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DESCRIPTION

FIELD OF THE INVENTION

[0001] The invention relates to nucleic acid expression cassettes and expression vectors for gene 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.

BACKGROUND OF THE INVENTION

[0002] 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 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-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, 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).

[0003] The severity of hemophilia A and hemophilia B has been classified by the subcommittee on 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 (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.

[0004] 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.

[0005] 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).

[0006] 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 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 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 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 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 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).

[0007] 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 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 (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.

[0008] 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.

[0009] 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).

[0010] 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.

[0011] 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.

[0012] 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).

[0013] 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).

[0014] In WO 2014/064277 expression vectors are described which combine the robust Serpin enhancer with codon-optimized transgenes encoding FIX or FVIII, resulting in increased liver-specific expression of FIX and FVIII, respectively.

[0015] 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.

SUMMARY OF THE INVENTION

[0016] 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 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.

[0017] 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 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 that are tandemly arranged with the known natural TTR enhancer further increases FIX expression by 6 to 10 fold. This increase in hFIX activity was shown to be 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 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 enhancer that are tandemly arranged 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.

[0018] The combination of the tandemly arranged triple repeat of the Serpin enhancer defined by SEQ ID NO:11 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 may be 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 a tandemly arranged triple repeat of the SerpEnh (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.

[0019] The invention therefore provides the following aspects:
Aspect 1. A nucleic acid expression cassette comprising: a tandemly arranged triple repeat, of a liver-specific nucleic acid regulatory element, said triple repeat consisting of the nucleic acid fragment defined by SEQ ID NO:11; and a nucleic acid regulatory element consisting of the nucleic acid fragment defined by SEQ ID NO:12 (TTRe); said triple repeat and said regulatory element being operably linked to a promoter and a transgene, preferably a codon-optimized transgene, wherein the promoter is a liver-specific promoter.

[0020] 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.

[0021] In another preferred embodiment, said liver-specific promoter is derived from the AAT promoter, e.g. as defined by SEQ ID NO.64.

[0022] In further embodiments, the liver-specific promotor is selected from the group comprising: the transthyretin (TTR) promoter or TTR-minimal promoter (TTRm), the alpha 1-antitrypsin (AAT) 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 lectin serine protease 2 (MASP2) promoter, the hepcidin antimicrobial peptide (HAMP) promoter, or the serpin peptidase inhibitor, clade C (antithrombin), member 1 (SERPINC1) promoter.

[0023] In an embodiment, the combination of the TTRe and TTRm nucleic acid modules is defined by SEQ ID NO.69.

[0024] Aspect 2, The nucleic acid expression cassette according to aspect 1, 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 promotor and a transgene, or the nucleic acid regulatory element as defined by SEQ ID NO:58, operably linked to a transgene.

[0025] Aspect 3. The nucleic acid expression cassette according to aspect 1 or 2, wherein said transgene encodes for coagulation factor VIII or coagulation factor IX.

[0026] Aspect 4. The nucleic acid expression cassette according to aspect 3, wherein said coagulation factor VIII has a deletion of the B domain.

[0027] Aspect 5. The nucleic acid expression cassette according to aspect 4, wherein said B domain of said FVIII is replaced by a linker defined by SEQ ID NO:59.

[0028] Aspect 6. The nucleic acid expression cassette according to any one of aspects 3 to 5, wherein said transgene encoding for coagulation factor VIII is defined by SEQ ID NO: 18.

[0029] Aspect 7. The nucleic acid expression cassette according to aspect 3, wherein said coagulation factor IX contains a hyper-activating mutation.

[0030] Aspect 8. The nucleic acid expression cassette according to aspect 7, wherein said hyper-activating mutation in coagulation factor IX corresponds to an R338L amino acid substitution.

[0031] Aspect 9. The nucleic acid expression cassette according to any one of aspects 3, 7 or 8, wherein said transgene encoding for coagulation factor IX is defined by SEQ ID NO:9.

[0032] Aspect 10. The nucleic acid expression cassette according to any one of aspects 1 to 9 wherein said liver-specific promoter is a promoter derived from the transthyretin (TTR) promoter, preferably the minimal TTR promotor as defined by SEQ ID NO:6.

[0033] Aspect 11. The nucleic acid expression cassette according to any one of aspects 1 to 10, further comprising a minute virus of mouse (MVM) intron, preferably the MVM intron as defined by SEQ ID NO:8.

[0034] Aspect 12. The nucleic acid expression cassette according to any one of aspects 1 to 11, 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.

[0035] Aspect 13. A vector comprising the nucleic acid expression cassette according to any one of aspects 1 to 12.

[0036] Aspect 14. The vector according to aspect 13, wherein said vector is a viral vector.

[0037] Aspect 15. The vector according to aspect 14, wherein said vector is derived from an adeno-associated virus (AAV).

[0038] Aspect 16. The vector according to aspect 15, wherein said vector is a single-stranded AAV vector, preferably a single-stranded AAV serotype 8 vector.

[0039] Aspect 17. The vector according to any one of aspects 13 to 16, 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.

[0040] Aspect 18. The vector according to aspect 15, wherein said vector is a self-complementary AAV vector, preferably a self-complementary AAV serotype 9 vector.

[0041] Aspect 19. The vector according to any one of aspects 13 to 15, or 18, 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 13 to 15, or 18, 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 20. The vector according to aspect 13, 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).

[0042] Aspect 21. The vector according to any one of aspects 13 to 17, or 20 comprising the FVIII transgene for use in the treatment of hemophilia A.

[0043] Aspect 22. The vector according to any one of aspects 13 to 15, 18 to 20 comprising the FIX transgene for use in the treatment of hemophilia B.

[0044] Aspect 23. A pharmaceutical composition comprising a vector according to any one of aspects 13 to 17, or 20 and a pharmaceutically acceptable carrier, optionally further comprising an active ingredient for treating hemophilia A when the transgene in said vector is FVIII.

[0045] Aspect 24. The vector for use according to aspect 21, wherein after transduction or transfection of the vector into a subject levels of factor VIII in plasma of the treated subject that are equal to or higher than the therapeutic threshold concentration of 10 mU/ml plasma in the subject are obtained.

[0046] Aspect 25. The vector for use according to any one of aspects 21 or 24, wherein said treatment comprises the transduction of the vector according to any one of aspects 13 to 17 into the subject at a dose lower than or equal than $2x10^{11}$ vg/kg.

[0047] Aspect 26. A pharmaceutical composition comprising a vector according to any one of aspects 13 to 15, 18 to 20 and a pharmaceutically acceptable carrier, optionally further comprising an active ingredient for treating hemophilia B when the transgene in said vector is FIX.

[0048] Aspect 27. The vector for use according to aspect 22, wherein after transduction or transfection of the vector into a subject 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 the subject are obtained, 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.

[0049] Aspect 28. The vector for use according to aspect 22 or 27, wherein said treatment comprises the transduction of the vector according to any one of aspects 13 to 15, 18 or 19 into the subject at a dose lower than or equal than $2x10^{11}$vg/kg.

BRIEF DESCRIPTION OF THE FIGURES

[0050] 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.

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 (cohFVIIIdeltaB). 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 1x10e9 vg/mouse (Low Dose) for the different vector systems described in Figure 1; 3b): the protein expression levels achieved upon transduction with 5x10e9 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 1x10e9 vg/mouse (Low Dose) for the different vector systems described in Figure 2; 4b): the protein expression levels achieved upon transduction with 5x10e9 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-coFVIIIdeltaB-Sv40pA vector

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

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

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

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-TTREnh-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** (SEQ ID NO:31); **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).

Figure 14: Nucleotide sequence of pAAVss-TTRm-MVM-coFVIIIdeltaB-Sv40pA (SEQ ID NO:14); pAAVss-SerpEnh-TTRm-MVM- coFVIIIdeltaB-Sv40pA (SEQ ID NO:15); pAAVss-3xSerpEnh-TTRm-MVM-coFVIIIdeltaB-Sv40pA (SEQ ID NO:16); pAAVss-TTRe-TTRm-MVM-coFVIIIdeltaB-Sv40pA (SEQ ID NO:17); codon-optimized transgene encoding B domain deleted human factor VIII (coFVIIIdeltaB) (SEQ ID NO:18); Simian virus 40 polyadenylation

signal (SV40polyA) (SEQ ID NO:19); pAAVss-3xSerpEnh-TTRm-MVM-coFVIIIdeltaB-Synt.pA (SEQ ID NO:20); pAAVss-3xSerpEnh-TTRm-coFVIIIdeltaB-Synt.pA (SEQ ID NO:21); pAAVss-3xSerpEnh-TTRe-TTRm-MVM-coFVIIIdeltaB-Sv40pA (SEQ ID NO:22); pAAVss-3xSerpEnh-TTRe-TTRm-coFVIIIdeltaB-Synt.pA (SEQ ID NO:23); pAAVss-TTRe-TTRm-coFVIIIdeltaB-Synt.pA (SEQ ID NO:24); **Flank**-3xSERP-*Flank* (SEQ ID NO:38); **Flank**-3xSERP-**Flank**-*TTRe* (SEQ ID NO:39); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank** (SEQ ID NO:40); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm (SEQ ID NO:41); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-**Flank** (SEQ ID NO:42); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-**Flank**-**coFVIIIdeltaB** (SEQ ID NO:43); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-**Flank**-**coFVIIIdeltaB**-**Flank** (SEQ ID NO:44); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-**Flank**-**coFVIIIdeltaB**-**Flank**-SV40pA (SEQ ID NO:45); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-**Flank**-**coFVIIIdeltaB**-**Flank**-SV40pA-**Flank** (SEQ ID NO:46); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-**Flank**-**coFVIIIdeltaB**-**Flank**-Synt.pA (SEQ ID NO:47); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-**Flank**-**coFVIIIdeltaB**-**Flank**-SyntpA-**Flank** (SEQ ID NO:48); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-*MVM*-**Flank** (SEQ ID NO:49); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-*MVM*-**Flank**-**coFVIIIdeltaB** (SEQ ID NO:50); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-*MVM*-**Flank**-**coFVIIIdeltaB**-**Flank** (SEQ ID NO:51); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-*MVM*-**Flank**-**coFVIIIdeltaB**-**Flank**-SV40pA (SEQ ID NO:52); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-*MVM*-**Flank**-**coFVIIIdeltaB**-**Flank**-SV40pA-**Flank** (SEQ ID NO:53); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-*MVM*-**Flank**-**coFVIIIdeltaB**-**Flank**-Synt.pA (SEQ ID NO:54); **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-*MVM*-**Flank**-**coFVIIIdeltaB**-**Flank**-Synt.pA-**Flank** (SEQ ID NO:55); synthetic polyadenylation signal (Synt.pA) (SEQ ID NO:56); 3xSERP-**Flank**-*TTRe*-**Flank** (SEQ ID NO:57); 3xSERP-**Flank**-*TTRe*-**Flank**-TTRm (SEQ ID NO:58).

Figure 15: FVIII protein levels in C57BL6 mice injected with the pAAVss-3XSerpEnh-TTREnh-TTRm-MVM-co-hFVIII-deltaB-SV40pA and pAAVss-TTREnh-TTRm-MVM-co-hFVIII-deltaB-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-TTRe-TTRm-MVM-co-FIX-R338L-Synt.pA vector

Figure 17: Plasmid map of the pAAVss-3xSerpEnh-TTRm-MVM-coFVIIIdeltaB-Synt.pA vector

Figure 18: Plasmid map of the pAAVss-3xSerpEnh-TTRm-coFVIIIdeltaB-Synt.pA vector

Figure 19: Plasmid map of the pAAVss-3xSerpEnh-TTRe-TTRm-MVM-coFVIIIdeltaB-Sv40pA vector

Figure 20: Plasmid map of the pAAVss-3xSerpEnh-TTRe-TTRm-coFVIIIdeltaB-Synt.pA vector

Figure 21: Plasmid map of the pAAVss-TTRe-TTRm-coFVIIIdeltaB-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-coFVIIIdeltaB-Sv40pA (SEQ ID NO.

14); pAAVss-3xSerpEnh-TTRm-MVM-coFVIIIdeltaB-Sv40pA (SEQ ID NO:16); pAAVss-TTRe-TTRm-MVM-coFVIIIdeltaB-Sv40pA (SEQ ID NO:17) and pAAVss-3xSerpEnh-TTRe-TTRm-MVM-coFVIIIdeltaB-Sv40pA (SEQ ID NO:22).

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 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 (SEQ ID NO:68).

Figure 25: a) Graph depicting the effect of the 3XSerp enhancer on the TTRenh-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. b) Graph comparing different constructs tested on FVIII expression as outlined in example 2.

