



(86) Date de dépôt PCT/PCT Filing Date: 2016/03/17  
(87) Date publication PCT/PCT Publication Date: 2016/09/22  
(85) Entrée phase nationale/National Entry: 2017/09/12  
(86) N° demande PCT/PCT Application No.: EP 2016/055825  
(87) N° publication PCT/PCT Publication No.: 2016/146757  
(30) Priorité/Priority: 2015/03/17 (EP15159395.1)

(51) Cl.Int./Int.Cl. *A61K 38/16* (2006.01),  
*A61K 38/36* (2006.01), *A61K 38/37* (2006.01),  
*A61K 48/00* (2006.01), *C12N 15/85* (2006.01),  
*C12N 15/86* (2006.01)

(71) Demandeur/Applicant:  
VRIJE UNIVERSITEIT BRUSSEL, BE

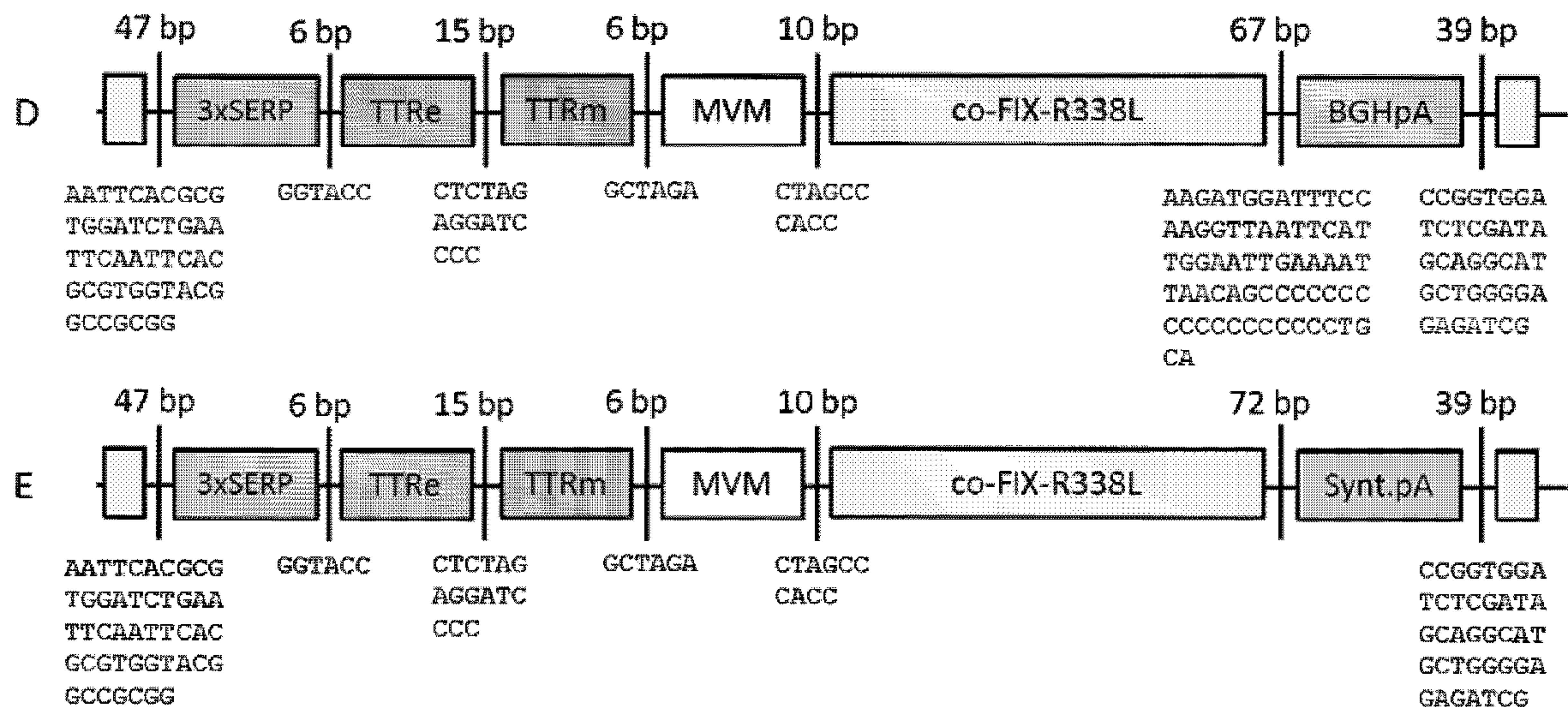
(72) Inventeurs/Inventors:  
CHUAH, MARINEE, BE;  
VANDENDRIESSCHE, THIERRY, BE

(74) Agent: GOWLING WLG (CANADA) LLP

(54) Titre : SYSTEMES D'EXPRESSION SPECIFIQUES DU FOIE OPTIMISES POUR FVIII ET FIX

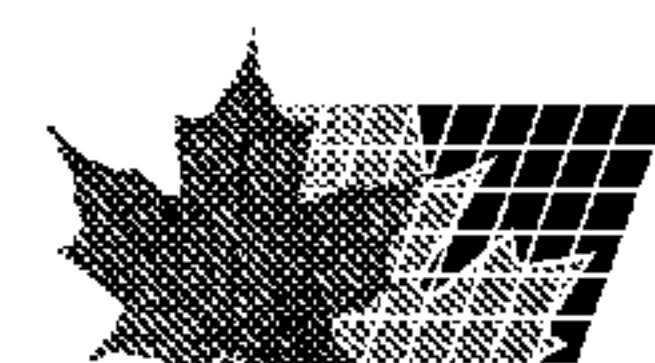
(54) Title: OPTIMIZED LIVER-SPECIFIC EXPRESSION SYSTEMS FOR FVIII AND FIX

Figure 1



(57) Abrégé/Abstract:

The present invention relates to nucleic acid expression cassettes and vectors containing liver- specific regulatory elements and codon-optimized factor IX or factor VIII transgenes, methods employing these expression cassettes and vectors and uses thereof. The present invention is particularly useful for applications using liver-directed gene therapy, in particular for the treatment of hemophilia A and B.



## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
22 September 2016 (22.09.2016)

WIPO | PCT

(10) International Publication Number  
**WO 2016/146757 A1**

## (51) International Patent Classification:

*A61K 38/16* (2006.01) *A61K 48/00* (2006.01)  
*A61K 38/36* (2006.01) *C12N 15/85* (2006.01)  
*A61K 38/37* (2006.01) *C12N 15/86* (2006.01)

## (21) International Application Number:

PCT/EP2016/055825

## (22) International Filing Date:

17 March 2016 (17.03.2016)

## (25) Filing Language:

English

## (26) Publication Language:

English

## (30) Priority Data:

15159395.1 17 March 2015 (17.03.2015) EP

(71) Applicant: **VRIJE UNIVERSITEIT BRUSSEL**  
[BE/BE]; Pleinlaan 2, 1050 Brussels (BE).

(72) Inventors: **CHUAH, Marinee**; Tiensesteenweg 250, 3360 Bierbeek (BE). **VANDENDRIESSCHE, Thierry**; Tiensesteenweg 250, 3360 Bierbeek (BE).

(74) Agents: **VANHALST, Koen** et al.; E. Gevaertdreef 10a, 9830 Sint-Martens-Latem (BE).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,

BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

## Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

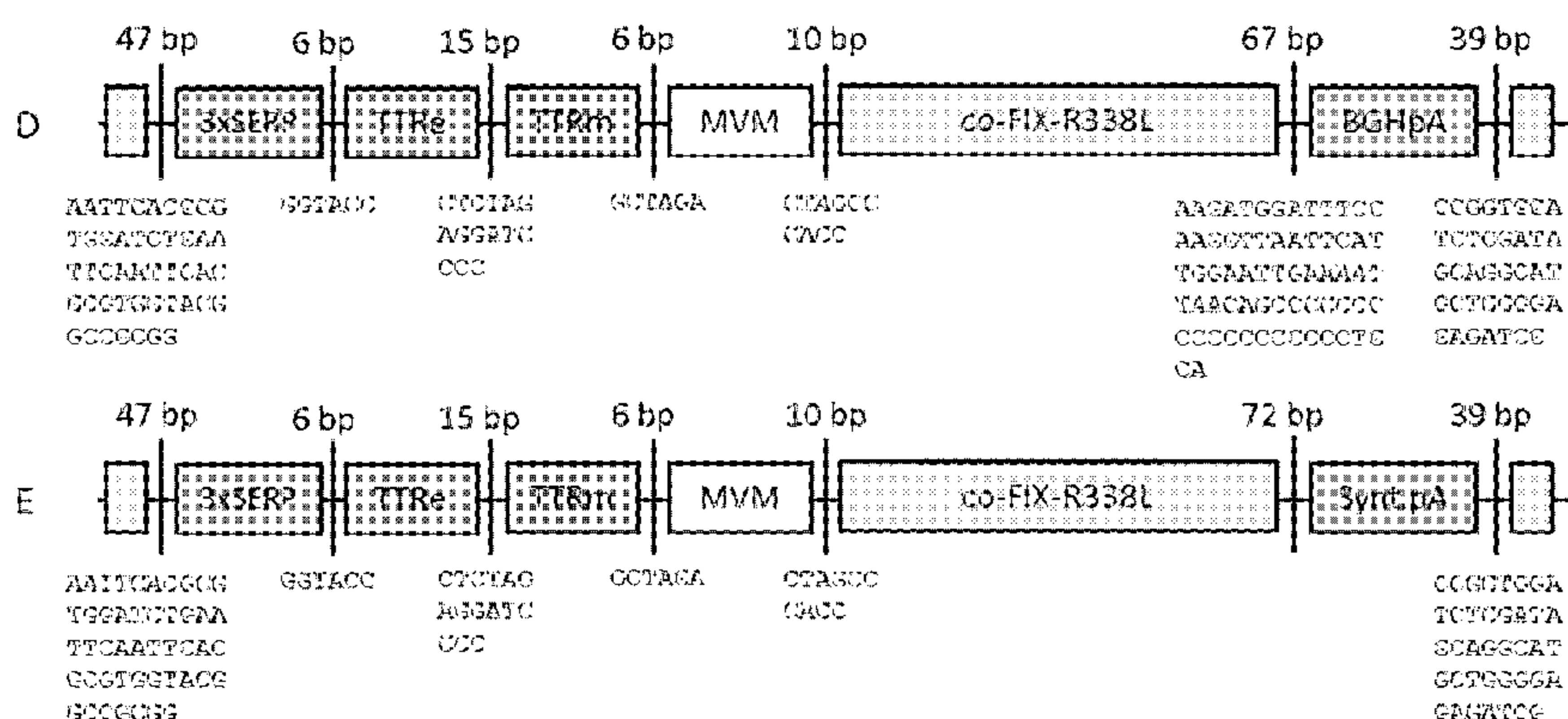
## Published:

— with international search report (Art. 21(3))

— with sequence listing part of description (Rule 5.2(a))

## (54) Title: OPTIMIZED LIVER-SPECIFIC EXPRESSION SYSTEMS FOR FVIII AND FIX

Figure 1



(57) Abstract: The present invention relates to nucleic acid expression cassettes and vectors containing liver- specific regulatory elements and codon-optimized factor IX or factor VIII transgenes, methods employing these expression cassettes and vectors and uses thereof. The present invention is particularly useful for applications using liver-directed gene therapy, in particular for the treatment of hemophilia A and B.

## OPTIMIZED LIVER-SPECIFIC EXPRESSION SYSTEMS FOR FVIII AND FIX

### FIELD OF THE INVENTION

The invention relates to nucleic acid expression cassettes and expression vectors for gene  
5 therapy with improved liver-specific expression capabilities, particularly for use as a gene  
therapy means for the treatment of hemophilia, more particularly for restoring coagulation  
factor IX (FIX) and/or coagulation factor VIII (FVIII) deficiency in liver-directed gene therapy of  
respectively, hemophilia B and hemophilia A.

### 10 BACKGROUND OF THE INVENTION

Hemophilia B is an X-linked, recessive bleeding disorder caused by deficiency of clotting factor  
IX (FIX). Hemophilia A is a serious bleeding disorder caused by a deficiency in, or complete  
absence of, the blood coagulation factor VIII (FVIII). The clinical presentation for hemophilia A  
and B is characterized by episodes of spontaneous and prolonged bleeding. There are an  
15 estimated 1 in 5,000 and 1 in 20,000 individuals suffer from hemophilia A and B, respectively.  
Currently, hemophilia A and B is treated with protein replacement therapy using either plasma-  
derived or recombinant FVIII or FIX. Although protein replacement markedly improved the life  
expectancy of patients suffering from hemophilia, they are still at risk for severe bleeding  
episodes and chronic joint damage, since prophylactic treatment is restricted by the short half-  
20 life, the limited availability and the high cost of purified clotting factors, which can approach  
100.000\$/patient/year. In addition, the use of plasma-derived factors obtained from  
contaminated blood sources increases the risk of viral transmission. Gene therapy offers the  
promise of a new method of treating hemophilia B, since the therapeutic window is relatively  
broad and levels slightly above 1% of normal physiologic levels are therapeutic. If successful,  
25 gene therapy could provide constant FVIII or FIX synthesis which may lead to a cure for this  
disease. The different modalities for gene therapy of hemophilia have been extensively  
reviewed (Chuah et al., 2012a, 2012b, 2012c; VandenDriessche et al., 2012; High 2001, 2011;  
Matrai et al., 2010a, 2010b).

The severity of hemophilia A and hemophilia B has been classified by the subcommittee on  
30 Factor VIII and Factor IX of the Scientific and Standardization Committee of the International  
Society on Thrombosis and Haemostasis into three forms, depending on respectively, the  
FVIII level and the FIX level: 1) severe form (FVIII or FIX level less than 0.01 international  
units (IU)/ml, i.e. less than 1% of normal FVIII or FIX level), 2) moderate form (FVIII or FIX  
level from 0.01 to 0.05 IU/ml, i.e. from 1 to 5% of normal FVIII or FIX level), and 3) mild from  
35 (FVIII or FIX level higher than 0.05 to 0.4 IU/ml, i.e. higher than 5 to 40% of normal FVIII or  
FIX level). Hemophilia A is the most common hereditary coagulation disorder with an  
incidence approaching approximately 1 in 5000 males.

Protein substitution therapy (PST) with purified or recombinant FVIII and FIX has significantly improved the patients' quality of life. However, PST is not curative and patients are still at risk of developing potentially life-threatening hemorrhages and crippling joint inflammation. Unfortunately, many patients suffering from hemophilia A (up to 40%) develop neutralizing antibodies to FVIII (i.e. "inhibitors") following PST. Similarly, an estimated 10% of patients suffering from hemophilia B develop "inhibitors" to FIX. These inhibitors complicate the management of bleeding episodes and can render further PST ineffective. These limitations of PST, justify the development of gene therapy as a potential alternative for hemophilia treatment. Furthermore, only a modest increase in FIX or FVIII plasma concentration is needed for therapeutic benefit, with levels of more than 1% of normal levels able to achieve markedly reduced rates of spontaneous bleeding and long-term arthropathy.

The liver is the main physiological site of FIX and FVIII synthesis and hence, hepatocytes are well suited target cells for hemophilia gene therapy. From this location, FIX or FVIII protein can easily enter into the circulation. Moreover, the hepatic niche may favor the induction of immune tolerance towards the transgene product (Annoni et al., 2007; Follenzi et al., 2004; Brown et al., 2007; Herzog et al., 1999; Matrai et al., 2011; Matsui et al., 2009). Liver-directed gene therapy for hemophilia can be accomplished with different viral vectors including retroviral (Axelrod et al., 1990; Kay et al., 1992; VandenDriessche et al., 1999, Xu et al., 2003, 2005), lentiviral (Ward et al., 2011, Brown et al., 2007, Matrai et al., 2011), adeno-associated viral (AAV) (Herzog et al., 1999) and adenoviral vectors (Brown et al., 2004; Ehrhardt & Kay, 2002). In particular, AAV is a naturally occurring replication defective non-pathogenic virus with a single stranded DNA genome. AAV vectors have a favorable safety profile and are capable of achieving persistent transgene expression. Long-term expression is predominantly mediated by episomally retained AAV genomes. More than 90% of the stably transduced vector genomes are extra-chromosomal, mostly organized as high-molecular-weight concatamers. Therefore, the risk of insertional oncogenesis is minimal, especially in the context of hemophilia gene therapy where no selective expansion of transduced cells is expected to occur. Nevertheless, oncogenic events have been reported following AAV-based gene transfer (Donsante et al., 2007) but it has been difficult to reproduce these findings in other model systems (Li et al., 2011). The major limitation of AAV vectors is the limited packaging capacity of the vector particles (i.e. approximately 5.0 kb, including the AAV inverted terminal repeats), constraining the size of the transgene expression cassette to obtain functional vectors (Jiang et al., 2006). Several immunologically distinct AAV serotypes have been isolated from human and non-human primates (Gao et al., 2002, Gao et al. 2004), although most vectors for hemophilia gene therapy were initially derived from the most prevalent AAV serotype 2. The first clinical success of AAV-based gene therapy for congenital blindness underscores the potential of this gene transfer technology (Bainbridge et al., 2008).

AAV-mediated hepatic gene transfer is an attractive alternative for gene therapy of hemophilia for both liver and muscle-directed gene therapy (Herzog et al., 1997, 1999, 2002; Arruda et al., 2010; Fields et al., 2001; Buchlis et al., 2012; Jiang et al., 2006; Kay et al., 2000). Preclinical studies with the AAV vectors in murine and canine models of hemophilia or non-human  
5 primates have demonstrated persistent therapeutic expression, leading to partial or complete correction of the bleeding phenotype in the hemophilic models (Snyder et al., 1997, 1999; Wang et al., 1999, 2000; Mount et al., 2002; Nathwani et al., 2002). Particularly, hepatic transduction conveniently induces immune tolerance to FIX that required induction of regulatory T cells (Tregs) (Mingozzi et al., 2003; Dobrzynski et al., 2006). Long-term correction  
10 of the hemophilia phenotype without inhibitor development was achieved in inhibitor-prone null mutation hemophilia B dogs treated with liver-directed AAV2-FIX gene therapy (Mount et al., 2002). In order to further reduce the vector dose, more potent FIX expression cassettes have been developed. This could be accomplished by using stronger promoter/enhancer elements, codon-optimized FIX or self-complementary, double-stranded AAV vectors (scAAV) that  
15 overcome one of the limiting steps in AAV transduction (i.e. single-stranded to double-stranded AAV conversion) (McCarty, 2001, 2003; Nathwani et al., 2002, 2006, 2011; Wu et al., 2008). Alternative AAV serotypes could be used (e.g. AAV8 or AAV5) that result in increased transduction into hepatocytes, improve intra-nuclear vector import and may reduce the risk of T cell activation (Gao et al., 2002; Vandenberghe et al., 2006) though it is not certain that this  
20 would necessarily also translate to human subjects since the epitopes are conserved between distinct AAV serotypes (Mingozzi et al., 2007). Liver-directed gene therapy for hemophilia B with AAV8 or AAV9 is more efficient than when lentiviral vectors are used, at least in mice, and resulted in less inflammation (VandenDriessche et al., 2007, 2002). Furthermore, recent studies indicate that mutations of the surface-exposed tyrosine residues allow the vector  
25 particles to evade phosphorylation and subsequent ubiquitination and, thus, prevent proteasome-mediated degradation, which resulted in a 10-fold increase in hepatic expression of FIX in mice (Zhong et al., 2008).

These liver-directed preclinical studies paved the way toward the use of AAV vectors for clinical gene therapy in patients suffering from severe hemophilia B. Hepatic delivery of AAV-FIX  
30 FIX vectors resulted in transient therapeutic FIX levels (maximum 12% of normal levels) in subjects receiving AAV-FIX by hepatic artery catheterization (Kay et al., 2000). However, the transduced hepatocytes were able to present AAV capsid-derived antigens in association with MHC class I to T cells (Manno et al., 2006, Mingozzi et al., 2007). Although antigen presentation was modest, it was sufficient to flag the transduced hepatocytes for T cell-mediated destruction. Recently, gene therapy for hemophilia made an important step forward  
35 (Nathwani et al., 2011; Commentary by VandenDriessche & Chuah, 2012). Subjects suffering from severe hemophilia B (<1% FIX) were injected intravenously with self-complementary (sc)

AAV8 vectors expressing codon-optimized FIX from a liver-specific promoter. This AAV8 serotype exhibits reduced cross-reactivity with pre-existing anti-AAV2 antibodies. Interestingly, its uptake by dendritic cells may be reduced compared to conventional AAV2 vectors, resulting in reduced T cell activation (Vandenberghe et al., 2006). In mice, AAV8 allows for a substantial increase in hepatic transduction compared to AAV2, though this advantage may be lost in higher species, like dog, rhesus monkeys and man. Subjects received escalating doses of the scAAV8-FIX vector, with two participants per dose. All of the treated subjects expressed FIX above the therapeutic 1% threshold for several months after vector administration, yielding sustained variable expression levels (i.e. 2 to 11% of normal levels). The main difference with the previous liver-directed AAV trial is that for the first time sustained therapeutic FIX levels could be achieved after gene therapy. Despite this progress, T-cell mediated clearance of AAV-transduced hepatocytes remains a concern consistent with elevated liver enzyme levels in some of the patients. Transient immune suppression using a short course of glucocorticoids was used in an attempt to limit this vector-specific immune response.

One of the significant limitations in the generation of efficient viral gene delivery systems for the treatment of hemophilia A by gene therapy is the large size of the FVIII cDNA. Previous viral vector-based gene therapy studies for hemophilia A typically relied on the use of small but weak promoters, required excessively high vector doses that were not clinically relevant or resulted in severely compromised vector titers. Several other *ad hoc* strategies were explored, such as the use of split or dual vector design to overcome the packaging constraints of AAV, but these approaches were overall relatively inefficient and raised additional immunogenicity concerns (reviewed in Petrus et al., 2010). It has been found that the FVIII B domain is dispensable for procoagulant activity. Consequently, FVIII constructs in which the B domain is deleted are used for gene transfer purposes since their smaller size is more easily incorporated into vectors. Furthermore, it has been shown that deletion of the B domain leads to a 17-fold increase in mRNA and primary translation product. FVIII wherein the B domain is deleted and replaced by a short 14-amino acid linker is currently produced as a recombinant product and marketed as Refacto® for clinical use (Wyeth Pharma) (Sandberg et al., 2001). Miao et al. (2004) added back a short B domain sequence to a B domain deleted FVIII, optimally 226 amino acids and retaining 6 sites for N-linked glycosylation, to improve secretion. McIntosh et al. (2013) replaced the 226 amino-acid spacer of Miao et al. with a 17 amino-acid peptide in which six glycosylation triplets from the B-domain were juxtaposed. Yet, production was still not sufficient for therapeutic purposes.

Non-viral vectors typically rely on a plasmid-based gene delivery system, where only the naked DNA is delivered, potentially in conjunction with physicochemical methods that facilitate transfection. Consequently, the non-viral approach may be less immunogenic and potentially safer than viral vectors, though innate immune response may still occur. The non-viral gene

transfer method is simple, but the efficiency is generally low compared to most viral vector-mediated gene transfer approaches. Efficient in vivo gene delivery of non-viral vectors remains a bottleneck. Typically, for hepatic gene delivery, plasmids are administered by hydrodynamic injection. In this case, a hydrodynamic pressure is generated by rapid injection of a large volume of DNA solution into the circulation, in order to deliver the gene of interest in the liver (Miao et al., 2000). Efforts are being made to adapt hydrodynamic injection towards a clinically relevant modality by reducing the volume of injection along with maintaining localized hydrodynamic pressure for gene transfer. Alternative approaches based on targetable nanoparticles are being explored to achieve target specific delivery of FIX into hepatocytes. Expression could be prolonged by removing bacterial backbone sequences which interfere with long term expression (i.e. mini-circle DNA). Finally, to increase the stability of FIX expression after non-viral transfection, transposons could be used that result in stable genomic transgene integration. We and others have shown that transposons could be used to obtain stable clotting factor expression following in vivo gene therapy (Yant et al., 2000; Mates, Chuah et al., 2009, VandenDriessche et al., 2009; Kren et al., 2009; Ohlfest et al., 2004 ).

An exemplary state of the art vector for liver-specific expression of FIX is described in WO 2009/130208 and is composed of a single-stranded AAV vector that contains the TTR/Serp regulatory sequences driving a factor cDNA. A FIX first intron was included in the vector, together with a poly-adenylation signal. Using said improved vector yielded about 25-30% stable circulating factor IX.

In order to translate viral-vector based gene therapy for hemophilia to the clinic, the safety concerns associated with administering large vector doses to the liver and the need for manufacturing large amounts of clinical-grade vector must be addressed. Increasing the potency (efficacy per dose) of gene transfer vectors is crucial towards achieving these goals. It would allow using lower doses to obtain therapeutic benefit, thus reducing potential toxicities and immune activation associated with in vivo administration, and easing manufacturing needs.

One way to increase potency is to engineer the transgene sequence itself to maximize expression and biological activity per vector copy. We have shown that FIX transgenes optimized for codon usage and carrying an R338L amino acid substitution associated with clotting hyperactivity and thrombophilia (Simioni et al., 2009), increase the efficacy of gene therapy using lentiviral vector up to 15-fold in hemophilia B mice, without detectable adverse effects, substantially reducing the dose requirement for reaching therapeutic efficacy and thus facilitating future scale up and its clinical translation (Cantore et al., 2012, Nair et al., 2014).

Also codon optimization of human factor VIII cDNAs leads to high-level expression. Significantly greater levels (up to a 44-fold increase and in excess of 200% normal human

levels) of active FVIII protein were detected in the plasma of neonatal hemophilia A mice transduced with lentiviral vector expressing FVIII from a codon-optimized cDNA sequence, thereby successfully correcting the disease model (Ward et al., 2011).

In WO 2014/064277 expression vectors are described which combine the robust Serpin  
5 enhancer with codon-optimized transgenes encoding FIX or FVIII, resulting in increased liver-specific expression of FIX and FVIII, respectively.

It is an object of the present invention to further increase the efficiency and safety of liver-directed gene therapy for hemophilia A and B.

## 10 SUMMARY OF THE INVENTION

It is an object of the present invention to increase the efficiency and safety of liver-directed gene therapy for hemophilia B. The above objective is accomplished by providing a nucleic acid expression cassette and a vector, either a viral vector, in particular an AAV-based vector, or a non-viral vector, comprising specific regulatory elements that enhance liver-directed gene  
15 expression, while retaining tissue specificity, in conjunction with the use of a transgene, preferably a codon-optimized transgene, encoding human FIX, preferably human FIX containing a hyper-activating mutation.

The resulting vector and nucleic acid expression cassette result in unexpectedly high expression levels of FIX in the liver, due to its unique combination of regulatory elements. The  
20 combined effect of these elements could not have been predicted. Previously, we reported on a new regulatory element that in combination with other vector elements represented a more than 20-fold increase in FIX levels (cf. WO2014/064277). In the present invention, it is shown that combining 3 copies of the serpin enhancer with the known natural TTR enhancer further increases FIX expression by 6 to 10 fold. This increase in hFIX activity was shown to be  
25 synergistic. It is another object of the present invention to increase the efficiency and safety of liver-directed gene therapy for hemophilia A. As shown in the experimental section, this objective is accomplished by providing a vector, either a viral vector, in particular an AAV-based vector, or a non-viral vector, comprising a nucleic acid expression cassette with specific regulatory elements that enhance liver-directed gene expression, while retaining tissue  
30 specificity, in conjunction with the use of a codon-optimized human FVIII construct, in particular a codon-optimized B domain deleted FVIII construct driven from a minimal transthyretin promoter. The resulting AAV-based vector and nucleic acid expression cassette resulted in unprecedented, supra-physiologic FVIII expression levels (cf. WO2014/064277). The inventors now demonstrated that the specific combination of three copies of the Serpin  
35 enhancer with the natural TTR enhancer, and the codon-optimized B domain deleted FVIII transgene or the codon optimized padua mutant FIX transgene driven from a minimal

transthyretin promoter provides for a synergistic effect on FVIII or FIX expression levels compared to expression cassettes containing the natural TTR enhancer and the codon-optimized B domain deleted FVIII transgene or the codon optimized padua mutant FIX transgene driven from a minimal transthyretin promoter.

- 5 The combination of the triple repeat of the Serpin enhancer defined by SEQ ID NO:5 and the transthyretin enhancer defined by SEQ ID NO:12 has been shown to be unexpectedly potent in increasing expression of a transgene operably linked to it. Said regulatory element is defined by SEQ ID NO:13. Said regulatory element can further be combined with the transthyretin minimal promotor as defined by SEQ ID NO:6. This creates a combination of 3x  
 10 the SerpEnh (3x SEQ ID NO:5, e.g. such as in SEQ ID NO:11) with the TTRe and TTRm nucleic acid sequence e.g. as defined by SEQ ID NO:69. For example, such a construct results in a regulatory element as defined by SEQ ID NO:58, which has been tested to increase the expression of both FVIII and FIX transgenes as shown herein.

The invention therefore provides the following aspects:

- 15 Aspect 1. A nucleic acid expression cassette comprising a triple repeat, preferably a tandem repeat, of a liver-specific nucleic acid regulatory element comprising or consisting of the nucleic acid fragment defined by SEQ ID NO:5 or a sequence having at least 95% identity to said sequence, preferably a liver-specific nucleic acid regulatory element of 150 nucleotides or less, comprising or consisting of the nucleic acid fragment defined by SEQ ID NO:5 or a  
 20 sequence having at least 95% identity to said sequence, more preferably the regulatory element (3xSERP) as defined by SEQ ID NO:11, operably linked to a promoter and a transgene, preferably a codon-optimized transgene, wherein the promoter is a liver-specific promoter.

- 25 Preferably said promoter is derived from the transthyretin (TTR) promoter, more preferably said promoter is the minimal TTR promotor (TTRm) as defined by SEQ ID NO:6.

In another preferred embodiment, said liver-specific promoter is derived from the AAT promoter, e.g. as defined by SEQ ID NO:64.

- In further embodiments, the liver-specific promoter is selected from the group comprising: the transthyretin (TTR) promoter or TTR-minimal promoter (TTRm), the alpha 1-antitrypsin (AAT)  
 30 promoter, the albumin promotor (ALB) or minimal albumin promoter (ALBm), the apolipoprotein A1 (APOA1) promoter, the complement factor B (CFB) promoter, the ketohexokinase (KHK) promoter, the hemopexin (HPX) promoter, the nicotinamide N-methyltransferase (NNMT) promoter, the (liver) carboxylesterase 1 (CES1) promoter, the protein C (PROC) promoter, the apolipoprotein C3 (APOC3) promoter, the mannan-binding  
 35 lectin serine protease 2 (MASP2) promoter, the hepcidin antimicrobial peptide (HAMP)

promoter, or the serpin peptidase inhibitor, clade C (antithrombin), member 1 (SERPINC1) promoter.

Aspect 2. The nucleic acid expression cassette according to aspect 1, further comprising a nucleic acid regulatory element comprising or consisting of the nucleic acid fragment defined by SEQ ID NO:12 (TTR<sub>e</sub>), or a sequence having at least 95% identity to said sequence, preferably a nucleic acid regulatory element of 150 nucleotides or less comprising or consisting of the nucleic acid fragment defined by SEQ ID NO:12, or a sequence having at least 95% identity to said sequence. In a preferred embodiment, the combination of the TTR<sub>e</sub> and TTR<sub>m</sub> nucleic acid modules is defined by SEQ ID NO:69.

Aspect 3, The nucleic acid expression cassette according to aspect 2, comprising the nucleic acid regulatory element as defined by SEQ ID NO:13, preferably the nucleic acid regulatory element as defined by SEQ ID NO:57, operably linked to a promoter and a transgene, or the nucleic acid regulatory element as defined by SEQ ID NO:58, operably linked to a transgene.

Aspect 4. The nucleic acid expression cassette according to any one of aspects 1 to 3, wherein said transgene encodes for coagulation factor VIII or coagulation factor IX.

Aspect 5. The nucleic acid expression cassette according to aspect 4, wherein said coagulation factor VIII has a deletion of the B domain.

Aspect 6. The nucleic acid expression cassette according to aspect 5, wherein said B domain of said FVIII is replaced by a linker defined by SEQ ID NO:59.

Aspect 7. The nucleic acid expression cassette according to any one of aspects 4 to 6, wherein said transgene encoding for coagulation factor VIII is defined by SEQ ID NO: 18.

Aspect 8. The nucleic acid expression cassette according to aspect 4, wherein said coagulation factor IX contains a hyper-activating mutation.

Aspect 9. The nucleic acid expression cassette according to aspect 8, wherein said hyper-activating mutation in coagulation factor IX corresponds to an R338L amino acid substitution.

Aspect 10. The nucleic acid expression cassette according to any one of aspects 4, 8 or 9, wherein said transgene encoding for coagulation factor IX is defined by SEQ ID NO:9.

Aspect 11. The nucleic acid expression cassette according to any one of aspects 1 to 10, wherein said promoter is a liver-specific promoter, preferably a promoter derived from the transthyretin (TTR) promoter, preferably the minimal TTR promoter as defined by SEQ ID NO:6.

Aspect 12. The nucleic acid expression cassette according to any one of aspects 1 to 11, further comprising a minute virus of mouse (MVM) intron, preferably the MVM intron as defined by SEQ ID NO:8.

Aspect 13. The nucleic acid expression cassette according to any one of aspects 1 to 12, further comprising a transcriptional termination signal derived from the bovine growth hormone polyadenylation signal (BGHpA), preferably the BGHpA as defined by SEQ ID NO:10, or derived from the Simian virus 40 polyadenylation signal (SV40pA), preferably the SV40pA as defined by SEQ ID NO:19, or a synthetic polyadenylation signal, preferably the synthetic polyadenylation signal as defined by SEQ ID NO: 56.

Aspect 14. A vector comprising the nucleic acid expression cassette according to any one of aspects 1 to 13.

Aspect 15. The vector according to aspect 14, wherein said vector is a viral vector.

Aspect 16. The vector according to aspect 15, wherein said vector is derived from an adeno-associated virus (AAV).

Aspect 17. The vector according to aspect 16, wherein said vector is a single-stranded AAV vector, preferably a single-stranded AAV serotype 8 vector.

Aspect 18. The vector according to any one of aspects 14 to 17, defined by SEQ ID NO: 16, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22 or SEQ ID NO:23, preferably SEQ ID NO:22 or SEQ ID NO:23, more preferably SEQ ID NO:22.

Aspect 19. The vector according to aspect 16, wherein said vector is a self-complementary AAV vector, preferably a self-complementary AAV serotype 9 vector.

Aspect 20. The vector according to any one of aspects 14 to 16, or 19, defined by SEQ ID NO: 2, SEQ ID NO:4, or SEQ ID NO:25, preferably SEQ ID NO:4 or SEQ ID NO:25, more preferably SEQ ID NO:4, or the vector according to any one of aspects 14 to 16, or 19, defined by SEQ ID NO: 65, SEQ ID NO:66, or SEQ ID NO:68, preferably SEQ ID NO:65 or 68, more preferably SEQ ID NO:65. Aspect 21. The vector according to aspect 14, wherein said vector is a non-viral vector, such as a transposon-based vector (e.g. a PiggyBac(PB)-based vector or a Sleeping Beauty(SB)-based vector).

Aspect 22. A method to obtain levels of factor VIII in plasma equal to or higher than the therapeutic threshold concentration of 10 mU/ml plasma in a subject, comprising the transduction or transfection of the vector according to any one of aspects 14 to 18, or 21 into a subject.

Aspect 23. The method according to aspect 22, wherein the transduction of the vector according to any one of aspects 14 to 18, or 21 into the subject is done at a dose lower than  $2.5 \times 10^{11}$  vg/kg.

Aspect 24. A method to obtain levels of factor IX in plasma equal to or higher than the therapeutic threshold concentration of 10mU/ml plasma in a subject, comprising the

transduction or transfection of the vector according to any one of aspects 14 to 16, or 19 to 21 into a subject.

Aspect 25. The method according to aspect 24, wherein the transduction of the vector according to any one of aspects 14 to 16, or 19 to 21 into the subject is done at a dose lower  
5 than  $2 \times 10^{11}$  vg/kg.

Aspect 26. The method according to any one of aspects 22 to 25, wherein said transduction or transfection is by intravenous administration.

Aspect 27. The method according to any one of aspects 22 to 26, wherein said subject is a mammalian subject, preferably a human subject.

10 Aspect 28. A method for treating hemophilia A in a mammalian subject, comprising performing the method according to any one of aspects 22, 23, 26 or 27.

Aspect 29. The use of the vector according to any one of aspects 14 to 18, or 21 for the manufacture of a medicament to treat hemophilia A.

15 Aspect 30. The vector according to any one of aspects 14 to 18, or 21 for use in the treatment of hemophilia A.

Aspect 31. A method for treating hemophilia B in a mammalian subject, comprising performing the method according to any one of aspects 24 to 27.

Aspect 32. The use of the vector according to any one of aspects 14 to 16, or 19 to 21 for the manufacture of a medicament to treat hemophilia B.

20 Aspect 33. The vector according to any one of aspects 14 to 16, 19 to 21 for use in the treatment of hemophilia B.

Aspect 34. A pharmaceutical composition comprising a vector according to any one of aspects 14 to 18, or 21 and a pharmaceutically acceptable carrier, optionally further comprising an active ingredient for treating hemophilia A.

25 Aspect 35. The pharmaceutical composition according to aspect 34 for use in treating hemophilia A.

Aspect 36. The pharmaceutical composition for use according to aspect 35, or the vector for use according to aspect 30, wherein said treatment results in levels of factor VIII in plasma of the treated subject that are equal to or higher than the therapeutic threshold concentration of  
30 10 mU/ml plasma in a subject.

Aspect 37. The pharmaceutical composition for use according to any one of aspects 35 or 35, or the vector for use according to any one of aspects 30 or 36, wherein said treatment

comprises the transduction of the vector according to any one of aspects 14 to 18 into the subject at a dose lower than or equal than  $2.5 \times 10^{11}$  vg/kg.

Aspect 38. A pharmaceutical composition comprising a vector according to any one of aspects 14 to 16, 19 to 21 and a pharmaceutically acceptable carrier, optionally further comprising an active ingredient for treating hemophilia B.

Aspect 39. The pharmaceutical composition according to aspect 38, for use in treating hemophilia B.

Aspect 40. The pharmaceutical composition for use according to aspect 39, or the vector for use according to aspect 33, wherein said treatment results in levels of factor IX in plasma of the treated subject that are equal to or higher than the therapeutic threshold concentration of 10 mU/ml plasma in a subject, preferably equal to or higher than the therapeutic concentration of 50 mU/ml plasma in a subject, more preferably equal to or higher than the therapeutic concentration of 100 mU/ml plasma in a subject, even more preferably equal to or higher than the therapeutic concentration of 150 mU/ml plasma in a subject and even more preferably equal to or higher than the therapeutic concentration of 200 mU/ml plasma in a subject.

Aspect 41. The pharmaceutical composition for use according to aspect 39 or 40, or the vector for use according to aspect 33 or 40, wherein said treatment comprises the transduction of the vector according to any one of aspects 14 to 16, 19 or 20 into the subject at a dose lower than or equal than  $2 \times 10^{12}$  vg/kg, preferably at a dose lower than or equal than  $6 \times 10^{11}$  vg/kg, more preferably at a dose lower than or equal than  $2 \times 10^{11}$  vg/kg.

## BRIEF DESCRIPTION OF THE FIGURES

The present invention is illustrated by the following figures which are to be considered for illustrative purposes only and in no way limit the invention to the embodiments disclosed therein:

**Figure 1:** Design of the self-complementary (sc), double-stranded adeno-associated viral (AAV) vectors AAVsc-SerpEnh-TTRm-MVM-co-FIX-R338L-BGHpA (2510 bp) (A), AAVsc-3xSerpEnh-TTRm-MVM-co-FIX-R338L-BGHpA (2683 bp) (B), AAVsc-TTREnh-TTRm-MVM-co-FIX-R338L-BGHpA (2540 bp) (C), AAVsc-3xSerpEnh-TTREnh-TTRm-MVM-co-FIX-R338L-BGHpA (2760 bp) (D), and AAVsc-3xSerpEnh-TTREnh-TTRm-MVM-co-FIX-R338L-Synt.pA (2519 bp) (E). The minimal transthyretin promoter (TTRm) is driving the expression of the codon-optimized human factor IX (co-FIX-R338L) containing the hyper-activating, thrombophilic FIX mutation (R338L). Either the native TTR enhancer (TTRE), the Serpin enhancer (SERP), a triplet of the Serpin enhancer (3xSERP), or a combination of a triplet of the Serpin enhancer (3xSERP) and the native TTR enhancer (TTRE) is cloned upstream of

TTRm. The minute virus of mouse intron (MVM), the bovine growth hormone polyadenylation site (BGHpA) or a synthetic polyadenylation site (Synt.pA), and the inverted terminal repeats (ITR) are indicated. The sequences flanking/linking the different elements are indicated. The indicated vector sizes includes both ITR's.

5 **Figure 2:** Design of the single-stranded (ss) adeno-associated viral (AAV) vectors AAVss-TTRm-MVM-co-hFVIII-ΔB-Sv40pA (5160 bp) (A), AAVss-SerpEnh-TTRm-MVM-co-hFVIII-ΔB-Sv40pA (5252 bp) (B), AAVss-3xSerpEnh-TTRm-MVM-co-hFVIII-ΔB-Sv40pA (5410 bp) (C), AAVss-TTREnh-TTRm-MVM-co-hFVIII-ΔB-Sv40pA (5272 bp) (D), AAVss-3xSerpEnh-TTRm-MVM-co-hFVIII-ΔB-Synt.pA (5325 bp) (E), AAVss-3xSerpEnh-TTRm-co-hFVIII-ΔB-Synt.pA (5217 bp) (F), AAVss-3xSerpEnh-TTREnh-TTRm-MVM-co-hFVIII-ΔB-Sv40pA (5493 bp) (G), AAVss-3xSerpEnh-TTREnh-TTRm-co-hFVIII-ΔB-Synt.pA (5307 bp) (H), and AAVss-TTREnh-TTRm-co-hFVIII-ΔB-Synt.pA (5083 bp) (I). The minimal transthyretin promoter (TTRm) is driving the expression of the human codon-optimized B-domain deleted factor VIII (cohFVIIIΔB). The native TTR enhancer (TTRe), the Serpin enhancer (SERP), a triplet of the Serpin enhancer (3xSERP), or a combination of a triplet of the Serpin enhancer (3xSERP) and the native TTR enhancer (TTRe) may be cloned upstream of TTRm. The minute virus of mouse intron (MVM), the Simian Virus 40 (SV40) polyadenylation site (SV40pA) or a synthetic polyadenylation site (Synt.pA), and the inverted terminal repeats (ITR) are indicated. The sequences flanking/linking the different elements are indicated. The indicated vector sizes include both ITR's.

**Figure 3:** FIX protein levels upon transduction of the described SC-vectors. 3a): the protein expression levels achieved upon transduction with  $1 \times 10^9$  vg/mouse (Low Dose) for the different vector systems described in Figure 1; 3b): the protein expression levels achieved upon transduction with  $5 \times 10^9$  vg/mouse (High Dose) for the different vector systems described in Figure 1.

**Figure 4:** FVIII protein levels upon transduction of the described SS-vectors. 4a): the protein expression levels achieved upon transduction with  $1 \times 10^9$  vg/mouse (Low Dose) for the different vector systems described in Figure 2; 4b): the protein expression levels achieved upon transduction with  $5 \times 10^9$  vg/mouse (High Dose) for the different vector systems described in Figure 2.

**Figure 5:** Plasmid map of the pAAVsc-SerpEnh-TTRm-MVM-co-FIX-R338L-BGHPA vector

**Figure 6:** Plasmid map of the pAAVsc-3xSerpEnh-TTRm-MVM-co-FIX-R338L-BGHPA vector

**Figure 7:** Plasmid map of the pAAVsc-TTRe-TTRm-MVM-co-FIX-R338L-BGHPA vector

**Figure 8:** Plasmid map of the pAAVsc-3xSerpEnh-TTRe-TTRm-MVM-co-FIX-R338L-BGHPA vector

**Figure 9:** Plasmid map of the pAAVss-TTRm-MVM-coFVIIIIdeltaB-Sv40pA vector

**Figure 10:** Plasmid map of the pAAVss-SerpEnh-TTRm-MVM-coFVIIIIdeltaB-Sv40pA vector

**Figure 11:** Plasmid map of the pAAVss-3xSerpEnh-TTRm-MVM-coFVIIIIdeltaB-Sv40pA vector

**Figure 12:** Plasmid map of the pAAVss-TTRe-TTRm-MVM-coFVIIIIdeltaB-Sv40pA vector

5 **Figure 13:** Nucleotide sequence of pAAVsc-SerpEnh-TTRm-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:1); pAAVsc-3xSerpEnh-TTRm-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:2); pAAVsc-TTRe-TTRm-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:3); pAAVsc-3xSerpEnh-TTRe-TTRm-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:4); the Serpin enhancer (SerpEnh) (SEQ ID NO:5); the minimal transthyretin (TTRm) promoter (SEQ ID NO:6); the 5' untranslated region (UTR) of TTRm (TTRm5'UTR) (SEQ ID NO:7); the Minute Virus of Mouse (MVM) intron (SEQ ID NO:8); the codon-optimized transgene encoding human FIX Padua mutant (Co-FIX-R338L) (SEQ ID NO:9); the Bovine Growth Hormone polyadenylation signal (BGHpA) (SEQ ID NO:10); triple tandem repeat of the Serpin enhancer (3xSERP) (SEQ ID NO:11, the nucleotide linking the repeats is indicated in bold); the transthyretin enhancer (TTRe) (SEQ ID NO:12); a triple tandem repeat of the Serpin enhancer (underlined) linked to the transthyretin enhancer (italics) (3xSERP-**Flank-TTRe**) (SEQ ID NO:13); pAAVsc-3xSerpEnh-TTRe-TTRm-MVM-co-FIX-R338L-Synt.pA (SEQ ID NO:25); **Flank-3xSERP-Flank-TTRe** (SEQ ID NO:26); **Flank-3xSERP-Flank-TTRe-Flank** (SEQ ID NO:27); **Flank-3xSERP-Flank-TTRe-Flank-TTRm** (SEQ ID NO:28); **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank** (SEQ ID NO:29); **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM** (SEQ ID NO:30); **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L** (SEQ ID NO:32); **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L-Flank** (SEQ ID NO:33); **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L-Flank-BGHpA** (SEQ ID NO:34); **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L-Flank-BGHpA-Flank** (SEQ ID NO:35); **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L-Flank-Synt.pA** (SEQ ID NO:36); **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L-Flank-Synt.pA-Flank** (SEQ ID NO:37).

30 **Figure 14:** Nucleotide sequence of pAAVss-TTRm-MVM-coFVIIIIdeltaB-Sv40pA (SEQ ID NO:14); pAAVss-SerpEnh-TTRm-MVM-coFVIIIIdeltaB-Sv40pA (SEQ ID NO:15); pAAVss-3xSerpEnh-TTRm-MVM-coFVIIIIdeltaB-Sv40pA (SEQ ID NO:16); pAAVss-TTRe-TTRm-MVM-coFVIIIIdeltaB-Sv40pA (SEQ ID NO:17); codon-optimized transgene encoding B domain deleted human factor VIII (coFVIIIIdeltaB) (SEQ ID NO:18); Simian virus 40 polyadenylation signal (SV40polyA) (SEQ ID NO:19); pAAVss-3xSerpEnh-TTRm-MVM-coFVIIIIdeltaB-Synt.pA (SEQ ID NO:20); pAAVss-3xSerpEnh-TTRm-coFVIIIIdeltaB-Synt.pA (SEQ ID NO:21); pAAVss-3xSerpEnh-TTRe-TTRm-MVM-coFVIIIIdeltaB-Sv40pA (SEQ ID NO:22); pAAVss-3xSerpEnh-

TTR $\epsilon$ -TTR $\mu$ -coFVIII $\Delta$ B-Synt.pA (SEQ ID NO:23); pAAVss-TTR $\epsilon$ -TTR $\mu$ -coFVIII $\Delta$ B-Synt.pA (SEQ ID NO:24); **Flank-3xSERP-Flank** (SEQ ID NO:38); **Flank-3xSERP-Flank-TTR $\epsilon$**  (SEQ ID NO:39); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank** (SEQ ID NO:40); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$**  (SEQ ID NO:41); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -Flank** (SEQ ID NO:42); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -Flank-coFVIII $\Delta$ B** (SEQ ID NO:43); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -Flank-coFVIII $\Delta$ B-Flank** (SEQ ID NO:44); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -Flank-coFVIII $\Delta$ B-Flank-SV40pA** (SEQ ID NO:45); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -Flank-coFVIII $\Delta$ B-Flank-SV40pA-Flank** (SEQ ID NO:46); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -Flank-coFVIII $\Delta$ B-Flank-Synt.pA** (SEQ ID NO:47); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -Flank-coFVIII $\Delta$ B-Flank-SyntpA-Flank** (SEQ ID NO:48); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -MVM-Flank** (SEQ ID NO:49); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -MVM-Flank-coFVIII $\Delta$ B** (SEQ ID NO:50); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -MVM-Flank-coFVIII $\Delta$ B-Flank** (SEQ ID NO:51); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -MVM-Flank-coFVIII $\Delta$ B-Flank-SV40pA** (SEQ ID NO:52); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -MVM-Flank-coFVIII $\Delta$ B-Flank-SV40pA-Flank** (SEQ ID NO:53); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -MVM-Flank-coFVIII $\Delta$ B-Flank-Synt.pA** (SEQ ID NO:54); **Flank-3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$ -MVM-Flank-coFVIII $\Delta$ B-Flank-Synt.pA-Flank** (SEQ ID NO:55); synthetic polyadenylation signal (Synt.pA) (SEQ ID NO:56); **3xSERP-Flank-TTR $\epsilon$ -Flank** (SEQ ID NO:57); **3xSERP-Flank-TTR $\epsilon$ -Flank-TTR $\mu$**  (SEQ ID NO:58).

**Figure 15:** FVIII protein levels in C57BL6 mice injected with the pAAVss-3XSerpEnh-TTRENh-TTR $\mu$ -MVM-co-hFVIII- $\Delta$ B-SV40pA and pAAVss-TTRENh-TTR $\mu$ -MVM-co-hFVIII- $\Delta$ B-SV40pA plasmids as described in Figure 2. C57BL6 mice were injected with 300 ng of the respective plasmids. FVIII protein levels were measured by ELISA in plasma samples collected on day 1 (black bar) and day 2 (white bar) post injection.

**Figure 16:** Plasmid map of the pAAVsc-3xSerpEnh-TTR $\epsilon$ -TTR $\mu$ -MVM-co-FIX-R338L-Synt.pA vector

**Figure 17:** Plasmid map of the pAAVss-3xSerpEnh-TTR $\mu$ -MVM-coFVIII $\Delta$ B-Synt.pA vector

**Figure 18:** Plasmid map of the pAAVss-3xSerpEnh-TTR $\mu$ -coFVIII $\Delta$ B-Synt.pA vector

**Figure 19:** Plasmid map of the pAAVss-3xSerpEnh-TTR $\epsilon$ -TTR $\mu$ -MVM-coFVIII $\Delta$ B-Sv40pA vector

**Figure 20:** Plasmid map of the pAAVss-3xSerpEnh-TTR $\epsilon$ -TTR $\mu$ -coFVIII $\Delta$ B-Synt.pA vector

**Figure 21:** Plasmid map of the pAAVss-TTR $\epsilon$ -TTR $\mu$ -coFVIII $\Delta$ B-Synt.pA vector.

**Figure 22:** Design of comparative example of self-complementary (sc), double-stranded adeno-associated viral (AAV) vectors expressing co-FVIII  $\Delta$ B. The following vectors were

compared for FVIII expression levels: pAAVss-TTRm-MVM-coFVIIIIdeltaB-Sv40pA (SEQ ID NO. 14); pAAVss-3xSerpEnh-TTRm-MVM-coFVIIIIdeltaB-Sv40pA (SEQ ID NO:16); pAAVss-TTRe-TTRm-MVM-coFVIIIIdeltaB-Sv40pA (SEQ ID NO:17) and pAAVss-3xSerpEnh-TTRe-TTRm-MVM-coFVIIIIdeltaB-Sv40pA (SEQ ID NO:22).

- 5 **Figure 23:** Design of comparative example of self-complementary (sc), double-stranded adeno-associated viral (AAV) vectors expressing co-FIX. The following vectors were compared for FIX expression: pAAVss-3xSerpEnh-TTRe-AAT-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:65); pAAVss-3xSerpEnh-TTRe-AAT-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:66); pAAVss-3xSerpEnh-TTRe-AAT-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:67); and  
10 pAAVss-3xSerpEnh-TTRe-AAT-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:68).

**Figure 24:** Nucleotide sequence of AAT promotor (SEQ ID 64); pAAVss-3xSerpEnh-TTRe-AAT-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:65); pAAVss-3xSerpEnh-TTRe-AAT-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:66); pAAVss-3xSerpEnh-TTRe-AAT-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:67); and pAAVss-3xSerpEnh-TTRe-AAT-MVM-co-FIX-R338L-BGHpA  
15 (SEQ ID NO:68).

**Figure 25:** a) Graph depicting the effect of the 3XSerp enhancer on the TTReh-TTRm promoter in regulating the FVIII expression in C57BL6 mice injected with 300ng of respective plasmids. The FVIII expression profile was tested using the ELISA, in the plasma samples collected Day 1. The presence of 3XSerp enhancer seems to elevate the FVIII expression by 8  
20 fold. b) Graph comparing different constructs tested on FVIII expression as outlined in example 2.

## DETAILED DESCRIPTION OF THE INVENTION

25 The present invention will be described with respect to particular embodiments and with reference to certain drawings but the invention is not limited thereto but only by the claims. Any reference signs in the claims shall not be construed as limiting the scope. The drawings described are only schematic and are non-limiting. In the drawings, the size of some of the elements may be exaggerated and not drawn on scale for illustrative purposes.

30 Where the term "comprising" is used in the present description and claims, it does not exclude other elements or steps. The term "comprising" also encompasses the more specific embodiments defined as "consisting of" and "consisting essentially of".

Where an indefinite or definite article is used when referring to a singular noun e.g. "a" or "an", "the", this includes a plural of that noun unless something else is specifically stated.

35 Furthermore, the terms first, second, third and the like in the description and in the claims, are

used for distinguishing between similar elements and not necessarily for describing a sequential or chronological order.

It is to be understood that the terms so used are interchangeable under appropriate circumstances and that the embodiments of the invention described herein are capable of  
5 operation in other sequences than described or illustrated herein.

The following terms or definitions are provided to aid in the understanding of the invention. Unless specifically defined herein, all terms used herein have the same meaning as they would to one skilled in the art of the present invention. Practitioners are particularly directed to  
10 Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Press, Plainsview, New York (1989); and Ausubel et al., Current Protocols in Molecular Biology (Supplement 47), John Wiley & Sons, New York (1999), for definitions and terms of the art.

The definitions provided herein should not be construed to have a scope less than understood by a person of ordinary skill in the art.

The invention relates to nucleic acid expression cassettes and expression vectors comprising  
15 said nucleic acid expression cassettes for enhancing liver-specific expression of a (trans)gene.

As used herein, the term “nucleic acid expression cassette” refers to nucleic acid molecules that include one or more transcriptional control elements (such as, but not limited to promoters, enhancers and/or regulatory elements, polyadenylation sequences, and introns) that direct (trans)gene expression in one or more desired cell types, tissues or organs.  
20 Typically, the nucleic acid expression cassettes described herein will contain the FIX transgene or the FVIII transgene as defined herein.

The invention provides nucleic acid expression cassettes comprising one or more liver-specific nucleic acid regulatory elements, operably linked to a promoter and a transgene.

The term “operably linked” as used herein refers to the arrangement of various nucleic acid  
25 molecule elements relative to each such that the elements are functionally connected and are able to interact with each other. Such elements may include, without limitation, a promoter, an enhancer and/or a regulatory element, a polyadenylation sequence, one or more introns and/or exons, and a coding sequence of a gene of interest to be expressed (i.e., the transgene). The nucleic acid sequence elements, when properly oriented or operably linked,  
30 act together to modulate the activity of one another, and ultimately may affect the level of expression of the transgene. By modulate is meant increasing, decreasing, or maintaining the level of activity of a particular element. The position of each element relative to other elements may be expressed in terms of the 5' terminus and the 3' terminus of each element, and the distance between any particular elements may be referenced by the number of intervening  
35 nucleotides, or base pairs, between the elements.

A “regulatory element” as used herein refers to transcriptional control elements, in particular non-coding cis-acting transcriptional control elements, capable of regulating and/or controlling transcription of a gene, in particular tissue-specific transcription of a gene. Regulatory elements comprise at least one transcription factor binding site (TFBS), more in particular at least one binding site for a tissue-specific transcription factor, most particularly at least one binding site for a liver-specific transcription factor. Typically, regulatory elements as used herein increase or enhance promoter-driven gene expression when compared to the transcription of the gene from the promoter alone, without the regulatory elements. Thus, regulatory elements particularly comprise enhancer sequences, although it is to be understood that the regulatory elements enhancing transcription are not limited to typical far upstream enhancer sequences, but may occur at any distance of the gene they regulate. Indeed, it is known in the art that sequences regulating transcription may be situated either upstream (e.g. in the promoter region) or downstream (e.g. in the 3'UTR) of the gene they regulate in vivo, and may be located in the immediate vicinity of the gene or further away. Of note, although regulatory elements as disclosed herein typically are naturally occurring sequences, combinations of (parts of) such regulatory elements or several copies of a regulatory element, i.e. non-naturally occurring sequences, are themselves also envisaged as regulatory element. Regulatory elements as used herein may be part of a larger sequence involved in transcriptional control, e.g. part of a promoter sequence. However, regulatory elements alone are typically not sufficient to initiate transcription, but require a promoter to this end.

The one or more regulatory elements contained in the nucleic acid expression cassettes and vectors disclosed herein are preferably liver-specific. Non-limiting examples of liver-specific regulatory elements are disclosed in WO 2009/130208, which is specifically incorporated by reference herein. Another example of a liver-specific regulatory element is a regulatory element derived from the transthyretin (TTR) gene, such as the regulatory element defined by SEQ ID NO:12, also referred to herein as “TTRe” or “TTREnh”(Wu et al., 2008). 'Liver-specific expression', as used in the application, refers to the preferential or predominant expression of a (trans)gene (as RNA and/or polypeptide) in the liver as compared to other tissues. According to particular embodiments, at least 50% of the (trans)gene expression occurs within the liver. According to more particular embodiments, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99% or 100% of the (trans)gene expression occurs within the liver. According to a particular embodiment, liver-specific expression entails that there is no 'leakage' of expressed gene product to other organs, such as spleen, muscle, heart and/or lung. The same applies mutatis mutandis for hepatocyte-specific expression, which may be considered as a particular form of liver-specific expression. Throughout the application, where liver-specific is mentioned in the context of expression, hepatocyte-specific expression is also explicitly envisaged. Similarly, where

tissue-specific expression is used in the application, cell-type specific expression of the cell type(s) predominantly making up the tissue is also envisaged.

Preferably, the one or more regulatory element in the nucleic acid expression cassettes and vectors disclosed herein is fully functional while being only of limited length. This allows its use in vectors or nucleic acid expression cassettes without unduly restricting their payload capacity. Accordingly, in embodiments, the one or more regulatory element in the expression cassettes and vectors disclosed herein is a nucleic acid of 1000 nucleotides or less, 800 nucleotides or less, or 600 nucleotides or less, preferably 400 nucleotides or less, such as 300 nucleotides or less, 200 nucleotides or less, 150 nucleotides or less, or 100 nucleotides or less (i.e. the nucleic acid regulatory element has a maximal length of 1000 nucleotides, 800 nucleotides, 600 nucleotides, 400 nucleotides, 300 nucleotides, 200 nucleotides, 150 nucleotides, or 100 nucleotides).

However, it is to be understood that the disclosed nucleic acid regulatory elements retain regulatory activity (i.e. with regard to specificity and/or activity of transcription) and thus they particularly have a minimum length of 20 nucleotides, 25 nucleotides, 30 nucleotides, 35 nucleotides, 40 nucleotides, 45 nucleotides, 50 nucleotides, 55 nucleotides, 60 nucleotides, 65 nucleotides, or 70 nucleotides. In preferred embodiments, the one or more regulatory element in the nucleic acid expression cassettes and vectors disclosed herein comprises a sequence from SERPINA1 regulatory elements, i.e. regulatory elements that control expression of the SERPINA1 gene *in vivo*. Said regulatory element preferably comprises, consists essentially of or consists of the sequence as defined in SEQ ID NO:5, a sequence having at least 85%, preferably at least 90%, more preferably at least 95%, such as 96%, 97%, 98% or 99%, identity to said sequence, or a functional fragment thereof. Also preferably, said regulatory element has a maximal length of 150 nucleotides or less, preferably 100 nucleotides or less, and comprises, consists essentially of or consists of the sequence as defined in SEQ ID NO:5, a sequence having at least 85%, preferably at least 90%, more preferably at least 95%, such as 96%, 97%, 98% or 99%, identity to said sequence, or a functional fragment thereof. The liver-specific nucleic acid regulatory element consisting of SEQ ID NO:5 is herein referred to as "the Serpin enhancer", "SerpEnh", or "Serp".

In particularly preferred embodiments, the nucleic acid expression cassettes and vectors disclosed herein comprise two or more, such as two, three, four, five or six, preferably three, (tandem) repeats of a liver-specific regulatory element comprising, consisting essentially of or consisting of SEQ ID NO:5, or a sequence having at least 85%, preferably at least 90%, more preferably at least 95%, such as 96%, 97%, 98% or 99%, identity to said sequence, more preferably a liver-specific regulatory element of 150 nucleotides or less, preferably 100 nucleotides or less, more preferably 80 nucleotides or less, comprising, consisting essentially

of or consisting of SEQ ID NO:5, or a sequence having at least 85%, preferably at least 90%, more preferably at least 95%, such as 96%, 97%, 98% or 99%, identity to said sequence. A preferred nucleic acid regulatory element comprising three tandem repeats of SEQ ID NO:5 is herein referred to as “3xSerp” and is defined by SEQ ID NO:11.

5 In further embodiments, the nucleic acid expression cassettes and vectors disclosed herein comprise two or more, such as two, three, four, five or six, more preferably three, (tandem) repeats of a liver-specific regulatory element comprising, consisting essentially of or consisting of SEQ ID NO:5, or a sequence having at least 85%, preferably at least 90%, more preferably at least 95%, such as 96%, 97%, 98% or 99%, identity to said sequence, preferably a liver-  
10 specific regulatory element of 150 nucleotides or less, preferably 100 nucleotides or less, more preferably 80 nucleotides or less, comprising, consisting essentially of or consisting of SEQ ID NO:5, or a sequence having at least 85%, preferably at least 90%, more preferably at least 95%, such as 96%, 97%, 98% or 99%, identity to said sequence; and a regulatory element comprising, consisting essentially of or consisting of SEQ ID NO:12, preferably a regulatory  
15 element of 150 nucleotides or less, preferably 120 nucleotides or less, comprising, consisting essentially of or consisting of SEQ ID NO:12. A preferred liver-specific nucleic acid regulatory element comprising three tandem repeats of SEQ ID NO:5, and SEQ ID NO:12, is herein referred to as “3xSerp-flank-TTRe” and is defined by SEQ ID NO:13. A further preferred liver-specific nucleic acid regulatory element comprising three tandem repeats of SEQ ID NO:5,  
20 and SEQ ID NO:12, is herein referred to as “3xSerp-flank-TTRe-flank” and is defined by SEQ ID NO:57. Preferably, the liver-specific nucleic acid regulatory element in the nucleic acid expression cassettes and vectors disclosed herein comprises three tandem repeats of SEQ ID NO:5, and SEQ ID NO:12; more preferably SEQ ID NO:13; even more preferably SEQ ID NO:57, such as SEQ ID NO:27 or SEQ ID NO:39. It has been shown herein that said specific  
25 combinations of liver-specific regulatory elements resulted in unexpectedly enhanced liver-specific expression of the transgene, in particular the FIX transgene or FVIII transgene described herein, operably linked thereto.

In further embodiments, said nucleic acid expression cassettes and vectors disclosed herein comprise three tandem repeats of SEQ ID NO:5 (such as SEQ ID NO:13), and a further  
30 enhancer element TTRe defined by SEQ ID NO:12, for example as defined by SEQ ID NO:13, in combination with a liver-specific promotor. In one particular example, said promotor is the TTRm minimal promotor as defined by SEQ ID NO:6. In an alternative embodiment, said liver-specific promotor is the AAT promotor, such as the promotor defined by SEQ ID NO:64. It has been shown herein that said specific combinations of liver-specific regulatory elements  
35 resulted in unexpectedly enhanced liver-specific expression of the transgene, in particular the FIX transgene or FVIII transgene described herein, operably linked thereto.

