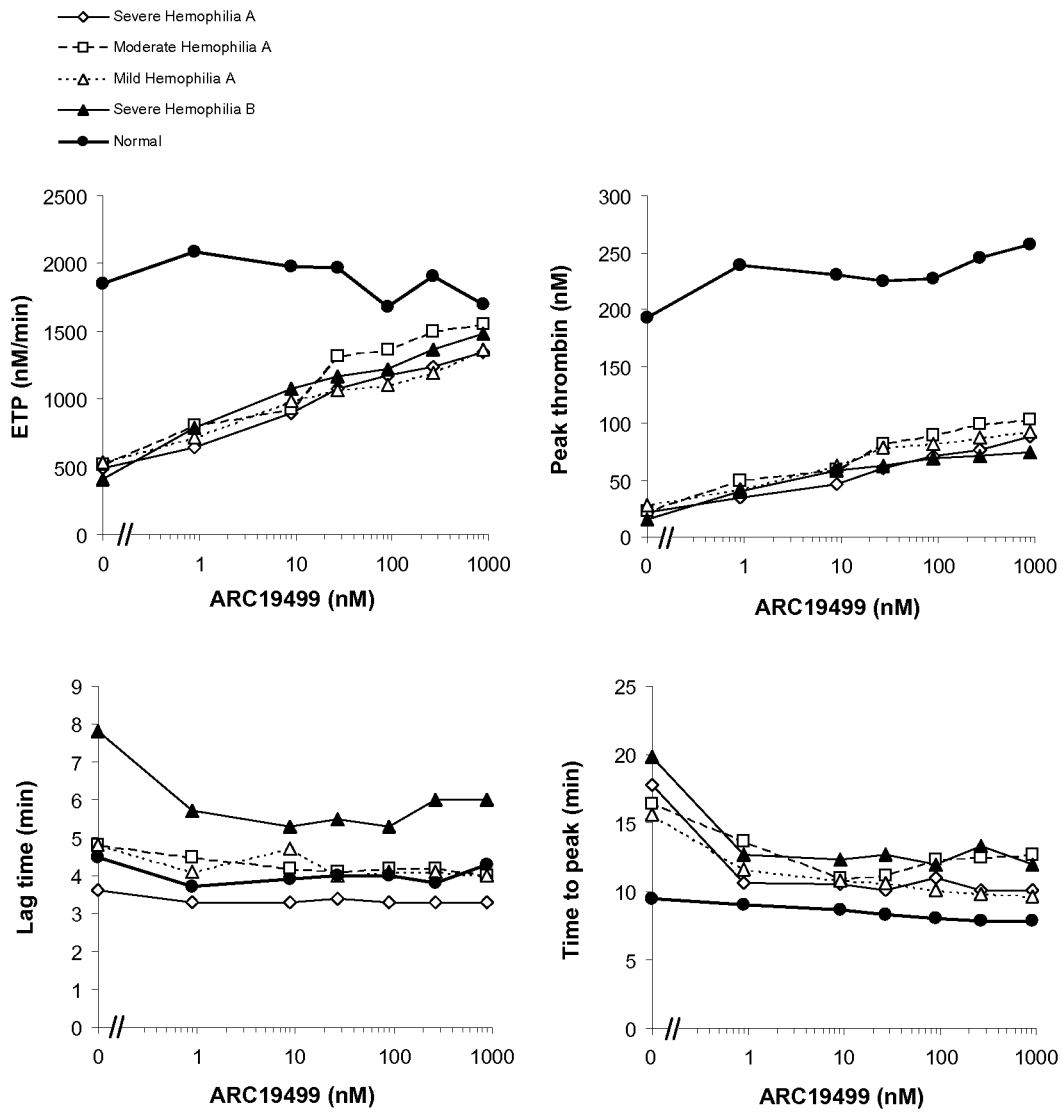

Severe Hemophilia A
Moderate Hemophilia A
Mild Hemophilia A
Severe Hemophilia B
Normal
ETP (nM/min)
ARC19499 (nM)
Peak thrombin (nM)
ARC19499 (nM)
Lag time (min)
ARC19499 (nM)
Time to peak (min)
ARC19499 (nM)

Figure 99

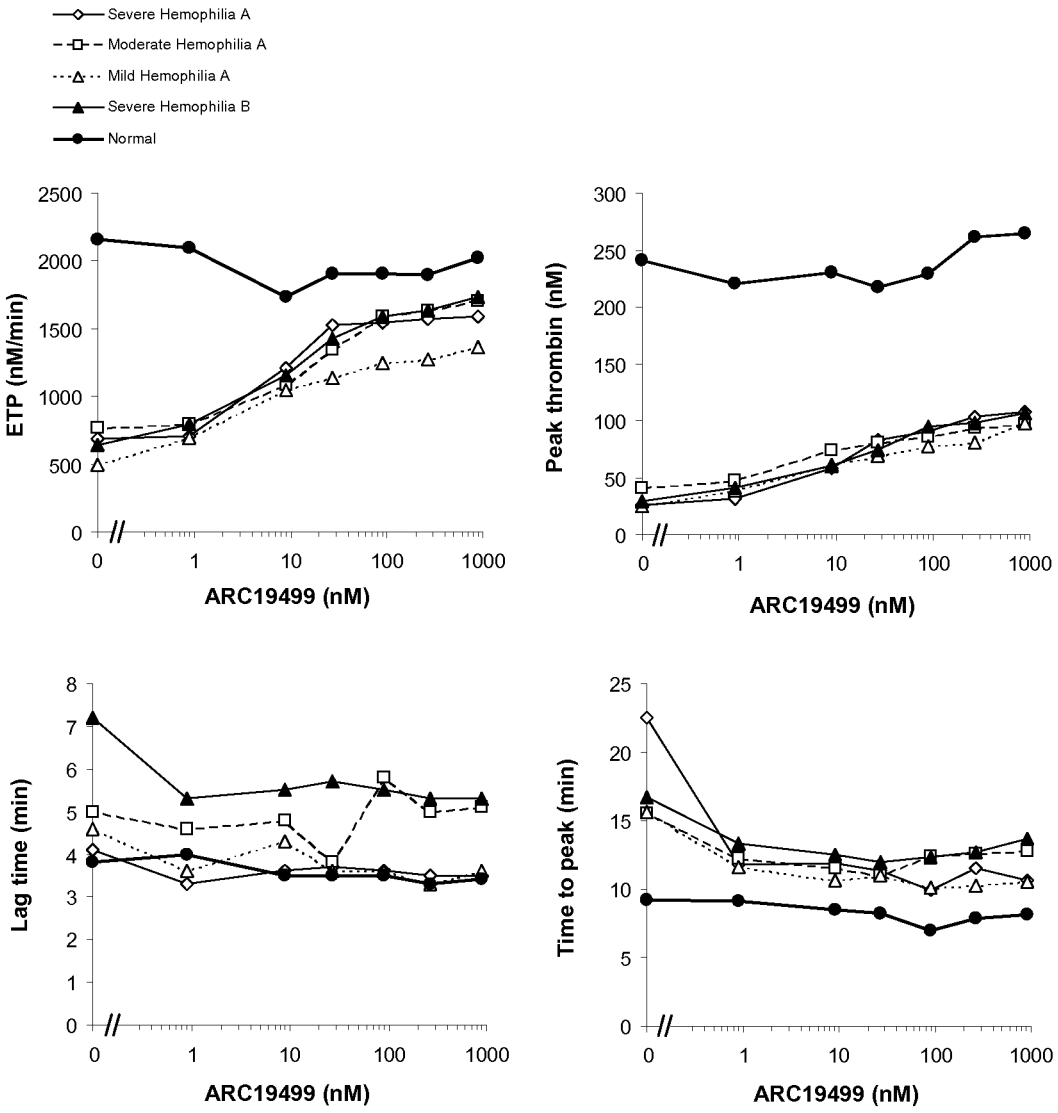
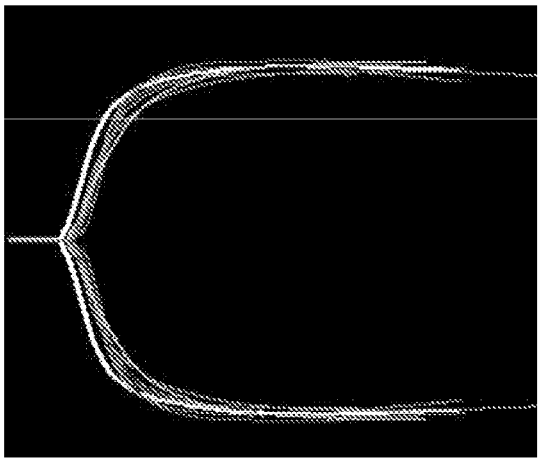

Severe Hemophilia A
Moderate Hemophilia A
Mild Hemophilia A
Severe Hemophilia B
Normal
ETP (nM/min)
ARC19499 (nM)
Peak thrombin (nM)
ARC19499 (nM)
Lag time (min)
ARC19499 (nM)
Time to peak (min)
ARC19499 (nM)

Figure 100

ARC HV 01

TEG - WB

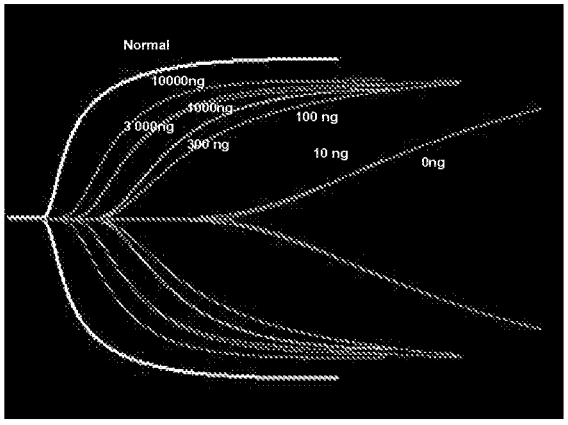


Factor Conc. iu/mL	R time(min) 5.4-11.2	K(min) 1.7-4.6	Angle(deg) 46.3 - 67.8
	8.9	2.4	55.0
10000	9.3	2.6	61.4
3000	8.3	2.3	61.7
1000	8.5	2.8	57.9
300	8.4	2.7	61.9
100	7.1	2.4	64.4
10	7.9	3.3	56.2
0	8.7	2.4	63.7

Figure 101

ARC SHA 02

TEG - WB



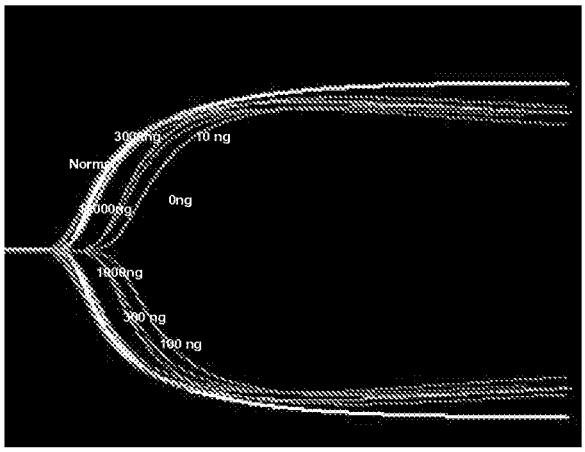
Factor Conc. iu/mL	R time(min) 5.4-11.2	K(min) 1.7-4.6	Angle(deg) 46.3 - 67.8
	8.9	2.4	55.0
10000	11.3	6.3	34.1
3000	16.7	7.4	30.5
1000	16.5	7.4	30.5
300	21.6	9.4	24.7
100	22.7	12.0	18.8
10	50.5	26.3	11.2
0	58.3	22.7	10.8

FVIII:C- 0.3 iu/dL

Figure 102

ARC MoHA 01

TFC - PVB



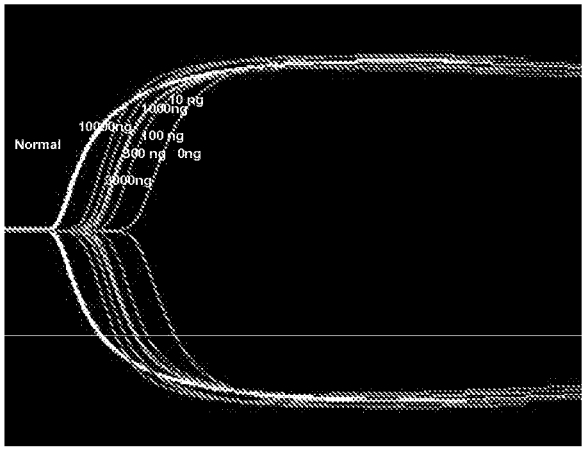
Inhib conc ug/mL	T thrombin (s) (95 % CI)	Ximelagatran (95 % CI)	Argatroban (95 % CI)
	8.9	2.4	55.0
10000	7.3	3.5	52.0
3000	6.8	3.9	50.2
1000	8.1	3.9	51.1
300	8.1	3.9	48.0
100	11.3	4.0	49.5
10	11.3	4.5	47.0
0	13.2	4.4	39.4

FVIII:C – 2.9 iu/dL

Figure 103

ARC MiHA 01

TFC - PVB



Inhib conc ug/mL	T thrombin (s) (95 % CI)	Ximelagatran (95 % CI)	Argatroban (95 % CI)
	8.9	2.4	55.0
10000	11.8	3.3	54.5
3000	12.8	3.4	52.6
1000	13.4	3.4	50.2
300	14.0	3.4	48.3
100	14.7	3.5	34.5
10	15.8	3.6	30.0
0	19.8	3.7	30.7