DETAILED DESCRIPTION OF THE INVENTION

[0051] 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.

[0052] 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".

[0053] 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. 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.

[0054] 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 operation in other sequences than described or illustrated herein.

[0055] 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 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.

[0056] The definitions provided herein should not be construed to have a scope less than understood by a person of ordinary skill in the art.

[0057] Disclosed herein are nucleic acid expression cassettes and expression vectors comprising said nucleic acid expression cassettes for enhancing liver-specific expression of a (trans)gene.

[0058] 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. Typically, the nucleic acid expression cassettes described herein will contain the FIX transgene or the FVIII transgene as defined herein.

[0059] Disclosed herein are nucleic acid expression cassettes comprising one or more liver-specific nucleic acid regulatory elements, operably linked to a promoter and a transgene.

[0060] The term "operably linked" as used herein refers to the arrangement of various nucleic acid 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, 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 nucleotides, or base pairs, between the elements.

[0061] 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.

[0062] 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. 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. At least 50% of the (trans)gene expression may occur within the liver, 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 97%, at least 99% or 100% of the (trans)gene expression may occur within the liver. Liver-specific expression may entail 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.

[0063] 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, the one or more regulatory element in the expression cassettes and vectors disclosed herein may be 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).

[0064] 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. Preferably, the one or more regulatory element in the nucleic acid expression cassettes and vectors disclosed herein comprise 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".

[0065] The nucleic acid expression cassettes and vectors disclosed herein preferably 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.

[0066] The nucleic acid expression cassettes and vectors disclosed herein may 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-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 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, 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 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.

[0067] Nucleic acid expression cassettes and vectors disclosed herein may comprise three tandem repeats of SEQ ID NO:5 (such as SEQ ID NO.13), and a further 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 promoter as defined by SEQ ID NO.6. In an alternative example, said liver-specific promoter is the AAT promoter, such as the promoter defined by SEQ ID NO.64. It has been shown herein that said specific 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

[0068] 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.

[0069] 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 particular, fragments may 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.

[0070] 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.

[0071] 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).

[0072] The promoter contained in the nucleic acid expression cassettes and vectors disclosed herein may be a liver-specific promoter. This is to increase liver specificity and/or avoid leakage of expression in other tissues. The liver-specific promoter may be from the transthyretin (TTR) gene or from the Alpha-1-antitrypsin (AAT) gene. The TTR promoter may be a minimal promoter (also referred to as TTRm or TRRmin herein), most particularly the minimal TTR promoter as defined in SEQ ID NO: 6. The AAT promoter may be as defined in SEQ ID NO: 64.

[0073] The promoter in the nucleic acid expression cassettes and vectors disclosed herein may be a minimal promoter.

[0074] 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.

[0075] 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) 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, 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.

[0076] The promoter is preferably a mammalian liver-specific promoter, in particular a murine or human liver-specific promoter. More preferably, said promoters are the respective minimal promoters

[0077] 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. 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 may occur within liver tissue or liver cells. Liver-specific expression may entail 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 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.

[0078] As used herein, the term "liver cells" encompasses the cells predominantly populating the liver and encompasses mainly hepatocytes, oval cells, liver sinusoidal endothelial cells (LSEC) and cholangiocytes (epithelial cells forming the bile ducts).

[0079] 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 dedifferentiated. The term includes cells in vivo and cells cultured ex vivo regardless of whether such cells are primary or passaged.

[0080] 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 passaged.

[0081] 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

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 in the context of the present application, it may for instance be through integration in the genome or as an episomal plasmid. Of note, expression of the 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 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.

[0082] Typically, the transgenes in the expression cassettes and vectors described herein encode coagulation factor IX or coagulation factor VIII.

[0083] 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.

[0084] 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). For example, the FIX mutant may be 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. The FIX transgene used in nucleic acid expression cassettes and expression vectors described herein may encode the human FIX protein, most preferably the FIX transgene encodes for the Padua mutant of the human FIX protein. Accordingly, the transgene

may have SEQ ID NO:9 (i.e. codon-optimized transgene encoding for the Padua mutant of the human FIX protein).

[0085] 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.

[0086] Said FVIII may be a FVIII wherein the B domain is deleted (i.e. B domain deleted FVIII, also referred to as BDD FVIII or FVIIIΔB or FVIIIdeltaB herein). The term "B domain 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.

[0087] For example, said FVIII may be B domain deleted FVIII wherein the B domain is replaced by a linker having the following sequence: SFSQNPPVLTRHQR (SEQ ID NO: 59) (i.e. SQ FVIII as defined in Ward et al. (2011)).Said transgene encoding FVIII may have 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.

[0088] 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).

[0089] 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 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.The intron may be 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 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.The nucleic acid expression cassette disclosed herein may further comprise 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) 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.

[0090] Any polyadenylation signal that directs the synthesis of a polyA tail is useful in the expression 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 β-gtobin (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).

[0091] Typically, the nucleic acid expression cassette described herein comprise a promotor, an enhancer, a (trans)gene, and a transcription terminator.

[0092] For example, a nucleic acid expression cassette as described herein may comprise:

- 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
- a transgene.

[0093] In another example, a nucleic acid expression cassette as described herein 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,
- 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.

[0094] In yet another example, a nucleic acid expression cassette as described herein 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,
- 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.

[0095] In still another example, a nucleic acid expression cassette as described herein may comprise:

- 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,
- 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.

[0096] In still another example, a nucleic acid expression cassette as desxcribed herein 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,
- the liver-specific AAT promoter, e.g. as defined by SEQ ID NO.64 , and
- a transgene.

[0097] In still another example, a nucleic acid expression cassette as described herein 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,
- 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.

[0098] In still another example, a nucleic acid expression cassette as described herein 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,
- 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.

[0099] For example, said nucleic acid expression cassette disclosed herein may comprise:

- 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,
- 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 polyA site as defined by SEQ ID NO:56.

[0100] In a further example, 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, 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,
- 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.

[0101] In another example, 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.

[0102] In another example, 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).

[0103] In another example, 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,
- 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. 66 (cf. Figure 25).

[0104] In another example, said nucleic acid expression cassette disclosed herein comprises:

- 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,
- 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.68 (cf. Figure 25).

[0105] The expression cassettes disclosed herein may be used as such, or typically, they may be part of a nucleic acid vector. Accordingly, also disclosed herein is the use of a nucleic acid expression cassette as described herein in a vector, in particular a nucleic acid vector.

[0106] Also disclosed herein is a vector comprising a nucleic acid expression cassette as disclosed herein.

[0107] 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 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.

[0108] 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 delivery systems can be used to combine viral and non-viral components, such as nanoparticles or virosomes (Yamada et al., 2003).

[0109] 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 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.

[0110] 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 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 dividing cells.

[0111] 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 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.

[0112] 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 limited. Accordingly, the vector used may be derived from adeno-associated virus (i.e. AAV vector).

[0113] 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 herein are preferably AAV serotype 9 vectors, and AAV vectors that comprise a FVIII transgene as disclosed herein are preferably AAV serotype 8 vectors.

[0114] 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 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.

[0115] Gene therapy with adeno-associated viral vectors disclosed herein was shown to induce immune tolerance towards the transgene comprised in the vector.

[0116] For example, the vector described herein may comprise 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 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).

[0117] 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.

[0118] In a further example, said vector comprises the following elements (cf. Fig. 8 and Fig. 16):

- 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") 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,
- 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).

[0119] 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.

[0120] In another example, 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),
- 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).

[0121] 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.

[0122] In a further example, 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).

[0123] 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.

[0124] 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 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.

[0125] In specific examples the following plamids/vectors are provided:

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

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

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,

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,

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,

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

pAAVsc-3xCRM8-TTRe-APOA1 p-MVM-FIXcoR338L-BGHpA,

pAAVss-3xCRM8-TTRe-APOA1 p-MVM-FVIIIcodeltaB-sv40pA

pAAVsc-TTRe-3xCRM8-APOA1 p-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-APOA1 p-MVM-FVIIIcodeltaB-sv40pA

pAAVsc-CRM8-TTRe-APOA1p-MVM-FIXcoR338L-BGHpA,

pAAVss-CRM8-TTRe-APOA1 p-MVM-FVIIIcodeltaB-sv40pA,

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,

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

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

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,

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,

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,

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

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

pAAVsc-3xCRM8-TTRe-CES1 p-MVM-FIXcoR338L-BGHpA,

pAAVss-3xCRM8-TTRe-CES1 p-MVM-FVIIIcodeltaB-sv40pA,

pAAVsc-TTRe-3xCRM8-CES1 p-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-CES1 p-MVM-FVIIIcodeltaB-sv40pA,

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

pAAVss-CRM8-TTRe-CES1 p-MVM-FVIIIcodeltaB-sv40pA,

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,

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,

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,

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,

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

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

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

[0126] 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).

[0127] The vector may also be 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 no enhance the tumorigenic risk. Furthermore, liver-directed 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.

[0128] 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 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).

[0129] Transposon/transposase constructs can be delivered by hydrodynamic injection or using non-viral nanoparticles to transfect hepatocytes.

[0130] 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 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).

[0131] 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). In particular, the use of the regulatory elements, expression cassettes or vectors may be for gene therapy, in particular liver-directed gene therapy, *in vivo.* More particularly, the use may be for a method of gene therapy, in particular liver-directed gene therapy, to treat hemophilia, in particular to treat hemophilia B or hemophilia A.

[0132] 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). Methods for expressing a protein in liver cells are also disclosed herein, said methods 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.

[0133] Methods of gene therapy for a subject in need thereof are also disclosed herein, said methods 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. The method may further comprise 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.

[0134] The therapeutic protein encoded by the transgene in the nucleic acid expression cassette or the vector may be factor IX, and the method may be 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). Alternatively, the therapeutic protein encoded by the transgene in the nucleic acid expression cassette or the vector may be factor VIII, and the method may be a method for treating hemophilia A.

[0135] 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.

[0136] 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) 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 undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

[0137] 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 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.

[0138] 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. For example, the term may imply 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 a vector

described herein into a subject. Due to the very high efficiency of the vectors and nucleic acid expression cassettes described herein, this high physiological level of factor IX in the subject can be obtained even by administering relatively low doses of vector. In another example, the term may imply 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 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 described herein 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.

[0139] In particular, the transduction of a vector described herein herein into the subject can be done at a dose lower than $2x10^{11}$ 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.

[0140] Alternatively, if a level of factor IX of 100 mU/ml plasma needs to be reached in a subject, the transduction of a vector described herein into the subject can be done at a dose lower than or equal to $6x10^{11}$ vg/kg.

[0141] Further, if a level of factor IX equal to 150 mU/ml plasma or higher needs to be reached, the transduction of a vector described herein into the subject can be done at a dose lower than or equal than $2x10^{12}$ vg/kg.

[0142] Preferably, a level of factor IX of 200 mU/ml plasma or higher can be reached in a subject, when the transduction of a vector described herein into the subject is done at a dose lower than or equal to $2x10^{12}$ vg/kg.

[0143] In particular, the transduction of a vector as described herein into the subject can be done at a dose lower than or equal to $2x10^{12}$ vg/kg (viral genomes per kilogram), such as lower than or equal to $1x10^{12}$ vg/kg, $5x10^{11}$ vg/kg, $2.5x10^{11}$ vg/kg, $1x10^{11}$ vg/kg, $5x10^{10}$ vg/kg, $1x10^{10}$ vg/kg, $5x10^{9}$ vg/kg, or $1x10^{9}$ vg/kg preferably at a dose lower than or equal to $2.5x10^{11}$ 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.

[0144] 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.

[0145] The nucleic acid expression cassette, the vector or the pharmaceutical composition as described herein 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 as described herein 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).

[0146] Further disclosed herein 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 as described herein 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.

[0147] A pharmaceutical composition is provided herein comprising a nucleic acid expression cassette containing a transgene encoding a therapeutic protein, and a pharmaceutically acceptable carrier. The pharmaceutical composition may comprise a vector containing the nucleic acid expression cassette containing a transgene encoding a therapeutic protein, and a pharmaceutically acceptable carrier.The transgene may encode factor IX and the pharmaceutical composition is for treating hemophilia B or the transgene may encode factor VIII and the pharmaceutical composition is for treating hemophilia A.

[0148] 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.

[0149] 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

[0150] 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 vector size (including both ITR's) is indicated.

[0151] 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 both ITR's) is indicated.

Materials and methods:

Cloning strategy

[0152] 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 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, 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.