As used herein, the terms “identity” and “identical” and the like refer to the sequence similarity between two polymeric molecules, e.g., between two nucleic acid molecules, e.g., two DNA molecules. Sequence alignments and determination of sequence identity can be done, e.g., using the Basic Local Alignment Search Tool (BLAST) originally described by Altschul et al. 1990 (J Mol Biol 215: 403-10), such as the “Blast 2 sequences” algorithm described by Tatusova and Madden 1999 (FEMS Microbiol Lett 174: 247-250). Typically, the percentage sequence identity is calculated over the entire length of the sequence. As used herein, the term “substantially identical” denotes at least 90%, preferably at least 95%, such as 95%, 96%, 97%, 98% or 99%, sequence identity.

The term “functional fragment” as used in the application refers to fragments of the sequences disclosed herein that retain the capability of regulating liver-specific expression, i.e. they still confer tissue specificity and they are capable of regulating expression of a (trans)gene in the same way (although possibly not to the same extent) as the sequence from which they are derived. Fragments comprise at least 10 contiguous nucleotides from the sequence from which they are derived. In further particular embodiments, fragments comprise at least 15, at least 20, at least 25, at least 30, at least 35 or at least 40 contiguous nucleotides from the sequence from which they are derived. Also preferably, functional fragments may comprise at least 1, more preferably at least 2, at least 3, or at least 4, even more preferably at least 5, at least 10, or at least 15, of the transcription factor binding sites (TFBS) that are present in the sequence from which they are derived.

As used in the application, the term “promoter” refers to nucleic acid sequences that regulate, either directly or indirectly, the transcription of corresponding nucleic acid coding sequences to which they are operably linked (e.g. a transgene or endogenous gene). A promoter may function alone to regulate transcription or may act in concert with one or more other regulatory sequences (e.g. enhancers or silencers). In the context of the present application, a promoter is typically operably linked to regulatory elements to regulate transcription of a transgene.

When a regulatory element as described herein is operably linked to both a promoter and a transgene, the regulatory element can (1) confer a significant degree of liver specific expression in vivo (and/or in hepatocytes/ hepatic cell lines in vitro) of the transgene, and/or (2) can increase the level of expression of the transgene in the liver (and/or in hepatocytes/hepatocyte cell lines in vitro).

According to a particular embodiment, the promoter contained in the nucleic acid expression cassettes and vectors disclosed herein is a liver-specific promoter. This is to increase liver specificity and/or avoid leakage of expression in other tissues. According to a further particular embodiment, the liver-specific promoter is from the transthyretin (TTR) gene or from the Alpha-1-antitrypsin (AAT) gene. According to yet a further particular embodiment, the TTR

promoter is a minimal promoter (also referred to as TTRm or TTRmin herein), most particularly the minimal TTR promoter as defined in SEQ ID NO: 6. According to yet a further particular embodiment, the AAT promoter is as defined in SEQ ID NO: 64.

According to particular embodiments, the promoter in the nucleic acid expression cassettes and vectors disclosed herein is a minimal promoter.

A 'minimal promoter' as used herein is part of a full-size promoter still capable of driving expression, but lacking at least part of the sequence that contributes to regulating (e.g. tissue-specific) expression. This definition covers both promoters from which (tissue-specific) regulatory elements have been deleted- that are capable of driving expression of a gene but have lost their ability to express that gene in a tissue-specific fashion and promoters from which (tissue-specific) regulatory elements have been deleted that are capable of driving (possibly decreased) expression of a gene but have not necessarily lost their ability to express that gene in a tissue-specific fashion. Minimal promoters have been extensively documented in the art, a non-limiting list of minimal promoters is provided in the specification.

The term "liver-specific promoter" encompasses any promoter that confers liver-specific expression to a (trans)gene. Non-limiting examples of liver-specific promoters are provided on the Liver Specific Gene Promoter Database (LSPD, <http://rulai.cshl.edu/LSPD/>), and include, for example, the transthyretin (TTR) promoter or TTR-minimal promoter (TTRm), the alpha 1-antitrypsin (AAT) promoter, the albumin (ALB) promoter or minimal promoter, the apolipoprotein A1 (APOA1) promoter or minimal promoter, the complement factor B (CFB) promoter, the ketohexokinase (KHK) promoter, the hemopexin (HPX) promoter or minimal promoter, the nicotinamide N-methyltransferase (NNMT) promoter or minimal promoter, the (liver) carboxylesterase 1 (CES1) promoter or minimal promoter, the protein C (PROC) promoter or minimal promoter, the apolipoprotein C3 (APOC3) promoter or minimal promoter, the mannan-binding lectin serine protease 2 (MASP2) promoter or minimal promoter, the hepcidin antimicrobial peptide (HAMP) promoter or minimal promoter, and the serpin peptidase inhibitor, clade C (antithrombin), member 1 (SERPINC1) promoter or minimal promoter.

In particularly preferred embodiments, the promoter is a mammalian liver-specific promoter, in particular a murine or human liver-specific promoter. More preferably, said promoters are the respective minimal promoters

The term "liver-specific expression" as used in the application, refers to the preferential or predominant expression of a (trans)gene (as RNA and/or polypeptide) in the liver, in liver tissue or in liver cells, as compared to other (i.e. non-liver) tissues or cells. According to particular embodiments, at least 50%, more particularly at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99% or

100% of the (trans)gene expression occurs within liver tissue or liver cells. According to a particular embodiment, liver-specific expression entails that there is no 'leakage' of expressed gene product to other organs or tissue than liver, such as lung, muscle, brain, kidney and/or spleen. The same applies mutatis mutandis for hepatocyte-specific expression and  
5 hepatoblast-specific expression, which may be considered as particular forms of liver-specific expression. Throughout the application, where liver-specific is mentioned in the context of expression, hepatocyte-specific expression and hepatoblast-specific expression are also explicitly envisaged.

As used herein, the term "liver cells" encompasses the cells predominantly populating the liver  
10 and encompasses mainly hepatocytes, oval cells, liver sinusoidal endothelial cells (LSEC) and cholangiocytes (epithelial cells forming the bile ducts).

The term "hepatocyte," as used herein, refers to a cell that has been differentiated from a progenitor hepatoblast such that it is capable of expressing liver-specific phenotype under appropriate conditions. The term "hepatocyte" also refers to hepatocytes that are de-  
15 differentiated. The term includes cells in vivo and cells cultured ex vivo regardless of whether such cells are primary or passaged.

The term "hepatoblast" as used herein, refers to an embryonic cell in the mesoderm that differentiates to give rise to a hepatocyte, an oval cell, or a cholangiocyte. The term includes cells in vivo and cells cultured ex vivo regardless of whether such cells are primary or  
20 passaged.

The term "transgene" or "(trans)gene" as used herein refers to particular nucleic acid sequences encoding a polypeptide or a portion of a polypeptide to be expressed in a cell into which the nucleic acid sequence is inserted. However, it is also possible that transgenes are expressed as RNA, typically to lower the amount of a particular polypeptide in a cell into which  
25 the nucleic acid sequence is inserted. These RNA molecules include but are not limited to molecules that exert their function through RNA interference (shRNA, RNAi), micro-RNA regulation (miRNA), catalytic RNA, antisense RNA, RNA aptamers, etc. How the nucleic acid sequence is introduced into a cell is not essential to the invention, it may for instance be through integration in the genome or as an episomal plasmid. Of note, expression of the  
30 transgene may be restricted to a subset of the cells into which the nucleic acid sequence is inserted. The term 'transgene' is meant to include (1) a nucleic acid sequence that is not naturally found in the cell (i.e., a heterologous nucleic acid sequence); (2) a nucleic acid sequence that is a mutant form of a nucleic acid sequence naturally found in the cell into which it has been introduced ; (3) a nucleic acid sequence that serves to add additional copies of the  
35 same (i.e., homologous) or a similar nucleic acid sequence naturally occurring in the cell into which it has been introduced ; or (4) a silent naturally occurring or homologous nucleic acid

sequence whose expression is induced in the cell into which it has been introduced. By 'mutant form' is meant a nucleic acid sequence that contains one or more nucleotides that are different from the wild-type or naturally occurring sequence, i.e., the mutant nucleic acid sequence contains one or more nucleotide substitutions, deletions, and/or insertions. In some cases, the transgene may also include a sequence encoding a leader peptide or signal sequence such that the transgene product will be secreted from the cell.

Typically, the transgenes in the expression cassettes and vectors described herein encode coagulation factor IX or coagulation factor VIII.

The term "coagulation factor IX" has the meaning as known in the art. Synonyms of coagulation factor IX are "FIX" or "Christmas factor" or "F9" and can be used interchangeably. In particular, the term "coagulation factor IX" encompasses the human protein encoded by the mRNA sequence as defined in Genbank accession number NM\_000133.

Preferably, said FIX is a mutated FIX, which is hyperactive or hyper-functional as compared to the wild type FIX. Modifying functional activity of human coagulation factor can be done by bioengineering e.g. by introduction of point mutations. By this approach a hyperactive R338A variant was reported, which showed a 3 fold increased clotting activity compared to the wild type human FIX in an *in vitro* activated partial thromboplastin time assay (APPT) (Chang et al., 1998) and a 2 to 6-fold higher specific activity in hemophilia B mice transduced with the mutant FIX gene (Schuettrumpf et al., 2005). Further exemplary FIX point-mutants or domain exchange mutants with even higher clotting activities have been described: FIX, with the EGF-1 domain replaced with the EGF-1 domain from FVII, alone or in combination with a R338A point mutation (Brunetti-Pierri et al., 2009), the V86A/E277A/R338A triple mutant (Lin et al., 2010), the Y259F, K265T, and/or Y345T single, double or triple mutants (Milanov, et al., 2012), and the G190V point mutant (Kao et al., 2010), all incorporated herein by reference. In a particularly preferred embodiment, the FIX mutant is the one described by Simioni et al., in 2009 and denominated as the "factor IX Padua" mutant, causing X-linked thrombophilia. Said mutant factor IX is hyperactive and carries an R338L amino acid substitution. In a preferred embodiment of the present invention, the FIX transgene used in nucleic acid expression cassettes and expression vectors described herein encodes the human FIX protein, most preferably the FIX transgene encodes for the Padua mutant of the human FIX protein. Accordingly, in a particularly preferred embodiment of the present invention, the transgene has SEQ ID NO:9 (i.e. codon-optimized transgene encoding for the Padua mutant of the human FIX protein).

The term "coagulation factor VIII" has the meaning as known in the art. Synonyms of coagulation factor VIII are "FVIII" or "anti-hemophilic factor" or "AHF" and can be used interchangeably herein. The term "coagulation factor VIII" encompasses, for example, the

human protein having the amino acid sequence as defined in Uniprot accession number P00451.

In embodiments, said FVIII is a FVIII wherein the B domain is deleted (i.e. B domain deleted FVIII, also referred to as BDD FVIII or FVIII $\Delta$ B or FVIIIdeltaB herein). The term “B domain  
5 deleted FVIII” encompasses for example, but without limitation, FVIII mutants wherein whole or a part of the B domain is deleted and FVIII mutants wherein the B domain is replaced by a linker. Non-limiting examples of B domain deleted FVIII are described in Ward et al. (2011) and WO 2011/005968, which are specifically incorporated by reference herein.

In preferred embodiments, said FVIII is B domain deleted FVIII wherein the B domain is  
10 replaced by a linker having the following sequence: SFSQNPPVLTRHQR (SEQ ID NO: 59) (i.e. SQ FVIII as defined in Ward et al. (2011)). In particularly preferred embodiments, said transgene encoding FVIII has SEQ ID NO:18 (i.e. codon-optimized transgene encoding B domain deleted human FVIII, also referred to herein as (h)FVIIIcopt or co(h)FVIIIdeltaB or co(h)FVIIIdeltaB transgene), as disclosed also in WO 2011/005968.

15 Other sequences may be incorporated in the nucleic acid expression cassette disclosed herein as well, typically to further increase or stabilize the expression of the transgene product (e.g. introns and/or polyadenylation sequences).

Any intron can be utilized in the expression cassettes described herein. The term “intron” encompasses any portion of a whole intron that is large enough to be recognized and spliced  
20 by the nuclear splicing apparatus. Typically, short, functional, intron sequences are preferred in order to keep the size of the expression cassette as small as possible which facilitates the construction and manipulation of the expression cassette. In some embodiments, the intron is obtained from a gene that encodes the protein that is encoded by the coding sequence within the expression cassette. The intron can be located 5' to the coding sequence, 3' to the coding  
25 sequence, or within the coding sequence. An advantage of locating the intron 5' to the coding sequence is to minimize the chance of the intron interfering with the function of the polyadenylation signal. In embodiments, the nucleic acid expression cassette disclosed herein further comprises an intron. Non-limiting examples of suitable introns are Minute Virus of Mice (MVM) intron, beta-globin intron (betaIVS-II), factor IX (FIX) intron A, Simian virus 40 (SV40)  
30 small-t intron, and beta-actin intron. Preferably, the intron is an MVM intron, more preferably the MVM mini-intron as defined by SEQ ID NO: 8. The cloning of the MVM intron into a nucleic acid expression cassette described herein was shown to result in unexpectedly high expression levels of the transgene operably linked thereto.

Any polyadenylation signal that directs the synthesis of a polyA tail is useful in the expression  
35 cassettes described herein, examples of those are well known to one of skill in the art. Exemplary polyadenylation signals include, but are not limited to, polyA sequences derived

from the Simian virus 40 (SV40) late gene, the bovine growth hormone (BGH) polyadenylation signal, the minimal rabbit  $\beta$ -globin (mRBG) gene, and the synthetic polyA (SPA) site as described in Levitt et al. (1989, Genes Dev 3:1019-1025) (SEQ ID NO:56). Preferably, the polyadenylation signal is the bovine growth hormone (BGH) polyadenylation signal (SEQ ID NO:10) or the Simian virus 40 (SV40) polyadenylation signal (SEQ ID NO:19).

Typically, the nucleic acid expression cassette according to the invention comprises a promotor, an enhancer, a (trans)gene, and a transcription terminator.

In a typical embodiment of the present invention, a nucleic acid expression cassette is disclosed and comprises:

- 10 - a liver-specific nucleic acid regulatory element, preferably a regulatory element comprising three tandem repeats of the Serpin enhancer (e.g. SEQ ID NO.5), such as a regulatory element comprising SEQ ID NO:11 and the transthyretin enhancer (TTRe) as defined by SEQ ID NO.12,
- a liver-specific promoter, and
- 15 - a transgene.

In a typical embodiment of the present invention, a nucleic acid expression cassette is disclosed and comprises:

- a liver-specific nucleic acid regulatory element, preferably a regulatory element comprising three tandem repeats of the Serpin enhancer (e.g. SEQ ID NO.5), such as a regulatory element comprising SEQ ID NO:11 and the transthyretin enhancer (TTRe) as defined by SEQ ID NO.12,
- 20 - the liver-specific TTRm promoter (e.g. defined by SEQ ID NO.6, and
- a transgene, preferably wherein the combination of the TTRe and TTRm nucleic acids is defined by SEQ ID NO.69.

25 In a typical embodiment of the present invention, a nucleic acid expression cassette is disclosed and comprises:

- a liver-specific nucleic acid regulatory element, preferably a regulatory element comprising three tandem repeats of the Serpin enhancer (e.g. SEQ ID NO.5), such as a regulatory element comprising SEQ ID NO:11 and the transthyretin enhancer (TTRe) as defined by SEQ ID NO.12,
- 30 - the liver-specific TTRm promoter, e.g. as defined by SEQ ID NO.6,
- an intron, preferably the MVM intron, e.g. as defined by SEQ ID NO.8, and

- a transgene preferably wherein the combination of the TTRe and TTRm nucleic acids is defined by SEQ ID NO.69.

In a typical embodiment of the present invention, a nucleic acid expression cassette is disclosed and comprises:

- 5 - a liver-specific nucleic acid regulatory element, preferably a regulatory element comprising three tandem repeats of the Serpin enhancer (e.g. SEQ ID NO.5), such as a regulatory element comprising SEQ ID NO:11 and the transthyretin enhancer (TTRe) as defined by SEQ ID NO.12,
- the liver-specific TTRm promoter, e.g. as defined by SEQ ID NO.6,
- 10 - an intron, preferably the MVM intron, e.g. as defined by SEQ ID NO.8, and
- a transgene, preferably the FIX or FVIII transgene as defined herein elsewhere and optionally a transcription terminator as defined herein elsewhere, preferably wherein the combination of the TTRe and TTRm nucleic acids is defined by SEQ ID NO.69.

In another preferred embodiment of the present invention, a nucleic acid expression cassette  
15 is disclosed and comprises:

- a liver-specific nucleic acid regulatory element, preferably a regulatory element comprising three tandem repeats of the Serpin enhancer (e.g. SEQ ID NO.5), such as a regulatory element comprising SEQ ID NO:11 and the transthyretin enhancer (TTRe) as defined by SEQ ID NO.12,
- 20 - the liver-specific AAT promoter, e.g. as defined by SEQ ID NO.64 , and
- a transgene.

In another preferred embodiment of the present invention, a nucleic acid expression cassette is disclosed and comprises:

- 25 - a liver-specific nucleic acid regulatory element, preferably a regulatory element comprising three tandem repeats of the Serpin enhancer (e.g. SEQ ID NO.5), such as a regulatory element comprising SEQ ID NO:11 and the transthyretin enhancer (TTRe) as defined by SEQ ID NO.12,
- the liver-specific AAT promoter, e.g. as defined by SEQ ID NO.64 , and
- an intron, preferably the MVM intron, e.g. as defined by SEQ ID NO.8, and
- 30 - a transgene.

In another preferred embodiment of the present invention, a nucleic acid expression cassette is disclosed and comprises:

- a liver-specific nucleic acid regulatory element, preferably a regulatory element comprising three tandem repeats of the Serpin enhancer (e.g. SEQ ID NO.5), such as a regulatory element comprising SEQ ID NO:11 and the transthyretin enhancer (TTRe) as defined by SEQ ID NO.12,

- 5 - the liver-specific AAT promoter, e.g. as defined by SEQ ID NO.64, and
- an intron, preferably the MVM intron, e.g. as defined by SEQ ID NO.8, and
- a transgene, preferably the FIX or FVIII transgene as defined herein elsewhere and optionally a transcription terminator as defined herein elsewhere.

10 In a typical embodiment of the invention, said nucleic acid expression cassette disclosed herein comprises:

- a liver-specific regulatory element, preferably three tandem repeats of the Serpin enhancer (SEQ ID NO.5), e.g. a regulatory element as defined by SEQ ID NO:11,

- a promoter, preferably the minimal TTR promoter,

15 - an intron, preferably the MVM intron

- a transgene, preferably codon-optimized factor IX cDNA, even more preferably codon-optimized factor IX Padua cDNA

- a transcription terminator, preferably a polyadenylation signal such as the bovine growth hormone polyadenylation signal (BGHpA) e.g. as defined by SEQ ID NO.10, or the synthetic

20 polyA site as defined by SEQ ID NO:56.

In a further typical embodiment of the present invention, said nucleic acid expression cassette disclosed herein comprises:

- a liver-specific regulatory element, preferably three tandem repeats of the Serpin enhancer and the transthyretin enhancer (TTRe) (e.g. a regulatory element comprising SEQ ID NO:13,

25 preferably comprising SEQ ID NO:57),

- a promoter, preferably the minimal TTR promoter,

- an intron, preferably the MVM intron,

- a (trans)gene, preferably codon-optimized factor IX cDNA, even more preferably codon-optimized factor IX Padua cDNA,

30 - a transcription terminator, preferably a polyadenylation signal such as the bovine growth hormone polyadenylation signal (BGHpA) or the synthetic polyA site as defined by SEQ ID NO:56.

In another typical embodiment of the present invention, said nucleic acid expression cassette disclosed herein comprises:

- a liver-specific regulatory element, preferably a regulatory element comprising three tandem repeats of the Serpin enhancer (e.g. a regulatory element comprising SEQ ID NO:11), more preferably three tandem repeats of the Serpin enhancer and the transthyretin enhancer (TTRe) (e.g. a regulatory element comprising SEQ ID NO:13, preferably comprising SEQ ID NO:57),
- a promoter, preferably the minimal TTR promoter,
- an intron, preferably the MVM intron,
- a (trans)gene, preferably codon-optimized factor VIII cDNA, even more preferably codon-optimized B domain deleted factor VIII cDNA,
- a transcription terminator, preferably a polyadenylation signal such as the Simian vacuolating virus 40 or Simian virus 40 (SV40) polyadenylation signal or the synthetic polyA site as defined by SEQ ID NO:56.

In another typical embodiment of the present invention, said nucleic acid expression cassette disclosed herein comprises:

- a liver-specific regulatory element, preferably a regulatory element comprising three tandem repeats of the Serpin enhancer (e.g. SEQ ID NO.5), such as a regulatory element comprising SEQ ID NO:11 and the transthyretin enhancer (TTRe) as defined by SEQ ID NO.12, such as the regulatory element comprising SEQ ID NO:13, preferably comprising SEQ ID NO:57,
- a promoter, preferably the AAT promoter such as the promoter as defined by SEQ ID NO. 64,
- an intron, preferably the MVM intron such as the MVM intron as defined by SEQ ID NO.8,
- a (trans)gene, preferably codon-optimized factor IX cDNA, even more preferably codon-optimized factor IX Padua cDNA,
- a transcription terminator, preferably a polyadenylation signal such as the bovine growth hormone polyadenylation signal (BGHpA) as defined by SEQ ID NO.10, or the synthetic polyA site as defined by SEQ ID NO:56. As a non-limiting example, such a vector is defined by SEQ ID NO. 65 (cf. Figure 25).

In another typical embodiment of the present invention, said nucleic acid expression cassette disclosed herein comprises:

- a liver-specific regulatory element, preferably a regulatory element comprising three tandem repeats of the Serpin enhancer (e.g. SEQ ID NO.5), such as a regulatory element comprising SEQ ID NO:11,

5 - a promoter, preferably the AAT promoter such as the promoter as defined by SEQ ID NO. 64,

- an intron, preferably the MVM intron such as the MVM intron as defined by SEQ ID NO.8 ,

a (trans)gene, preferably codon-optimized factor IX cDNA, even more preferably codon-optimized factor IX Padua cDNA,

10 - a transcription terminator, preferably a polyadenylation signal such as the bovine growth hormone polyadenylation signal (BGHpA) as defined by SEQ ID NO.10, or the synthetic polyA site as defined by SEQ ID NO:56. As a non-limiting example, such a vector is defined by SEQ ID NO. 66 (cf. Figure 25).

In another typical embodiment of the present invention, said nucleic acid expression cassette disclosed herein comprises:

15 - a liver-specific regulatory element, preferably a regulatory element comprising the transthyretin enhancer (TTRe) as defined by SEQ ID NO.12, operably linked to three tandem repeats of the Serpin enhancer (e.g. SEQ ID NO.5), more preferably as defined by SEQ ID NO:11,

20 - a promoter, preferably the AAT promoter such as the promoter as defined by SEQ ID NO. 64,

- an intron, preferably the MVM intron such as the MVM intron as defined by SEQ ID NO.8,

a (trans)gene, preferably codon-optimized factor IX cDNA, even more preferably codon-optimized factor IX Padua cDNA,

25 - a transcription terminator, preferably a polyadenylation signal such as the bovine growth hormone polyadenylation signal (BGHpA) as defined by SEQ ID NO.10, or the synthetic polyA site as defined by SEQ ID NO:56. As a non-limiting example, such a vector is defined by SEQ ID NO.68 (cf. Figure 25).

30 The expression cassettes disclosed herein may be used as such, or typically, they may be part of a nucleic acid vector. Accordingly, a further aspect relates to the use of a nucleic acid expression cassette as described herein in a vector, in particular a nucleic acid vector.

In an aspect, the invention also provides a vector comprising a nucleic acid expression cassette as disclosed herein.

The term 'vector' as used in the application refers to nucleic acid molecules, usually double-stranded DNA, which may have inserted into it another nucleic acid molecule (the insert nucleic acid molecule) such as, but not limited to, a cDNA molecule. The vector is used to transport the insert nucleic acid molecule into a suitable host cell. A vector may contain the  
5 necessary elements that permit transcribing the insert nucleic acid molecule, and, optionally, translating the transcript into a polypeptide. The insert nucleic acid molecule may be derived from the host cell, or may be derived from a different cell or organism. Once in the host cell, the vector can replicate independently of, or coincidental with, the host chromosomal DNA, and several copies of the vector and its inserted nucleic acid molecule may be generated.

10 The term "vector" may thus also be defined as a gene delivery vehicle that facilitates gene transfer into a target cell. This definition includes both non-viral and viral vectors. Non-viral vectors include but are not limited to cationic lipids, liposomes, nanoparticles, PEG, PEI, etc. Viral vectors are derived from viruses including but not limited to: retrovirus, lentivirus, adeno-associated virus, adenovirus, herpesvirus, hepatitis virus or the like. Alternatively, gene  
15 delivery systems can be used to combine viral and non-viral components, such as nanoparticles or virosomes (Yamada et al., 2003).

Typically, but not necessarily, viral vectors are replication-deficient as they have lost the ability to propagate in a given cell since viral genes essential for replication have been eliminated from the viral vector. However, some viral vectors can also be adapted to replicate specifically  
20 in a given cell, such as e.g. a cancer cell, and are typically used to trigger the (cancer) cell-specific (onco)lysis. Preferred vectors are derived from adeno-associated virus, adenovirus, retroviruses and Antiviruses.

Retroviruses and Antiviruses are RNA viruses that have the ability to insert their genes into host cell chromosomes after infection. Retroviral and lentiviral vectors have been developed  
25 that lack the genes encoding viral proteins, but retain the ability to infect cells and insert their genes into the chromosomes of the target cell (Miller, 1990; Naldini et al., 1996, VandenDriessche et al., 1999). The difference between a lentiviral and a classical Moloney-murine leukemia-virus (MLV) based retroviral vector is that lentiviral vectors can transduce both dividing and non-dividing cells whereas MLV-based retroviral vectors can only transduce  
30 dividing cells.

Adenoviral vectors are designed to be administered directly to a living subject. Unlike retroviral vectors, most of the adenoviral vector genomes do not integrate into the chromosome of the host cell. Instead, genes introduced into cells using adenoviral vectors are maintained in the nucleus as an extrachromosomal element (episome) that persists for an extended period of  
35 time. Adenoviral vectors will transduce dividing and nondividing cells in many different tissues in vivo including airway epithelial cells, endothelial cells, hepatocytes and various tumors

(Trapnell, 1993; Chuah et al., 2003). Another viral vector is derived from the herpes simplex virus, a large, double-stranded DNA virus. Recombinant forms of the vaccinia virus, another dsDNA virus, can accommodate large inserts and are generated by homologous recombination.

- 5 Adeno-associated virus (AAV) is a small ssDNA virus which infects humans and some other primate species, not known to cause disease and consequently causing only a very mild immune response. AAV can infect both dividing and non-dividing cells and may incorporate its genome into that of the host cell. These features make AAV a very attractive candidate for creating viral vectors for gene therapy, although the cloning capacity of the vector is relatively  
10 limited. Accordingly, in preferred embodiments of the invention, the vector used is derived from adeno-associated virus (i.e. AAV vector).

Different serotypes of AAVs have been isolated and characterized, such as, for example AAV serotype 2, AAV serotype 5, AAV serotype 8, and AAV serotype 9, and all AAV serotypes are contemplated herein. In particular, AAV vectors that comprise a FIX transgene as disclosed  
15 herein are preferably AAV serotype 9 vectors, and AAV vectors that comprise a FVIII transgene as disclosed herein are preferably AAV serotype 8 vectors.

The AAV vectors disclosed herein may be single-stranded (i.e. ssAAV vectors) or self-complementary (i.e. scAAV vectors). In particular, AAV vectors that comprise a FIX transgene as disclosed herein are preferably self-complementary, and AAV vectors that comprise a FVIII  
20 transgene as disclosed herein are preferably single-stranded. With the term “self-complementary AAV” is meant herein a recombinant AAV-derived vector wherein the coding region has been designed to form an intra-molecular double-stranded DNA template.

Gene therapy with adeno-associated viral vectors disclosed herein was shown to induce immune tolerance towards the transgene comprised in the vector.

- 25 In embodiments, the vector according to the invention comprises the following elements (cfr. Fig. 6):

- an Inverted Terminal Repeat sequence (ITR), optionally mutated,
- a liver-specific regulatory element, preferably a regulatory element comprising three tandem repeats of the Serpin enhancer (“Serp” or “SerpEnh”) (e.g. a regulatory element comprising  
30 the nucleic acid fragment defined by SEQ ID NO:11),
- a promoter, preferably the minimal TTR promoter (TTRm),
- an intron, preferably the MVM intron,
- a (trans)gene, preferably codon-optimized factor IX cDNA, even more preferably codon-optimized factor IX Padua cDNA,

- a transcription terminator, preferably a polyadenylation signal such as the BGHpA or the synthetic polyA site as defined by SEQ ID NO:56,
- an Inverted Terminal Repeat sequence (ITR).

5 Preferably, the vector is an adeno-associated virus-derived vector, more preferably a self-complementary AAV vector, even more preferably a self-complementary AAV serotype 9 vector, such as the vector as defined by SEQ ID NO:2.

In a further typical embodiment of the present invention, said vector comprises the following elements (cf. Fig. 8 and Fig. 16):

- an Inverted Terminal Repeat sequence (ITR), optionally mutated,
- 10 - a liver-specific regulatory element, preferably a regulatory element comprising three tandem repeats of the Serpin enhancer ("Serp" or "SerpEnh") and the transthyretin enhancer (TTRe) (e.g. a regulatory element comprising SEQ ID NO:13, preferably comprising SEQ ID NO:57),
- a promoter, preferably the minimal TTR promoter (TTRm),
- an intron, preferably the MVM intron,
- 15 - a (trans)gene, preferably codon-optimized factor IX cDNA, even more preferably codon-optimized factor IX Padua cDNA,
- a transcription terminator, preferably a polyadenylation signal such as the BGHpA or the synthetic polyA site as defined by SEQ ID NO:56, and
- an Inverted Terminal Repeat sequence (ITR).

20 The combination of said elements resulted in an unexpectedly high expression level of FIX, and in particular of the Padua mutant thereof, in the liver of subjects. Preferably, the vector is an adeno-associated virus-derived vector, more preferably a self-complementary AAV vector, even more preferably a self-complementary AAV serotype 9 vector, such as the vector as defined by SEQ ID NO:4 or SEQ ID NO:25.

25 In another typical embodiment of the present invention, said vector comprises the following elements (cfr. Fig. 11, 17 or 18):

- an Inverted Terminal Repeat sequence (ITR), optionally mutated,
- a liver-specific regulatory element, preferably a regulatory element comprising three tandem repeats of the Serpin enhancer (e.g. a regulatory element comprising SEQ ID NO:11),
- 30 - a promoter, preferably the minimal TTR promoter,
- an intron, preferably the MVM intron,

- a (trans)gene, preferably codon-optimized factor VIII cDNA, even more preferably codon-optimized B domain deleted factor VIII cDNA,
- a transcription terminator, preferably a polyadenylation signal such as the Simian vacuolating virus 40 or Simian virus 40 (SV40) polyadenylation signal or the synthetic polyA site as defined by SEQ ID NO:56, and
- an Inverted Terminal Repeat sequence (ITR).

The combination of said elements resulted in an unexpectedly high expression level of FVIII specifically in the liver of subjects. Preferably, the vector is an adeno-associated virus(AAV)-derived vector, more preferably a single-stranded AAV vector, even more preferably a single-stranded AAV serotype 8 vector, such as the vector as defined by SEQ ID NO:16, SEQ ID NO:20 or SEQ ID NO:21.

In a further embodiment, said vector comprises the following elements (cfr. Fig. 19 or 20):

- an Inverted Terminal Repeat sequence (ITR), optionally mutated,
- a liver-specific regulatory element, preferably preferably a regulatory element comprising three tandem repeats of the Serpin enhancer ("Serp" or "SerpEnh") and the transthyretin enhancer (TTRe) (e.g. a regulatory element comprising SEQ ID NO:13, preferably comprising SEQ ID NO:57),
- a promoter, preferably the minimal TTR promoter,
- an intron, preferably the MVM intron,
- a (trans)gene, preferably codon-optimized factor VIII cDNA, even more preferably codon-optimized B domain deleted factor VIII cDNA,
- a transcription terminator, preferably a polyadenylation signal such as the Simian vacuolating virus 40 or Simian virus 40 (SV40) polyadenylation signal or the synthetic polyA site as defined by SEQ ID NO:56, and
- an Inverted Terminal Repeat sequence (ITR).

The combination of said elements resulted in an unexpectedly high expression level of FVIII specifically in the liver of subjects. Preferably, the vector is an adeno-associated virus(AAV)-derived vector, more preferably a single-stranded AAV vector, even more preferably a single-stranded AAV serotype 8 vector, such as the vector as defined by SEQ ID NO:22 or SEQ ID NO:23.

The combination of the triple repeat of the Serpin enhancer defined by SEQ ID NO. 5 and the transthyretin enhancer defined by SEQ ID NO:12 including a specific spacer fragment has been shown to be unexpectedly potent in increasing expression of a transgene operably linked

to it. Said regulatory element is defined by SEQ ID NO:13. Said regulatory element can further be combined with the transthyretin minimal promotor as defined by SEQ ID NO.6. This creates a combination of 3x the SerpEnh (3x SEQ ID NO.5, e.g. such as in SEQ ID NO.11) with the TTRe and TTRm nucleic acid sequence e.g. as defined by SEQ ID NO.69. For example, such

5 a construct results in a regulatory element as defined by SEQ ID NO:58, which has been tested to increase the expression of both FVIII and FIX transgenes as shown herein.

In specific embodiments the following plamids/vectors are provided:

pAAVsc-3xCRM8-TTRe-TTRm-MVM-FIXcoR338L-BGHpA,

pAAVss-3xCRM8-TTRe-TTRm-MVM-FVIIIcodeltaB-sv40pA,

10 pAAVsc-TTRe-3xCRM8-TTRm-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-TTRm-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-CRM8-TTRe-TTRm-MVM-FIXcoR338L-BGHpA,

pAAVss-CRM8-TTRe-TTRm-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-3xCRM8-TTRe-AAT-MVM-FIXcoR338L-BGHpA,

15 pAAVss-3xCRM8-TTRe-AAT-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-TTRe-3xCRM8-AAT-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-AAT-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-CRM8-TTRe-AAT-MVM-FIXcoR338L-BGHpA,

pAAVss-CRM8-TTRe-AAT-MVM-FVIIIcodeltaB-sv40pA,

20 pAAVsc-3xCRM8-TTRe-ALBp-MVM-FIXcoR338L-BGHpA,

pAAVss-3xCRM8-TTRe-ALBp-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-TTRe-3xCRM8-ALBp-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-ALBp-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-CRM8-TTRe-ALBp-MVM-FIXcoR338L-BGHpA,

25 pAAVss-CRM8-TTRe-ALBp-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-3xCRM8-TTRe-APOA1p-MVM-FIXcoR338L-BGHpA,

pAAVss-3xCRM8-TTRe-APOA1p-MVM-FVIIIcodeltaB-sv40pA

pAAVsc-TTRe-3xCRM8-APOA1p-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-APOA1p-MVM-FVIIIcodeltaB-sv40pA

- pAAVsc-CRM8-TTRe-APOA1p-MVM-FIXcoR338L-BGHpA,  
 pAAVss-CRM8-TTRe-APOA1p-MVM-FVIIIcodeltaB-sv40pA,  
 pAAVsc-3xCRM8-TTRe-CFBp-MVM-FIXcoR338L-BGHpA,  
 pAAVss-3xCRM8-TTRe-CFBp-MVM-FVIIIcodeltaB-sv40pA,  
 5 pAAVsc-TTRe-3xCRM8-CFBp-MVM-FIXcoR338L-BGHpA,  
 pAAVss-TTRe-3xCRM8-CFBp-MVM-FVIIIcodeltaB-sv40pA,  
 pAAVsc-CRM8-TTRe-CFBp-MVM-FIXcoR338L-BGHpA,  
 pAAVss-CRM8-TTRe-CFBp-MVM-FVIIIcodeltaB-sv40pA,  
 pAAVsc-3xCRM8-TTRe-KHKp-MVM-FIXcoR338L-BGHpA,  
 10 pAAVss-3xCRM8-TTRe-KHKp-MVM-FVIIIcodeltaB-sv40pA,  
 pAAVsc-TTRe-3xCRM8-KHKp-MVM-FIXcoR338L-BGHpA,  
 pAAVss-TTRe-3xCRM8-KHKp-MVM-FVIIIcodeltaB-sv40pA,  
 pAAVsc-CRM8-TTRe-KHKp-MVM-FIXcoR338L-BGHpA,  
 pAAVss-CRM8-TTRe-KHKp-MVM-FVIIIcodeltaB-sv40pA,  
 15 pAAVsc-3xCRM8-TTRe-HPXp-MVM-FIXcoR338L-BGHpA,  
 pAAVss-3xCRM8-TTRe-HPXp-MVM-FVIIIcodeltaB-sv40pA,  
 pAAVsc-TTRe-3xCRM8-HPXp-MVM-FIXcoR338L-BGHpA,  
 pAAVss-TTRe-3xCRM8-HPXp-MVM-FVIIIcodeltaB-sv40pA,  
 pAAVsc-CRM8-TTRe-HPXp-MVM-FIXcoR338L-BGHpA,  
 20 pAAVss-CRM8-TTRe-HPXp-MVM-FVIIIcodeltaB-sv40pA,  
 pAAVsc-3xCRM8-TTRe-NNMTp-MVM-FIXcoR338L-BGHpA,  
 pAAVss-3xCRM8-TTRe-NNMTp-MVM-FVIIIcodeltaB-sv40pA,  
 pAAVsc-TTRe-3xCRM8-NNMTp-MVM-FIXcoR338L-BGHpA,  
 pAAVss-TTRe-3xCRM8-NNMTp-MVM-FVIIIcodeltaB-sv40pA,  
 25 pAAVsc-CRM8-TTRe-NNMTp-MVM-FIXcoR338L-BGHpA,  
 pAAVss-CRM8-TTRe-NNMTp-MVM-FVIIIcodeltaB-sv40pA,  
 pAAVsc-3xCRM8-TTRe-CES1p-MVM-FIXcoR338L-BGHpA,  
 pAAVss-3xCRM8-TTRe-CES1p-MVM-FVIIIcodeltaB-sv40pA,

- pAAVsc-TTRe-3xCRM8-CES1p-MVM-FIXcoR338L-BGHpA,  
pAAVss-TTRe-3xCRM8-CES1p-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-CRM8-TTRe-CES1p-MVM-FIXcoR338L-BGHpA,  
pAAVss-CRM8-TTRe-CES1p-MVM-FVIIIcodeltaB-sv40pA,  
5 pAAVsc-3xCRM8-TTRe-PROCp-MVM-FIXcoR338L-BGHpA,  
pAAVss-3xCRM8-TTRe-PROCp-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-TTRe-3xCRM8-PROCp-MVM-FIXcoR338L-BGHpA,  
pAAVss-TTRe-3xCRM8-PROCp-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-CRM8-TTRe-PROCp-MVM-FIXcoR338L-BGHpA,  
10 pAAVss-CRM8-TTRe-PROCp-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-3xCRM8-TTRe-APOC3p-MVM-FIXcoR338L-BGHpA,  
pAAVss-3xCRM8-TTRe-APOC3p-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-TTRe-3xCRM8-APOC3p-MVM-FIXcoR338L-BGHpA,  
pAAVss-TTRe-3xCRM8-APOC3p-MVM-FVIIIcodeltaB-sv40pA,  
15 pAAVsc-CRM8-TTRe-APOC3p-MVM-FIXcoR338L-BGHpA,  
pAAVss-CRM8-TTRe-APOC3p-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-3xCRM8-TTRe-MASP2p-MVM-FIXcoR338L-BGHpA,  
pAAVss-3xCRM8-TTRe-MASP2p-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-TTRe-3xCRM8-MASP2p-MVM-FIXcoR338L-BGHpA,  
20 pAAVss-TTRe-3xCRM8-MASP2p-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-CRM8-TTRe-MASP2p-MVM-FIXcoR338L-BGHpA,  
pAAVss-CRM8-TTRe-MASP2p-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-3xCRM8-TTRe-SERPINC1p-MVM-FIXcoR338L-BGHpA,  
pAAVss-3xCRM8-TTRe-SERPINC1p-MVM-FVIIIcodeltaB-sv40pA,  
25 pAAVsc-TTRe-3xCRM8-SERPINC1p-MVM-FIXcoR338L-BGHpA,  
pAAVss-TTRe-3xCRM8-SERPINC1p-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-CRM8-TTRe-SERPINC1p-MVM-FIXcoR338L-BGHpA,  
pAAVss-CRM8-TTRe-SERPINC1p-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-3xCRM8-TTRe-HAMPp-MVM-FIXcoR338L-BGHpA,

pAAVss-3xCRM8-TTRe-HAMPp-MVM-FVIIIcodeltaB-sv40pA

pAAVsc-TTRe-3xCRM8-HAMPp-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-HAMPp-MVM-FVIIIcodeltaB-sv40pA

- 5 pAAVsc-CRM8-TTRe-HAMPp-MVM-FIXcoR338L-BGHpA, or  
pAAVss-CRM8-TTRe-HAMPp-MVM-FVIIIcodeltaB-sv40pA.

In any one of said plasmids the poly adenylation signal can be replaced by any other poly adenylation signal such as e.g. the synthetic polyA site as defined by SEQ ID NO:56 (Synth.pA).

- 10 In other embodiments, the vector is a non-viral vector, such as a transposon-based vector. Preferably, said transposon-based vectors are derived from Sleeping Beauty (SB) or PiggyBac (PB). A preferred SB transposon has been described in Ivics et al. (1997) and its hyperactive versions, including SB100X, as described in Mates et al. (2009). PiggyBac-based transposons are safe vectors in that they do not enhance the tumorigenic risk. Furthermore, liver-directed  
15 gene therapy with these vectors was shown to induce immune tolerance towards the transgene, in particular the hFIX or hFVIII transgene, comprised in the vector.

- The transposon-based vectors are preferably administered in combination with a vector encoding a transposase for gene therapy. For example, the PiggyBac-derived transposon-based vector can be administered with wild-type PiggyBac transposase (Pbase) or mouse  
20 codon-optimized PiggyBac transposase (mPBase). Preferably, said transposases are hyperactive transposases, such as, for example, hyperactive PB (hyPB) transposase containing seven amino acid substitutions (I30V, S103P, G165S, M282V, S509G, N538K, N570S) as described in Yusa et al. (2011), which is specifically incorporated by reference herein.

- 25 Transposon/transposase constructs can be delivered by hydrodynamic injection or using non-viral nanoparticles to transfect hepatocytes.

- In a further aspect, the nucleic acid regulatory elements, the nucleic acid expression cassettes and the vectors described herein can be used in gene therapy. Gene therapy protocols, intended to achieve therapeutic gene product expression in target cells, *in vitro*, but also  
30 particularly *in vivo*, have been extensively described in the art. These include, but are not limited to, intramuscular injection of plasmid DNA (naked or in liposomes), interstitial injection, instillation in airways, application to endothelium, intra-hepatic parenchyme, and intravenous or intra-arterial administration (e.g. intra-hepatic artery, intra-hepatic vein). Various devices have been developed for enhancing the availability of DNA to the target cell. A simple

approach is to contact the target cell physically with catheters or implantable materials containing DNA. Another approach is to utilize needle-free, jet injection devices which project a column of liquid directly into the target tissue under high pressure. These delivery paradigms can also be used to deliver viral vectors. Another approach to targeted gene delivery is the use of molecular conjugates, which consist of protein or synthetic ligands to which a nucleic acid-or DNA- binding agent has been attached for the specific targeting of nucleic acids to cells (Cristiano et al., 1993).

According to particular embodiments, the use of the nucleic acid expression cassettes and vectors as described herein is envisaged for gene therapy of liver cells (i.e. liver-directed gene therapy). According to a further particular embodiment, the use of the regulatory elements, expression cassettes or vectors is for gene therapy, in particular liver-directed gene therapy, *in vivo*. According to yet a further particular embodiment, the use is for a method of gene therapy, in particular liver-directed gene therapy, to treat hemophilia, in particular to treat hemophilia B or hemophilia A.

Gene transfer into mammalian hepatocytes has been performed using both *ex vivo* and *in vivo* procedures. The *ex vivo* approach requires harvesting of the liver cells, *in vitro* transduction with long-term expression vectors, and reintroduction of the transduced hepatocytes into the portal circulation (Kay et al., 1992; Chowdhury et al., 1991 ). *In vivo* targeting has been done by injecting DNA or viral vectors into the liver parenchyma, hepatic artery, or portal vein, as well as via transcriptional targeting (Kuriyama et al., 1991; Kistner et al., 1996). Recent methods also include intraportal delivery of naked DNA (Budker et al., 1996) and hydrodynamic tail vein transfection (Liu et al., 1999; Zhang et al., 1999). According to a further aspect, methods for expressing a protein in liver cells are provided, comprising the steps of introducing in liver cells the nucleic acid expression cassette or a vector as described herein and expressing the transgene protein product in the liver cells. These methods may be performed both *in vitro* and *in vivo*.

Methods of gene therapy for a subject in need thereof are also provided, comprising the steps of introducing in the liver of the subject a nucleic acid expression cassette containing a transgene encoding a therapeutic protein, and expressing a therapeutic amount of the therapeutic protein in the liver. According to a further embodiment, the method comprises the steps of introducing in the liver of the subject a vector comprising the nucleic acid expression cassette containing a transgene encoding a therapeutic protein, and expressing a therapeutic amount of the therapeutic protein in the liver.

According to a very specific embodiment, the therapeutic protein encoded by the transgene in the nucleic acid expression cassette or the vector is factor IX, and the method is a method for treating hemophilia B. By expressing factor IX in the liver via gene therapy, hemophilia B can

be treated (Snyder et al., 1999). According to another very specific embodiment, the therapeutic protein encoded by the transgene in the nucleic acid expression cassette or the vector is factor VIII, and the method is a method for treating hemophilia A.

5 Except when noted differently, the terms "subject" or "patient" are used interchangeably and refer to animals, preferably vertebrates, more preferably mammals, and specifically includes human patients and non-human mammals, such as e.g. mice. Preferred patients or subjects are human subjects.

As used herein, the terms "treat" or "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen)  
10 an undesired physiological change or disorder, such as the development or spread of proliferative disease, e.g., cancer. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilised (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or  
15 undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

As used herein, a phrase such as "a subject in need of treatment" includes subjects, such as mammalian subjects, that would benefit from treatment of a given condition, such as, hemophilia B or hemophilia A. Such subjects will typically include, without limitation, those that  
20 have been diagnosed with the condition, those prone to have or develop the said condition and/or those in whom the condition is to be prevented.

The term "therapeutically effective amount" refers to an amount of a compound or pharmaceutical composition effective to treat a disease or disorder in a subject, i.e., to obtain a desired local or systemic effect and performance. In a particular embodiment, the term implies  
25 that levels of factor IX in plasma equal to or higher than the therapeutic threshold concentration of 10mU/ml (milli-units per milliliter) plasma, 50mU/ml plasma, 100mU/ml plasma, 150mU/ml or 200mU/ml plasma in a subject can be obtained by transduction or transfection of the vector according to any one the embodiments described herein into a subject. Due to the very high efficiency of the vectors and nucleic acid expression cassettes of  
30 the present invention, this high physiological level of factor IX in the subject can be obtained even by administering relatively low doses of vector. In another particular embodiment, the term implies that levels of factor VIII in plasma equal to or higher than the therapeutic threshold concentration of 10mU/ml (milli-units per milliliter) plasma, 50mU/ml plasma, 100mU/ml plasma, 150mU/ml plasma, 200mU/ml plasma or higher can be obtained by  
35 transduction or transfection of any of the vectors disclosed herein into a subject. Due to the very high efficiency of the vectors and nucleic acid expression cassettes disclosed herein,

these high physiological levels of factor VIII in the subject can be obtained even by administering relatively low doses of vector. The term thus refers to the quantity of compound or pharmaceutical composition that elicits the biological or medicinal response in a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the hemophilia being treated. In particular, these terms refer to the quantity of compound or pharmaceutical composition according to the invention which is necessary to prevent, cure, ameliorate, or at least minimize the clinical impairment, symptoms, or complications associated with hemophilia, in particular hemophilia B or hemophilia A, in either a single or multiple dose.

10 In particular, the transduction of the vector according to any one of the embodiments defined herein into the subject can be done at a dose lower than  $2 \times 10^{11}$  vg/kg (viral genomes per kilogram) to obtain a therapeutic factor IX level of 10mU/ml plasma or of 50mU/ml plasma in a subject.

Alternatively, if a level of factor IX of 100 mU/ml plasma needs to be reached in a subject, the transduction of the vector according to any one of the embodiments defined herein into the subject can be done at a dose lower than or equal to  $6 \times 10^{11}$  vg/kg.

Further, if a level of factor IX equal to 150 mU/ml plasma or higher needs to be reached, the transduction of the vector according to any one of the embodiments defined herein into the subject can be done at a dose lower than or equal than  $2 \times 10^{12}$  vg/kg.

20 In a preferred embodiment, a level of factor IX of 200 mU/ml plasma or higher can be reached in a subject, when the transduction of the vector according to any one of the embodiments defined herein into the subject is done at a dose lower than or equal to  $2 \times 10^{12}$  vg/kg.

In particular, the transduction of the vector according to any one of the embodiments defined herein into the subject can be done at a dose lower than or equal to  $2 \times 10^{12}$  vg/kg (viral genomes per kilogram), such as lower than or equal to  $1 \times 10^{12}$  vg/kg,  $5 \times 10^{11}$  vg/kg,  $2.5 \times 10^{11}$  vg/kg,  $1 \times 10^{11}$  vg/kg,  $5 \times 10^{10}$  vg/kg,  $1 \times 10^{10}$  vg/kg,  $5 \times 10^9$  vg/kg, or  $1 \times 10^9$  vg/kg preferably at a dose lower than or equal to  $2.5 \times 10^{11}$  vg/kg, to obtain a therapeutic factor VIII level of 10 mU/ml plasma, 50 mU/ml plasma, 100 mU/ml plasma, 150 mU/ml plasma, 200 mU/ml plasma, or higher in a subject.

30 For hemophilia therapy, efficacy of the treatment can, for example, be measured by assessing the hemophilia-caused bleeding in the subject. In vitro tests such as, but not limited to the in vitro activated partial thromboplastin time assay (APPT), test factor IX chromogenic activity assays, blood clotting times, factor IX or human factor VIII-specific ELISAs are also available. Any other tests for assessing the efficacy of the treatment known in the art can of course be used.

The nucleic acid expression cassette, the vector or the pharmaceutical composition of the invention may be used alone or in combination with any of the know hemophilia therapies, such as the administration of recombinant or purified clotting factors. The nucleic acid expression cassette, the vector or the pharmaceutical composition of the invention can thus be administered alone or in combination with one or more active compounds. The latter can be administered before, after or simultaneously with the administration of the said agent(s).

A further object of the invention are pharmaceutical preparations which comprise a therapeutically effective amount of the nucleic acid expression cassette or the expression vector as defined herein, and a pharmaceutically acceptable carrier, i.e., one or more pharmaceutically acceptable carrier substances and/or additives, e.g., buffers, carriers, excipients, stabilisers, etc. The term "pharmaceutically acceptable" as used herein is consistent with the art and means compatible with the other ingredients of a pharmaceutical composition and not deleterious to the recipient thereof. The term "pharmaceutically acceptable salts" as used herein means an inorganic acid addition salt such as hydrochloride, sulfate, and phosphate, or an organic acid addition salt such as acetate, maleate, fumarate, tartrate, and citrate. Examples of pharmaceutically acceptable metal salts are alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminum salt, and zinc salt. Examples of pharmaceutically acceptable ammonium salts are ammonium salt and tetramethylammonium salt. Examples of pharmaceutically acceptable organic amine addition salts are salts with morpholine and piperidine. Examples of pharmaceutically acceptable amino acid addition salts are salts with lysine, glycine, and phenylalanine. The pharmaceutical composition according to the invention can be administered orally, for example in the form of pills, tablets, lacquered tablets, sugar-coated tablets, granules, hard and soft gelatin capsules, aqueous, alcoholic or oily solutions, syrups, emulsions or suspensions, or rectally, for example in the form of suppositories. Administration can also be carried out parenterally, for example subcutaneously, intramuscularly or intravenously in the form of solutions for injection or infusion. Other suitable administration forms are, for example, percutaneous or topical administration, for example in the form of ointments, tinctures, sprays or transdermal therapeutic systems, or the inhalative administration in the form of nasal sprays or aerosol mixtures, or, for example, microcapsules, implants or rods. The pharmaceutical composition can be prepared in a manner known per se to one of skill in the art. For this purpose, the nucleic acid expression cassette or the expression vector as defined herein, one or more solid or liquid pharmaceutically acceptable excipients and, if desired, in combination with other pharmaceutical active compounds, are brought into a suitable administration form or dosage form which can then be used as a pharmaceutical in human medicine or veterinary medicine.

According to another aspect, a pharmaceutical composition is provided comprising a nucleic acid expression cassette containing a transgene encoding a therapeutic protein, and a pharmaceutically acceptable carrier. According to another embodiment, the pharmaceutical composition comprises a vector containing the nucleic acid expression cassette containing a transgene encoding a therapeutic protein, and a pharmaceutically acceptable carrier.

5 According to further particular embodiments, the transgene encodes factor IX and the pharmaceutical composition is for treating hemophilia B or the transgene encodes factor VIII and the pharmaceutical composition is for treating hemophilia A.

The use of the nucleic acid expression cassette, its regulatory elements and the vector components as disclosed herein for the manufacture of these pharmaceutical compositions for use in treating hemophilia, preferably hemophilia B or hemophilia A, is also envisaged.

10

It is to be understood that although particular embodiments, specific constructions and configurations, as well as materials, have been discussed herein for methods and applications according to the present invention, various changes or modifications in form and detail may be made without departing from the scope and spirit of this invention.

15

The following examples are provided to better illustrate particular embodiments, and they should not be considered limiting the application. The application is limited only by the claims.

## EXAMPLES

### Example 1: Design of the AAV vectors used

20 The design of the self-complementary (sc), double-stranded adeno-associated viral (AAV) vectors is depicted in Figure 1. The minimal transthyretin promoter (TTRm) is driving the expression of the human codon-optimized factor IX (co-FIX-R338L) containing the hyper-activating, thrombophilic FIX mutation (R338L). The minimal TTR promoter (TTRm) is used in conjunction with either the Serpin enhancer (SERP), a triple repeat of the Serpin enhancer (3xSERP), the native TTR enhancer (TTRe), or a combination of a triple repeat of the Serpin enhancer and the native TTR enhancer (3xSERP-TTRe). The minute virus of mouse intron (MVM), the bovine growth hormone polyadenylation site (BGHpA) or a synthetic polyadenylation site (Synt.pA), and the inverted terminal repeats (ITR) are indicated; 3xSerpEnh means that this element was cloned as a triplet repeat upstream of the TTRm. The

25

30 vector size (including both ITR's) is indicated.

Figure 2 shows the design of the single-stranded (ss) adeno-associated viral (AAV) vectors. The minimal transthyretin promoter (TTRm) is driving the expression of the human codon-optimized B-domain deleted factor VIII (cohFVIIIdeltaB). Optionally, the Serpin enhancer (SERP), a triple repeat of the Serpin enhancer (3xSERP), the native TTR enhancer (TTRe), or

a combination of a triple repeat of the Serpin enhancer and the native TTR enhancer (3xSERP-TTRe) are cloned upstream of the TTRm. The minute virus of mouse intron (MVM), the Simian Virus 40 (SV40) polyadenylation site (Sv40pA) or a synthetic polyadenylation site (Synt.pA), and the inverted terminal repeats (ITR) are indicated. The vector size (including  
5 both ITR's) is indicated.

## **Materials and methods:**

### **Cloning strategy**

FIX constructs: The basic AAVsc-SerpEnh-TTRm-MVM-co-FIX-R338L-BGHpA plasmid (Nair et al. Blood, 2014) was used to create the other AAV-FIX constructs. This plasmid contains the  
10 Serp enhancer (SerpEnh), a liver-specific transthyretin (TTRm) promoter, a minute virus of mouse (MVM) small intron, a codon optimized human FIX transgene containing a R338L mutation, and a bovine growth hormone poly A (BGHpA). The 3xSerpEnh-TTRm-MVM sequence was synthesized by GeneArt (Life Technologies, Regensburg, Germany) and cloned into the basic construct using AscI and NheI, thereby replacing SerpEnh-TTRm-MVM,  
15 creating pAAVsc-3xSerpEnh-TTRm-MVM-co-FIX-R338L-BGHpA. Into this plasmid, the 3xSerpEnh sequence was replaced by the TTR enhancer (TTREnh) or 3xSerpEnh-TTREnh (constructed by GeneArt), thereby respectively creating pAAVsc-TTREnh-TTRm-MVM-co-FIX-R338L-BGHpA and pAAVsc-3xSerpEnh-TTREnh-TTRm-MVM-co-FIX-R338L-BGHpA respectively.

FVIII constructs: The basic AAVss-SerpEnh-TTRm-MVM-FVIIIcopt-Sv40pA plasmid was used to create the other AAV-FVIII constructs. This plasmid contains the Serp enhancer (SerpEnh), a liver-specific transthyretin (TTRm) promoter, an MVM intron, a codon optimized human FVIII transgene (Di Matteo et al., 2014), and an SV40 poly A. The SerpEnh was removed using KpnI, followed by re-ligation of the backbone, thereby creating pAAVss-TTRm-MVM-FVIIIcopt-Sv40pA. To create pAAVsc-3xSerpEnh-TTRm-MVM-FVIIIcopt-Sv40pA, the 3xSerpEnh was  
25 first cloned into a FVIIIcopt plasmid with a different backbone, after which the entire expression cassette (3xSerpEnh-TTRm-MVM-FVIIIcopt-Sv40pA) was cloned into the AAVss backbone using NotI and XhoI. From this final plasmid, 3xSerpEnh was removed and replaced with the TTREnh (constructed by GeneArt), thereby creating pAAVss-TTREnh-TTRm-MVM-FVIIIcopt-Sv40pA. In order to generate pAAVss-3XSerpEnh-TTREnh-TTRm-MVM-cohFVIIIdeltaB-SV40pA (5493bp), pAAVss-TTREnh-TTRm-MVM-cohFVIIIdeltaB-SV40pA (the  
30 vector) was restricted with NotI-Acc65I. A fragment with 3XSerp flanked by NotI/Acc65I was synthesized by GenArt and ligated into the restricted vector.

### AAV vector production, purification and titration

AAV vectors were produced by calcium phosphate (Invitrogen Corp, Carlsbad, CA) co-transfection of AAV-293 human embryonic kidney carcinoma cells (Stratagene, Carlsbad, CA, catalog No 240073; with the pAAV plasmid of interest, an adenoviral helper plasmid and a

5 chimeric packaging constructs that delivers the AAV2 Rep gene together with the AAV8 or AAV9 Cap gene, as described previously (VandenDriessche et al, 2007, VandenDriessche et al; 2007, J. Thromb. Haemost. JTH 5:16–24). For the AAV-FIX vectors, the AAV9 serotype was used and for the AAV-FVIII vectors the AAV8 serotype. The AAV-293 cells are free of microbial contamination as determined by PCR for detection of mycoplasma. Briefly, two days

10 post transfection, cells were harvested and vector particles were purified using isopycnic centrifugation methods. Harvested cells were lysed by successive freeze/thaw cycles and sonication, treated with benzonase (Novagen, Madison, WI) and deoxycholic acid (Sigma-Aldrich, St. Louis, MO) and subsequently subjected to 2 successive rounds of cesium chloride (Invitrogen Corp, Carlsbad, CA) density gradient ultracentrifugation. Fractions containing the

15 AAV vector were collected, concentrated in 1mM MgCl<sub>2</sub> in Dulbecco's phosphate buffered saline (PBS) (Gibco, BRL) and stored at -80°C. The vector titers (in viral genomes (vg)/ml) were determined by quantitative real-time PCR using specific primers. For the FIX vectors, primers specific for the bovine growth hormone poly A sequence were used. The forward and reverse primers used were 5'-GCCTTCTAGTTGCCAGCCAT-3' (SEQ ID NO:60) and 5'-GGCACCTTCCAGGGTCAAG-3' (SEQ ID NO:61), respectively. For the FVIII vectors, primers

20 specific for the FVIII gene sequence were used. The forward and reverse primers used were 5'- AACGGCTACGTGAACAGAAG -3' (SEQ ID NO:62) and 5'-GATAGGGCTGATTTCCAGGC -3' (SEQ ID NO:63), respectively. Reactions were performed in SybrGreen PCR Master Mix (Applied Biosystems, Foster City,CA,USA), on an ABI 7500

25 Real-Time PCR System (Applied Biosystems, Foster City,CA,USA). Known copy numbers (102–107) of the respective vector plasmids used to generate the corresponding AAV vectors, carrying the appropriate cDNAs were used to generate the standard curves.

### Animal study and blood collection

AAV vector administration is carried out by tail vein injection on adult C57B6 mice at two

30 different doses:  $1 \times 10^9$  (low dose) and  $5 \times 10^9$  (high dose) vector genomes (vg) per mouse as detailed below. Mice were bled at different time points after gene transfer in order to evaluate the FIX/FVIII gene expression. The pAAVss-TTRENh-TTRm-MVM-co-hFVIII-deltaB-SV40pA and pAAVss-3XSerpEnh-TTRENh-TTRm-MVM-co-hFVIII-deltaB-SV40pA plasmid constructs were administered by hydrodynamic delivery into C57BL/6 mice at a dose of 300 ng per

35 mouse. Animals were anesthetized using isoflurane and blood samples were taken by retro-

orbital bleeding on trisodium citrate. Plasma was prepared immediately after blood collection by centrifugation at 14000rpm for 3 minutes at 4°C. Plasma was immediately stored at -80°C for further analysis.

### **FIX ELISA**

5 The concentration of hFIX antigens in citrated plasma was measured by enzyme-linked immunosorbent assay (ELISA) using manufacturer's protocol (Diagnostica Stago, France). The hFIX standards (available in the kit) were serially diluted using the dilution buffer and used for calibration. Here the 100% of the standard corresponds to 5000ng of FIX protein. The aliquots of the plasma samples were thawed and diluted in order to make their reading fall in  
10 the linear range of standards. Standards and samples were then added to a 96 well plate pre-coated with primary anti-human FIX antibodies. After an incubation of 1 hour at room temperature, the plate was washed and a solution containing secondary antibodies coupled to peroxidase were added followed by another incubation of 1 hour at room temperature. After incubation, the peroxidase substrate TMB (chromogenic solution) was added which resulted in  
15 color development. After exact 5 minutes of incubation 1M H<sub>2</sub>SO<sub>4</sub> was added to all wells to stop the reaction. After an incubation of 15minutes the absorbance was measured at 450 nm using the microplate reader. Using the obtained standard curve, FIX levels were determined.

### **FVIII ELISA**

The concentration of hFVIII antigens in citrated plasma was measured by enzyme-linked  
20 immunosorbent assay (ELISA) using manufacturer's protocol (Diagnostica Stago, France). The hFVIII standards (available in the kit) were serially diluted using the dilution buffer and used for calibration. Here the 100% of the standard corresponds to 200ng of FVIII protein. The aliquots of the plasma samples were thawed and diluted in order to make their reading fall in the linear range of standards. Standards and samples were then added to a 96 well plate pre-  
25 coated with primary anti-human FVIII antibodies. After an incubation of 2 hour at room temperature, the plate was washed and a solution containing secondary antibodies coupled to peroxidase was added followed by another incubation of 2 hour at room temperature. After incubation, the peroxidase substrate TMB (chromogenic solution) was added which resulted in color development. After exact 5 minutes of incubation 1M H<sub>2</sub>SO<sub>4</sub> was added to all wells to  
30 stop the reaction. After an incubation of 15 minutes the absorbance was measured at 450 nm using the microplate reader. Using the obtained standard curve, FIX levels were determined.

### **STATISTICS**

Data were analyzed using Microsoft Excel Statistics package. Values shown in Figures 3 and 4 are the mean + SEM. Significance values were obtained by comparison using t-test.