FVIII:C – 8.8 iu/dL

Figure 104

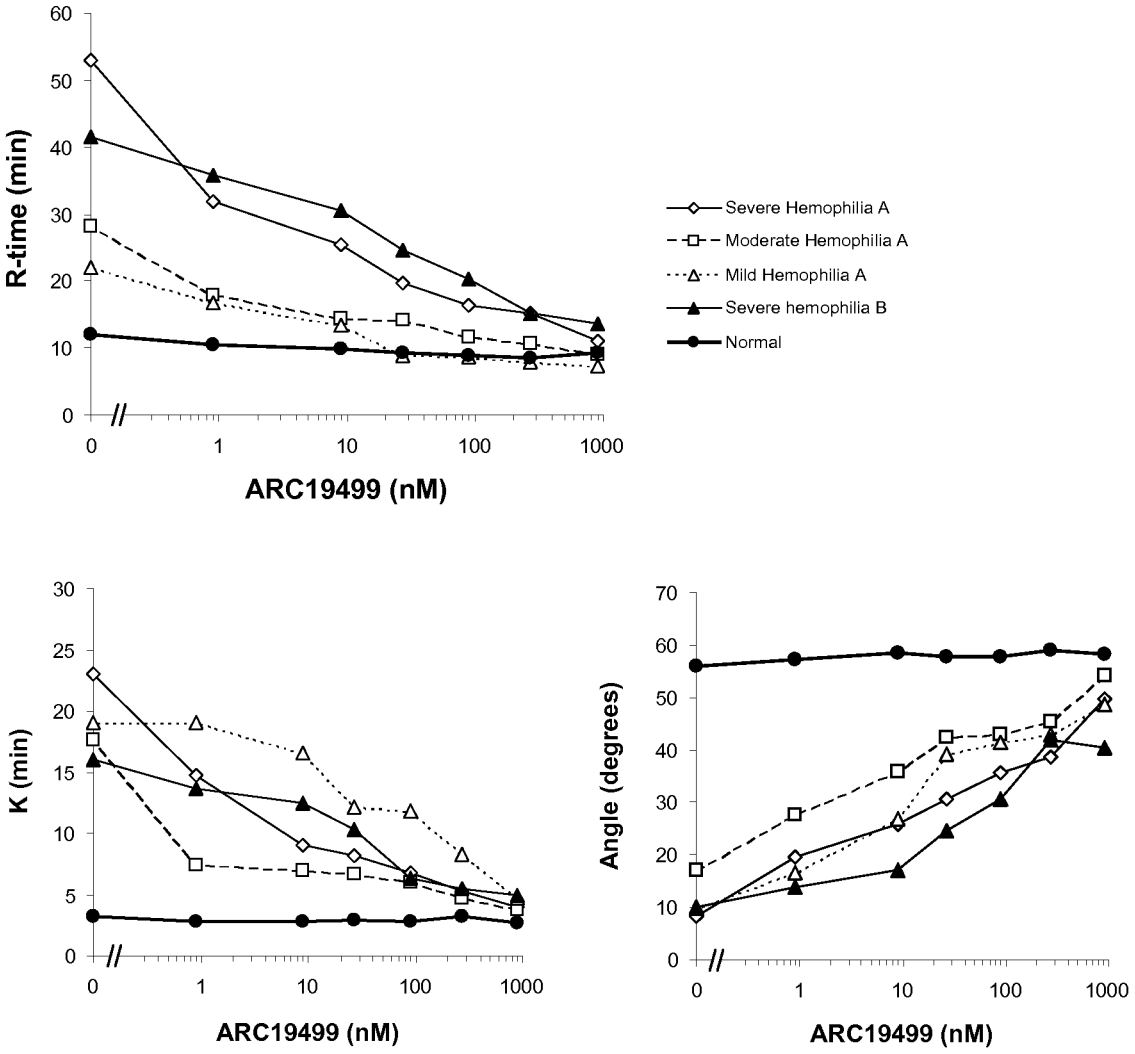
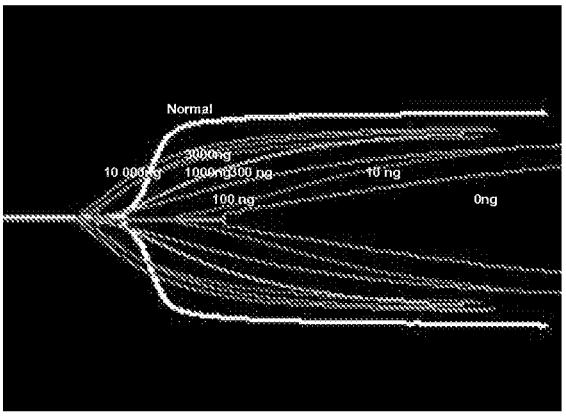

R-time (min)
ARC19499 (nM)
Severe Hemophilia A
Moderate Hemophilia A
Mild Hemophilia A
Severe hemophilia B
Normal
K (min)
ARC19499 (nM)
Angle (degrees)
ARC19499 (nM)

Figure 105

ARC SHA 02

TEG - PPP



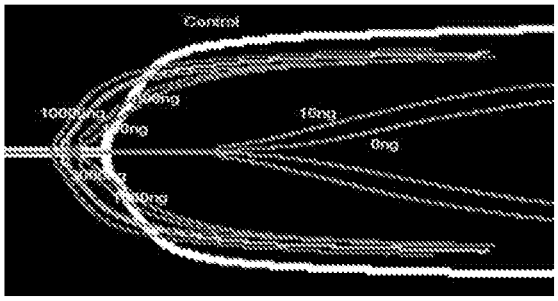
rFVIIFC (IU/mL)	R (minutes)	Alpha (°)	Angle (mm)
	14.8	4.6	49.4
10000	9.6	12.9	38.8
3000	10.7	14.9	29.0
1000	11.4	18.0	25.0
300	14.2	21.0	14.4
100	14.6	21.0	14.2
10	23.6	22.0	9.9
0	26.7	23.0	8.2

FVIIFC = 0.2

Figure 106

ARC MoHA 01

TEG - PPP



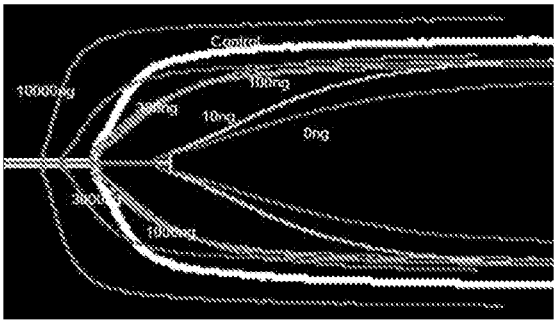
rFVIIFC (IU/mL)	R (minutes)	Alpha (°)	Angle (mm)
	14.8	4.6	49.4
10000	12.8	13.2	21.9
3000	13.7	14.5	20.9
1000	10.6	20.1	18.3
300	12.8	21.3	16.4
100	15.6	22.5	15.2
10	16.5	25.3	10.2
0	25.2	30.1	4.2

FVIIFC = 2.9

Figure 107

ARC MiHA 03

TEG - HPP



rFVIIIFC (ng/ml)	R (minutes) 2.3 - 8.2	Kinetics 1.7 - 4.6	Angle (deg) 52.6 - 72.5
	14.8	4.6	49.4
10000	3.8	2.1	69.7
3000	5.5	10.9	49.7
1000	8.0	12.1	46.3
300	7.7	15.0	39.4
100	13.3	15.6	38.2
10	13.6	19.0	16.9
0	35.8	22.0	10.2

rFVIIIFC - 16.4

Figure 108

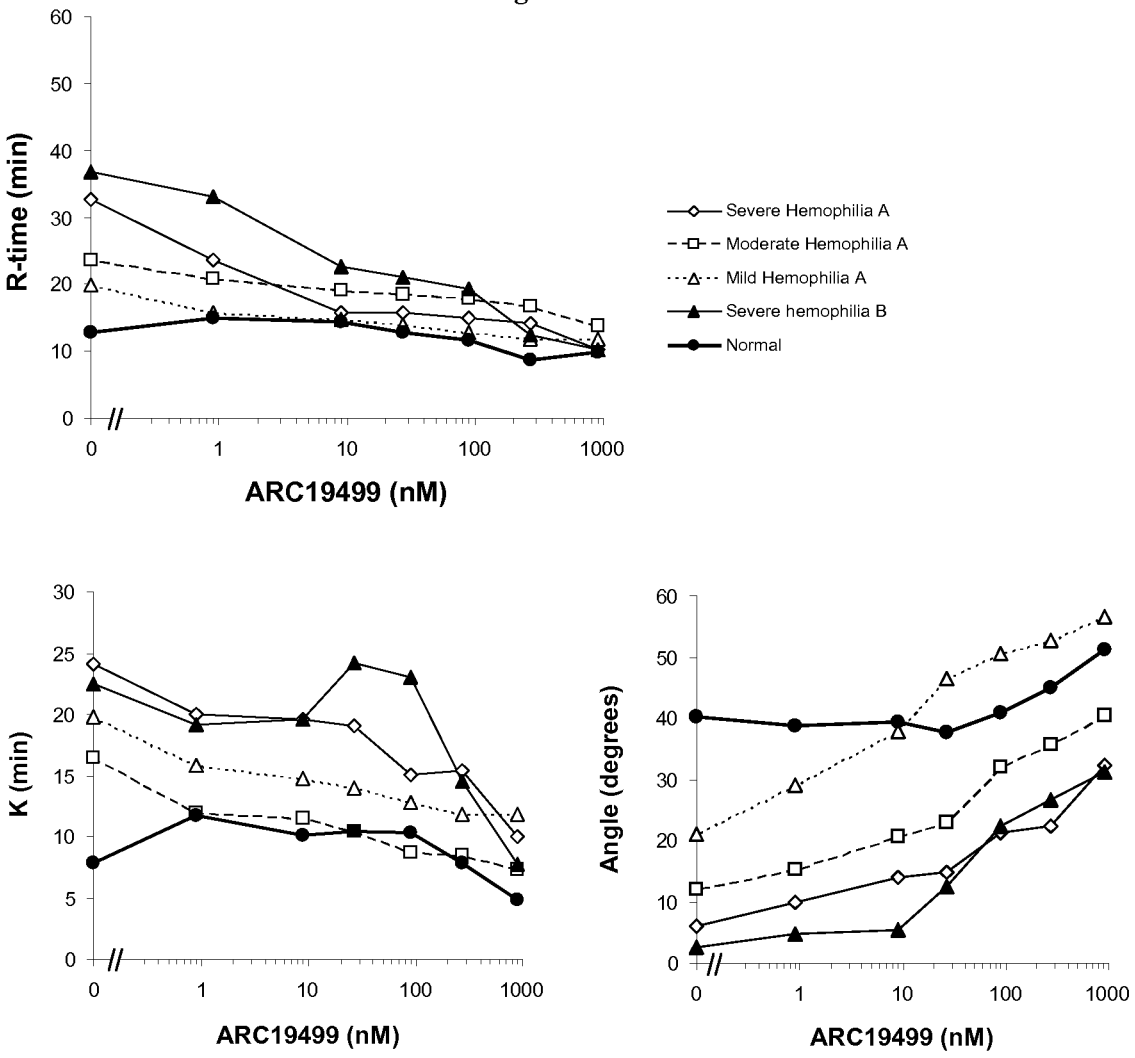

R-time (min)
60
50
40
30
20
10
0
0
1
10
100
1000
ARC19499 (nM)
Severe Hemophilia A
Moderate Hemophilia A
Mild Hemophilia A
Severe hemophilia B
Normal
K (min)
30
25
20
15
10
5
0
0
1
10
100
1000
ARC19499 (nM)
Angle (degrees)
60
50
40
30
20
10
0
0
1
10
100
1000
ARC19499 (nM)

Figure 109

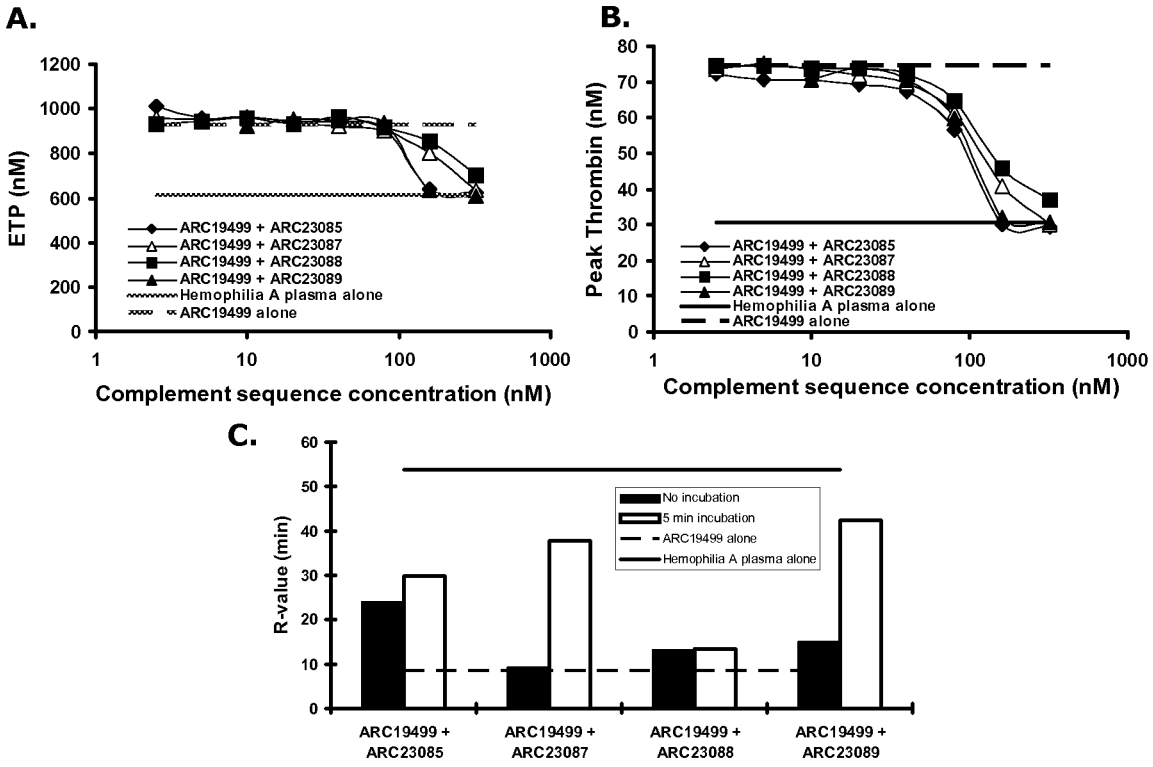

A.
ETP (nM)
1200
1000
800
600
400
200
0
1
10
100
1000
Complement sequence concentration (nM)
ARC19499 + ARC23085
ARC19499 + ARC23087
ARC19499 + ARC23088
ARC19499 + ARC23089
Hemophilia A plasma alone
ARC19499 alone
B.
Peak Thrombin (nM)
80
70
60
50
40
30
20
10
0
1
10
100
1000
Complement sequence concentration (nM)
ARC19499 + ARC23085
ARC19499 + ARC23087
ARC19499 + ARC23088
ARC19499 + ARC23089
Hemophilia A plasma alone
ARC19499 alone
C.
R-value (min)
60
50
40
30
20
10
0
No incubation
5 min incubation
ARC19499 alone
Hemophilia A plasma alone
ARC19499 + ARC23085
ARC19499 + ARC23087
ARC19499 + ARC23088
ARC19499 + ARC23089