[0153] 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 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 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

[0154] 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 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 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 AAV vector were collected, concentrated in 1mM $MgCl_2$ 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 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 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

[0155] AAV vector administration is carried out by tail vein injection on adult C57B6 mice at two different doses: $1x10^9$ (low dose) and $5x10^9$ (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 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

[0156] 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 the linear range of standards. Standards and samples were then added to a 96 well plate precoated 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 color development. After exact 5 minutes of incubation 1M H2SO4 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

[0157] The concentration of hFVIII antigens in citrated plasma was measured by enzyme-linked 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 precoated 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 H2SO4 was added to all wells to 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

[0158] 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

[0159] 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 $1x10^9$ vg/mouse and $5x10^9$ vg/mouse.

Construct	Size	Dose	Mice
AAV9sc-SerpEnh-TTRm-MVM-co-FIX-R338L-BGHpolyA	2510 bp	1×10^9	4
		5×10^9	4

Construct	Size	Dose	Mice
AAV9sc-3xSerpEnh-TTRm-MVM-co-FIX-R338L-BGHpolyA	2682 bp	1 x 10^9	4
		5 x 10^9	4
AAV9sc-TTREnh-TTRm-MVM-co-FIX-R338L-BGHpolyA	2540 bp	1 x 10^9	4
		5 x 10^9	4
AAV9sc-3xSerpEnh-TTREnh-TTRm-MVM-co-FIX-R338L-BGHpolyA	2760 bp	1 x 10^9	4
		5 x 10^9	4

[0160] Male adult CB17SCID mice (18-20 grams) were administrated with AAV8 XVIII vectors (see the table below) by tail vain injection at doses of 1x10^9 vg/mouse and 5x10^9 vg/mouse.

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

Plasmid administration

[0161] 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

Results

Factor IX:

[0162] 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.

[0163] 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).

[0164] 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.

[0165] 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

[0166] 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.

[0167] 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.

[0168] 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.

[0169] 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.

[0170] 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.

[0171] Constructs: The following vectors were compared for FVIII expression levels (cf. Figure 22):

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

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

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

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

[0172] In a first experiment, the following conditions were used:
Mouse model: CB17-SCID, male, adult mice of 18-20 grams
Doses: 150 ng plasmid/mouse
Analysis points: Blood collection at Day1
No of mice: 3 per condition
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

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 TTRenh-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.

[0173] In a second experiment the following conditions were used:
Mouse model: CB17-SCID, male, adult mice of 18-20 grams
Doses: 150 ng plasmid/mouse
Analysis points: Blood collection at Day1
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.

[0174] In this experiment, the TTRm minimal promotor is replaced by another liver-specific promotor to show the versatility of the regulator element.

[0175] As a first example, the AAT liver-specific promoter (AAT) is tested.

[0176] 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);

[0177] All constructs tested make use of the AAT promoter (SEQ ID NO.64).

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

Doses: 1 µg and 2 µg plasmid/mouse

Analysis points: Blood collection at D1, D2

No of mice: 3 per condition

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

[0178] Also the corresponding FVIII constructs will be tested for FVIII expression with the AAT 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.

[0179] 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.

[0180] In further examples, the albumin promotor (ALBp) is used to replace the TTRm promotor in 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.

[0181] In further examples, the apolipoprotein A1 promotor (APOA1p) is used to replace the TTRm promotor in said constructs, hence encompassing the following construct:

pAAVsc-3xCRM8-TTRe-APOA1 p-MVM-FIXcoR338L-BGHpA,

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

pAAVsc-TTRe-3xCRM8-APOA1 p-MVM-FIXcoR338L-BGHpA,

pAAVss-TTRe-3xCRM8-APOA1 p-MVM-FVIIIcodeltaB-sv40pA

pAAVsc-CRM8-TTRe-APOA1 p-MVM-FIXcoR338L-BGHpA, or

pAAVss-CRM8-TTRe-APOA1 p-MVM-FVIIIcodeltaB-sv40pA.

[0182] In further examples, the complement factor B promoter (CFBp) is used to replace the TTRm promotor in said constructs, hence encompassing the following construct:

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

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

[0183] 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,

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.

[0184] 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,

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.

[0185] 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,

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.

[0186] 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,

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

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

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

[0187] 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,

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.

[0188] 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,

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

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

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

[0189] 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,

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

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

[0190] 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,

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.

[0191] 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

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.

[0192] Results: The expression level of FIX or FVIII will be analysed and compared as explained in Example 2.

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[0193]

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cttacagaca agctgtgacc gtctccgggg gctgcatgtg tcagaggttt tcaccgtcat 4140

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gaaagtaaaa gatgctgaag atcagttggg tgcacgagtg ggttacatcg aactggatct 4500

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cgagcgcagc gagtcagtga gcgaggaagc ggaagagcgc ccaatacgca aaccgcctct 6180

ccccgcgcgt tggccgattc attaatg 6207

<210> 26
<211> 371
<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe

<400> 26
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gggggaggct gctggtgaat attaaccaag gtcaccccag ttatcggagg agcaaacagg 180

ggctaagtcc accgggggag gctgctggtg aatattaacc aaggtcaccc cagttatcgg 240

aggagcaaac aggggctaag tccacggtac ccactgggag gatgttgagt aagatggaaa 300

actactgatg acccttgcag agacagagta ttaggacatg tttgaacagg ggccgggcga 360

tcagcaggta g 371

<210> 27
<211> 386

<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe-Flank

<400> 27
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gggggaggct gctggtgaat attaaccaag gtcaccccag ttatcggagg agcaaacagg 180

ggctaagtcc accgggggag gctgctggtg aatattaacc aaggtcaccc cagttatcgg 240

aggagcaaac aggggctaag tccacggtac ccactgggag gatgttgagt aagatggaaa 300

actactgatg acccttgcag agacagagta ttaggacatg tttgaacagg ggccgggcga 360

tcagcaggta gctctagagg atcccc 386

<210> 28
<211> 588
<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe-Flank-TTRm

<400> 28
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gggggaggct gctggtgaat attaaccaag gtcaccccag ttatcggagg agcaaacagg 180

ggctaagtcc accgggggag gctgctggtg aatattaacc aaggtcaccc cagttatcgg 240

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actactgatg acccttgcag agacagagta ttaggacatg tttgaacagg ggccgggcga 360

tcagcaggta gctctagagg atccccgtct gtctgcacat ttcgtagagc gagtgttccg 420

atactctaat ctccctaggc aaggttcata tttgtgtagg ttacttattc tccttttgtt 480

gactaagtca ataatcagaa tcagcaggtt tggagtcagc ttggcaggga tcagcagcct 540

gggttggaag gaggggtat aaaagcccct tcaccaggag aagccgtc 588

<210> 29
<211> 615
<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank

<400> 29
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gggggaggct gctggtgaat attaaccaag gtcaccccag ttatcggagg agcaaacagg      180
ggctaagtcc accgggggag gctgctggtg aatattaacc aaggtcaccc cagttatcgg      240
aggagcaaac aggggctaag tccacggtac ccactgggag gatgttgagt aagatggaaa      300
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aagctcctgg ctaga                                                      615
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<210> 30
<211> 707
<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM

<400> 30

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gggggaggct gctggtgaat attaaccaag gtcaccccag ttatcggagg agcaaacagg      180
ggctaagtcc accgggggag gctgctggtg aatattaacc aaggtcaccc cagttatcgg      240
aggagcaaac aggggctaag tccacggtac ccactgggag gatgttgagt aagatggaaa      300
actactgatg acccttgcag agacagagta ttaggacatg tttgaacagg ggccgggcga      360
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atactctaat ctccctaggc aaggttcata tttgtgtagg ttacttattc tccttttgtt      480
gactaagtca ataatcagaa tcagcaggtt tggagtcagc ttggcaggga tcagcagcct      540
gggttggaag gaggggtat aaaagcccct tcaccaggag aagccgtcac acagatccac      600
aagctcctgg ctagaaagag gtaagggttt aagggatggt tggttggtgg ggtattaatg      660
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<210> 31
<211> 718
<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank

<400> 31

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gggggaggct gctggtgaat attaaccaag gtcaccccag ttatcggagg agcaaacagg 180

ggctaagtcc accgggggag gctgctggtg aatattaacc aaggtcaccc cagttatcgg 240

aggagcaaac aggggctaag tccacggtac ccactgggag gatgttgagt aagatggaaa 300

actactgatg acccttgcag agacagagta ttaggacatg tttgaacagg ggccgggcga 360

tcagcaggta gctctagagg atccccgtct gtctgcacat ttcgtagagc gagtgttccg 420

atactctaat ctccctaggc aaggttcata tttgtgtagg ttacttattc tccttttgtt 480

gactaagtca ataatcagaa tcagcaggtt tggagtcagc ttggcaggga tcagcagcct 540

gggttggaag gaggggggtat aaaagcccct tcaccaggag aagccgtcac acagatccac 600

aagctcctgg ctagaaagag gtaagggttt aagggatggt tggttggtgg ggtattaatg 660

tttaattacc tggagcacct gcctgaaatc actttttttc aggttgggct agcccacc 718

<210> 32
<211> 2107
<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L

<400> 32
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gggggaggct gctggtgaat attaaccaag gtcaccccag ttatcggagg agcaaacagg 180

ggctaagtcc accgggggag gctgctggtg aatattaacc aaggtcaccc cagttatcgg 240

aggagcaaac aggggctaag tccacggtac ccactgggag gatgttgagt aagatggaaa 300

actactgatg acccttgcag agacagagta ttaggacatg tttgaacagg ggccgggcga 360

tcagcaggta gctctagagg atccccgtct gtctgcacat ttcgtagagc gagtgttccg 420

atactctaat ctccctaggc aaggttcata tttgtgtagg ttacttattc tccttttgtt 480

gactaagtca ataatcagaa tcagcaggtt tggagtcagc ttggcaggga tcagcagcct 540

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gcgcgagtgc atggaggaga agtgcagctt cgaggaggcc cgcgaggtgt tcgagaacac 960

cgagcgcacc accgagttct ggaagcagta cgtggacggc gaccagtgcg agagcaaccc 1020

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caccagcttc ctgaccggca tcatcagctg gggcgaggag tgcgccatga agggcaagta     2040
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<210> 33
<211> 2174
<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L-F lank

<400> 33

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aagctcctgg ctagaaagag gtaagggttt aagggatggt tggttggtgg ggtattaatg      660
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<210> 34
<211> 2469
<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L-Flank-BGHpA

<400> 34

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<210> 35
<211> 2508
<212> DNA
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<220>
<223> Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L-Flank-BGHpA-Flank

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aggagcaaac aggggctaag tccacggtac ccactgggag gatgttgagt aagatggaaa 300

actactgatg acccttgcag agacagagta ttaggacatg tttgaacagg ggccgggcga 360

tcagcaggta gctctagagg atccccgtct gtctgcacat ttcgtagagc gagtgttccg 420

atactctaat ctccctaggc aaggttcata tttgtgtagg ttacttattc tccttttgtt 480

gactaagtca ataatcagaa tcagcaggtt tggagtcagc ttggcaggga tcagcagcct 540

gggttggaag gaggggtat aaaagcccct tcaccaggag aagccgtcac acagatccac 600

aagctcctgg ctagaaagag gtaagggttt aagggatggt tggttggtgg ggtattaatg 660

tttaattacc tggagcacct gcctgaaatc actttttttc aggttgggct agcccaccat 720

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<211> 2223
<212> DNA
<213> Artificial Sequence

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<223> Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L-Flank-Synt.pA

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<210> 37
<211> 2262
<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-MVM-Flank-co-FIX-R338L-Flank-Synt.pA-Flank

<400> 37

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gggggaggct gctggtgaat attaaccaag gtcaccccag ttatcggagg agcaaacagg      180
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aggagcaaac aggggctaag tccacggtac ccactgggag gatgttgagt aagatggaaa      300
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atactctaat ctccctaggc aaggttcata tttgtgtagg ttacttattc tccttttgtt 480

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<210> 38

<211> 239

<212> DNA

<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank

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tattaaccaa ggtcacccca gttatcggag gagcaaacag gggctaagtc cacggtacc 239

<210> 39
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe

<400> 39
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<210> 40
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe-Flank

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<210> 41
<211> 556

<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe-Flank-TTRm

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<210> 42
<211> 561
<212> DNA
<213> Artificial Sequence

<220>
<223> Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank

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<210> 43
<211> 4938
<212> DNA
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<220>

<223> Flank-3xSERP-Flank-TTRe-Flank-TTRm-Flank-coFVIIIdeltaB

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PATENTKRAV

1. Nukleinsyreekspressionskassette omfattende:

- et i tandem arrangeret tredobbelt repeat af et leverspecifikt regulatorisk element fra en nukleinsyre, hvilket tredobbelte repeat består af nukleinsyrefragmentet defineret af SEQ ID NO:11, og

- et regulatorisk element fra en nukleinsyre bestående af nukleinsyrefragmentet defineret af SEQ ID NO:12;

idet det tredobbelte repeat og det regulatoriske element er operabelt forbundet til en leverspecifik promotor og et transgen.