### Viral administration

Male adult C57BL/6 mice (18-20 grams) were administrated with AAV9 FIX vectors (see the table below) by tail vain injection at doses of  $1 \times 10^9$  vg/mouse and  $5 \times 10^9$  vg/mouse.

| Construct                                              | Size    | Dose            | Mice |
|--------------------------------------------------------|---------|-----------------|------|
| AAV9sc-SerpEnh-TTRm-MVM-co-FIX-R338L-BGHpolyA          | 2510 bp | $1 \times 10^9$ | 4    |
|                                                        |         | $5 \times 10^9$ | 4    |
| AAV9sc-3xSerpEnh-TTRm-MVM-co-FIX-R338L-BGHpolyA        | 2682 bp | $1 \times 10^9$ | 4    |
|                                                        |         | $5 \times 10^9$ | 4    |
| AAV9sc-TTREnh-TTRm-MVM-co-FIX-R338L-BGHpolyA           | 2540 bp | $1 \times 10^9$ | 4    |
|                                                        |         | $5 \times 10^9$ | 4    |
| AAV9sc-3xSerpEnh-TTREnh-TTRm-MVM-co-FIX-R338L-BGHpolyA | 2760 bp | $1 \times 10^9$ | 4    |
|                                                        |         | $5 \times 10^9$ | 4    |

Male adult CB17SCID mice (18-20 grams) were administrated with AAV8 XVIII vectors (see the table below) by tail vain injection at doses of  $1 \times 10^9$  vg/mouse and  $5 \times 10^9$  vg/mouse.

| Construct/condition                        | Size    | Dose            | Mice |
|--------------------------------------------|---------|-----------------|------|
| AAV8ss-TTRm-MVM-FVIIIcopt-sv40pA           | 5160 bp | $1 \times 10^9$ | 4    |
|                                            |         | $5 \times 10^9$ | 4    |
| AAV8ss-SerpEnh-TTRm-MVM-FVIIIcopt-sv40pA   | 5252 bp | $1 \times 10^9$ | 4    |
|                                            |         | $5 \times 10^9$ | 4    |
| AAV8ss-3xSerpEnh-TTRm-MVM-FVIIIcopt-sv40pA | 5410 bp | $1 \times 10^9$ | 4    |
|                                            |         | $5 \times 10^9$ | 4    |
| AAV8ss-TTREnh-TTRm-MVM-FVIIIcopt-sv40pA    | 5272 bp | $1 \times 10^9$ | 4    |
|                                            |         | $5 \times 10^9$ | 4    |

Plasmid administration

Male adult C57BL/6 mice (22-24 grams) were administrated with respective plasmids (see the table below) by hydrodynamic tail vein injection at doses of 300 ng.

| Construct/condition                                        | Size    | Dose   | Mice |
|------------------------------------------------------------|---------|--------|------|
| pAAVss-TTREnh-TTRm-MVM-co-hFVIII-deltaB-SV40pA             | 5272 p  | 300 ng | 2    |
| pAAVss-3XSerpEnh-TTREnh-TTRm-MVM-co-hFVIII-deltaB - SV40pA | 5493 bp | 300 ng | 2    |

5     Results

Factor IX:

The AAV vector containing **3XSerpEnh-TTREnh-TTRm**, with 3 copies of the Serp enhancer combined with the natural TTRe enhancer, and in combination with the TTRm promoter, led to the highest FIX levels compared to any of the other expression cassettes, over 4 time points until at least day 39 after AAV vector injection. The FIX expression showed a continuous increase over time.

The AAV vector containing the most robust **3XSerpEnh-TTREnh-TTRm** regulatory elements showed about **11 to 6 fold** (at low and high vector dose, respectively) higher FIX expression when compared to a control AAV vector that expressed FIX from the **TTREnh-TTRm** enhancer/promoter (i.e. lacking the SerpEnh enhancer).

The AAV vector containing the most robust **3XSerpEnh-TTREnh-TTRm** regulatory elements showed about **4 to 3 fold** (low and high vector dose, respectively) higher FIX expression when compared to a vector that expressed FIX from the **SerpEnh-TTRm** enhancer/promoter, which contains only one instead of 3 copies of the Serp enhancer, and no TTRe enhancer.

The AAV vector containing the most robust **3XSerpEnh-TTREnh-TTRm** showed about **3 to 2 fold** (low and high vector dose, respectively) higher expression when compared to a vector

that expressed FIX from the **3XSerpEnh-TTRm** enhancer/promoter which also 3 copies of the Serp enhancer, but is devoid of the TTR enhancer.

### Factor VIII

The AAV vector containing **3XSerpEnh-TTRm**, with 3 copies of the Serp enhancer, led to the highest FVIII levels compared to any of the other expression cassettes, until at least day 40 after AAV vector injection. The FVIII expression showed a continuous increase over time.

The AAV vector containing the **3XSerpEnh-TTRm** regulatory elements showed about **30 to 12 fold** (low and high vector dose, respectively) higher FVIII expression when compared to a reference control cassette (**TTRm**) which consist of only the TTR minimal promoter and that do not contain any enhancer.

The AAV vector containing the **3XSerpEnh-TTRm** regulatory elements showed about **10 to 1.5-fold** (low and high vector dose, respectively) higher FVIII expression when compared to an AAV vector containing **SerpEnh-TTRm** with only one copy of the Serp enhancer.

The AAV vector containing the **3XSerpEnh-TTRm** regulatory elements showed about 5 to 2 fold (low and high vector dose, respectively) higher expression when compared to an AAV vector containing the **TTREnh-TTRm** enhancer/promoter. The 3x SerpEnh regulatory element could further increase FVIII expression from the TTREnh-TTRm enhancer/promoter (Fig. 15). FVIII protein levels were about 8 to 5 fold higher in mice injected with the pAAVss-3XSerpEnh-TTREnh-TTRm-MVM-co-hFVIII-deltaB-SV40pA plasmid as compared to the pAAVss-TTREnh-TTRm-MVM-co-hFVIII-deltaB-SV40pA plasmid.

### Example 2 Studying the in vivo effect of 3xCRM8 and TTREnhancer on FVIII expression in various constructs by hydrodynamic injection (2ml) into CB17-SCID mice.

The aim of this example was to study the in vivo effect of 3xCRM8 and TTREnhancer on FVIII expression in various constructs by hydrodynamic injection (2ml) into CB17-SCID mice.

**Constructs:** The following vectors were compared for FVIII expression levels (cf. Figure 22):

pAAVss-TTRm-MVM-coFVIIIIdeltaB-Sv40pA (SEQ ID NO. 14);

pAAVss-3xSerpEnh-TTRm-MVM-coFVIIIIdeltaB-Sv40pA (SEQ ID NO:16);

pAAVss-TTRe-TTRm-MVM-coFVIIIIdeltaB-Sv40pA (SEQ ID NO:17); and

pAAVss-3xSerpEnh-TTRe-TTRm-MVM-coFVIIIIdeltaB-Sv40pA (SEQ ID NO:22).

In a first experiment, the following conditions were used:

**Mouse model:** CB17-SCID, male, adult mice of 18-20 grams

5 **Doses:** 150 ng plasmid/mouse

**Analysis points:** Blood collection at Day1

**No of mice:** 3 per condition

10

**Design:** See the table below

| Construct/condition                             | Dose   | Mice |
|-------------------------------------------------|--------|------|
| PBS control                                     | -      | 3    |
| 1. pAAVss-TTRe-TTRm-MVM-FVIIIcoΔB-sv40pA        | 300 ng | 3    |
| 2. pAAVss-3xCRM8-TTRe-TTRm-MVM-FVIIIcoΔB-sv40pA | 300 ng | 3    |

15 **Results:** The expression level of FVIII was analysed and compared. Figure 25a example shows a graph depicting the effect of the 3XSerp enhancer on the TTReh-TTRm promoter in regulating the FVIII expression in C57BL6 mice injected with 300ng of respective plasmids. The FVIII expression profile was tested using the ELISA, in the plasma samples collected Day 1. The presence of 3XSerp enhancer seems to elevate the FVIII expression by 8 fold.

20

In a second experiment the following conditions were used:

**Mouse model:** CB17-SCID, male, adult mice of 18-20 grams

25

**Doses:** 150 ng plasmid/mouse

**Analysis points:** Blood collection at Day1

30 **No of mice:** 3 per condition

**Design:** See the table below

| Construct/condition                         | Dose   | Mice |
|---------------------------------------------|--------|------|
| PBS control                                 | -      | 3    |
| 1. pAAVss-TTRm-MVM-FVIIIcoΔB-sv40pA         | 150 ng | 3    |
| 2. pAAVss-3xCRM8-TTRm-MVM-FVIIIcoΔB -sv40pA | 150 ng | 3    |

|                                                 |        |   |
|-------------------------------------------------|--------|---|
|                                                 |        |   |
| 3. pAAVss-TTRe-TTRm-MVM-FVIIIcoΔB-sv40pA        | 150 ng | 3 |
|                                                 |        |   |
| 4. pAAVss-3xCRM8-TTRe-TTRm-MVM-FVIIIcoΔB-sv40pA | 150 ng | 3 |
|                                                 |        |   |

**Results:** Figure 25b shows the compiled data from comparing the 4 constructs (see table below for actual FVIII expression values). Addition of 3xSERP to the TTRm construct enhances FVIII expression 17 fold. Addition of 3xSERP to the TTRe-TTRm construct enhances FVIII expression 13 fold. Addition of TTRe to the 3xSERP-TTRm construct still enhances FVIII expression 4 fold.

| Vectors          | FVIII level (ng/ml) |
|------------------|---------------------|
| TTRm             | 0,68                |
| 3xCRM8-TTRm      | 11,74               |
| TTRe-TTRm        | 3,52                |
| 3xCRM8-TTRe-TTRm | 46,67               |

**Example 3: Studying the in vivo effect of 3xCRM8 and TTRenhancer in combination with an AAT promoter on FIX expression in various constructs by hydrodynamic injection (2ml) into C57BL/6 mice.**

In this experiment, the TTRm minimal promotor is replaced by another liver-specific promotor to show the versatility of the regulator element.

As a first example, the AAT liver-specific promoter (AAT) is tested.

**Constructs:** Four different constructs were prepared as depicted in Figure 23 (the sequences are depicted in Figure 24):

- pAAVss-3xSerpEnh-TTRe-AAT-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:65);
- pAAVss-3xSerpEnh-AAT-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:66);
- pAAVss-TTRe-AAT-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:67); and
- pAAVss-TTRe-3xSerpEnh-AAT-MVM-co-FIX-R338L-BGHpA (SEQ ID NO:68);

All constructs tested make use of the AAT promoter (SEQ ID NO.64).

**Mouse model:** C57BL/6, male, adult mice of 18-20 grams

5     **Doses:** 1 µg and 2 µg plasmid/mouse

**Analysis points:** Blood collection at D1, D2

**No of mice:** 3 per condition

10

**Design:** See the table below

| Construct/condition                            | Dose | Mice |
|------------------------------------------------|------|------|
| PBS control                                    | -    | 3    |
| 1. pAAVsc-3xCRM8-TTRe-AAT-MVM-FIXcoR338L-BGHpA | 1 µg | 3    |
|                                                | 2 µg | 3    |
| 2. pAAVsc-3xCRM8-AAT-MVM-FIXcoR338L-BGHpA      | 1 µg | 3    |
|                                                | 2 µg | 3    |
| 3. pAAVsc-TTRe-AAT-MVM-FIXcoR338L-BGHpA        | 1 µg | 3    |
|                                                | 2 µg | 3    |
| 4. pAAVsc-TTRe-3xCRM8-AAT-MVM-FIXcoR338L-BGHpA | 1 µg | 3    |
|                                                | 2 µg | 3    |

Also the corresponding FVIII constructs will be tested for FVIII expression with the AAT  
15     promotor, hence encompassing the following constructs:

pAAVss-CRM8-TTRe-AAT-MVM-FVIIIcodeltaB-sv40pA.

pAAVss-3xCRM8-AAT-MVM-FVIIIcodeltaB-sv40pA.

pAAVss-3xCRM8-TTRe-AAT-MVM-FVIIIcodeltaB-sv40pA and

pAAVss-TTRe-3xCRM8-AAT-MVM-FVIIIcodeltaB-sv40pA.

20

In analogy, the following examples follow the outline of the example with the AAT promoter  
above, but each time with a different liver-specific promoter or minimal promoter.

In further examples, the albumin promotor (ALBp) is used to replace the TTRm promotor in  
25     said constructs, hence encompassing the following constructs:

pAAVsc-3xCRM8-TTRe-ALBp-MVM-FIXcoR338L-BGHpA,

pAAVss-3xCRM8-TTRe-ALBp-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-TTRe-3xCRM8-ALBp-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-ALBp-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-CRM8-TTRe-ALBp-MVM-FIXcoR338L-BGHpA, or  
pAAVss-CRM8-TTRe-ALBp-MVM-FVIIIcodeltaB-sv40pA.

In further examples, the apolipoprotein A1 promotor (APOA1p) is used to replace the TTRm  
5 promotor in said constructs, hence encompassing the following construct:

pAAVsc-3xCRM8-TTRe-APOA1p-MVM-FIXcoR338L-BGHpA,  
pAAVss-3xCRM8-TTRe-APOA1p-MVM-FVIIIcodeltaB-sv40pA  
pAAVsc-TTRe-3xCRM8-APOA1p-MVM-FIXcoR338L-BGHpA,  
pAAVss-TTRe-3xCRM8-APOA1p-MVM-FVIIIcodeltaB-sv40pA  
10 pAAVsc-CRM8-TTRe-APOA1p-MVM-FIXcoR338L-BGHpA, or  
pAAVss-CRM8-TTRe-APOA1p-MVM-FVIIIcodeltaB-sv40pA.

In further examples, the complement factor B promoter (CFBp) is used to replace the TTRm  
promotor in said constructs, hence encompassing the following construct:

15 pAAVsc-3xCRM8-TTRe-CFBp-MVM-FIXcoR338L-BGHpA,  
pAAVss-3xCRM8-TTRe-CFBp-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-TTRe-3xCRM8-CFBp-MVM-FIXcoR338L-BGHpA,  
pAAVss-TTRe-3xCRM8-CFBp-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-CRM8-TTRe-CFBp-MVM-FIXcoR338L-BGHpA, or  
20 pAAVss-CRM8-TTRe-CFBp-MVM-FVIIIcodeltaB-sv40pA.

In further examples, the ketohexokinase promoter (KHKp) is used to replace the TTRm  
promotor in said constructs, hence encompassing the following construct:

pAAVsc-3xCRM8-TTRe-KHKp-MVM-FIXcoR338L-BGHpA,  
25 pAAVss-3xCRM8-TTRe-KHKp-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-TTRe-3xCRM8-KHKp-MVM-FIXcoR338L-BGHpA,  
pAAVss-TTRe-3xCRM8-KHKp-MVM-FVIIIcodeltaB-sv40pA,  
pAAVsc-CRM8-TTRe-KHKp-MVM-FIXcoR338L-BGHpA, or  
pAAVss-CRM8-TTRe-KHKp-MVM-FVIIIcodeltaB-sv40pA.

In further examples, the hemopexin promoter (HPXp) is used to replace the TTRm promotor in said constructs, hence encompassing the following construct:

pAAVsc-3xCRM8-TTRe-HPXp-MVM-FIXcoR338L-BGHpA,

5 pAAVss-3xCRM8-TTRe-HPXp-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-TTRe-3xCRM8-HPXp-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-HPXp-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-CRM8-TTRe-HPXp-MVM-FIXcoR338L-BGHpA, or

pAAVss-CRM8-TTRe-HPXp-MVM-FVIIIcodeltaB-sv40pA.

10

In further examples, the nicotinamide N-methyltransferase promoter (NNMTp) is used to replace the TTRm promotor in said constructs, hence encompassing the following construct:

pAAVsc-3xCRM8-TTRe-NNMTp-MVM-FIXcoR338L-BGHpA,

pAAVss-3xCRM8-TTRe-NNMTp-MVM-FVIIIcodeltaB-sv40pA,

15 pAAVsc-TTRe-3xCRM8-NNMTp-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-NNMTp-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-CRM8-TTRe-NNMTp-MVM-FIXcoR338L-BGHpA, or

pAAVss-CRM8-TTRe-NNMTp-MVM-FVIIIcodeltaB-sv40pA.

20 In further examples, the (liver) carboxylesterase 1 promoter (CES1p) is used to replace the TTRm promotor in said constructs, hence encompassing the following construct:

pAAVsc-3xCRM8-TTRe-CES1p-MVM-FIXcoR338L-BGHpA,

pAAVss-3xCRM8-TTRe-CES1p-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-TTRe-3xCRM8-CES1p-MVM-FIXcoR338L-BGHpA,

25 pAAVss-TTRe-3xCRM8-CES1p-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-CRM8-TTRe-CES1p-MVM-FIXcoR338L-BGHpA, or

pAAVss-CRM8-TTRe-CES1p-MVM-FVIIIcodeltaB-sv40pA.

In further examples, the protein C promoter (PROCp) is used to replace the TTRm promotor in said constructs, hence encompassing the following construct:

pAAVsc-3xCRM8-TTRe-PROCp-MVM-FIXcoR338L-BGHpA,

pAAVss-3xCRM8-TTRe-PROCp-MVM-FVIIIcodeltaB-sv40pA,

5 pAAVsc-TTRe-3xCRM8-PROCp-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-PROCp-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-CRM8-TTRe-PROCp-MVM-FIXcoR338L-BGHpA, or

pAAVss-CRM8-TTRe-PROCp-MVM-FVIIIcodeltaB-sv40pA.

10 In further examples, the apolipoprotein C3 promoter (APOC3p) is used to replace the TTRm promotor in said constructs, hence encompassing the following construct:

pAAVsc-3xCRM8-TTRe-APOC3p-MVM-FIXcoR338L-BGHpA,

pAAVss-3xCRM8-TTRe-APOC3p-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-TTRe-3xCRM8-APOC3p-MVM-FIXcoR338L-BGHpA,

15 pAAVss-TTRe-3xCRM8-APOC3p-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-CRM8-TTRe-APOC3p-MVM-FIXcoR338L-BGHpA, or

pAAVss-CRM8-TTRe-APOC3p-MVM-FVIIIcodeltaB-sv40pA.

20 In further examples, the mannan-binding lectin serine protease 2 (MASP2p) is used to replace the TTRm promotor in said constructs, hence encompassing the following construct:

pAAVsc-3xCRM8-TTRe-MASP2p-MVM-FIXcoR338L-BGHpA,

pAAVss-3xCRM8-TTRe-MASP2p-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-TTRe-3xCRM8-MASP2p-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-MASP2p-MVM-FVIIIcodeltaB-sv40pA,

25 pAAVsc-CRM8-TTRe-MASP2p-MVM-FIXcoR338L-BGHpA, or

pAAVss-CRM8-TTRe-MASP2p-MVM-FVIIIcodeltaB-sv40pA.

In further examples, the serpin peptidase inhibitor, clade C (antithrombin) promoter (SERPINC1p) is used to replace the TTRm promotor in said constructs, hence encompassing the following construct:

pAAVsc-3xCRM8-TTRe-SERPINC1p-MVM-FIXcoR338L-BGHpA,

5 pAAVss-3xCRM8-TTRe-SERPINC1p-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-TTRe-3xCRM8-SERPINC1p-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-SERPINC1p-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-CRM8-TTRe-SERPINC1p-MVM-FIXcoR338L-BGHpA, or

pAAVss-CRM8-TTRe-SERPINC1p-MVM-FVIIIcodeltaB-sv40pA.

10

In further examples, the serpin peptidase inhibitor promoter (HAMPp) is used to replace the TTRm promotor in said constructs, hence encompassing the following construct:

pAAVsc-3xCRM8-TTRe-HAMPp-MVM-FIXcoR338L-BGHpA,

pAAVss-3xCRM8-TTRe-HAMPp-MVM-FVIIIcodeltaB-sv40pA

15 pAAVsc-TTRe-3xCRM8-HAMPp-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-HAMPp-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-CRM8-TTRe-HAMPp-MVM-FIXcoR338L-BGHpA, or

pAAVss-CRM8-TTRe-HAMPp-MVM-FVIIIcodeltaB-sv40pA.

20 **Results:** The expression level of FIX or FVIII will be analysed and compared as explained in Example 2.

## References

- 25 ANNONI A, BROWN BD, CANTORE A, SERGI LS, NALDINI L, and RONCAROLO MG. (2009). In vivo delivery of a microRNA-regulated transgene induces antigen-specific regulatory T cells and promotes immunologic tolerance. Blood 114, 5152–5161
- ARRUDA VR, STEDMAN HH, HAURIGOT V, and BUCHLIS G. (2010). Peripheral transvenular delivery of adeno-associated viral vectors to skeletal muscle as a novel therapy
- 30 for hemophilia B. Blood 115, 4678-88.

AXELROD JH, READ MS, BRINKHOUS KM, and VERMA IM. (1990). Phenotypic correction of factor IX deficiency in skin fibroblasts of hemophilic dogs. *Proc Natl Acad Sci USA*; 87, 5173-7.

BROWN BD, SHI CX, POWELL S, HURLBUT D, GRAHAM FL, and LILLICRAP D. (2004). Helper-dependent adenoviral vectors mediate therapeutic factor VIII expression for several months with minimal accompanying toxicity in a canine model of severe hemophilia A. *Blood* 103, 804-10.

BROWN BD, CANTORE A, ANNONI A, SERGI LS, LOMBARDO A, DELLA VALLE P, D'ANGELO A, and NALDINI L. (2007). A microRNA-regulated lentiviral vector mediates stable correction of hemophilia B mice. *Blood* 110, 4144-52.

Brunetti-Pierri N, Grove NC, Zuo Y, Edwards R, Palmer D, Cerullo V, Teruya J, Ng P.

Bioengineered factor IX molecules with increased catalytic activity improve the therapeutic index of gene therapy vectors for hemophilia B. *Hum Gene Ther.* 2009 May;20(5):479-85.

BUCHLIS G, PODSAKOFF GM, RADU A, HAWK SM, FLAKE AW, MINGOZZI F, and HIGH KA. (2012). Factor IX expression in skeletal muscle of a severe hemophilia B patient 10 years after AAV-mediated gene transfer. *Blood* 119, 3038-41.

BUDKER V, ZHANG G, KNECHTLE S, WOLFF JA. Naked DNA delivered intraportally expresses efficiently in hepatocytes. (1996) *Gene Ther.* Jul;3(7):593-8.

CANTORE A, NAIR N, DELLA VALLE P, DI MATTEO M, MÀTRAI J, SANVITO F, BROMBIN C, DI SERIO C, D'ANGELO A, CHUAH M, NALDINI L, VANDENDRIESSCHE T. Hyper-functional coagulation factor IX improves the efficacy of gene therapy in hemophilic mice. *Blood.* 2012. Oct 4.

CHANG, J., JIN, J., LOLLAR, P., BODE, W., BRANDSTETTER, H., HAMAGUCHI, N., STRAIGHT, D. L. & STAFFORD, D. W. (1998). Changing residue 338 in human factor IX from arginine to alanine causes an increase in catalytic activity. *J Biol Chem* 273(20): 12089-12094.

CHOWDHURY JR, GROSSMAN M, GUPTA S, CHOWDHURY NR, BAKER JR JR, WILSON JM. (1991) Long-term improvement of hypercholesterolemia after ex vivo gene therapy in LDLR-deficient rabbits. *Science.* Dec 20;254(5039):1802-5.

CHUAH MK, SCHIEDNER G, THORREZ L, BROWN B, JOHNSTON M, GILLIJNS V, HERTEL S, VAN ROOIJEN N, LILLICRAP D, COLLEN D, VANDENDRIESSCHE T, and KOCHANNEK S. (2003). Therapeutic factor VIII levels and negligible toxicity in mouse and dog models of hemophilia A following gene therapy with high-capacity adenoviral vectors. *Blood* 101, 1734-43.

Chuah MK, Nair N, VandenDriessche T. Recent progress in gene therapy for hemophilia.

Hum Gene Ther. 2012a Jun;23(6):557-65.

Chuah MK, Nair N, VandenDriessche T. Recent progress in gene therapy for hemophilia.

Hum Gene Ther. 2012b Jun;23(6):557-65.

5 Chuah MK, VandenDriessche T. Platelet-directed gene therapy overcomes inhibitory antibodies to factor VIII. J Thromb Haemost. 2012c Aug;10(8):1566-9

DONSANTE A, MILLER DG, LI Y, VOGLER C, BRUNT EM, RUSSELL DW, and SANDS MS. (2007). AAV vector integration sites in mouse hepatocellular carcinoma. Science 317, 477.

10 DOBRZYNSKI E, FITZGERALD JC, CAO O, MINGOZZI F, WANG L, and HERZOG RW (2006) Prevention of cytotoxic T lymphocyte responses to factor IX-expressing hepatocytes by gene transfer-induced regulatory T cells. Proc Natl Acad Sci USA 103, 4592 – 4597.

EHRHARDT A, and KAY MA. (2002). A new adenoviral helper-dependent vector results in long-term therapeutic levels of human coagulation factor IX at low doses in vivo. Blood 99, 3923-30.

15 FIELDS PA, ARRUDA VR, ARMSTRONG E, KIRK CHU, MINGOZZI, F. HAGSTROM, J., HERZOG R, HIGH KA. (2001). Risk and prevention of anti-factor IX formation in AAV-mediated gene transfer in the context of a large deletion of F9. Mol. Ther. 4, 201–210.

20 FOLLENZI A, BATTAGLIA M, LOMBARDO A, ANNONI A, RONCAROLO MG, and NALDINI L. (2004). Targeting lentiviral vector expression to hepatocytes limits transgene-specific immune response and establishes long-term expression of human antihemophilic factor IX in mice. Blood 103, 3700-9.

GAO GP, ALVIRA MR, WANG L, JOHNSTON J, WILSON JM. (2002). Novel adeno-associated viruses from rhesus monkeys as vectors for human gene therapy. Proc Natl Acad Sci USA 99, 11854 -9.

25 GAO G, VANDENBERGH LH, ALVIRA MR LU Y, CALCEDO R, ZHOU X, and WILSON JM. (2004). Clades of Adeno-associated viruses are widely disseminated in human tissues. J. Viro 78, 6381 – 6388.

30 HERZOG RW, YANG EY, COUTO LB, HAGSTROM JN, ELWELL D, FIELDS PA, BURTON M, BELLINGER DA, READ MS, BRINKHOUS KM, PODSAKOFF GM, NICHOLS TC, KURTZMAN GJ, and HIGH KA. (1999). Long-term correction of canine hemophilia B by gene transfer of blood coagulation factor IX mediated by adeno-associated viral vector. Nat Med. 5, 56–63.

HERZOG RW, MOUNT JD, ARRUDA VR, HIGH KA, and LOTHROP CD Jr. (2001). Muscle-directed gene transfer and transient immune suppression result in sustained partial correction of canine hemophilia B caused by a null mutation. *Mol Ther.* 4, 192-200.

HERZOG RW, HAGSTROM JN, KUNG SH, TAI SJ, WILSON JM, FISHER KJ, and HIGH KA.  
5 (1997) Stable gene transfer and expression of human blood coagulation factor IX after intramuscular injection of recombinant adeno-associated virus. *Proc Natl Acad Sci USA.* 94, 5804 – 5809.

HERZOG RW, FIELDS PA, ARRUDA VR, BRUBAKER JO, ARMSTRONG E, MCCLINTOCK D, BELLINGER DA, COUTO LB, NICHOLS TC, HIGH KA (2002) Influence of vector dose on  
10 factor IX-specific T and B cell responses in muscle- directed gene therapy. *Hum Gene Ther* 13, 1281–1291.

HIGH KA. (2001). Gene Transfer as an approach to treating Hemophilia. *Circ Res.* 88, 137-144.

HIGH KA. (2011) Gene therapy for hemophilia: a long and winding road. *J Thromb Haemost.* 9  
15 Suppl. 1: 2-11.

BAINBRIDGE J, SMITH AJ, BARKER S, et al. (2008) Effect of Gene Therapy on Visual Function in Leber's Congenital Amaurosis. *N Engl J Med.* 358, 2231-2239.

JIANG H, LILLICRAP D, and PATARROYO-WHITE S. (2006). Multiyear therapeutic benefit of AAV serotypes 2, 6, and 8 delivering factor VIII to hemophilia A mice and dogs. *Blood.* 108,  
20 107-15.

KAO, C. Y., LIN, C. N., YU, I. S., TAO, M. H., WU, H. L., SHI, G. Y., YANG, Y. L., KAO, J. T. & LIN, S. W. (2010). FIX-Triple, a gain-of-function factor IX variant, improves haemostasis in mouse models without increased risk of thrombosis. *Thromb Haemost* 104(2): 355-365.

KAY MA, BAILEY P, ROTHENBERG S, LELAND F, FLEMING L, PONDER KP, LIU T, FINEGOLD M, DARLINGTON G, POKORNY W, WOO SLC. (1992) Expression of human alpha 1 -antitrypsin in dogs after autologous transplantation of retroviral transduced hepatocytes. *Proc Natl Acad Sci U S A.* Jan 1 ;89(1 ):89-93.  
25

KAY MA, MANNO CS, RAGNI MV, COUTO LB, MCCLELLAND A, GLADER B, CHEW AJ, TAI SJ, HERZOG RW, ARRUDA V, JOHNSON F, SCALLAN C, SKARSGARD E, FLAKE AW, and HIGH KA. (2000). Evidence for gene transfer and expression of factor IX in hemophilia B  
30 patients treated with an AAV vector. *Nat Genet.* 24, 257- 61.

KISTNER A, GOSSEN M, ZIMMERMANN F, JERECIC J, ULLMER C, LYBBERT H, BUJARD H. (1996) Doxycycline- mediated quantitative and tissue-specific control of gene expression in transgenic mice. *Proc Natl Acad Sci U S A.* Oct 1;93(20): 10933-8.

KREN BT, UNGER GM, SJEKLOCHA L, TROSSEN AA, KORMAN V, DIETHELEM-OKITA BM, REDING MT, and STEER CJ. (2009). Nanocapsule-delivered Sleeping Beauty mediates therapeutic Factor VIII expression in liver sinusoidal endothelial cells of hemophilia A mice. *J Clin Invest.* 19, 2086-99.

- 5 KURIYAMA S, YOSHIKAWA M, ISHIZAKA S, TSUJII T, LKENAKA K, KAGAWA T, MORITA N, MIKOSHIBA K. (1991) A potential approach for gene therapy targeting hepatoma using a liver-specific promoter on a retroviral vector. *Cell Struct Funct.* Dec;16(6):503-10.

LI H, MALANI N, HAMILTON SR, SCHLACHTERMAN A, BUSSADORI G, EDMONSON SE, SHAH R, ARRUDA VR, MINGOZZI F, WRIGHT JF, BUSHMAN FD, and HIGH KA. (2011).

- 10 Assessing the potential for AAV vector genotoxicity in a murine model. *Blood.* 117, 3311-9.

LIN, C. N., KAO, C. Y., MIAO, C. H., HAMAGUCHI, N., WU, H. L., SHI, G. Y., LIU, Y. L., HIGH, K. A. & LIN, S. W. (2010). Generation of a novel factor IX with augmented clotting activities in vitro and in vivo. *J Thromb Haemost* 8(8): 1773-1783.

- 15 LIU F, SONG Y, LIU D. (1999) Hydrodynamics-based transfection in animals by systemic administration of plasmid DNA. *Gene Ther.* Jul;6(7):1258-66.

MANNO CS, PIERCE GF, and ARRUDA VR. (2006). Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response. *Nat Med.* 12, 342-7.

- 20 MÁTÉS L, CHUAH MK, BELAY E, JERCHOW B, MANOJ N, ACOSTA-SANCHEZ A, GRZELA DP, SCHMITT A, BECKER K, MATRAI J, MA L, SAMARA-KUKO E, GYSEMANS C, PRYPUTNIEWICZ D, MISKEY C, FLETCHER B, VANDENDRIESSCHE T., IVICS Z, and IZSVAK Z. (2009). Molecular evolution of a novel hyperactive Sleeping Beauty transposase enables robust stable gene transfer in vertebrates. *Nat Genet.* 41, 753-61.

- 25 MÁTRAI J, CHUAH MK, and VANDENDRIESSCHE T. (2010a). Pre clinical and clinical progress in hemophilia gene therapy. *Curr Opin Hematol.* 17, 387-92.

MÁTRAI J, CHUAH MK, and VANDENDRIESSCHE T. (2010b). Recent advances in lentiviral vector development and applications. *Mol Ther.* 18, 477-90.

- 30 MÁTRAI J, CANTORE A, BARTHOLOMAE CC, ANNONI A, WANG W, ACOSTA-SANCHEZ A, SAMARA-KUKO E, DE WAELE L, MA L, GENOVESE P, DAMO M, ARENS A, GOUDY K, NICHOLS TC, VON KALLE C, L CHUAH MK, RONCAROLO MG, SCHMIDT M, VANDENDRIESSCHE T, and NALDINI L. (2011). Hepatocyte-targeted expression by integrase-defective lentiviral vectors induces antigen-specific tolerance in mice with low genotoxic risk. *Hepatology* 53, 1696-707.

- MATSUI H, SHIBATA M, BROWN B, LABELLE A, HEGADRON C, ANDREWS C, CHUAH M, VANDENDRIESSCHE T, MIAO CH, HOUGH C, and LILLICRAP D. (2009). A murine model for induction of long-term immunologic tolerance to factor VIII does not require persistent detectable levels of plasma factor VIII and involves contributions from Foxp3+ T regulatory  
5 cells. *Blood*. 114, 677-85.
- MATSUI H, HEGADORN C, OZELO M, BURNETT E, TUTTLE A, LABELLE A, McCARY PB Jr., NALDINI L, BROWN B, HOUGH C, and LILLICRAP D. (2011). A microRNA-regulated and GP64-pseudotyped lentiviral vector mediates stable expression of FVIII in a murine model of Hemophilia A. *Mol Ther*. 19, 723-30.
- 10 McCARTY DM, MONAHAN PE, and SAMULSKI RJ. (2001). Self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis. *Gene Ther*. 8, 1248-54.
- McCARTY DM, FU H, MONAHAN PE, TOULSON CE, NAIK P, and SAMULSKI RJ. (2003). Adeno-associated virus terminal repeat (TR) mutant generates self-complementary vectors to  
15 overcome the rate-limiting step to transduction in vivo. *Gene Ther*. 10, 2112-8.
- McIntosh, J. *et al*. Therapeutic levels of FVIII following a single peripheral vein administration of rAAV vector encoding a novel human factor VIII variant. *Blood* (2013).
- MIAO CH, OHASHI K, PATIJN GA, MEUSE L, YE X, THOMPSON AR, and KAY MA. (2000). Inclusion of the hepatic locus control region, an intron, and untranslated region increases and  
20 stabilizes hepatic factor IX gene expression in vivo but not in vitro. *Mol Ther*. 1, 522-32.
- MIAO H.Z., SIRACHAINAN N., PALMER L., et al. (2004). Bioengineering of coagulation factor VIII for improved secretion. *Blood* 103(9):3412-3419.
- MILANOV, ET AL., 2012 Engineered factor IX variants bypass FVIII and correct hemophilia A phenotype in mice *Blood* 119:602-611.
- 25 MILLER AD. (1990) Retrovirus packaging cells. *Hum Gene Ther*. Spring;1 (1 ):5-14.
- MINGOZZI F, LIU YL, DOBRZYNSKI E, KAUFHOLD A, LIU JH, WANG Y, ARRUDA VR, HIGH KA, and HERZOG RW. (2003). Induction of immune tolerance to coagulation factor IX antigen by in vivo hepatic gene transfer. *J Clin Invest*. 111, 1347-56.
- MINGOZZI F, MAUS MV, HUI DJ, SABATINO DE, MURPHY SL, RASKO JE, RAGINI MV,  
30 MANNO CS, SOMMER J, JIANG H, PIERCE GF, ERTL HC, and HIGH KA. (2007). CD8(+) T-cell responses to adeno-associated virus capsid in humans. *Nat Med*. 13, 419-22.
- MOUNT JD, HERZOG RW, TILLSON DM, GOODMAN SA, ROBINSON N, MCCLELAND ML, BELLINGER D, NICHOLS TC, ARRUDA VR, LOTHROP CD JR, and HIGH KA. (2002).

Sustained phenotypic correction of hemophilia B dogs with a factor IX null mutation by liver-directed gene therapy. *Blood* 99, 2670-6.

5 NAIR N, RINCON MY, EVENS H, SARCAR S, DASTIDAR S, SAMARA-KUKO E, GHANDEHARIAN O, MAN VIECELLI H, THÖNY B, DE BLESER P, VANDENDRIESSCHE T, CHUAH MK. (2014). Computationally designed liver-specific transcriptional modules and hyperactive factor IX improve hepatic gene therapy. *Blood* 123,3195-9.

NALDINI L, BLOMER U, GALLAY P, ORY D, MULLIGAN R, GAGE FH, VERMA IM, TRONO D. (1996) In vivo gene delivery and stable transduction of nondividing cells by a lentiviral vector. *Science*. Apr 12;272(5259):263-7.

10 NATHWANI AC, DAVIDOFF AM, HANAWA H, YUNYU HU, HOFFER FA, NIKANOROV A, SLAUGHTER C, NG CYC, ZHOU J, LOZIER J, MANDRELL TD, VANIN EF, and NIENHUIS AW. (2002). Sustained high- level expression of human factor IX (hFIX) after liver-targeted delivery of recombinant adeno-associated virus encoding the hFIX gene in rhesus macaques. *Blood* 100, 1662–1669.

15 NATHWANI AC, GRAY JT, NG CY, ZHOU J, SPENCE Y, WADDINGTON SN, TUDDENHAM EG, KEMBALL COOK G, McINTOSH J, BOON-SPIJKER M, MERTENS K, DAVIDOFF AM. (2006). Self-complementary adeno-associated virus vectors containing a novel liver-specific human factor IX expression cassette enable highly efficient transduction of murine and nonhuman primate liver. *Blood* 107, 2653-61.

20 NATHWANI AC, TUDDENHAM EG, RANGARAJAN S, ROSALES C, MCINTOSH J, LINCH DC, CHOWDARY P, RIDDELL A, PIE AJ, HARRINGTON C, O'BEIRNE J, SMITH K, PASI J, GLADER B, RUSTAGI P, NG CY, KAY MA, ZHOU J, SPENCE Y, MORTON CL, ALLAY J, COLEMAN J, SLEEP S, CUNNINGHAM JM, SRIVASTAVA D, BASNER-TSCHAKARJAN E, MINGOZZI F, HIGH KA, GRAY JT, REISS UM, NIENHUIS AW, and DAVIDOFF AM. (2011). Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. *N Engl J Med*. 365, 2357-2365.

30 OHLFEST JR, FRANSEN JL, FRITZ S, LOBITZ PD, PERKINSON SG, CLARK KJ, NELSESTUEN G, KEY NS, MCLVOR RS, HACKETT PB, and LARGAESPADA DA. (2004). Phenotypic correction and long-term expression of factor VIII in hemophilic mice by immunotolerization and nonviral gene transfer using the Sleeping Beauty transposon system. *Blood* 105, 2691-8.

Petrus, I., Chuah, M. & VandenDriessche, T. Gene therapy strategies for hemophilia: benefits versus risks. *J Gene Med* 12, 797-809 (2010). SANDBERG H, ALMSTEDT A, BRANDT J, et al. (2001). Structural and functional characteristics of the B domain-deleted recombinant factor VIII proteint, r-VIII SQ. *Thromb Haemost*. 85(1): 93-100.

35

SCHUETTRUMPF, J., HERZOG, R. W., SCHLACHTERMAN, A., KAUFHOLD, A., STAFFORD, D. W. & ARRUDA, V. R. (2005). Factor IX variants improve gene therapy efficacy for hemophilia B. *Blood* 105(6): 2316-2323.

5 SIMIONI, P., TORMENE, D., TOGNIN, G., GAVASSO, S., BULATO, C., IACOBELLI, N. P., FINN, J. D., SPIEZIA, L., RADU, C. & ARRUDA, V. R. (2009). X-linked thrombophilia with a mutant factor IX (factor IX Padua). *N Engl J Med* 361(17): 1671-1675.

10 SNYDER RO, MIAO CH, PATIJN GA, SPRATT SK, DANOS O, NAGY D, GOWN AM, WINTHER B, MEUSE L, COHEN LK, THOMPSON AR, and KAY MA. (1997). Persistent and therapeutic concentrations of human factor IX in mice after hepatic gene transfer of recombinant AAV vectors. *Nat Genet.* 16, 270 – 276.

SNYDER RO, MIAO C, MEUSE L, TUBB J, DONAHUE BA, HUI-FENG LIN, STAFFORD DW, PATEL S, THOMPSON AR, NICHOLS T, READ MS, BELLINGER DA, BRINKHOUS KM, and KAY MA. (1999). Correction of hemophilia B in canine and murine models using recombinant adeno-associated viral vectors. *Nat Med.* 5, 64–70.

15 TRAPNELL BC. (1993) Adenoviral vectors for gene transfer. *Adv. Drug Del. Rev.* 12: 185-199.

VANDENBERGHE LH, WANG L, SOMANATHAN S, ZHI Y, FIGUEREDO J, CALCEDO R, SANMIGUEL J, DESAI RA, CHEN CS, JOHNSTON J, GRANT RL, GAO G, and WILSON JM. (2006). Heparin binding directs activation of T cells against adeno-associated virus serotype 2 capsid. *Nat Med.* 12, 967-71.

20 VANDENDRIESSCHE T, VANSLEMBROUCK V, GOOVAERTS I, ZWINNEN H, VANDERHAEGHEN ML, COLLEN D, and CHUAH MK. (1999). Long-term expression of human coagulation factor VIII and correction of hemophilia A after in vivo retroviral gene transfer in factor VIII-deficient mice. *Proc Natl Acad Sci USA.* 96, 10379-84.

25 VANDENDRIESSCHE T, THORREZ L, NALDINI L, FOLLENZI A, MOONS L, ZWIERNEMAN, COLLEN D, and CHUAH MK. (2002). Lentiviral vectors containing the human immunodeficiency virus type-1 central polypurine tract can efficiently transduce nondividing hepatocytes and antigen-presenting cells in vivo. *Blood* 100, 813-22.

30 VANDENDRIESSCHE T, THORREZ L, ACOSTA-SANCHEZ A, PETRUS I, WANG L, MA L, DE WAELE L, IWASAKI Y, GILLIJNS V, WILSON JM, COLLEN D, and CHUAH MK. (2007). Efficacy and safety of adeno-associated viral vectors based on serotype 8 and 9 vs. lentiviral vectors for hemophilia B gene therapy. *J Thromb Haemost.* 5, 16-24.

VANDENDRIESSCHE T, IVICS Z, IZSVÁK Z, and CHUAH MK. (2009). Emerging potential of transposons for gene therapy and generation of induced pluripotent stem cells. *Blood* 114, 1461-8.

VANDENDRIESSCHE T, and CHUAH MK. (2012). Clinical progress in gene therapy: sustained partial correction of the bleeding disorder in patients suffering from severe hemophilia B. *Hum Gene Ther.* 23, 4-6.

5 WANG L, TAKABE K, BIDLINGMAIER SM, ILL CR, and VERMA IM. (1999). Sustained correction of bleeding disorder in hemophilia B mice by gene therapy. *Proc Natl Acad Sci USA* 96, 3906–3910.

WANG L, NICHOLS TC, READ MS, BELLINGER DA, and VERMA IM. (2000). Sustained expression of therapeutic level of factor IX in hemophilia B dogs by AAV-mediated gene therapy in liver. *Mol Ther.* 1, 154–158.

10 WANG L, CAO O, SWALM B, DOBRZYNSKI E, MINGOZZI F, and HERZOG RW (2005) Major role of local immune responses in antibody formation to factor IX in AAV gene transfer. *Gene Ther* 12, 1453-464.

WARD NJ, BUCKLEY SM, WADDINGTON SN, VANDENDRIESSCHE T, CHUAH MK, NATHWANI AC, McLINTOSH J, TUDDENHAM EG, KINNON C, THRASHER AJ, and McVEY  
15 JH (2010) Codon optimization of human factor VIII cDNAs leads to high-level expression. *Blood* 117, 798-807.

Ward, N.J. *et al.* Codon optimization of human factor VIII cDNAs leads to high-level expression. *Blood* **117**, 798-807 (2011).

20 WU Z, SUN J, ZHANG T, YIN C, YIN F, VAN DYKE T, SAMULSKI RJ, and MONAHAN PE. (2008). Optimization of self-complementary AAV vectors for liver-directed expression results in sustained correction of hemophilia B at low vector dose. *Mol Ther.* 16, 280-9.

XU L, GAO C, and SANDS MS. (2003). Neonatal or hepatocyte growth factor-potentiated adult gene therapy with a retroviral vector results in therapeutic levels of canine factor IX for hemophilia B. *Blood* 101, 3924 – 3932.

25 XU L, NICHOLS TC, SARKAR R, Mc CORQUODALE S, BELLINGER DA, PONDER KP. (2005). Absence of a desmopressin response after therapeutic expression of factor VIII in hemophilia A dogs with liver-directed neonatal gene therapy. *Proc Natl Acad Sci USA* 102, 6080–6085.

30 YAMADA T, IWASAKI Y, TADA H, IWABUKI H, CHUAH MK, VANDENDRIESSCHE T, FUKUDA H, KONDO A, UEDA M, SENO M, TANIZAWA K, KURODA S. (2003) Nanoparticles for the delivery of genes and drugs to human hepatocytes. *Nat Biotechnol.* Aug;21 (8):885-90.

YANT SR, MEUSE L, CHIU W, IVICS Z, IZSVAK Z, and KAY MA. (2000). Somatic integration and long-term transgene expression in normal and haemophilic mice using a DNA transposon system. *Nat Genet.* 25, 35-41.

Yusa et al. A hyperactive piggyBac transposase for mammalian applications. Proc Natl Acad Sci U S A. 2011;108(4):1531-6.

5 ZHANG G, BUDKER V, WOLFF JA. (1999) High levels of foreign gene expression in hepatocytes after tail vein injections of naked plasmid DNA. Hum Gene Ther. Jul 1 ;10(10):1735-7.

ZHONG L, LI B, MAH CS, GOVINDASAMY L, AGBANDJE-MCKENNA, COOPER M, HERZOG RW, ZOLOTUKHIN I, WARRINGTON JR. KH, WEIGEL-VAN AKEN K, HOBBS JA, ZOLOTUKHIN S, MUZYCZKA N, and SRIVASTAVA A (2008). Next generation of adeno-associated virus 2 vectors: point mutations in tyrosines lead to high-efficiency transduction at  
10 lower doses. Proc Natl Acad Sci USA 105, 7827-32.

**CLAIMS**

1. A nucleic acid expression cassette comprising a triple repeat, preferably tandemly arranged, of a liver-specific nucleic acid regulatory element comprising or consisting of the nucleic acid fragment defined by SEQ ID NO:5 or a sequence having at least 95% identity to said  
5 sequence; and a nucleic acid regulatory element comprising or consisting of the nucleic acid fragment defined by SEQ ID NO:12 or a sequence having at least 95% identity to said sequence; operably linked to a liver-specific promoter and a transgene.
2. The nucleic acid expression cassette according to claim 1, wherein the liver-specific promoter is selected from the group comprising: the minimal TTR promotor (TTRm), the AAT  
10 promoter, the albumin (ALB) promotor or minimal promoter, the apolipoprotein A1 (APOA1) promoter or minimal promoter, the complement factor B (CFB) promoter, the ketohexokinase (KHK) promoter, the hemopexin (HPX) promoter or minimal promoter, the nicotinamide N-methyltransferase (NNMT) promoter or minimal promoter, the (liver) carboxylesterase 1 (CES1) promoter or minimal promoter, the protein C (PROC) promoter or minimal promoter,  
15 the apolipoprotein C3 (APOC3) promoter or minimal promoter, the mannan-binding lectin serine protease 2 (MASP2) promoter or minimal promoter, the hepcidin antimicrobial peptide (HAMP) promoter or minimal promoter, or the serpin peptidase inhibitor, clade C (antithrombin), member 1 (SERPINC1) promoter or minimal promoter.
3. The nucleic acid expression cassette according to claim 1 or 2, wherein said liver-specific  
20 promoter is the minimal TTR promotor (TTRm) as defined by SEQ ID NO:6.
4. The nucleic acid expression cassette according to claim 1 or 2, wherein said liver-specific promoter is the AAT promoter as defined by SEQ ID NO:64.
5. The nucleic acid expression cassette according to any one of claims 1 to 4, wherein said triple repeat consists of the nucleic acid fragment defined by SEQ ID NO:11 or a sequence  
25 having at least 95% identity to said sequence.
6. The nucleic acid expression cassette according to any one of claims 1 to 5, comprising the regulatory element as defined by SEQ ID NO:13, more preferably a regulatory element as defined by SEQ ID NO:57, operably linked to a promoter and a transgene, operably linked to a transgene.
- 30 7. The nucleic acid expression cassette according to any one of claims 1 to 6, wherein said transgene encodes for coagulation factor IX (FIX), preferably wherein said transgene is codon-optimized coagulation factor FIX, or wherein said coagulation factor FIX contains a hyper-activating mutation, preferably wherein said hyper-activating mutation corresponds to an R338L amino acid substitution, more preferably wherein said transgene encoding for  
35 coagulation factor FIX has a nucleic acid sequence as defined by SEQ ID NO:9.

8. The nucleic acid expression cassette according to any one of claims 1 to 7, wherein said transgene encodes for coagulation factor VIII (FVIII), preferably wherein said transgene is codon-optimized coagulation factor FVIII, or wherein said coagulation factor VIII has a deletion of the B domain, preferably wherein said B domain of said FVIII is replaced by a linker defined by SEQ ID NO:59, more preferably wherein said transgene encoding for coagulation factor VIII has a nucleic acid sequence defined by SEQ ID NO:18.
9. The nucleic acid expression cassette according to any one of claims 1 to 3 and 5 to 8, wherein the promoter is the transthyretin (TTR) promoter, thereby comprising the combination of the TTR<sub>e</sub> and TTR<sub>m</sub> nucleic acids as defined by SEQ ID NO:69.
10. The nucleic acid expression cassette according to any one of claims 1 to 9, further comprising a minute virus of mouse (MVM) intron, preferably the MVM intron defined by SEQ ID NO:8.
11. The nucleic acid expression cassette according to any one of claims 1 to 10, further comprising a transcriptional termination signal derived from the bovine growth hormone polyadenylation signal (BGHpA), preferably the BGHpA as defined by SEQ ID NO:10, or derived from the Simian virus 40 polyadenylation signal (SV40pA), preferably the SV40pA as defined by SEQ ID NO:19, or the synthetic polyadenylation signal as defined by SEQ ID NO:56.
12. A vector comprising the nucleic acid expression cassette according to any one of claims 1 to 11, preferably wherein said vector is a viral vector, more preferably wherein said vector is derived from an adeno-associated virus (AAV).
13. The vector according to claim 12, comprising the FVIII transgene for use in treating hemophilia A; or the vector according to claim 12, comprising the FIX transgene for use in treating hemophilia B.
14. The vector for use according to claim 13, wherein after transduction or transfection of the vector according to claim 12 into a subject, levels of factor IX or FVIII in plasma equal to or higher than the therapeutic threshold concentration of 10mU/ml plasma in the subject are obtained.
15. The vector for use according to claim 14, wherein the transduction of the viral vector into the subject is done at a dose lower than  $2 \times 10^{11}$  vg/kg.
16. The vector for use according to claim 15, wherein the transduction of the viral vector into the subject is done at a dose lower than or equal than  $6 \times 10^{11}$  vg/kg, and wherein levels of factor IX or FVIII in plasma equal to or higher than the therapeutic concentration of 100 mU/ml are obtained in said subject; or wherein the transduction of the viral vector into the subject is done at a dose lower than or equal than  $6 \times 10^{11}$  vg/kg, and wherein levels of factor IX or FVIII

in plasma equal to or higher than the therapeutic concentration of 50 mU/ml are obtained in said subject; or wherein the transduction of the viral vector into the subject is done at a dose lower than or equal than  $2 \times 10^{12}$  vg/kg, and wherein levels of factor IX or FVIII in plasma equal to or higher than the therapeutic concentration of 200 mU/ml are obtained in said subject; or  
5 wherein the transduction of the viral vector into the subject is done at a dose lower than or equal than  $2 \times 10^{12}$  vg/kg, and wherein levels of factor IX or FVIII in plasma equal to or higher than the therapeutic concentration of 150 mU/ml are obtained in said subject.

17. A pharmaceutical composition comprising a vector according to claim 12 and a pharmaceutically acceptable carrier, optionally further comprising an active ingredient for  
10 treating hemophilia A when the transgene in said vector is FVIII; or an active ingredient for treating hemophilia B when the transgene in said vector is FIX.

Figure 1

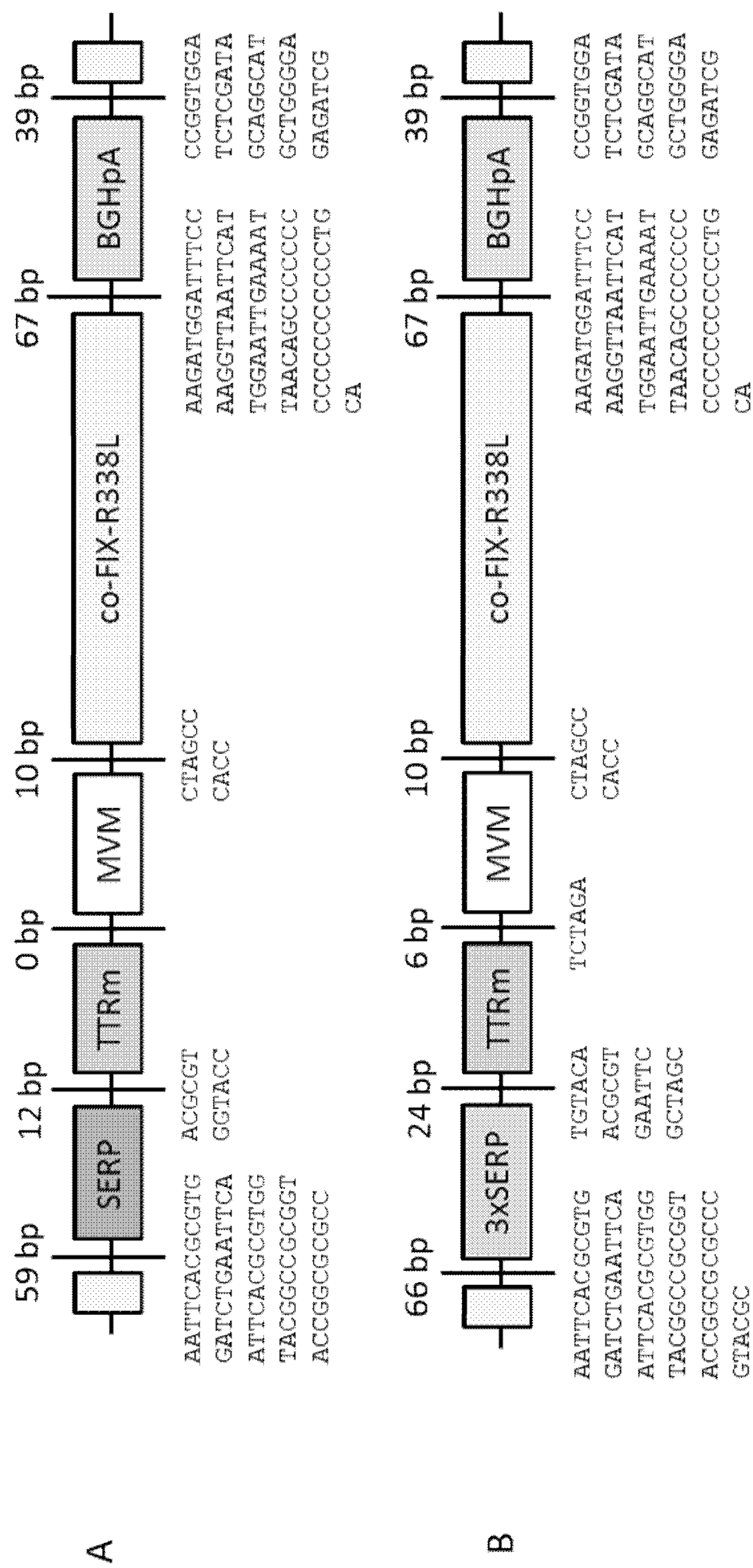


Figure 1 (continued)

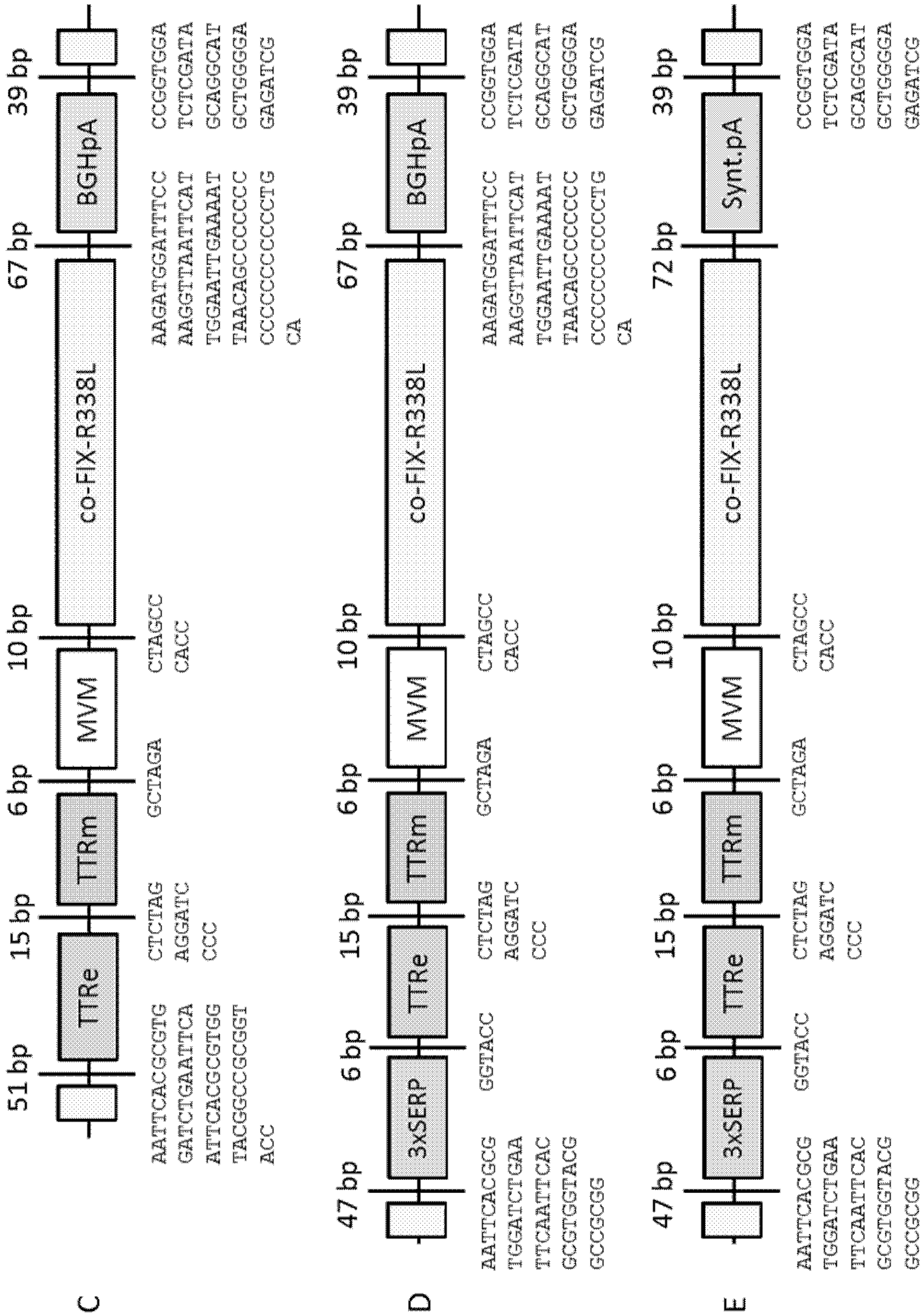


Figure 2

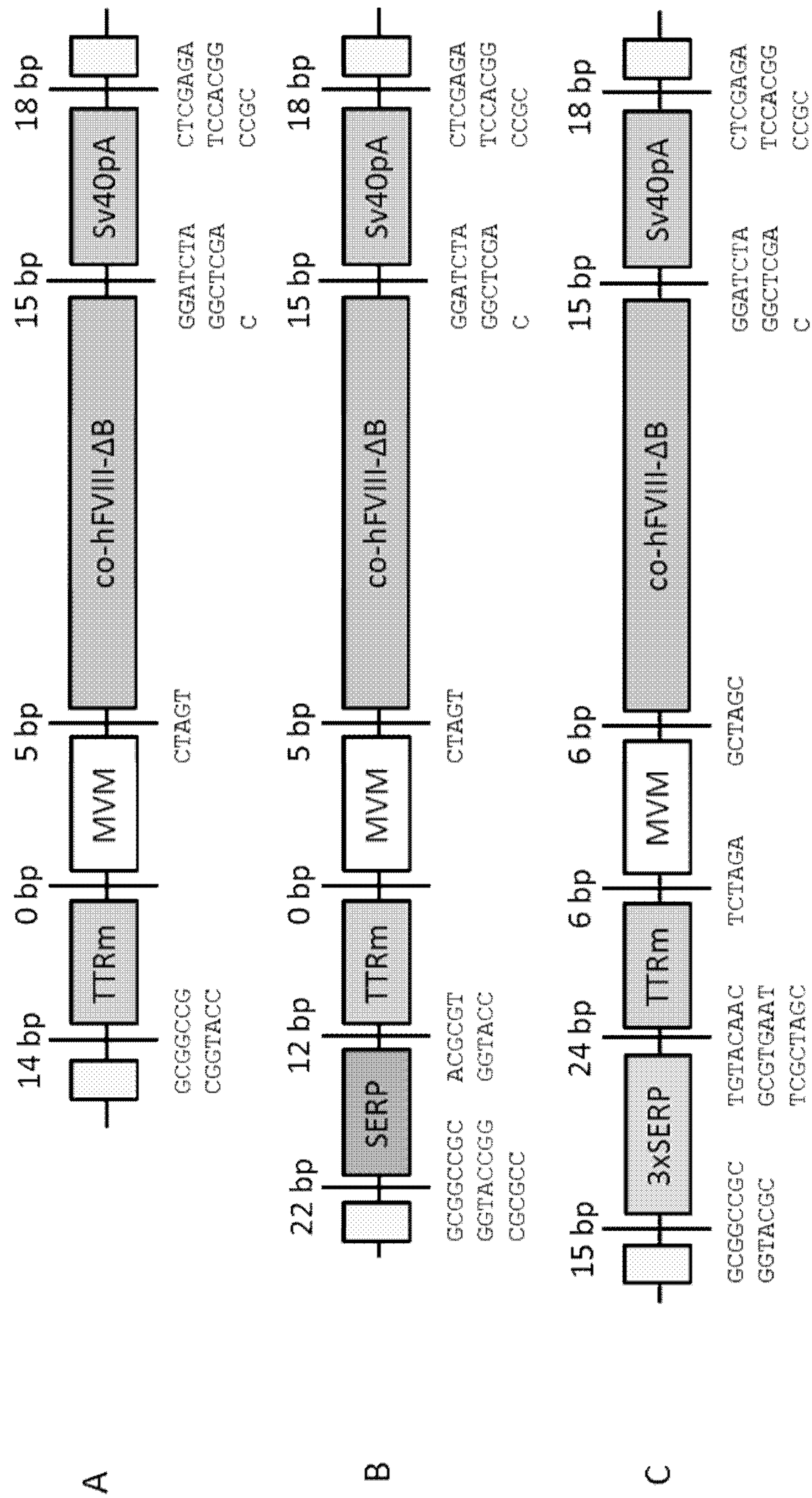


Figure 2 (continued)

