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Figure 1B

CS12-FL-AA

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Figure 2

CS12-CRM8.2-Vr

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Figure 3B

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CRM8

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Kozak

ccacc (SEQ ID NO:7)

Poly-A

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3'-ITR

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CS12-CRM8.2-Vrp

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Figure 5A

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(Continued)

Figure 5B

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CS12-CRM8.2-V

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(Continued)

Figure 6A

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Figure 6B

12/28

CS04-FL-NA

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(Continued)

Figure 7A

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NG1: V S N N V S N N A T N A T N (SEQ ID NO:11)
GTG AGC AAC AAT GTG AGC AAC AAT GCC ACC AAT AAT GCT ACC AAC (SEQ ID NO:12)

NG4: V S N N A T N N V S N (SEQ ID NO:13)
GTG AGC AAC AAT GCC ACC AAC AAT GTG AGC AAC (SEQ ID NO:14)

NG5: V S N N A T N (SEQ ID NO:15)
GTG AGC AAT AAT GCC ACC AAC (SEQ ID NO:16)

NG6: V S N N (SEQ ID NO:17)
GTG AGC AAT AAT (SEQ ID NO:18)

NG9: R S L (SEQ ID NO:19)
AGG AGC CTG (SEQ ID NO:20)

NG10: A T N V S N N S A T S A D S A V S (SEQ ID NO:21)
GCC ACT AAT GTG TCT AAC AAC TCT GCT ACC TCT GCT GAC TCT GCT GTG AGC (SEQ ID NO:22)

NG16: A T N Y V N R S L (SEQ ID NO:23)
GCC ACC AAC TAT GTG AAC AGG AGC CTG (SEQ ID NO:24)

Figure 8A

NG17: A T N Y V N R S L S A T S A D S A V S Q N (SEQ ID NO:25)
GCC ACC AAC TAT GTG AAC AGG AGC CTG TCT GCC ACC TCT GCT GAC TCT GCT GTG AGC CAG AAT (SEQ ID NO:26)

NG18: V S N N V S N A V S A V S A (SEQ ID NO:27)
GTG AGC AAC AAT GTG AGC AAT GCT GTG TCT GCT GTG TCT GCT (SEQ ID NO:28)

NG19: I T V A S A T S N I T V A S A D (SEQ ID NO:29)
ATC ACT GTG GCC TCT GCC ACC TCT AAC ATC ACT GTG GCC TCT GCT GAC (SEQ ID NO:30)

NG20: I T V T N I T V T A (SEQ ID NO:31)
ATC ACT GTG ACC AAC ATC ACT GTG ACT GCC (SEQ ID NO:32)

NG21: Q T V T N I T V T A (SEQ ID NO:33)
CAG ACT GTG ACC AAC ATC ACT GTG ACT GCC (SEQ ID NO:34)

NGV: A T N V S N N S N T S N D S N V S (SEQ ID NO:35)
GCC ACT AAT GTG TCT AAC AAC AGC AAC ACC AGC AAT GAC AGC AAT GTG TCT (SEQ ID NO:36)