Figure 110

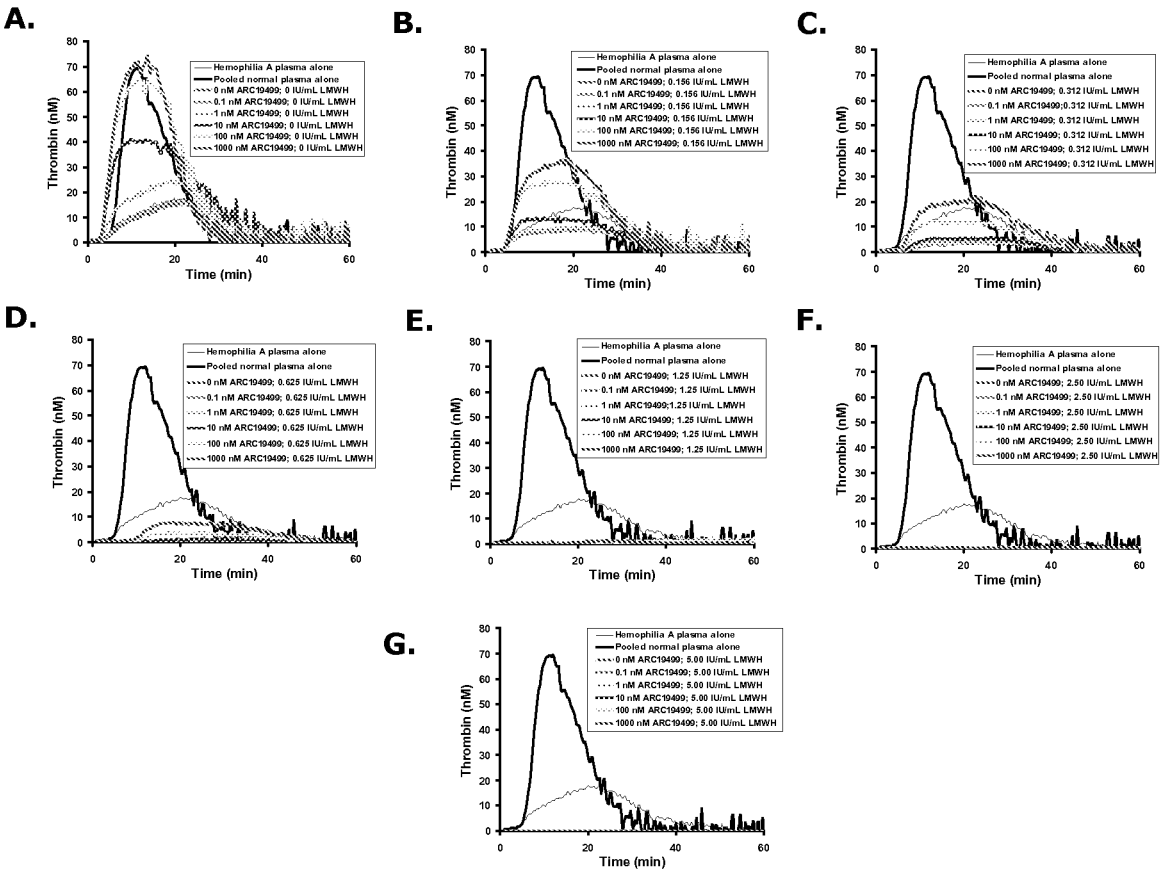

A.
Thrombin (nM)
Time (min)
Hemophilia A plasma alone
Pooled normal plasma alone
0 nM ARC19499; 0 IU/mL LMWH
0.1 nM ARC19499; 0 IU/mL LMWH
1 nM ARC19499; 0 IU/mL LMWH
10 nM ARC19499; 0 IU/mL LMWH
100 nM ARC19499; 0 IU/mL LMWH
1000 nM ARC19499; 0 IU/mL LMWH
B.
Thrombin (nM)
Time (min)
Hemophilia A plasma alone
Pooled normal plasma alone
0 nM ARC19499; 0.156 IU/mL LMWH
0.1 nM ARC19499; 0.156 IU/mL LMWH
1 nM ARC19499; 0.156 IU/mL LMWH
10 nM ARC19499; 0.156 IU/mL LMWH
100 nM ARC19499; 0.156 IU/mL LMWH
1000 nM ARC19499; 0.156 IU/mL LMWH
C.
Thrombin (nM)
Time (min)
Hemophilia A plasma alone
Pooled normal plasma alone
0 nM ARC19499; 0.312 IU/mL LMWH
0.1 nM ARC19499;0.312 IU/mL LMWH
1 nM ARC19499; 0.312 IU/mL LMWH
10 nM ARC19499; 0.312 IU/mL LMWH
100 nM ARC19499; 0.312 IU/mL LMWH
1000 nM ARC19499; 0.312 IU/mL LMWH
D.
Thrombin (nM)
Time (min)
Hemophilia A plasma alone
Pooled normal plasma alone
0 nM ARC19499; 0.625 IU/mL LMWH
0.1 nM ARC19499; 0.625 IU/mL LMWH
1 nM ARC19499; 0.625 IU/mL LMWH
10 nM ARC19499; 0.625 IU/mL LMWH
100 nM ARC19499; 0.625 IU/mL LMWH
1000 nM ARC19499; 0.625 IU/mL LMWH
E.
Thrombin (nM)
Time (min)
Hemophilia A plasma alone
Pooled normal plasma alone
0 nM ARC19499; 1.25 IU/mL LMWH
0.1 nM ARC19499; 1.25 IU/mL LMWH
1 nM ARC19499;1.25 IU/mL LMWH
10 nM ARC19499; 1.25 IU/mL LMWH
100 nM ARC19499; 1.25 IU/mL LMWH
1000 nM ARC19499; 1.25 IU/mL LMWH
F.
Thrombin (nM)
Time (min)
Hemophilia A plasma alone
Pooled normal plasma alone
0 nM ARC19499; 2.50 IU/mL LMWH
0.1 nM ARC19499; 2.50 IU/mL LMWH
1 nM ARC19499; 2.50 IU/mL LMWH
10 nM ARC19499; 2.50 IU/mL LMWH
100 nM ARC19499; 2.50 IU/mL LMWH
1000 nM ARC19499; 2.50 IU/mL LMWH
G.
Thrombin (nM)
Time (min)
Hemophilia A plasma alone
Pooled normal plasma alone
0 nM ARC19499; 5.00 IU/mL LMWH
0.1 nM ARC19499; 5.00 IU/mL LMWH
1 nM ARC19499; 5.00 IU/mL LMWH
10 nM ARC19499; 5.00 IU/mL LMWH
100 nM ARC19499; 5.00 IU/mL LMWH
1000 nM ARC19499; 5.00 IU/mL LMWH

Figure 111

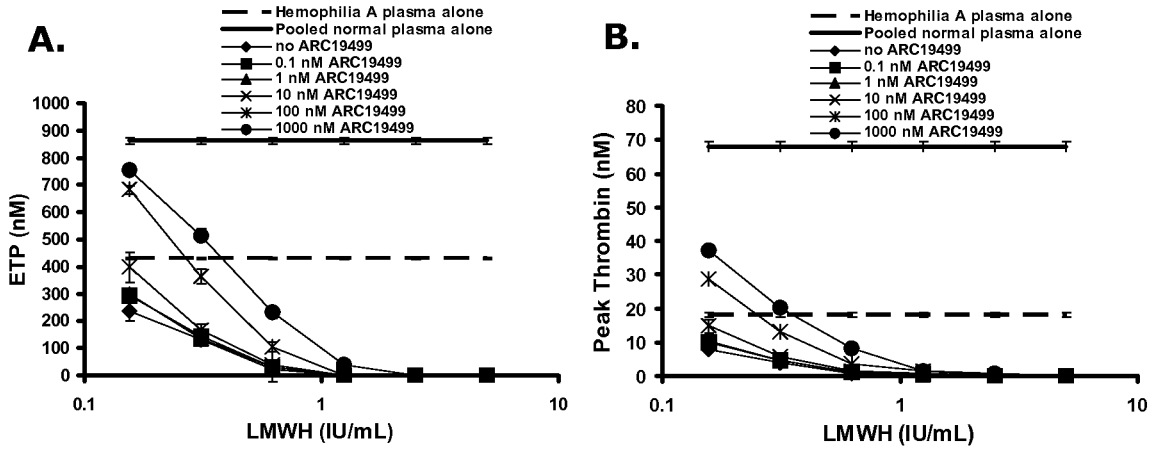
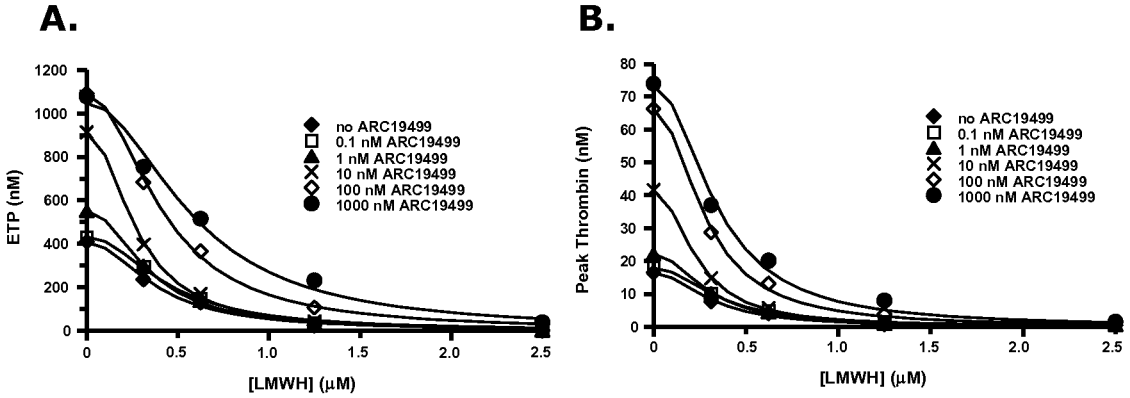


Figure 112



[ARC19499] nM	LMWH IC_{50}			
	ETP		Peak Thrombin	
	IC_{50} (nM)	Std Error	IC_{50} (nM)	Std Error
0	381	24.3	299	18.0
0.1	449	13.3	353	13.6
1.0	345	9.4	290	8.2
10	274	7.7	226	5.9
100	418	16.5	268	5.9
1000	561	36.2	318	10.6

Figure 113

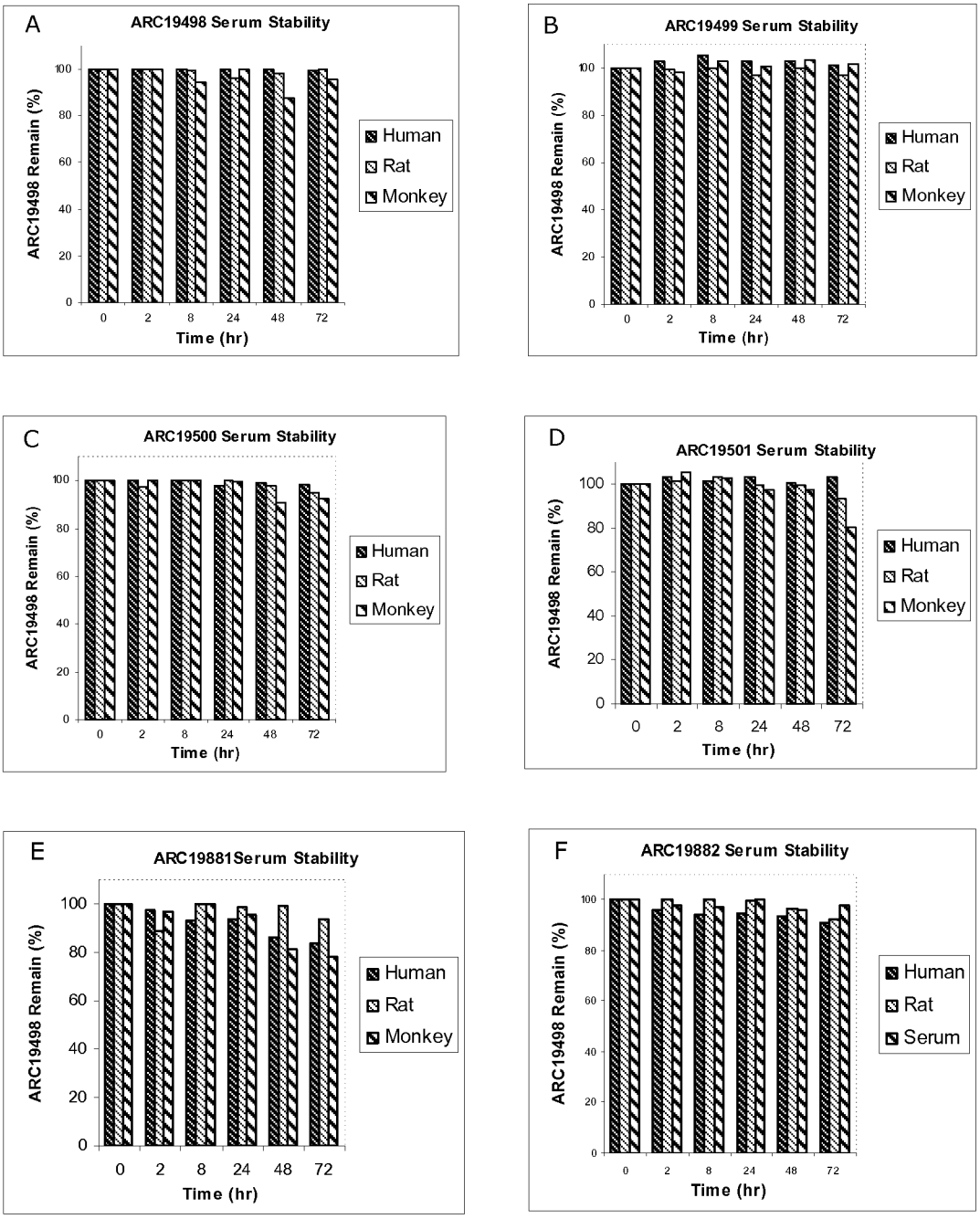

A
ARC19498 Serum Stability
ARC19498 Remain (%)
Time (hr)
Human
Rat
Monkey
B
ARC19499 Serum Stability
ARC19498 Remain (%)
Time (hr)
Human
Rat
Monkey
C
ARC19500 Serum Stability
ARC19498 Remain (%)
Time (hr)
Human
Rat
Monkey
D
ARC19501 Serum Stability
ARC19498 Remain (%)
Time (hr)
Human
Rat
Monkey
E
ARC19881Serum Stability
ARC19498 Remain (%)
Time (hr)
Human
Rat
Monkey
F
ARC19882 Serum Stability
ARC19498 Remain (%)
Time (hr)
Human
Rat
Serum