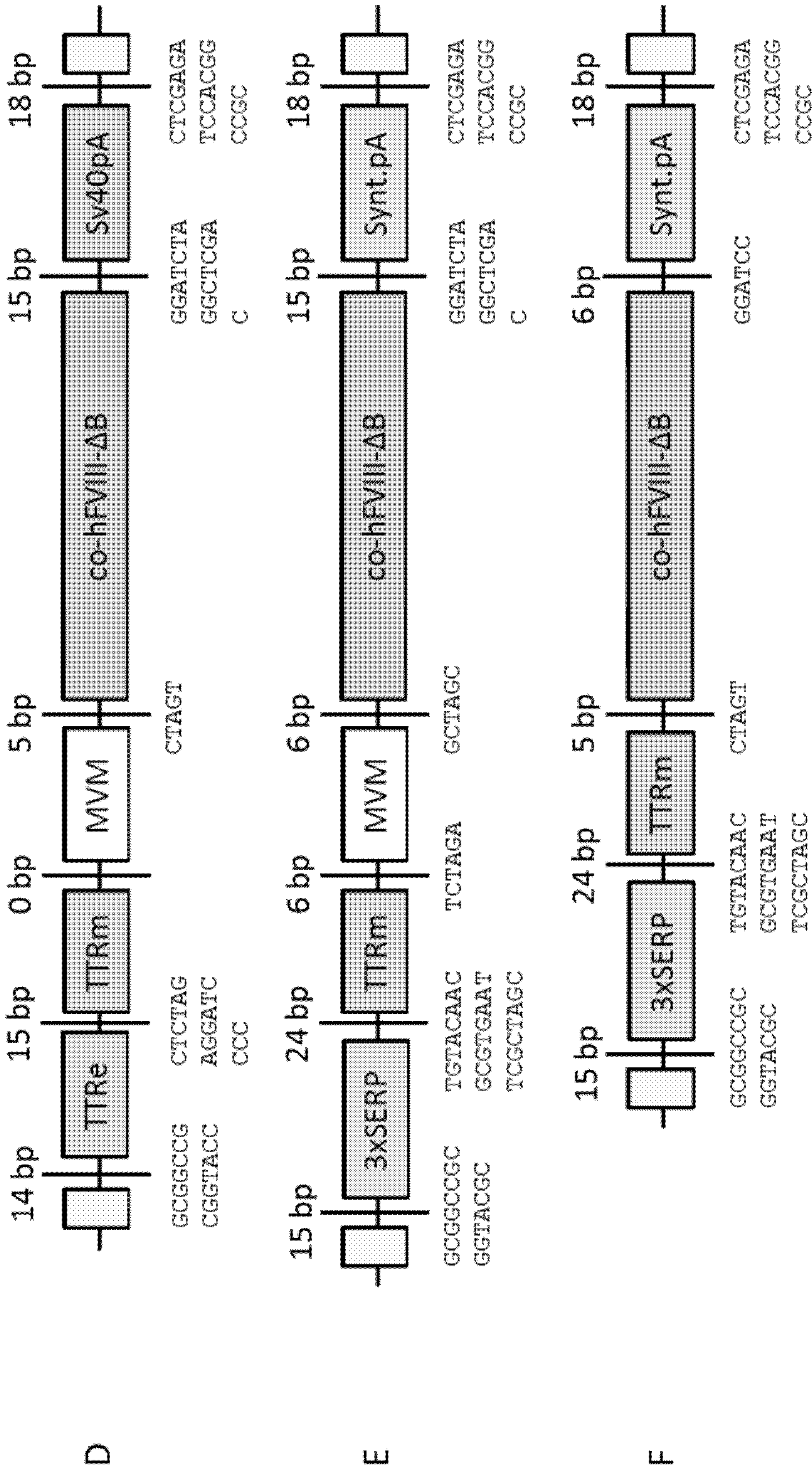


Figure 2 (continued)

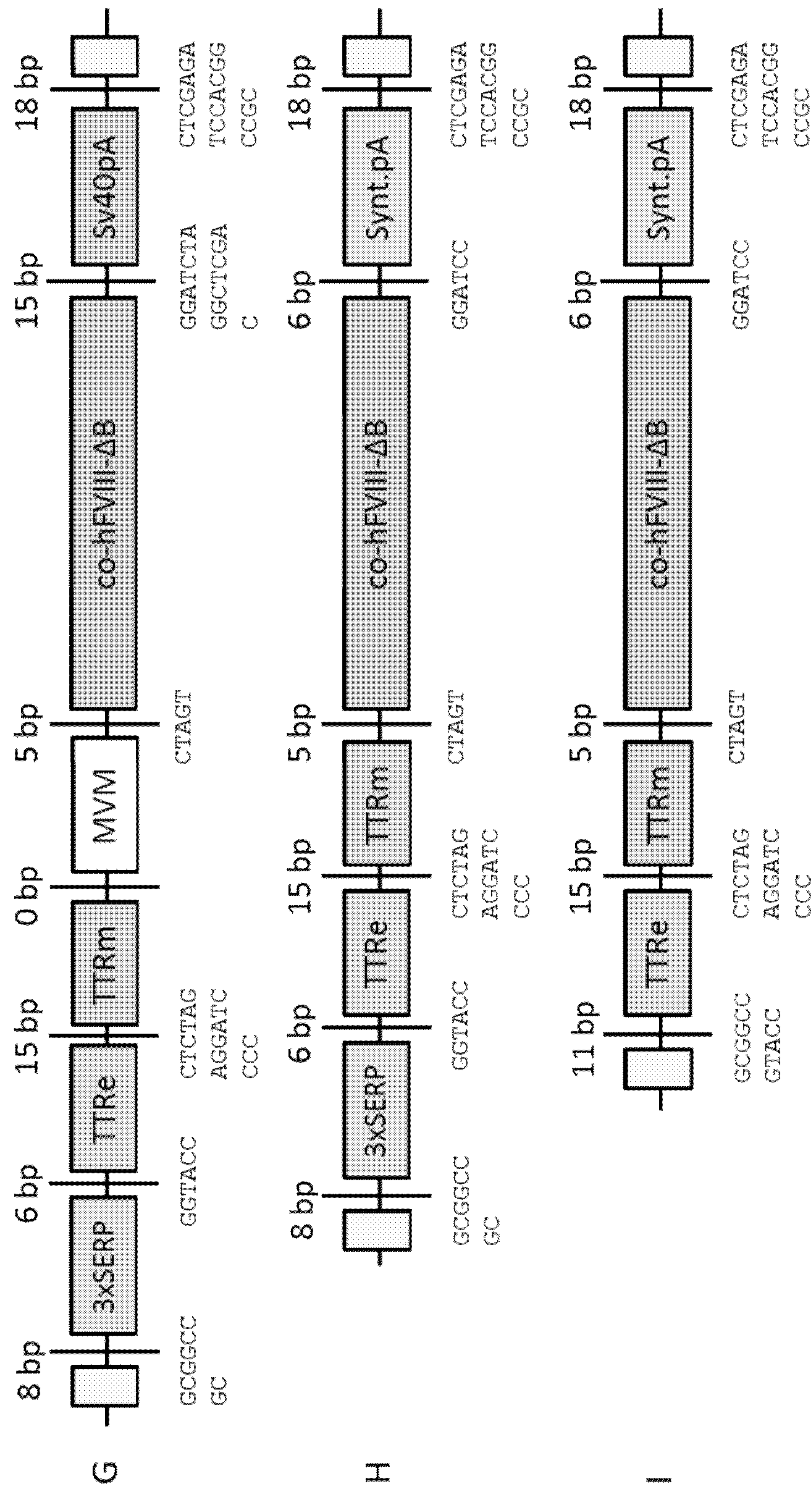


Figure 3a

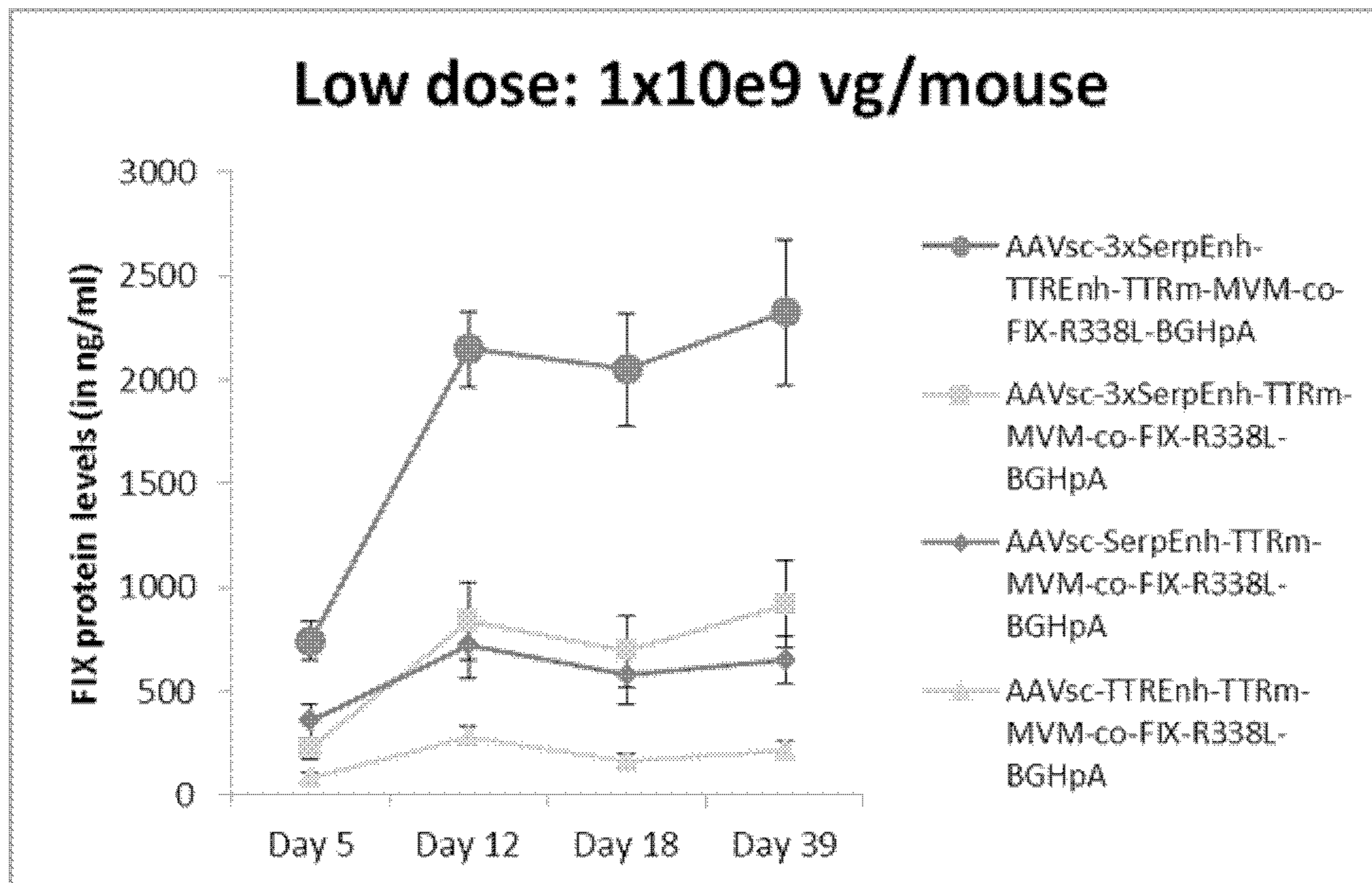


Figure 3b

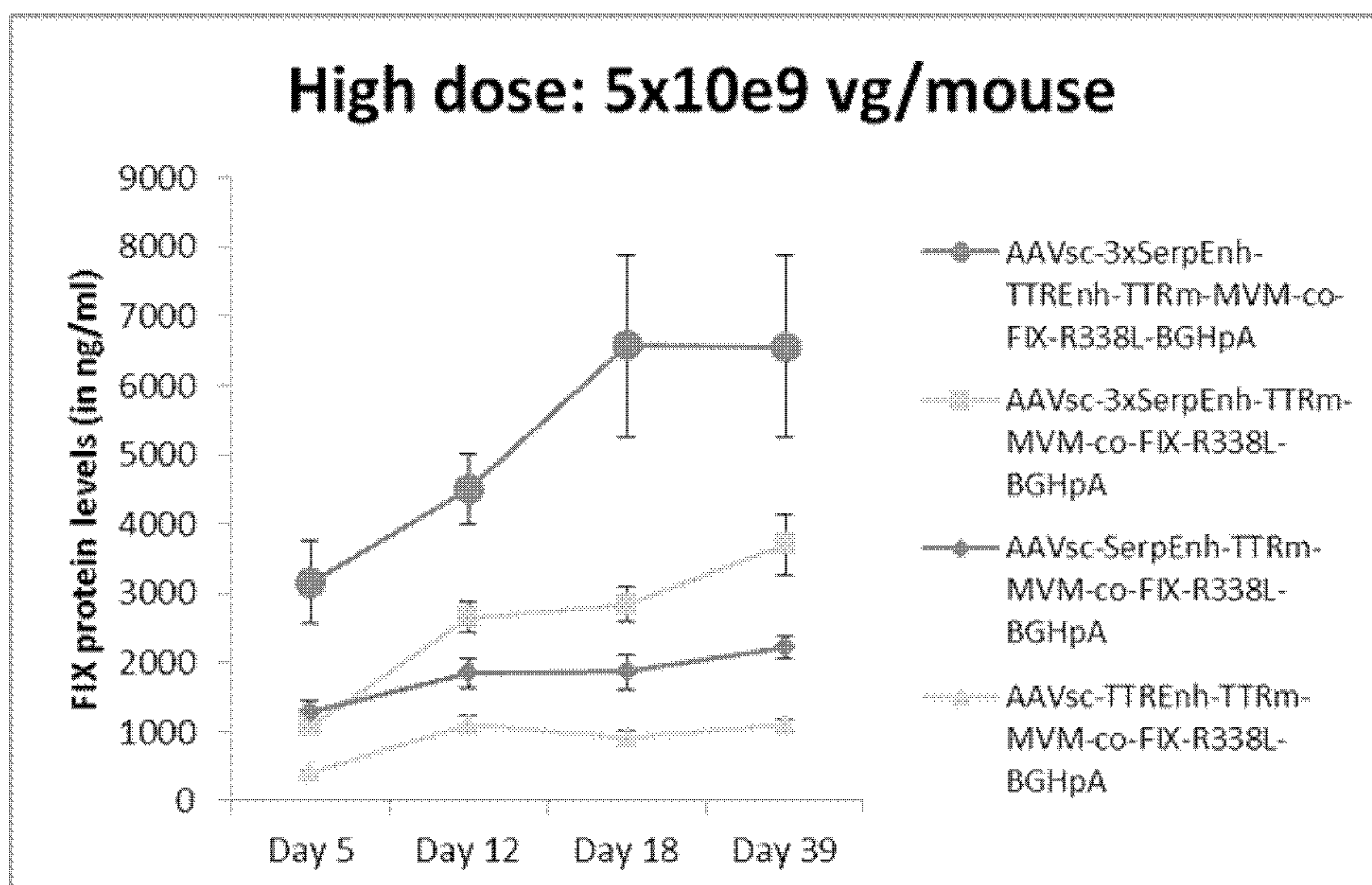


Figure 4a

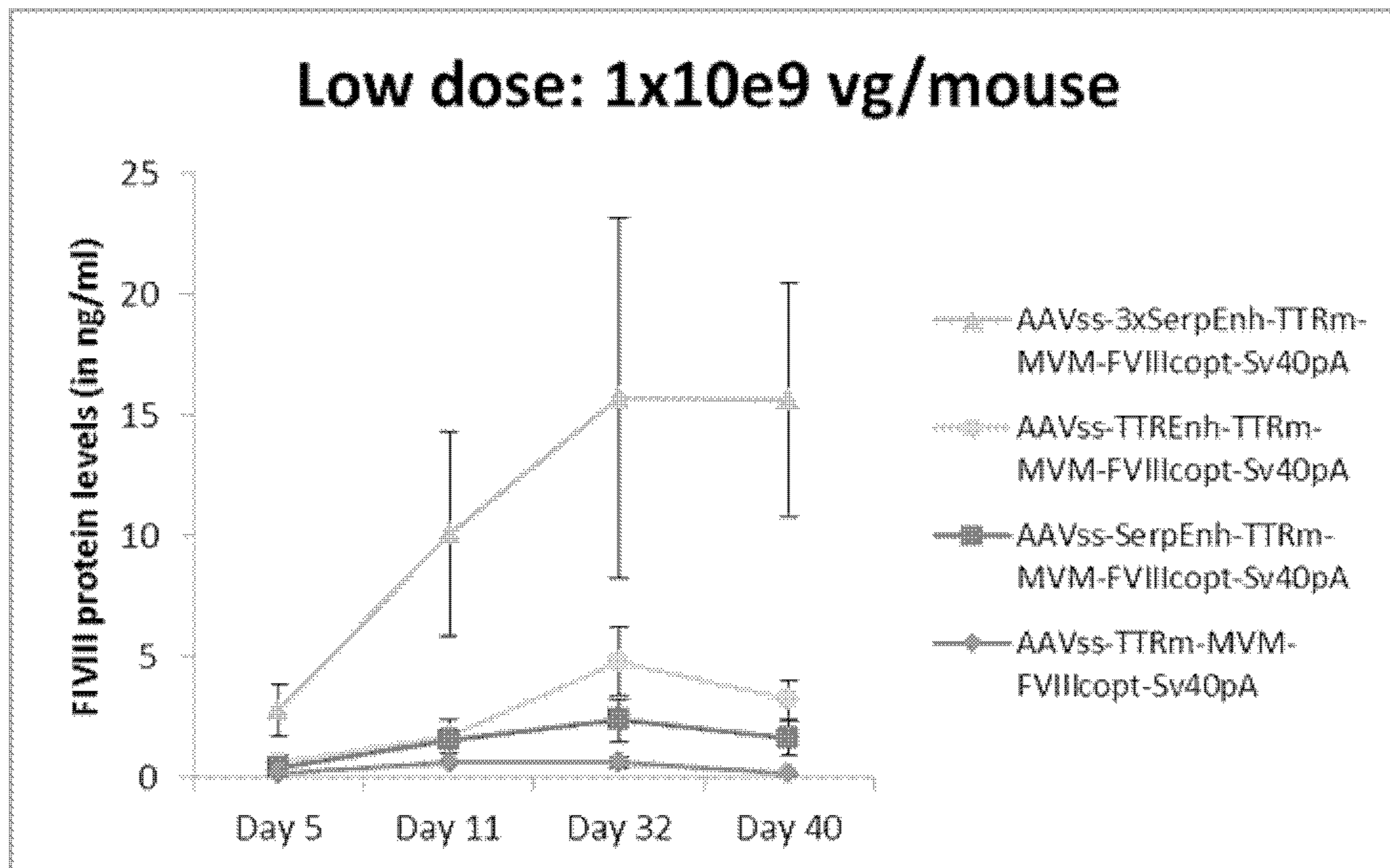


Figure 4b

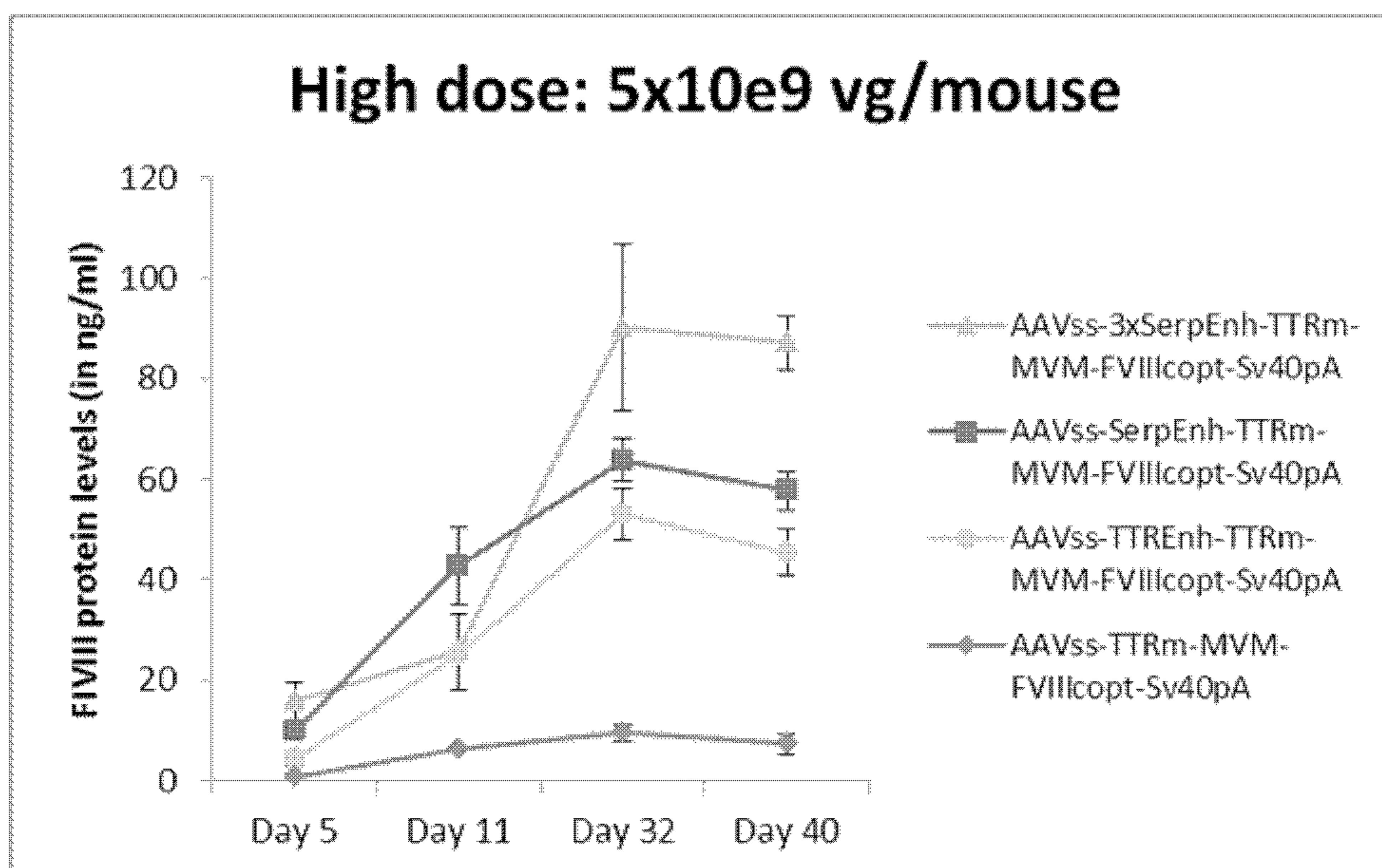


Figure 5

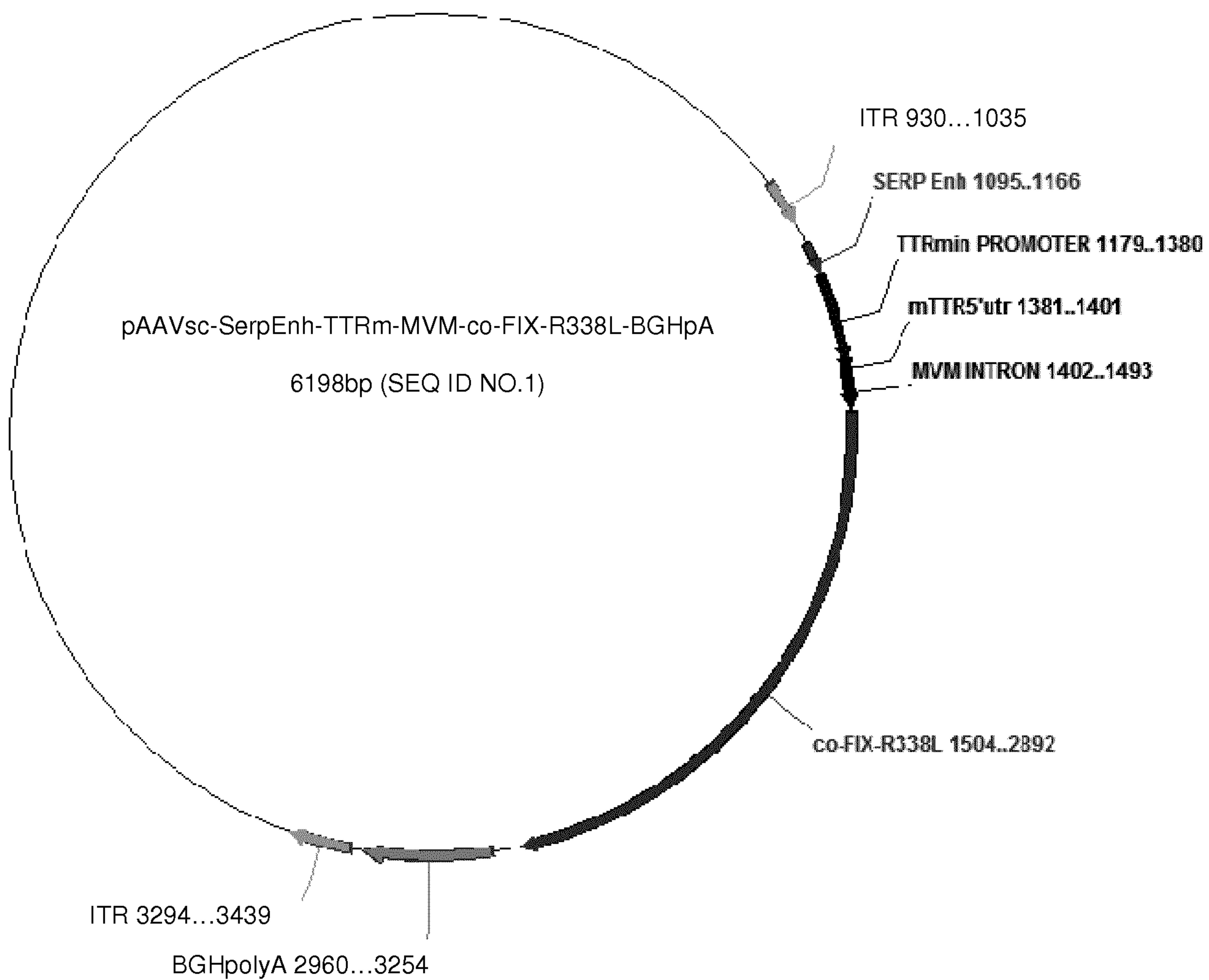


Figure 6

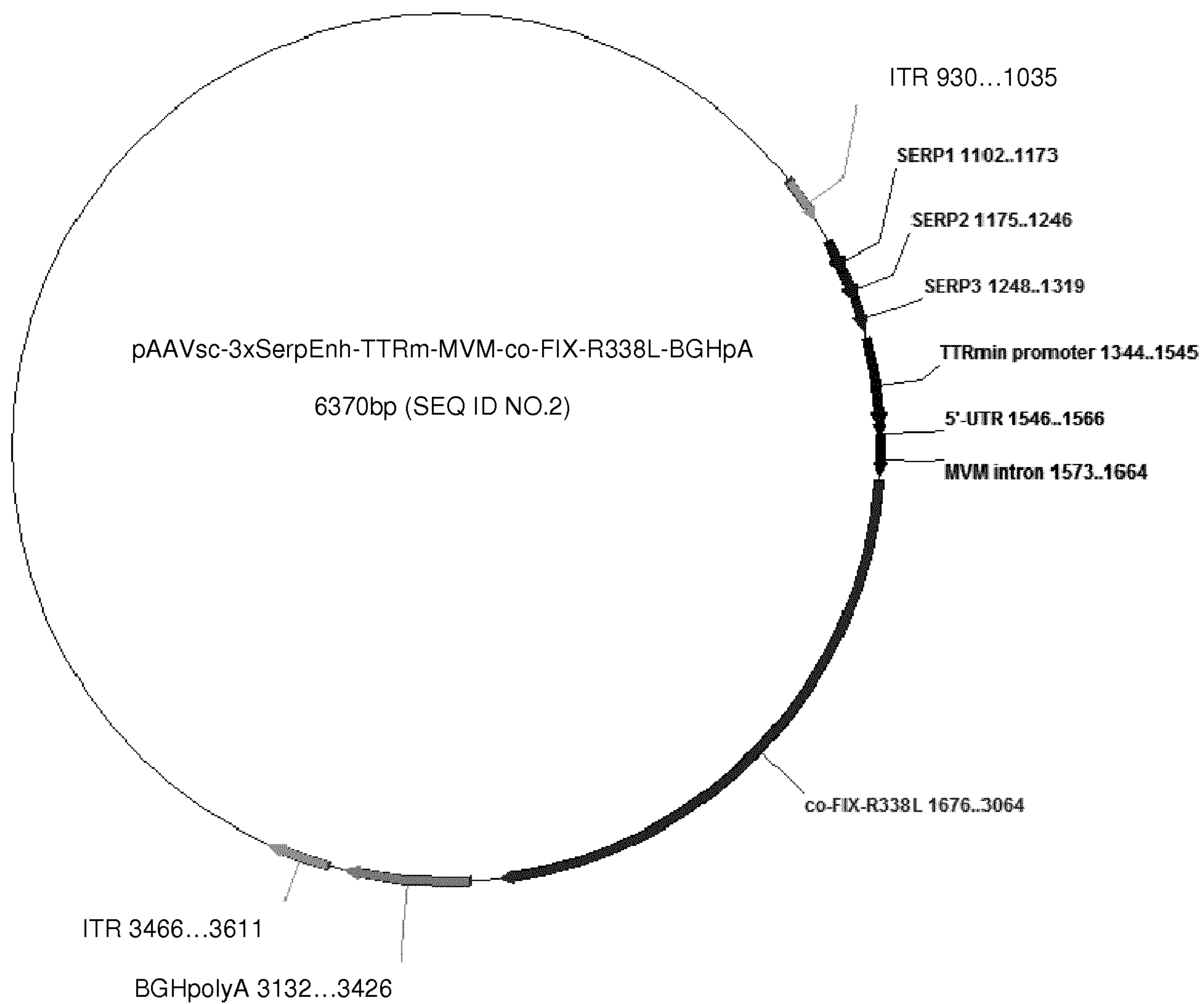


Figure 7

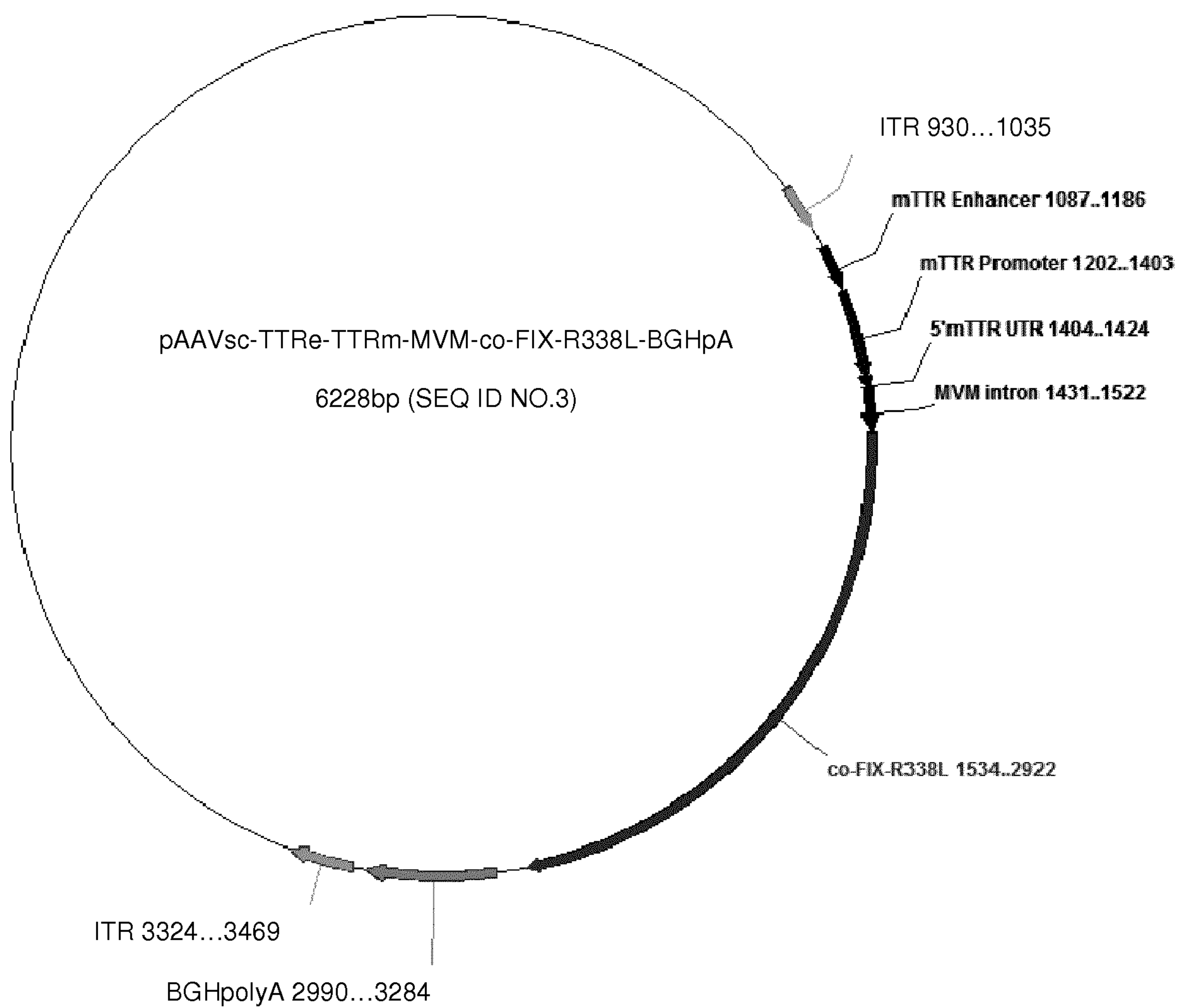


Figure 8

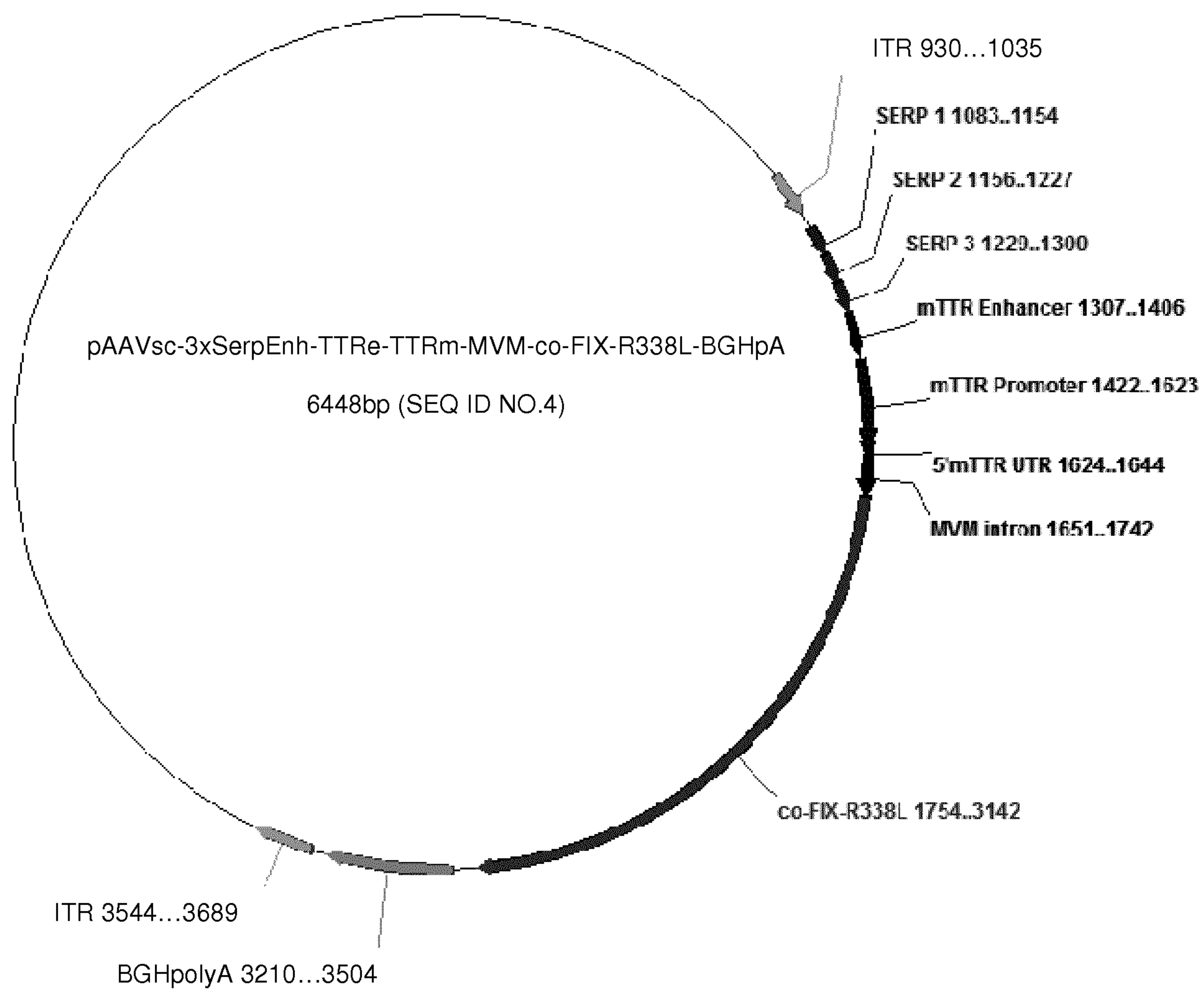


Figure 9

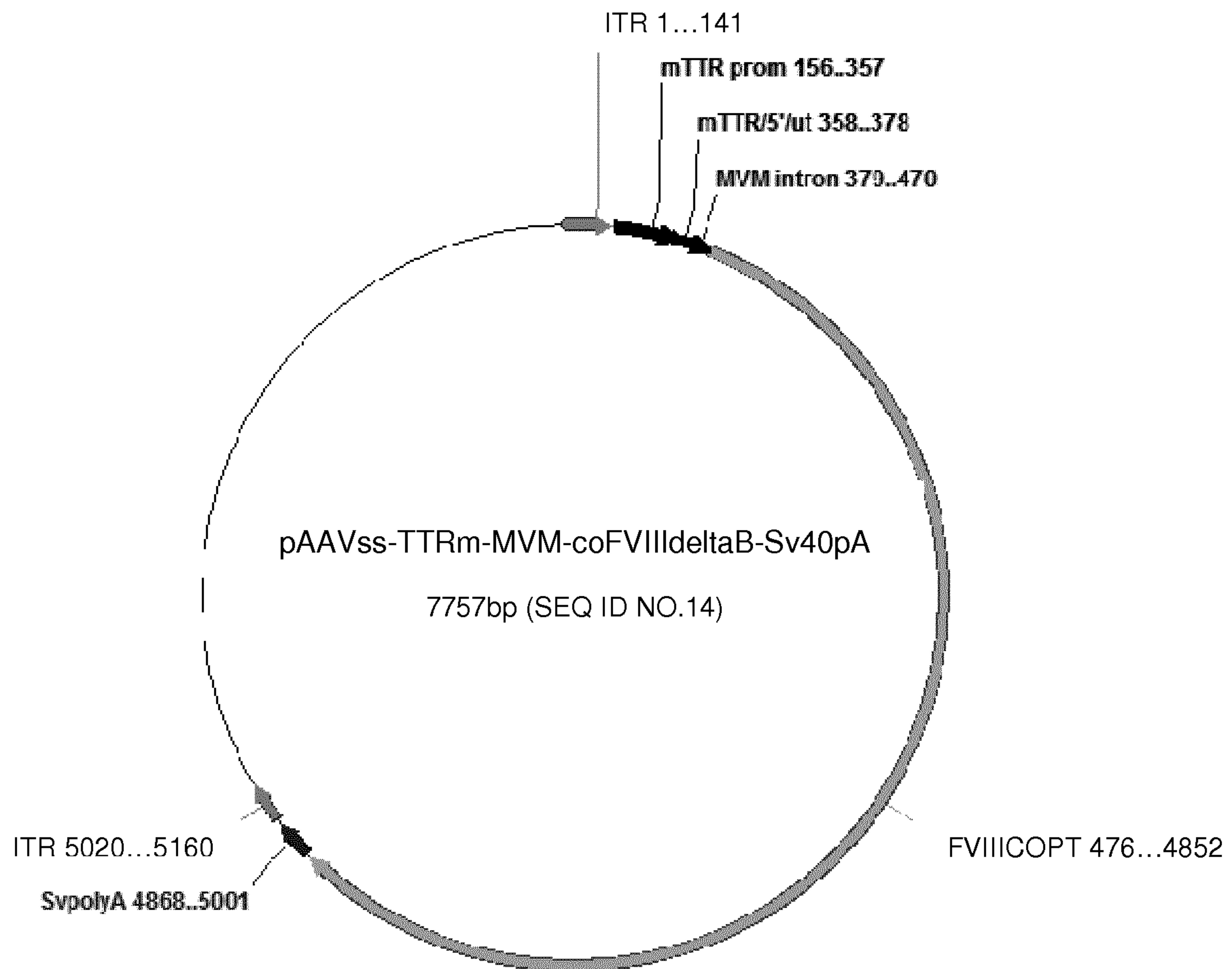


Figure 10

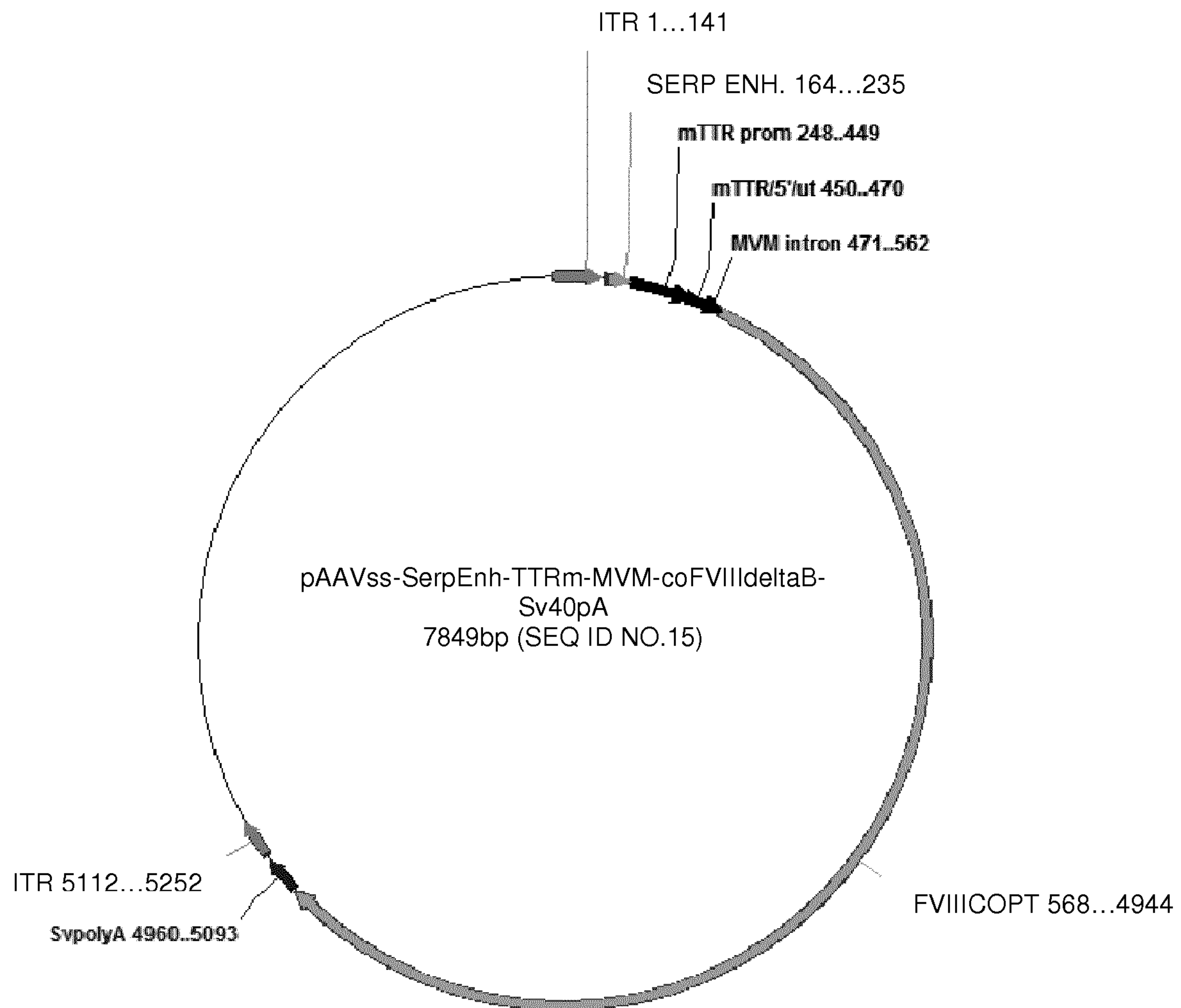


Figure 11

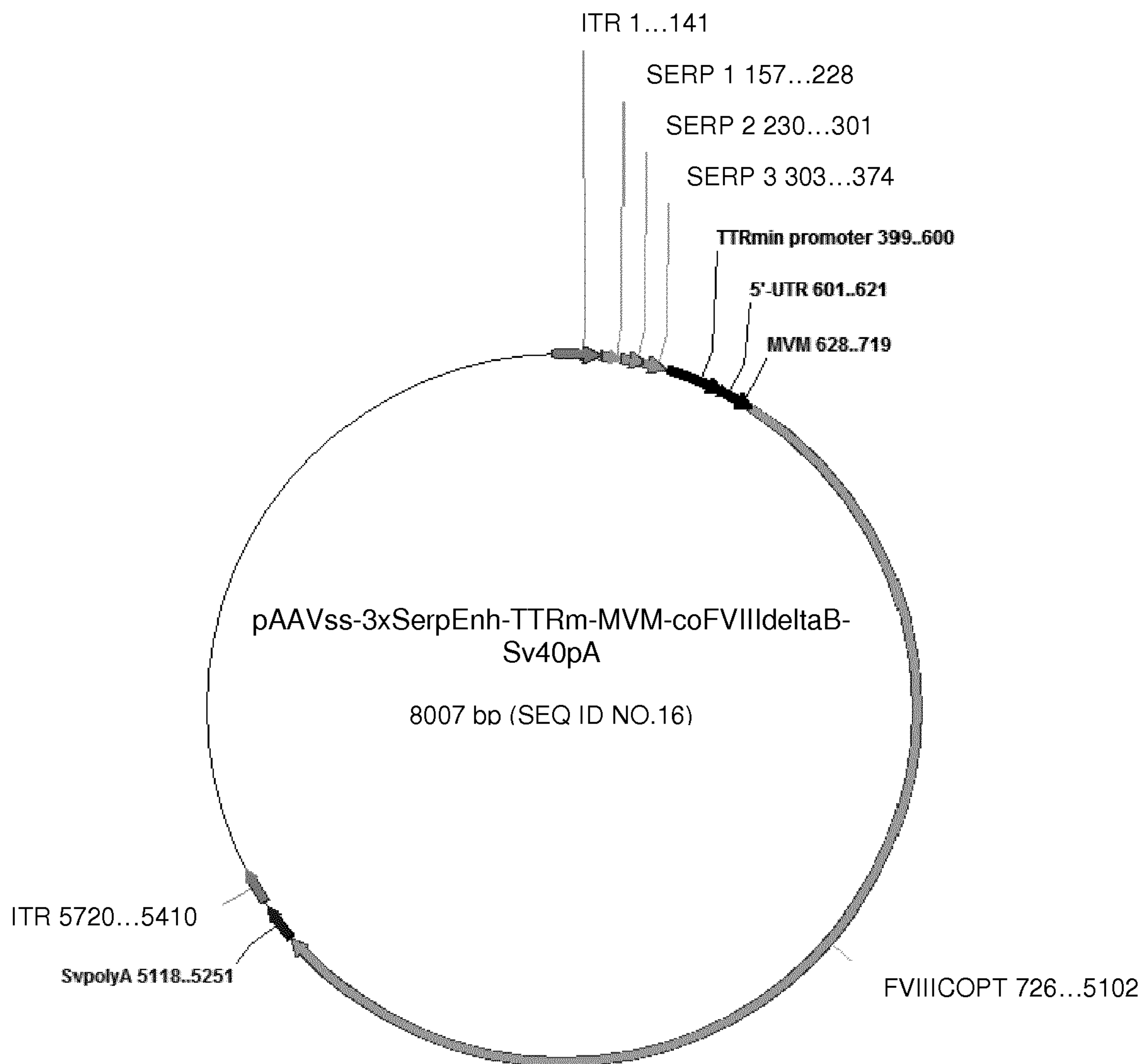


Figure 12

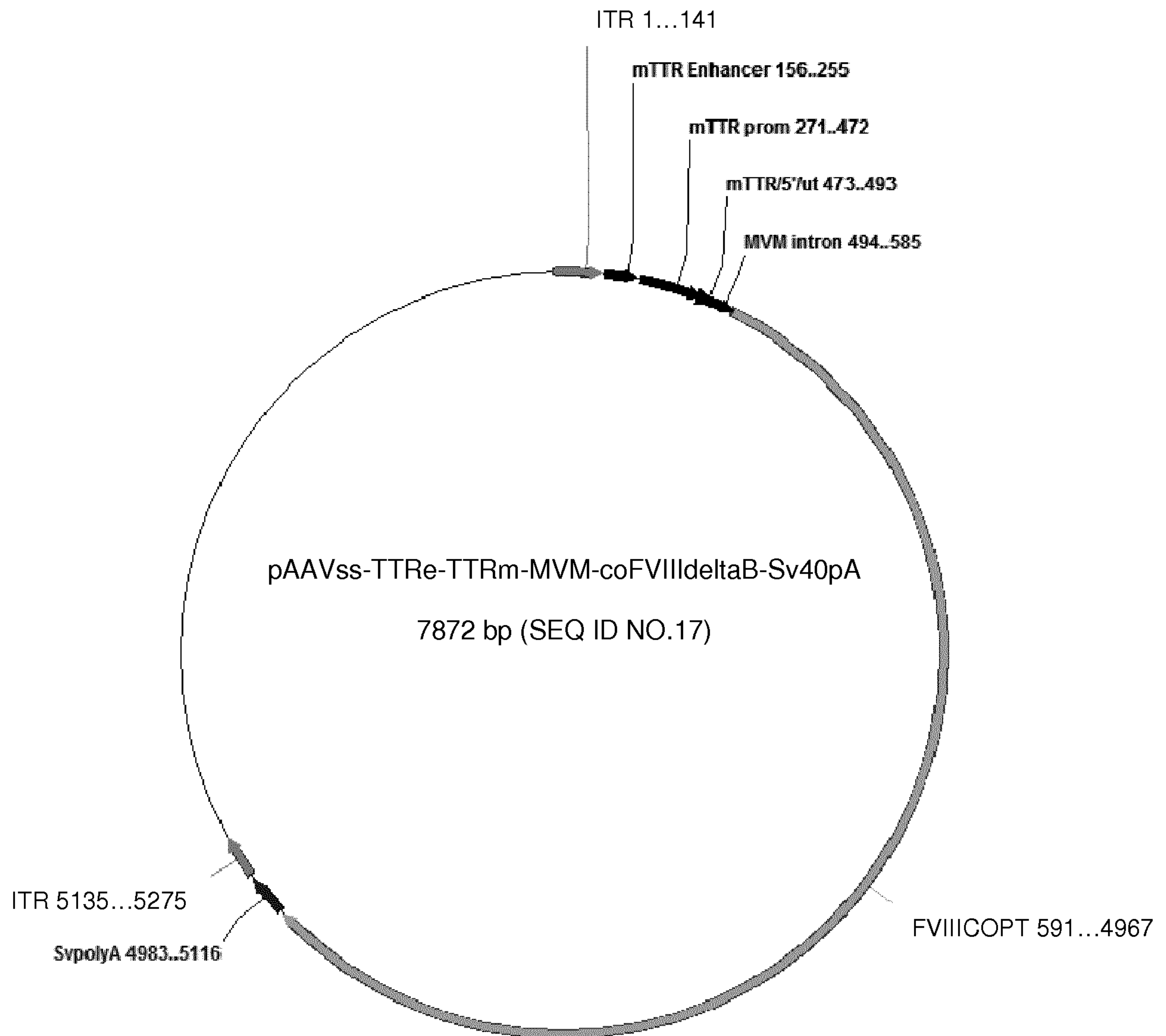


**Figure 13**

SEQ ID NO.1: pAAVsc-SerpEnh-TTRm-MVM-co-FIX-R338L-BGHpA

AGCTGGCGTAATAGCGAAGAGGCCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATG  
GCGATTCCGTTGCAATGGCTGGCGGTAATATTGTTCTGGATATTACCAGCAAGGCCGATAGTTTGAGTTCT  
TCTACTCAGGCAAGTGATGTTATTACTAATCAAAGAAGTATTGCGACAACGGTTAATTTGCGTGATGGACA  
GACTCTTTTACTCGGTGGCCTCACTGATTATAAAAACACTTCTCAGGATTCTGGCGTACCGTTCCTGTCTA  
AAATCCCTTTAATCGGCCTCCTGTTTAGCTCCCGCTCTGATTCTAACGAGGAAAGCACGTTATACGTGCTC  
GTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCG  
TGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTT  
GCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCT  
CGACCCCAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTTCGCC  
CTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAACTGGAACAACACTCAACCCTATC  
TCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAAAATGAGCTGATTTA  
ACAAAAATTTAACGCGAACTTTAACAAAAATATTAACGTTTACAATTTAAATATTTGCTTATACAATCTTCC  
TGTTTTTTGGGGCTTTTCTGATTATCAACCGGGGTACATATGATTGACATGCTAGTTTTTACGATTACCGTTC  
ATCGCCCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCG  
CCCGGCCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGAATTCACGCGTGGATCTGAATTCAATTAC  
GCGTGGTACGGCCGCGGTACCGGCGCGCCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTT  
ATCGGAGGAGCAAACAGGGGCTAAGTCCACACGCGTGGTACCGTCTGTCTGCACATTTTCGTAGAGCGAGTG  
TTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTAA  
GTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTGGAAGGAGGGGG  
TATAAAAGCCCCTTCACCAGGAGAAGCCGTCACACAGATCCACAAGCTCCTGAAGAGGTAAGGGTTTAAGG  
GATGGTTGGTTGGTGGGGTATTAATGTTTAAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTTCAGGTT  
GGCTAGCCCAACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCT  
GGGCTACCTGCTGAGCGCCGAGTGACCGTGTTTCCTGGACCACGAGAACGCCAACAAGATCCTGAACCGCC  
CCAAGCGCTACAACAGCGGCAAGCTGGAGGAGTTTCGTGCAGGGCAACCTGGAGCGCGAGTGCAATGGAGGAG  
AAGTGCAGCTTCGAGGAGGCCCGCGAGGTGTTTCGAGAACACCGAGCGCACCAACCGAGTTCTGGAAGCAGTA  
CGTGGACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCT  
ACGAGTGCTGGTGCCCCCTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAAC  
GGCCGCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCG  
CCTGGCCGAGAACCAGAAGAGCTGCGAGCCCCGCCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGA  
CCAGCAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCGAGGCCGAGACC  
ATCCTGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGC  
CAAGCCCGGCCAGTTCCCCTGGCAGGTGGTGCTGAACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCG  
TGAACGAGAAGTGATCGTGACCGCCGCCCACTGCGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGC  
GAGCACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCCACCACAA  
CTACAACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCTGGTGCTGA  
ACAGCTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGC  
TACGTGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGCGAGCGCCCTGGTGCTGCAGTACCTGCGCGTGCC  
CCTGGTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCT  
TCCACGAGGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACC  
AGCTTCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAA  
GGTGAGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGAAAGATGGATTTCCAAGGTT  
AATTCATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCCCCTGCAGATCTGAGCCGAATTCCTGCAGC  
CCGGGGGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCCTCCCCCGTGCCCTTCC  
TTGACCCTGGAAGGTGCCACTCCCCTGTCTTTTCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAG  
TAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCA  
GGCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGGGGACCGGTGGATCTC  
GATAGCAGGCATGCTGGGGAGAGATCGATCTGAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGC  
GCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCA  
GTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACCCCCCCCCCCCCCCCCCGGCGATTCTCTTGTTT  
GCTCCAGACTCTCAGGCAATGACCTGATAGCCTTTGTAGAGACCTCTCAAAAATAGCTACCCTCTCCGGCA  
TGAATTTATCAGCTAGAACGGTTGAATATCATATTGATGGTGAATTTGACTGTCTCCGGCCTTCTCACCCG

TTTGAATCTTTACCTACACATTACTCAGGCATTGCATTTTAAAATATATGAGGGTTCTAAAAATTTTTATCC  
TTGCGTTGAAATAAAGGCTTCTCCCGCAAAGTATTACAGGGTCATAATGTTTTTGGTACAACCGATTTAG  
CTTTATGCTCTGAGGCTTTATTGCTTAATTTTGCTAATTCTTTGCCTTGCCTGTATGATTTATTGGATGTT  
GGAATCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTACACCCGCATATGGTGCACCTCTC  
AGTACAATCTGCTCTGATGCCGCATAGTTATATGGTGCACCTCTCAGTACAATCTGCTCTGATGCCGCATAG  
TTAAGCCAGCCCCGACACCCGCCAACACAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGAC  
GGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGG  
TTTTACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTAAATGT  
CATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTT  
TATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTCAATAATATT  
GAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTT  
CCTGTTTTTGGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGG  
TTACATCGAACTGGATCTCAACAGCGGTAAAGATCCTTGAGAGTTTTTCGCCCCGAAGAACGTTTTTCCAATGA  
TGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGT  
CGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGG  
CATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGA  
CAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGAT  
CGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGC  
AACAACGTTGCGCAAACCTATTAAC TGCGCAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGA  
TGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAA  
TCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTAT  
CGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTG  
CCTCACTGATTAAGCATTGGTAACGTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACCTT  
CATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGA  
GTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGC  
GCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTGTTGCCGGATCAAGAGCTA  
CCAACCTCTTTTTCCGAAGGTAAC TGCTTCAGCAGAGCGCAGATACCAAATACTGTCCCTTCTAGTGTAGCC  
GTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAG  
TGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCG  
CAGCGGTGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGAGCGAACGACCTACACCGAACTGAG  
ATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAA  
GCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCT  
GTCGGGTTTTCGCCACCTCTGACTTGAGCGTCGATTTTTTGATGCTCGTCAGGGGGGCGGAGCCTATGGAA  
AAACGCCAGCAACGCGGCCTTTTTACGGTTCTTGCCCTTTTGCTGGCCTTTTGCTCACATGTTCTTTCCTG  
CGTTATCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGA  
ACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGC  
GCGTTGGCCGATTCATTAATG

SEQ ID NO.2: pAAVsc-3xSerpEnh-TTRm-MVM-co-FIX-R338L-BGHPA

AGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATG  
GCGATTCCGTTGCAATGGCTGGCGGTAATATTGTTCTGGATATTACCAGCAAGGCCGATAGTTTGAGTTCT  
TCTACTCAGGCAAGTGATGTTATTACTAATCAAAGAAGTATTGCGACAACGGTTAATTTGCGTGATGGACA  
GACTCTTTTACTCGGTGGCCTCACTGATTATAAAAACACTTCTCAGGATTCTGGCGTACCGTTTCTGTCTA  
AAATCCCTTTAATCGGCCTCCTGTTTTAGCTCCCGCTCTGATTCTAACGAGGAAAGCACGTTATACGTGCTC  
GTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCG  
TGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCGCTTCTTCCCTTCCCTTCTCGCCACGTTT  
GCCGGCTTTCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCT  
CGACCCCAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTTCGCC  
CTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATC  
TCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAAAATGAGCTGATTTA  
ACAAAAATTTAACGCGAACTTTAACAAAAATATTAACGTTTACAATTTAAATATTTGCTTATACAATCTTCC  
TGTTTTTGGGGCTTTTCTGATTATCAACCGGGGTACATATGATTGACATGCTAGTTTTACGATTACCGTTC  
ATCGCCCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTGC  
CCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGAATTCACGCGTGGATCTGAATTCAATTAC

GCGTGGTACGGCCGCGGTACCGGCGCGCCCGTACGCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCAC  
CCCAGTTATCGGAGGAGCAAACAGGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTC  
ACCCCAGTTATCGGAGGAGCAAACAGGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGG  
TCACCCCAGTTATCGGAGGAGCAAACAGGGGGCTAAGTCCACTGTACAACGCGTGAATTCGCTAGCGTCTGT  
CTGCACATTTTCGTAGAGCGAGTGTTCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTA  
CTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAG  
CAGCCTGGGTTGGAAGGAGGGGGGTATAAAAGCCCCCTTCACCAGGAGAAGCCGTCACACAGATCCACAAGCT  
CCTGTCTAGAAAGAGGTAAGGGTTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGC  
ACCTGCCTGAAATCACTTTTTTTTCAGGTTGGGCTAGCCCACCATGCAGCGCGTGAACATGATCATGGCCGA  
GAGCCCCGGCCTGATCACCATCTGCCTGCTGGGCTACCTGCTGAGCGCCGAGTGCACCGTGTTCCTGGACC  
ACGAGAACGCCAACAAGATCCTGAACCGCCCCAAGCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAG  
GGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGTGCAGCTTCGAGGAGGGCCCGCGAGGTGTTTCGAGAACAC  
CGAGCGCACCCACCGAGTTCTGGAAGCAGTACGTGGACGGCGACCAGTGCAGAGAGCAACCCCTGCCTGAACG  
GCGGCAGCTGCAAGGACGACATCAACAGCTACGAGTGTGGTGCCCCCTTCGGCTTCGAGGGCAAGAACTGC  
GAGCTGGACGTGACCTGCAACATCAAGAACGGCCGCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAA  
GGTGGTGTGCAGCTGCACCGAGGGGCTACCGCCTGGCCGAGAACCAGAAGAGCTGCGAGCCCCGCCGTGCCCT  
TCCCCGTGCGGCCGCGTGAGCGTGAGCCAGACCAGCAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTG  
GACTACGTGAACAGCACCCGAGGCCGAGACCATCCTGGACAACATCACCAGAGCACCCAGAGCTTCAACGA  
CTTCACCCGCGTGTTGGTGGGCGGCGAGGACGCCAAGCCCCGGCCAGTTCCCCTGGCAGGTGGTGTGCTGAACGGCA  
AGGTGGACGCCCTTCTGCGGCGGCAGCATCGTGAACGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGGAG  
ACCGGCGTGAAAGATCACCGTGGTGGCCGGCGAGCACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCG  
CAACGTGATCCGCATCATCCCCACCACAACACTACAACGCCGCCATCAACAAGTACAACCACGACATCGCCC  
TGCTGGAGCTGGACGAGCCCCCTGGTGCTGAACAGCTACGTGACCCCCATCTGCATCGCCGACAAGGAGTAC  
ACCAACATCTTCCTGAAGTTCGGCAGCGGCTACGTGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGCGAG  
CGCCCTGGTGTGCTGCAGTACCTGCGCGTGCCCTGGTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCA  
CCATCTACAACAACATGTTCTGCGCCGGCTTCCACGAGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGC  
GGCCCCCACGTGACCGAGGTGGAGGGCACCAGCTTCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGC GC  
CATGAAGGGCAAGTACGGCATCTACACCAAGGTGAGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGC  
TGACCTAATGAAAGATGGATTTCCAAGGTTAATTCATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCC  
CCCTGCAGATCTGAGCCGAATTCCTGCAGCCCCGGGGGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCA  
TCTGTTGTTTGCCCCCTCCCCCGTGCCCTTCCTTGACCCCTGGAAGGTGCCACTCCCCTGTCCCTTTCCTAATA  
AAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACA  
GCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCG  
GAAAGAACCAGCTGGGGACCGGTGGATCTCGATAGCAGGCATGCTGGGGAGAGATCGATCTGAGGAACCCC  
TAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCCGGG  
CGTCGGGCGACCTTTGGTGCGCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACCCCCC  
CCCCCCCCCCCCCGGCGATTCTCTTGTTTGCTCCAGACTCTCAGGCAATGACCTGATAGCCTTTGTAGAG  
ACCTCTCAAAAATAGCTACCCCTCTCCGGCATGAATTTATCAGCTAGAACGGTTGAATATCATATTGATGGT  
GATTTGACTGTCTCCGGCCTTTCTCACCCGTTTGAATCTTTACCTACACATTACTCAGGCATTGCATTTAA  
AATATATGAGGGTTCTAAAAATTTTTATCCTTGCGTTGAAATAAAGGCTTCTCCCGCAAAGTATTACAGG  
GTCATAATGTTTTTGGTACAACCGATTTAGCTTTATGCTCTGAGGCTTTATTGCTTAATTTTGCTAATTCT  
TTGCCTTGCTGTATGATTTATTGGATGTTGGAATCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGC  
GGTATTTACACCGCATATGGTGCACCTCTCAGTACAATCTGCTCTGATGCCGCATAGTTATATGGTGCACCT  
CTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACAGCCAGCCCCGAC  
ACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTG  
ACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTACCGTTCATCACCAGAACGCGCGAGACGAAAGGGCCT  
CGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTC  
GGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGA  
CAATAACCCCTGATAAATGCTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCC  
CTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAGA  
TGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGA  
GTTTTCGCCCCGAAGAACGTTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCC  
CGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTC  
ACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGA  
GTGATAAACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCCTTTTTTGCAC

AACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGA  
GCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACCTATTAAGTGGCGAACTACTTACTC  
TAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCC  
CTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGC  
ACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATG  
AACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAAGTGTGACACCAAGTTTAC  
TCATATATACTTTAGATTGATTTAAACTTCATTTTTTAATTTAAAGGATCTAGGTGAAGATCCTTTTTGA  
TAATCTCATGACCAAAATCCCTTAACGTGAGTTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCA  
AAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCA  
GCGGTGGTTTGTGTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAAGTGGCTTCAGCAGAGCGCA  
GATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTA  
CATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTG  
GACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAG  
CTTGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCG  
AAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCA  
GGGGGAAACGCCTGGTATCTTTATAGTCCTGTGCGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTG  
ATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTT  
GCTGGCCTTTTGCTCACATGTTCTTTCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTT  
GAGTGAGCTGATACCGCTCGCCGAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAGA  
GCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCAATTAATG

SEQ ID NO.3: pAAVsc-TTRe-TTRm-MVM-co-FIX-R338L-BGHPA

AGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATG  
GCGATTCCGTTGCAATGGCTGGCGGTAATATTGTTCTGGATATTACCAGCAAGGCCGATAGTTTGAGTTCT  
TCTACTCAGGCAAGTGATGTTATTACTAATCAAAGAAGTATTGCGACAACGGTTAATTTGCGTGATGGACA  
GACTCTTTTTACTCGGTGGCCTCACTGATTATAAAAACACTTCTCAGGATTCTGGCGTACCGTTTCTGTCTA  
AAATCCCTTTAATCGGCCTCCTGTTTAGCTCCCGCTCTGATTCTAACGAGGAAAGCACGTTATACGTGCTC  
GTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCG  
TGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTGCTTTCTTCCCTTCCCTTCTCGCCACGTTT  
GCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCT  
CGACCCCAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCC  
CTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATC  
TCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTGCGCCTATTGGTTAAAAAATGAGCTGATTTA  
ACAAAAATTTAACGCGAACTTTAACAAAAATATTAACGTTTACAATTTAAATATTTGCTTATACAATCTTCC  
TGTTTTTGGGGCTTTTCTGATTATCAACCGGGGTACATATGATTGACATGCTAGTTTTACGATTACCGTTT  
ATCGCCCTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCG  
CCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGAATTCACGCGTGGATCTGAATTCAATTCAC  
GCGTGGTACGGCCGCGGTACCCACTGGGAGGATGTTGAGTAAGATGGAAACTACTGATGACCCTTGACAG  
GACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAGCTCTAGAGGATCCCCGTCTGT  
CTGCACATTTCTGATAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTA  
CTTATTCTCCTTTTGTTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAG  
CAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCCTTACCAGGAGAAGCCGTCACACAGATCCACAAGCT  
CCTGGCTAGAAAGAGGTAAGGGTTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGC  
ACCTGCCTGAAATCACTTTTTTTTTCAGGTTGGGCTAGCCACCATGCAGCGCGTGAACATGATCATGGCCGA  
GAGCCCCGGCCTGATCACCATCTGCCTGCTGGGCTACCTGCTGAGCGCCGAGTGCACCGTGTTTCTGGACC  
ACGAGAACGCCAACAAGATCCTGAACCGCCCCAAGCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAG  
GGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGTGCAGCTTCGAGGAGGCCCGCGAGGTGTTTCGAGAACAC  
CGAGCGCACCAACCGAGTTCTGGAAGCAGTACGTGGACGGCGACCAGTGCAGAGCAACCCCTGCCTGAACG  
GCGGCAGCTGCAAGGACGACATCAACAGCTACGAGTGCTGGTGCCCTTCGGCTTCGAGGGCAAGAACTGC  
GAGCTGGACGTGACCTGCAACATCAAGAACGGCCGCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAA  
GGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTGGCCGAGAACCAGAAGAGCTGCGAGCCCGCCGTGCCCT  
TCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAGCAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTG  
GACTACGTGAACAGCACCGAGGCCGAGACCATCCTGGACAACATACCCAGAGCACCCAGAGCTTCAACGA  
CTTACCCCGCGTGGTGGGCGGCGAGGACGCCAAGCCCGGCCAGTTCCTTGGCAGGTGGTGCTGAACGGCA

AGGTGGACGCCTTCTGCGGGCGGCAGCATCGTGAACGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGGAG  
ACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGCACAAACATCGAGGAGACCGAGCACACCGAGCAGAAGCG  
CAACGTGATCCGCATCATCCCCACCACAACACTACAACGCCGCCATCAACAAGTACAACCACGACATCGCCC  
TGCTGGAGCTGGACGAGCCCCCTGGTGCTGAACAGCTACGTGACCCCCATCTGCATCGCCGACAAGGAGTAC  
ACCAACATCTTCCTGAAGTTCGGCAGCGGCTACGTGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGCAG  
CGCCCTGGTGCTGCAGTACCTGCGCGTGCCCTGGTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCA  
CCATCTACAACAACATGTTCTGCGCCGGCTTCCACGAGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGC  
GGCCCCCACGTGACCGAGGTGGAGGGCACCAGCTTCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGC  
CATGAAGGGCAAGTACGGCATCTACACCAAGGTGAGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGC  
TGACCTAATGAAAGATGGATTTCOAAGGTTAATTCATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCC  
CCCTGCAGATCTGAGCCGAATTCCTGCAGCCCCGGGGGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCA  
TCTGTTGTTTGCCCCCTCCCCCGTGCCCTTCCTTGACCCTGGAAGGTGCCACTCCCCTGTCTTTCCTAATA  
AAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTTCTGGGGGGTGGGGTGGGGCAGGACA  
GCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCG  
GAAAGAACCAGCTGGGGACCGGTGGATCTCGATAGCAGGCATGCTGGGGAGAGATCGATCTGAGGAACCCC  
TAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGG  
CGTCGGGCGACCTTTGGTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACCCCCC  
CCCCCCCCCCCCCGGCGATTCTCTTGTGTTTGCTCCAGACTCTCAGGCAATGACCTGATAGCCTTTGTAGAG  
ACCTCTCAAAAATAGCTACCCCTCTCCGGCATGAATTTATCAGCTAGAACGGTTGAATATCATATTGATGGT  
GATTTGACTGTCTCCGGCCTTTCTCACCCGTTTGAATCTTTACCTACACATTACTCAGGCATTGCATTTAA  
AATATATGAGGGTTCTAAAAATTTTATCCTTGCGTTGAAATAAAGGCTTCTCCCGCAAAGTATTACAGG  
GTCATAATGTTTTTGGTACAACCGATTTAGCTTTATGCTCTGAGGCTTTATTGCTTAATTTTGCTAATTCT  
TTGCCTTGCTGTATGATTTATTGGATGTTGGAATCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGC  
GGTATTTACACCCGCATATGGTGCACCTCTCAGTACAATCTGCTCTGATGCCGCATAGTTATATGGTGCAC  
CTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACAGCCAGCCCCGAC  
ACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTG  
ACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTACCGTTCATCACCGAAACGCGCGAGACGAAAGGGCCT  
CGTGATACGCCTATTTTTATAGGTAAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTC  
GGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGA  
CAATAACCCCTGATAAATGCTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTGCGC  
CTTATTCCCTTTTTTGCGGCATTTTGCCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAGA  
TGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGA  
GTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCC  
CGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTC  
ACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGA  
GTGATAAACAACCTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCCTTTTTTGCAC  
AACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGA  
GCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACCTATTAACCTGGCGAACTACTTACTC  
TAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCC  
CTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTTGCAGC  
ACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATG  
AACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACCTGTCAGACCAAGTTTAC  
TCATATATACTTTAGATTGATTTAAAACTTCATTTTTTAATTTAAAGGATCTAGGTGAAGATCCTTTTTGA  
TAATCTCATGACCAAAAATCCCTTAACGTGAGTTTTCTGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCA  
AAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCA  
GCGGTGGTTTGTGTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACCTGGCTTCAGCAGAGCGCA  
GATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTA  
CATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTG  
GACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTGCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAG  
CTTGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCG  
AAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCA  
GGGGGAAACGCCTGGTATCTTTATAGTCCTGTGCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTG  
ATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTT  
GCTGGCCTTTTGCTCACATGTTCTTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTT

GAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAGA  
GCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTTCATTAATG

SEQ ID NO.4: pAAVsc-3xSerpEnh-TTRe-TTRm-MVM-co-FIX-R338L-BGHPA

AGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATG  
GCGATTCCGTTGCAATGGCTGGCGGTAATATTGTTCTGGATATTACCAGCAAGGCCGATAGTTTGAGTTCT  
TCTACTCAGGCAAGTGATGTTATTACTAATCAAAGAAGTATTGCGACAACGGTTAATTTGCGTGATGGACA  
GACTCTTTTACTCGGTGGCCTCACTGATTATAAAAACACTTCTCAGGATTCTGGCGTACCGTTTCTGTCTA  
AAATCCCTTTAATCGGCCTCCTGTTTAGCTCCCGCTCTGATTCTAACGAGGAAAGCACGTTATACGTGCTC  
GTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCG  
TGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCGCTTTCTTCCCTTCCCTTCTCGCCACGTTT  
GCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCT  
CGACCCCAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCC  
CTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATC  
TCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAAAATGAGCTGATTTA  
ACAAAAATTTAACGCGAACTTTAACAAAAATATTAACGTTTACAATTTAAATATTTGCTTATACAATCTTCC  
TGTTTTTTGGGGCTTTTCTGATTATCAACCGGGGTACATATGATTGACATGCTAGTTTTTACGATTACCGTTC  
ATCGCCCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTGC  
CCCGGCCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGAATTCACGCGTGGATCTGAATTCATTCAC  
GCGTGGTACGGCCGCGGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTTATCGGAGGAGCA  
AACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTTATCGGAGGAG  
CAAACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTTATCGGAGG  
AGCAAACAGGGGCTAAGTCCACGGTACCCACTGGGAGGATGTTGAGTAAGATGGAAAACTACTGATGACCC  
TTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAGCTCTAGAGGATCCC  
CGTCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTG  
TAGGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAG  
GGATCAGCAGCCTGGGTGGAAGGAGGGGGTATAAAAGCCCCCTTACCAGGAGAAGCCGTCACACAGATCC  
ACAAGCTCCTGGCTAGAAAGAGGTAAGGGTTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTAC  
CTGGAGCACCTGCCTGAAATCACTTTTTTTTCAGGTTGGGCTAGCCCACCATGCAGCGCGTGAACATGATCA  
TGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGCTACCTGCTGAGCGCCGAGTGACCGTGTTT  
CTGGACCACGAGAACGCCAACAAGATCCTGAACCGCCCCAAGCGCTACAACAGCGGCAAGCTGGAGGAGTT  
CGTGCAGGGCAACCTGGAGCGCGAGTGATGGAGGAGAAGTGACGTTTCGAGGAGGCCCGCGAGGTGTTTCG  
AGAACACCGAGCGCACCAACCGAGTTCTGGAAGCAGTACGTGGACGGCGACCAGTGCGAGAGCAACCCCTGC  
CTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGAGTGCTGGTGCCCCCTTCGGCTTCGAGGGCAA  
GAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCCGCTGCGAGCAGTTCTGCAAGAACAGCGCCG  
ACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTGGCCGAGAACCAGAAGAGCTGCGAGCCCGCC  
GTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAGCAAGCTGACCCGCGCCGAGGCCGTGTTCCC  
CGACGTGGACTACGTGAACAGCACCGAGGCCGAGACCATCCTGGACAACATCACCCAGAGCACCCAGAGCT  
TCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGCCAAGCCCGGCCAGTTCCCCTGGCAGGTGGTGCTG  
AACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAACGAGAAGTGATCGTGACCGCCGCCCACTG  
CGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGCACAACATCGAGGAGACCGAGCACACCGAGC  
AGAAGCGCAACGTGATCCGCATCATCCCCACCACAACACTACAACGCCGCCATCAACAAGTACAACCACGAC  
ATCGCCCTGCTGGAGCTGGACGAGCCCCCTGGTGCTGAACAGCTACGTGACCCCCATCTGCATCGCCGACAA  
GGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACGTGAGCGGCTGGGGCCGCGTGTTCCACAAGG  
GCCGAGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCCCTGGTGGACCGCGCCACCTGCCTGCTGAGCACC  
AAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCACGAGGGCGGCCGCGACAGCTGCCAGGGCGA  
CAGCGGCGGCCCCACGTGACCGAGGTGGAGGGCACCAAGCTTCTGACCGGCATCATCAGCTGGGGCGAGG  
AGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTGAGCCGCTACGTGAACTGGATCAAGGAGAAG  
ACCAAGCTGACCTAATGAAAGATGGATTTCCAAGGTTAATTCATTGGAATTGAAAATTAACAGCCCCCCCC  
CCCCCCCCCTGCAGATCTGAGCCGAATTCCTGCAGCCCGGGGGATCAGCCTCGACTGTGCCTTCTAGTTG  
CCAGCCATCTGTTGTTTGCCCCCTCCCCCGTGCCCTTCCTTGACCCTGGAAGGTGCCACTCCCCTGTCTTT  
CCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCTATTCTATTTCTGGGGGGTGGGGTGGGG  
CAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGATGCGGTGGGCTCTATGGCTTC  
TGAGGCGGAAAGAACCAGCTGGGGACCGGTGGATCTCGATAGCAGGCATGCTGGGGAGAGATCGATCTGAG

GAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAA  
GCCCCGGGCGTCGGGCGACCTTTGGTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCA  
ACCCCCCCCCCCCCCCCCCCCCGGCGATTCTCTTGTTTGCTCCAGACTCTCAGGCAATGACCTGATAGCCTT  
TGTAGAGACCTCTCAAAAATAGCTACCCTCTCCGGCATGAATTTATCAGCTAGAACGGTTGAATATCATAT  
TGATGGTGATTTGACTGTCTCCGGCCTTTCTCACCCGTTTGAATCTTTACCTACACATTACTCAGGCATTG  
CATTTAAAATATATGAGGGTTCTAAAAATTTTTATCCTTGCGTTGAAATAAAGGCTTCTCCCGCAAAAGTA  
TTACAGGGTCATAATGTTTTTGGTACAACCGATTTAGCTTTATGCTCTGAGGCTTTATTGCTTAATTTTGC  
TAATTCCTTTGCCTTGCCTGTATGATTTATTGGATGTTGGAATCGCCTGATGCGGTATTTTCTCCTTACGCA  
TCTGTGCGGTATTTTACACCGCATATGGTGCACCTCTCAGTACAATCTGCTCTGATGCCGCATAGTTATATG  
GTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACAGCCAG  
CCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACA  
AGCTGTGACCGTCTCCGGGAGCTGCATGTGTGAGAGGTTTTACCGTCATCACCGAAACGCGCGAGACGAA  
AGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTTCTTAGACGTCAGGTGGC  
ACTTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCT  
CATGAGACAATAACCCTGATAAATGCTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCG  
TGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAG  
TAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACTGGATCTCAACAGCGGTAAGATC  
CTTGAGAGTTTTTCGCCCCGAAGAACGTTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGT  
ATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTGCGCGCATACACTATTCTCAGAATGACTTGGTTG  
AGTACTCACCGATCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATA  
ACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTT  
TTTGACACAACATGGGGGATCATGTAACCTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAA  
ACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACCTATTAAGTGGCGAACTA  
CTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCG  
CTCGGCCCTTCCGGCTGGCTGGTTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCA  
TTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACT  
ATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAAGTGTGACACCA  
AGTTTACTCATATATACTTTAGATTGATTTAAACCTTCATTTTTTAATTTAAAAGGATCTAGGTGAAGATCC  
TTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAA  
AAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACC  
GCTACCAGCGGTGGTTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTTCCGAAGGTAAGTGGCTTCAGCA  
GAGCGCAGATACCAAATACTGTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCA  
CCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTAC  
CGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTTCGTGCACAC  
AGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACG  
CTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGA  
GCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTGCGGTTTTCGCCACCTCTGACTTGAGCGTCGAT  
TTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGAAAAACGCCAGCAACGCGGCCTTTTTTACGGTTCCTG  
GCCTTTTGCTGGCCTTTTGCTCACATGTTCTTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTAC  
CGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAG  
CGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATG

SEQ ID NO.5: SerpEnh

GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCA  
C

SEQ ID NO.6: TTRm (TTR minimal promotor)

GTCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGT  
AGGTTACTTATTCTCCTTTTTGTTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGG  
GATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCCTTACCAGGAGAAGCCGTC

SEQ ID NO.7: TTRm5' UTR  
ACACAGATCCACAAGCTCCTG

SEQ ID NO.8: MVM intron

AAGAGGTAAGGGTTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGA  
AATCACTTTTTTTCAGGTTGG

SEQ ID NO.9: Co-FIX-R338L

ATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGCTACCTGCT  
GAGCGCCGAGTGCACCGTGTTCTTGGACCACGAGAACGCCAACAAGATCCTGAACCGCCCCAAGCGCTACA  
ACAGCGGCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGTGCAGCTTC  
GAGGAGGCCCGCGAGGTGTTTCGAGAACACCGAGCGCACCCAGAGTTCTGGAAGCAGTACGTGGACGGCGA  
CCAGTGCAGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGAGTGCTGGT  
GCCCCCTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCCGCTGCGAG  
CAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGGTACCGCCTGGCCGAGAA  
CCAGAAGAGCTGCGAGCCCGCCGTGCCCTTCCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAGCAAGCTGA  
CCCGCGCCGAGGCGGTGTTCCCCGACGTGGACTACGTGAACAGCACCGAGGCCGAGACCATCCTGGACAAC  
ATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCAGGACGCCAAGCCCGGCCA  
GTTCCCCCTGGCAGGTGGTGTGTAACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAACGAGAAGT  
GGATCGTGACCGCCGCCCACTGCGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGCACAACATC  
GAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCACCACAACACTACAACGCCGC  
CATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCCTGGTGCTGAACAGCTACGTGA  
CCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACGTGAGCGGC  
TGGGGCCGCGTGTTCCACAAGGGCCGCAGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCCCTGGTGGACCG  
CGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCACGAGGGCG  
GCCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCACGTGACCGAGGTGGAGGGCACCAGCTTCCTGACC  
GGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTGAGCCGCTA  
CGTGAACCTGGATCAAGGAGAAGACCAAGCTGACCTAATGA

SEQ ID NO.10: BGHpolyA

GATCTGAGCCGAATTCCTGCAGCCCGGGGGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTG  
TTTGCCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCCTGTCTTTTCTAATAAAATGAG  
GAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGG  
GGAGGATTGGGAAGACAATAGCAGGCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAA  
CCAGCTGGGGA

SEQ ID NO.11: 3xSERP

GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCA  
CCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTC  
CACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAG  
TCCAC

SEQ ID NO.12: TTRe (TTR Enhancer)

CACTGGGAGGATGTTGAGTAAGATGGAAAACACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTT  
TGAACAGGGGCCGGGCGATCAGCAGGTAG

SEQ ID NO.13: 3xSERP-**Flank**-TTRe

GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCA  
CCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTC  
CACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAG  
TCCACGGTACCCACTGGGAGGATGTTGAGTAAGATGGAAAACACTGATGACCCTTGCAGAGACAGAGTAT  
TAGGACATGTTTGAACAGGGGGCCGGGCGATCAGCAGGTAG

SEQ ID NO.25: pAAVsc-3xSerpEnh-TTRENh-TTRm-MVM-co-FIX-R338L-Synt.pA

AGCTGGCGTAATAGCGAAGAGGCCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATG  
GCGATTCCGTTGCAATGGCTGGCGGTAAATATTGTTCTGGATATTACCAGCAAGGCCGATAGTTTGAGTTCT  
TCTACTCAGGCAAGTGATGTTATTACTAATCAAAGAAGTATTGCGACAACGGTTAATTTGCGTGATGGACA  
GACTCTTTTACTCGGTGGCCTCACTGATTATAAAAACACTTCTCAGGATTCTGGCGTACCGTTCCTGTCTA  
AAATCCCTTTAATCGGCCTCCTGTTTAGCTCCCGCTCTGATTCTAACGAGGAAAGCACGTTATACGTGCTC  
GTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCG  
TGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTC  
GCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCT  
CGACCCCAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCC  
CTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCATATC  
TCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAAAATGAGCTGATTTA  
ACAAAAATTTAACGCGAACTTTAACAAAAATATTAACGTTTACAATTTAAATATTTGCTTATACAATCTTCC  
TGTTTTTGGGGCTTTTCTGATTATCAACCGGGGTACATATGATTGACATGCTAGTTTTACGATTACCGTTC  
ATCGCCCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCG  
CCCGGCCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGAATTCACGCGTGATCTGAATTCAATTAC  
GCGTGGTACGGCCGCGGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTTATCGGAGGAGCA  
AACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTTATCGGAGGAG  
CAAACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTTATCGGAGG  
AGCAAACAGGGGCTAAGTCCACGGTACCCACTGGGAGGATGTTGAGTAAGATGGAAAACACTGATGACCC  
TTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAGCTCTAGAGGATCCC  
CGTCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTG  
TAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAG  
GGATCAGCAGCCTGGGTGGAAGGAGGGGGTATAAAAGCCCCCTTACCAGGAGAAGCCGTCACACAGATCC  
ACAAGCTCCTGGCTAGAAAGAGGTAAGGGTTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTAC  
CTGGAGCACCTGCCTGAAATCACTTTTTTTTCAGGTTGGGCTAGCCCACCATGCAGCGCGTGAACATGATCA  
TGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGCTACCTGCTGAGCGCCGAGTGCACCGTGTTT  
CTGGACCACGAGAACGCCAACAGATCCTGAACCGCCCCAAGCGCTACAACAGCGGCAAGCTGGAGGAGTT  
CGTGCAGGGCAACCTGGAGCGCGAGTGATGGAGGAGAAGTGCAGCTTCGAGGAGGCCCGCGAGGTGTTTCG  
AGAACACCGAGCGCACCCAGGTTCTGGAAGCAGTACGTGGACGGCGACCAGTGCGAGAGCAACCCCTGC  
CTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGAGTGCTGGTGCCCCCTTCGGCTTCGAGGGCAA  
GAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCCGCTGCGAGCAGTTCTGCAAGAACAGCGCCG  
ACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTGGCCGAGAACCAGAAGAGCTGCGAGCCCCGCC  
GTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAGCAAGCTGACCCGCGCCGAGGCCGTGTTCCC  
CGACGTGGACTACGTGAACAGCACCGAGGCCGAGACCATCCTGGACAACATCACCCAGAGCACCCAGAGCT  
TCAACGACTTCACCCGCGTGTTGGGCGGCGAGGACGCCAAGCCCGGCCAGTTCCCCTGGCAGGTGGTGCTG  
AACGGCAAGGTGGACGCCCTTCTGCGGCGGCAGCATCGTGAACGAGAAGTGGATCGTGACCGCCGCCCACTG  
CGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGCACAAACATCGAGGAGACCGAGCACACCGAGC  
AGAAGCGCAACGTGATCCGCATCATCCCCACCACAACACTACAACGCCGCCATCAACAAGTACAACCACGAC  
ATCGCCCTGCTGGAGCTGGACGAGCCCCCTGGTGCTGAACAGCTACGTGACCCCCATCTGCATCGCCGACAA  
GGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACGTGAGCGGCTGGGGCCGCGTGTTCCACAAGG  
GCCGCAGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCCCTGGTGGACCGCGCCACCTGCCTGCTGAGCACC  
AAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCACGAGGGCGGCCGCGACAGCTGCCAGGGCGA  
CAGCGGCGGCCCCACGTGACCGAGGTGGAGGGCACAGCTTCTGACCGGCATCATCAGCTGGGGCGAGG  
AGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTGAGCCGCTACGTGAACTGGATCAAGGAGAAG  
ACCAAGCTGACCTAATGAAAGATGGATTTCCAAGGTTAATTCATTGGAATTGAAAATTAACAGCCCCCCCC  
CCCCCCCCCTGCAGATCTAATAAAAGATCTTTATTTTCATTAGATCTGTGTGTTGGTTTTTTGTGTGCCG  
GTGGATCTCGATAGCAGGCATGCTGGGGAGAGATCGATCTGAGGAACCCCTAGTGATGGAGTTGGCCACTC  
CCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGC  
CCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACCCCCCCCCCCCCCCCCCGGCGATT  
CTCTTGTTTTGCTCCAGACTCTCAGGCAATGACCTGATAGCCTTTGTAGAGACCTCTCAAAAATAGCTACCC  
TCTCCGGCATGAATTTATCAGCTAGAACGGTTGAATATCATATTGATGGTGATTTGACTGTCTCCGGCCTT  
TCTCACCCGTTTGAATCTTTACCTACACATTACTCAGGCATTGCATTTAAATATATGAGGGTTCTAAAAA

TTTTTATCCTTGCGTTGAAATAAAGGCTTCTCCCGCAAAAGTATTACAGGGTCATAATGTTTTTGGTACAA  
 CCGATTTAGCTTTTATGCTCTGAGGCTTTATTGCTTAATTTTGCTAATTCTTTGCCTTGCCTGTATGATTTA  
 TTGGATGTTGGAATCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTACACCCGCATATGG  
 TGCCTCTCAGTACAATCTGCTCTGATGCCGCATAGTTATATGGTGCCTCTCAGTACAATCTGCTCTGAT  
 GCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACAGCCAGCCCCGACACCCGCCAACACCCGCTGACG  
 CGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATG  
 TGTCAGAGGTTTTACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTTATA  
 GGTTAATGTCATGATAATAATGGTTTTCTTAGACGTCAGGTGGCACTTTTTCGGGGAAATGTGCGCGGAACCC  
 CTATTTGTTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTC  
 AATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTTCGGGCA  
 TTTTGCCTTCCTGTTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGC  
 ACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTTCGCCCCGAAGAACGTT  
 TTCCAATGATGAGCACTTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAG  
 CAACTCGGTGCGCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCT  
 TACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACT  
 TACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGACAAACATGGGGGATCATGTAACT  
 CGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGT  
 AGCAATGGCAACAACGTTGCGCAAACCTATTAAC TGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAA  
 TAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTTATT  
 GCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCC  
 CTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTG  
 AGATAGGTGCCTCACTGATTAAGCATTGGTAACGTGTCAGACCAAGTTTACTCATATATACTTTAGATTGAT  
 TTAAAACTTCATTTTTAATTTAAAGGATCTAGGTGAAGATCCTTTTTTGATAATCTCATGACCAAAATCCC  
 TTAACGTGAGTTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTT  
 TTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGAT  
 CAAGAGCTACCAACTCTTTTTCCGAAGGTAAC TGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCT  
 AGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCC  
 TGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCG  
 GATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACAC  
 CGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGT  
 ATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTT  
 TATAGTCCTGTCGGGTTTTCGCCACCTCTGACTTGAGCGTCGATTTTTTGATGCTCGTCAGGGGGGCGGAG  
 CCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT  
 TCTTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGC  
 CGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCAATACGCAAACCGCC  
 TCTCCCCGCGCGTTGGCCGATTCATTAATG

SEQ ID NO.26: **Flank-3xSERP-Flank-TTRe**

**AATTCACGCGTGGATCTGAATTCAATTACGCGTGGTACGGCCGCGG**GGGGGAGGCTGCTGGTGAATATTA  
 ACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAATAT**  
 TAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAAT**  
 ATTAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATG  
 TTGAGTAAGATGGAAAAC**TA**CTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGGCCG  
 GGCGATCAGCAGGTAG

SEQ ID NO.27: **Flank-3xSERP-Flank-TTRe-Flank**

**AATTCACGCGTGGATCTGAATTCAATTACGCGTGGTACGGCCGCGG**GGGGGAGGCTGCTGGTGAATATTA  
 ACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAATAT**  
 TAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAAT**  
 ATTAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATG  
 TTGAGTAAGATGGAAAAC**TA**CTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGGCCG  
 GGCGATCAGCAGGTAG**CTCTAGAGGATCCCC**

SEQ ID NO.28: **Flank-3xSERP-Flank-TTRe-Flank-TTRm**

**AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGG**GGGGGAGGCTGCTGGTGAATATTA  
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAATAT**  
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAAT**  
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*  
*TTGAGTAAGATGGAAA***CTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG**  
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCTAGAGCGAGTGTTCCGATACTC  
TAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCA  
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC  
CTTACCAGGAGAAGCCGTC

SEQ ID NO.29: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank**

**AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGG**GGGGGAGGCTGCTGGTGAATATTA  
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAATAT**  
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAAT**  
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*  
*TTGAGTAAGATGGAAA***CTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG**  
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCTAGAGCGAGTGTTCCGATACTC  
TAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCA  
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC  
CTTACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA**

SEQ ID NO.30: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM**

**AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGG**GGGGGAGGCTGCTGGTGAATATTA  
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAATAT**  
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAAT**  
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*  
*TTGAGTAAGATGGAAA***CTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG**  
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCTAGAGCGAGTGTTCCGATACTC  
TAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCA  
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC  
CTTACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGAAAGAGGTAAGGGTTTAAGGGATGG**  
*TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTCAGGTTGG*

SEQ ID NO.31: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank**

**AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGG**GGGGGAGGCTGCTGGTGAATATTA  
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAATAT**  
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAAT**  
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*  
*TTGAGTAAGATGGAAA***CTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG**  
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCTAGAGCGAGTGTTCCGATACTC  
TAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCA  
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC  
CTTACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGAAAGAGGTAAGGGTTTAAGGGATGG**  
*TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTCAGGTTGGGCT*  
**AGCCCACC**

SEQ ID NO.32: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L**

**AATTCACGCGTGGATCTGAATTCAATTACGCGTGGTACGGCCGCGG**GGGGGAGGCTGCTGGTGAATATTA  
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAATAT**  
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAAT**  
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*  
*TTGAGTAAGATGGAAA***CTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG**  
**GGCGATCAGCAGGTAGCTCTAGAGGATCCCC**GTCTGTCTGCACATTTCTAGAGCGAGTGTTCCGATACTC  
 TAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCA  
 GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC  
 CTTACACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA**AAGAGGTAAGGGTTTAAGGGATGG  
*TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTTCAGGTTGGGCT*  
**AGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGC**  
**TACCTGCTGAGCGCCGAGTGCACCGTGTTCTTGGACCACGAGAACGCCAACAAAGATCCTGAACCGCCCCAA**  
**GCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGT**  
**GCAGCTTCGAGGAGGCCCCGCGAGGTGTTGAGAACACCGAGCGCACCACCGAGTTCTGGAAGCAGTACGTG**  
**GACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGA**  
**GTGCTGGTGCCCTTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCC**  
**GCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGAGCTGCACCGAGGGCTACCGCCTG**  
**GCCGAGAACCAGAAGAGCTGCGAGCCCCGCCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAG**  
**CAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCCGAGGCCGAGACCATCC**  
**TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGCCAAG**  
**CCCGGCCAGTTCCCCTGGCAGGTGGTGTGTAACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAA**  
**CGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGCGCAGC**  
**ACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCACCACA****ACTAC**  
**AACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCCTGGTGCTGAACAG**  
**CTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCTGAAGTTCGGCAGCGGCTACG**  
**TGAGCGGCTGGGGCCGCGTGTTCACAAGGGCCGACGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCTG**  
**GTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCA**  
**CGAGGGCGGCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCT**  
**TCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTG**  
**AGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGA**

SEQ ID NO.33: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L-Flank**

**AATTCACGCGTGGATCTGAATTCAATTACGCGTGGTACGGCCGCGG**GGGGGAGGCTGCTGGTGAATATTA  
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAATAT**  
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAAT**  
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*  
*TTGAGTAAGATGGAAA***CTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG**  
**GGCGATCAGCAGGTAGCTCTAGAGGATCCCC**GTCTGTCTGCACATTTCTAGAGCGAGTGTTCCGATACTC  
 TAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCA  
 GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC  
 CTTACACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA**AAGAGGTAAGGGTTTAAGGGATGG  
*TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTTCAGGTTGGGCT*  
**AGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGC**  
**TACCTGCTGAGCGCCGAGTGCACCGTGTTCTTGGACCACGAGAACGCCAACAAAGATCCTGAACCGCCCCAA**  
**GCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGT**  
**GCAGCTTCGAGGAGGCCCCGCGAGGTGTTGAGAACACCGAGCGCACCACCGAGTTCTGGAAGCAGTACGTG**  
**GACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGA**  
**GTGCTGGTGCCCTTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCC**  
**GCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGAGCTGCACCGAGGGCTACCGCCTG**  
**GCCGAGAACCAGAAGAGCTGCGAGCCCCGCCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAG**  
**CAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCCGAGGCCGAGACCATCC**  
**TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGCCAAG**  
**CCCGGCCAGTTCCCCTGGCAGGTGGTGTGTAACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAA**

CGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGC  
 ACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCACCACAACACTAC  
 AACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCCTGGTGCTGAACAG  
 CTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACG  
 TGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGACGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCTG  
 GTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCA  
 CGAGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCT  
 TCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTG  
 AGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGAAAGATGGATTTCOAAGGTTAATT  
 CATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCCCCTGCA

SEQ ID NO.34: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-  
 FIX-R338L-Flank-BGHPA**

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGAGGCTGCTGGTGAATATTA  
 ACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATAT  
 TAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAAT  
 ATTAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCACCGGTACCCTGTTGGAGGATG  
 TTGAGTAAGATGGAAAACCTACTGATGACCCCTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG  
 GGCGATCAGCAGGTAGCTCTAGAGGATCCCCGTCTGTCTGCACATTTCTGATAGAGCGAGTGTTCCGATACTC  
 TAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCA  
 GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC  
 CTTACACCAGGAGAAGCCGTCACACAGATCCACAAGCTCCTGGCTAGAAGAGGTAAGGGTTTAAGGGATGG  
 TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTTCAGGTTGGGCT  
 AGCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGC  
 TACCTGCTGAGCGCCGAGTGCACCGTGTTCTTGGACCACGAGAACGCCAACAAGATCCTGAACCGCCCCAA  
 GCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGT  
 GCAGCTTCGAGGAGGCCCCGCGAGGTGTTGAGAACACCGAGCGCACCCAGGTTCTGGAAGCAGTACGTG  
 GACGGCGACCAAGTGCAGAGACAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGA  
 GTGCTGGTGCCCTTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCC  
 GCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTG  
 GCCGAGAACCAGAAGAGCTGCGAGCCCCGCCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAG  
 CAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCCGAGGCCGAGACCATCC  
 TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGCCAAG  
 CCCGGCCAGTTCCCCTGGCAGGTGGTGCTGAACGGCAAGGTGGACGCCCTTCTGCGGCGGCAGCATCGTGAA  
 CGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGC  
 ACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCACCACAACACTAC  
 AACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCCTGGTGCTGAACAG  
 CTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACG  
 TGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGACGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCTG  
 GTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCA  
 CGAGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCT  
 TCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTG  
 AGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGAAAGATGGATTTCOAAGGTTAATT  
 CATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCCCCTGCAGATCTGAGCCGAATTCCTGCAGCCCCG  
 GGGATCAGCCTCGACTGTGCCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCTCCCCCGTGCTTCTTGA  
 CCCTGGAAGGTGCCACTCCCCTGTCTTTCTTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGG  
 TGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCA  
 TGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGGGGA

SEQ ID NO.35: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-  
 FIX-R338L-Flank-BGHPA-Flank**

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGAGGCTGCTGGTGAATATTA  
 ACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATAT

TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAAT**  
 ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATG  
 TTGAGTAAGATGGAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGGCCG  
 GGCGATCAGCAGGTAG**CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCTGTAGAGCGAGTGTTCCGATACTC  
 TAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCA  
 GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC  
 CTTACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA**AAGAGGTAAGGGTTTAAGGGATGG  
 TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTTCAGGTTGGGCT  
**AGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGC**  
**TACCTGCTGAGCGCCGAGTGCACCGTGTTCTGGACCACGAGAACGCCAACAAGATCCTGAACCGCCCCAA**  
**GCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGT**  
**GCAGCTTCGAGGAGGCCCCGCGAGGTGTTGAGAACACCGAGCGCACCCAGGTTCTGGAAGCAGTACGTG**  
**GACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGA**  
**GTGCTGGTGCCCCCTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCC**  
**GCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTG**  
**GCCGAGAACCAGAAGAGCTGCGAGCCCCGCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAG**  
**CAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCCGAGGCCGAGACCATCC**  
**TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGCCAAG**  
**CCCGGCCAGTTCCTTGGCAGGTGGTGTGTAACGGCAAGGTGGACGCCCTTCTGCGGCGGCAGCATCGTGAA**  
**CGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGC**  
**ACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCACCACAACCTAC**  
**AACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCCTGGTGCTGAACAG**  
**CTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCTGAAGTTCGGCAGCGGCTACG**  
**TGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGACGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCTG**  
**GTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCA**  
**CGAGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCACGTGACCGAGGTGGAGGGCACCAGCT**  
**TCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTG**  
**AGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGAAAGATGGATTTCCAAGGTTAATT**  
**CATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCCCCTGCAGATCTGAGCCGAATTCCTGCAGCCCGG**  
 GGGATCAGCCTCGACTGTGCCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCTCCCCCGTGCTTCCCTTGA  
 CCCTGGAAGGTGCCACTCCCCTGTCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGG  
 TGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCA  
 TGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGGGGAC**CCGGTGGATCTCGATA**  
**GCAGGCATGCTGGGGAGAGATCG**

SEQ ID NO.36: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L-Flank-Synt.pA**

**AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGG**GGGGGAGGCTGCTGGTGAATATTA  
 ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAATAT**  
 TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGGCTAAGTCCAC**CGGGGGAGGCTGCTGGTGAAT**  
 ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATG  
 TTGAGTAAGATGGAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGGCCG  
 GGCGATCAGCAGGTAG**CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCTGTAGAGCGAGTGTTCCGATACTC  
 TAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCA  
 GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC  
 CTTACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA**AAGAGGTAAGGGTTTAAGGGATGG  
 TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTTCAGGTTGGGCT  
**AGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGC**  
**TACCTGCTGAGCGCCGAGTGCACCGTGTTCTGGACCACGAGAACGCCAACAAGATCCTGAACCGCCCCAA**  
**GCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGT**  
**GCAGCTTCGAGGAGGCCCCGCGAGGTGTTGAGAACACCGAGCGCACCCAGGTTCTGGAAGCAGTACGTG**  
**GACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGA**  
**GTGCTGGTGCCCCCTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCC**  
**GCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTG**

GCCGAGAACCAGAAGAGCTGCGAGCCCCGCCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAG  
CAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCGAGGCCGAGACCATCC  
TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGCCAAG  
CCCGGCCAGTTCCCCTGGCAGGTGGTGCTGAACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAA  
CGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGC  
ACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCACCACAACACTAC  
AACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCCTGGTGCTGAACAG  
CTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACG  
TGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGACGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCTG  
GTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCA  
CGAGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCT  
TCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTG  
AGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGAAAGATGGATTTCCAAGGTTAATT  
CATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCCCCTGCAAATAAAAGATCTTTATTTTCATTAGAT  
 CTGTGTGTTGGTTTTTTGTGTG

SEQ ID NO.37: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-**  
**FIX-R338L-Flank-Synt.pA-Flank**

**AATTACGCGTGGATCTGAATTCAATTACGCGTGGTACGGCCGCGGGGGGAGGCTGCTGGTGAATATTA**  
**ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATAT**  
**TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAAT**  
**ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGGCTAAGTCCACGGTACC****ACTGGGAGGATG**  
**TTGAGTAAGATGGAAA****ACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG**  
**GGCGATCAGCAGGTAGCTCTAGAGGATCCCCGTCTGTCTGCACATTTCTAGAGCGAGTGTTCCGATACTC**  
**TAATCTCCCTAGGCAAGGTT****CATATTTGTGTAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCA**  
**GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC**  
**CTTACCAGGAGAAGCCGTCACACAGATCCACAAGCTCCTGGCTAGA****AAGAGGTAAGGGTTTAAGGGATGG**  
**TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTCAGGTTGGGCT**  
**AGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGC**  
**TACCTGCTGAGCGCCGAGTGCACCGTGTTCTTGGAACACGAGAACGCCAACAAGATCCTGAACCGCCCCAA**  
**GCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGT**  
**GCAGCTTCGAGGAGGCCCCGCGAGGTGTTGAGAACACCGAGCGCACCACCGAGTTCTGGAAGCAGTACGTG**  
**GACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGA**  
**GTGCTGGTGCCCTTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCC**  
**GCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTG**  
**GCCGAGAACCAGAAGAGCTGCGAGCCCGCCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAG**  
**CAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCGAGGCCGAGACCATCC**  
**TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGCCAAG**  
**CCCGGCCAGTTCCCCTGGCAGGTGGTGCTGAACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAA**  
**CGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGC**  
**ACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCACCACAACACTAC**  
**AACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCCTGGTGCTGAACAG**  
**CTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACG**  
**TGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGACGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCTG**  
**GTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCA**  
**CGAGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCT**  
**TCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTG**  
**AGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGAAAGATGGATTTCCAAGGTTAATT**  
**CATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCCCCTGCA**AATAAAAGATCTTTATTTTCATTAGAT  
 CTGTGTGTTGGTTTTTTGTGTGCCGGTGGATCTCGATAGCAGGCATGCTGGGGAGAGATCG

**Figure 14**

SEQ ID NO.14: pAAVss-TTRm-MVM-coFVIIIdeltaB-Sv40pA

CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCCGGGCGTCGGGCGACCTTT  
GGTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTG  
CGGCCGCGGTACCGTCTGTCTGCACATTTCTGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGG  
TTCATATTTGTGTAGGTACTTATTCTCCTTTTGTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAG  
TCAGCTTGGCAGGGATCAGCAGCCTGGGTGGAAGGAGGGGGTATAAAAGCCCCCTTCACCAGGAGAAGCCG  
TCACACAGATCCACAAGCTCCTGAAGAGGTAAGGGTTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTT  
AATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTTCAGGTTGGCTAGTATGCAGATCGAGCTGTCCACCT  
GCTTTTTTCTGTGCCTGCTGCGGTCTGCTTCAGCGCCACCCGGCGGTACTACCTGGGCGCCGTGGAGCTG  
TCCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCGTGGACGCCCGGTTCCCCCCCCAGAGTGCCCCA  
GAGCTTCCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCTGTTTCGTGGAGTTCACCGACCACCTGTTCA  
ATATCGCCAAGCCCAGGCCCCCTGGATGGGCCTGCTGGGCCCCACCATCCAGGCCGAGGTGTACGACACC  
GTGGTGATCACCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAA  
GGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAAGAAGATGACAAGGTGTTCCCTG  
GCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGGCCCCATGGCCTCCGACCCCCCTGTGCCTG  
ACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGCCTGATCGGCGCTCTGCTCGT  
CTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAGTTCATCCTGCTGTTCCCGTGT  
TCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCAGGACCGGGACGCCGCCTCTGCC  
AGAGCCTGGCCCAAGATGCACACCCTGAACGGCTACGTGAACAGAAGCCTGCCCGGCCTGATTGGCTGCCA  
CCGGAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACACCCGAGGTGCACAGCATCTTTCTGGAAG  
GGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAGCCCTATCACCTTCCTGACCGCC  
CAGACACTGCTGATGGACCTGGGCCAGTTCTGCTGTTTTGCCACATCAGCTCTCACCAGCACGACGGCAT  
GGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCAGCTGCGGATGAAGAACAACGAGGAAGCCG  
AGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCGGTTCGACGACGACAACAGCCCCAGC  
TTCATCCAGATCAGAAGCGTGGCCAAAGAAGCACCCCAAGACCTGGGTGCATATATCGCCGCCGAGGAAGA  
GGACTGGGACTACGCCCCCTGGTGTGCGCCCCGACGACAGAAGCTACAAGAGCCAGTACCTGAACAATG  
GCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTTTCATGGCCTACACCGACGAGACATTCAAGACC  
CGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGCGAAGTGGGCGACACACTGCT  
GATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTACCCCCACGGCATCACCGACGTGCGGCCCC  
TGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTC  
AAGTACAAGTGGACCGTGACCGTGAGGACGGCCCCACCAAGAGCGACCCCAGATGCCTGACCCGGTACTA  
CAGCAGCTTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGACCTCTGCTGATCTGCTACAAAG  
AAAGCGTGGACCAGCGGGGCAACCAGATCATGAGCGACAAGCGGAACGTGATCCTGTTTCAGCGTGTTTCGAT  
GAGAACCGGTCTTGGTATCTGACCGAGAACATCCAGCGGTTTCTGCCCAACCCTGCCGGCGTGACGCTGGA  
AGATCCCGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGCTACGTGTTTCGACTCTCTGCAGCTCT  
CCGTGTGTCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCCAGACCGACTTCCTGAGCGTG  
TTCTTCAGCGGCTACACCTTCAAGCACAAAGATGGTGTACGAGGACACCCTGACCCTGTTCCCTTTCAGCGG  
CGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCCTGTGGATTCTGGGCTGCCACAACAGCGACTTCCGGA  
ACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGCTGCGACAAGAACACCGGCGACTACTACGAGGACAGC  
TACGAGGATATCAGCGCCTACCTGCTGTCCAAGAACAACGCCATCGAACCCCGGAGCTTCAGCCAGAACCC  
CCCCGTGCTGACGCGTCACCAGCGGGAGATCACCCGGACAACCCTGCAGTCCGACCAGGAAGAGATCGATT  
ACGACGACACCATCAGCGTGGAGATGAAGAAAGAGGATTTTCGATATCTACGACGAGGACGAGAACCAGAGC  
CCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTTTCATTGCCGCCGTGGAGAGGCTGTGGGACTACGGCAT  
GAGTTCTAGCCCCCACGTGCTGCGGAACCGGGCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAAGTGGTGT  
TCCAGGAATTCACAGACGGCAGCTTCACCCAGCCTCTGTATAGAGGCGAGCTGAACGAGCACCTGGGGCTG  
CTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAACATCATGGTGACCTTCCGGAATCAGGCCAGCAGACC  
CTACTCCTTCTACAGCAGCCTGATCAGCTACGAAGAGGACCAGCGGCAGGGCGCCGAACCCCGGAAGAACT  
TCGTGAAGCCCAACGAAACCAAGACCTACTTCTGGAAAGTGCAGCACCATGGCCCCCACCAGGACGAG  
TTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTGGATCTGGAAAAGGACGTGCACCTCTGGACTGATTGG  
CCCCTCCTGGTCTGCCACACTAACCCCTCAACCCCGCCACGGCCGCCAGGTGACCGTGCAGGAATTTCG  
CCCTGTTCTTCACCATCTTCGACGAGACAAAGTCCTGGTACTTCACCGAGAATATGGAACGGAACTGCAGA  
GCCCCCTGCAACATCCAGATGGAAGATCCTACCTTCAAAGAGAACTACCGGTTCCACGCCATCAACGGCTA

CATCATGGACACCCTGCCTGGCCTGGTGATGGCCCAGGACCAGAGAATCCGGTGGTATCTGCTGTCCATGG  
GCAGCAACGAGAATATCCACAGCATCCACTTCAGCGGCCACGTGTTACCGTGCGGAAGAAAGAAGAGTAC  
AAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTTCGAGACAGTGGAGATGCTGCCCAGCAAGGCCGGCAT  
CTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGCACGCTGGCATGAGCACCCCTGTTTCTGGTGTACAGCA  
ACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGCCACATCCGGGACTTCCAGATCACCGCCTCCGGCCAG  
TACGGCCAGTGGGGCCCCAAGCTGGCCAGACTGCACTACAGCGGCAGCATCAACGCCTGGTCCACCAAAGA  
GCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCTATGATCATCCACGGCATTAAAGACCCAGGGCGCCA  
GGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTGGACGGCAAGAAGTGGCAG  
ACCTACCGGGGCAACAGCACCGGCACCCTGATGGTGTCTTTCGGCAATGTGGACAGCAGCGGCATCAAGCA  
CAACATCTTCAACCCCCCATCATTTGCCCGGTACATCCGGCTGCACCCCACTACAGCATTAGATCCA  
CACTGAGAATGGAAGTGTGGGCTGCGACCTGAACTCCTGCAGCATGCCTCTGGGCATGGAAAGCAAGGCC  
ATCAGCGACGCCCAGATCACAGCCAGCAGCTACTTCACCAACATGTTTCGCCACCTGGTCCCCCTCCAAGGC  
CAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGCGGCCTCAGGTCAACAACCCCAAAGAATGGCTGCAGG  
TGGACTTTCAGAAAACCATGAAGGTGACCGGCGTGACCACCCAGGGCGTGAAAAGCCTGCTGACCAGCATG  
TACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGATGGCCACCAGTGGACCCCTGTTCTTTCAGAACGGCAA  
GGTGAAAGTGTTCAGGGCAACCAGGACTCCTTCACCCCGTGGTGAAGTCCCTGGACCCCCCTGCTGA  
CCCGCTACCTGAGAATCCACCCCCAGTCTTGGGTGCACCAGATCGCCCTCAGGATGGAAGTCCTGGGATGT  
GAGGCCCAGGATCTGTACTGATGAGGATCTAGGCTCGACATGCTTTATTTGTGAAATTTGTGATGCTATTG  
CTTTATTTGTAACCATTATAAGCTGCAATAAACAAGTTAACAACAACAATTGCATTTCATTTTATGTTTCAG  
GTTTCAGGGGGAGGTGTGGGAGGTTTTTTAAACTCGAGATCCACGGCCGCAGGAACCCCTAGTGATGGAGTT  
GGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCGGGCGACCAAGGTGCGCCGACGCCCGGGCT  
TTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTC  
CTTACGCATCTGTGCGGTATTTACACCGCATACTGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCA  
TTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCC  
TTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTTCGCCGGCTTTCCCGTCAAGCTCTAAATCGGGGGCTCC  
CTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAACCTTGATTTGGGTGATGGTTCACGT  
AGTGGGCCATCGCCCTGATAGACGGTTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACT  
CTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGA  
TTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACG  
TTTACAATTTTATGGTGCACCTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCC  
GCCAACACCCGCTGACGCGCCCTGACGGGCTTGCTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCG  
TCTCCGGGAGCTGCATGTGTCAGAGGTTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTG  
ATACGCCATTTTTTATAGGTAAATGTCATGATAATAATGGTTTTCTTAGACGTCAGGTGGCACTTTTCGGGG  
AAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAAT  
AACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTC AACATTTCCGTGTCGCCCTT  
ATTCCCTTTTTTTCGGGCATTTTGCCTTCCTGTTTTTGTCTACCCAGAAACGCTGGTGAAAGTAAAAGATGC  
TGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTT  
TTCGCCCCGAAGAACGTTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGT  
ATTGACGCCGGGCAAGAGCAACTCGGTGCGCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACC  
AGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTG  
ATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAAC  
ATGGGGGATCATGTAACCTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCG  
TGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACCTATTAAGTGGCGAACTACTTACTCTAG  
CTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTT  
CCGGCTGGCTGGTTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTTGCAGCACT  
GGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAAC  
GAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAAGTGTGAGACCAAGTTTACTCA  
TATATACTTTAGATTGATTTAAACTTCATTTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTTGATAA  
TCTCATGACCAAAAATCCCTTAACGTGAGTTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAG  
GATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCG  
GTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAAGTGGCTTCAGCAGAGCGCAGAT  
ACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACAT  
ACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGAC  
TCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTTCGTGCACACAGCCCAGCTT  
GGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAG

GGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGG  
GGAAACGCCTGGTATCTTTATAGTCCTGTCTGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATG  
CTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCT  
GGCCTTTTGCTCACATGT

SEQ ID NO.15: pAAVss-SerpEnh-TTRm-MVM-coFVIIIdeltaB-Sv40pA

CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCCGGGCGTCGGGCGACCTTT  
GGTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACCTCCATCACTAGGGGTTCCTG  
CGGCCGCGGTACCGGCGCGCCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGG  
AGCAAACAGGGGCTAAGTCCACACGCGTGGTACCGTCTGTCTGCACATTTCTGTAGAGCGAGTGTTCCGATA  
CTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTAAGTCAATAA  
TCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGGTATAAAAG  
CCCCTTTACCAGGAGAAGCCGTCACACAGATCCACAAGCTCCTGAAGAGGTAAGGGTTTAAGGGATGGTTG  
GTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTTCAGGTTGGCTAGTA  
TGCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGCGCCACCCGGCGGTAC  
TACCTGGGCGCCGTGGAGCTGTCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCCGTGGACGCCCCG  
GTTCCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCCTGTTTCGTGG  
AGTTCACCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCTGGATGGGCCTGCTGGGCCCCACCATC  
CAGGCCGAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGC  
CGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAAG  
AAGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGGCCCCATG  
GCCTCCGACCCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGG  
CCTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAGT  
TCATCCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCAG  
GACCGGGACGCCGCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGAAGCCT  
GCCCCGGCCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACACCCGAGG  
TGCACAGCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAGC  
CCTATCACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCTCTGCTGTTTTGCCACATCAG  
CTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCAGCTGCGGA  
TGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCGGTTC  
GACGACGACAACAGCCCCAGCTTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTGCA  
CTATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCGACGACAGAAGCTACA  
AGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTTTCATGGCCTAC  
ACCGACGAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGG  
CGAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTACCCCCACG  
GCATCACCGACGTGCGGCCCCGTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCC  
ATCCTGCCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACCC  
CAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGAC  
CTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGCGACAAGCGGAACGTG  
ATCCTGTTTCAGCGTGTTTCGATGAGAACCGGTCTTGGTATCTGACCGAGAACATCCAGCGGTTTCTGCCCAA  
CCCTGCCGGCGTGAGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGCTACG  
TGTTGCACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCC  
CAGACCGACTTCCTGAGCGTGTTCTTTCAGCGGCTACACCTTCAAGCACAAAGATGGTGTACGAGGACACCCT  
GACCCTGTTCCCTTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCCTGTGGATTCTGGGCT  
GCCACAACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGCTGCGACAAGAACACC  
GGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAACAACGCCATCGAACC  
CCGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCCGGACAACCCTGCAGT  
CCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAGGATTTTCGATATCTAC  
GACGAGGACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTTCATTGCCGCCGTGGA  
GAGGCTGTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGGCCAGAGCGGCAGCGTGC  
CCCAGTTCAAGAAAGTGGTGTTCAGGAATTCACAGACGGCAGCTTCACCCAGCCTCTGTATAGAGGCGAG  
CTGAACGAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAACATCATGGTGACCTT  
CCGGAATCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAGAGGACCAGCGGCAGG  
GCGCCGAACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGGAAGGTGCAGCACCAC

ATGGCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTGGATCTGGAAAAGGA  
CGTGCACTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCCTCAACCCCGCCACGGCCGCC  
AGGTGACCGTGCAGGAATTCGCCCTGTTCTTCACCATCTTCGACGAGACAAAGTCCTGGTACTTCACCGAG  
AATATGGAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTTCAAAGAGAACTACCG  
GTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGATGGCCCAGGACCAGAGAATCC  
GGTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGCGGCCACGTGTTACCC  
GTGCGGAAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTTCGAGACAGTGGAGAT  
GCTGCCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGCACGCTGGCATGAGCA  
CCCTGTTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGCCACATCCGGGACTTC  
CAGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCACTACAGCGGCAGCAT  
CAACGCCTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCTATGATCATCCACG  
GCATTAAGACCCAGGGCGCCAGGCAGAAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGC  
CTGGACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGTGTCTTCGGCAATGT  
GGACAGCAGCGGCATCAAGCACAAACATCTTCAACCCCCCATCATTTGCCCGGTACATCCGGCTGCACCCCA  
CCCCTACAGCATTAGATCCACACTGAGAATGGAAGTGTGGGCTGCGACCTGAACTCCTGCAGCATGCCT  
CTGGGCATGGAAAGCAAGGCCATCAGCGACGCCAGATCACAGCCAGCAGCTACTTCACCAACATGTTTCGC  
CACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGCGGCCCTCAGGTCAACA  
ACCCCAAAGAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGTGACCACCCAGGGCGTG  
AAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGATGGCCACCAGTGGAC  
CCTGTTCTTTCAGAACGGCAAGGTGAAAGTGTTCCAGGGCAACCAGGACTCCTTCACCCCCGTGGTGAAGT  
CCCTGGACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGTCTTGGGTGCACCAGATCGCCCTC  
AGGATGGAAGTCTGGGATGTGAGGCCAGGATCTGTACTGATGAGGATCTAGGCTCGACATGCTTTATTT  
GTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAAGTTAACAACAACAAT  
TGCATTCATTTTATGTTTCAGGTTTCAGGGGGAGGTGTGGGAGGTTTTTTAAACTCGAGATCCACGGCCGCA  
GGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAA  
AGGTGCCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGG  
CGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTACACCCGCATACGTCAAAGCAACCATAG  
TACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGC  
CAGCGCCCTAGCGCCCGCTCCTTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTTCGCCGGCTTTCCCCGTC  
AAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAACTT  
GATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTTCGCCCTTTGACGTTGGAGTC  
CACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGGCTATTCTTTTG  
ATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAATAAATTTAACGCG  
AATTTTAACAATAATTAACGTTTACAATTTTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATA  
GTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCG  
CTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTGAGAGGTTTTTCACCGTCATCACCGAAACGC  
GCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTAAATGTCATGATAATAATGGTTTCTTAGAC  
GTCAGGTGGCAGTTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATA  
TGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATT  
CAACATTTCCGTGTCGCCCTTATTCCCTTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGTCTACCCAGAAAC  
GCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACTGGATCTCAACA  
GCGGTAAGATCCTTGAGAGTTTTTCGCCCCGAAGAAGCTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTA  
TGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTGCGCGCATACTACTATTCTCAGAA  
TGACTTGGTTGAGTACTCACCAGTCAAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCA  
GTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAG  
CTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACCTCGCCTTGATCGTTGGGAACCGGAGCTGAATGA  
AGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACCTATTAA  
CTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGA  
CCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTATTATGCTGATAAATCTGGAGCCGGTGAGCGTGGGTC  
TCGCGGTATCATTTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGA  
GTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTTGGTAA  
CTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAACTTCATTTTTTAATTTAAAGGATCTA  
GGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTTCGTTCCACTGAGCGTCAG  
ACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACA  
AAAAAACACCGCTACCAGCGGTGGTTTGTGTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAAC

TGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGA  
ACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAG  
TCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGG  
TTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAG  
AAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAG  
CGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTGCGGGTTTCGCCACCTCTGACT  
TGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTT  
TACGGTTCCTGGCCTTTTGTGCTGGCCTTTTGTCTCACATGT

SEQ ID NO.16: pAAVss-3xSerpEnh-TTRm-MVM-coFVIIIdeltaB-Sv40pA

CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCCGGGCGTCGGGCGACCTTT  
GGTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTG  
CGGCCGCGGTACGCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAAC  
AGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAA  
ACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGC  
AAACAGGGGGCTAAGTCCACTGTACAACGCGTGAATTCGCTAGCGTCTGTCTGCACATTTCTGTAGAGCGAGT  
GTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTA  
AGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGG  
GTATAAAAGCCCCCTTCACCAGGAGAAGCCGTCACACAGATCCACAAGCTCCTGTCTAGAAAGAGGTAAGGG  
TTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTT  
TCAGGTTGGGCTAGCATGCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAG  
CGCCACCCGGCGGTACTACCTGGGCGCCGTGGAGCTGTCTGGGACTACATGCAGAGCGACCTGGGCGAGC  
TGCCCGTGGACGCCCGGTTCCCCCCCCAGAGTGCCCAAGAGCTTCCCCCTTCAACACCAGCGTGGTGTACAAG  
AAAACCTGTTCGTGGAGTTCACCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCTGGATGGGCCT  
GCTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACC  
CCGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACC  
AGCCAGCGGGAGAAAGAAGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAA  
AGAAAACGGCCCCATGGCCTCCGACCCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGA  
AGGACCTGAACAGCGGCCTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACC  
CAGACCCTGCACAAGTTCATCCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAA  
GAACAGCCTGATGCAGGACCGGGACGCCGCCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCT  
ACGTGAACAGAAGCCTGCCCCGGCCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATG  
GGCACCACACCCGAGGTGCACAGCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGC  
CAGCCTGGAAATCAGCCCTATCACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCTCTGC  
TGTTTTGCCACATCAGCTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAG  
GAACCCCAGCTGCGGATGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGAT  
GGACGTGGTGCGGTTTCGACGACGACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACC  
CCAAGACCTGGGTGCACTATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCC  
GACGACAGAAGCTACAAGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGT  
GCGGTTTCATGGCCTACACCGACGAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGG  
GCCCCCTGCTGTACGGCGAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTAC  
AACATCTACCCCCACGGCATCACCGACGTGCGGCCCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCA  
CCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCC  
CCACCAAGAGCGACCCCAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCC  
TCCGGGCTGATCGGACCTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAG  
CGACAAGCGGAACGTGATCCTGTTTCAGCGTGTTTCGATGAGAACCGGTCCTGGTATCTGACCGAGAACATCC  
AGCGGTTTCTGCCCAACCCTGCCGGCGTGACGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCAC  
TCCATCAATGGCTACGTGTTTCGACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACAT  
CCTGAGCATCGGCGCCAGACCGACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAAGATGG  
TGTACGAGGACACCCTGACCTGTTCCCTTTCAGCGGCGAGACAGTGTTCATGAGCATGGAAAACCCCGGC  
CTGTGGATTCTGGGCTGCCACAACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAG  
CTGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGA  
ACAACGCCATCGAACCCCGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACC  
CGGACAACCCTGCAGTCCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGA

GGATTTTCGATATCTACGACGAGGACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACT  
TCATTGCCGCCGTGGAGAGGCTGTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCC  
CAGAGCGGCAGCGTGCCCCAGTTCAAGAAAGTGGTGTTCAGGAATTCACAGACGGCAGCTTCACCCAGCC  
TCTGTATAGAGGCGAGCTGAACGAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACA  
ACATCATGGTGACCTTCCGGAATCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAA  
GAGGACCAGCGGCAGGGCGCCGAACCCCGGAAGAAGTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTG  
GAAAGTGCAGCACCACATGGCCCCCACCAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACG  
TGGATCTGGAAAAGGACGTGCACTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCCTCAAC  
CCCGCCACCGCCGCCAGGTGACCGTGAGGAATTCGCCCTGTTCTTCACCATCTTCGACGAGACAAAGTC  
CTGGTACTTCACCGAGAATATGGAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCT  
TCAAAGAGAACTACCGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGATGGCC  
CAGGACCAGAGAATCCGGTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAG  
CGGCCACGTGTTACCGTGCGGAAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGT  
TCGAGACAGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTG  
CACGCTGGCATGAGCACCTGTTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGG  
CCACATCCGGGACTTCCAGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGC  
ACTACAGCGGCAGCATCAACGCCTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCC  
CCTATGATCATCCACGGCATTAAAGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTT  
CATCATCATGTACAGCCTGGACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCCGGCACCTGATGG  
TGTTCTTCGGCAATGTGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCATCATTGCCCGGTAC  
ATCCGGCTGCACCCCACTACTACAGCATTAGATCCACACTGAGAATGGAAGTGTGGGCTGCGACCTGAA  
CTCCTGCAGCATGCCTCTGGGCATGGAAAGCAAGGCCATCAGCGACGCCCAGATCACAGCCAGCAGCTACT  
TCACCAACATGTTGCCCACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGG  
CGGCCTCAGGTCAACAACCCCAAGAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGT  
GACCACCCAGGGCGTGAAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGG  
ATGGCCACCAGTGGACCCTGTTCTTTTCAAGAACGGCAAGGTGAAAGTGTTCAGGGCAACCAGGACTCCTTC  
ACCCCGTGGTGAAGTCCCTGGACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGTCTTGCGT  
GCACCAGATCGCCCTCAGGATGGAAGTCTTGGGATGTGAGGCCCAGGATCTGTACTGATGAGGATCTAGGC  
TCGACATGCTTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACA  
AGTTAACAACAACAATTGCATTCATTTTATGTTTCAGGTTTCAGGGGGAGGTGTGGGAGGTTTTTTAACTC  
GAGATCCACGGCCGCAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACT  
GAGGCCGGGCGACCAAAGGTGCCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCG  
CAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTACACCCGCATAC  
GTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCG  
TGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTT  
GCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCT  
CGACCCCAAAAACCTTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTTCGCC  
CTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATC  
TCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAAAATGAGCTGATTTA  
ACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTTACAATTTTATGGTGCACCTCTCAGTACAATCT  
GCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGT  
CTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTTCACC  
GTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTTATAGGTTAATGTCATGATAA  
TAATGGTTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTTATTTTC  
TAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAG  
GAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTT  
TTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATC  
GAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCAC  
TTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTGCGCGCA  
TACACTATTCTCAGAATGACTTGGTTGAGTACTACCCAGTCACAGAAAAGCATCTTACGGATGGCATGACA  
GTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAAAGTGCAGGCAACTTACTTCTGACAACGAT  
CGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACCTGCCTTGATCGTTGGG  
AACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACG  
TTGCGCAAACTATTAAGTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGC  
GGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTTATTGCTGATAAATCTGGAG

CCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTT  
ATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACT  
GATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAACTTCATTTTT  
AATTTAAAAGGATCTAGGTGAAGATCCTTTTTTGATAATCTCATGACCAAATCCCTTAACGTGAGTTTTCG  
TTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAAT  
CTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTGTTGCCGGATCAAGAGCTACCAACTC  
TTTTTCCGAAGGTAACCTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCTTCTAGTGTAGCCGTAGTTA  
GGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGC  
TGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGT  
CGGGCTGAACGGGGGGTTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTA  
CAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAG  
GGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTGCGGT  
TTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCC  
AGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT

SEQ ID NO.17: pAAVss-TTRe-TTRm-MVM-coFVIIIdeltaB-Sv40pA

CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTT  
GGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACCTCCATCACTAGGGGTTCCTG  
CGGCCGCGGTACCCACTGGGAGGATGTTGAGTAAGATGGAAAATACTGATGACCCTTGCAGAGACAGAGT  
ATTAGGACATGTTTGAACAGGGGGCCGGGCGATCAGCAGGTAGCTCTAGAGGATCCCCGTCTGTCTGCACAT  
TTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCT  
CCTTTTGTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGG  
GTTGGAAGGAGGGGGTATAAAAGCCCCCTTCACCAGGAGAAGCCGTCACACAGATCCACAAGCTCCTGAAGA  
GGTAAGGGTTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATC  
ACTTTTTTTCAGGTGGCTAGTATGCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTCTCT  
GCTTCAGCGCCACCCGGCGGTACTACCTGGGCGCCGTGGAGCTGTCTGGGACTACATGCAGAGCGACCTG  
GGCGAGCTGCCCGTGGACGCCCGGTTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGT  
GTACAAGAAAACCCTGTTCTGTGGAGTTCACCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCCTGGA  
TGGGCCTGCTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCC  
AGCCACCCCGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGGCGCCGAGTACGACGA  
CCAGACCAGCCAGCGGGAGAAAGAAGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGG  
TGCTGAAAGAAAACGGCCCCATGGCCTCCGACCCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGAC  
CTGGTGAAGGACCTGAACAGCGGCCTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGA  
GAAAACCCAGACCTTGCACAAGTTCATCCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCG  
AGACAAAGAACAGCCTGATGCAGGACCGGGACGCCGCCCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTG  
AACGGCTACGTGAACAGAAGCCTGCCCGGCCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGAT  
CGGCATGGGCACCACACCCGAGGTGCACAGCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACC  
GGCAGGCCAGCCTGGAAATCAGCCCTATCACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAG  
TTCTGCTGTTTTTGCCACATCAGCTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTG  
CCCCGAGGAACCCAGCTGCGGATGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACA  
GCGAGATGGACGTGGTGCGGTTTCGACGACGACAACAGCCCCAGCTTTCATCCAGATCAGAAGCGTGGCCAAG  
AAGCACCCCAAGACCTGGGTGCACTATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCCTGGTGCT  
GGCCCCCGACGACAGAAGCTACAAGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACA  
AGAAAGTGCGGTTCATGGCCTACACCGACGAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGC  
ATCCTGGGCCCCCTGCTGTACGGCGAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCG  
GCCCTACAACATCTACCCCCACGGCATCACCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCG  
TGAAGCACCTGAAGGACTTCCCCATCTGCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAG  
GACGGCCCCACCAAGAGCGACCCCAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGA  
CCTGGCCTCCGGGCTGATCGGACCTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGA  
TCATGAGCGACAAGCGGAACGTGATCCTGTTTCAGCGTGTTTCGATGAGAACCGGTCCTGGTATCTGACCGAG  
AACATCCAGCGGTTTTCTGCCCAACCCTGCCGGCGTGACGCTGGAAGATCCCGAGTTCCAGGCCAGCAACAT  
CATGCACTCCATCAATGGCTACGTGTTTCGACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACT  
GGTACATCCTGAGCATCGGCGCCCAGACCGACTTCCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCAC  
AAGATGGTGTACGAGGACACCCTGACCCTGTTCCCTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAA

CCCCGGCCTGTGGATTCTGGGCTGCCACAACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGG  
TGTCAGCTGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTG  
TCCAAGAACAACGCCATCGAACCCCGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGA  
GATCACCCGGACAACCCTGCAGTCCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGA  
AGAAAGAGGATTTTCGATATCTACGACGAGGACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGG  
CACTACTTCATTGCCGCCGTGGAGAGGCTGTGGGACTACGGCATGAGTTCTAGCCCCCACGTGCTGCGGAA  
CCGGGCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAAGTGGTGTTCCAGGAATTCACAGACGGCAGCTTCA  
CCCAGCCTCTGTATAGAGGCGAGCTGAACGAGCACCTGGGGCTGCTGGGGGCCCTACATCAGGGCCGAAGTG  
GAGGACAACATCATGGTGACCTTCCGGAATCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAG  
CTACGAAGAGGACCAGCGGCAGGGCGCCGAACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCT  
ACTTCTGGAAAGTGCAGCACCATATGGCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTC  
AGCGACGTGGATCTGGAAAAGGACGTGCACTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACAC  
CCTCAACCCCGCCACGGCCGCCAGGTGACCGTGCAGGAATTCGCCCTGTTCTTCACCATCTTCGACGAGA  
CAAAGTCCTGGTACTTCACCGAGAATATGGAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGAT  
CCTACCTTCAAAGAGAACTACCGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGT  
GATGGCCAGGACCAGAGAATCCGGTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCC  
ACTTCAGCGGCCACGTGTTACCGTGCGGAAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCC  
GGCGTGTTTCGAGACAGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGA  
GCACCTGCACGCTGGCATGAGCACCTGTCTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGG  
CCTCTGGCCACATCCGGGACTTCCAGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCC  
AGACTGCACTACAGCGGCAGCATCAACGCCTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCT  
GCTGGCCCCCTATGATCATCCACGGCATTAAAGACCCAGGGCGCCAGGCAGAAAGTTCAGCAGCCTGTACATCA  
GCCAGTTCATCATCATGTACAGCCTGGACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACC  
CTGATGGTGTCTTCGGCAATGTGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCATCATTTGC  
CCGGTACATCCGGCTGCACCCCACTACTACAGCATTAGATCCACACTGAGAATGGAAGTGTTCAGGGCAACCAGGA  
ACCTGAACTCCTGCAGCATGCCTCTGGGCATGGAAAGCAAGGCCATCAGCGACGCCAGATCACAGCCAGC  
AGCTACTTCACCAACATGTTTCGCCACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAA  
CGCCTGGCGGCCTCAGGTCAACAACCCCAAGAAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGA  
CCGGCGTGACCACCCAGGGCGTGAAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGC  
TCTCAGGATGGCCACCAGTGGACCCTGTCTTTTCAGAACGGCAAGGTGAAAGTGTTCAGGGCAACCAGGA  
CTCCTTCACCCCCGTGGTGAAGTCCCTGGACCCCCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGT  
CTTGGGTGCACCAGATCGCCCTCAGGATGGAAGTCTGGGATGTGAGGCCAGGATCTGTACTGATGAGGA  
TCTAGGCTCGACATGCTTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTTATAAGCTGCA  
ATAAACAAGTTAACAACAACAATTGCATTCATTTTATGTTTCAGGTTTCAGGGGGAGGTGTGGGAGGTTTTT  
TAAACTCGAGATCCACGGCCGCAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTC  
GCTCACTGAGGCCGGGCGACCAAAGGTGCCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGC  
GAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTACAC  
CGCATAAGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACG  
CGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTGCTTTCTTCCCTTCCTTTCTCGC  
CACGTTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTAC  
GGCACCTCGACCCCAAAAACCTTGATTTGGGTGATGGTTACGTAAGTGGGCCATCGCCCTGATAGACGGTT  
TTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAA  
CCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTGGCCTATTGGTTAAAAAATGAGC  
TGATTTAACAAAAATTTAACGCGAATTTTAAACAAAATATTAACGTTTACAATTTTATGGTGCACCTCTCAGT  
ACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACG  
GGCTTGCTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGT  
TTTACACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTTATAGGTTAATGTC  
ATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTT  
ATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATT  
GAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCTT  
CCTGTTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGG  
TTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTTCGCCCCGAAGAAGCTTTTCCAATGA  
TGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGT  
CGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTACCAGTCACAGAAAAGCATCTTACGGATGG  
CATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGA

CAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGAT  
CGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGC  
AACAAACGTTGCGCAAACCTATTAACCTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGA  
TGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAA  
TCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTAT  
CGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTG  
CCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAACTT  
CATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGA  
GTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGC  
GCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTA  
CCAACCTCTTTTTCCGAAGGTAACCTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCTTCTAGTGTAGCC  
GTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAG  
TGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCG  
CAGCGGTGCGGCTGAACGGGGGGTTCGTGCACACAGCCAGCTTGAGAGCGAACGACCTACACCGAACTGAG  
ATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAA  
GCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCT  
GTCGGGTTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAA  
AAACGCCAGCAACGCGGCCTTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT

SEQ ID NO.18: coFVIIIdeltaB

ATGCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGCGCCACCCGGCGGTA  
CTACCTGGGCGCCGTGGAGCTGTCCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCCGTGGACGCCC  
GGTTCCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCCTGTTCTGTG  
GAGTTCACCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCTGGATGGGCCTGCTGGGCCCCACCAT  
CCAGGCCGAGGTGTACGACACCGTGGTGTATCACCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACG  
CCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAA  
GAAGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGGCCCCAT  
GGCCTCCGACCCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCG  
GCCTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAG  
TTCATCCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCA  
GGACCGGGACGCCGCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAAACGGCTACGTGAACAGAAGCC  
TGCCCGGCCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACACCCGAG  
GTGCACAGCATCTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAG  
CCCTATCACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCCTGCTGTTTTGCCACATCA  
GCTCTCACACAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCCAGCTGCGG  
ATGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCGGTT  
CGACGACGACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTGC  
ACTATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGTGCGCCCCGACGACAGAAGCTAC  
AAGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTTTCATGGCCTA  
CACCGACGAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACG  
GCGAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTACCCCCAC  
GGCATCACCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCC  
CATCCTGCCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACC  
CCAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGA  
CCTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGCGACAAGCGGAACGT  
GATCCTGTTTCAGCGTGTTCGATGAGAACCGGTCCTGGTATCTGACCGGAAACATCCAGCGGTTTCTGCCCA  
ACCCTGCCGGCGTGACGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGCTAC  
GTGTTGACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGC  
CCAGACCGACTTCCTGAGCGTGTTCCTCAGCGGCTACACCTTCAAGCACAAAGATGGTGTACGAGGACACCC  
TGACCCTGTTCCCTTTTACGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCCTGTGGATTCTGGGC  
TGCCACAACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGCTGCGACAAGAACAC  
CGGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAACAACGCCATCGAAC  
CCCGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCCGGACAACCCTGCAG  
TCCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAGGATTTTCGATATCTA

CGACGAGGACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTTCATTGCCGCCGTGG  
AGAGGCTGTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCCAGAGCGGCAGCGTG  
CCCCAGTTCAAGAAAGTGGTGTTCAGGAATTCACAGACGGCAGCTTCACCCAGCCTCTGTATAGAGGCGA  
GCTGAACGAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAACATCATGGTGACCT  
TCCGGAATCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAGAGGACCAGCGGCAG  
GGCGCCGAACCCCGGAAGAACTTCGTGAAGCCCCAACGAAACCAAGACCTACTTCTGGAAAGTGCAGCACCA  
CATGGCCCCCACCAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTGGATCTGGAAAAGG  
ACGTGCACTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCCTCAACCCCGCCACGGCCGC  
CAGGTGACCGTGCAGGAATTCGCCCTGTTCTTACCATCTTCGACGAGACAAAGTCCTGGTACTTCACCGA  
GAATATGGAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTTCAAAGAGAACTACC  
GGTTCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGATGGCCCAGGACCAGAGAATC  
CGGTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGCGGCCACGTGTTTAC  
CGTGCGGAAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTTCGAGACAGTGGAGA  
TGCTGCCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGCACGCTGGCATGAGC  
ACCCTGTTTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGCCACATCCGGGACTT  
CCAGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCACTACAGCGGCAGCA  
TCAACGCCTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCTATGATCATCCAC  
GGCATTAAGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAG  
CCTGGACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGTGTCTTTCGGCAATG  
TGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCATCATTTGCCCGGTACATCCGGCTGCACCCC  
ACCCACTACAGCATTAGATCCACACTGAGAATGGAAGTGTGGGCTGCGACCTGAACTCCTGCAGCATGCC  
TCTGGGCATGGAAAGCAAGGCCATCAGCGACGCCCAGATCACAGCCAGCAGCTACTTCACCAACATGTTTCG  
CCACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGCGGCCTCAGGTCAAC  
AACCCCAAAGAATGGCTGCAGGTGGACTTTTCAGAAAACCATGAAGGTGACCGGCGTGACCACCCAGGGCGT  
GAAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGATGGCCACCAGTGGA  
CCCTGTTCTTTCAGAACGGCAAGGTGAAAGTGTTCAGGGCAACCAGGACTCCTTCACCCCGTGGTGAAC  
TCCCTGGACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGTCTTGGGTGCACCAGATCGCCCT  
CAGGATGGAAGTCTGGGATGTGAGGCCCAGGATCTGTACTGATGA

SEQ ID NO.19: SV40polyA

ATGCTTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAAGTTA  
ACAACAACAATTGCATTTCATTTTATGTTTCAGGTTTCAGGGGGAGGTGTGGGAGGTTTTTTTAA

SEQ ID NO.20: pAAVss-3xSerpEnh-TTRm-MVM-coFVIIIdeltaB-Synt.pA

CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCCGGGCGTCGGGCGACCTTT  
GGTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACCTCCATCACTAGGGGTTCTTG  
CGGCCGCGGTACGCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAAC  
AGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAA  
ACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGC  
AAACAGGGGCTAAGTCCACTGTACAACGCGTGAATTCGCTAGCGTCTGTCTGCACATTTTCGTAGAGCGAGT  
GTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTA  
AGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGG  
GTATAAAAGCCCCCTTCACCAGGAGAAGCCGTCACACAGATCCACAAGCTCCTGTCTAGAAAGAGGTAAGGG  
TTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTT  
TCAGGTTGGGCTAGCATGCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAG  
CGCCACCCGGCGGTACTACCTGGGCGCCGTGGAGCTGTCTGGGACTACATGCAGAGCGACCTGGGCGAGC  
TGCCCGTGGACGCCCGGTTCCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAG  
AAAACCTGTTCGTGGAGTTCACCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCCTGGATGGGCCT  
GCTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACC  
CCGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACC  
AGCCAGCGGGAGAAAGAAGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAA  
AGAAAACGGCCCCATGGCCTCCGACCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGA  
AGGACCTGAACAGCGGCCTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACC

CAGACCCTGCACAAGTTCATCCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAA  
GAACAGCCTGATGCAGGACCGGGACGCCGCCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCT  
ACGTGAACAGAAGCCTGCCCCGGCCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATG  
GGCACCACACCCGAGGTGCACAGCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCAACCGGCAGGC  
CAGCCTGGAAATCAGCCCTATCACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCTGC  
TGTTTTGCCACATCAGCTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAG  
GAACCCCAGCTGCGGATGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGAT  
GGACGTGGTGCGGTTTCGACGACGACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACC  
CCAAGACCTGGGTGCATATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCCTGGTGCTGGCCCCC  
GACGACAGAAGCTACAAGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGT  
GCGGTTTCATGGCCTACACCGACGAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGG  
GCCCCCTGCTGTACGGCGAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTAC  
AACATCTACCCCCACGGCATCACCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCA  
CCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCC  
CCACCAAGAGCGACCCCAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCC  
TCCGGGCTGATCGGACCTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAG  
CGACAAGCGGAACGTGATCCTGTTTCAGCGTGTTTCGATGAGAACCGGTCTTGGTATCTGACCGAGAACATCC  
AGCGGTTTCTGCCCAACCCTGCCGGCGTGACGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCAC  
TCCATCAATGGCTACGTGTTTCGACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACAT  
CCTGAGCATCGGCGCCCAGACCGACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAGATGG  
TGTACGAGGACACCCTGACCCGTGTTCCCTTTCAGCGGCGAGACAGTGTTCATGAGCATGGAAAACCCCGGC  
CTGTGGATTCTGGGCTGCCACAACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAG  
CTGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGA  
ACAACGCCATCGAACCCCCGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACC  
CGGACAACCCTGCAGTCCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGA  
GGATTTTCGATATCTACGACGAGGACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACT  
TCATTGCCGCCGTGGAGAGGCTGTGGGACTACGGCATGAGTTCTAGCCCCCACGTGCTGCGGAACCGGGCC  
CAGAGCGGCAGCGTGCCCCAGTTCAAGAAAGTGGTGTTCCAGGAATTCACAGACGGCAGCTTCACCCAGCC  
TCTGTATAGAGGCGAGCTGAACGAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACA  
ACATCATGGTGACCTTCCGGAATCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAA  
GAGGACCAGCGGCAGGGCGCCGAACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTG  
GAAAGTGCAGCACCACATGGCCCCCACCAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACG  
TGGATCTGGAAGAGGACGTGCACTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCCTCAAC  
CCCGCCCACGGCCGCCAGGTGACCGTGACGGAATTGCCCCTGTTCTTCACCATCTTCGACGAGACAAAGTC  
CTGGTACTTCACCGAGAATATGGAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCT  
TCAAAGAGAACTACCGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGATGGCC  
CAGGACCAGAGAATCCGGTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAG  
CGGCCACGTGTTACCGTGCGGAAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGT  
TCGAGACAGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTG  
CACGCTGGCATGAGCACCCCTGTTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGG  
CCACATCCGGGACTTCCAGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGC  
ACTACAGCGGCAGCATCAACGCCTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCC  
CCTATGATCATCCACGGCATTAAAGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTT  
CATCATCATGTACAGCCTGGACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCCGGCACCCCTGATGG  
TGTTCTTCGGCAATGTGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCATCATTGCCCGGTAC  
ATCCGGCTGCACCCCAACCACTACAGCATTAGATCCACACTGAGAATGGAAGTGTTCAGGGTGCAGCTGAA  
CTCCTGCAGCATGCCTCTGGGCATGGAAAGCAAGGCCATCAGCGACGCCCAGATCACAGCCAGCAGCTACT  
TCACCAACATGTTTCGCCACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGG  
CGGCCTCAGGTCAACAACCCCAAGAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGT  
GACCACCCAGGGCGTGAAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGG  
ATGGCCACCAGTGGACCCCTGTTCTTTTCAGAACGGCAAGGTGAAAGTGTTCAGGGCAACCAGGACTCCTTC  
ACCCCGTGGTGAACCTCCCTGGACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCAAGTCTTGGGT  
GCACCAGATCGCCCTCAGGATGGAAGTCTTGGGATGTGAGGCCCAGGATCTGTACTGATGAGGATCTAGGC  
TCGACAATAAAAGATCTTTATTTTCATTAGATCTGTGTGTTGGTTTTTTGTGTGCTCGAGATCCACGGCCG  
CAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACC

AAAGGTCGCCCCGACGCCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGG  
 GGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTACACCCGCATACGTCAAAGCAACCAT  
 AGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTT  
 GCCAGCGCCCTAGCGCCCCGCTCCTTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTTCGCCGGCTTTCCCCG  
 TCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCCAAAAAC  
 TTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTTCGCCCTTTGACGTTGGAG  
 TCCACGTTCTTTAATAGTGGACTCTTGTTCCAACTGGAACAACACTCAACCCTATCTCGGGCTATTCTTT  
 TGATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACG  
 CGAATTTTAACAAAAATATTAACGTTTACAATTTTATGGTGCACCTCTCAGTACAATCTGCTCTGATGCCGCA  
 TAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGCTGCTCCCGGCATC  
 CGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTTCACCGTCATCACCGAAAC  
 GCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAG  
 ACGTCAGGTGGCACTTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTTATTTTTCTAAATACATTCAA  
 TATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTA  
 TTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTTCGGGCATTTTGCCTTCCTGTTTTTGTCTACCCAGAA  
 ACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACTGGATCTCAA  
 CAGCGGTAAGATCCTTGAGAGTTTTTCGCCCCGAAGAACGTTTTTCCAATGATGAGCACTTTTAAAGTTCTGC  
 TATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTGCGCGCATACACTATTCTCAG  
 AATGACTTGGTTGAGTACTCACCAGTCCAGAGAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATG  
 CAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGG  
 AGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACCTCGCCTTGATCGTTGGGAACCGGAGCTGAAT  
 GAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACCTATT  
 AACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAG  
 GACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGG  
 TCTCGCGGTATCATTCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGG  
 GAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGT  
 AACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACCTTCATTTTTTAATTTAAAAGGATC  
 TAGGTGAAGATCCTTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTTCGTTCCACTGAGCGTC  
 AGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAA  
 CAAAAAACCACCGCTACCAGCGGTGGTTTGTGTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTA  
 ACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAA  
 GAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATA  
 AGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTTCGGGCTGAACGGGG  
 GGTTTCGTGCACACAGCCCAGCTTGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATG  
 AGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAG  
 AGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTGCGGGTTTCGCCACCTCTGA  
 CTTGAGCGTCGATTTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTT  
 TTTACGGTTCCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT

SEQ ID NO.21: pAAVss-3xSerpEnh-TTRm-coFVIIIdeltaB-Synt.pA

CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCCGGGCGTCGGGCGACCTTT  
 GGTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCTTG  
 CGGCCGCGGTACGCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAAC  
 AGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAA  
 ACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGC  
 AAACAGGGGCTAAGTCCACTGTACAACGCGTGAATTCGCTAGCGTCTGTCTGCACATTTTCGTAGAGCGAGT  
 GTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTGACTA  
 AGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTGGAAGGAGGGG  
 GTATAAAAGCCCCTTCACCAGGAGAAGCCGTCACACAGATCCACAAGCTCCTGCTAGTATGCAGATCGAGC  
 TGTCCACCTGCTTTTTTCTGTGCTGCTGCGGTTCTGCTTCAGCGCCACCCGGCGGTACTACCTGGGCGCC  
 GTGGAGCTGTCCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCCTGGACGCCCGGTTCCCCCCCAG  
 AGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCCTGTTTCGTGGAGTTCACCGACC  
 ACCTGTTCAATATCGCCAAGCCCAGGCCCCCCTGGATGGGCCTGCTGGGCCCCACCATCCAGGCCGAGGTG  
 TACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGCCGTGGGCGTGAG

CTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAAAGAAGATGACAAGG  
TGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGGCCCCATGGCCTCCGACCCC  
CTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGCCTGATCGGCGC  
TCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAGTTCATCCTGCTGT  
TCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCAGGACCGGGACGCC  
GCCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGAAGCCTGCCCCGGCCTGAT  
TGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACACCCGAGGTGCACAGCATCT  
TTCTGGAAGGGCACACCTTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAGCCCTATCACCTTC  
CTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCTGCTGTTTTGCCACATCAGCTCTCACCAGCA  
CGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCCAGCTGCGGATGAAGAACAACG  
AGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCGGTTCGACGACGACAAC  
AGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTGCACTATATCGCCGC  
CGAGGAAGAGGACTGGGACTACGCCCCCCTGGTGCTGGCCCCCGACGACAGAAGCTACAAGAGCCAGTACC  
TGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTTCATGGCCTACACCGACGAGACA  
TTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGCGAAGTGGGCGA  
CACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTACCCCCACGGCATCACCGACG  
TGCGGCCCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTGCCCGGC  
GAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACCCCAGATGCCTGAC  
CCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGACCTCTGCTGATCT  
GCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGCGACAAGCGGAACGTGATCCTGTTTACG  
GTGTTTCGATGAGAACCGGTCCCTGGTATCTGACCGAGAACATCCAGCGGTTTCTGCCCCAACCTGCCGGCGT  
GCAGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGCTACGTGTTTCGACTCTC  
TGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCCAGACCGACTTC  
CTGAGCGTGTTCTTTCAGCGGCTACACCTTCAAGCACAAAGATGGTGTACGAGGACACCCTGACCCTGTTCCC  
TTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCCTGTGGATTCTGGGCTGCCACAACAGCG  
ACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGCTGCGACAAGAACACCGGCGACTACTAC  
GAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAACAACGCCATCGAACCCCGGAGCTTCAG  
CCAGAACCCCCCGTGCTGACGCGTCAACCAGCGGGAGATCACCCGGACAACCCTGCAGTCCGACCAGGAAG  
AGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAGGATTTTCGATATCTACGACGAGGACGAG  
AACCAGAGCCCCAGAAGCTTCAGAAAGAAAACCCGGCACTACTTCATTGCCGCCGTGGAGAGGCTGTGGGA  
CTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCCAGAGCGGCAGCGTGCCCCAGTTCAAGA  
AAGTGGTGTTCAGGAATTCACAGACGGCAGCTTCACCCAGCCTCTGTATAGAGGCGAGCTGAACGAGCAC  
CTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAACATCATGGTGACCTTCCGGAATCAGGC  
CAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAGAGGACCAGCGGCAGGGCGCCGAACCCC  
GGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGGAAAGTGCAGCACCATGCCCCCACC  
AAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTGGATCTGGAAAAGGACGTGCACTCTGG  
ACTGATTGGCCCACTCCTGGTCTGCCACACTAACCCCTCAACCCCGCCACGGCCGCCAGGTGACCGTGC  
AGGAATTCGCCCTGTTCTTCACCATCTTCGACGAGACAAAGTCCTGGTACTTCACCGAGAATATGGAACGG  
AACTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTTCAAAGAGAACTACCGGTTCCACGCCAT  
CAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGTGATGGCCCAGGACCAGAGAATCCGGTGGTATCTGC  
TGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGCGGCCACGTGTTTACCGTGCGGAAGAAA  
GAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTTCGAGACAGTGGAGATGCTGCCCAGCAA  
GGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGCACGCTGGCATGAGCACCTGTTTCTGG  
TGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGCCACATCCGGGACTTCCAGATCACCGCC  
TCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCACTACAGCGGCAGCATCAACGCCTGGTC  
CACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCTATGATCATCCACGGCATTAAGACCC  
AGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTGGACGGCAAG  
AAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGTGTTCCTTCGGCAATGTGGACAGCAGCGG  
CATCAAGCACAAACATCTTCAACCCCCCATCATTTGCCCGGTACATCCGGCTGCACCCCACCCACTACAGCA  
TTAGATCCACACTGAGAATGGAACGTGATGGGCTGCGACCTGAACTCCTGCAGCATGCCTCTGGGCATGGAA  
AGCAAGGCCATCAGCGACGCCAGATCACAGCCAGCAGCTACTTCACCAACATGTTTCGCCACCTGGTCCCC  
CTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGCGGCCTCAGGTCAACAACCCCAAAGAAT  
GGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGTGACCACCCAGGGCGTGAAAAGCCTGCTG  
ACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGATGGCCACCAGTGGACCCTGTTCTTTCA  
GAACGGCAAGGTGAAAGTGTTCCAGGGCAACCAGGACTCCTTCACCCCGTGGTGAACCTCCTGGACCCCC

CCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGTCTTGGGTGCACCAGATCGCCCTCAGGATGGAAGTC  
CTGGGATGTGAGGCCCAGGATCTGTACTGATGAGGATCCAATAAAAGATCTTTATTTTCATTAGATCTGTG  
TGTTGGTTTTTTTGTGTGCTCGAGATCCACGGCCGCAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTC  
TGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCC  
TCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTG  
CGGTATTTTACACCCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGG  
TGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCGCTTTCTTCC  
CTTCCTTTCTCGCCACGTTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGA  
TTTAGTGCTTTACGGCACCTCGACCCCAAAAACTTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCC  
CTGATAGACGGTTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTG  
GAACAACACTCAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGG  
TTAAAAAATGAGCTGATTTAAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTTACAATTTTATG  
GTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTG  
ACGCGCCCTGACGGGCTTGCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGC  
ATGTGTCAGAGGTTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCATTTTTT  
ATAGGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAA  
CCCCATTTTGTTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATG  
CTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGC  
GGCATTTTGCC TTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGG  
GTGCACGAGTGGGTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTTCGCCCCGAAGAA  
CGTTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCA  
AGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGC  
ATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAAACTGCGGCC  
AACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCCTTTTTTGCACAACATGGGGGATCATGT  
AACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATAACCAACGACGAGCGTGACACCACGATGC  
CTGTAGCAATGGCAACAACGTTGCGCAAACTATTAAGTGGCGAACTACTTACTCTAGCTTCCCGGCAACAA  
TTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTT  
TATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGACGCACTGGGGCCAGATGGTA  
AGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATC  
GCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGAT  
TGATTTAAAACTTCATTTTTTAATTTAAAGGATCTAGGTGAAGATCCTTTTTTGATAATCTCATGACCAAAA  
TCCCTTAACGTGAGTTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGAT  
CCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTTGTTGCC  
GGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAAGTGGCTTCAGCAGAGCGCAGATACCAATACTGTCC  
TTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTA  
ATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTT  
ACCGGATAAGGCGCAGCGGTGCGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCT  
ACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGAC  
AGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTA  
TCTTTATAGTCCTGTGCGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGC  
GGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCAC  
ATGT

SEQ ID NO.22: pAAVss-3xSerpEnh-TTRe-TTRm-MVM-coFVIIIdeltaB-Sv40pA

CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCGGGCAAAGCCCGGGCGTCGGGCGACCTTT  
GGTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCCTG  
CGGCCGCGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCT  
AAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGG  
CTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGG  
GGCTAAGTCCACGGTACCCACTGGGAGGATGTTGAGTAAGATGGAAAATACTGATGACCCTTGACAGAGAC  
AGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAGCTCTAGAGGATCCCCGTCTGTCTG  
CACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTT  
ATTCTCCTTTTTGTTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAG  
CCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCTTACCAGGAGAAGCCGTCACACAGATCCACAAGCTCCT

GAAGAGGTAAGGGTTTAAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAAATTACCTGGAGCACCTGCCTG  
AAATCACTTTTTTTCAGGTTGGCTAGTATGCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCG  
GTTCTGCTTTCAGCGCCACCCGGCGGTACTACCTGGGCGCCGTGGAGCTGTCTGGGACTACATGCAGAGCG  
ACCTGGGCGAGCTGCCCCTGGACGCCCCGGTTCCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGC  
GTGGTGTACAAGAAAACCCTGTTCTGTGGAGTTCACCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCC  
CTGGATGGGCCTGCTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCTGAAGAACA  
TGGCCAGCCACCCCGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTAC  
GACGACCAGACCAGCCAGCGGGAGAAAGAAGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTG  
GCAGGTGCTGAAAGAAAACGGCCCCATGGCCTCCGACCCCCCTGTGCCTGACCTACAGCTACCTGAGCCACG  
TGGACCTGGTGAAGGACCTGAACAGCGGCCTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCC  
AAAGAGAAAACCCAGACCCTGCACAAGTTCATCCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCA  
CAGCGAGACAAAGAACAGCCTGATGCAGGACCGGGACGCCGCCTCTGCCAGAGCCTGGCCCCAAGATGCACA  
CCGTGAACGGCTACGTGAACAGAAGCCTGCCCCGGCCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCAC  
GTGATCGGCATGGGCACCACACCCGAGGTGCACAGCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAA  
CCACCGGCAGGCCAGCCTGGAAATCAGCCCTATCACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGG  
GCCAGTTCCTGCTGTTTTGCCACATCAGCTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGAC  
TCTTGCCCCGAGGAACCCAGCTGCGGATGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGAC  
CGACAGCGAGATGGACGTGGTGCGGTTCGACGACGACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGG  
CCAAGAAGCACCCCAAGACCTGGGTGCACTATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCCTG  
GTGCTGGCCCCCGACGACAGAAGCTACAAGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAA  
GTACAAGAAAGTGCGGTTCATGGCCTACACCGACGAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGA  
GCGGCATCCTGGGCCCCCTGCTGTACGGCGAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCT  
AGCCGGCCCTACAACATCTACCCCCACGGCATCACCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAA  
GGGCGTGAAGCACCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCG  
TGGAGGACGGCCCCACCAAGAGCGACCCAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAA  
CGGGACCTGGCCTCCGGGCTGATCGGACCTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAA  
CCAGATCATGAGCGACAAGCGGAACGTGATCCTGTTACGCGTGTTTCGATGAGAACCGGTCCTGGTATCTGA  
CCGAGAACATCCAGCGGTTTTCTGCCCAACCCTGCCGGCGTGACGCTGGAAGATCCCGAGTTCCAGGCCAGC  
AACATCATGCACTCCATCAATGGCTACGTGTTTCGACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGC  
CTACTGGTACATCCTGAGCATCGGCGCCCAGACCGACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCA  
AGCACAAGATGGTGTACGAGGACACCCTGACCCTGTTCCCTTTTCAGCGGCGAGACAGTGTTTCATGAGCATG  
GAAAACCCCGGCCTGTGGATTCTGGGCTGCCACAACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCT  
GAAGGTGTCCAGCTGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACC  
TGCTGTCCAAGAACAAACGCCATCGAACCCCGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAG  
CGGGAGATCACCCGGACAACCCTGCAGTCCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGA  
GATGAAGAAAGAGGATTTTCGATATCTACGACGAGGACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAA  
CCCGGCACTACTTTCATTGCCGCCGTGGAGAGGCTGTGGGACTACGGCATGAGTTCTAGCCCCCACGTGCTG  
CGGAACCGGGCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAAGTGGTGTTCAGGAATTCACAGACGGCAG  
CTTCACCCAGCCTCTGTATAGAGGCGAGCTGAACGAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCG  
AAGTGGAGGACAACATCATGGTGACCTTCCGGAATCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTG  
ATCAGCTACGAAGAGGACCAGCGGCAGGGCGCCGAACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAA  
GACCTACTTCTGGAAAGTGCAGCACCATGGCCCCCACCAGGACGAGTTCGACTGCAAGGCCTGGGCCT  
ACTTCAGCGACGTGGATCTGGAAAAGGACGTGCACTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACT  
AACACCCCTCAACCCCGCCACGGCCGCCAGGTGACCGTGCAGGAATTCGCCCTGTTCTTCACCATCTTCGA  
CGAGACAAAGTCTTGGTACTTCACCGAGAATATGGAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGG  
AAGATCCTACCTTCAAAGAGAACTACCGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGC  
CTGGTGTATGGCCCAGGACCAGAGAATCCGGTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAG  
CATCCACTTCAGCGGCCACGTGTTACCGTGCGGAAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGT  
ACCCCGGCGTGTTTCGAGACAGTGGAGATGCTGCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATC  
GGCGAGCACCTGCACGCTGGCATGAGCACCTGTTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGG  
CATGGCCTCTGGCCACATCCGGGACTTCCAGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGC  
TGGCCAGACTGCACTACAGCGGCAGCATCAACGCCTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTG  
GACCTGCTGGCCCCCTATGATCATCCACGGCATTAAGACCCAGGGCGCCAGGCAGAAAGTTCAGCAGCCTGTA  
CATCAGCCAGTTCATCATCATGTACAGCCTGGACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCG  
GCACCCTGATGGTGTTCCTTCGGCAATGTGGACAGCAGCGGCATCAAGCACAAACATCTTCAACCCCCCATC

ATTGCCCCGGTACATCCGGCTGCACCCCACCCACTACAGCATTAGATCCACACTGAGAATGGAAC TGATGGG  
CTGCGACCTGAACTCCTGCAGCATGCCTCTGGGCATGGAAAGCAAGGCCATCAGCGACGCCCAGATCACAG  
CCAGCAGCTACTTCACCAACATGTTTCGCCACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGG  
TCCAACGCCTGGCGGCCTCAGGTCAACAACCCCAAAGAATGGCTGCAGGTGGACTTTCAGAAAACCATGAA  
GGTGACCGGCGTGACCACCCAGGGCGTGAAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCA  
GCAGCTCTCAGGATGGCCACCAGTGGACCCTGTTCTTTCAGAACGGCAAGGTGAAAGTGTTCCAGGGCAAC  
CAGGACTCCTTCACCCCCGTGGTGAAC TCCCTGGACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCC  
CCAGTCTTGGGTGCACCAGATCGCCCTCAGGATGGAAGTCCCTGGGATGTGAGGCCCAGGATCTGTACTGAT  
GAGGATCTAGGCTCGACATGCTTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTTATAAG  
CTGCAATAAACAAGTTAACAACAACAATTGCATTTCATTTTATGTTTTCAGGTTTCAGGGGGAGGTGTGGGAGG  
TTTTTTAAACTCGAGATCCACGGCCGCAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCT  
CGCTCGCTCACTGAGGCCGGGCGACCAAAGGTGCCCCGACGCCCGGGCTTTGCCCCGGGCGGCCTCAGTGAG  
CGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTT  
CACACCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGG  
TTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCGCTTTCTTCCCTTCCTTT  
CTCGCCACGTTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGC  
TTTACGGCACCTCGACCCCAAAAACTTGATTTGGGTGATGGTTTCAGTAGTGGGCCATCGCCCTGATAGA  
CGGTTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACA  
CTCAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAAAA  
TGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTTACAATTTTATGGTGCCTC  
TCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCC  
TGACGGGCTTGCTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCA  
GAGGTTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTTATAGGTTA  
ATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATT  
TGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATA  
ATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTTCGCGCATTTT  
GCCTTCCTGTTTTTTCGTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGA  
GTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTTCGCCCCGAAGAACGTTTTTC  
AATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAAC  
TCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTACCAGTCAACAGAAAAGCATCTTACG  
GATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAA CACTGCGGCCAACTTACT  
TCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAAC TCGCC  
TTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCA  
ATGGCAACAACGTTGCGCAAACTATTA ACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGA  
CTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTTATTGCTG  
ATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCC  
CGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGAT  
AGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAA  
AACTTCATTTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTTGATAATCTCATGACCAAAATCCCTTAA  
CGTGAGTTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTT  
TCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAG  
AGCTACCAACTCTTTTTCCGAAGGTA ACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTG  
TAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACTCGCTCTGCTAATCCTGTT  
ACCA GTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATA  
AGGCGCAGCGGTTCGGGCTGAACGGGGGGTTCTGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAA  
CTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCC  
GGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATA  
GTCCTGTGCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTA  
TGGA AAAACGCCAGCAACGCGGCCTTTTTACGGTTCTTGGCCTTTTGCTGGCCTTTTGCTCACATGT

SEQ ID NO.23: pAAVss-3xSerpEnh-TTRe-TTRm-coFVIIIdeltaB-Synt.pA

CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCCGGGCGTCGGGCGACCTTT  
GGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCA ACTCCATCACTAGGGGTTCCTG  
CGGCCGCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCT

AAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGG  
CTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGG  
GGCTAAGTCCACGGTACCCACTGGGAGGATGTTGAGTAAGATGGAAAAC TACTGATGACCCTTG CAGAGAC  
AGAGTATTAGGACATGTTTGAACAGGGGGCCGGGCGATCAGCAGGTAGCTCTAGAGGATCCCCGTCTGTCTG  
CACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTT  
ATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAG  
CCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCCTTCACCAGGAGAAGCCGTCACACAGATCCACAAGCTCCT  
GCTAGTATGCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGCGCCACCCG  
GCGGTACTACCTGGGCGCCGTGGAGCTGTCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCCGTGG  
ACGCCCCGTTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCTGT  
TTCGTGGAGTTCACCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCCTGGATGGGCCTGCTGGGCCC  
CACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCCCGTGAGCC  
TGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGG  
GAGAAAGAAGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGG  
CCCCATGGCCTCCGACCCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGA  
ACAGCGGCCTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTG  
CACAAGTTCATCCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCT  
GATGCAGGACCGGGACGCCGCCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACA  
GAAGCCTGCCCGGCCTGATTGGCTGCCACCGGAAGAGCGTG TACTGGCACGTGATCGGCATGGGCACCACA  
CCCGAGGTGCACAGCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGA  
AATCAGCCCTATCACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCTGCTGTTTTGCC  
ACATCAGCTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCCGAG  
CTGCGGATGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGT  
GCGGTTTCGACGACGACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCCCAAGACCT  
GGGTGCACTATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCGACGACAGA  
AGCTACAAGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTTTCAT  
GGCCTACACCGACGAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGC  
TGTACGGCGAAGTG GGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTAC  
CCCCACGGCATCACCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCACCTGAAGGA  
CTTCCCCATCCTGCCCGGCGAGATCTTCAAGTACAAGTG GACCGTGACCGTGGAGGACGGCCCCACCAAGA  
GCGACCCAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTG  
ATCGGACCTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGCGACAAGCG  
GAACGTGATCCTGTTTCAGCGTGTTTCGATGAGAACCGGTCCTGGTATCTGACCGAGAACATCCAGCGGTTTC  
TGCCCAACCCTGCCGGCGTG CAGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACTCCATCAAT  
GGCTACGTGTTTCGACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATCCTGAGCAT  
CGGCGCCCAGACCGACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAAGATGGTGTACGAGG  
ACACCCTGACCCTGTTCCCTTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCCTGTGGATT  
CTGGGCTGCCACAACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGCTGCGACAA  
GAACACCGGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAACACGCCA  
TCGAACCCCGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCCGGACAACC  
CTGCAGTCCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAGGATTTCGA  
TATCTACGACGAGGACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTTCATTGCCG  
CCGTGGAGAGGCTGTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCCAGAGCGGC  
AGCGTGCCCCAGTTCAAGAAAGTGGTGTTCAGGAATTCACAGACGGCAGCTTCACCCAGCCTCTGTATAG  
AGGCGAGCTGAACGAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAACATCATGG  
TGACCTTCCGGAATCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAGAGGACCAG  
CGGCAGGGCGCCGAACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGGAAGTGCA  
GCACCACATGGCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTGGATCTGG  
AAAAGGACGTGCACTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCCTCAACCCCGCCAC  
GGCCGCCAGGTGACCGTGCAGGAATTCGCCCTGTTCTTCACCATCTTCGACGAGACAAAGTCCTGGTACTT  
CACCGAGAATATGGAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTTCAAAGAGA  
ACTACCGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGATGGCCCAGGACCAG  
AGAATCCGGTGGTATCTGCTGTCCATGGGCAGCAACGAGAAATCCACAGCATCCACTTCAGCGGCCACGT  
GTTACACGTGCGGAAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTTCGAGACAG  
TGGAGATGCTGCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGCACGCTGGC

ATGAGCACCCCTGTTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGCCACATCCG  
GGACTTCCAGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCAAGCTGGCCAGACTGCACTACAGCG  
GCAGCATCAACGCCTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCTATGATC  
ATCCACGGCATTAAGACCCAGGGCGCCAGGCAGAAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCAT  
GTACAGCCTGGACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGTGTCTTTCG  
GCAATGTGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCATCATTTGCCCGGTACATCCGGCTG  
CACCCACCCACTACAGCATTAGATCCACACTGAGAATGGAAGTGTGGGCTGCGACCTGAAGTCCCTGCAG  
CATGCCTCTGGGCATGGAAAGCAAGGCCATCAGCGACGCCCAGATCACAGCCAGCAGCTACTTCACCAACA  
TGTTTCGCCACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGCGGCCTCAG  
GTCAACAACCCCAAAGAATGGCTGCAGGTGGACTTTTCAGAAAACCATGAAGGTGACCGGCGTGACCACCCA  
GGGCGTGAAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGATGGCCACC  
AGTGGACCCTGTTCCTTTCAGAACGGCAAGGTGAAAGTGTTCAGGGCAACCAGGACTCCTTCACCCCCGTG  
GTGAACTCCCTGGACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGTCTTGGGTGCACCAGAT  
CGCCCTCAGGATGGAAGTCCTGGGATGTGAGGCCCAGGATCTGTACTGATGAGGATCCAATAAAAGATCTT  
TATTTTCATTAGATCTGTGTGTTGGTTTTTTGTGTGCTCGAGATCCACGGCCGCAGGAACCCCTAGTGATG  
GAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCC  
GGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATT  
TTCTCCTTACGCATCTGTGCGGTATTTTACACCCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCG  
GCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCC  
GCTCCTTTCGCTTTTCTTCCCTTCCTTTCTCGCCACGTTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGG  
GCTCCCTTTAGGGTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAACTTGATTTGGGTGATGGTT  
CACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGT  
GGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTT  
GCCGATTTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAAAT  
TAACGTTTACAATTTTATGGTGCCTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGA  
CACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGT  
GACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTTACCGTTCATCACCGAAACGCGCGAGACGAAAGGGCC  
TCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTTCTTAGACGTCAGGTGGCACTTTT  
CGGGGAAATGTGCGCGGAACCCCTATTTGTTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAG  
ACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTGCG  
CCCTTATTCCCTTTTTTTGCGGCATTTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAA  
GATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGA  
GAGTTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTTAAAGTTCTGCTATGTGGCGCGGTATTAT  
CCCGTATTGACGCCGGGCAAGAGCAACTCGGTGCGCGCATACACTATTCTCAGAATGACTTGGTGAGTAC  
TCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCAT  
GAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGC  
ACAACATGGGGGATCATGTAACCTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGAC  
GAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACCTATTAAGTGGCGAACTACTTAC  
TCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGG  
CCCTTCCGGCTGGCTGGTTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCA  
GCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGA  
TGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAAGTGTGAGACCAAGTTT  
ACTCATATATACTTTAGATTGATTTAAACTTTCATTTTTTAATTTAAAGGATCTAGGTGAAGATCCTTTTT  
GATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGAT  
CAAAGGATCTTCTTGAGATCCTTTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTAC  
CAGCGGTGGTTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTTCCGAAGGTAAGTGGCTTCAGCAGAGCG  
CAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCC  
TACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGT  
TGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTGCGGGCTGAACGGGGGGTTCGTGCACACAGCCC  
AGCTTGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCC  
CGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTC  
CAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTTCGCCACCTCTGACTTGAGCGTCGATTTTTG  
TGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTT  
TTGCTGGCCTTTTGCTCACATGT

SEQ ID NO.24: pAAVss-TTRe-TTRm-coFVIIIdeltaB-Synt.pA

CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCCGGGCGTCGGGCGACCTTT  
GGTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTG  
CGGCCGTACCCACTGGGAGGATGTTGAGTAAGATGGAAAACCTACTGATGACCCTTGCGAGAGACAGAGTATT  
AGGACATGTTTGAACAGGGGGCCGGGCGATCAGCAGGTAGCTCTAGAGGATCCCCGTCTGTCTGCACATTTTC  
GTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTTACTTATTCTCCT  
TTTGTTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTT  
GGAAGGAGGGGGTATAAAAGCCCCCTTACCAGGAGAAGCCGTCACACAGATCCACAAGCTCCTGCTAGTAT  
GCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGCGCCACCCGGCGGTACT  
ACCTGGGCGCCGTGGAGCTGTCCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCCGTGGACGCCCCGG  
TTCCCCCCCCAGAGTGCCCAAGAGCTTCCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCTGTTTCGTGGA  
GTTACCCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCTGGATGGGCCTGCTGGGCCCCACCATCC  
AGGCCGAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGCC  
GTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAAGA  
AGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGGCCCCATGG  
CCTCCGACCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGC  
CTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAGTT  
CATCCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCAGG  
ACCGGGACGCCGCCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGAAGCCTG  
CCCGGCCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACACCCGAGGT  
GCACAGCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAGCC  
CTATCACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCTCTGCTGTTTTGCCACATCAGC  
TCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCCACTGCGGAT  
GAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCGGTTCG  
ACGACGACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTGCAC  
TATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGTCTGGCCCCGACGACAGAAGCTACAA  
GAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTTCATGGCCTACA  
CCGACGAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGC  
GAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTACCCCCACGG  
CATCACCGACGTGCGGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCA  
TCCTGCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACCCC  
AGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGACC  
TCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGCGACAAGCGGAACGTGA  
TCCTGTTTCAGCGTGTTTCGATGAGAACCGGTCTTGGTATCTGACCGAGAACATCCAGCGGTTTCTGCCAAC  
CCTGCCGGCGTGCGAGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGCTACGT  
GTTTCGACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCC  
AGACCGACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAGATGGTGTACGAGGACACCCTG  
ACCCTGTTCCCTTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCCTGTGGATTCTGGGCTG  
CCACAACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGCTGCGACAAGAACACCG  
GCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAACAACGCCATCGAACCC  
CGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCCGGACAACCTGCGAGTC  
CGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAGGATTTTCGATATCTACG  
ACGAGGACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTTCATTGCCGCCGTGGAG  
AGGCTGTGGGACTACGGCATGAGTTCTAGCCCCCACGTGCTGCGGAACCGGGCCCAGAGCGGCAGCGTGCC  
CCAGTTCAAGAAAGTGGTGTTCCAGGAATTCACAGACGGCAGCTTCACCCAGCCTCTGTATAGAGGCGAGC  
TGAACGAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGGCCGAAGTGGAGGACAACATCATGGTGACCTTC  
CGGAATCAGGCCAGCAGACCCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAGAGGACCAGCGGCAGGG  
CGCCGAACCCCGGAAGAAGTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGGAAAGTGCAGCACCA  
TGCCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTGGATCTGGAAAAGGAC  
GTGCACTCTGGACTGATTGGCCCCACTCCTGGTCTGCCACACTAACACCCTCAACCCCGCCCACGGCCGCCA  
GGTGACCGTGCAGGAATTGCCCCGTGTTCTTCACCATCTTCGACGAGACAAAGTCCTGGTACTTCACCGAGA  
ATATGGAACGGAACTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTTCAAAGAGAACTACCGG  
TTCCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGTATGGCCCAGGACCAGAGAATCCG  
GTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGCGGCCACGTGTTACCG

TGCGGAAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTTCGAGACAGTGGAGATG  
CTGCCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGCACGCTGGCATGAGCAC  
CCTGTTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGCCACATCCGGGACTTCC  
AGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCACTACAGCGGCAGCATC  
AACGCCTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCTATGATCATCCACGG  
CATTAAGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCC  
TGGACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGTGTTCCTTCGGCAATGTG  
GACAGCAGCGGCATCAAGCACAAACATCTTCAACCCCCCATCATTGCCCGGTACATCCGGCTGCACCCAC  
CCACTACAGCATTAGATCCACACTGAGAATGGAAGTGTGGGCTGCGACCTGAACTCCTGCAGCATGCCTC  
TGGGCATGGAAAGCAAGGCCATCAGCGACGCCCAGATCACAGCCAGCAGCTACTTCACCAACATGTTTCGCC  
ACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGCGGCCTCAGGTCAACAA  
CCCCAAAGAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGTGACCACCCAGGGCGTGA  
AAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGATGGCCACCAGTGGACC  
CTGTTCTTTTCAGAACGGCAAGGTGAAAGTGTTCAGGGCAACCAGGACTCCTTCACCCCCGTGGTGAAGTC  
CCTGGACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGTCTTGGGTGCACCAGATCGCCCTCA  
GGATGGAAGTCCTGGGATGTGAGGCCCAGGATCTGTACTGATGAGGATCCAATAAAAGATCTTTATTTTCA  
TTAGATCTGTGTGTTGGTTTTTGTGTGCTCGAGATCCACGGCCGCAGGAACCCCTAGTGATGGAGTTGGC  
CACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTG  
CCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTT  
ACGCATCTGTGCGGTATTTACACCCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATT  
AGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTT  
CGCTTTCTTCCCTTCCTTTCTCGCCACGTTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTT  
TAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCCAAAAACTTGATTTGGGTGATGGTTCACGTAGT  
GGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTT  
GTTCCAAACTGGAACAACACTCAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTT  
CGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAAATATTAACGTTT  
ACAATTTTATGGTGCACCTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCC  
AACACCCGCTGACGCGCCCTGACGGGCTTGCTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCT  
CCGGGAGCTGCATGTGTCAGAGGTTTTACCGTTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATA  
CGCCTATTTTTATAGGTAAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAA  
TGTGCGCGGAACCCCTATTTGTTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAAC  
CCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATT  
CCCTTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAGATGCTGA  
AGATCAGTTGGGTGCACGAGTGGGTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTTC  
GCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATT  
GACGCCGGGCAAGAGCAACTCGGTGCGCGCATACTATTTCTCAGAATGACTTGGTGAGTACTCACCAGT  
CACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATA  
ACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTTGCACAACATG  
GGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATAACCAAACGACGAGCGTGA  
CACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACCTATTAAGTGGCGAACTACTTACTCTAGCTT  
CCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCCTTCTGCGCTCGGCCCTTCCG  
GCTGGCTGGTTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGG  
GCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAA  
ATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAAGTGTGAGACCAAGTTTACTCATAT  
ATACTTTAGATTGATTTAAACTTTCATTTTTTAATTTAAAGGATCTAGGTGAAGATCCTTTTTTGATAATCT  
CATGACCAAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGAT  
CTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTG  
GTTTGTGTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAAGTGGCTTCAGCAGAGCGCAGATACC  
AAATACTGTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACC  
TCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCA  
AGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTTCGTGCACACAGCCCAGCTTGGA  
GCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGA  
GAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGA  
AACGCCTGGTATCTTTATAGTCCTGTGCGGTTTTCGCCACCTCTGACTTGAGCGTCGATTTTTTGTGATGCTC

GTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGC  
CTTTTGCTCACATGT

SEQ ID NO.38: **Flank-3xSERP-Flank**

**GCGGCCGCGGTACGC**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
CAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
CAACAGGGGCTAAGTCCAC**GGTACC**

SEQ ID NO.39: **Flank-3xSERP-Flank-TTRe**

**GCGGCCGCGGTACGC**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
CAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
CAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAA**ACTACTGATGACCCTT**  
GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAG

SEQ ID NO.40: **Flank-3xSERP-Flank-TTRe-Flank**

**GCGGCCGCGGTACGC**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
CAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
CAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAA**ACTACTGATGACCCTT**  
GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAG**CTCTAGAGGATCCCC**

SEQ ID NO.41: **Flank-3xSERP-Flank-TTRe-Flank-TTRm**

**GCGGCCGCGGTACGC**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
CAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
CAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAA**ACTACTGATGACCCTT**  
GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAG**CTCTAGAGGATCCCCG**  
TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTA  
GGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGG  
ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCTTCACCAGGAGAAGCCGTC

SEQ ID NO.42: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank**

**GCGGCCGCGGTACGC**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
CAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
CAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAA**ACTACTGATGACCCTT**  
GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAG**CTCTAGAGGATCCCCG**  
TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTA  
GGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGG  
ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCTTCACCAGGAGAAGCCGTC**CTAGT**

SEQ ID NO.43: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-coFVIIIdeltaB**

**GCGGCCGCGGTACGC**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
CAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
CAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAA**ACTACTGATGACCCTT**  
GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAG**CTCTAGAGGATCCCCG**  
TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTA

GGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGG  
ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCCTTCACCAGGAGAAGCCGTCC**CTAGTATGCAGA**  
**TCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGCGCCACCCGGCGGTACTACCTG**  
**GGCGCCGTGGAGCTGTCTTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCGTGGACGCCCGGTTCCC**  
**CCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCCTGTTCTGTGGAGTTCA**  
**CCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCCCTGGATGGGCCTGCTGGGCCCCACCATCCAGGCC**  
**GAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGCCGTGGG**  
**CGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAAGAAGATG**  
**ACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGGCCCCATGGCCTCC**  
**GACCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGCCTGAT**  
**CGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAGTTCATCC**  
**TGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCAGGACCGG**  
**GACGCCGCCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGAAGCCTGCCCGG**  
**CCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACACCCGAGGTGCACA**  
**GCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAGCCCTATC**  
**ACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCTGCTGTTTTGCCACATCAGCTCTCA**  
**CCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCAGCTGCGGATGAAGA**  
**ACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCGGTTCGACGAC**  
**GACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTGCACTATAT**  
**CGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCGACGACAGAAGCTACAAGAGCC**  
**AGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTTTCATGGCCTACACCGAC**  
**GAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGCGAAGT**  
**GGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTACCCCCACGGCATCA**  
**CCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTG**  
**CCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACCCAGATG**  
**CCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGACCTCTGC**  
**TGATCTGCTACAAAGAAAGCGTGGACCAGCGGGCAACCAGATCATGAGCGACAAGCGGAACGTGATCCTG**  
**TTCAGCGTGTTTCGATGAGAACCGGTCTGGTATCTGACCGAGAACATCCAGCGGTTTCTGCCCAACCCTGC**  
**CGGCGTGACGTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGCTACGTGTTTCG**  
**ACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCCAGACC**  
**GACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAGATGGTGTACGAGGACACCCTGACCCCT**  
**GTTCCCTTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCCTGTGGATTCTGGGCTGCCACA**  
**ACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGCTGCGACAAGAACACCGGCGAC**  
**TACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAACAACGCCATCGAACCCCGGAG**  
**CTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCCGGACAACCCTGCAGTCCGACC**  
**AGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAGGATTTTCGATATCTACGACGAG**  
**GACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTTCATTGCCGCCGTGGAGAGGCT**  
**GTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCCAGAGCGGCAGCGTGCCCCAGT**  
**TCAAGAAAGTGGTGTTCCAGGAATTCACAGACGGCAGCTTCACCCAGCCTCTGTATAGAGGCGAGCTGAAC**  
**GAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAACATCATGGTGACCTTCCGGAA**  
**TCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAGAGGACCAGCGGCAGGGCGCCG**  
**AACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGGAAAGTGCAGCACCATGGCC**  
**CCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTGGATCTGGAAAAGGACGTGCA**  
**CTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCTCAACCCCGCCACGGCCGCCAGGTGA**  
**CCGTGCAGGAATTCGCCCTGTTCTTCACCATCTTCGACGAGACAAAGTCCTGGTACTTCACCGAGAATATG**  
**GAACGGAACCTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTTCAAAGAGAACTACCGGTTCCA**  
**CGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGTATGGCCCAGGACCAGAGAATCCGGTGGT**  
**ATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGCGGCCACGTGTTACCGTGCGG**  
**AAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTTCGAGACAGTGGAGATGCTGCC**  
**CAGCAAGGCCCGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGCACGCTGGCATGAGCACCCCTGT**  
**TTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGCCACATCCGGGACTTCCAGATC**  
**ACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCACTACAGCGGCAGCATCAACGC**  
**CTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCTATGATCATCCACGGCATT**  
**AGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTGGAC**  
**GGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGTGTTCCTTCGGCAATGTGGACAG**

CAGCGGCATCAAGCACAACATCTTCAACCCCCCATCATTTGCCCGGTACATCCGGCTGCACCCCACCCACT  
ACAGCATTAGATCCACACTGAGAATGGAAGTGAATGGGCTGCGACCTGAACTCCTGCAGCATGCCTCTGGGC  
ATGGAAAGCAAGGCCATCAGCGACGCCCAGATCACAGCCAGCAGCTACTTCACCAACATGTTTCGCCACCTG  
GTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGCGGCCTCAGGTCAACAACCCCA  
AAGAATGGCTGCAGGTGGACTTTTCAGAAAACCATGAAGGTGACCGGCGTGACCACCCAGGGCGTGAAAAGC  
CTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGATGGCCACCAGTGGACCCTGTT  
CTTTCAGAACGGCAAGGTGAAAGTGTTCCAGGGCAACCAGGACTCCTTCACCCCCGTGGTGAAGTCCCTGG  
ACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGTCTTGGGTGCACCAGATCGCCCTCAGGATG  
GAAGTCCTGGGATGTGAGGCCAGGATCTGTACTGATGA

SEQ ID NO.44: **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-**Flank**-coFVIIIdeltaB-**Flank**

GCGGCCGCGGTACGCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
CAGGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
AACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
CAAACAGGGGCTAAGTCCACGGTACCCACTGGGAGGATGGAAAACTACTGATGACCCT  
GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGCGGATCAGCAGGTAGCTCTAGAGGATCCCCG  
TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTCATATTTGTGTA  
GGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGG  
ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCTTACCAGGAGAAGCCGTCTAGTATGCAGA  
TCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGCGCCACCCGGCGGTACTACCTG  
GGCGCCGTGGAGCTGTCCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCGTGACGCCCCGTTCCC  
CCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCCTGTTTCGTGGAGTTCA  
CCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCTGGATGGGCCTGCTGGGCCCCACCATCCAGGCC  
GAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGCCGTGGG  
CGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAAGAAGATG  
ACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGGCCCCATGGCCTCC  
GACCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGCCTGAT  
CGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAGTTCATCC  
TGCTGTTGCGCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCAGGACCGG  
GACGCCGCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGAAGCCTGCCCGG  
CCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGGCACCCGAGGTGCA  
GCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAGCCCTATC  
ACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCTGCTGTTTTTGCCACATCAGCTCTCA  
CCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCAGCTGCGGATGAAGA  
ACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCGGTTCGACGAC  
GACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTGCACTATAT  
CGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCGACGACAGAAGCTACAAGAGCC  
AGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTTTCATGGCCTACACCGAC  
GAGACATTCAAGACCCGGAGGCCATCCAGCAGAGCGGCATCCTGGGCCCCTGCTGTACGGCGAAGT  
GGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTACCCCCACGGCATCA  
CCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTG  
CCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACCCCAGATG  
CCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGACCTCTGC  
TGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGCGACAAGCGGAACGTGATCCTG  
TTCAGCGTGTTTCGATGAGAACCGGTCCTGGTATCTGACCGAGAACATCCAGCGGTTTCTGCCCAACCCTGC  
CGGCGTGACGTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGCTACGTGTTTCG  
ACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCCAGACC  
GACTTCCTGAGCGTGTTCTTTCAGCGGCTACACCTTCAAGCACAAAGATGGTGTACGAGGACACCCTGACCCT  
GTTCCCTTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCCTGTGGATTCTGGGCTGCCACA  
ACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGCTGCGACAAGAACACCGGCGAC  
TACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAAACAACGCCATCGAACCCCGGAG  
CTTCAGCCAGAACCCCCCGTGCTGACGCGTACCAGCGGGAGATCACCCGGACAACCCTGCAGTCCGACC  
AGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAGGATTTTCGATATCTACGACGAG

GACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGGCACTACTTCATTGCCGCCGTGGAGAGGCT  
 GTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCCAGAGCGGCAGCGTGCCCCAGT  
 TCAAGAAAGTGGTGTTCCAGGAATTCACAGACGGCAGCTTCACCCAGCCTCTGTATAGAGGCGAGCTGAAC  
 GAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAACATCATGGTGACCTTCCGGAA  
 TCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAGAGGACCAGCGGCAGGGCGCCG  
 AACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGGAAAGTGCAGCACCACATGGCC  
 CCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTGGATCTGGAAAAGGACGTGCA  
 CTCTGGACTGATTGGCCCCACTCCTGGTCTGCCACACTAACACCCTCAACCCCGCCACGGCCGCCAGGTGA  
 CCGTGCGAGGAATTCGCCCTGTTCTTACCATCTTCGACGAGACAAAGTCCTGGTACTTCACCGAGAATATG  
 GAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTTCAAAGAGAACTACCGGTTCCA  
 CGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGATGGCCCAGGACCAGAGAATCCGGTGGT  
 ATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGCGGCCACGTGTTACCGTGCGG  
 AAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTTCGAGACAGTGGAGATGCTGCC  
 CAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGCACGCTGGCATGAGCACCCCTGT  
 TTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGCCACATCCGGGACTTCCAGATC  
 ACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCACTACAGCGGCAGCATCAACGC  
 CTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCTATGATCATCCACGGCATT  
 AGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTGGAC  
 GGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGTGTTCTTCGGCAATGTGGACAG  
 CAGCGGCATCAAGCACAACATCTTCAACCCCCCATCATTGCCCGGTACATCCGGCTGCACCCACCCACT  
 ACAGCATTAGATCCACACTGAGAAATGGAAGTATGGGCTGCGACCTGAACTCCTGCAGCATGCCTCTGGGC  
 ATGGAAAGCAAGGCCATCAGCGACGCCAGATCACAGCCAGCAGCTACTTCACCAACATGTTTCGCCACCTG  
 GTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGCGGCCTCAGGTCAACAACCCCA  
 AAGAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGTGACCACCCAGGGCGTGAAAGC  
 CTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGATGGCCACCAGTGGACCCTGTT  
 CTTTCAGAACGGCAAGGTGAAAGTGTTCAGGGCAACCAGGACTCCTTCACCCCCGTGGTGAAGTCCCTGG  
 ACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGTCTTGGGTGCACCAGATCGCCCTCAGGATG  
 GAAGTCCTGGGATGTGAGGCCAGGATCTGTACTGATGAGGATCC

SEQ ID NO.45: **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-**Flank**-coFVIIIdeltaB-**Flank**-SV40pA

GCGGCCGCGGTACGC GGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
 CAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
 AACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
 CAAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAAACCTACTGATGACCTT  
 GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGGCCGGGCGATCAGCAGGTAG**CTCTAGAGGATCCCCG**  
 TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTA  
 GGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGAGTTCAGCTTGGCAGGG  
 ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCTTCACCAGGAGAAGCCGT**CCTAGTATGCAGA**  
**TCGAGCTGTCCACCTGCTTTTTTCTGTGCTGCTGCGGTTCTGCTTCAGCGCCACCCGGCGGTACTACCTG**  
**GGCGCCGTGGAGCTGTCTTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCGTGGACGCCCGGTTCCC**  
**CCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCCTGTTCTGTGGAGTTCA**  
**CCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCTGGATGGGCCTGCTGGGCCCCACCATCCAGGCC**  
**GAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGCCGTGGG**  
**CGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAAGAAGATG**  
**ACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGGCCCCATGGCCTCC**  
**GACCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGCCTGAT**  
**CGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAGTTCATCC**  
**TGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCAGGACCGG**  
**GACGCCGCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGAAGCCTGCCCGG**  
**CCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACACCCGAGGTGCACA**  
**GCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAGCCCTATC**  
**ACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCTGCTGTTTTGCCACATCAGCTCTCA**  
**CCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCAGCTGCGGATGAAGA**

ACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCGGTTCGACGAC  
 GACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTGCACTATAT  
 CGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCGACGACAGAAGCTACAAGAGCC  
 AGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTTCATGGCCTACACCGAC  
 GAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGCGAAGT  
 GGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTACCCCCACGGCATCA  
 CCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTG  
 CCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGAGGACGGCCCCACCAAGAGCGACCCCAGATG  
 CCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGACCTCTGC  
 TGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGCGACAAGCGGAACGTGATCCTG  
 TTCAGCGTGTTGATGAGAACCGGTCCTGGTATCTGACCGAGAACATCCAGCGGTTTCTGCCAACCCTGC  
 CGGCGTGACGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGCTACGTGTTG  
 ACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCCAGACC  
 GACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAGATGGTGTACGAGGACACCCTGACCCT  
 GTTCCCTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCCCTGTGGATTCTGGGCTGCCACA  
 ACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGCTGCGACAAGAACACCGGCGAC  
 TACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAACAACGCCATCGAACCCCGGAG  
 CTTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCCGGACAACCCTGCAGTCCGACC  
 AGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAGGATTTTCGATATCTACGACGAG  
 GACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTTCATTGCCGCCGTGGAGAGGCT  
 GTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCCAGAGCGGCAGCGTGCCCCAGT  
 TCAAGAAAGTGGTGTTCCAGGAATTCACAGACGGCAGCTTCACCCAGCCTCTGTATAGAGGCGAGCTGAAC  
 GAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAACATCATGGTGACCTTCCGGAA  
 TCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAGAGGACCAGCGGCAGGGCGCCG  
 AACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGGAAAGTGCAGCACCATGGCC  
 CCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTGGATCTGGAAAAGGACGTGCA  
 CTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCCTCAACCCCGCCACGGCCGCCAGGTGA  
 CCGTGACAGGAATTCGCCCTGTTCTTACCATCTTCGACGAGACAAAGTCCTGGTACTTCACCGAGAATATG  
 GAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTTCAAAGAGAACTACCGGTTCCA  
 CGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGATGGCCCAGGACCAGAGAATCCGGTGGT  
 ATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGCGGCCACGTGTTACCGTGCGG  
 AAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCGGCGTGTTTCGAGACAGTGGAGATGCTGCC  
 CAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGCACGCTGGCATGAGCACCCCTGT  
 TTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGCCACATCCGGGACTTCCAGATC  
 ACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCACTACAGCGGCAGCATCAACGC  
 CTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCTATGATCATCCACGGCATT  
 AGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTGGAC  
 GGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGTGTTCTTCGGCAATGTGGACAG  
 CAGCGGCATCAAGCACAACATCTTCAACCCCCCATCATTGCCCGGTACATCCGGCTGCACCCACCCACT  
 ACAGCATTAGATCCACACTGAGAATGGAAGTGAATGGGCTGCGACCTGAACTCCTGCAGCATGCCTCTGGGC  
 ATGGAAAGCAAGGCCATCAGCGACGCCAGATCACAGCCAGCAGCTACTTCACCAACATGTTTCGCCACCTG  
 GTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGCGGCCTCAGGTCAACAACCCCA  
 AAGAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGTGACCACCCAGGGCGTGAAAAGC  
 CTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGATGGCCACCAGTGGACCCTGTT  
 CTTTCAGAACGGCAAGGTGAAAGTGTTCCAGGGCAACCAGGACTCCTTCACCCCGTGTTGAACTCCCTGG  
 ACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCAAGTCTTGGGTGCACCAGATCGCCCTCAGGATG  
 GAAGTCCTGGGATGTGAGGCCAGGATCTGTACTGATGAGGATCCATGCTTTATTTGTGAAATTTGTGATG  
 CTATTGCTTTATTTGTAACCATTTATAAGCTGCAATAAACAAGTTAACAACAACAATTGCATTTCATTTTATG  
 TTTCAGGTTTCAGGGGGAGGTGTGGGAGGTTTTTTTAA

SEQ ID NO.46: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-coFVIIIdeltaB-  
 Flank-SV40pA-Flank**

GCGGCCGCGGTACGCGGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAAGTTATCGGAGGAGCAAA  
 CAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAAGTTATCGGAGGAGCA

AACAGGGGCTAAGTCCAC**CGGGGG**GAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
CAAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAA**ACTACTGATGACCCTT**  
GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCGGGCGATCAGCAGGTAG**CTCTAGAGGATCCCCG**  
TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTA  
GGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGG  
ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCTTCACCAGGAGAAGCCGT**CCTAGTATGCAGA**  
**TCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGCGCCACCCGGCGGTACTACCTG**  
**GGCGCCGTGGAGCTGTCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCCGTGGACGCCCGGTTCCC**  
**CCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCCTGTTTCGTGGAGTTCA**  
**CCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCCCTGGATGGGCCTGCTGGGCCCCACCATCCAGGCC**  
**GAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGCCGTGGG**  
**CGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAAGAAGATG**  
**ACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGGCCCCATGGCCTCC**  
**GACCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGCCTGAT**  
**CGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAGTTCATCC**  
**TGCTGTTGCGCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCAGGACCGG**  
**GACGCCGCCTCTGCCAGAGCCTGGCCCCAAGATGCACACCGTGAACGGCTACGTGAACAGAAGCCTGCCCCG**  
**CCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACACCCGAGGTGCACA**  
**GCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAGCCCTATC**  
**ACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCTGCTGTTTTGCCACATCAGCTCTCA**  
**CCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCAGCTGCGGATGAAGA**  
**ACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCGGTTTCGACGAC**  
**GACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTGCACTATAT**  
**CGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCGACGACAGAAGCTACAAGAGCC**  
**AGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTTTCATGGCCTACACCGAC**  
**GAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGCGAAGT**  
**GGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTACCCCCACGGCATCA**  
**CCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTG**  
**CCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACCCCAGATG**  
**CCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGACCTCTGC**  
**TGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGCGACAAGCGGAACGTGATCCTG**  
**TTCAGCGTGTTTCGATGAGAACCGGTCCTGGTATCTGACCGAGAACATCCAGCGGTTTCTGCCCAACCCTGC**  
**CGGCGTGACGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGCTACGTGTTGC**  
**ACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCCAGACC**  
**GACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAAGATGGTGTACGAGGACACCCTGACCCT**  
**GTTCCCTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCTGTGGATTCTGGGCTGCCACA**  
**ACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGCTGCGACAAGAACACCGGCGAC**  
**TACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAACAACGCCATCGAACCCCGGAG**  
**CTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCCGGACAACCCTGCAGTCCGACC**  
**AGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAGGATTTTCGATATCTACGACGAG**  
**GACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTTCATTGCCGCCGTGGAGAGGCT**  
**GTGGGACTACGGCATGAGTTCTAGCCCCCACGTGCTGCGGAACCGGGCCCAGAGCGGCAGCGTGCCCCAGT**  
**TCAAGAAAGTGGTGTTCCAGGAATTCACAGACGGCAGCTTCACCCAGCCTCTGTATAGAGGCGAGCTGAAC**  
**GAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAACATCATGGTGACCTTCCGGAA**  
**TCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAGAGGACCAGCGGCAGGGCGCCG**  
**AACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGGAAAGTGCAGCACCATG GCC**  
**CCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTGGATCTGGAAAAGGACGTGCA**  
**CTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCCTCAACCCCGCCACGGCCGCCAGGTGA**  
**CCGTGCAGGAATTCGCCCTGTTCCTTACCATCTTCGACGAGACAAAGTCCTGGTACTTCACCGAGAATATG**  
**GAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTTCAAAGAGAACTACCGGTTCCA**  
**CGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGATGGCCCAGGACCAGAGAATCCGGTGGT**  
**ATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGCGGCCACGTGTTACCGTGCGG**  
**AAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTTCGAGACAGTGGAGATGCTGCC**  
**CAGCAAGGCCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGCACGCTGGCATGAGCACCCCTGT**  
**TTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGCCACATCCGGGACTTCCAGATC**

ACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCACTACAGCGGCAGCATCAACGC  
CTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCTATGATCATCCACGGCATT  
AGACCCAGGGCGCCAGGCAGAAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTGGAC  
GGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCCTGATGGTGTTCTTCGGCAATGTGGACAG  
CAGCGGCATCAAGCACAAACATCTTCAACCCCCCATCATTGCCCCGGTACATCCGGCTGCACCCACCCACT  
ACAGCATTAGATCCACACTGAGAATGGAAC TGATGGGCTGCGACCTGAACTCCTGCAGCATGCCTCTGGGC  
ATGGAAGCAAGGCCATCAGCGACGCCAGATCACAGCCAGCAGCTACTTCACCAACATGTTGCGCACCTG  
GTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGCGGCCTCAGGTCAACAACCCCA  
AAGAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGTGACCACCCAGGGCGTGAAAAGC  
CTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGATGGCCACCAGTGGACCCTGTT  
CTTTCAGAACGGCAAGGTGAAAGTGTTCCAGGGCAACCAGGACTCCTTCACCCCCGTGGTGAAC TCCCTGG  
ACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGTCTTGGGTGCACCAGATCGCCCTCAGGATG  
GAAGTCCTGGGATGTGAGGCCCAGGATCTGTACTGATGAGGATCCATGCTTTATTTGTGAAATTTGTGATG  
 CTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAAGTTAACAACAACAATTGCATT CATTTTATG  
 TTTCAGGTT CAGGGGGAGGTGTGGGAGGTTTTTTAAACTCGAGATCCACGGCCGC

SEQ ID NO.47: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-coFVIIIdeltaB-**  
**Flank-Synt.pA**

GCGGCCGCGGTACGCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
 CAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
 AACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
 CAAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAAAC TACTGATGACCCTT  
 GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCGGGCGATCAGCAGGTAG**CTCTAGAGGATCCCCG**  
 TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTCATATTTGTGTA  
 GGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGG  
 ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCCTTCACCAGGAGAAGCCGT**CTAGTATGCAGA**  
**TCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGCGCCACCCGGCGGTACTACCTG**  
**GGCGCCGTGGAGCTGTCCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCGTGGACGCCCGGTTCCC**  
**CCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCCTGTTTCGTGGAGTTCA**  
**CCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCCCTGGATGGGCCTGCTGGGCCCCACCATCCAGGCC**  
**GAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGCCGTGGG**  
**CGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAAGAAGATG**  
**ACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGGCCCCATGGCCTCC**  
**GACCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGCCTGAT**  
**CGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAGTTCATCC**  
**TGCTGTTGCGCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCAGGACCGG**  
**GACGCCGCCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGAAGCCTGCCCGG**  
**CCTGATTGGCTGCCACCGGAAGAGCGTG TACTGGCACGTGATCGGCATGGGCACCACACCCGAGGTGCACA**  
**GCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAGCCCTATC**  
**ACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCTGCTGTTTTTGCCACATCAGCTCTCA**  
**CCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCAGCTGCGGATGAAGA**  
**ACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCGGTTCGACGAC**  
**GACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTGCACTATAT**  
**CGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCGACGACAGAAGCTACAAGAGCC**  
**AGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTT CATGGCCTACACCGAC**  
**GAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGCGAAGT**  
**GGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTACCCCCACGGCATCA**  
**CCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTG**  
**CCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACCCAGATG**  
**CCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGACCTCTGC**  
**TGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGCGACAAGCGGAACGTGATCCTG**  
**TTCAGCGTGTTTCGATGAGAACCGGTCTGGTATCTGACCGAGAACATCCAGCGGTTTTCTGCCCAACCCTGC**  
**CGGCGTGAGCTGGAAGATCCCAGATTCCAGGCCAGCAACATCATGCACTCCATCAATGGCTACGTGTTTCG**  
**ACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCCAGACC**

GACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAAGATGGTGTACGAGGACACCCTGACCCT  
 GTTCCCTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCTGTGGATTCTGGGCTGCCACA  
 ACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGCTGCGACAAGAACACCGGCGAC  
 TACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAACAACGCCATCGAACCCCGGAG  
 CTTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCCGGACAACCCTGCAGTCCGACC  
 AGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAGGATTTTCGATATCTACGACGAG  
 GACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTTCATTGCCGCCGTGGAGAGGCT  
 GTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCCAGAGCGGCAGCGTGCCCCAGT  
 TCAAGAAAGTGGTGTTCAGGAATTCACAGACGGCAGCTTCACCCAGCCTCTGTATAGAGGCGAGCTGAAC  
 GAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAACATCATGGTGACCTTCCGGAA  
 TCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAGAGGACCAGCGGCAGGGCGCCG  
 AACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGGAAAGTGCAGCACCACATGGCC  
 CCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTGGATCTGGAAAAGGACGTGCA  
 CTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCCTCAACCCCGCCACGGCCGCCAGGTGA  
 CCGTGCGAGGAATTCGCCCTGTTCTTCACCATCTTCGACGAGACAAAGTCTGGTACTTCACCGAGAATATG  
 GAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTTCAAAGAGAACTACCGGTTCCA  
 CGCCATCAACGGCTACATCATGGACACCCTGCCTGGCTGGTGTATGGCCCAGGACCAGAGAATCCGGTGGT  
 ATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGCGGCCACGTGTTACCGTGCGG  
 AAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTTCGAGACAGTGGAGATGCTGCC  
 CAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGCACGCTGGCATGAGCACCTGT  
 TTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGCCACATCCGGGACTTCCAGATC  
 ACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCACTACAGCGGCAGCATCAACGC  
 CTGGTCCACCAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCTATGATCATCCACGGCATT  
 AGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTGGAC  
 GGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGTGTTCCTTCGGCAATGTGGACAG  
 CAGCGGCATCAAGCACAAACATCTTCAACCCCCCATCATTTGCCCGGTACATCCGGCTGCACCCCACT  
 ACAGCATTAGATCCACACTGAGAATGGAAGTGTGGCTGCGACCTGAACTCCTGCAGCATGCCTCTGGGC  
 ATGGAAAGCAAGGCCATCAGCGACGCCAGATCACAGCCAGCAGCTACTTCACCAACATGTTTCGCCACCTG  
 GTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGCGGCCTCAGGTCAACAACCCCA  
 AAGAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGTGACCACCCAGGGCGTGAAAAGC  
 CTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGATGGCCACCAGTGGACCCTGTT  
 CTTTCAGAACGGCAAGGTGAAAGTGTTCCAGGGCAACCAGGACTCCTTCACCCCGTGTTGAACTCCCTGG  
 ACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCAAGTCTTGGGTGCACCAGATCGCCCTCAGGATG  
 GAAGTCCTGGGATGTGAGGCCAGGATCTGTACTGATGAGGATCCAATAAAAGATCTTTATTTTCATTAGA  
 TCTGTGTGTTGGTTTTTTGTGTG

SEQ ID NO.48: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-coFVIIIdeltaB-  
 Flank-SyntpA-Flank**

GCGGCCGCGGTACGCGGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAAGTTATCGGAGGAGCAAA  
 CAGGGGCTAAGTCCACCGGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAAGTTATCGGAGGAGCA  
 AACAGGGGCTAAGTCCACCGGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAAGTTATCGGAGGAG  
 CAAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAAAC**TA**CTGATGACCCTT  
 GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCGGGCGATCAGCAGG**TAGCTCTAGAGGATCCCCG**  
 TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTA  
 GGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGAGTCACTTGGCAGGG  
 ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCTTCACCAGGAGAAGCCGT**C**TAGTATGCAGA  
**TCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGCGCCACCCGGCGGTACTACCTG**  
**GGCGCCGTGGAGCTGTCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCCTGGACGCCCGGTTCCC**  
**CCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCCTGTTTCGTGGAGTTCA**  
**CCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCTGGATGGGCCTGCTGGGCCCCACCATCCAGGCC**  
**GAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGCCGTGGG**  
**CGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAAGAAGATG**  
**ACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGGCCCCATGGCCTCC**  
**GACCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGCCTGAT**

CGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAGTTCATCC  
TGCTGTTCCGCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCAGGACCGG  
GACGCCGCCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGAAGCCTGCCCCG  
CCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACACCCGAGGTGCACA  
GCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAGCCCTATC  
ACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCTGCTGTTTTGCCACATCAGCTCTCA  
CCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCAGCTGCGGATGAAGA  
ACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCGGTTCGACGAC  
GACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTGCACTATAT  
CGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCGACGACAGAAGCTACAAGAGCC  
AGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTTTCATGGCCTACACCGAC  
GAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGCGAAGT  
GGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTACCCCCACGGCATCA  
CCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTG  
CCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACCCCAGATG  
CCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGACCTCTGC  
TGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGCGACAAGCGGAACGTGATCCTG  
TTCAGCGTGTTTCGATGAGAACCGGTCTTGGTATCTGACCGAGAACATCCAGCGGTTTTCTGCCCAACCCTGC  
CGGCGTGACGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGCTACGTGTTTCG  
ACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCCAGACC  
GACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAAGATGGTGACGAGGACACCCTGACCCT  
GTTCCCTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCCTGTGGATTCTGGGCTGCCACA  
ACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGCTGCGACAAGAACACCGGCGAC  
TACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAACAACGCCATCGAACCCCGGAG  
CTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCCGGACAACCCTGCAGTCCGACC  
AGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAGGATTTTCGATATCTACGACGAG  
GACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTTCATTGCCGCCGTGGAGAGGCT  
GTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCCAGAGCGGCAGCGTGCCCCAGT  
TCAAGAAAGTGGTGTTCCAGGAATTCACAGACGGCAGCTTCACCCAGCCTCTGTATAGAGGCGAGCTGAAC  
GAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAACATCATGGTGACCTTCCGGAA  
TCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAGAGGACCAGCGGCAGGGCGCCG  
AACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGGAAAGTGCAGCACCACATGGCC  
CCCACCAAGGACGAGTTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTGGATCTGGAAAAGGACGTGCA  
CTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCCTCAACCCCGCCACGGCCGCCAGGTGA  
CCGTGCAGGAATTCGCCCTGTTCTTACCATCTTCGACGAGACAAAGTCCTGGTACTTCACCGAGAATATG  
GAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTTCAAAGAGAACTACCGGTTCCA  
CGCCATCAACGGCTACATCATGGACACCCTGCCTGGCTGGTGATGGCCCAGGACCAGAGAATCCGGTGGT  
ATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGCGGCCACGTGTTACCGTGCGG  
AAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTTCGAGACAGTGGAGATGCTGCC  
CAGCAAGGCCGCGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGCACGCTGGCATGAGCACCCCTGT  
TTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGCCACATCCGGGACTTCCAGATC  
ACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCACTACAGCGGCAGCATCAACGC  
CTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCTATGATCATCCACGGCATT  
AGACCCAGGGCGCCAGGCAGAAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTGGAC  
GGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGTGTTCTTCGGCAATGTGGACAG  
CAGCGGCATCAAGCACAAACATCTTCAACCCCCCATCATTTGCCCGGTACATCCGGCTGCACCCACCCACT  
ACAGCATTAGATCCACACTGAGAATGGAAGTGAATGGGCTGCGACCTGAACTCCTGCAGCATGCCTCTGGGC  
ATGGAAAGCAAGGCCATCAGCGACGCCCAGATCACAGCCAGCAGCTACTTCACCAACATGTTTCGCCACCTG  
GTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGCGGCCTCAGGTCAACAACCCCA  
AAGAATGGCTGCAGGTGGACTTTTCAGAAAACCATGAAGGTGACCGGCGTGACCACCCAGGGCGTGAAAGC  
CTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGATGGCCACCAGTGGACCCTGTT  
CTTTCAGAACGGCAAGGTGAAAGTGTTCCAGGGCAACCAGGACTCCTTCACCCCCGTGGTGAACTCCCTGG  
ACCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCAAGTCTTGGGTGCACCAGATCGCCCTCAGGATG  
GAAGTCCTGGGATGTGAGGCCCAGGATCTGTACTGATGAGGATCCAATAAAAGATCTTTATTTTCATTAGA  
TCTGTGTGTTGGTTTTTTGTGTGCTCGAGATCCACGGCCGC

SEQ ID NO.49: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-MVM-Flank**

**GCGGCCGCGGTACGC**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
CAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
CAAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAAAC**TACTGATGACCCTT**  
**GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAGCTCTAGAGGATCCCCG**  
TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTA  
GGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGG  
ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCTTCACCAGGAGAAGCCGTCAAGAGGTAAGGG  
TTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTT  
TCAGGTTGG**CTAGT**

SEQ ID NO.50: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-MVM-Flank-coFVIIIdeltaB**

**GCGGCCGCGGTACGC**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
CAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
CAAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAAAC**TACTGATGACCCTT**  
**GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAGCTCTAGAGGATCCCCG**  
TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTA  
GGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGG  
ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCTTCACCAGGAGAAGCCGTCAAGAGGTAAGGG  
TTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTT  
TCAGGTTGG**CTAGTATGCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGC**  
**GCCACCCGCGGTACTACCTGGGCGCCGTGGAGCTGTCCTGGGACTACATGCAGAGCGACCTGGGCGAGCT**  
**GCCCGTGGACGCCCGGTTCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGA**  
**AAACCCTGTTTCGTGGAGTTCACCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCTGGATGGGCTG**  
**CTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCC**  
**CGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCA**  
**GCCAGCGGGAGAAAGAAGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAA**  
**GAAAACGGCCCCATGGCCTCCGACCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAA**  
**GGACCTGAACAGCGGCCTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCC**  
**AGACCCTGCACAAGTTCATCCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAG**  
**AACAGCCTGATGCAGGACCGGGACGCCGCCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTA**  
**CGTGAACAGAAGCCTGCCCGGCCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGG**  
**GCACCACACCCGAGGTGCACAGCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCC**  
**AGCCTGGAAATCAGCCCTATCACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCCTGCT**  
**GTTTTTGCCACATCAGCTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGG**  
**AACCCAGCTGCGGATGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATG**  
**GACGTGGTGCGGTTTCGACGACGACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCC**  
**CAAGACCTGGGTGCACTATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCG**  
**ACGACAGAAGCTACAAGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTG**  
**CGGTTTCATGGCCTACACCGACGAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGG**  
**CCCCCTGCTGTACGGCGAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACA**  
**ACATCTACCCCCACGGCATCACCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCAC**  
**CTGAAGGACTTCCCCATCCTGCCCGGCAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCC**  
**CACCAAGAGCGACCCCAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCT**  
**CCGGGCTGATCGGACCTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGC**  
**GACAAGCGGAACGTGATCCTGTTTCAGCGTGTTTCGATGAGAACCGGTCCTGGTATCTGACCGAGAACATCCA**  
**GCGGTTTCTGCCCAACCCTGCCGGCGTGACGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACT**  
**CCATCAATGGCTACGTGTTTCGACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATC**  
**CTGAGCATCGGCGCCCAGACCGACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAAGATGGT**

GTACGAGGACACCCCTGACCCTGTTCCCTTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCC  
 TGTGGATTCTGGGCTGCCACAACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGC  
 TGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAA  
 CAACGCCATCGAACCCCGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCC  
 GGACAACCCTGCAGTCCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAG  
 GATTTCGATATCTACGACGAGGACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTT  
 CATTGCCGCCGTGGAGAGGCTGTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCC  
 AGAGCGGCAGCGTGCCCCAGTTCAAGAAAGTGGTGTTCCAGGAATTACAGACGGCAGCTTCACCCAGCCT  
 CTGTATAGAGGCGAGCTGAACGAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAA  
 CATCATGGTGACCTTCCGGAATCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAG  
 AGGACCAGCGGCAGGGCGCCGAACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGG  
 AAAGTGCAGCACCACATGGCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGT  
 GGATCTGGAAGGACGTGCACTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCCTCAACC  
 CCGCCACGGCCGCCAGGTGACCGTGCAAGAAATTCGCCCTGTTCTTCACCATCTTCGACGAGACAAAGTCC  
 TGGTACTTCACCGAGAATATGGAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTT  
 CAAAGAGAACTACCGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGATGGCCC  
 AGGACCAGAGAATCCGGTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGC  
 GGCCACGTGTTACCGTGCGGAAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTT  
 CGAGACAGTGGAGATGCTGCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGC  
 ACGCTGGCATGAGCACCTGTCTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGC  
 CACATCCGGGACTTCCAGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCA  
 CTACAGCGGCAGCATCAACGCCTGGTCCACCAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCC  
 CTATGATCATCCACGGCATTAAAGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTC  
 ATCATCATGTACAGCCTGGACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGT  
 GTTCTTCGGCAATGTGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCATCATTGCCCGGTACA  
 TCCGGCTGCACCCCACTACAGCATTAGATCCACACTGAGAATGGAAGTGAAGGTGGGCTGCGACCTGAAC  
 TCCTGCAGCATGCCTCTGGGCATGGAAAGCAAGGCCATCAGCGACGCCAGATCACAGCCAGCAGCTACTT  
 CACCAACATGTTCGCCACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGC  
 GGCTCAGGTCAACAACCCCAAGAAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGTG  
 ACCACCCAGGGCGTGAAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGA  
 TGGCCACCAGTGGACCCTGTTCTTTCAGAACGGCAAGGTGAAAGTGTTCCAGGGCAACCAGGACTCCTTCA  
 CCCCCGTGGTGAAGTCCCTGGACCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGTCTTGGGTG  
 CACCAGATCGCCCTCAGGATGGAAGTCTGGGATGTGAGGCCAGGATCTGTACTGATGA

SEQ ID NO.51: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-MVM-Flank-**  
**coFVIIIdeltaB-Flank**

GCGGCCGCGGTACGCCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
 CAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
 AACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
 CAAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAAACCTACTGATGACCCTT  
 GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCGGGCGATCAGCAGGTAG**CTCTAGAGGATCCCCG**  
 TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTA  
 GGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGG  
 ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCTTCACCAGGAGAAGCCGTCAGAGGTAAGGG  
 TTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTT  
 TCAGGTTGGCTAGTATGCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGC  
 GCCACCCGCGGTACTACCTGGGCGCCGTGGAGCTGTCTGGGACTACATGCAGAGCGACCTGGGCGAGCT  
 GCCCGTGGACGCCCGGTTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGA  
 AAACCCTGTTCTGTTGGAGTTCACCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCTGGATGGGCCTG  
 CTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCC  
 CGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCA  
 GCCAGCGGGAGAAAGAAGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAA  
 GAAAACGGCCCCATGGCCTCCGACCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAA  
 GGACCTGAACAGCGGCCTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCC

AGACCCTGCACAAGTTTCATCCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAG  
AACAGCCTGATGCAGGACCGGGACGCCGCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTA  
CGTGAACAGAAGCCTGCCCCGGCCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGG  
GCACCACACCCGAGGTGCACAGCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACGGCAGGCC  
AGCCTGGAAATCAGCCCTATCACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCTGCT  
GTTTTGCCACATCAGCTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGG  
AACCCCAGCTGCGGATGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATG  
GACGTGGTGCGGTTTCGACGACGACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCC  
CAAGACCTGGGTGCACTATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCCTGGTGCTGGCCCCCG  
ACGACAGAAGCTACAAGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGGCCGGAAGTACAAGAAAGTG  
CGGTTCATGGCCTACACCGACGAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGG  
CCCCCTGCTGTACGGCGAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACA  
ACATCTACCCCCACGGCATCACCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCAC  
CTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCC  
CACCAAGAGCGACCCCAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCT  
CCGGGCTGATCGGACCTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGC  
GACAAGCGGAACGTGATCCTGTTCAGCGTGTTCGATGAGAACCGGTCCTGGTATCTGACCGAGAACATCCA  
GCGGTTTCTGCCCAACCTGCCGGCGTGCAGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACT  
CCATCAATGGCTACGTGTTCGACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATC  
CTGAGCATCGGCGCCCAGACCGACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAGATGGT  
GTACGAGGACACCTGACCTGTTCCCTTTCAGCGCGAGACAGTGTTCATGAGCATGGAAAACCCCGGCC  
TGTGGATTCTGGGCTGCCACAACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGC  
TGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAA  
CAACGCCATCGAACCCCGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCC  
GGACAACCTGCAGTCCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAG  
GATTTCGATATCTACGACGAGGACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTT  
CATTGCCGCCGTGGAGAGGCTGTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCC  
AGAGCGGCAGCGTGCCCCAGTTCAAGAAAGTGGTGTTCCAGGAATTCACAGACGGCAGCTTCACCCAGCCT  
CTGTATAGAGGCGAGCTGAACGAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAA  
CATCATGGTGACCTTCCGGAATCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAG  
AGGACCAGCGGCAGGGCGCCGAACCCCGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGG  
AAAGTGCAGCACCACATGGCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGT  
GGATCTGGAAAAGGACGTGCACTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCTCAACC  
CCGCCCACGGCCGCCAGGTGACCGTGCAGGAATTCGCCCTGTTCTTCACCATCTTCGACGAGACAAAGTCC  
TGGTACTTCACCGAGAATATGGAACGGAACTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTT  
CAAAGAGAACTACCGGTTCCACGCCATCAACGGCTACATCATGGACACCCCTGCCTGGCCTGGTGATGGCCC  
AGGACCAGAGAATCCGGTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGC  
GGCCACGTGTTCACCGTGCGGAAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTT  
CGAGACAGTGGAGATGCTGCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGC  
ACGCTGGCATGAGCACCTGTTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGC  
CACATCCGGGACTTCCAGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCA  
CTACAGCGGCAGCATCAACGCCTGGTCCACCAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCC  
CTATGATCATCCACGGCATTAAGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTC  
ATCATCATGTACAGCCTGGACGGCAAGAAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCTGATGGT  
GTTCTTCGGCAATGTGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCATCATTGCCCGGTACA  
TCCGGCTGCACCCCACCCACTACAGCATTAGATCCACACTGAGAATGGAACTGATGGGCTGCGACCTGAAC  
TCCTGCAGCATGCCTCTGGGCATGGAAGCAAGGCCATCAGCGACGCCAGATCACAGCCAGCAGCTACTT  
CACCAACATGTTCGCCACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGC  
GGCTCAGGTCAACAACCCCAAGAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGTG  
ACCACCCAGGGCGTGAAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGA  
TGGCCACCAGTGGACCTGTTCTTTCAGAACGGCAAGGTGAAAGTGTTCCAGGGCAACCAGGACTCCTTCA  
CCCCCGTGGTGAACTCCCTGGACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCAGTCTTGGGTG  
CACCAGATCGCCCTCAGGATGGAAGTCTGGGATGTGAGGCCAGGATCTGTACTGATGAGGATCC

SEQ ID NO.52: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-MVM-Flank-coFVIIIdeltaB-Flank-SV40pA**

**GCGGCCGCGGTACGC**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
CAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
CAAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAA**ACTACTGATGACCCTT**  
**GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAGCTCTAGAGGATCCCCG**  
**TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTA**  
**GGTTACTTATTCTCCTTTTGTGTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGG**  
**ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCCTTCACCAGGAGAAGCCGTCAAGAGGTAAGGG**  
**TTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTT**  
**TCAGGTTGGCTAGTATGCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGC**  
**GCCACCCGGCGGTACTACCTGGGCGCCGTGGAGCTGTCCTGGGACTACATGCAGAGCGACCTGGGCGAGCT**  
**GCCCGTGGACGCCCCGGTTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGA**  
**AAACCCTGTTTCGTGGAGTTCACCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCTGGATGGGCCTG**  
**CTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCC**  
**CGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCA**  
**GCCAGCGGGAGAAAGAAGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAA**  
**GAAAACGGCCCCATGGCCTCCGACCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAA**  
**GGACCTGAACAGCGGCCTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCC**  
**AGACCCTGCACAAGTTCATCCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAG**  
**AACAGCCTGATGCAGGACCGGGACGCCGCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTA**  
**CGTGAACAGAAGCCTGCCCGGCCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGG**  
**GCACCACACCCGAGGTGCACAGCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCC**  
**AGCCTGGAAATCAGCCCTATCACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCCTGCT**  
**GTTTTGCCACATCAGCTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGG**  
**AACCCAGCTGCGGATGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATG**  
**GACGTGGTGCGGTTTCGACGACGACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCC**  
**CAAGACCTGGGTGCACTATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCG**  
**ACGACAGAAGCTACAAGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGGCCGGAAGTACAAGAAAGTG**  
**CGGTTTCATGGCCTACACCGACGAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGG**  
**CCCCCTGCTGTACGGCGAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACA**  
**ACATCTACCCCCACGGCATCACCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCAC**  
**CTGAAGGACTTCCCCATCCTGCCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCC**  
**CACCAAGAGCGACCCCAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCT**  
**CCGGGCTGATCGGACCTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGC**  
**GACAAGCGGAACGTGATCCTGTTTCAGCGTGTTTCGATGAGAACCGGTCCCTGGTATCTGACCGAGAACATCCA**  
**GCGGTTTCTGCCCAACCCTGCCGGCGTGACGTGGAAGATCCCGAGTTCAGGCCAGCAACATCATGCACT**  
**CCATCAATGGCTACGTGTTTCGACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATC**  
**CTGAGCATCGGCGCCCAGACCGACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAAGATGGT**  
**GTACGAGGACACCCTGACCCTGTTCCCTTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCC**  
**TGTGGATTCTGGGCTGCCACAACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGC**  
**TGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAA**  
**CAACGCCATCGAACCCCGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCC**  
**GGACAACCCTGCAGTCCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAG**  
**GATTTGATATCTACGACGAGGACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTT**  
**CATTGCCGCCGTGGAGAGGCTGTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCC**  
**AGAGCGGCAGCGTGCCCCAGTTCAAGAAAGTGGTGTTCCAGGAATTCACAGACGGCAGCTTCACCCAGCCT**  
**CTGTATAGAGGCGAGCTGAACGAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAA**  
**CATCATGGTGACCTTCCGGAATCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAG**  
**AGGACCAGCGGCAGGGCGCCGAACCCCGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGG**  
**AAAGTGCAGCACCATGGCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGT**  
**GGATCTGGAAGGACGTGCACTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCCTCAACC**  
**CCGCCACGGCCGCCAGGTGACCGTGACGAATTGCCCTGTTCTTCACCATCTTCGACGAGACAAAGTCC**

TGGTACTTCACCGAGAATATGGAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTT  
 CAAAGAGAACTACCGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGATGGCCC  
 AGGACCAGAGAATCCGGTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGC  
 GGCCACGTGTTACCGTGCGGAAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTT  
 CGAGACAGTGGAGATGCTGCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGC  
 ACGCTGGCATGAGCACCTGTCTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGC  
 CACATCCGGGACTTCCAGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCA  
 CTACAGCGGCAGCATCAACGCCTGGTCCACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCC  
 CTATGATCATCCACGGCATTAAAGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTC  
 ATCATCATGTACAGCCTGGACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGT  
 GTTCTTCGGCAATGTGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCATCATTGCCCGGTACA  
 TCCGGCTGCACCCCACTACAGCATTAGATCCACACTGAGAAATGGAAGTATGAGGCTGCGACCTGAAC  
 TCCTGCAGCATGCCTCTGGGCATGGAAGCAAGGCCATCAGCGACGCCAGATCACAGCCAGCAGCTACTT  
 CACCAACATGTTGCGCACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGC  
 GGCTCAGGTCAACAACCCCAAGAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGTG  
 ACCACCCAGGGCGTGAAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGA  
 TGGCCACCAGTGGACCTGTTCTTTCAGAACGGCAAGGTGAAAGTGTTCAGGGCAACCAGGACTCCTTCA  
 CCCCCGTGGTGAAGTCCCTGGACCCCCCTGCTGACCCGCTACCTGAGAAATCCACCCCCAGTCTTGGGTG  
 CACCAGATCGCCCTCAGGATGGAAGTCTTGGGATGTGAGGCCAGGATCTGTACTGATGAGGATCCATGCT  
 TTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAAGTTAACAAC  
 AACAATTGCATTCATTTTATGTTTCAGGTTCAAGGGGAGGTGTGGGAGGTTTTTTTAA

SEQ ID NO.53: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-MVM-Flank-**  
**coFVIIIdeltaB-Flank-SV40pA-Flank**

GCGGCCGCGGTACGC GGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
 CAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
 AACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
 CAAACAGGGGCTAAGTCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAAAC**TA**CTGATGAC**CC**TT  
 GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGG**TA**CT**CTAGAGGATCCCCG**  
 TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTA  
 GGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGAGAGTCACTTGGCAGGG  
 ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCTTCACCAGGAGAAGCCGTCAGAGGTAAGGG  
 TTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTT  
 TCAGGTTGGCTAGTATGCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGC  
 GCCACCCGGCGGTACTACCTGGGCGCCGTGGAGCTGTCCTGGGACTACATGCAGAGCGACCTGGGCGAGCT  
 GCCCGTGGACGCCCGGTTCCCCCCCAGAGTGCCCAAGAGCTTCCCTTCAACACCAGCGTGCTGTACAAGA  
 AAACCTGTTCGTGGAGTTCACCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCCCTGGATGGGCCTG  
 CTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCC  
 CGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCA  
 GCCAGCGGGAGAAAGAAGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAA  
 GAAAACGGCCCCATGGCCTCCGACCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAA  
 GGACCTGAACAGCGGCCTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCC  
 AGACCCTGCACAAGTTCATCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAG  
 AACAGCCTGATGCAGGACCGGGACGCCGCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTA  
 CGTGAACAGAAGCCTGCCCGCCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGG  
 GCACCACACCCGAGGTGCACAGCATCTTCTGGAAGGGCACACCTTCTGGTCCGGAACCACCGGCAGGCC  
 AGCCTGGAAATCAGCCCTATCACCTTCTGACCGCCAGACACTGCTGATGGACCTGGGCCAGTTCCTGCT  
 GTTTTGCCACATCAGCTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGG  
 AACCCAGCTGCGGATGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATG  
 GACGTGGTGCGGTTTCGACGACGACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCC  
 CAAGACCTGGGTGCACTATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCG  
 ACGACAGAAGCTACAAGAGCCAGTACCTGAACAATGGCCCCAGCGGATCGGCGGGAAGTACAAGAAAGTG  
 CGGTTTCATGGCCTACACCGACGAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGG  
 CCCCCTGCTGTACGGCGAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACA

ACATCTACCCCCACGGCATCACCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCAC  
CTGAAGGACTTCCCCATCCTGCCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCC  
CACCAAGAGCGACCCCAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCT  
CCGGGCTGATCGGACCTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGC  
GACAAGCGGAACGTGATCCTGTTTCAGCGTGTTTCGATGAGAACCGGTCCTGGTATCTGACCGAGAACATCCA  
GCGGTTTCTGCCCAACCTGCGGCGGTGCAGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACT  
CCATCAATGGCTACGTGTTTCGACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATC  
CTGAGCATCGGCGCCCAGACCGACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAAGATGGT  
GTACGAGGACACCCTGACCCTGTTCCCTTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCC  
TGTGGATTCTGGGCTGCCACAACAGCGACTTCGGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGC  
TGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAA  
CAACGCCATCGAACCCCGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCC  
GGACAACCCTGCAGTCCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAG  
GATTTTCGATATCTACGACGAGGACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTT  
CATTGCCGCCGTGGAGAGGCTGTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCC  
AGAGCGGCAGCGTGCCCCAGTTCAAGAAAGTGGTGTTCCAGGAATTCACAGACGGCAGCTTCACCCAGCCT  
CTGTATAGAGGCGAGCTGAACGAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAA  
CATCATGGTGACCTTCCGGAATCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAG  
AGGACCAGCGGCAGGGCGCCGAACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGG  
AAAGTGCAGCACCCACATGGCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGT  
GGATCTGGAAAAGGACGTGCACTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCCTCAACC  
CCGCCACGGCCGCCAGGTGACCGTGCAGGAATTCGCCCTGTTCTTCACCATCTTCGACGAGACAAAGTCC  
TGGTACTTCACCGAGAAATATGGAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTT  
CAAAGAGAACTACCGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGATGGCCC  
AGGACCAGAGAATCCGGTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGC  
GGCCACGTGTTACCCGTGCGGAAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTT  
CGAGACAGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGC  
ACGCTGGCATGAGCACCTGTCTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGC  
CACATCCGGGACTTCCAGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCA  
CTACAGCGGCAGCATCAACGCCTGGTCCACCAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCC  
CTATGATCATCCACGGCATTAAAGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTC  
ATCATCATGTACAGCCTGGACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGT  
GTTCTTCGGCAATGTGGACAGCAGCGGCATCAAGCACAAACATCTTCAACCCCCCATCATTGCCCGGTACA  
TCCGGCTGCACCCCACTACTACAGCATTAGATCCACACTGAGAATGGAAGTGAATGGGCTGCGACCTGAAC  
TCCTGCAGCATGCCTCTGGGCATGGAAAGCAAGGCCATCAGCGACGCCCAGATCACAGCCAGCAGCTACTT  
CACCAACATGTTTCGCCACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGC  
GGCCTCAGGTCAACAACCCCAAGAAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGTG  
ACCACCCAGGGCGTGAAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGA  
TGGCCACCAGTGGACCCTGTTCTTTCAGAACGGCAAGGTGAAAGTGTTCCAGGGCAACCAGGACTCCTTCA  
CCCCCGTGGTGAACTCCCTGGACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGTCTTGGGTG  
CACCAGATCGCCCTCAGGATGGAAGTCTTGGGATGTGAGGCCAGGATCTGTACTGATGAGGATCCATGCT  
TTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTATAAGCTGCAATAAACAAGTTAACAAC  
AACAATTGCATTCATTTTATGTTTCAGGTTTCAGGGGGAGGTGTGGGAGGTTTTTTTAAACTCGAGATCCACG  
GCCGC

SEQ ID NO.54: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-MVM-Flank-coFVIIIdeltaB-Flank-Synt.pA**

GCGGCCGCGGTACGC GGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAAGTTATCGGAGGAGCAAA  
CAGGGGCTAAGTCCACCGGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAAGTTATCGGAGGAGCA  
AACAGGGGCTAAGTCCACCGGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAAGTTATCGGAGGAG  
CAAACAGGGGCTAAGTCCACGGTACC CACTGGGAGGATGTTGAGTAAGATGGAAAACCTACTGATGACCCTT  
GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCGGGCGATCAGCAGGTAGCTCTAGAGGATCCCCG  
TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTA  
GGTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGG

ATCAGCAGCCTGGGTTGGAAGGAGGGGGGTATAAAAGCCCCTTCACCAGGAGAAGCCGTCAAGAGGTAAGGG  
TTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTT  
TCAGGTTGGCTAGTATGCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGC  
GCCACCCGGCGGTACTACCTGGGCGCCGTGGAGCTGTCCTGGGACTACATGCAGAGCGACCTGGGCGAGCT  
GCCCCTGGACGCCCGGTTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGA  
AAACCCTGTTTCGTGGAGTTCACCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCCTGGATGGGCCTG  
CTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGTATCACCTGAAGAACATGGCCAGCCACCC  
CGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCA  
GCCAGCGGGAGAAAGAAGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAA  
GAAAACGGCCCCATGGCCTCCGACCCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAA  
GGACCTGAACAGCGGCCTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCC  
AGACCCTGCACAAGTTCATCCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAG  
AACAGCCTGATGCAGGACCGGGACGCCGCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTA  
CGTGAACAGAAGCCTGCCCGGCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGG  
GCACCACACCCGAGGTGCACAGCATCTTCTGGAAGGGCACACCTTCTGGTCCGGAACCACCGGCAGGCC  
AGCCTGGAAATCAGCCCTATCACCTTCCTGACCGCCAGACACTGCTGATGGACCTGGGCCAGTTCCTGCT  
GTTTTGCCACATCAGCTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGG  
AACCCAGCTGCGGATGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATG  
GACGTGGTGCGGTTTCGACGACGACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCC  
CAAGACCTGGGTGCACTATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCCTGGTGCTGGCCCCG  
ACGACAGAAGCTACAAGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTG  
CGGTTTCATGGCCTACACCGACGAGACATTCAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGG  
CCCCCTGCTGTACGGCGAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACA  
ACATCTACCCCCACGGCATCACCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCAC  
CTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCC  
CACCAAGAGCGACCCCAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCT  
CCGGGCTGATCGGACCTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGC  
GACAAGCGGAACGTGATCCTGTTTCAGCGTGTTCGATGAGAACCGGTCTTGGTATCTGACCGAGAACATCCA  
GCGGTTTCTGCCCAACCTTGCCGGCGTGAGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACT  
CCATCAATGGCTACGTGTTTCGACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATC  
CTGAGCATCGGCGCCCAGACCGACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAGATGGT  
GTACGAGGACACCCTGACCCTGTTCCCTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCC  
TGTGGATTCTGGGCTGCCACAACAGCGACTTCGGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGC  
TGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAA  
CAACGCCATCGAACCCCGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCC  
GGACAACCTGCAGTCCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAG  
GATTCGATATCTACGACGAGGACGAGAACCAGAGCCCCAGAAGCTTCAGAGAAGAAAACCCGGCACTACTT  
CATTGCCGCCGTGGAGAGGCTGTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCC  
AGAGCGGCAGCGTGCCCCAGTTCAAGAAAGTGGTGTTCCAGGAATTCACAGACGGCAGCTTCACCCAGCCT  
CTGTATAGAGGCGAGCTGAACGAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAA  
CATCATGGTGACCTTCCGGAATCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAG  
AGGACCAGCGGCAGGGCGCCGAACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGG  
AAAGTGCAGCACCACATGGCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGT  
GGATCTGGAAGGACGTGCACTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCTCAACC  
CCGCCCACGGCCGCCAGGTGACCGTGCAGGAATTCGCCCTGTTCTTCACCATCTTCGACGAGACAAAGTCC  
TGGTACTTCACCGAGAAATATGGAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTT  
CAAAGAGAACTACCGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGATGGCCC  
AGGACCAGAGAATCCGGTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGC  
GGCCACGTGTTACACGTGCGGAAGAAAGAAGGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTT  
CGAGACAGTGGAGATGCTGCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGC  
ACGCTGGCATGAGCACCTGTCTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGC  
CACATCCGGGACTTCCAGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCA  
CTACAGCGGCAGCATCAACGCCTGGTCCACCAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCC  
CTATGATCATCCACGGCATTAAGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTC  
ATCATCATGTACAGCCTGGACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGT

GTTCTTCGGCAATGTGGACAGCAGCGGCATCAAGCACAAACATCTTCAACCCCCCATCATTGCCCGGTACA  
TCCGGCTGCACCCCACTACTACAGCATTAGATCCACACTGAGAATGGAAGTATGGGCTGCGACCTGAAC  
TCCTGCAGCATGCCTCTGGGCATGGAAAGCAAGGCCATCAGCGACGCCAGATCACAGCCAGCAGCTACTT  
CACCAACATGTTTCGCCACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGC  
GGCTCAGGTCAACAACCCCAAAGAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGTG  
ACCACCCAGGGCGTGAAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGA  
TGGCCACCAGTGGACCCTGTTCTTTCAGAACGGCAAGGTGAAAGTGTTCAGGGCAACCAGGACTCCTTCA  
CCCCGTGGTGAACTCCCTGGACCCCCCCTGCTGACCCGCTACCTGAGAAATCCACCCCCAGTCTTGGGTG  
CACCAGATCGCCCTCAGGATGGAAGTCTTGGGATGTGAGGCCAGGATCTGTACTGATGAGGATCCAATAA  
 AAGATCTTTATTTTCATTAGATCTGTGTGTTGGTTTTTTGTGTG

SEQ ID NO.55: **Flank-3xSERP-Flank-TTRe-Flank-TTRm-MVM-Flank-**  
**coFVIIIdeltaB-Flank-Synt.pA-Flank**

GCGGCCGCGGTACGCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA  
 CAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA  
 AACAGGGGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG  
 CAAACAGGGGCTAAGTCCACGGTACCCACTGGGAGGATGTTGAGTAAGATGGAAAACACTACTGATGACCCTT  
 GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCGGGCGATCAGCAGGTAGCTCTAGAGGATCCCCG  
 TCTGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTA  
 GGTTACTTATTCTCCTTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGAGTTCAGCTTGGCAGGG  
 ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCTTCACCAGGAGAAGCCGTCAGAGGTAAGGG  
 TTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTT  
 TCAGGTTGGCTAGTATGCAGATCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGC  
GCCACCCGGCGGTACTACCTGGGCGCCGTGGAGCTGTCCTGGGACTACATGCAGAGCGACCTGGGCGAGCT  
GCCCGTGGACGCCCCGGTTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGA  
AAACCTGTTCGTGGAGTTCACCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCCCTGGATGGGCCTG  
CTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCTGAAGAACATGGCCAGCCACCC  
CGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCA  
GCCAGCGGGAGAAAGAAGATGACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAA  
GAAAACGGCCCCATGGCCTCCGACCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAA  
GGACCTGAACAGCGGCCTGATCGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCC  
AGACCCTGCACAAGTTCATCCTGCTGTTTCGCCGTGTTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAG  
AACAGCCTGATGCAGGACCGGGACGCGCCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTA  
CGTGAACAGAAGCCTGCCCCGGCCTGATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGG  
GCACCACACCCGAGGTGCACAGCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCC  
AGCCTGGAAATCAGCCCTATCACCTTCTGACCGCCAGACACTGCTGATGGACCTGGGCCAGTTCTCTGCT  
GTTTTGCCACATCAGCTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGG  
AACCCAGCTGCGGATGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATG  
GACGTGGTGCGGTTCGACGACGACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCC  
CAAGACCTGGGTGCACTATATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCG  
ACGACAGAAGCTACAAGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGCGGGAAGTACAAGAAAGTG  
CGGTTTCATGGCCTACACCGACGAGACATTCAAGACCCGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGG  
CCCCCTGCTGTACGGCGAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACA  
ACATCTACCCCCACGGCATCACCGACGTGCGGCCCTGTACAGCAGGCGGCTGCCCAAGGGCGTGAAGCAC  
CTGAAGGACTTCCCCATCCTGCCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCC  
CACCAAGAGCGACCCCAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCT  
CCGGGCTGATCGGACCTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGC  
GACAAGCGGAACGTGATCCTGTTTCAGCGTGTTCGATGAGAACCGGTCTTGGTATCTGACCGGAGAACATCA  
GCGGTTTTCTGCCCAACCTGCCGGCGTGACGTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACT  
CCATCAATGGCTACGTGTTTCGACTCTCTGCAGCTCTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATC  
CTGAGCATCGGCGCCCAGACCGACTTCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAGATGGT  
GTACGAGGACACCTGACCCTGTTCCCTTTCAGCGGCGAGACAGTGTTTCATGAGCATGGAAAACCCCGGCC  
TGTGGATTCTGGGCTGCCACAACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAGGTGTCCAGC  
TGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTACCTGCTGTCCAAGAA

CAACGCCATCGAACCCCGGAGCTTCAGCCAGAACCCCCCGTGCTGACGCGTCACCAGCGGGAGATCACCC  
 GGACAACCCTGCAGTCCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAG  
 GATTTCGATATCTACGACGAGGACGAGAACCAGAGCCCCAGAAGCTTCCAGAAGAAAACCCGGCACTACTT  
 CATTGCCGCGCTGGAGAGGCTGTGGGACTACGGCATGAGTTCTAGCCCCACGTGCTGCGGAACCGGGCCC  
 AGAGCGGCAGCGTGCCCCAGTTCAAGAAAGTGGTGTTCAGGAATTCACAGACGGCAGCTTCACCCAGCCT  
 CTGTATAGAGGCGAGCTGAACGAGCACCTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAA  
 CATCATGGTGACCTTCCGGAATCAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAG  
 AGGACCAGCGGCAGGGCGCCGAACCCCGGAAGAACTTCGTGAAGCCCAACGAAACCAAGACCTACTTCTGG  
 AAAGTGCAGCACCACATGGCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGT  
 GGATCTGGAAAAGGACGTGCACTCTGGACTGATTGGCCCACTCCTGGTCTGCCACACTAACACCCTCAACC  
 CCGCCACGGCCGCCAGGTGACCGTGCCAGGAATTCGCCCTGTTCTTCACCATCTTCGACGAGACAAAGTCC  
 TGGTACTTCACCGAGAAATATGGAACGGAAGTGCAGAGCCCCCTGCAACATCCAGATGGAAGATCCTACCTT  
 CAAAGAGAACTACCGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGCCTGGTGATGGCCC  
 AGGACCAGAGAATCCGGTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATCCACAGCATCCACTTCAGC  
 GGCCACGTGTTACCGTGCGGAAGAAAGAAGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTT  
 CGAGACAGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGCGGGTGGAGTGTCTGATCGGCGAGCACCTGC  
 ACGCTGGCATGAGCACCTGTCTTCTGGTGTACAGCAACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGC  
 CACATCCGGGACTTCCAGATCACCGCCTCCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGACTGCA  
 CTACAGCGGCAGCATCAACGCCTGGTCCACCAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCC  
 CTATGATCATCCACGGCATTAAAGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTC  
 ATCATCATGTACAGCCTGGACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGT  
 GTTCTTCGGCAATGTGGACAGCAGCGGCATCAAGCACAAACATCTTCAACCCCCCATCATTGCCCGGTACA  
 TCCGGCTGCACCCCACTACTACAGCATTAGATCCACACTGAGAATGGAAGTGGGCTGCGACCTGAAC  
 TCCTGCAGCATGCCTCTGGGCATGGAAAGCAAGGCCATCAGCGACGCCAGATCACAGCCAGCAGCTACTT  
 CACCAACATGTTGCGCACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAACGCCTGGC  
 GGCTCAGGTCAACAACCCCAAGAAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAGGTGACCGGCGTG  
 ACCACCCAGGGCGTGAAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTGATCAGCAGCTCTCAGGA  
 TGGCCACCAGTGGACCCTGTTCTTTTCAGAACGGCAAGGTGAAAGTGTTCCAGGGCAACCAGGACTCCTTCA  
 CCCCCGTGGTGAACCTCCCTGGACCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGTCTTGGGTG  
 CACCAGATCGCCCTCAGGATGGAAGTCTGGGATGTGAGGCCAGGATCTGTACTGATGAGGATCCAATAA  
 AAGATCTTTATTTTCATTAGATCTGTGTGTTGGTTTTTTGTGTGCTCGAGATCCACGGCCGC

SEQ ID NO.56: Synt.pA

AATAAAAGATCTTTATTTTCATTAGATCTGTGTGTTGGTTTTTTGTGTG

SEQ ID NO.57: 3xSERP-**Flank**-*TRe*-**Flank**

GGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCA  
 CCGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTC  
 CACCGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAG  
 TCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAAAC**TA**CTGATGACCCTTGCAGAGACAGAGTAT  
 TAGGACATGTTTGAACAGGGGGCCGGGCGATCAGCAGGTAG**CTCTAGAGGATCCCC**

SEQ ID NO.58: 3xSERP-**Flank**-*TRe*-**Flank**-*T*Rm

GGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCA  
 CCGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTC  
 CACCGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAG  
 TCCAC**GGTACC**CACTGGGAGGATGTTGAGTAAGATGGAAAAC**TA**CTGATGACCCTTGCAGAGACAGAGTAT  
 TAGGACATGTTTGAACAGGGGGCCGGGCGATCAGCAGGTAG**CTCTAGAGGATCCCC**GTCTGTCTGCACATTT  
 CGTAGAGCGAGTGTTCGATACTCTAATCTCCCTAGGCAAGGTTTCATATTTGTGTAGGTACTTATTCTCC  
 TTTTGTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGT  
 TGGAAGGAGGGGGTATAAAAGCCCCTTCACCAGGAGAAGCCGTC