2. Nukleinsyreekspressionskassette ifølge krav 1, hvor den leverspecifikke promotor er valgt fra gruppen omfattende: den minimale TTR-promotor (TTRm), AAT-promotoren, albumin-(ALB)-promotoren eller den minimale promotor, apolipoprotein A1-(APOA1)-promotoren eller den minimale promotor, komplementfaktor B-(CFB)-promotoren, ketohexokinase-(KHK)-promotoren, hemopexin-(HPX)-promotoren eller den minimale promotor, nikotinamid-N-methyltransferase-(NNMT)-promotoren eller den minimale promotor, (lever)carboxylesterase 1-(CES1)-promotoren eller den minimale promotor, protein C-(PROC)-promotoren eller den minimale promotor, apolipoprotein C3-(APOC3)-promotoren eller den minimale promotor, mannan-bindende lektinserinprotease 2-(MASP2)-promotoren eller den minimale promotor, hepcidin-antimikrobielt peptid-(HAMP)-promotoren eller den minimale promotor eller serpinpeptidaseinhibitor, clade C (antithrombin), medlem 1-(SERPINC1)-promotoren eller den minimale promotor.

3. Nukleinsyreekspressionskassette ifølge krav 1 eller 2, hvor den leverspecifikke promotor er den minimale TTR-promotor (TTRm) som defineret af SEQ ID NO:6.

4. Nukleinsyreekspressionskassette ifølge krav 1 eller 2, hvor den leverspecifikke promotor er AAT-promotoren som defineret af SEQ ID NO:64.

5. Nukleinsyreekspressionskassette ifølge et hvilket som helst af kravene 1 til 4, som omfatter det regulatoriske element som defineret af SEQ ID NO:13, mere foretrukket et

regulatorisk element som defineret af SEQ ID NO:57, operabelt forbundet til en promotor og et transgen.

6. Nukleinsyreekspressionskassette ifølge et hvilket som helst af kravene 1 til 5, hvor transgenet koder for koagulationsfaktor IX (FIX), fortrinsvis hvor transgenet er kodonoptimeret koagulationsfaktor FIX, eller hvor koagulationsfaktoren FIX indeholder en hyperaktiverende mutation, fortrinsvis hvor den hyperaktiverende mutation svarer til en R338L-aminosyresubstitution, mere foretrukket hvor det transgen, der koder for koagulationsfaktor FIX, har en nukleinsyresekvens som defineret af SEQ ID NO:9.

7. Nukleinsyreekspressionskassette ifølge et hvilket som helst af kravene 1 til 6, hvor transgenet koder for koagulationsfaktor VIII (FVIII), fortrinsvis hvor transgenet er kodonoptimeret koagulationsfaktor FVIII, eller hvor nævnte koagulationsfaktor VIII har en deletion af B-domænet, fortrinsvis hvor B-domænet i nævnte FVIII er erstattet af en linker defineret af SEQ ID NO:59, mere foretrukket hvor det transgen, der koder for koagulationsfaktor VIII, har en nukleinsyresekvens defineret af SEQ ID NO:18.

8. Nukleinsyreekspressionskassette ifølge et hvilket som helst af kravene 1 til 3 og 5 til 7, hvor promotoren er transthyretin-(TTR)-promotoren, hvorved den omfatter kombinationen af TTRe- og TTRm-nukleinsyrerne som defineret af SEQ ID NO:69.

9. Nukleinsyreekspressionskassette ifølge et hvilket som helst af kravene 1 til 8, som yderligere omfatter et "minute virus of mouse"-(MVM)-intron, fortrinsvis MVM-intronet defineret af SEQ ID NO:8.

10. Nukleinsyreekspressionskassette ifølge et hvilket som helst af kravene 1 til 9, som yderligere omfatter et transkriptionelt termineringssignal afledt fra bovint væksthormon-polyadenyleringssignalet (BGHpA), fortrinsvis BGHpA som defineret af SEQ ID NO:10, eller afledt fra Simian virus 40-polyadenyleringssignalet (SV40pA), fortrinsvis SV40pA som defineret af SEQ ID NO:19, eller det syntetiske polyadenyleringssignal som defineret af SEQ ID NO:56.

11. Vektor omfattende nukleinsyreekspressionskassetten ifølge et hvilket som helst af kravene 1 til 10, fortrinsvis hvor nævnte vektor er en viral vektor, mere foretrukket hvor

vektoren er afledt fra et adenoassocieret virus (AAV).

12. Vektor ifølge krav 11, som omfatter FVIII-transgenet, til anvendelse til behandling af hæmofili A; eller vektor ifølge krav 11, som omfatter FIX-transgenet, til anvendelse til behandling af hæmofili B.

13. Vektor til anvendelse ifølge krav 12, hvor der efter transduktion eller transfektion af vektoren ifølge krav 11 til et individ opnås niveauer af faktor IX eller FVIII i plasma, som er lig med eller højere end den terapeutiske tærskelkoncentration på 10 mU/ml plasma i individet.

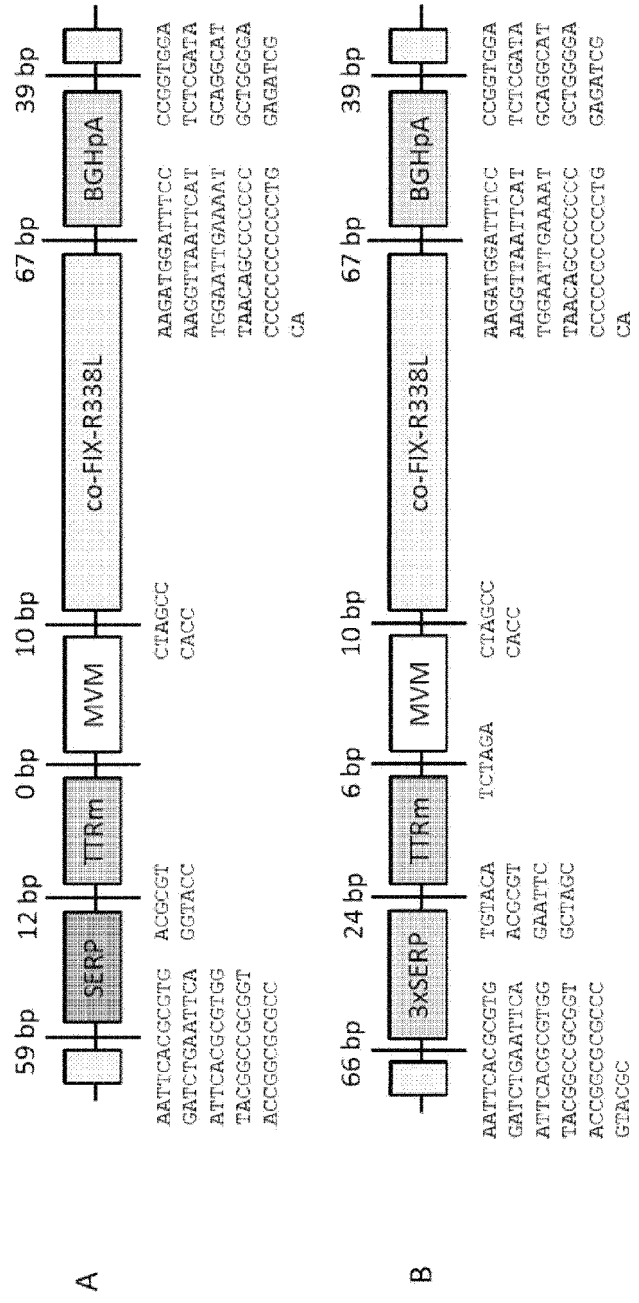
14. Vektor til anvendelse ifølge krav 13, hvor transduktionen af den virale vektor til individet udføres i en dosis, der er lavere end $2x10^{11}$ vg/kg.

15. Vektor til anvendelse ifølge krav 14, hvor transduktionen af den virale vektor til individet udføres i en dosis, der er lavere end eller lig med $6x10^{11}$ vg/kg, og hvor der i nævnte individ opnås niveauer af faktor IX eller FVIII i plasma, der er lig med eller højere end den terapeutiske koncentration på 100 mU/ml; eller hvor transduktionen af den virale vektor til individet udføres i en dosis, der er lavere end eller lig med $6x10^{11}$ vg/kg, og hvor der i nævnte individ opnås niveauer af faktor IX eller FVIII i plasma, der er lig med eller højere end den terapeutiske koncentration på 50 mU/ml; eller hvor transduktionen af den virale vektor til individet udføres i en dosis, der er lavere end eller lig med $2x10^{12}$ vg/kg, og hvor der i nævnte individ opnås niveauer af faktor IX eller FVIII i plasma, der er lig med eller højere end den terapeutiske koncentration på 200 mU/ml; eller hvor transduktionen af den virale vektor til individet udføres i en dosis, der er lavere end eller lig med $2x10^{12}$ vg/kg, og hvor der i nævnte individ opnås niveauer af faktor IX eller FVIII i plasma, der er lig med eller højere end den terapeutiske koncentration på 150 mU/ml.

16. Farmaceutisk præparat, som omfatter en vektor ifølge krav 11 og en farmaceutisk acceptabel bærer, og som eventuelt yderligere omfatter en aktiv ingrediens til behandling af hæmofili A, når transgenet i nævnte vektor er FVIII; eller en aktiv ingrediens til behandling af hæmofili B, når transgenet i nævnte vektor er FIX.