Figure 114

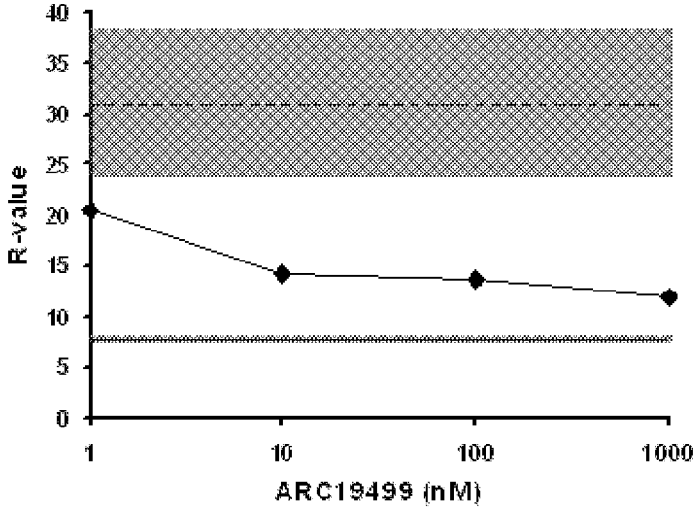


Figure 115

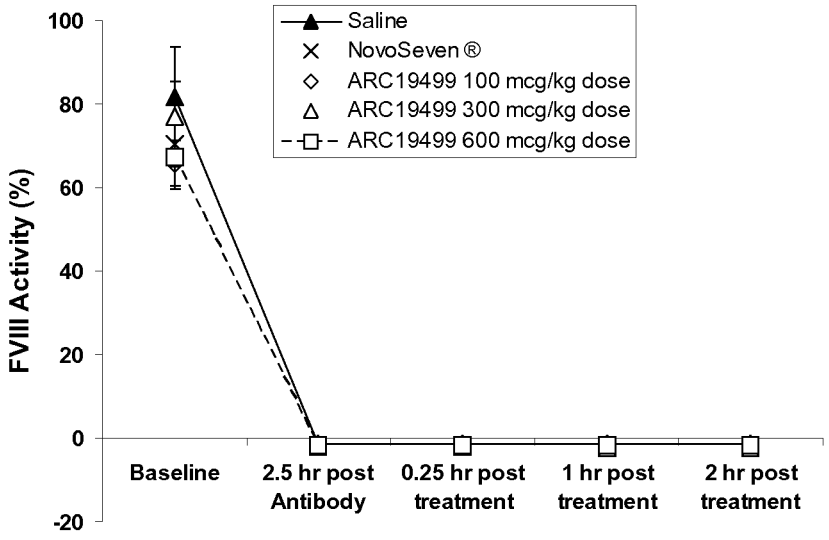


Figure 116

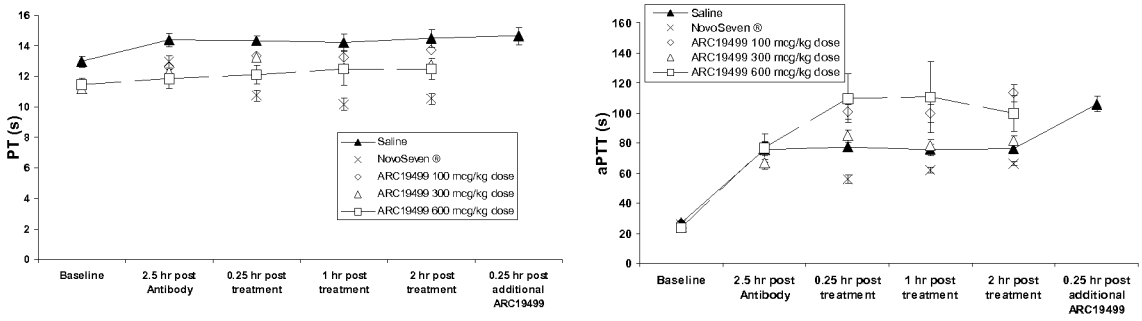


Figure 117

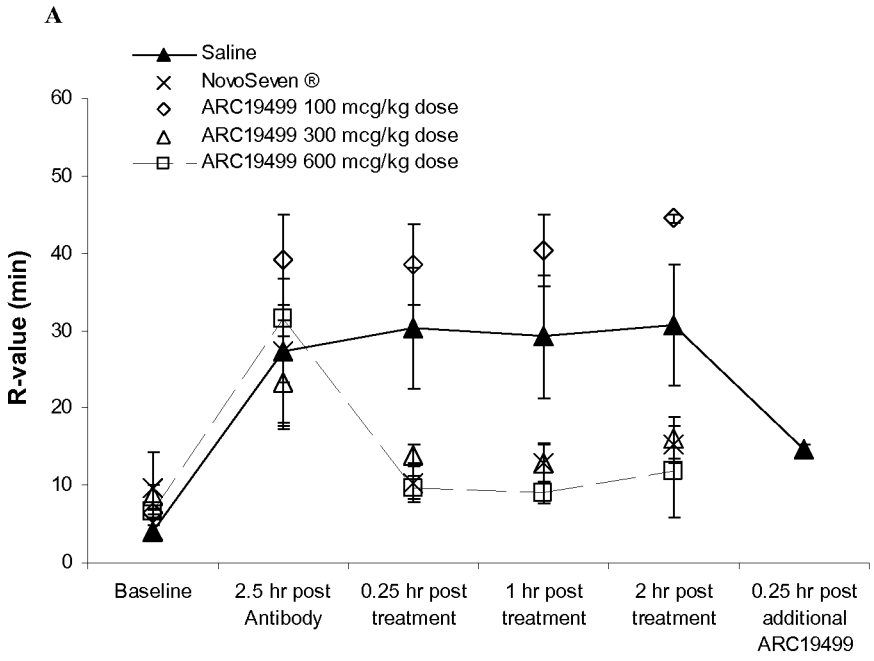
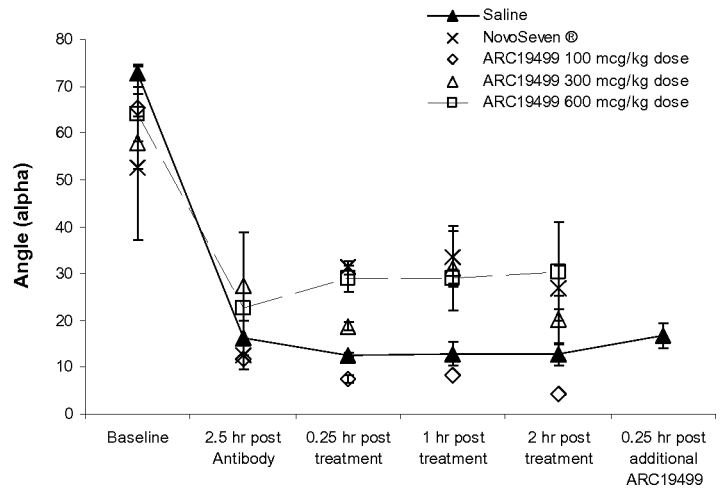


Figure 117 cont.

B



C

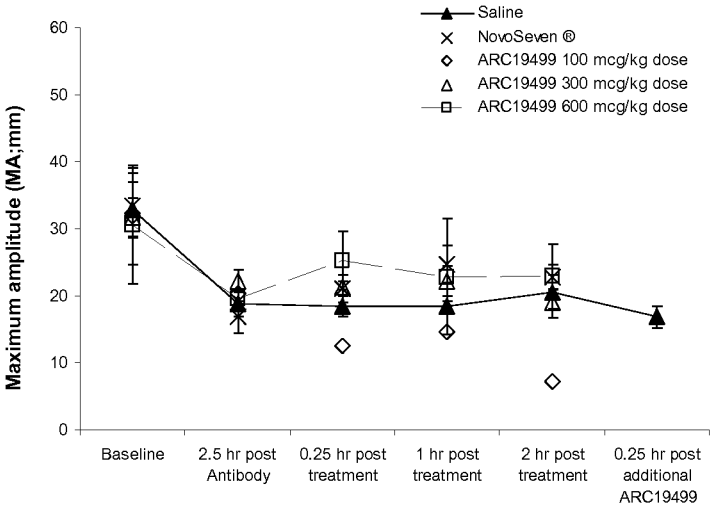


Figure 118

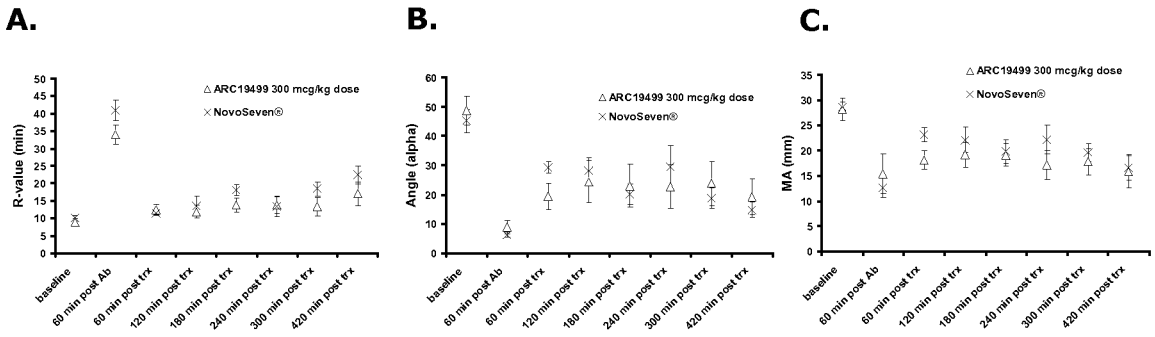


Figure 119

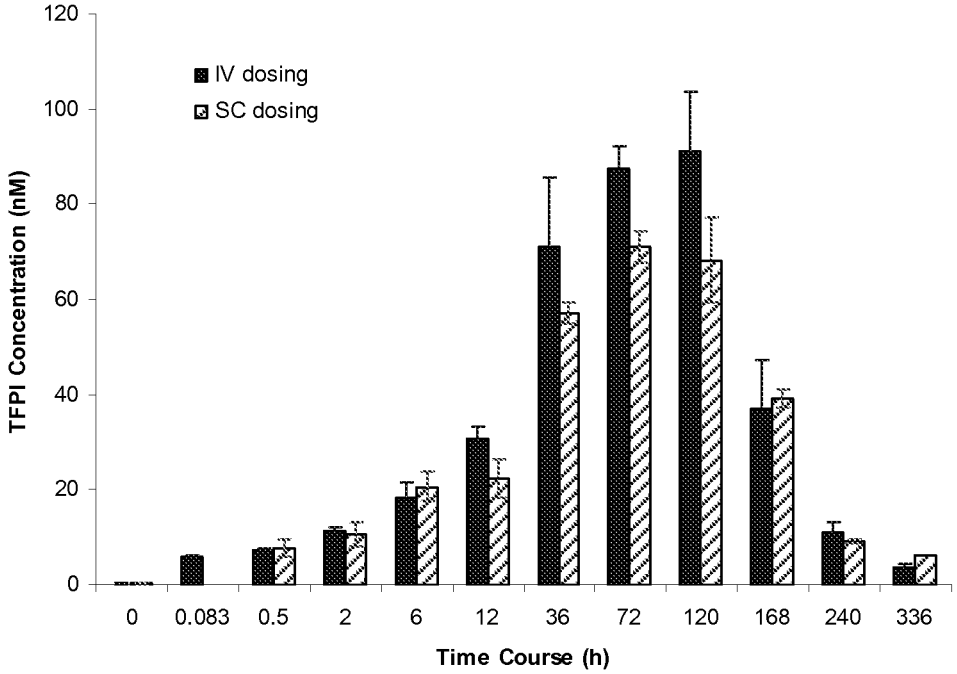
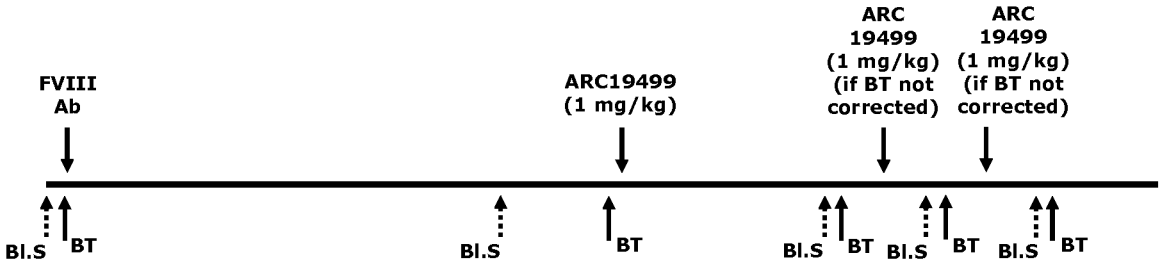


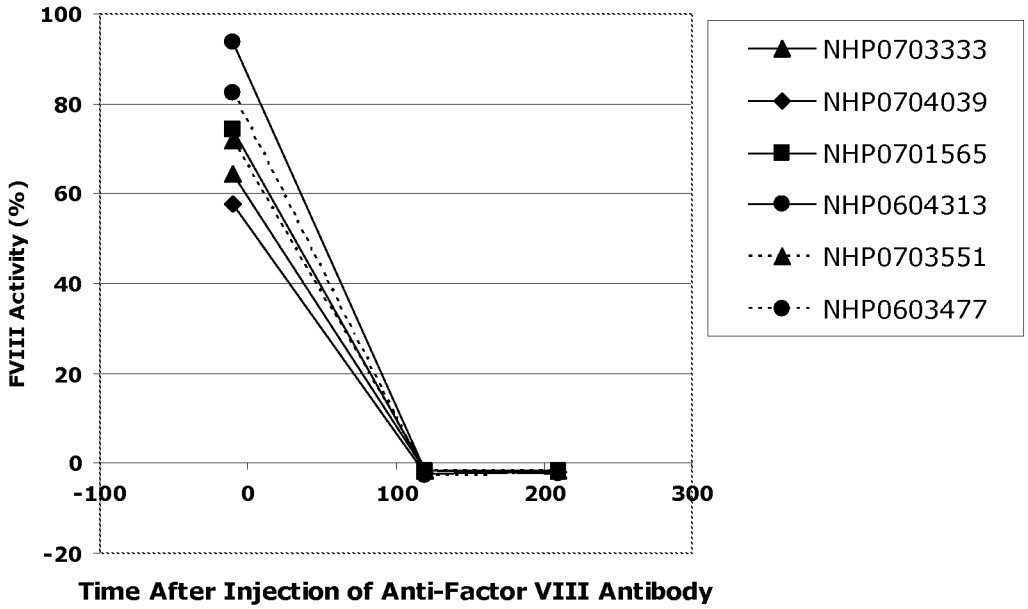
Figure 120



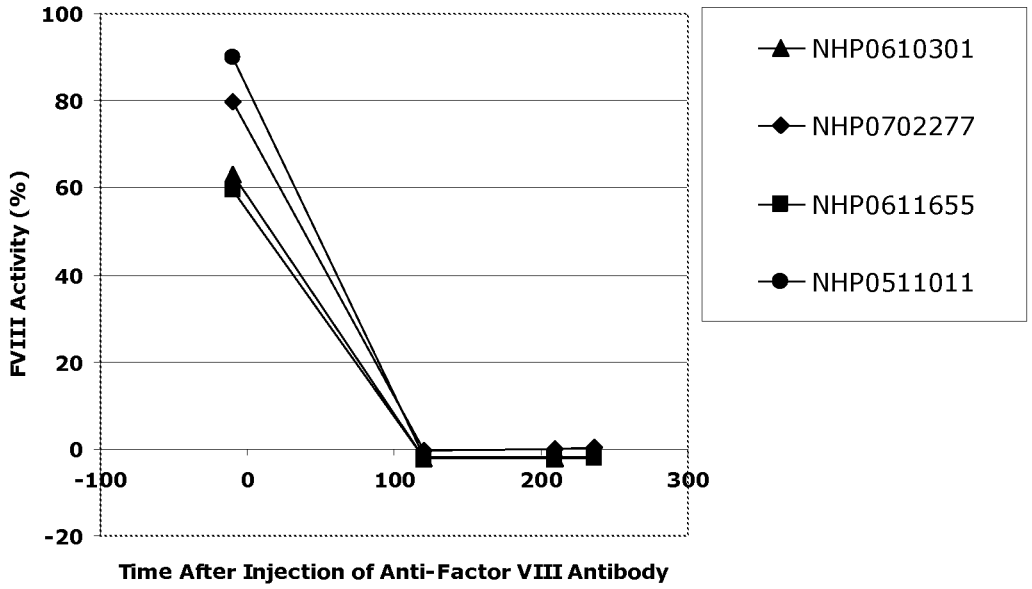
Bl.S Blood sampling
BT Bleeding time
FVIII Ab IV administration of anti-Factor VIII antibody
ARC19499 IV administration of 1 mg/kg ARC19499

Figure 121

A

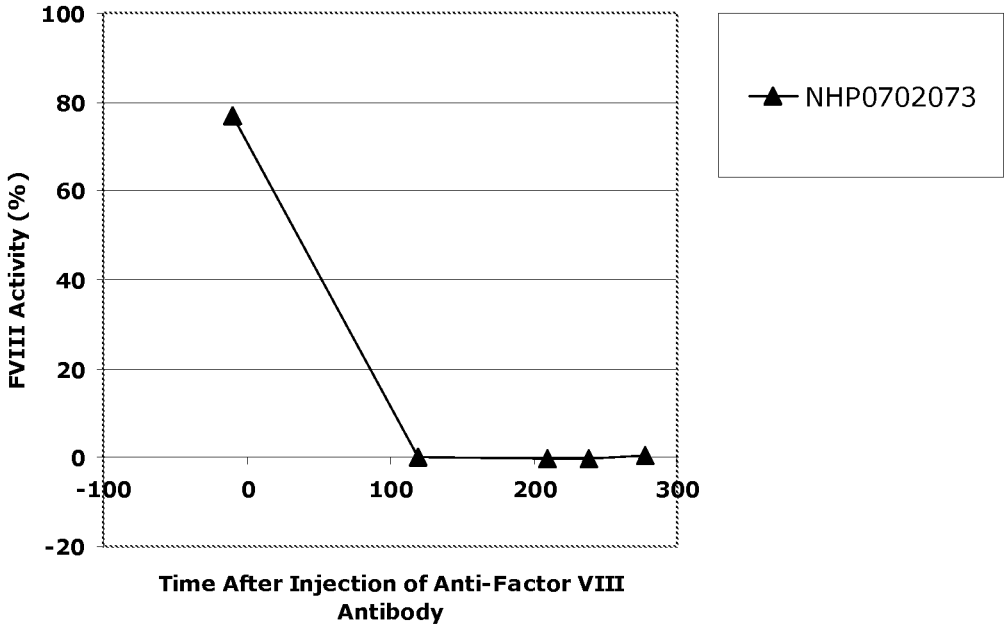


B



C

Figure 121 cont.