Figure 15

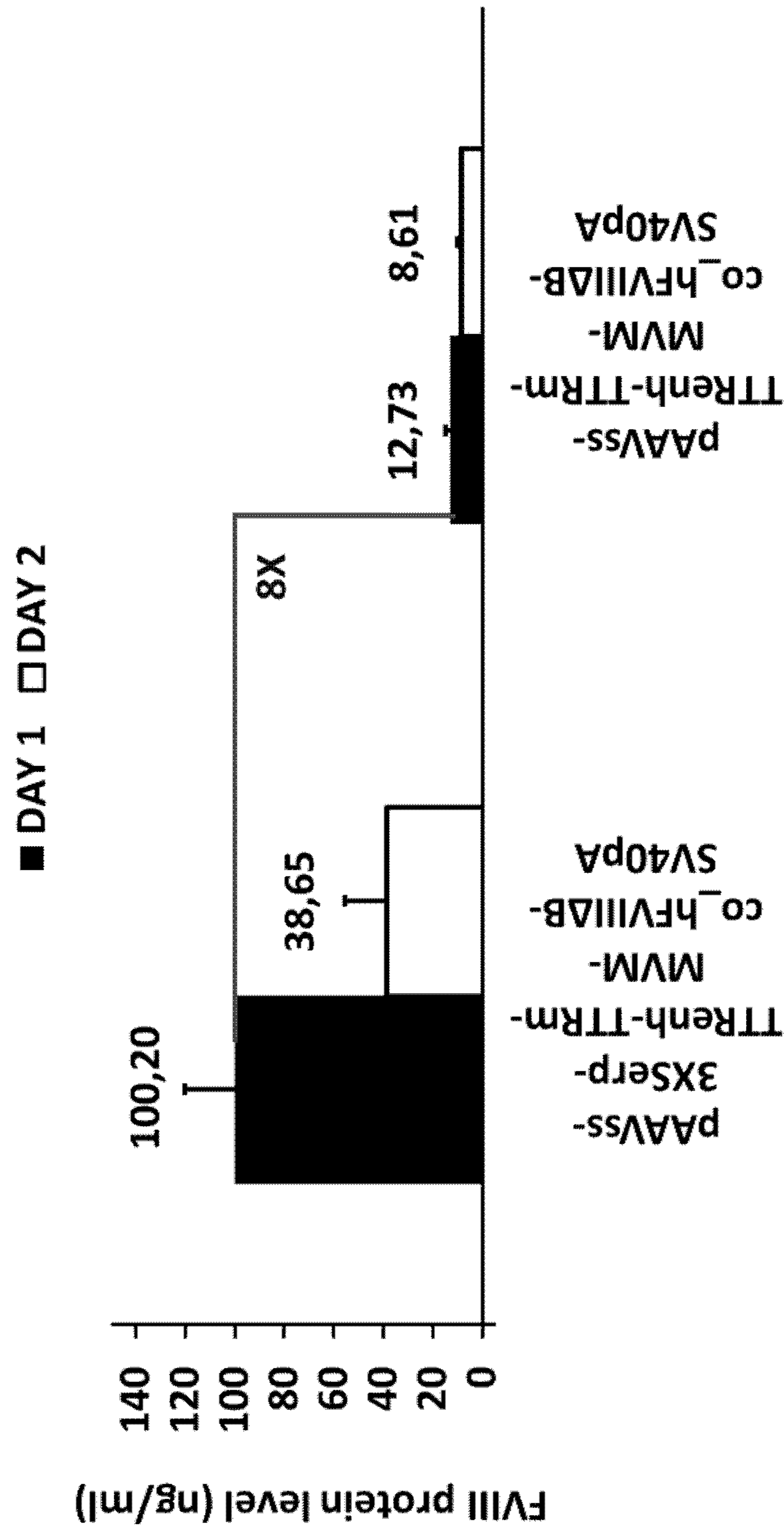


Figure 16

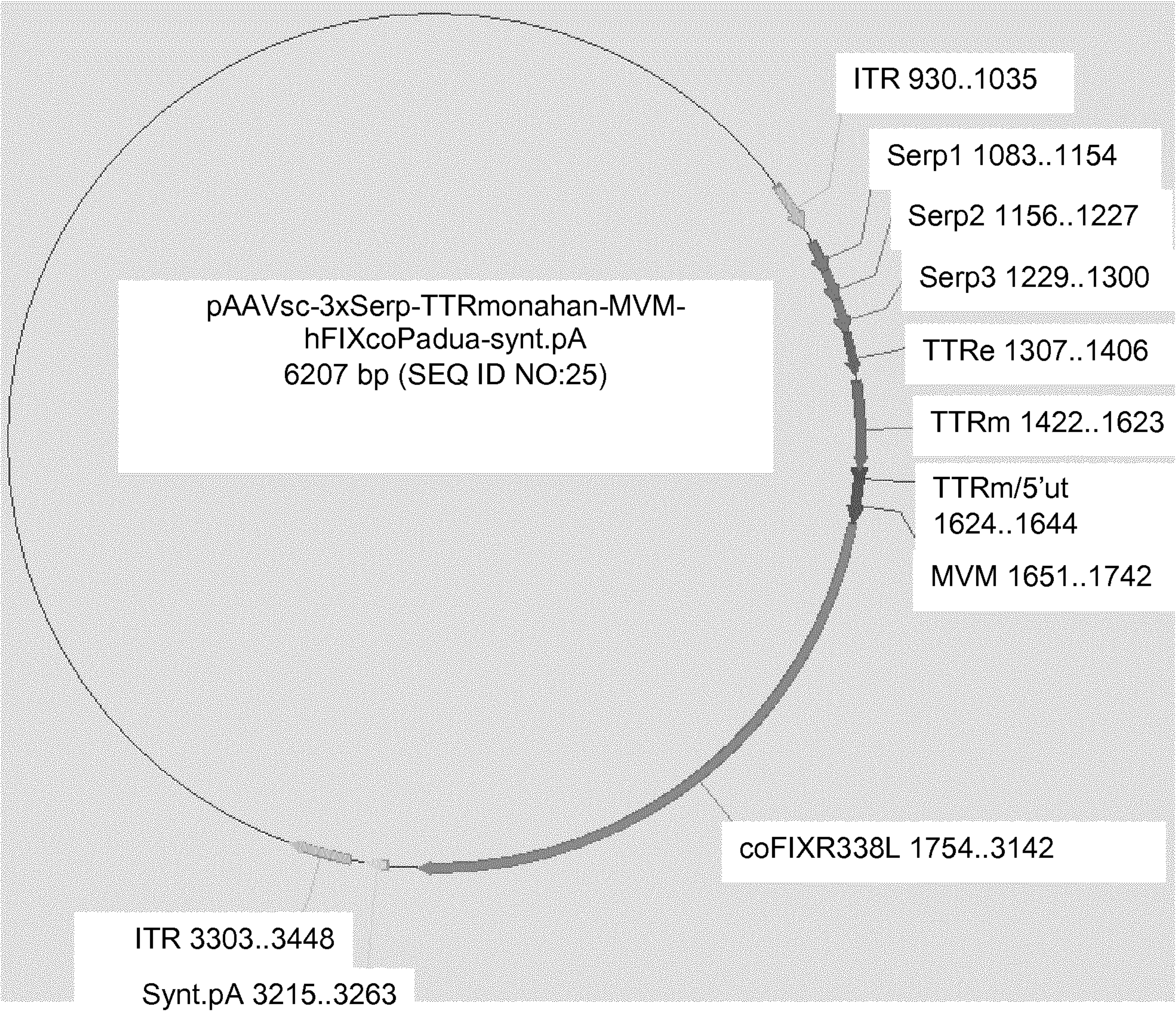


Figure 17

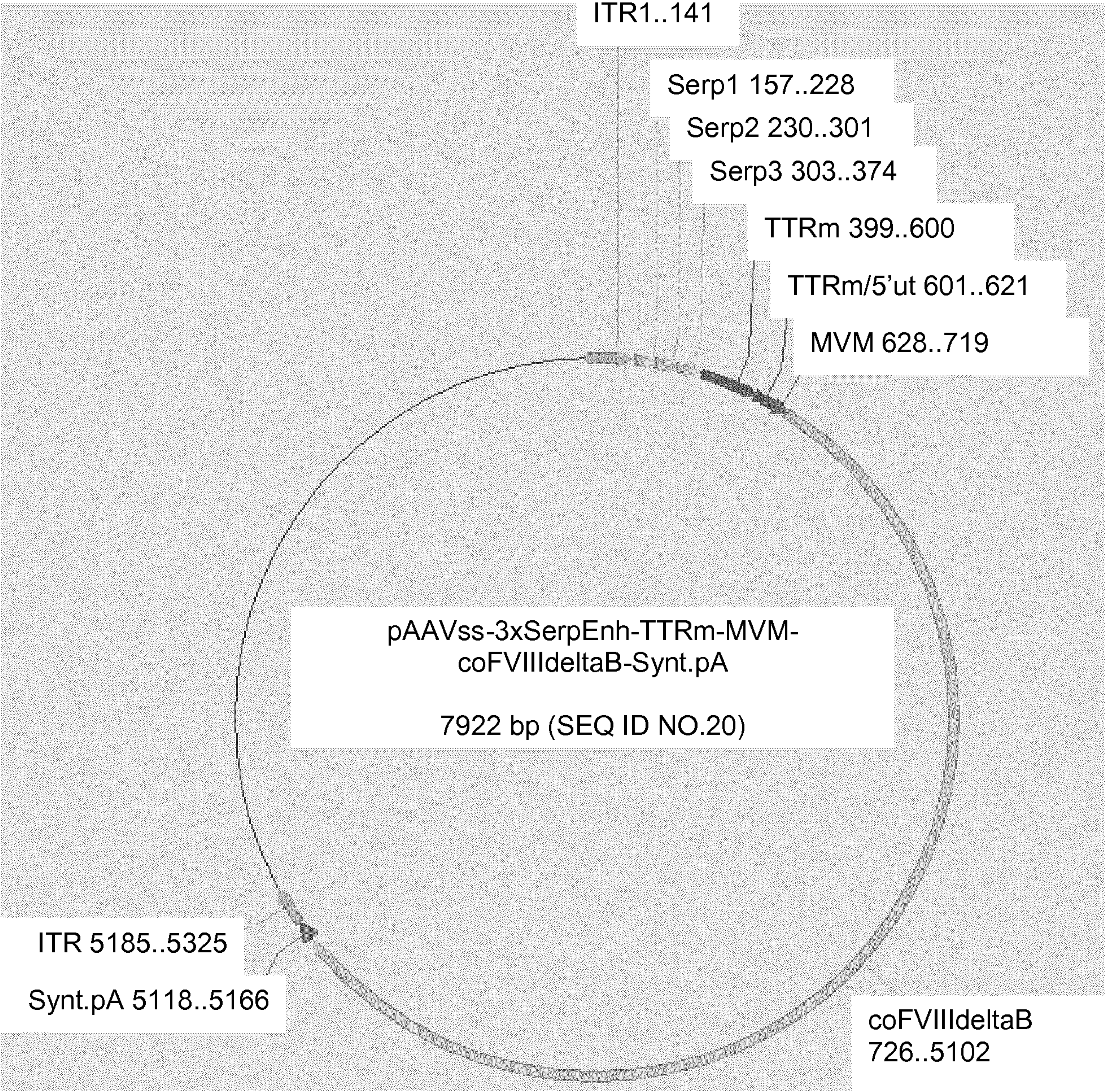


Figure 18

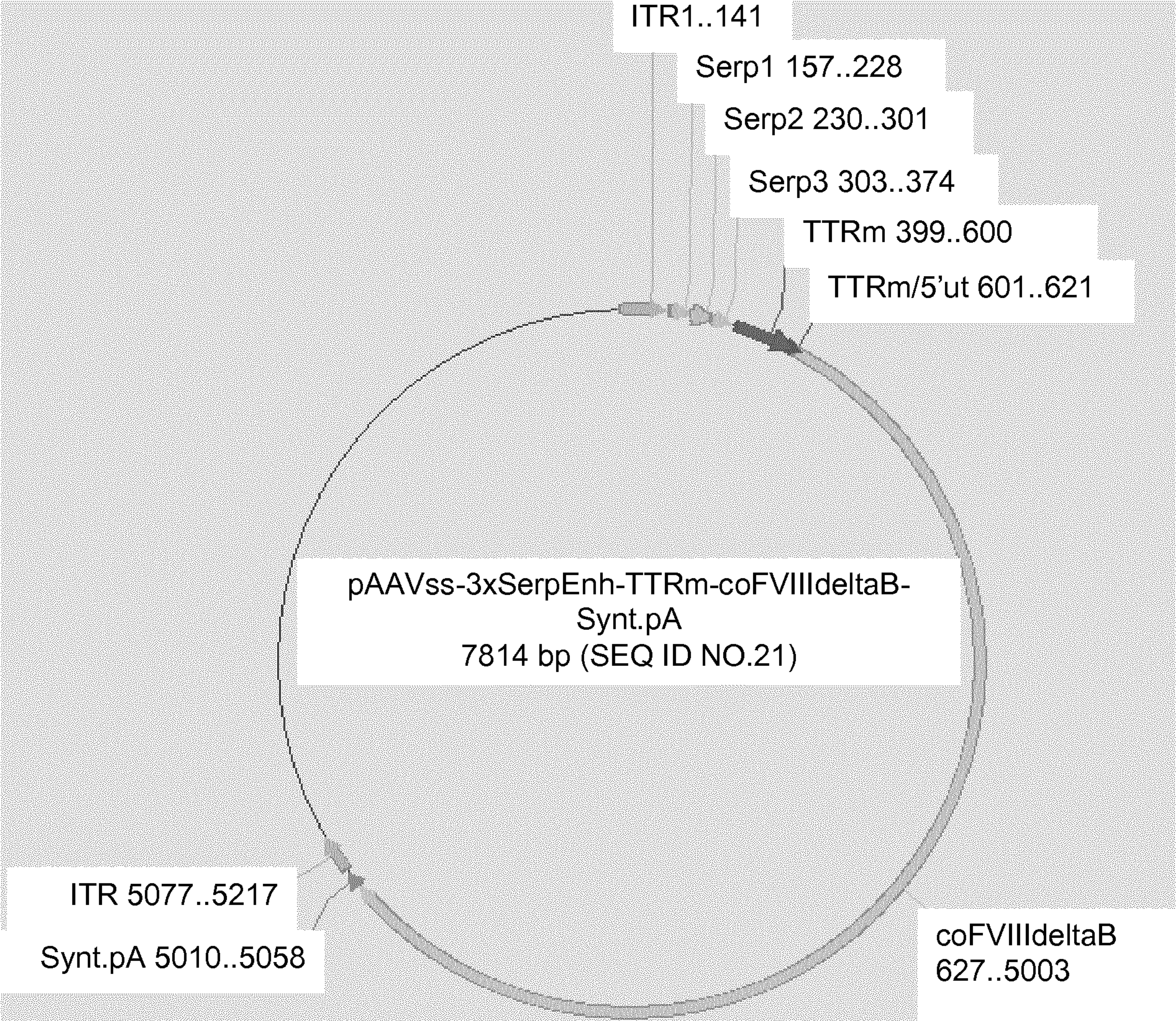


Figure 19

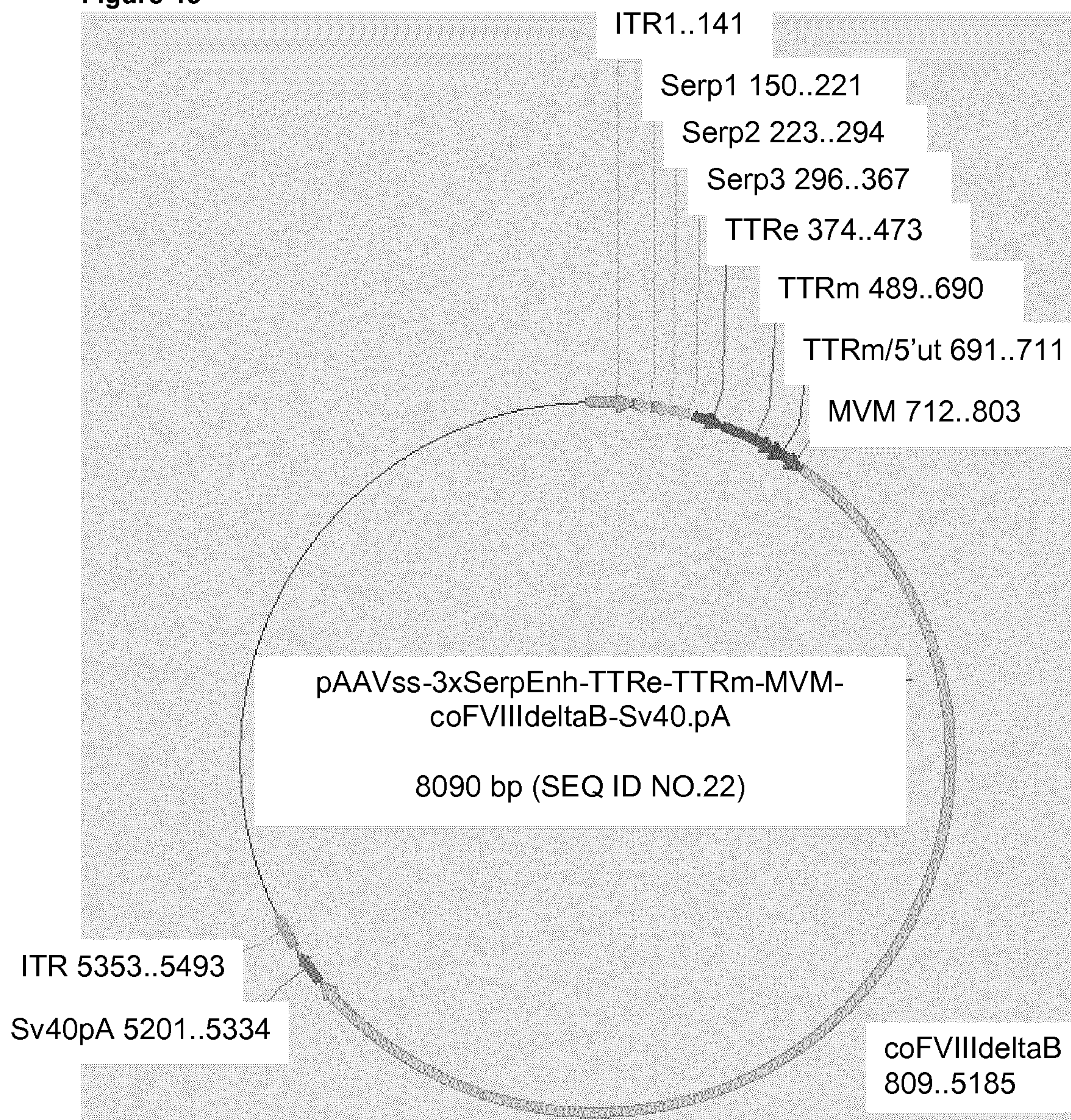


Figure 20

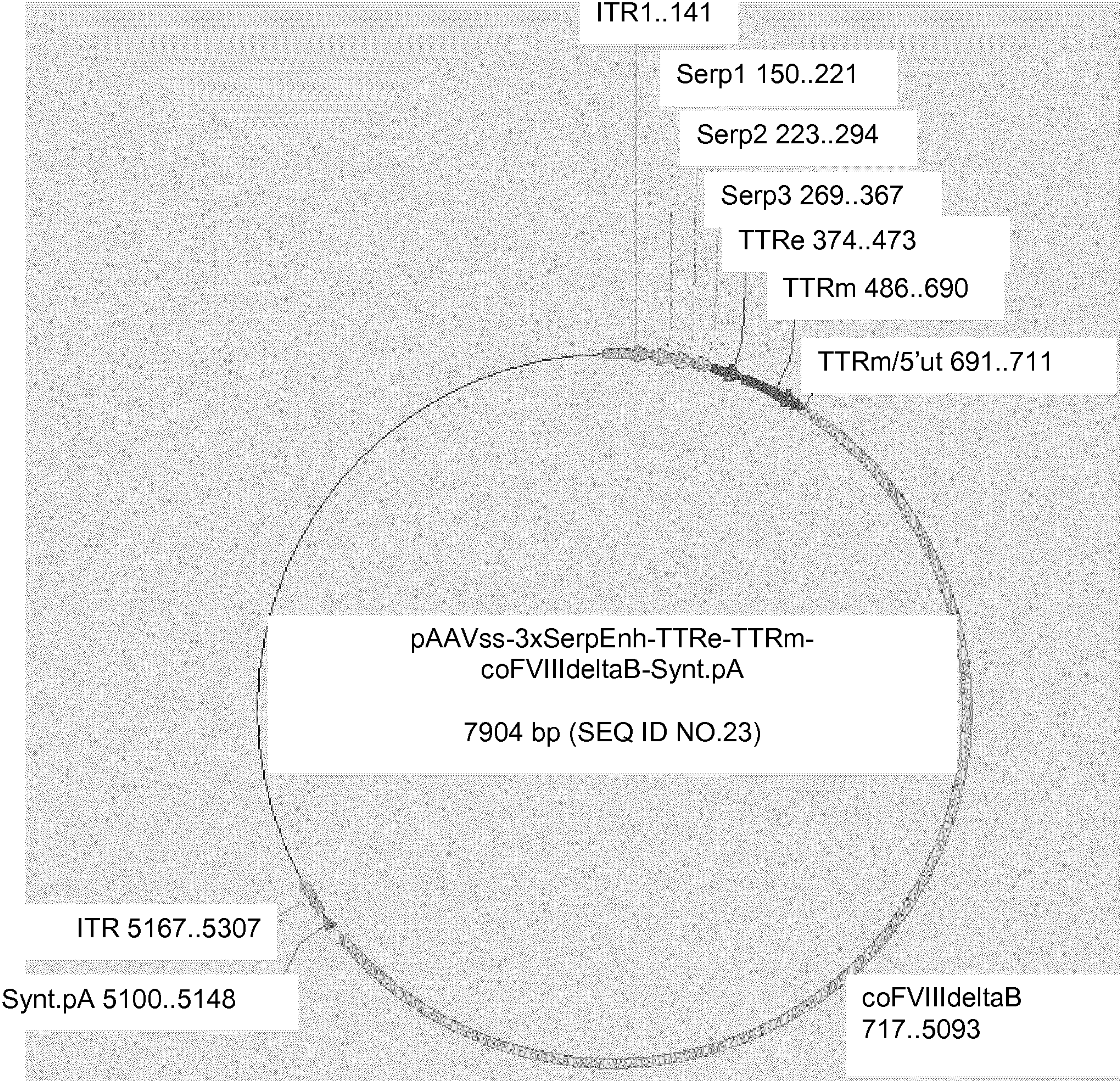


Figure 21

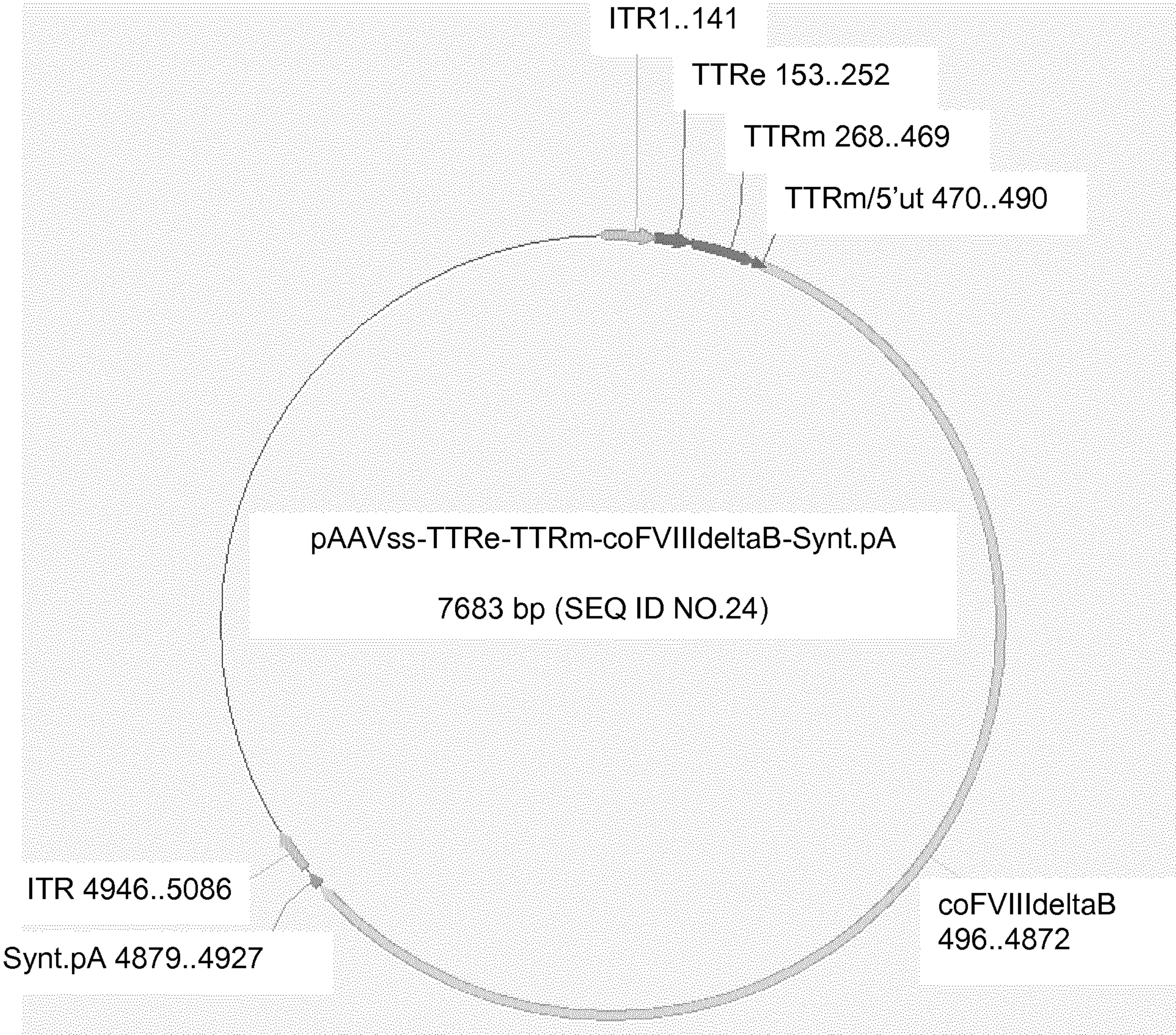


Figure 22

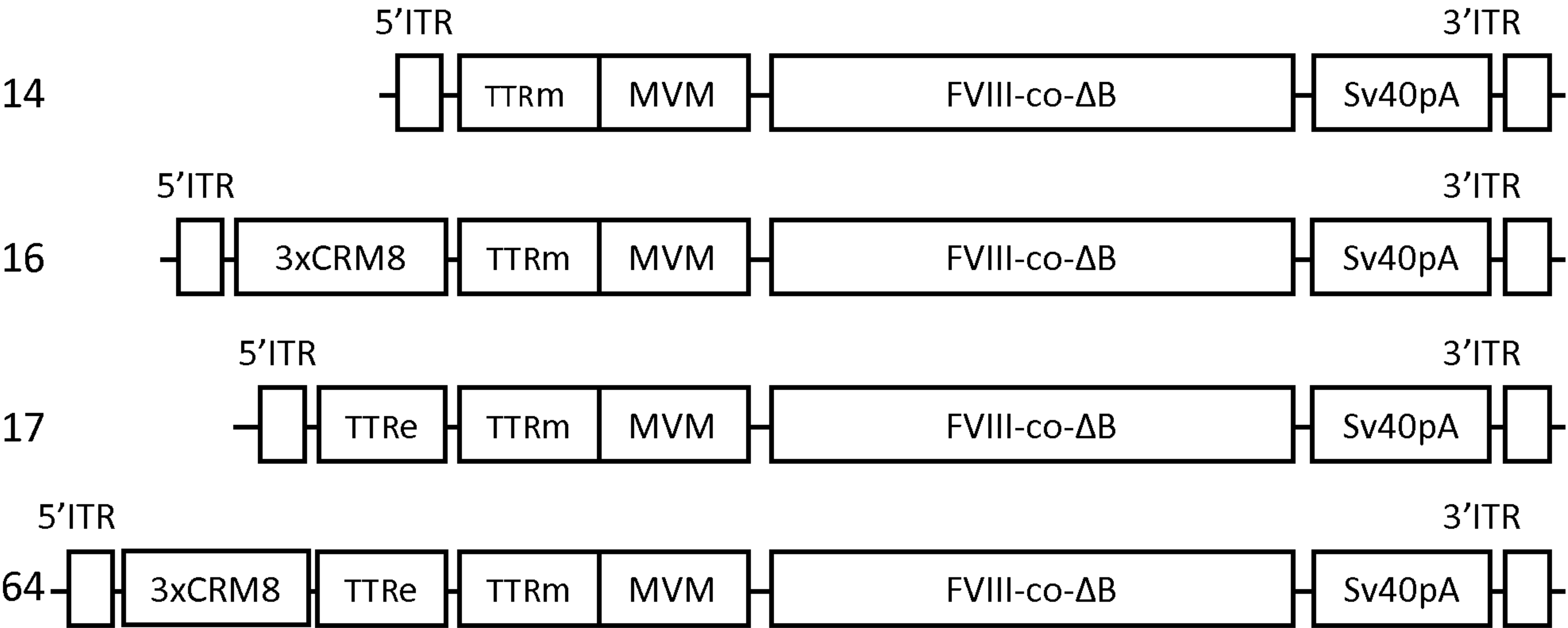


Figure 23

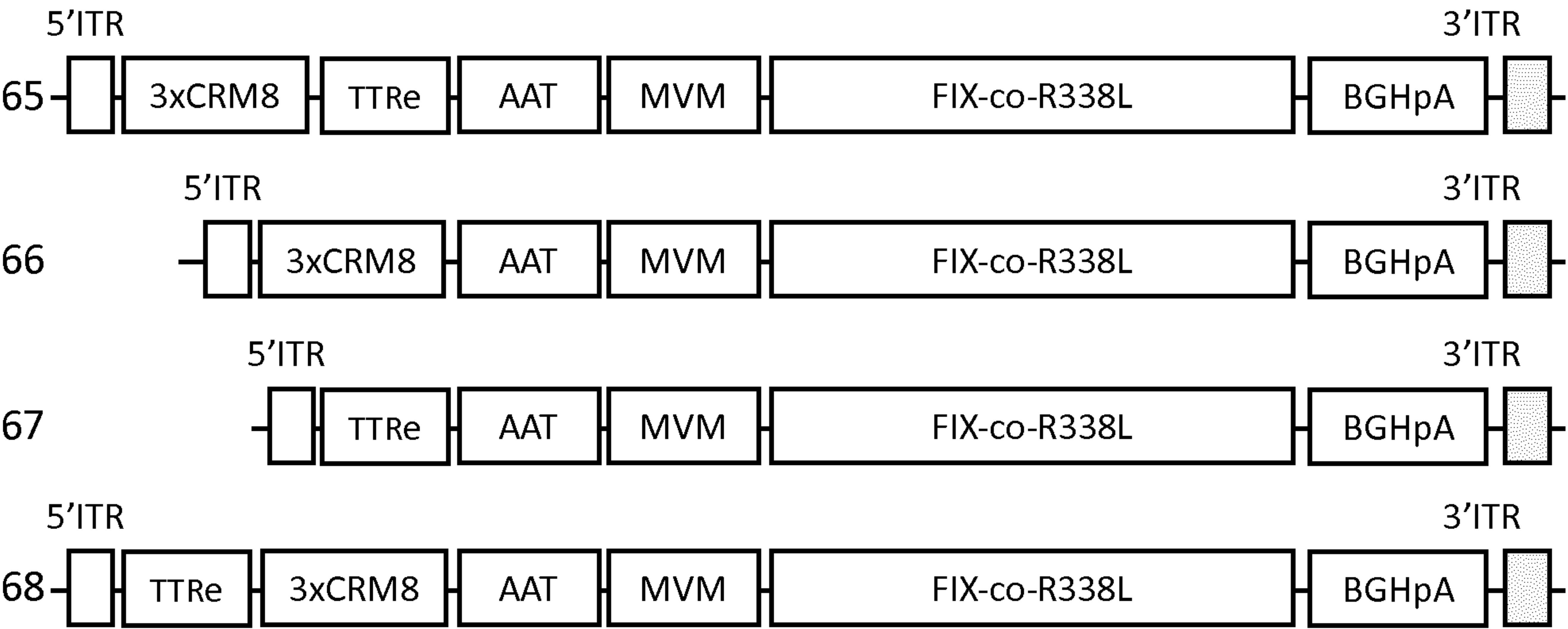


**Figure 24**

SEQ ID NO:64: AAT promoter

GGATCTTGCTACCAGTGGAAACAGCCACTAAGGATTCTGCAGTGAGAGCAGAGGGGCCAGC  
TAAGTGGTACTCTCCCAGAGACTGTCTGACTCACGCCACCCCCTCCACCTTGGACACAG  
GACGCTGTGGTTTCTGAGCCAGGTACAATGACTCCTTTTCGGTAAGTGCAGTGGAAGCTG  
TACACTGCCCAGGCAAAGCGTCCGGGCAGCGTAGGCGGGCGACTCAGATCCCAGCCAGT  
GGACTTAGCCCCCTGTTTGCTCCTCCGATAACTGGGGTGACCTTGGTTAATATTCACCAG  
CAGCCTCCCCCGTTGCCCCCTCTGGATCCACTGCTTAAATACGGACGAGGACAGGGGCCCT  
GTCTCCTCAGCTTCAGGCACCACCCTGACCTGGGACAGTGAATGATCCCCCTGATCTG  
CGGCC

SEQ ID NO:65: pAAVsc-3xSerpEnh-TTRe-AAT-FIX-co-R338L-BGHPA

AGCTGGCGTAATAGCGAAGAGGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCT  
GAATGGCGAATGGCGATTCCGTTGCAATGGCTGGCGGTAATATTGTTCTGGATATTACC  
AGCAAGGCCGATAGTTTGAGTTCTTCTACTCAGGCAAGTGATGTTATTACTAATCAAAG  
AAGTATTGCGACAACGGTTAATTTGCGTGATGGACAGACTCTTTTACTCGGTGGCCTCA  
CTGATTATAAAAACACTTCTCAGGATTCTGGCGTACCGTTCCTGTCTAAAATCCCTTTA  
ATCGGCCTCCTGTTTAGCTCCCGCTCTGATTCTAACGAGGAAAGCACGTTATACGTGCT  
CGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGGCGGGTGTGGTG  
GTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCGCTTT  
CTTCCCTTCCTTTCTCGCCACGTTGCGCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGC  
TCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAACTTGATTAG  
GGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTTCGCCCTTTGACGTT  
GGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTA  
TCTCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAA  
AATGAGCTGATTTAACAAAAATTTAACGCGAACTTTAACAAAATATTAACGTTTACAAT  
TTAAATATTTGCTTATACAATCTTCCTGTTTTTTGGGGCTTTTCTGATTATCAACCGGGG  
TACATATGATTGACATGCTAGTTTTACGATTACCGTTTCATCGCCCTGCGCGCTCGCTCG  
CTCACTGAGGCCGCCCCGGGCAAAGCCCCGGGCGTCGGGCGACCTTTGGTCGCCCCGGCCTC  
AGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGAATTCACGCGTCGGGGGAGGCTGCTGG  
TGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCACCG  
GGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGG  
GGCTAAGTCCACCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCG  
GAGGAGCAAACAGGGGCTAAGTCCACGGCGCGCCCACTGGGAGGATGTTGAGTAAGATG  
GAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG  
GGCGATCAGCAGGTAGGGTACCGGATCTTGCTACCAGTGGAACAGCCACTAAGGATTCT  
GCAGTGAGAGCAGAGGGCCAGCTAAGTGGTACTCTCCAGAGACTGTCTGACTCACGCC  
ACCCCCTCCACCTTGGACACAGGACGCTGTGGTTTTCTGAGCCAGGTACAATGACTCCTT  
TCGGTAAGTGCAGTGGAAGCTGTACACTGCCCAGGCAAAGCGTCCGGGCAGCGTAGGCG  
GGCGACTCAGATCCCAGCCAGTGGACTTAGCCCCCTGTTTGCTCCTCCGATAACTGGGGT  
GACCTTGGTTAATATTCACCAGCAGCCTCCCCCGTTGCCCCCTCTGGATCCACTGCTTAA  
ATACGGACGAGGACAGGGCCCTGTCTCCTCAGCTTCAGGCACCACCCTGACCTGGGAC  
AGTGAATGATCCCCCTGATCTGCGGCCTCTAGAAAGAGGTAAGGGTTTAAGGGATGGTT

GGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTC  
AGGTTGGGCTAGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCT  
GATCACCATCTGCCTGCTGGGCTACCTGCTGAGCGCCGAGTGCACCGTGTTCCCTGGACC  
ACGAGAACGCCAACAAGATCCTGAACCGCCCCAAGCGCTACAACAGCGGCAAGCTGGAG  
GAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGTGCAGCTTCGAGGA  
GGCCCGCGAGGTGTTTCGAGAACACCGAGCGCACCCACCGAGTTCTGGAAGCAGTACGTGG  
ACGGCGACCAGTGCAGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATC  
AACAGCTACGAGTGCTGGTGCCCCCTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGT  
GACCTGCAACATCAAGAACGGCCGCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACA  
AGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTGGCCGAGAACCAGAAGAGCTGCGAG  
CCCGCCGTGCCCTTCCCCCTGCGGGCCGCGTGAGCGTGAGCCAGACCAGCAAGCTGACCCG  
CGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCGAGGCCGAGACCATCC  
TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGTTGGGCGGC  
GAGGACGCCAAGCCCCGGCCAGTTCCCCCTGGCAGGTGGTGCTGAACGGCAAGGTGGACGC  
CTTCTGCGGGCGGCAGCATCGTGAACGAGAAGTGGATCGTGACCGCCGCCCACTGCGTG  
AGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGCACAACATCGAGGAGACCGAGCAC  
ACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCCACCACAACCTACAACGCCGCCAT  
CAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCTGGTGCTGAACA  
GCTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTC  
GGCAGCGGCTACGTGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGCGAGCGCCCTGGT  
GCTGCAGTACCTGCGCGTGCCCCCTGGTGGACCGCGCCACCTGCCTGCTGAGCACCAAGT  
TCACCATCTACAACAACATGTTCTGCGCCGGCTTCCACGAGGGCGGCGCGACAGCTGC  
CAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCTTCCTGACCGG  
CATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGG  
TGAGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGAAAGATGGAT  
TTCCAAGGTTAATTTCATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCCCCTGCAG  
ATCTGAGCCGAATTCCTGCAGCCCGGGGGATCAGCCTCGACTGTGCCTTCTAGTTGCCA  
GCCATCTGTTGTTTGCCCCCTCCCCCGTGCCCTTCCTTGACCCTGGAAGGTGCCACTCCCA  
CTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCT  
ATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAG  
GCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGGGGAC  
CGGTGGATCTCGATAGCAGGCATGCTGGGGAGAGATCGATCTGAGGAACCCCTAGTGAT  
GGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGC  
CCGGGCGTCGGGCGACCTTTGGTTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAG  
GGAGTGGCCAACCCCCCCCCCCCCCCCCCCCCCGGCGATTCTCTTGTGTTTGCTCCAGACTCT  
CAGGCAATGACCTGATAGCCTTTGTAGAGACCTCTCAAAAATAGCTACCCTCTCCGGCA  
TGAATTTATCAGCTAGAACGGTTGAATATCATATTGATGGTGATTTGACTGTCTCCGGC  
CTTTCTCACCCGTTTGAATCTTTACCTACACATTACTCAGGCATTGCATTTAAAATATA  
TGAGGGTTCTAAAAATTTTTATCCTTGCGTTGAAATAAAGGCTTCTCCCGCAAAGTAT  
TACAGGGTCATAATGTTTTTGGTACAACCGATTTAGCTTTATGCTCTGAGGCTTTATTG  
CTTAATTTTGCTAATTCTTTGCCTTGCTGTATGATTTATTGGATGTTGGAATCGCCTG  
ATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTACACCGCATATGGTGCACTCT  
CAGTACAATCTGCTCTGATGCCGCATAGTTATATGGTGCACTCTCAGTACAATCTGCTC  
TGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACAGCCAGCCCCGACACCCG  
CCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACA  
AGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTTCACCGTCATCACCGAAAC

GCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATA  
ATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTG  
TTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAA  
TGCTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTGCGCCCTTA  
TTCCCTTTTTTTCGCGGCATTTTGCCTTCCTGTTTTTGTCTACCCAGAAACGCTGGTGAAA  
GTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACTGGATCTCAA  
CAGCGGTAAGATCCTTGAGAGTTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTT  
TTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTC  
GGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAA  
GCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTG  
ATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCT  
TTTTTGCACAACATGGGGGATCATGTAACCTGCCTTGATCGTTGGGAACCGGAGCTGAA  
TGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGT  
TGCGCAAACCTATTAACCTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGAC  
TGGATGGAGGCGGATAAAGTTGCAGGACCCTTCTGCGCTCGGCCCTTCCGGCTGGCTG  
GTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTCAGCAC  
TGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCA  
ACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTG  
GTAACCTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCATTTTT  
AATTTAAAGGATCTAGGTGAAGATCCTTTTTTGATAATCTCATGACCAAATCCCTTAA  
CGTGAGTTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTG  
AGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAG  
CGGTGGTTTGTGTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTC  
AGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGCTAGCCGTAGTTAGGCCACCACTT  
CAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTG  
CTGCCAGTGCGGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGAT  
AAGGCGCAGCGGTCTGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAAC  
GACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCG  
AAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACG  
AGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCTGGGTTTCGCCACCT  
CTGACTTGAGCGTCGATTTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACG  
CCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGTTT  
TTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGA  
TACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAG  
AGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATG

SEQ ID NO:66: pAAVsc-3xSerpEnh-AAT-FIX-co-R338L-BGHpA

AGCTGGCGTAATAGCGAAGAGGCCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCT  
GAATGGCGAATGGCGATTCCGTTGCAATGGCTGGCGGTAATATTGTTCTGGATATTACC  
AGCAAGGCCGATAGTTTGAGTTCTTCTACTCAGGCAAGTGATGTTATTACTAATCAAAG  
AAGTATTGCGACAACGGTTAATTTGCGTGATGGACAGACTCTTTTACTCGGTGGCCTCA  
CTGATTATAAAAACACTTCTCAGGATTCTGGCGTACCGTTCCTGTCTAAAATCCCTTTA  
ATCGGCCTCCTGTTTAGCTCCCGCTCTGATTCTAACGAGGAAAGCACGTTATACGTGCT  
CGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTG  
GTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCGCTTT

CTTCCCTTCCTTTCTCGCCACGTTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGC  
TCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAACTTGATTAG  
GGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTT  
GGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTA  
TCTCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAA  
AATGAGCTGATTTAACAAAAATTTAACGCGAACTTTAACAAAAATATTAACGTTTACAAT  
TTAAATATTTGCTTATACAATCTTCCTGTTTTTGGGGCTTTTCTGATTATCAACCGGGG  
TACATATGATTGACATGCTAGTTTTACGATTACCGTTCATCGCCCTGCGCGCTCGCTCG  
CTCACTGAGGCCGCCCGGGCAAAGCCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTC  
AGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGAATTCACGCGCCCCGGGGGAGGCTGCTG  
GTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGGCTAAGTCCACC  
GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAG  
GGGCTAAGTCCACCGGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATC  
GGAGGAGCAAACAGGGGGCTAAGTCCACGGTACCGGATCTTGCTACCAGTGGAACAGCCA  
CTAAGGATTCTGCAGTGAGAGCAGAGGGCCAGCTAAGTGGTACTCTCCCAGAGACTGTC  
TGA CTCACGCCACCCCCCTCCACCTTGGACACAGGACGCTGTGGTTTTCTGAGCCAGGTAC  
AATGACTCCTTTTCGGTAAGTGCAGTGGAAGCTGTACACTGCCCAGGCAAAGCGTCCGGG  
CAGCGTAGGCGGGCGACTCAGATCCCAGCCAGTGGACTTAGCCCCCTGTTTGCTCCTCCG  
ATAACTGGGGTGACCTTGGTTAATATTCACCAGCAGCCTCCCCCGTTGCCCTCTGGAT  
CCACTGCTTAAATACGGACGAGGACAGGGCCCTGTCTCCTCAGCTTCAGGCACCACCAC  
TGACCTGGGACAGTGAATGATCCCCCTGATCTGCGGCCTCTAGAAAGAGGTAAGGGTTT  
AAGGGATGGTTGGTTGGTTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAAT  
CACTTTTTTTTCAGGTTGGGCTAGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAG  
AGCCCCGGCCTGATCACCATCTGCCTGCTGGGCTACCTGCTGAGCGCCGAGTGCACCGT  
GTTCTTGACACGAGAACGCCAACAAGATCCTGAACCGCCCCAAGCGCTACAACAGCG  
GCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGTGC  
AGCTTCGAGGAGGCCCGCGAGGTGTTGAGAACACCGAGCGCACCCACCGAGTTCTGGAA  
GCAGTACGTGGACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCA  
AGGACGACATCAACAGCTACGAGTGCTGGTGCCCCCTTCGGCTTCGAGGGCAAGAACTGC  
GAGCTGGACGTGACCTGCAACATCAAGAACGGCCGCTGCGAGCAGTTCTGCAAGAACAG  
CGCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTGGCCGAGAACCAGA  
AGAGCTGCGAGCCCCGCCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAGC  
AAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCGAGGC  
CGAGACCATCCTGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCG  
TGGTGGGCGGCGAGGACGCCAAGCCCGGCCAGTTCCCCTGGCAGGTGGTGCTGAACGGC  
AAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAACGAGAAGTGGATCGTGACCGCCGC  
CCACTGCGTGAGACCGGCGTGAAATCACCGTGGTGGCCGGCGAGCACAACATCGAGG  
AGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCACCACAACACTAC  
AACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCT  
GGTGCTGAACAGCTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCT  
TCCTGAAGTTCGGCAGCGGCTACGTGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGC  
AGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCCCTGGTGGACCGCGCCACCTGCCTGCT  
GAGCACCAGTTACCATCTACAACAACATGTTCTGCGCCGGCTTCACAGAGGGCGGCC  
GCGACAGCTGCCAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGC  
TTCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCAT  
CTACACCAAGGTGAGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAAT

GAAAGATGGATTTCCAAGGTTAATTCATTGGAATTGAAAATTAACAGCCCCCCCCCCCCC  
CCCCCCTGCAGATCTGAGCCGAATTCCTGCAGCCCGGGGGATCAGCCTCGACTGTGCCT  
TCTAGTTGCCAGCCATCTGTTGTTTGCCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGG  
TGCCACTCCCCTGTCTTTCCTAATAAAATGAGGAAATTGCATCGCATTTGTCTGAGTA  
GGTGTCATTTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAA  
GACAATAGCAGGCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAAC  
CAGCTGGGGACCGGTGGATCTCGATAGCAGGCATGCTGGGGAGAGATCGATCTGAGGAA  
CCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGC  
CCGGGCAAAGCCCCGGGCGTCGGGCGACCTTTGGTCGCCCCGGCCTCAGTGAGCGAGCGAG  
CGCGCAGAGAGGGAGTGGCCAACCCCCCCCCCCCCCCCCCCCCCGGCGATTCTCTTGTGTTG  
CTCCAGACTCTCAGGCAATGACCTGATAGCCTTTGTAGAGACCTCTCAAAAATAGCTAC  
CCTCTCCGGCATGAATTTATCAGCTAGAACGGTTGAATATCATATTGATGGTGATTTGA  
CTGTCTCCGGCCTTTCTCACCCGTTTGAATCTTTACCTACACATTACTCAGGCATTGCA  
TTTAAAATATATGAGGGTTCTAAAATTTTTATCCTTGCGTTGAAATAAAGGCTTCTCC  
CGCAAAGTATTACAGGGTCATAATGTTTTTGGTACAACCGATTTAGCTTTATGCTCTG  
AGGCTTTATTGCTTAATTTTGCTAATTCTTTGCCTTGCTGTATGATTTATTGGATGTT  
GGAATCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTACACCCGCATA  
TGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTATATGGTGCACTCTCAGT  
ACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACAGCCAGC  
CCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCC  
GCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTTCACCGTC  
ATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTTATAGGTTAATG  
TCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTTCGGGGAAATGTGCGCGGA  
ACCCCTATTTGTTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATA  
ACCCTGATAAATGCTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCG  
TGTCGCCCCTTATTCCCTTTTTTTGCGGCATTTTGCCTTCCTGTTTTTTGCTCACCCAGAAA  
CGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAA  
CTGGATCTCAACAGCGGTAAAGATCCTTGAGAGTTTTTCGCCCCGAAGAACGTTTTCCAAT  
GATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGC  
AAGAGCAACTCGGTGCGCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTACCA  
GTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCAT  
AACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGG  
AGCTAACCGCTTTTTTTGCACAACATGGGGGATCATGTAACCTCGCCTTGATCGTTGGGAA  
CCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAAT  
GGCAACAACGTTGCGCAAACCTATTAACCTGGCGAACTACTTACTCTAGCTTCCCGGCAAC  
AATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTT  
CCGGCTGGCTGGTTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTAT  
CATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGG  
GGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTG  
ATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAA  
ACTTCATTTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTTGATAATCTCATGACCA  
AAATCCCTTAACGTGAGTTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAA  
GGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACC  
ACCGCTACCAGCGGTGGTTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGG  
TAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTA  
GGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTT

ACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGAT  
AGTTACCGGATAAGGCGCAGCGGTTCGGGCTGAACGGGGGGTTTCGTGCACACAGCCCAGC  
TTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGC  
CACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAG  
GAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCTGGG  
TTTCGCCACCTCTGACTTGAGCGTCGATTTTTTGTGATGCTCGTCAGGGGGGCGGAGCCT  
ATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTG  
CTCACATGTTCTTTCTGCGTTATCCCCCTGATTCTGTGGATAACCGTATTACCGCCTTT  
GAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGA  
GGAAGCGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATT  
AATG

SEQ ID NO:67: pAAV<sub>sc</sub>-TTR<sub>e</sub>-AAT-FIX-co-R338L-BGHpA

AGCTGGCGTAATAGCGAAGAGGCCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCT  
GAATGGCGAATGGCGATTCCGTTGCAATGGCTGGCGGTAATATTGTTCTGGATATTACC  
AGCAAGGCCGATAGTTTGAGTTCTTCTACTCAGGCAAGTGATGTTATTACTAATCAAAG  
AAGTATTGCGACAACGGTTAATTTGCGTGATGGACAGACTCTTTTACTCGGTGGCCTCA  
CTGATTATAAAAACACTTCTCAGGATTCTGGCGTACCGTTCCTGTCTAAAATCCCTTTA  
ATCGGCCTCCTGTTTAGCTCCCGCTCTGATTCTAACGAGGAAAGCACGTTATACGTGCT  
CGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTG  
GTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCGCTTT  
CTTCCCTTCCTTTCTCGCCACGTTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGC  
TCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAACTTGATTAG  
GGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTTCGCCCTTTGACGTT  
GGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTA  
TCTCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAA  
AATGAGCTGATTTAACAAAAATTTAACGCGAACTTTAACAAAATATTAACGTTTACAAT  
TTAAATATTTGCTTATAACAATCTTCCTGTTTTTTGGGGCTTTTCTGATTATCAACCGGGG  
TACATATGATTGACATGCTAGTTTTACGATTACCGTTCATCGCCCTGCGCGCTCGCTCG  
CTCACTGAGGCCGCCCGGGCAAAGCCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTC  
AGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGAATTCACGCGCCCACTGGGAGGATGTT  
GAGTAAGATGGAAAACACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGA  
ACAGGGGCGGGCGATCAGCAGGTAGGGTACCGGATCTTGCTACCAGTGGAACAGCCAC  
TAAGGATTCTGCAGTGAGAGCAGAGGGCCAGCTAAGTGGTACTCTCCCAGAGACTGTCT  
GACTCACGCCACCCCCTCCACCTTGGACACAGGACGCTGTGGTTTTCTGAGCCAGGTACA  
ATGACTCCTTTTCGGTAAGTGCAAGTGAAGCTGTACACTGCCCAGGCAAAGCGTCCGGGC  
AGCGTAGGCGGGCGACTCAGATCCCAGCCAGTGGACTTAGCCCCCTGTTTGCTCCTCCGA  
TAACTGGGGTGACCTTGGTTAATATTCACCAGCAGCCTCCCCCGTTGCCCTCTGGATC  
CACTGCTTAAATACGGACGAGGACAGGGCCCTGTCTCCTCAGCTTCAGGCACCACCCT  
GACCTGGGACAGTGAATGATCCCCCTGATCTGCGGCCTCTAGAAAGAGGTAAGGGTTTA  
AGGGATGGTTGGTTGGTGGGGTATTAATGTTTAAATTACCTGGAGCACCTGCCTGAAATC  
ACTTTTTTTCAGGTTGGGCTAGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGA  
GCCCCGGCCTGATCACCATCTGCCTGCTGGGCTACCTGCTGAGCGCCGAGTGCACCGTG  
TTCTTGGAACACGAGAACGCCAACAAGATCCTGAACCGCCCCAAGCGCTACAACAGCGG  
CAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGTGCA

GCTTCGAGGAGGCCCCGCGAGGTGTTCGAGAACACCGAGCGCACCCACCGAGTTCTGGAAG  
CAGTACGTGGACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAA  
GGACGACATCAACAGCTACGAGTGCTGGTGCCCCCTTCGGCTTCGAGGGCAAGAACTGCG  
AGCTGGACGTGACCTGCAACATCAAGAACGGCCGCTGCGAGCAGTTCTGCAAGAACAGC  
GCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTGGCCGAGAACCAGAA  
GAGCTGCGAGCCCCGCCGTGCCCTTCCCCCTGCGGGCCGCGTGAGCGTGAGCCAGACCAGCA  
AGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCCGAGGCC  
GAGACCATCCTGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGT  
GGTGGGCGGGCGAGGACGCCAAGCCCCGGCCAGTTCCCCCTGGCAGGTGGTGTGCTGAACGGCA  
AGGTGGACGCCTTCTGCGGGCGGCAGCATCGTGAACGAGAAGTGGATCGTGACCGCCGCC  
CACTGCGTGAGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGCACAAACATCGAGGA  
GACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCCACCACAACACTACA  
ACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCTG  
GTGCTGAACAGCTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTT  
CCTGAAGTTCGGCAGCGGCTACGTGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGCA  
GCGCCCTGGTGTGCTGCAGTACCTGCGCGTGCCCCCTGGTGGACCGCGCCACCTGCCTGCTG  
AGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCACGAGGGCGGGCCG  
CGACAGCTGCCAGGGCGACAGCGGGCGGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCT  
TCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATC  
TACACCAAGGTGAGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATG  
AAAGATGGATTTCCAAGGTTAATTCATTGGAATTGAAAATTAACAGCCCCCCCCCCCCC  
CCCCCTGCAGATCTGAGCCGAATTCCTGCAGCCCCGGGGGATCAGCCTCGACTGTGCCTT  
CTAGTTGCCAGCCATCTGTTGTTTGCCCCCTCCCCCGTGCTTCCTTGACCCTGGAAGGT  
GCCACTCCCCTGTCTTTTCTAATAAAATGAGGAAATTGCATCGCATTTGTCTGAGTAG  
GTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAG  
ACAATAGCAGGCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACC  
AGCTGGGGACCGGTGGATCTCGATAGCAGGCATGCTGGGGAGAGATCGATCTGAGGAAC  
CCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGCC  
CGGGCAAAGCCCCGGGCGTCGGGCGACCTTTGGTTCGCCCGGCCCTCAGTGAGCGAGCGAGC  
GCGCAGAGAGGGAGTGGCCAACCCCCCCCCCCCCCCCCCCCCCGGCGATTCTCTTGTTC  
TCCAGACTCTCAGGCAATGACCTGATAGCCTTTGTAGAGACCTCTCAAAAATAGCTACC  
CTCTCCGGCATGAATTTATCAGCTAGAACGGTTGAATATCATATTGATGGTGATTTGAC  
TGTCTCCGGCCTTTCTCACCCGTTTGAATCTTTACCTACACATTACTCAGGCATTGCAT  
TTAAAATATATGAGGGTTCTAAAAATTTTTATCCTTGCGTTGAAATAAAGGCTTCTCCC  
GCAAAAGTATTACAGGGTCATAATGTTTTTGGTACAACCGATTTAGCTTTTATGCTCTGA  
GGCTTTTATTGCTTAATTTTGCTAATTCTTTGCCTTGCTGTATGATTTATTGGATGTTG  
GAATCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTTACACCGCATAT  
GGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTATATGGTGCACTCTCAGTA  
CAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACAGCCAGCC  
CCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCG  
CTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTTACCGTCA  
TCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTTATAGGTTAATGT  
CATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAA  
CCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAA  
CCCTGATAAATGCTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGT  
GTCGCCCTTATTCCCTTTTTTTCGCGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAAC

GCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAAC  
TGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTTCGCCCCGAAGAACGTTTTTCCAATG  
ATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCA  
AGAGCAACTCGGTGCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAG  
TCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATA  
ACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGA  
GCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAAC  
CGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATG  
GCAACAACGTTGCGCAAACCTATTAACCTGGCGAACTACTTACTCTAGCTTCCCGGCAACA  
ATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTC  
CGGCTGGCTGGTTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATC  
ATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGG  
GAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGA  
TTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAA  
CTTCATTTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTTGATAATCTCATGACCAA  
AATCCCTTAACGTGAGTTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAG  
GATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAACCA  
CCGCTACCAGCGGTGGTTTGTGTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGT  
AACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAG  
GCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTA  
CCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATA  
GTTACCGGATAAGGCGCAGCGGTGCGGCTGAACGGGGGGTTTCGTGCACACAGCCCAGCT  
TGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCC  
ACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGG  
AGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGT  
TTCGCCACCTCTGACTTGAGCGTCGATTTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTA  
TGGA AAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGC  
TCACATGTTCTTTCTGCGTTATCCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTG  
AGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAG  
GAAGCGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTTCATTA  
ATG

SEQ ID NO:68: pAAVsc-TTRe-3xSerpEnh-AAT-FIX-co-R338L-BGHPA

AGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCT  
GAATGGCGAATGGCGATTCCGTTGCAATGGCTGGCGGTAATATTGTTCTGGATATTACC  
AGCAAGGCCGATAGTTTGAGTTCTTCTACTCAGGCAAGTGATGTTATTACTAATCAAAG  
AAGTATTGCGACAACGGTTAATTTGCGTGATGGACAGACTCTTTTACTCGGTGGCCTCA  
CTGATTATAAAAACACTTCTCAGGATTCTGGCGTACCGTTCCTGTCTAAAATCCCTTTA  
ATCGGCCTCCTGTTTAGCTCCCGCTCTGATTCTAACGAGGAAAGCACGTTATACGTGCT  
CGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTG  
GTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCGCTTT  
CTTCCCTTCCTTTCTCGCCACGTTGCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGC  
TCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAACTTGATTAG  
GGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTTCGCCCTTTGACGTT  
GGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTA

TCTCGGTCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTTCGGCCTATTGGTTAAAA  
AATGAGCTGATTTAACAAAAATTTAACGCGAACTTTAACAAAATATTAACGTTTACAAT  
TTAAATATTTGCTTATACAATCTTCCTGTTTTTGGGGCTTTTCTGATTATCAACCGGGG  
TACATATGATTGACATGCTAGTTTTACGATTACCGTTCATCGCCCTGCGCGCTCGCTCG  
CTCACTGAGGCCGCCCGGGCAAAGCCCCGGGCGTCGGGCGACCTTTGGTCGCCCCGGCCTC  
AGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGAATTCACGCGTCACTGGGAGGATGTTG  
AGTAAGATGGAAAACACTGATGACCCTTGACAGAGACAGAGTATTAGGACATGTTTGAA  
CAGGGGCCGGGCGATCAGCAGGTAGGGCGCGCCCCGGGGGAGGCTGCTGGTGAATATTAA  
CCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCACCGGGGGAGGCTG  
CTGGTGAATATTAAACCAAGGTCACCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCC  
ACCGGGGGAGGCTGCTGGTGAATATTAAACCAAGGTCACCCAGTTATCGGAGGAGCAA  
CAGGGGCTAAGTCCACGGTACCGGATCTTGCTACCAGTGGAACAGCCACTAAGGATTCT  
GCAGTGAGAGCAGAGGGCCAGCTAAGTGGTACTCTCCAGAGACTGTCTGACTCACGCC  
ACCCCTCCACCTTGACACAGGACGCTGTGGTTTTCTGAGCCAGGTACAATGACTCCTT  
TCGGTAAGTGCAGTGGAAGCTGTACACTGCCCAGGCAAAGCGTCCGGGCAGCGTAGGCG  
GGCGACTCAGATCCCAGCCAGTGGACTTAGCCCCCTGTTTGCTCCTCCGATAACTGGGGT  
GACCTTGGTTAATATTCACCAGCAGCCTCCCCCGTTGCCCTCTGGATCCACTGCTTAA  
ATACGGACGAGGACAGGGCCCTGTCTCCTCAGCTTCAGGCACCACCAGTACCTGGGAC  
AGTGAATGATCCCCCTGATCTGCGGCCTCTAGAAAGAGGTAAGGGTTTAAGGGATGGTT  
GGTTGGTGGGGTATTAATGTTTAAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTC  
AGGTTGGGCTAGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCT  
GATCACCATCTGCCTGCTGGGCTACCTGCTGAGCGCCGAGTGCACCGTGTTCTTGACC  
ACGAGAACGCCAACAAGATCCTGAACCGCCCCAAGCGCTACAACAGCGGCAAGCTGGAG  
GAGTTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGTGCAGCTTCGAGGA  
GGCCCGCGAGGTGTTTCGAGAACACCGAGCGCACCAACCGAGTTCTGGAAGCAGTACGTGG  
ACGGCGACCAAGTGCAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATC  
AACAGCTACGAGTGCTGGTGCCCCCTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGT  
GACCTGCAACATCAAGAACGGCCGCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACA  
AGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTGGCCGAGAACCAGAAGAGCTGCGAG  
CCCGCCGTGCCCTTCCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAGCAAGCTGACCCG  
CGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCGAGGCCGAGACCATCC  
TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGC  
GAGGACGCCAAGCCCCGGCCAGTTCCCCCTGGCAGGTGGTGCTGAACGGCAAGGTGGACGC  
CTTCTGCGGCGGCAGCATCGTGAACGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGG  
AGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGCACAAACATCGAGGAGACCGAGCAC  
ACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCCACCACAACACTACAACGCCGCCAT  
CAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCTGGTGCTGAACA  
GCTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTC  
GGCAGCGGCTACGTGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGAGCGCCCTGGT  
GCTGCAGTACCTGCGCGTGCCCCCTGGTGGACCGCGCCACCTGCCTGCTGAGCACCAAGT  
TCACCATCTACAACAACATGTTCTGCGCCGGCTTCCACGAGGGCGGCGCGACAGCTGC  
CAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAAGCTTCCTGACCGG  
CATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGG  
TGAGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGAAAGATGGAT  
TTCCAAGGTTAATTCATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCCCCTGCAG  
ATCTGAGCCGAATTCCTGCAGCCCCGGGGGATCAGCCTCGACTGTGCCTTCTAGTTGCCA

GCCATCTGTTGTTTGCCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCA  
CTGTCCTTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCT  
ATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAG  
GCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGGGGAC  
CGGTGGATCTCGATAGCAGGCATGCTGGGGAGAGATCGATCTGAGGAACCCCTAGTGAT  
GGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGC  
CCGGGCGTCGGGCGACCTTTGGTCGCCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAG  
GGAGTGGCCAACCCCCCCCCCCCCCCCCCCCCCGGCGATTCTCTTGTTTGCTCCAGACTCT  
CAGGCAATGACCTGATAGCCTTTGTAGAGACCTCTCAAAAATAGCTACCCTCTCCGGCA  
TGAATTTATCAGCTAGAACGGTTGAATATCATATTGATGGTGATTTGACTGTCTCCGGC  
CTTTCTCACCCGTTTGAATCTTTACCTACACATTACTCAGGCATTGCATTTAAAATATA  
TGAGGGTTCTAAAAATTTTTATCCTTGCGTTGAAATAAAGGCTTCTCCCGCAAAGTAT  
TACAGGGTCATAATGTTTTTGGTACAACCGATTTAGCTTTATGCTCTGAGGCTTTATTG  
CTTAATTTTGCTAATTCTTTGCCTTGCTGTATGATTTATTGGATGTTGGAATCGCCTG  
ATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTACACCGCATATGGTGCACTCT  
CAGTACAATCTGCTCTGATGCCGCATAGTTATATGGTGCACTCTCAGTACAATCTGCTC  
TGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACAGCCAGCCCCGACACCCG  
CCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACA  
AGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTACCGTCATCACCGAAAC  
GCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATA  
ATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTG  
TTTATTTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAA  
TGCTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTGCCCCTTA  
TTCCCTTTTTTTCGCGGCATTTTGCCTTCCTGTTTTTGTCTACCCAGAAACGCTGGTGAAA  
GTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTACATCGAACTGGATCTCAA  
CAGCGGTAAGATCCTTGAGAGTTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTT  
TTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTC  
GGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTACCAGTCACAGAAAA  
GCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTG  
ATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCT  
TTTTTGCACAACATGGGGGATCATGTAACCTCGCCTTGATCGTTGGGAACCGGAGCTGAA  
TGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGT  
TGCGCAAACCTATTAACCTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGAC  
TGGATGGAGGCGGATAAAGTTGCAGGACCACCTTCTGCGCTCGGCCCTTCCGGCTGGCTG  
GTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCAC  
TGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCA  
ACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTG  
GTAACCTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACCTTCATTTTT  
AATTTAAAAGGATCTAGGTGAAGATCCTTTTTTGATAATCTCATGACCAAAATCCCTTAA  
CGTGAGTTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTG  
AGATCCTTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAG  
CGGTGGTTTGTGTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTC  
AGCAGAGCGCAGATAACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTT  
CAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTG  
CTGCCAGTGGCGATAAGTCGTGCTTACCGGGTTGGACTCAAGACGATAGTTACCGGAT  
AAGGCGCAGCGGTGCGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAAC

GACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCG  
AAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACG  
AGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCT  
CTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACG  
CCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGTTC  
TTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGA  
TACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAG  
AGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATG

SEQ ID NO:69: TTRe-TTRm

CACTGGGAGGATGTTGAGTAAGATGGAAAACCTACTGATGACCCTTGCAGAGACAGAGTA  
TTAGGACATGTTTGAACAGGGGCGGGCGATCAGCAGGTAGCTCTAGAGGATCCCCGTC  
TGTCTGCACATTTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTCA  
TATTTGTGTAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCAGAATCAGCAG  
GTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGC  
CCCTTCACCAGGAGAAGCCGTC

Figure 25a

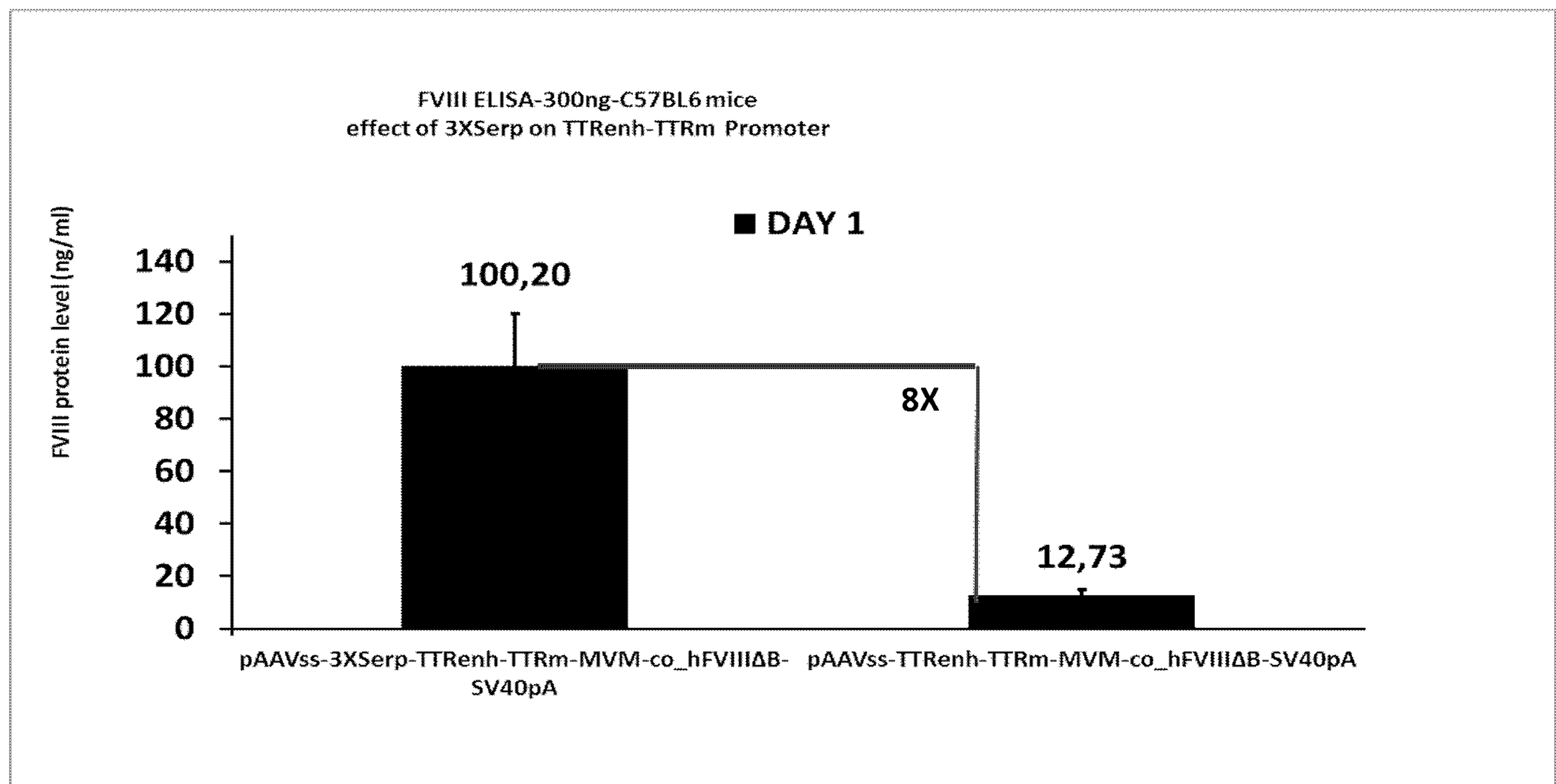


Figure 25b

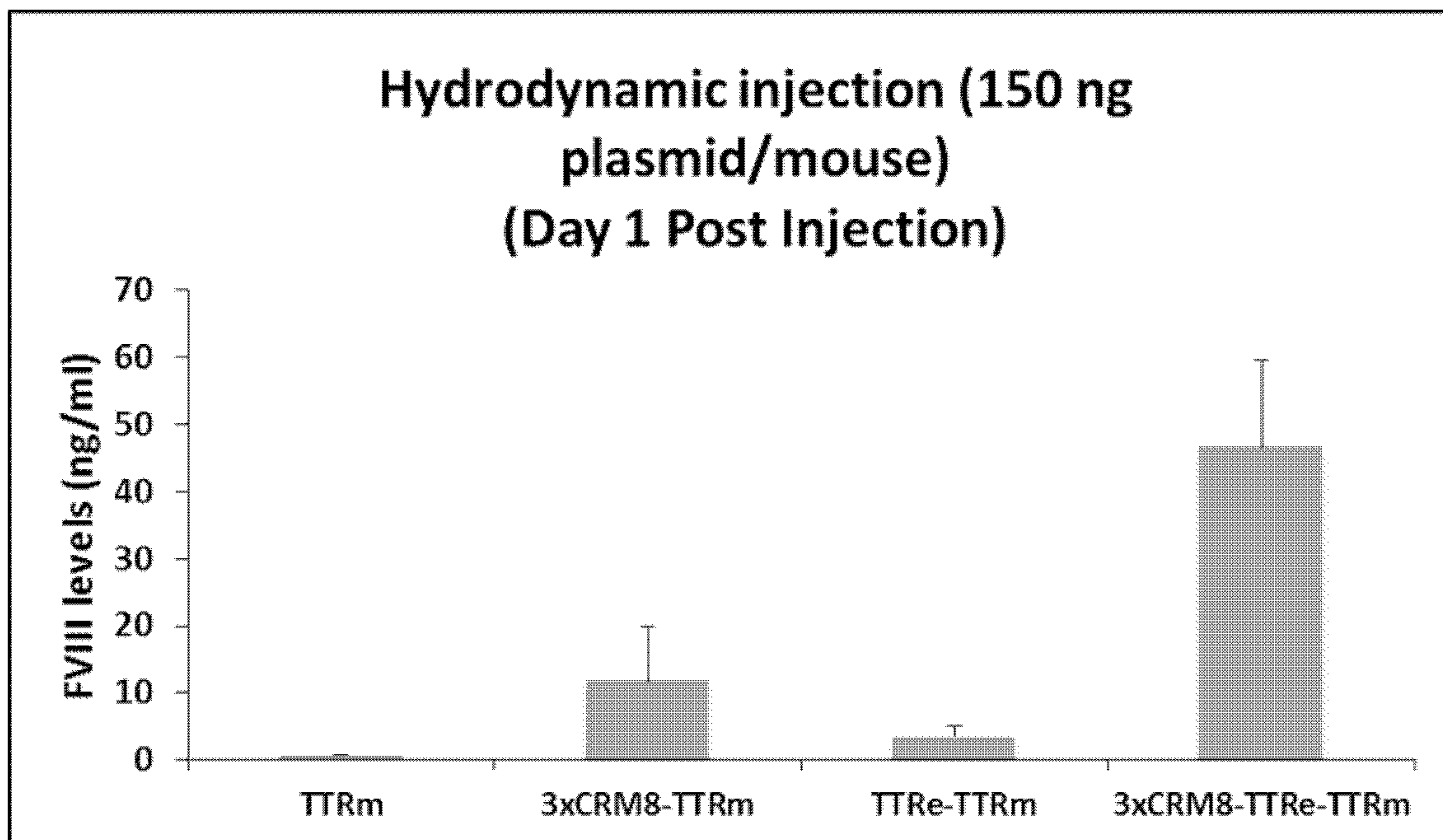


Figure 1