Figure 8B

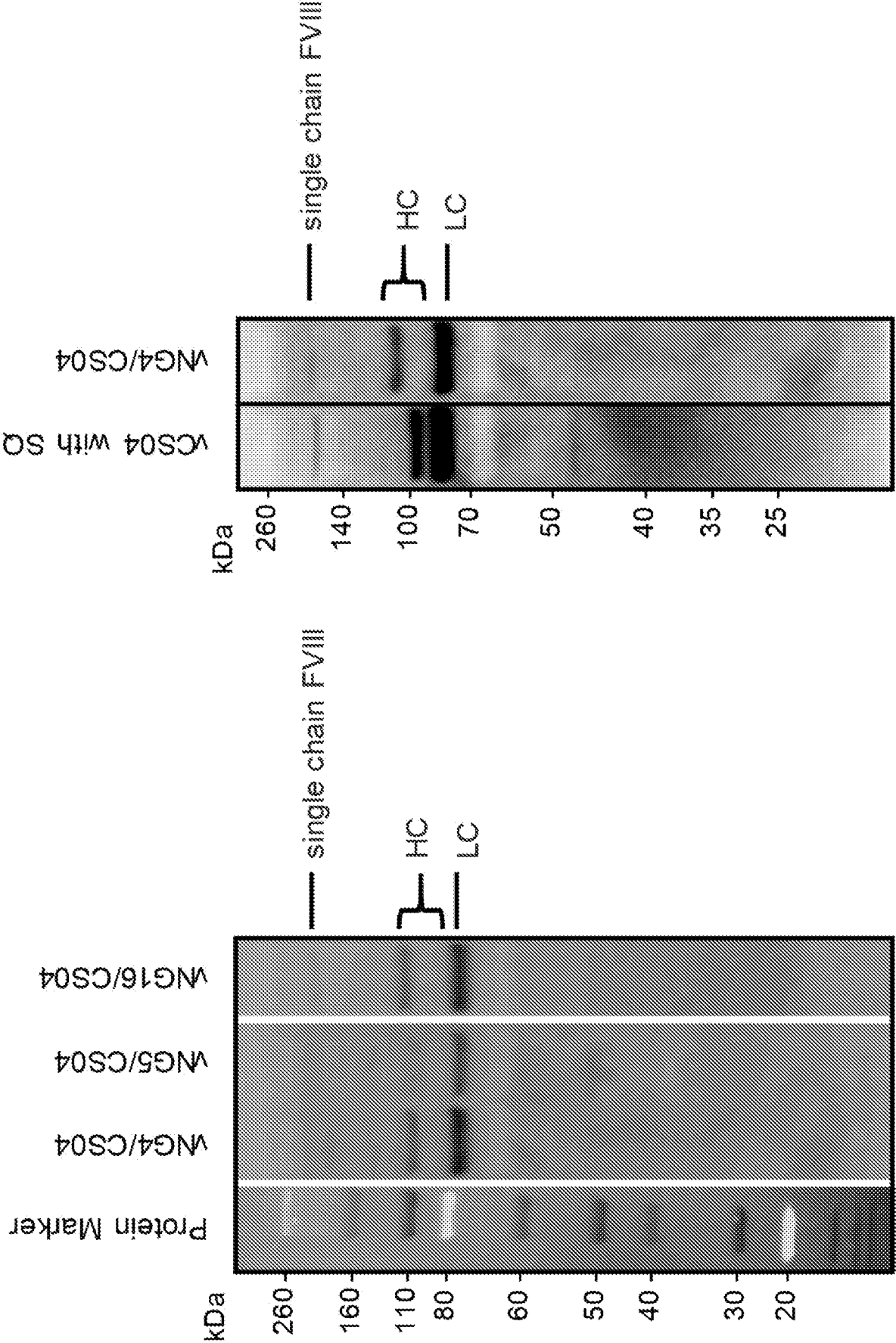


Figure 9

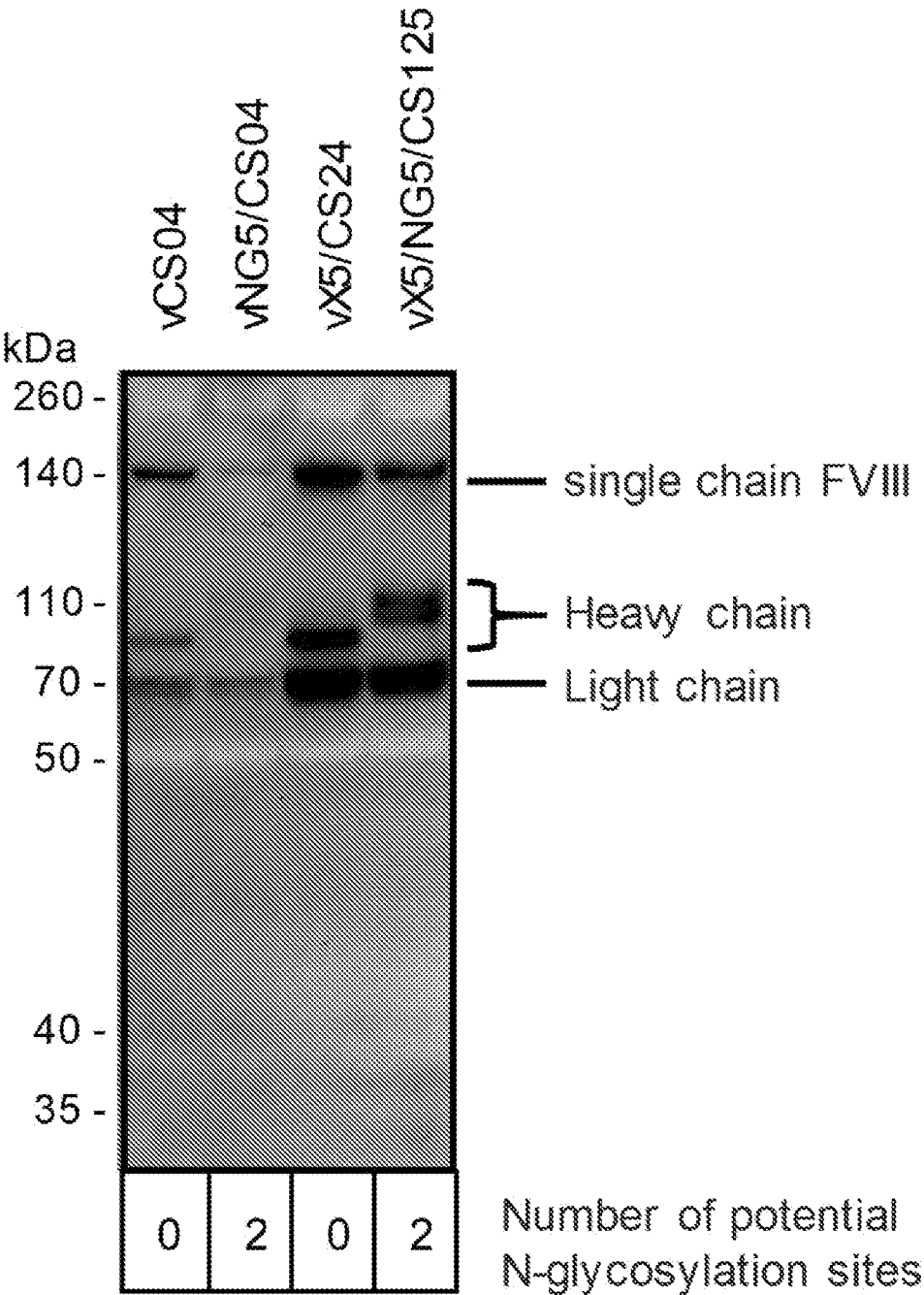


Figure 10

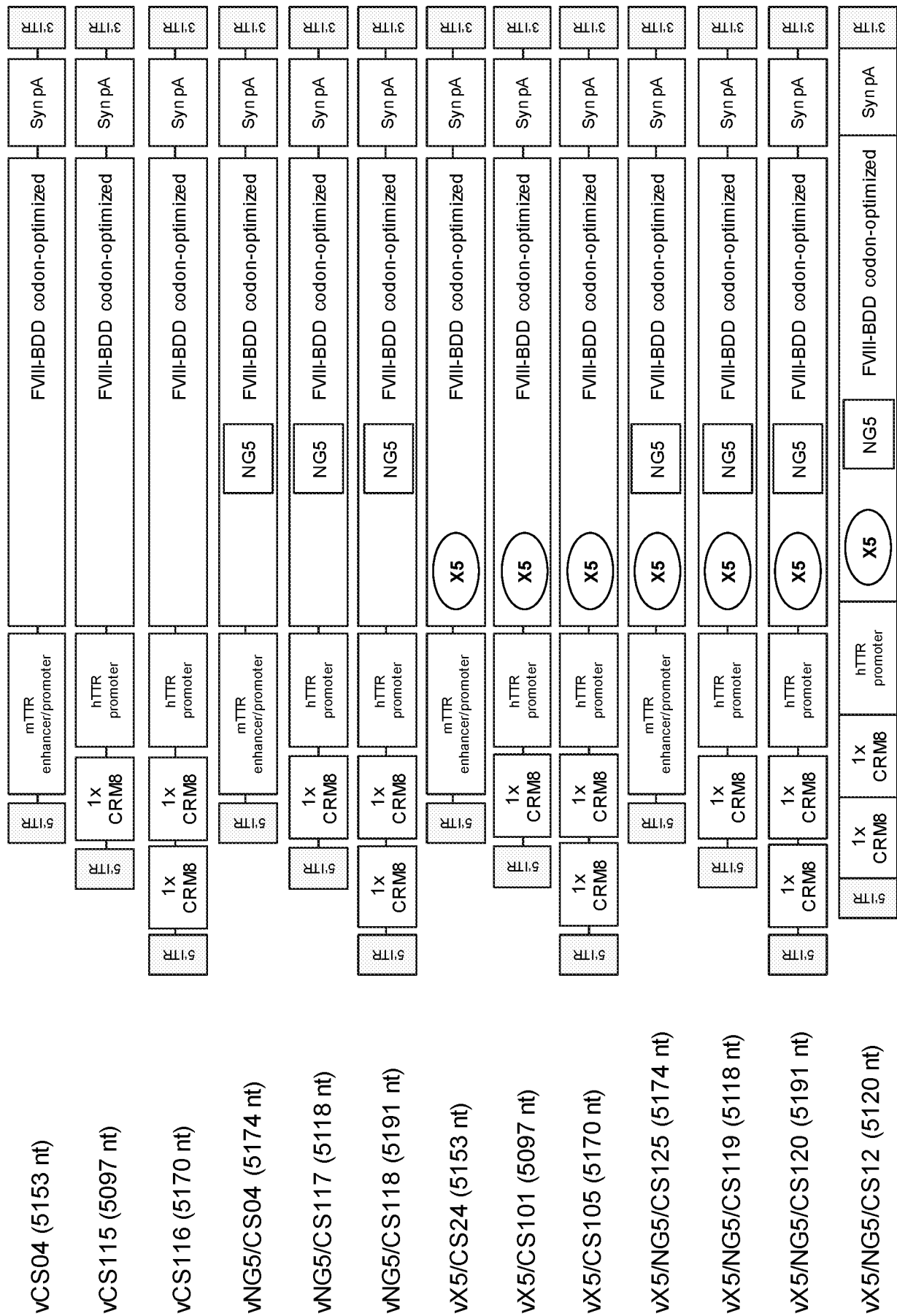


Figure 11

19/28

Vector	Promoter	CDS	Sequence modi- fication(s)	In vivo biopotency ("Line E" mice)				In vitro biopotency (HepG2 cells)		
				Number of mice	Average FVIII Expression at day 14 [IU/mL]	Standard Deviation	Fold expression increase	BPU	Standard Deviation	Fold expression increase*