DRAWINGS

Figure 1



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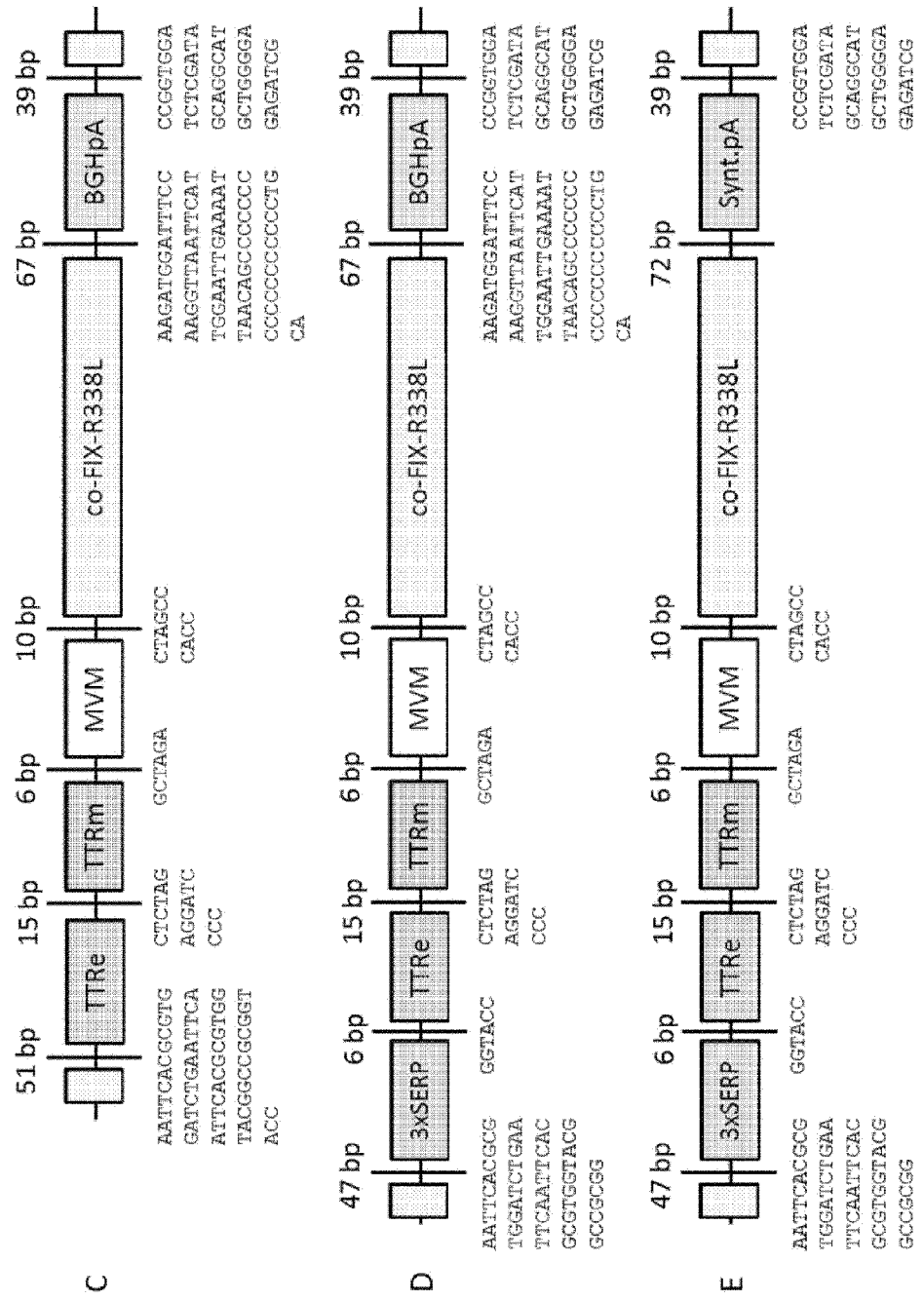
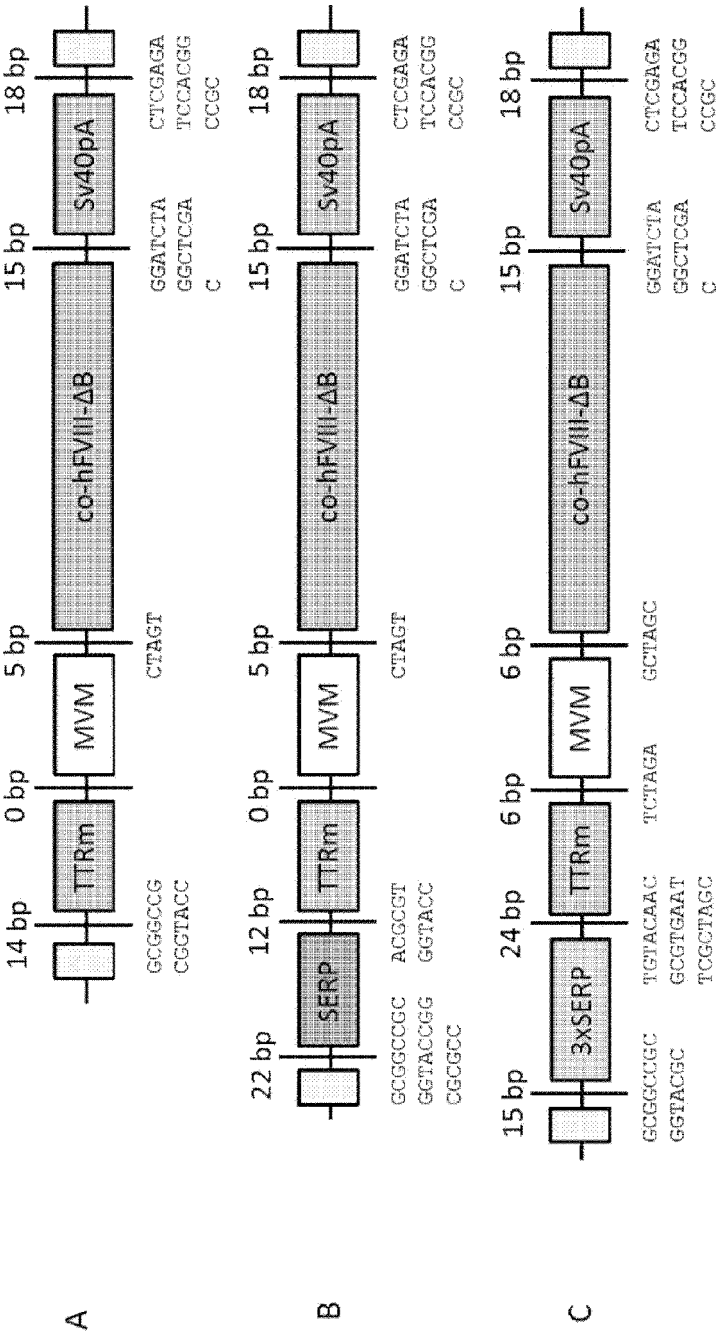


Figure 2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CTAGT
GGATCTA
GGCTCGA
C
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TCCACGG
CCGC
B
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SERP
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TTRm
0 bp
MVM
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C
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TTRm
6 bp
MVM
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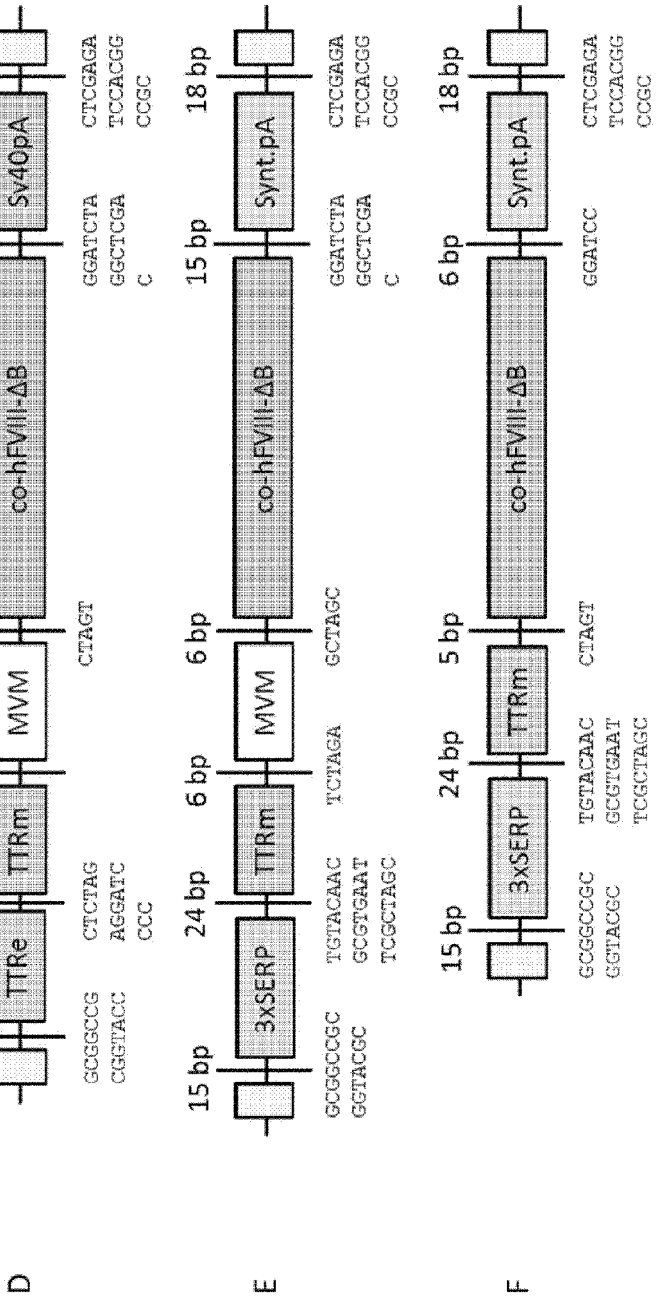
Figure 2 (continued)



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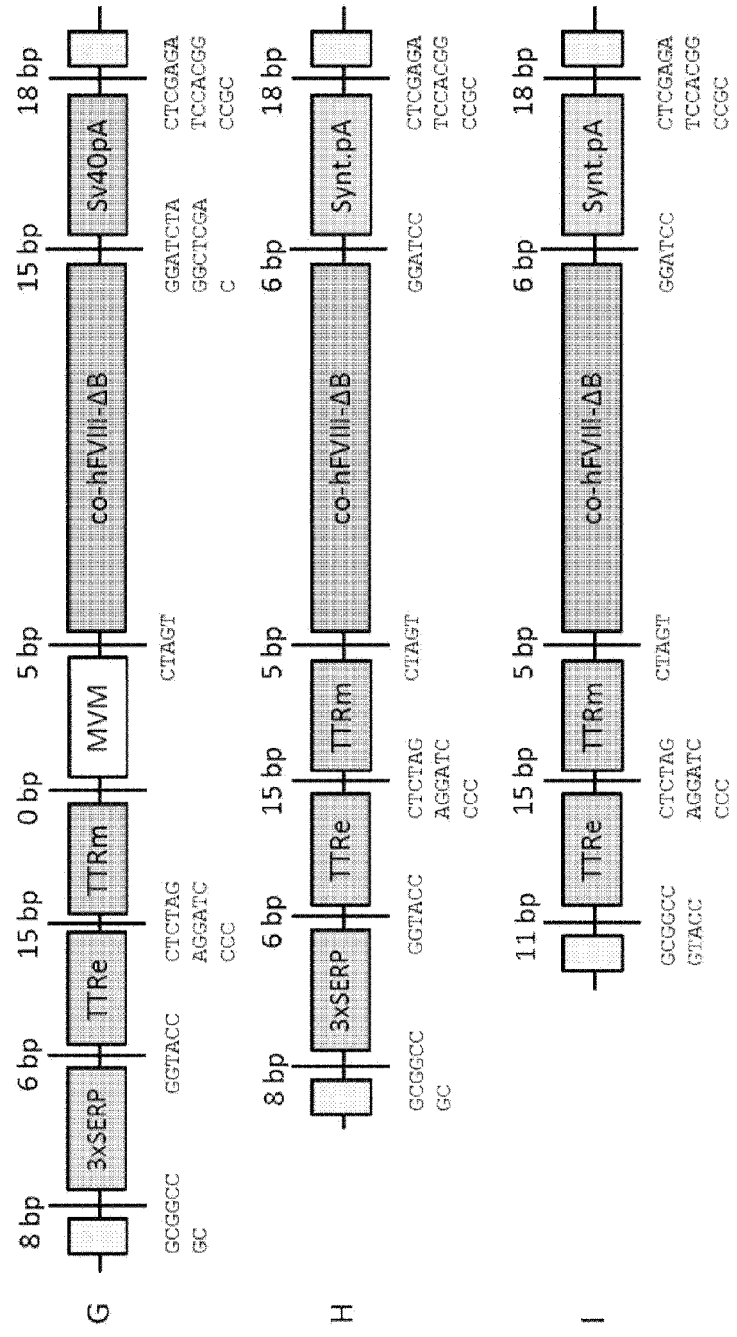