D

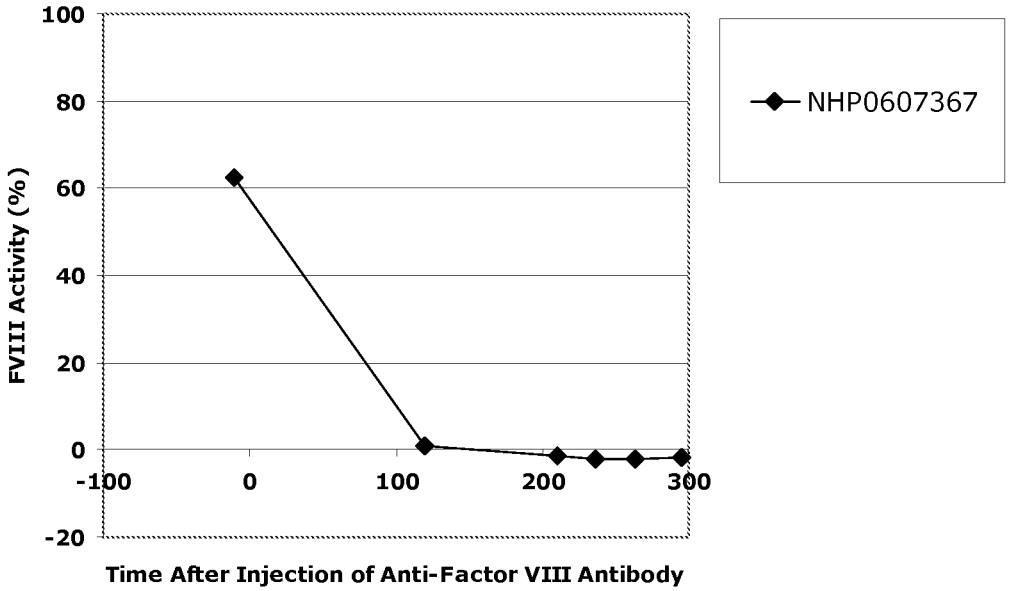
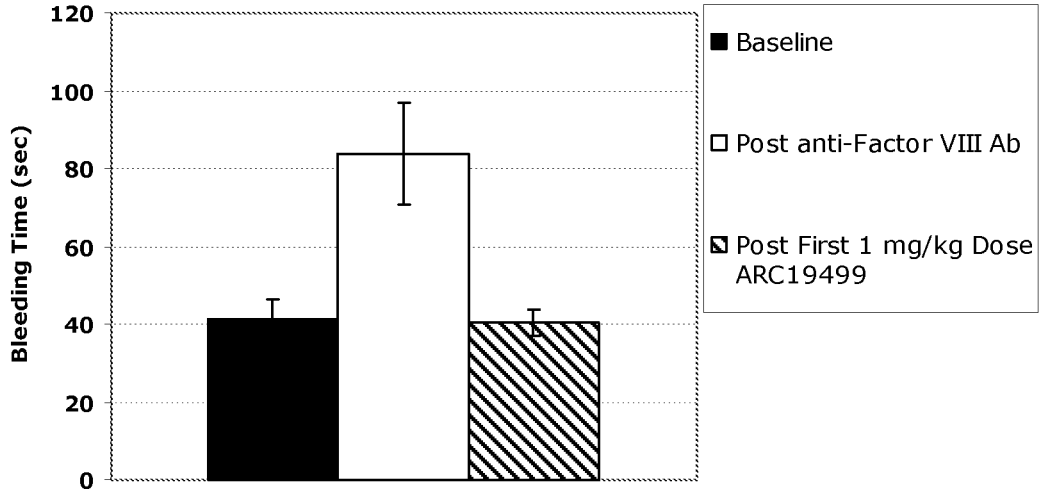


Figure 122

A



B

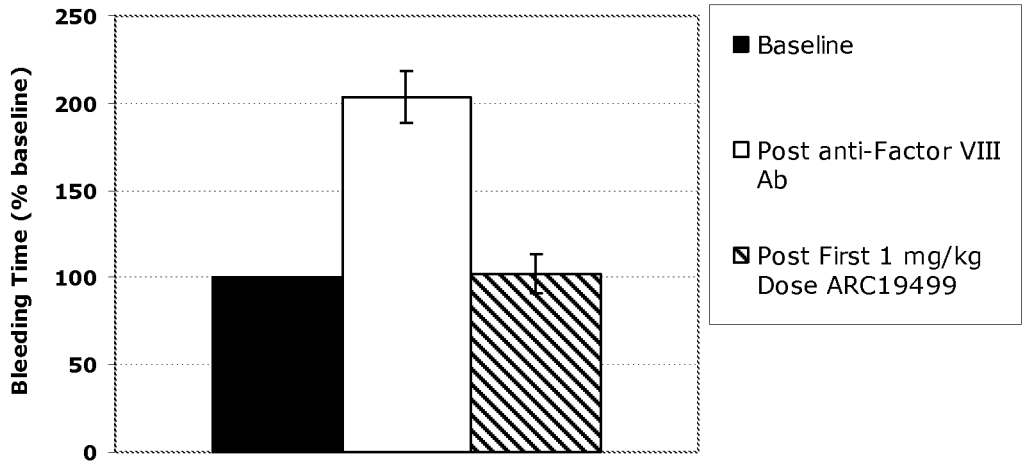
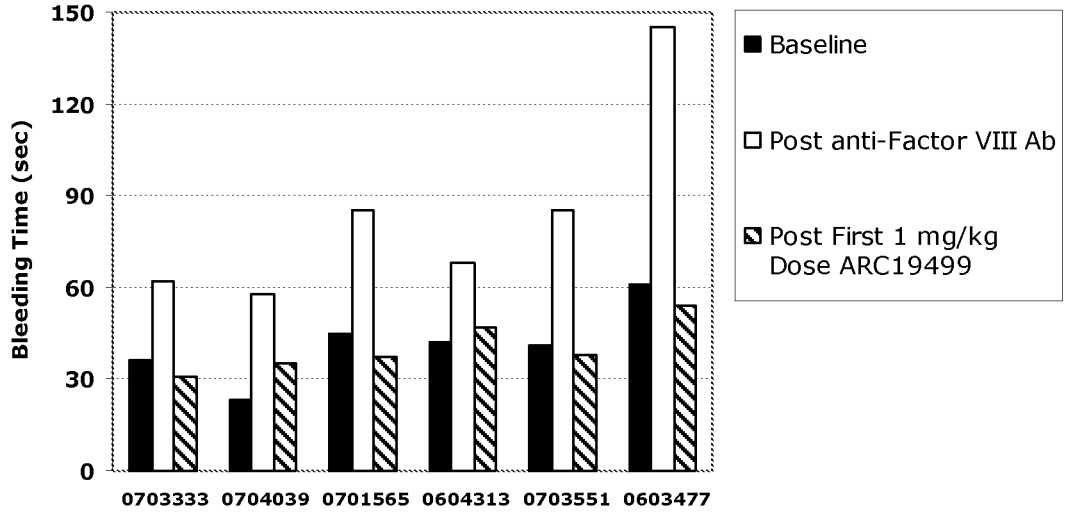


Figure 123

A



B

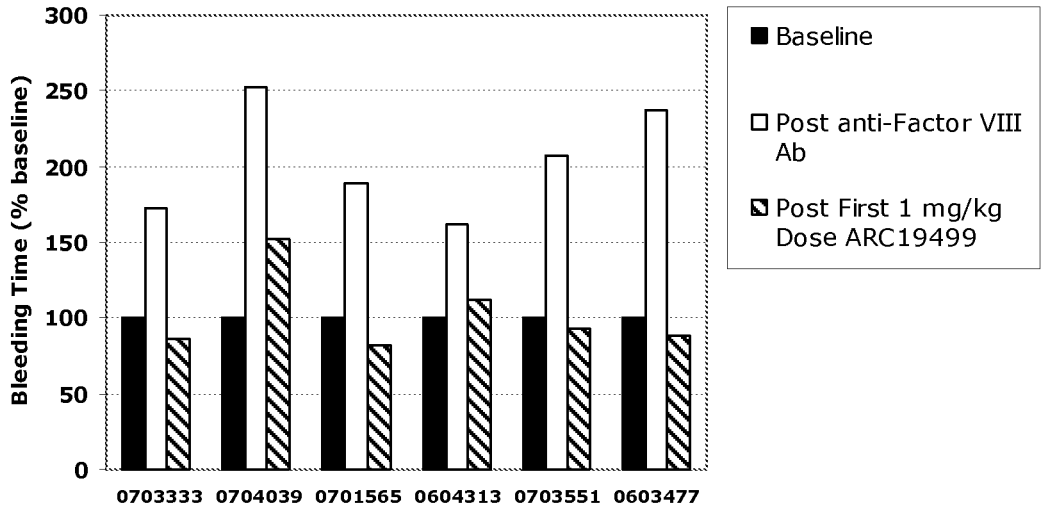
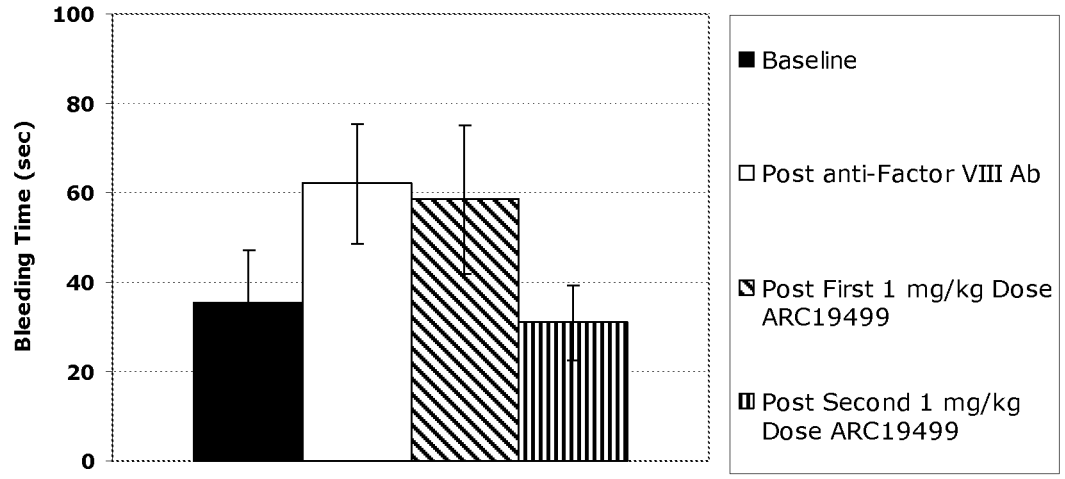


Figure 124

A



B

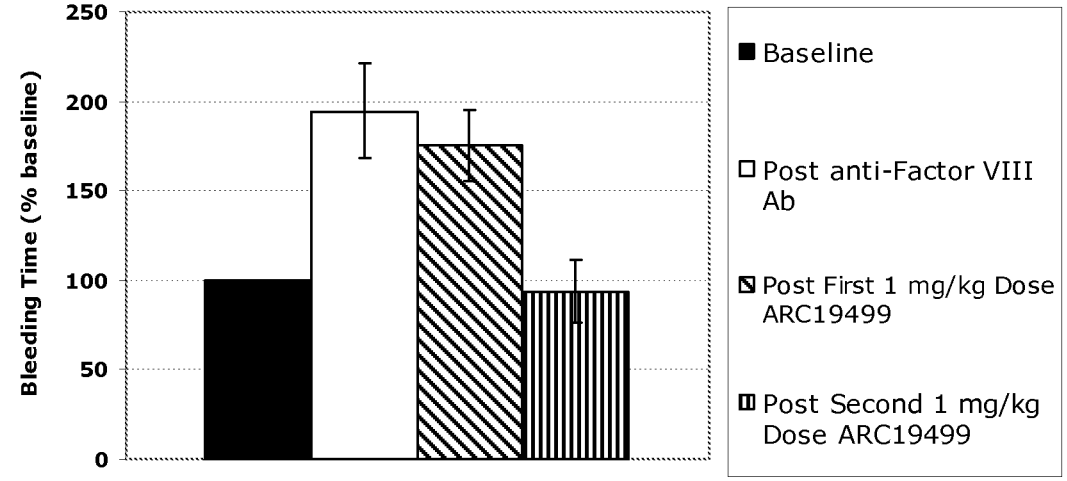
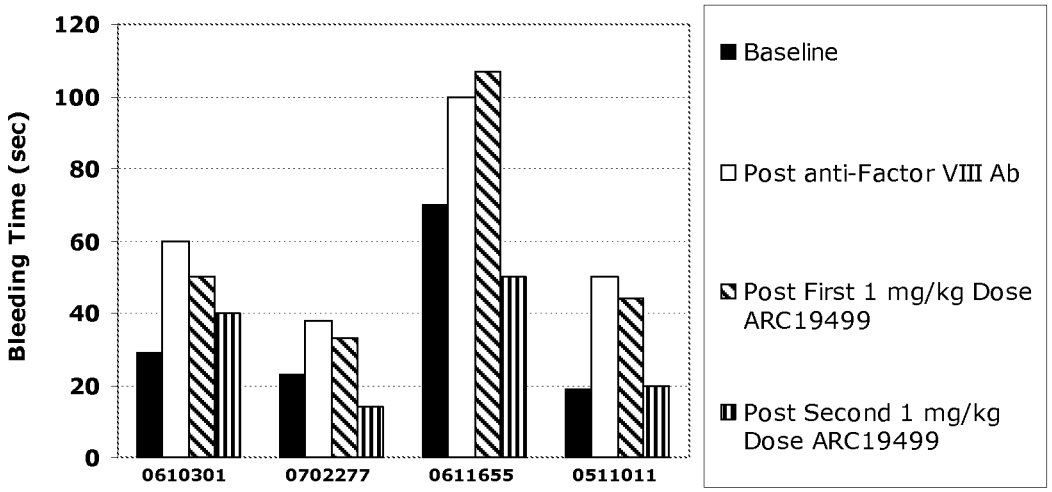