vCS04	mTTR promoter/enhancer	CS04	-	44	2.1	1.7	1.0 (ref.)	1.0	0.6	1.0 (ref.)
vCS115	1xCRM8/hTTR	CS04	-	8	2.5	0.9	1.2	2.1	n.a.	2.2
vCS116	2xCRM8/hTTR	CS04	-	8	1.9	0.6	0.9	3.6	n.a.	3.7
vNG5/CS04	mTTR promoter/enhancer	CS04	NG5	8	4.0	2.6	1.9	0.6	n.a.	0.6
vNG5/CS117	1xCRM8/hTTR	CS04	NG5	7	3.2	1.0	1.5	1.5	0.1	1.5
vNG5/CS118	2xCRM8/hTTR	CS04	NG5	7	2.9	1.8	1.4	2.3	n.a.	2.4
vX5/CS24	mTTR promoter/enhancer	CS04	X5	16	6.5	2.1	3.1	3.8	1.9	4.0
vX5/CS101	1xCRM8/hTTR	CS04	X5	7	5.2	3.2	2.5	7.0	n.a.	7.3
vX5/CS105	2xCRM8/hTTR	CS04	X5	8	5.1	2.8	2.5	20.3	n.a.	21.2
vX5/NG5/CS125	mTTR promoter/enhancer	CS04	NG / X5	8	9.3	2.8	4.5	3.0	1.0	3.2
vX5/NG5/CS119	1xCRM8/hTTR	CS04	NG / X5	8	7.6	5.8	3.6	13.6	4.4	14.2
vX5/NG5/CS120	2xCRM8/hTTR	CS04	NG / X5	8	11.4	5.0	5.5	19.0	n.a.	19.8