Figure 3a

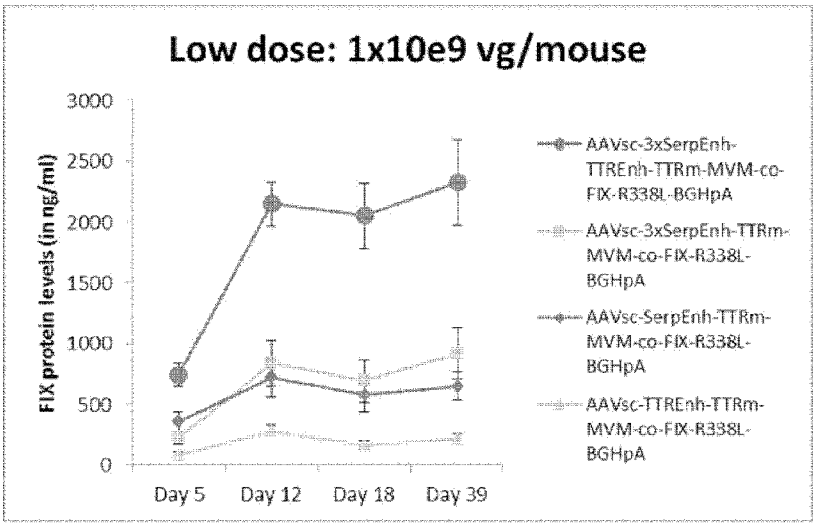


Figure 3b

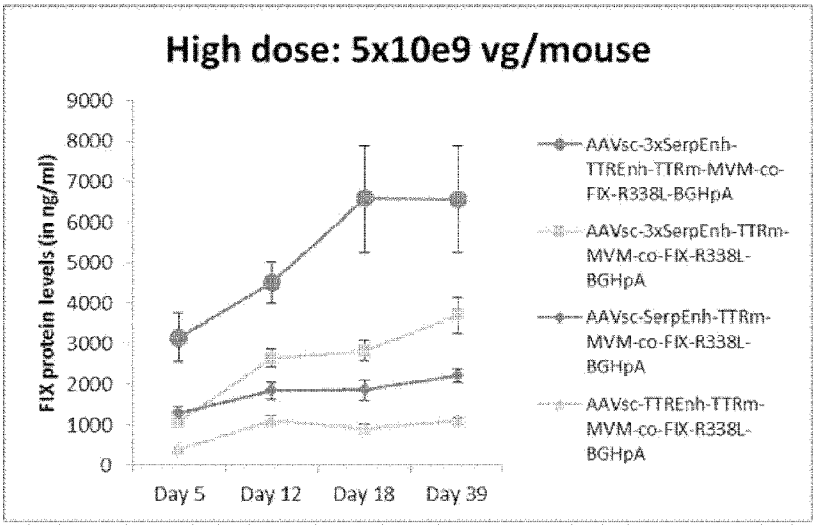


Figure 4a

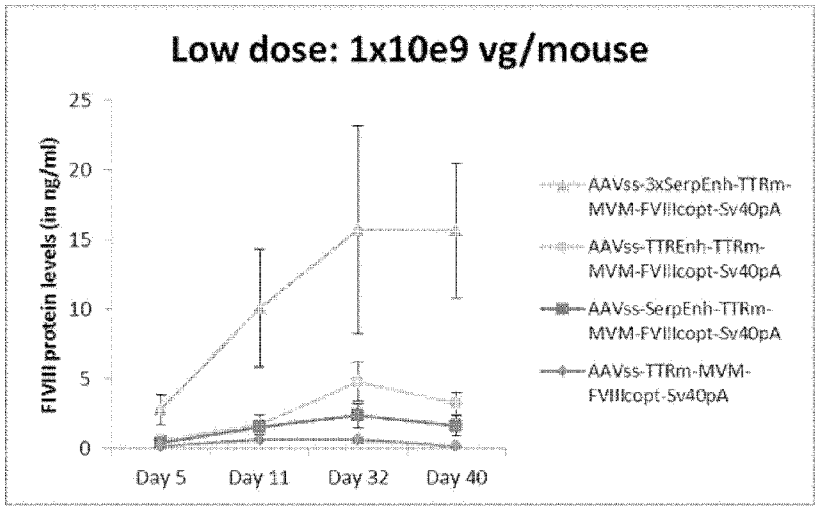


Figure 4b

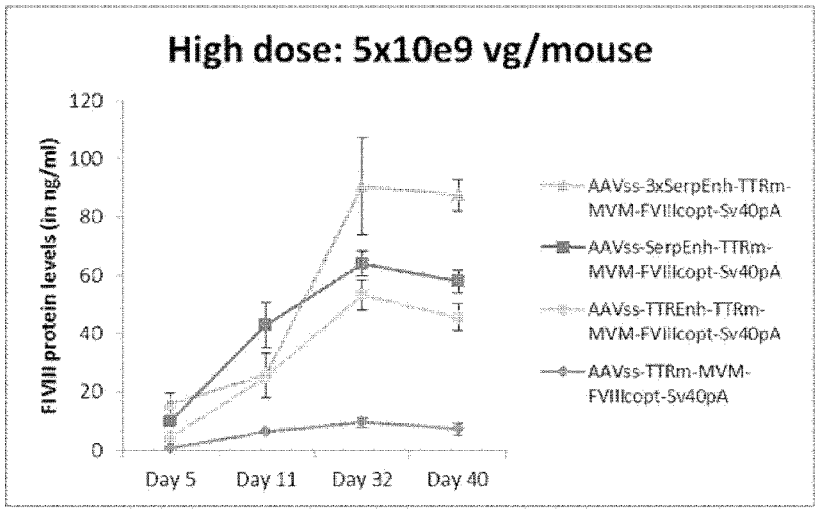
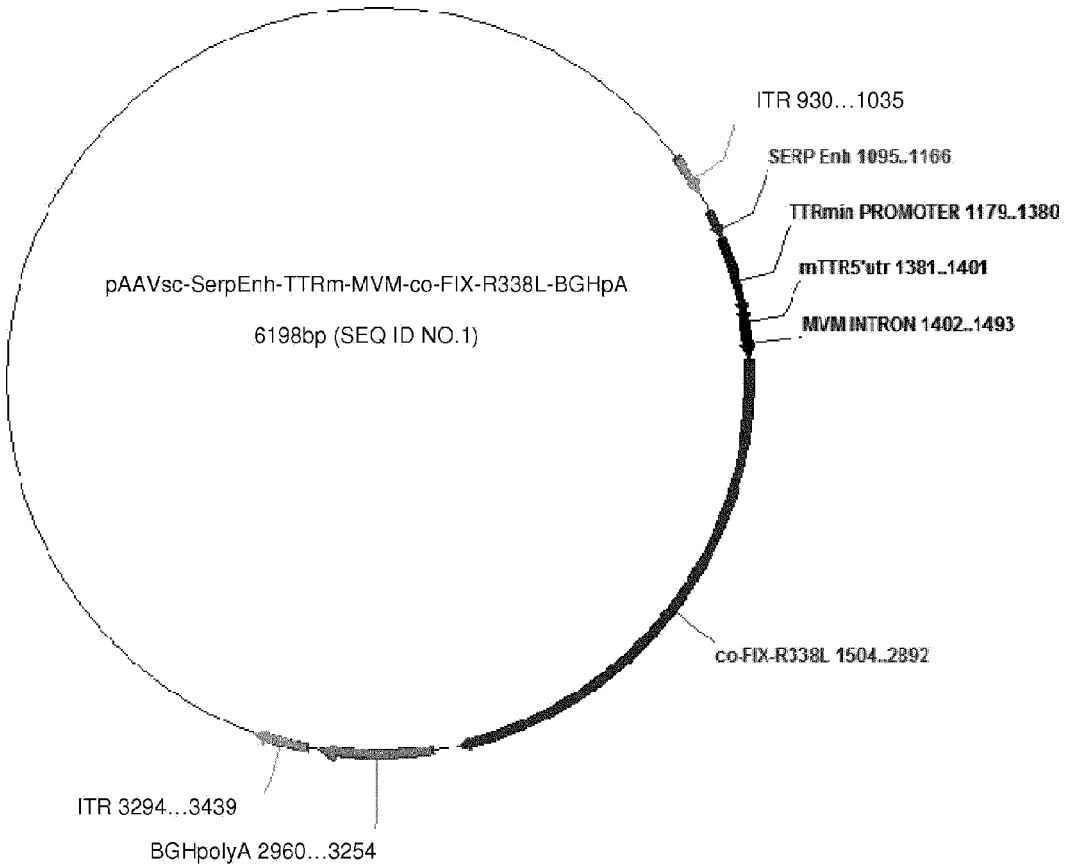


Figure 5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SERP Enh 1095..1166
TTRmin PROMOTER 1179..1380
mTTR5'utr 1381..1401
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Figure 6

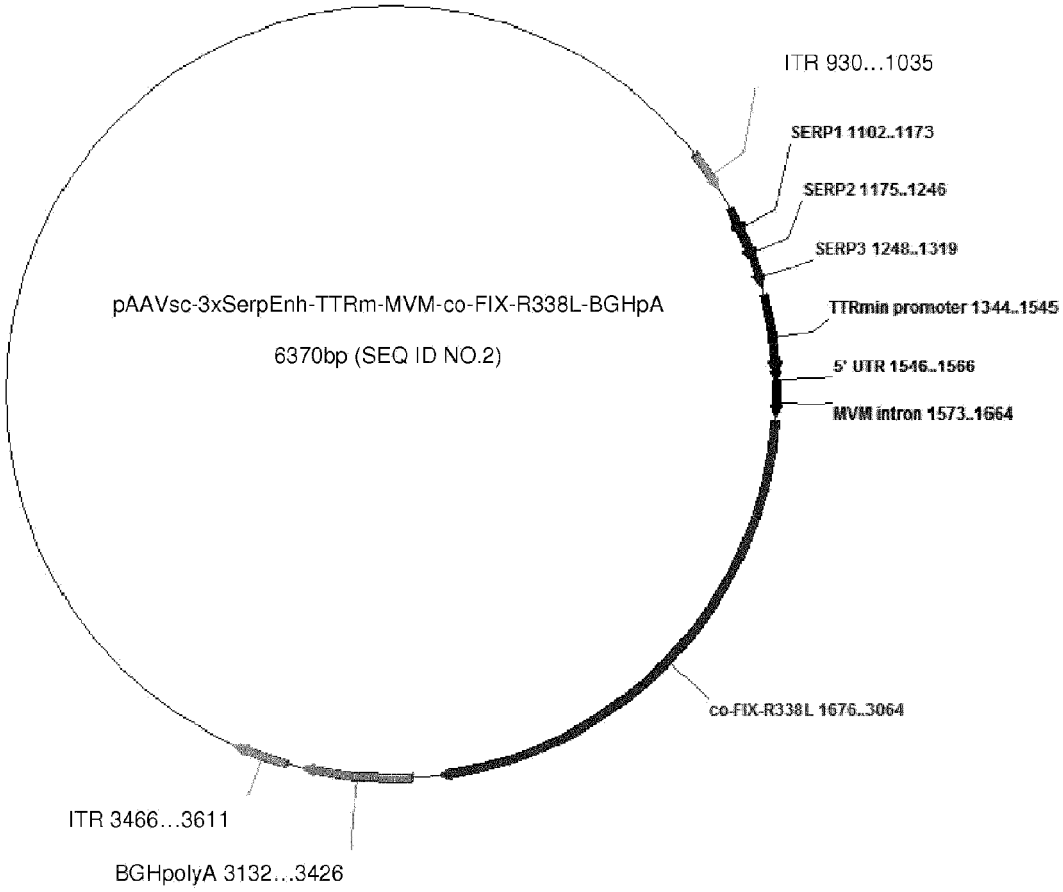
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Figure 7