Figure 125

A



B

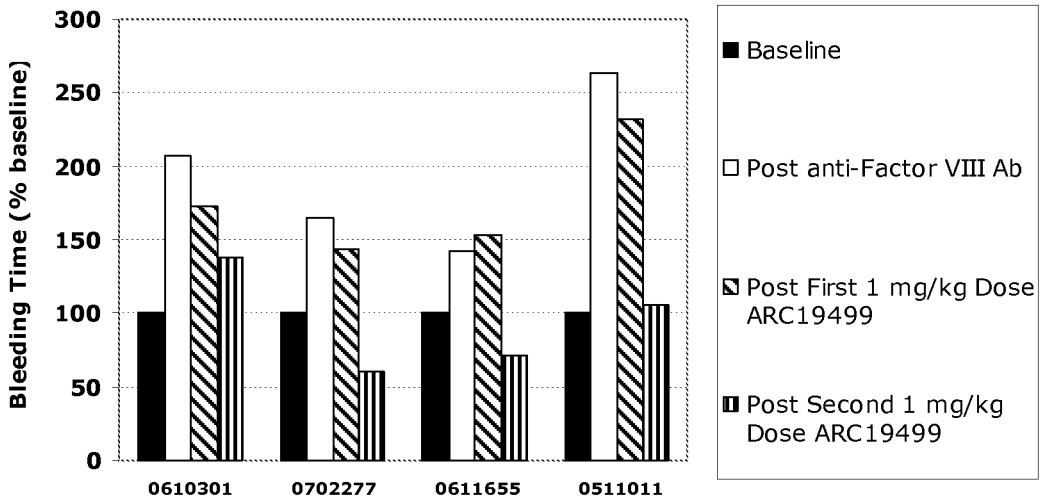
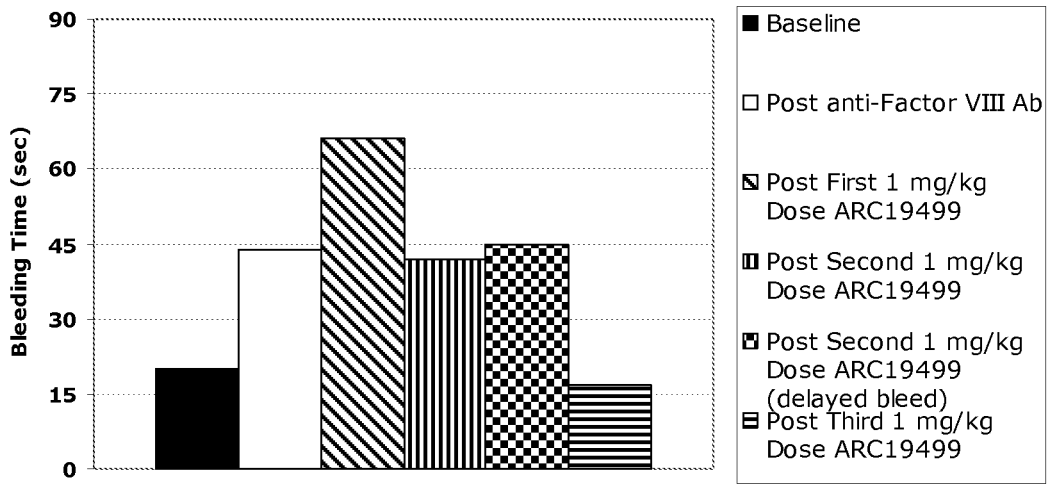


Figure 126

A



B

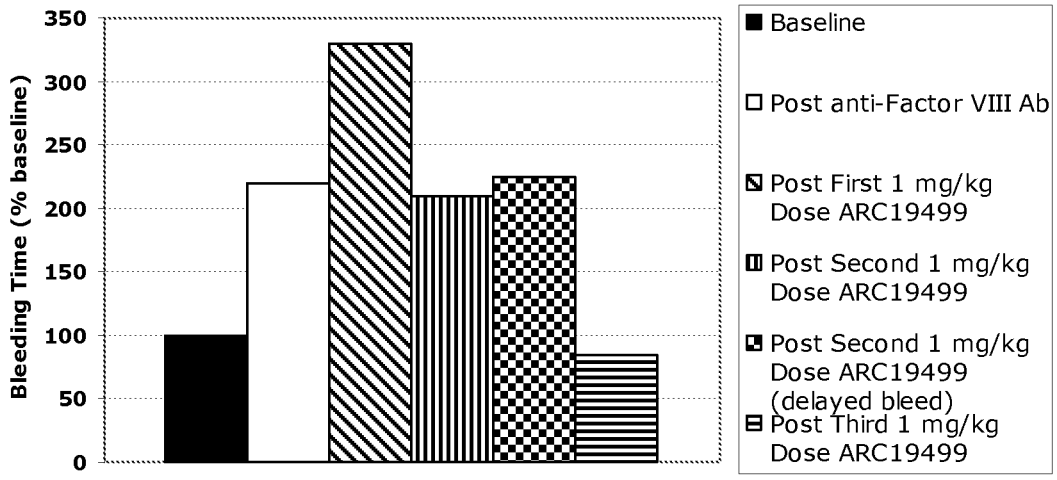
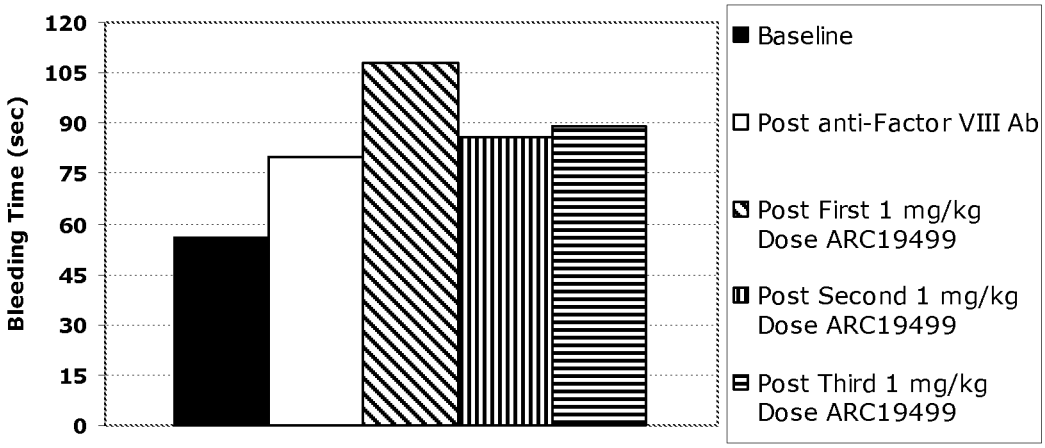