Figure 12

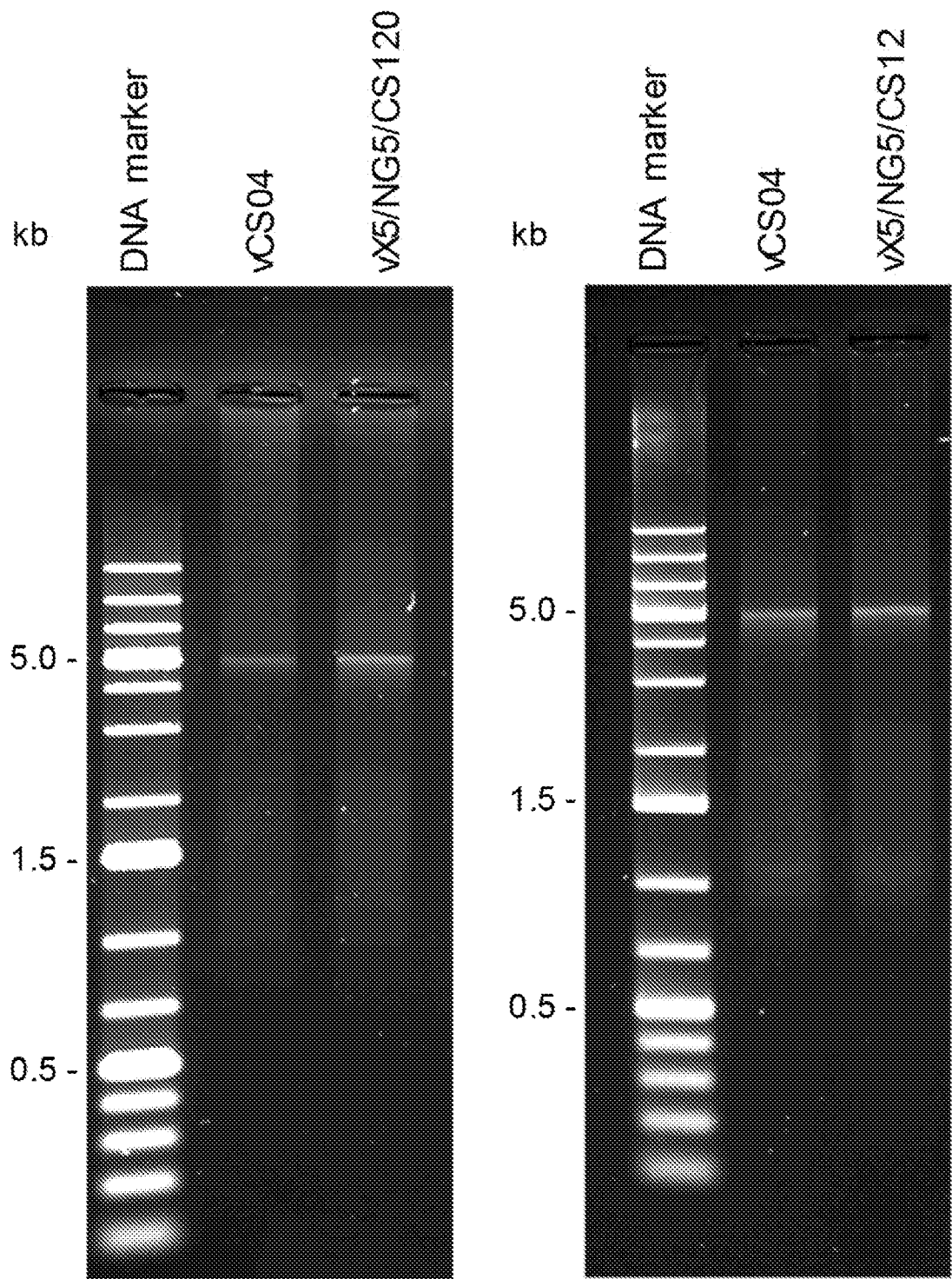


Figure 13

Vector	Promoter	CDS	Sequence modification (s)	In vivo biopotency					In vitro biopotency		
				Dosis [µg/kg]	Number of mice	Average FVIII Expression at day 14 [IU/mL]	Standard Deviation	Fold expression increase	BPU	Standard Deviation	Fold expression increase*
vCS04	mTTR promoter/enhancer	CS04	-	1.0E+12	16	0.3	0.1	1.0*	1.0	0.1	1
				4.0E+12	16	2.5	0.9	-			
vX5/NG5/CS120	2xCRM8/hTTR	CS04	NG / X5	1.0E+12	7	4.3	1.7	14.5*	16.7	5.1	17
vX5/NG5/CS12	2xCRM8/hTTR	CS04	NG / X5, size-reduced	5.0E+11	24	1.5	0.8	-	24.2	8.1	24
				1.0E+12	24	4.2	1.3	14.0*			

Figure 14

Human wild-type FVIII



Refacto-type BDD-FVIII



Figure 15

hFVIII-FL-AA

```

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Figure 16

Plasmid backbone of CS12-CRM8.2-Vrp

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