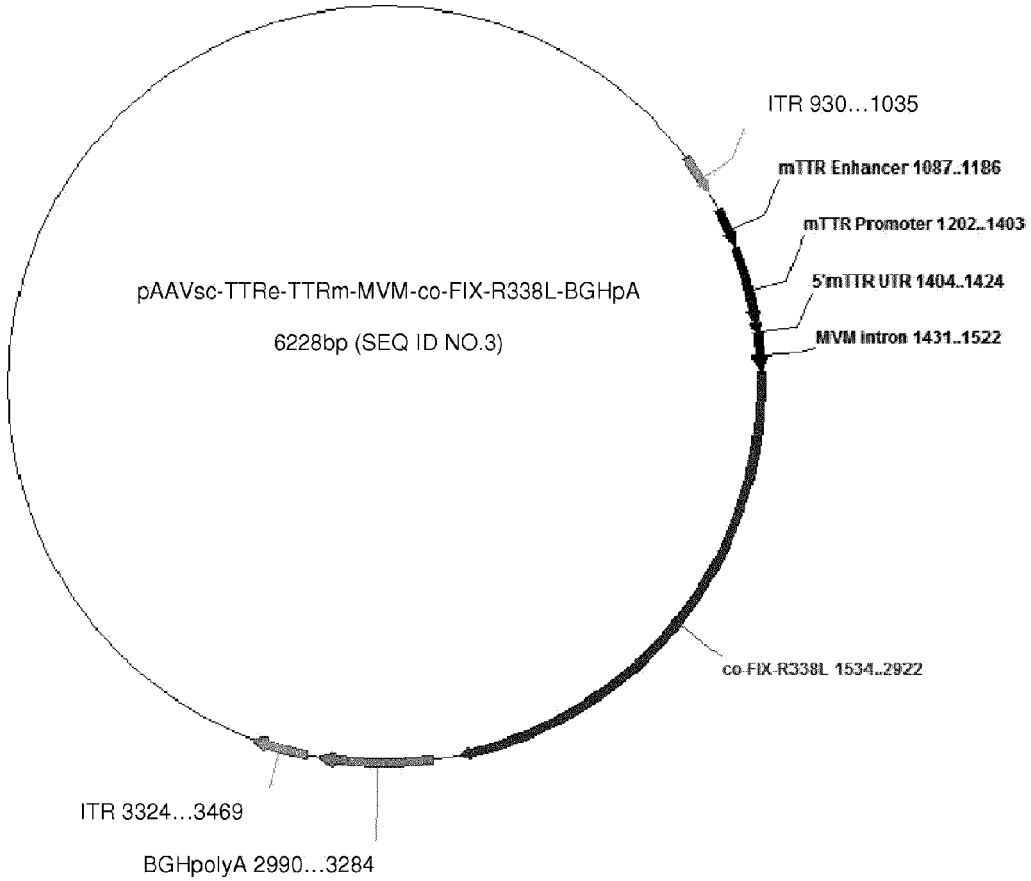
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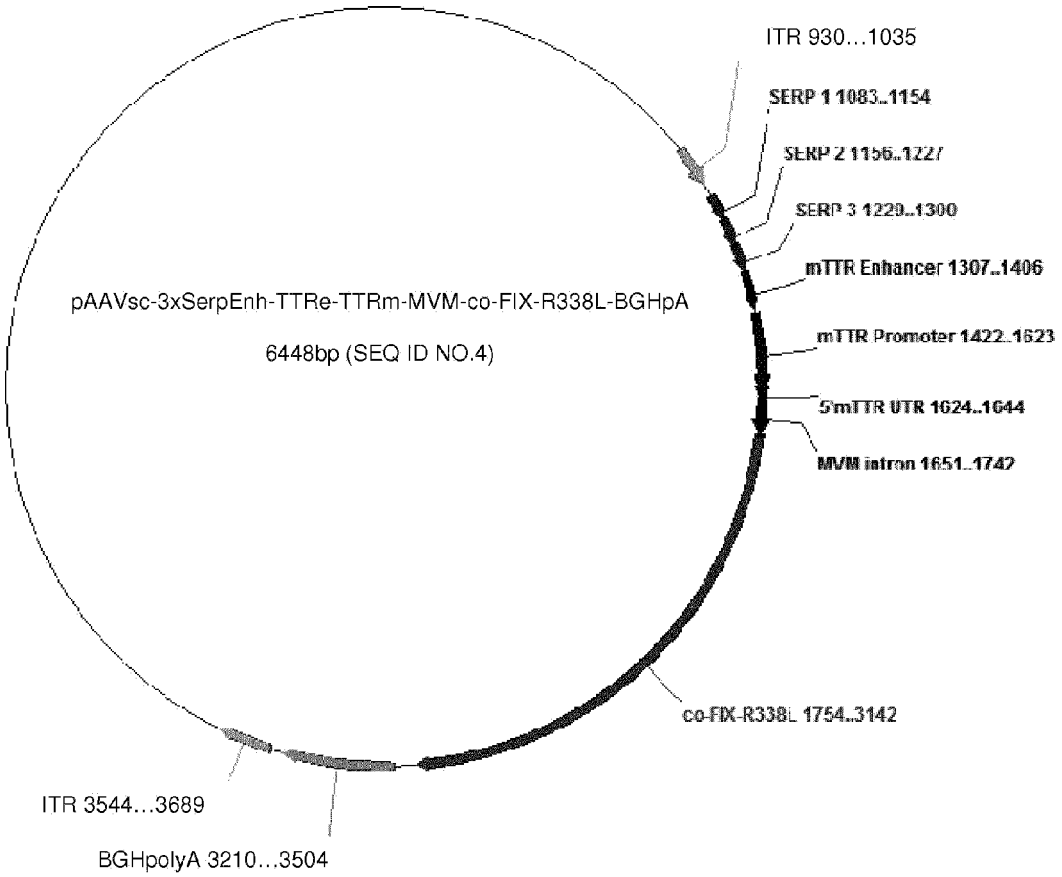
Figure 8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5'mTTR UTR 1624..1644
MVM intron 1651..1747
pAAVsc-3xSerpEnh-TTRe-TTRm-MVM-co-FIX-R338L-BGHpA
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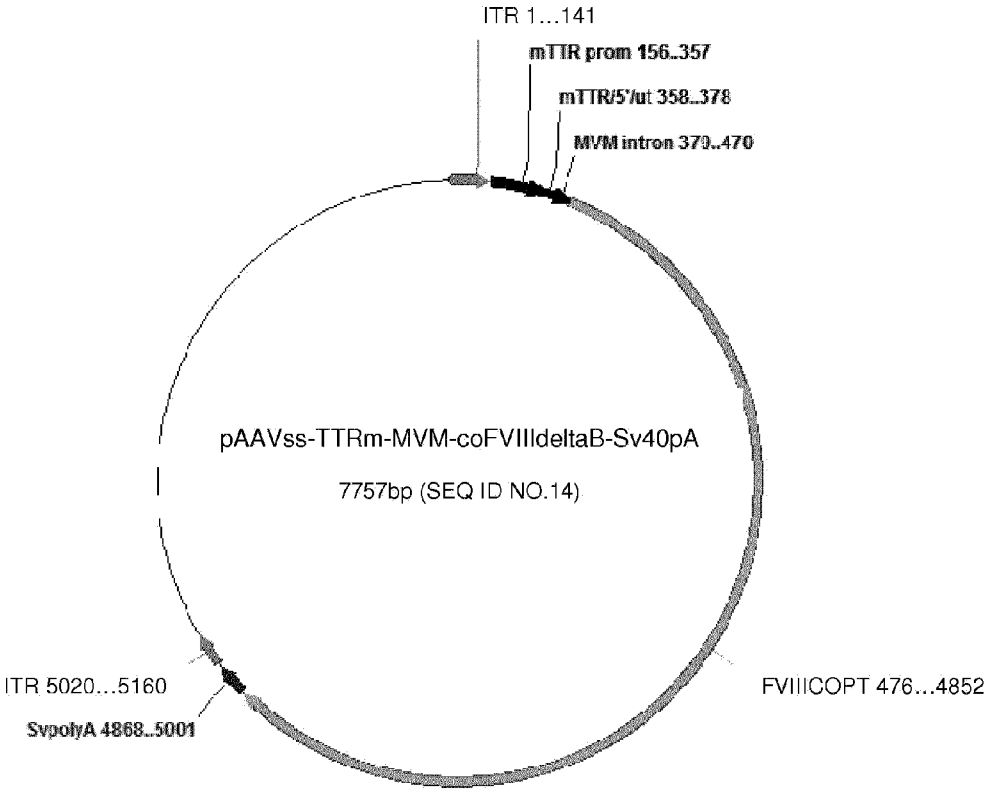
co-FIX-R338L 1754..3142
ITR 3544…3689
BGHpolyA 3210…3504

Figure 9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mTTR/5'ut 358..378
MVM intron 379..470
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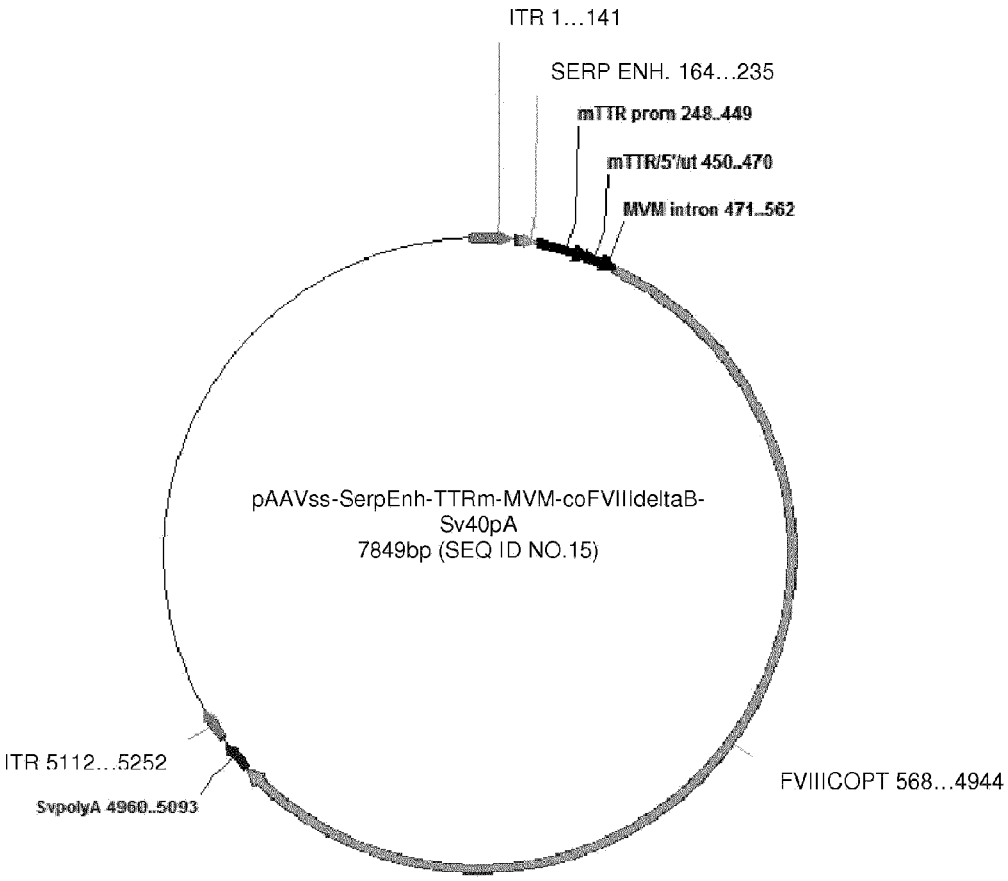
SvpolyA 4868..5001
FVIIICOPT 476...4852

Figure 10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SERP ENH. 164...235
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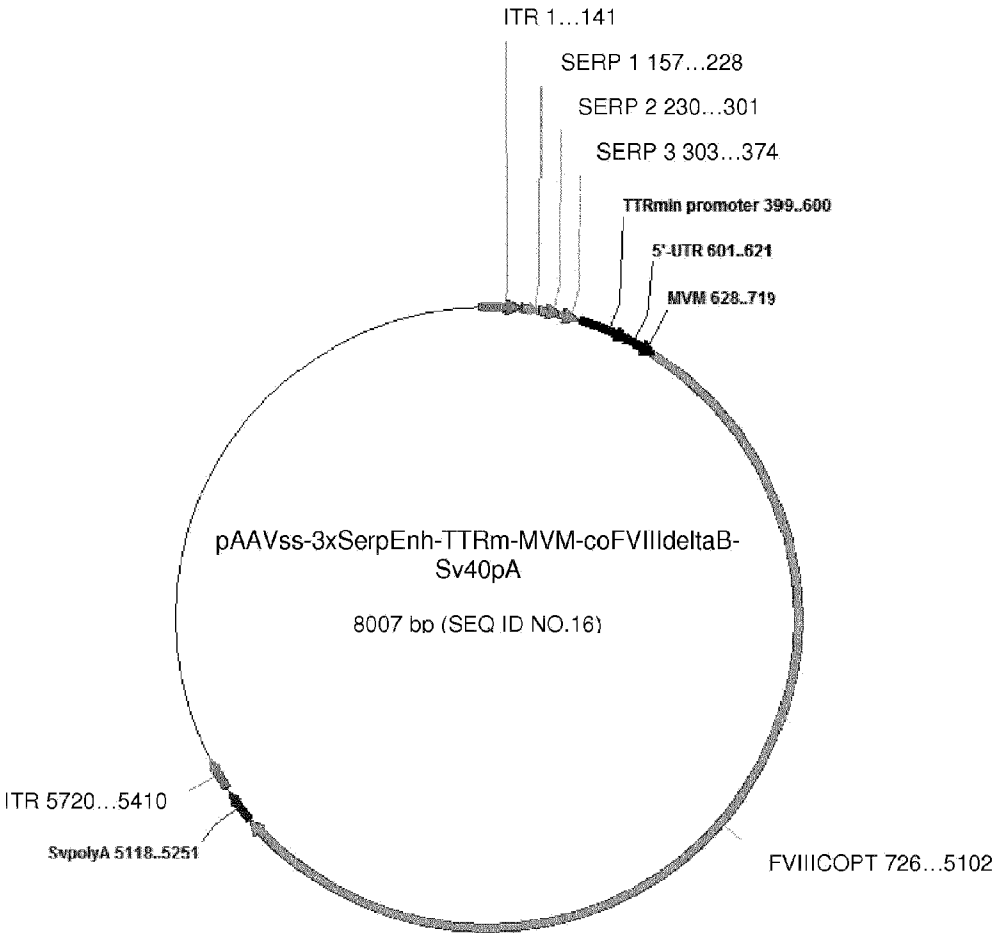
SvpolyA 4960..5093
FVIIICOPT 568...4944