Figure 127

A



B

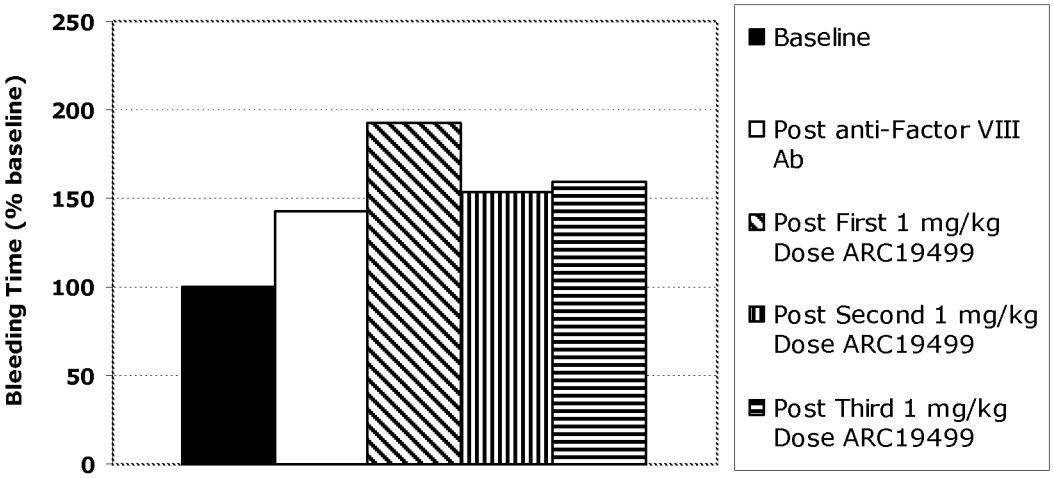


Figure 128

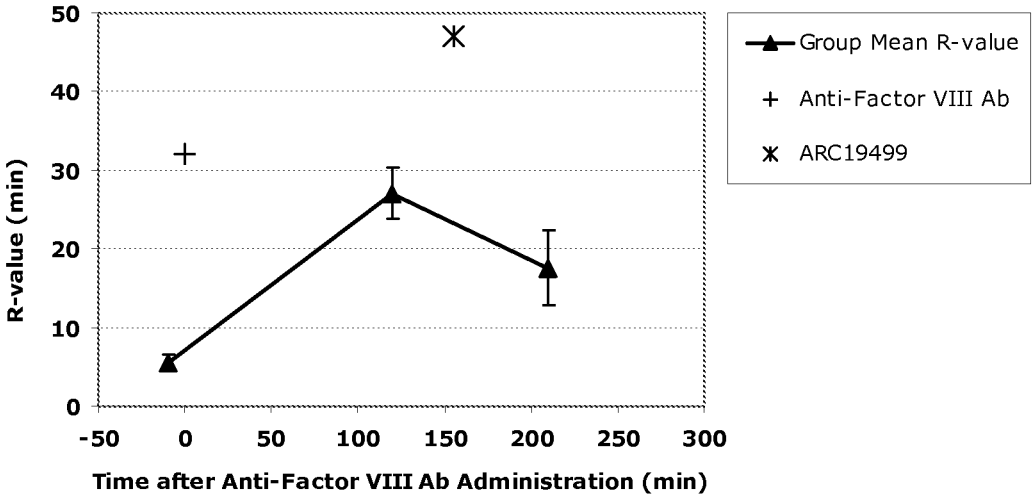


Figure 129

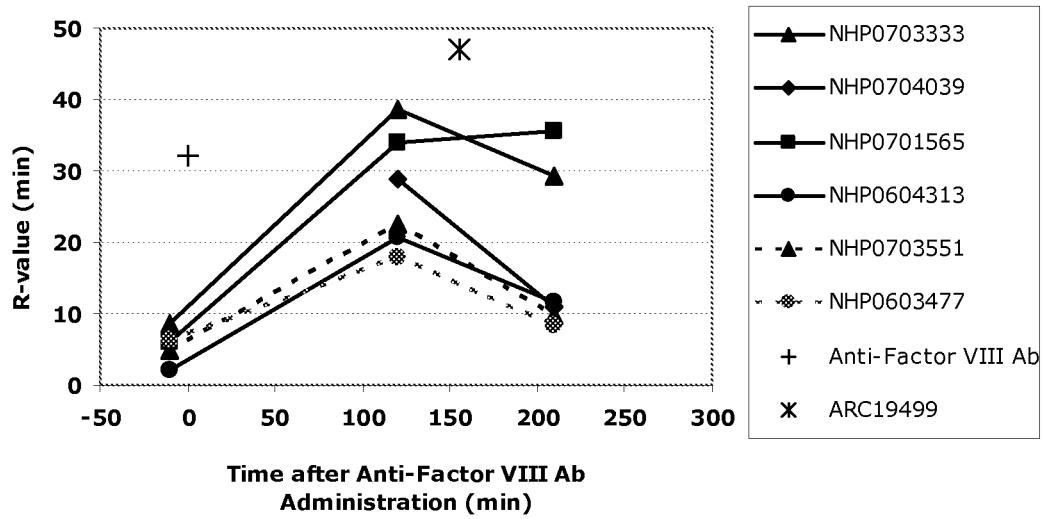


Figure 130

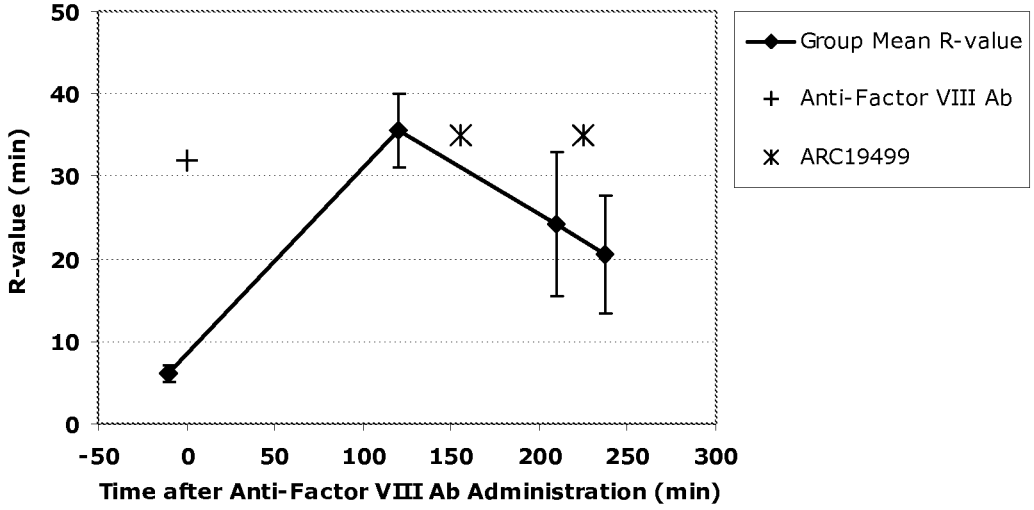


Figure 131

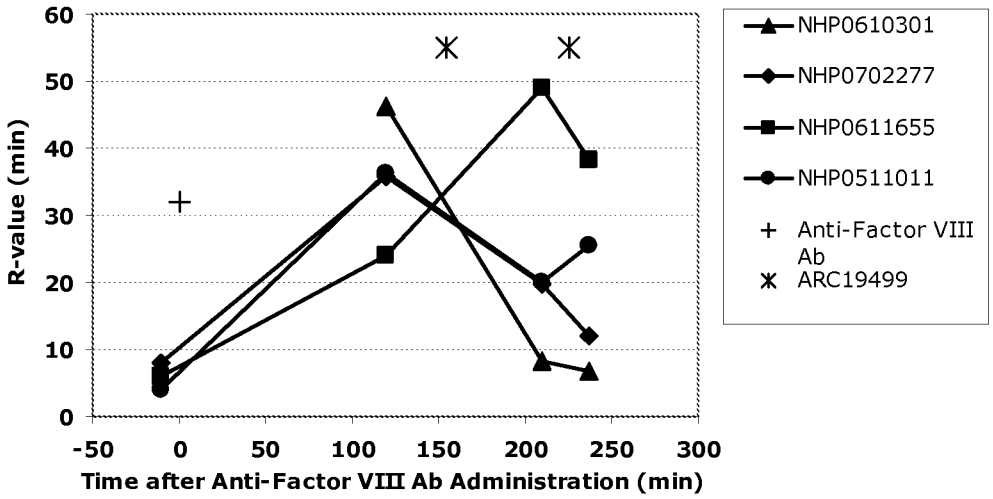


Figure 132

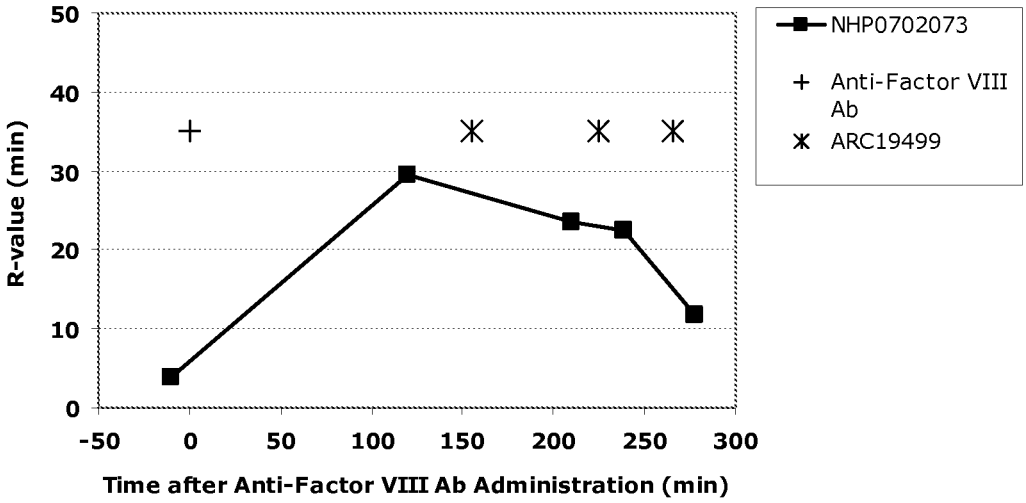


Figure 133

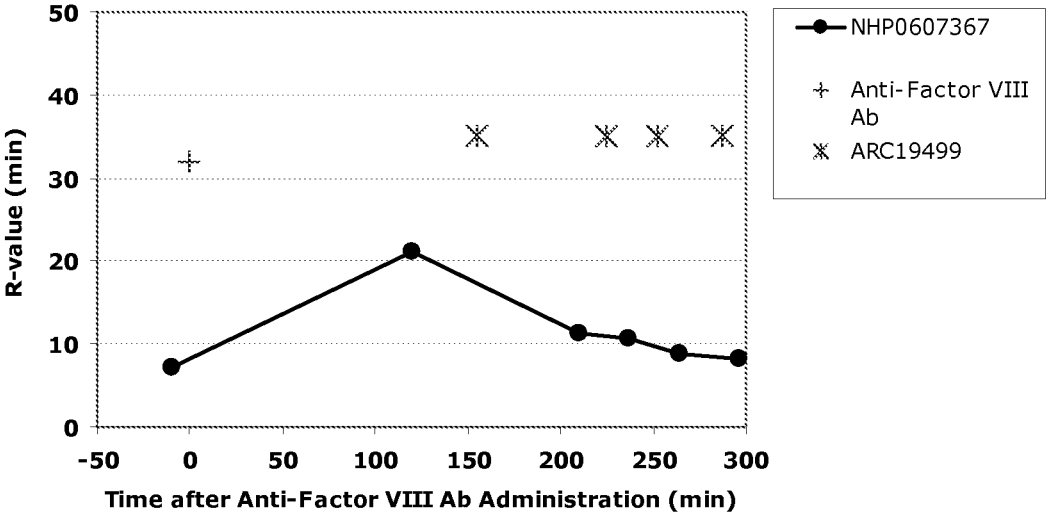


Figure 134

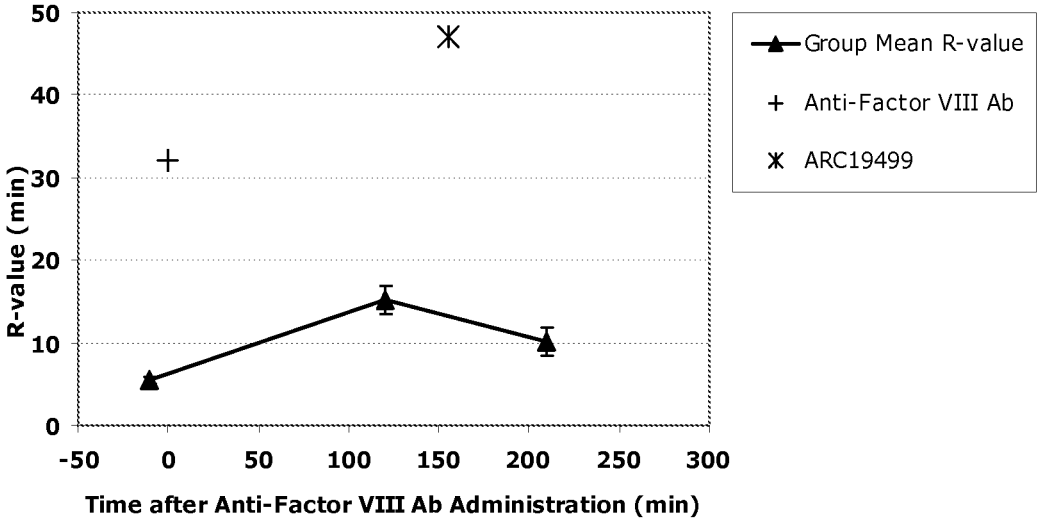


Figure 135

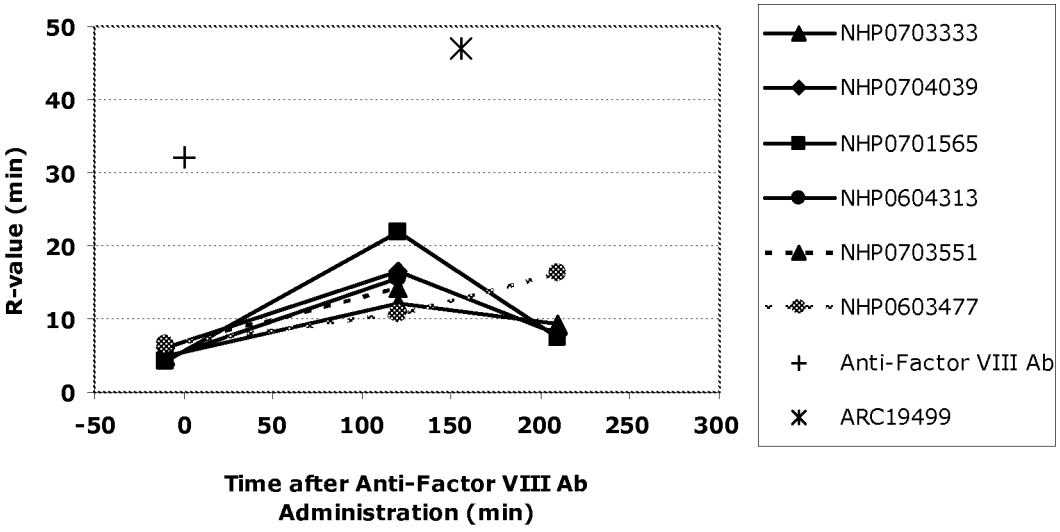


Figure 136

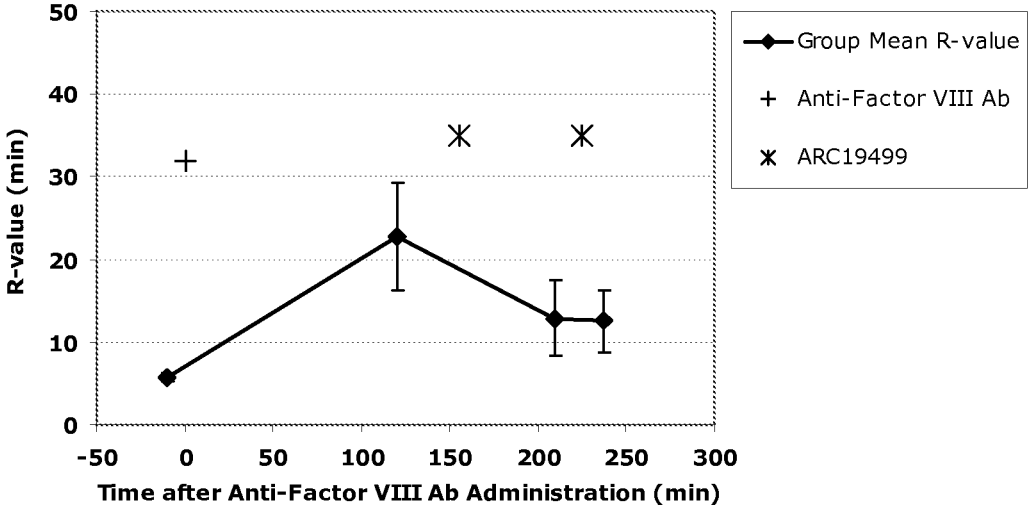


Figure 137

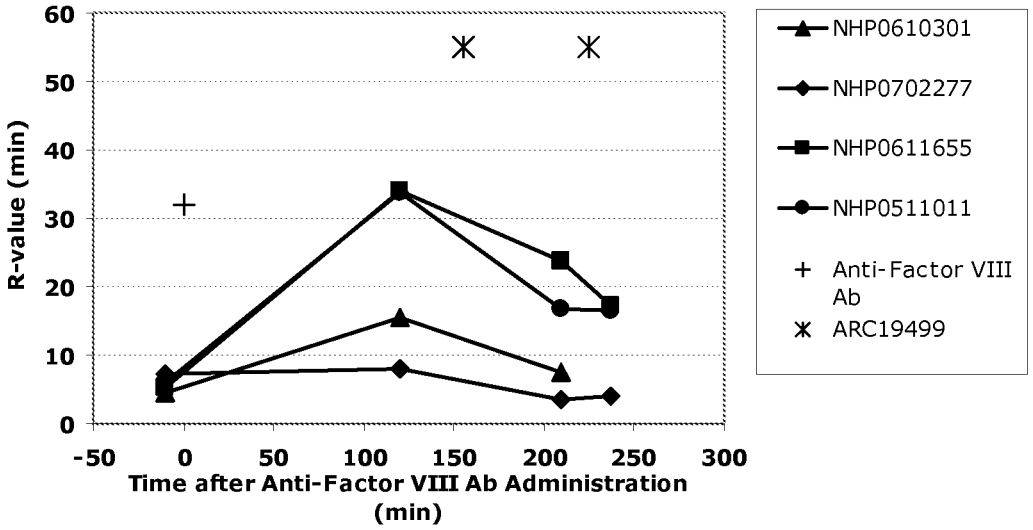


Figure 138

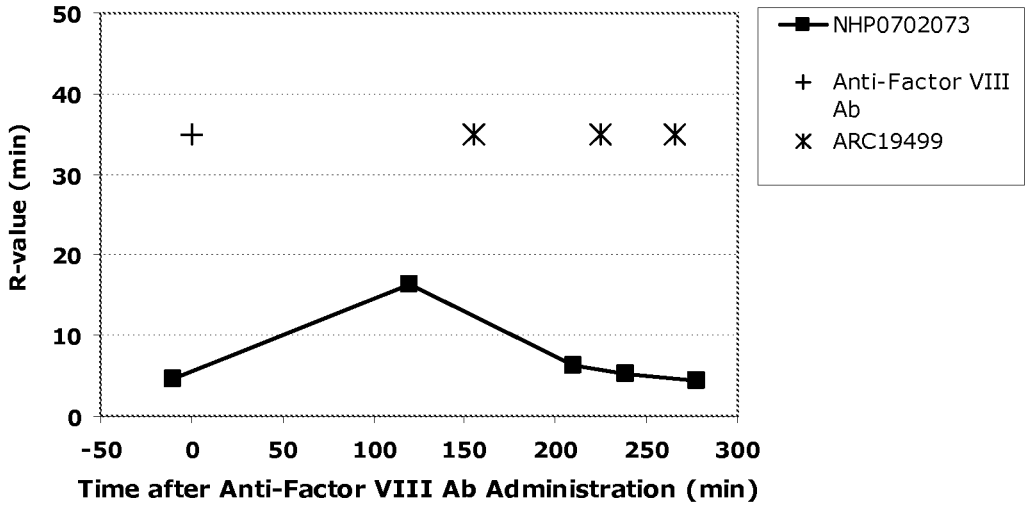


Figure 139

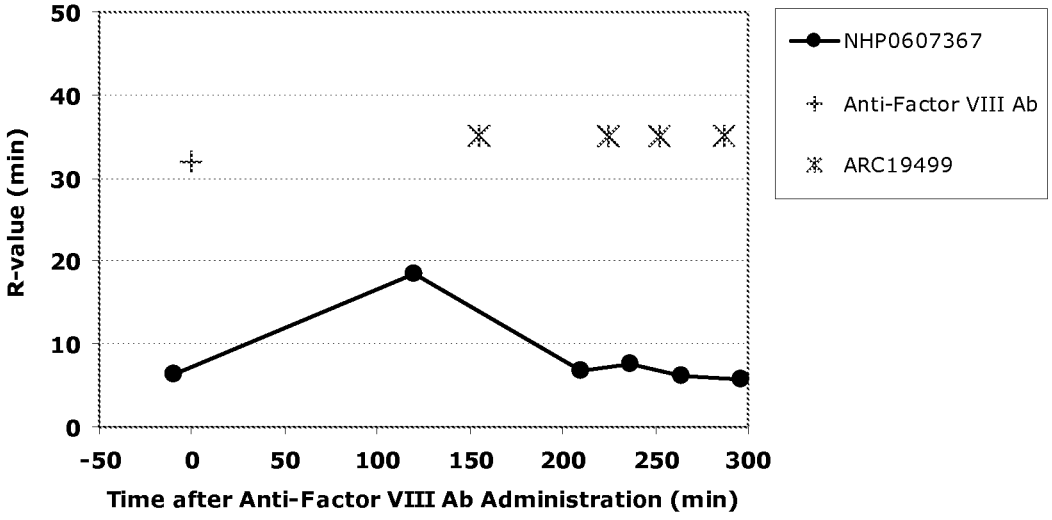


Figure 140

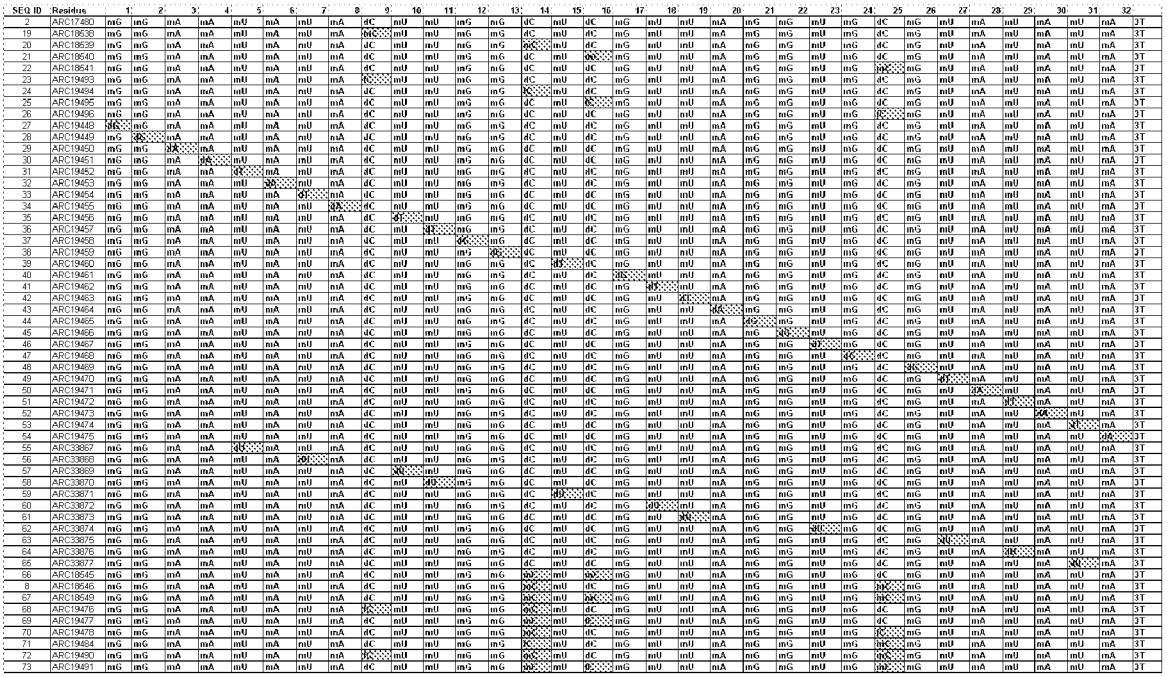


Figure 141

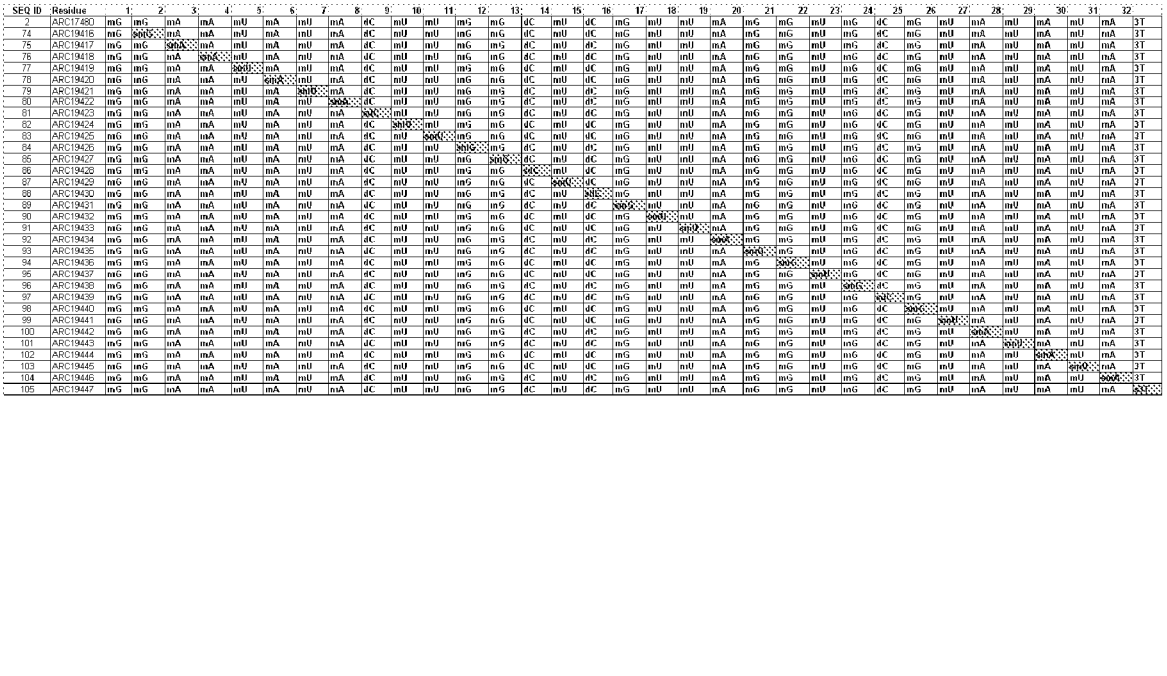
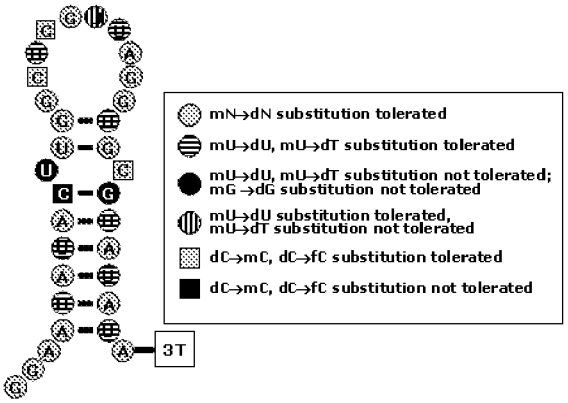


Figure 142

A.



SEQ ID NO: 2

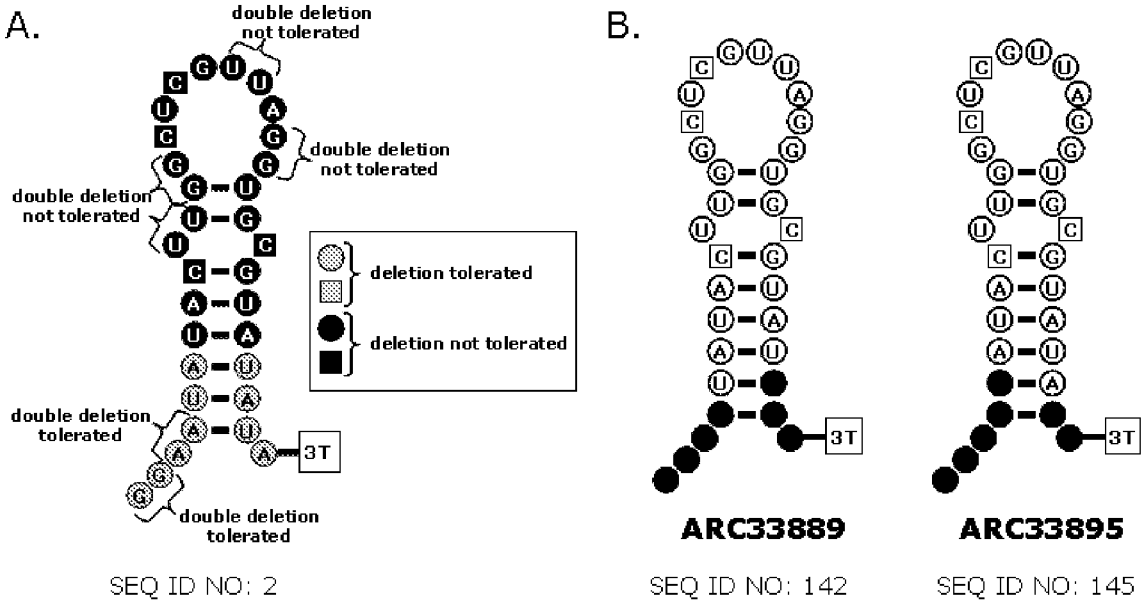
B.

SEQ ID		residue 9	residue 14	residue 16	residue 25	tolerated?
2	ARC17450	dC	dC	dC	fC	Yes
66	ARC18545	dC	mC	mC	dC	Yes
9	ARC18546	fC	mC	dC	mC	Yes
67	ARC18548	dC	mC	mC	mC	Yes
68	ARC18478	fC	mC	dC	fC	Yes
69	ARC18477	dC	mC	fC	dC	Yes
70	ARC18476	dC	mC	dC	fC	Yes
71	ARC18484	dC	fC	dC	mC	Yes
72	ARC18483	fC	mC	dC	mC	Yes
73	ARC18481	dC	mC	fC	mC	Yes

Figure 143

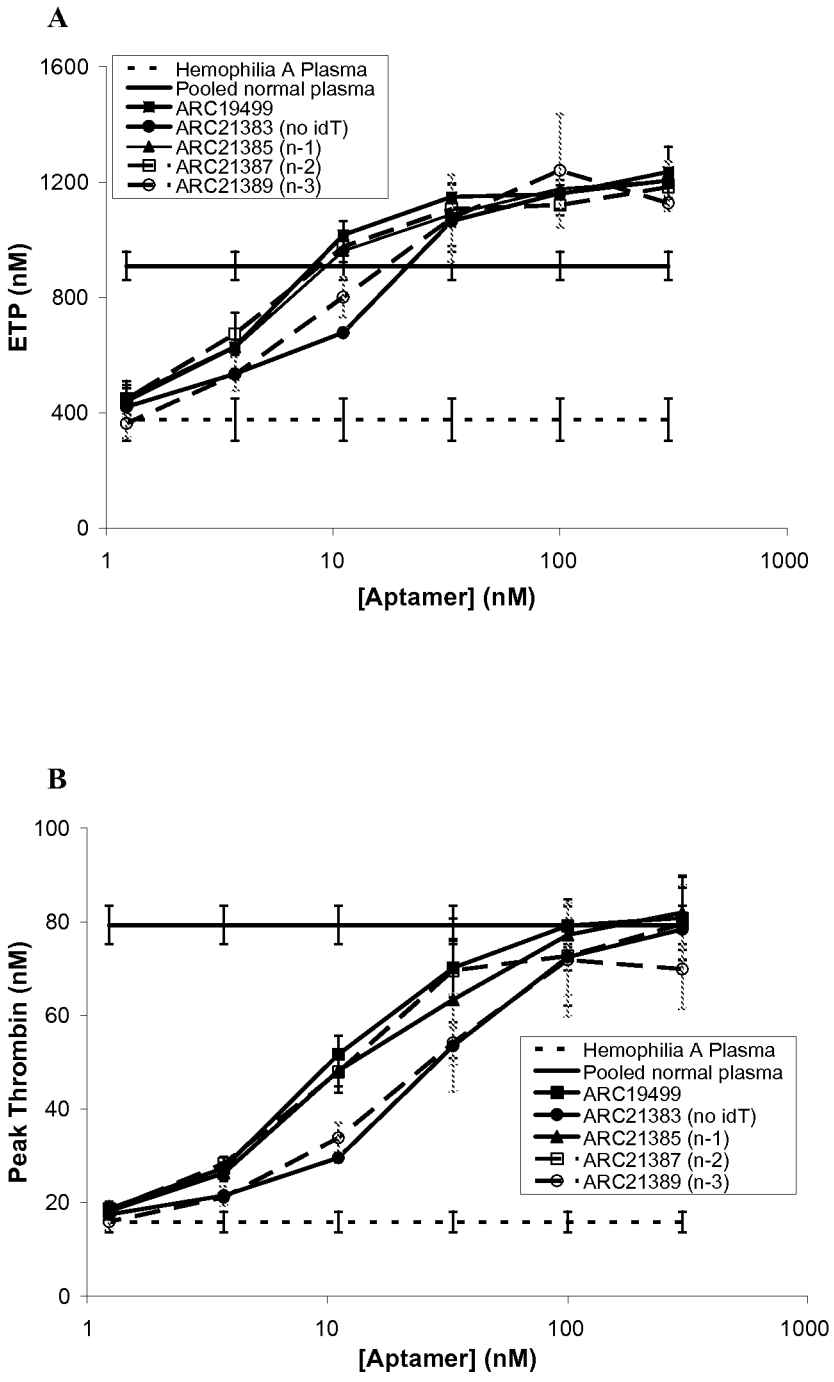
SEQ ID	Residue	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	
2	ARC17480	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
106	ARC32301		mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
107	ARC33120	mG	mG		mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
108	ARC33121	mG	mG	mA	mA		mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
109	ARC33122	mG	mG	mA	mA	mU		mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
110	ARC33123	mG	mG	mA	mA	mU	mA		mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
111	ARC33124	mG	mG	mA	mA	mU	mA	mU		dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
112	ARC33125	mG	mG	mA	mA	mU	mA	mU	mA		mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
113	ARC33126	mG	mG	mA	mA	mU	mA	mU	mA	dC		mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
114	ARC33127	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU		mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
115	ARC33128	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG		mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
116	ARC33129	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC		dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
117	ARC33130	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU		mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
118	ARC33131	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC		mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
119	ARC33132	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG		mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
120	ARC33133	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU		mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
121	ARC33134	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU		mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
122	ARC33135	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA		mG	mG	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
123	ARC33136	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG		mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
124	ARC33137	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG		mG	mU	mA	mU	mA	mU	mA	mU	mA	3T
125	ARC33138	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU		dC	mU	mA	mU	mA	mU	mA	mA	3T
126	ARC33139	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG		mG	mA	mU	mA	mU	mA	mA	3T
127	ARC33140	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC		mU	mA	mU	mA	mU	mA	3T
128	ARC33141	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG		mA	mU	mA	mU	mA	3T
129	ARC33142	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU		mU	mA	mU	mA	3T
130	ARC33143	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA		mA	mU	mA	3T
131	ARC18555	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU		mU	mA	3T
132	ARC32302			mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA		mA	3T
133	ARC33144	mG	mG			mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU		3T
134	ARC33145	mG	mG	mA	mA	mU	mA	mU	mA	dC			mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
135	ARC33146	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU			dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
136	ARC33147	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG			mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
137	ARC33148	mG	mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA			mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
138	ARC32303				mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T
139	ARC32305		mG	mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU		3T
140	ARC32306			mA	mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA			3T
141	ARC32307				mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU				3T
142	ARC33889					mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU				3T
143	ARC33890				mA	mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA			3T
144	ARC33891					mU	mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA			3T
145	ARC33895						mA	mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA			3T
146	ARC33900					mU		mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA			3T
147	ARC33907	mG	mG	mA	mA			mU	mA	dC	mU	mU	mG	mG	dC	mU	dC	mG	mU	mU	mA	mG	mG	mU	mG	dC	mG	mU	mA	mU	mA	mU	mA	3T

Figure 144



SEQ ID NO: 2 SEQ ID NO: 142 SEQ ID NO: 145

Figure 145


A
1600
1200
800
400
0
ETP (nM)
1
10
100
1000
[Aptamer] (nM)
Hemophilia A Plasma
Pooled normal plasma
ARC19499
ARC21383 (no idT)
ARC21385 (n-1)
ARC21387 (n-2)
ARC21389 (n-3)
B
100
80
60
40
20
0
Peak Thrombin (nM)
1
10
100
1000
[Aptamer] (nM)
Hemophilia A Plasma
Pooled normal plasma
ARC19499
ARC21383 (no idT)
ARC21385 (n-1)
ARC21387 (n-2)
ARC21389 (n-3)