Figure 11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SERP 1 157...228
SERP 2 230...301
SERP 3 303...374
TTRmin promoter 399..600
5'-UTR 601..621
MVM 628..719
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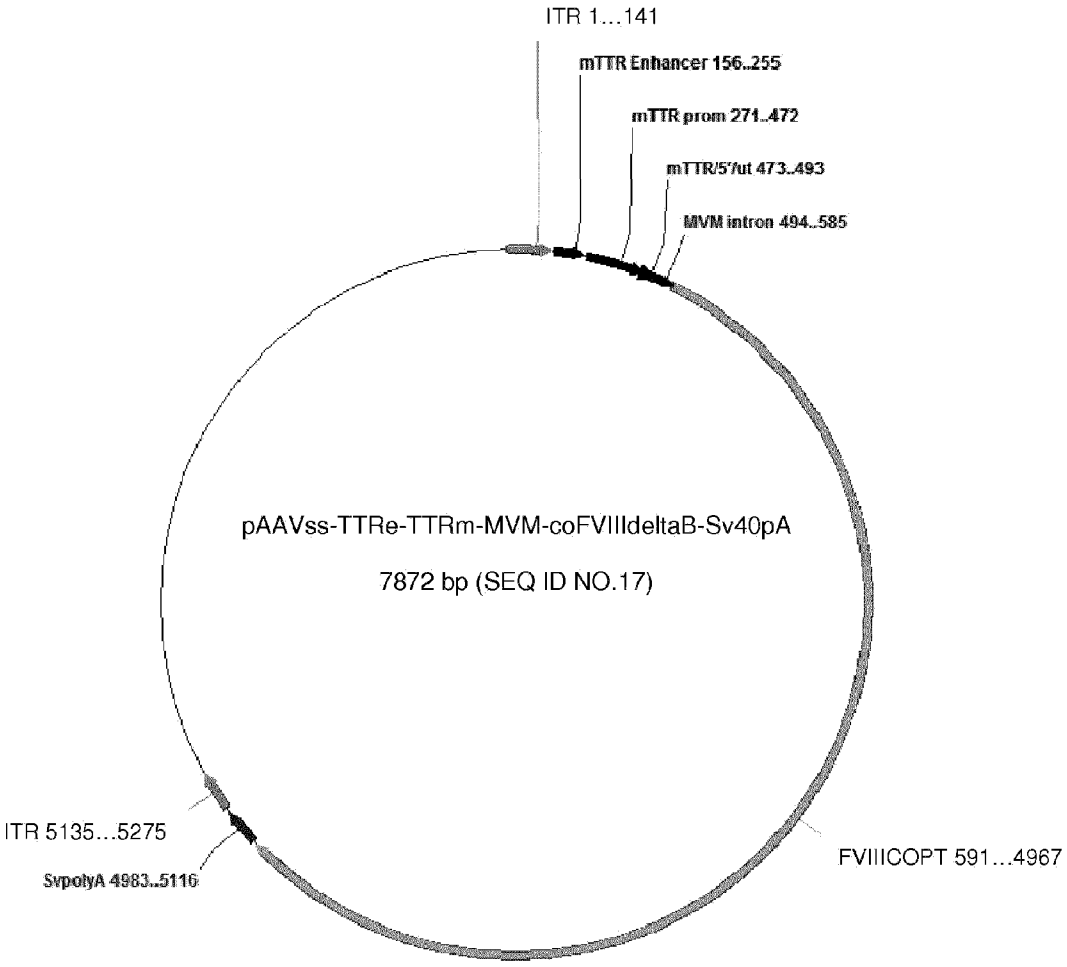
8007 bp (SEQ ID NO.16)
ITR 5720...5410
SvpolyA 5118..5251
FVIIICOPT 726...5102

Figure 12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mTTR prom 271..472
mTTR/5'ut 473..493
MVM intron 494..585
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7872 bp (SEQ ID NO.17)
ITR 5135...5275
SvpolyA 4983..5116
FVIIICOPT 591...4967

Figure 13

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

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SEQ ID NO.5: SerpEnh

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

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SEQ ID NO.7: TTRm5'UTR
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SEQ ID NO.8: MVM intron

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SEQ ID NO.9: Co-FIX-R338L

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SEQ ID NO.10: BGHpolyA

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SEQ ID NO.11: 3xSERP
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SEQ ID NO.12: TTRe (TTR Enhancer)

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

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

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AACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAACGAGAAGTGGATCGTGACCGCCGCCCACTG
CGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGCACAACATCGAGGAGACCGAGCACACCGAGC
AGAAGCGCAACGTGATCCGCATCATCCCCCACCACAACTACAACGCCGCCATCAACAAGTACAACCACGAC
ATCGCCCTGCTGGAGCTGGACGAGCCCCTGGTGCTGAACAGCTACGTGACCCCCATCTGCATCGCCGACAA
GGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACGTGAGCGGCTGGGGCCGCGTGTTCCACAAGG
GCCGCAGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCCTGGTGGACCGCGCCACCTGCCTGCTGAGCACC
AAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCACGAGGGCGGCCGCGACAGCTGCCAGGGCGA
CAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCTTCCTGACCGGCATCATCAGCTGGGGCGAGG
AGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTGAGCCGCTACGTGAACTGGATCAAGGAGAAG
ACCAAGCTGACCTAATGAAAGATGGATTTCCAAGGTTAATTCATTGGAATTGAAAATTAACAGCCCCCCCC
CCCCCCCCCCTGCAGATCTAATAAAAGATCTTTATTTTCATTAGATCTGTGTGTTGGTTTTTTGTGTGCCG
GTGGATCTCGATAGCAGGCATGCTGGGGAGAGATCGATCTGAGGAACCCCTAGTGATGGAGTTGGCCACTC
CCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGC
CCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACCCCCCCCCCCCCCCCCGGCGATT
CTCTTGTTTGCTCCAGACTCTCAGGCAATGACCTGATAGCCTTTGTAGAGACCTCTCAAAAATAGCTACCC
TCTCCGGCATGAATTTATCAGCTAGAACGGTTGAATATCATATTGATGGTGATTTGACTGTCTCCGGCCTT
TCTCACCCGTTTGAATCTTTACCTACACATTACTCAGGCATTGCATTTAAAATATATGAGGGTTCTAAAAA

TTTTTATCCTTGCGTTGAAATAAAGGCTTCTCCCGCAAAAGTATTACAGGGTCATAATGTTTTTGGTACAA
CCGATTTAGCTTTATGCTCTGAGGCTTTATTGCTTAATTTTGCTAATTCTTTGCCTTGCCTGTATGATTTA
TTGGATGTTGGAATCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATATGG
TGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTATATGGTGCACTCTCAGTACAATCTGCTCTGAT
GCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACAGCCAGCCCCGACACCCGCCAACACCCGCTGACG
CGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATG
TGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATA
GGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCC
CTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTC
AATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCA
TTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGC
ACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTT
TTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAG
CAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCT
TACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACT
TACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACT
CGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGT
AGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAA
TAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATT
GCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCC
CTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTG
AGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGAT
TTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCC
TTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTT
TTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGAT
CAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCT
AGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCC
TGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCG
GATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACAC
CGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGT
ATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTT
TATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAG
CCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT
TCTTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGC
CGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCAATACGCAAACCGCC
TCTCCCCGCGCGTTGGCCGATTCATTAATG

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

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGGAGGCTGCTGGTGAATATTA
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATAT
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAAT
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*
TTGAGTAAGATGGAAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG
GGCGATCAGCAGGTAG

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

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGGAGGCTGCTGGTGAATATTA
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATAT
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAAT
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*
TTGAGTAAGATGGAAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**

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

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGGAGGCTGCTGGTGAATATTA
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATAT
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAAT
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*
TTGAGTAAGATGGAAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTC
TAATCTCCCTAGGCAAGGTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCA
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC
CTTCACCAGGAGAAGCCGTC

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

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGGAGGCTGCTGGTGAATATTA
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATAT
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAAT
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*
TTGAGTAAGATGGAAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTC
TAATCTCCCTAGGCAAGGTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCA
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC
CTTCACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA**

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

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGGAGGCTGCTGGTGAATATTA
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATAT
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAAT
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*
TTGAGTAAGATGGAAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTC
TAATCTCCCTAGGCAAGGTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCA
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC
CTTCACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA***AAGAGGTAAGGGTTTAAGGGATGG*
TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTCAGGTTGG

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

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGGAGGCTGCTGGTGAATATTA
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATAT
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAAT
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*
TTGAGTAAGATGGAAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTC
TAATCTCCCTAGGCAAGGTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCA
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC
CTTCACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA***AAGAGGTAAGGGTTTAAGGGATGG*
*TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTCAGGTTGG***GCT**
AGCCCACC

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

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGGAGGCTGCTGGTGAATATTA
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATAT
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAAT
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*
TTGAGTAAGATGGAAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTC
TAATCTCCCTAGGCAAGGTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCA
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC
CTTCACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA***AAGAGGTAAGGGTTTAAGGGATGG*
*TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTCAGGTTGG***GCT**
AGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGC
TACCTGCTGAGCGCCGAGTGCACCGTGTTCCTGGACCACGAGAACGCCAACAAGATCCTGAACCGCCCCAA
GCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGT
GCAGCTTCGAGGAGGCCCGCGAGGTGTTCGAGAACACCGAGCGCACCACCGAGTTCTGGAAGCAGTACGTG
GACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGA
GTGCTGGTGCCCCTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCC
GCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTG
GCCGAGAACCAGAAGAGCTGCGAGCCCGCCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAG
CAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCGAGGCCGAGACCATCC
TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGCCAAG
CCCGGCCAGTTCCCCTGGCAGGTGGTGCTGAACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAA
CGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGC
ACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCCACCACAACTAC
AACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCTGGTGCTGAACAG
CTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACG
TGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGCAGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCCTG
GTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCA
CGAGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCT
TCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTG
AGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGA

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

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGGAGGCTGCTGGTGAATATTA
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATAT
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAAT
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*
TTGAGTAAGATGGAAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTC
TAATCTCCCTAGGCAAGGTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCA
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC
CTTCACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA***AAGAGGTAAGGGTTTAAGGGATGG*
*TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTCAGGTTGG***GCT**
AGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGC
TACCTGCTGAGCGCCGAGTGCACCGTGTTCCTGGACCACGAGAACGCCAACAAGATCCTGAACCGCCCCAA
GCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGT
GCAGCTTCGAGGAGGCCCGCGAGGTGTTCGAGAACACCGAGCGCACCACCGAGTTCTGGAAGCAGTACGTG
GACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGA
GTGCTGGTGCCCCTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCC
GCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTG
GCCGAGAACCAGAAGAGCTGCGAGCCCGCCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAG
CAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCGAGGCCGAGACCATCC
TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGCCAAG
CCCGGCCAGTTCCCCTGGCAGGTGGTGCTGAACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAA

CGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGC
ACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCCACCACAACTAC
AACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCTGGTGCTGAACAG
CTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACG
TGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGCAGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCCTG
GTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCA
CGAGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCT
TCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTG
AGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGAAAGATGGATTTCCAAGGTTAATT
CATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCCCCCTGCA

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

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGGAGGCTGCTGGTGAATATTA
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATAT
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAAT
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*
TTGAGTAAGATGGAAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTC
TAATCTCCCTAGGCAAGGTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCA
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC
CTTCACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA***AAGAGGTAAGGGTTTAAGGGATGG*
*TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTCAGGTTGG***GCT**
AGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGC
TACCTGCTGAGCGCCGAGTGCACCGTGTTCCTGGACCACGAGAACGCCAACAAGATCCTGAACCGCCCCAA
GCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGT
GCAGCTTCGAGGAGGCCCGCGAGGTGTTCGAGAACACCGAGCGCACCACCGAGTTCTGGAAGCAGTACGTG
GACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGA
GTGCTGGTGCCCCTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCC
GCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTG
GCCGAGAACCAGAAGAGCTGCGAGCCCGCCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAG
CAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCGAGGCCGAGACCATCC
TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGCCAAG
CCCGGCCAGTTCCCCTGGCAGGTGGTGCTGAACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAA
CGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGC
ACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCCACCACAACTAC
AACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCTGGTGCTGAACAG
CTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACG
TGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGCAGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCCTG
GTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCA
CGAGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCT
TCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTG
AGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGAAAGATGGATTTCCAAGGTTAATT
CATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCCCCCTGCAGATCTGAGCCGAATTCCTGCAGCCCGG
GGGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGA
CCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGG
TGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCA
TGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGGGGA

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

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGGAGGCTGCTGGTGAATATTA
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATAT

TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAAT
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*
TTGAGTAAGATGGAAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTC
TAATCTCCCTAGGCAAGGTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCA
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC
CTTCACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA***AAGAGGTAAGGGTTTAAGGGATGG*
*TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTCAGGTTGG***GCT**
AGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGC
TACCTGCTGAGCGCCGAGTGCACCGTGTTCCTGGACCACGAGAACGCCAACAAGATCCTGAACCGCCCCAA
GCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGT
GCAGCTTCGAGGAGGCCCGCGAGGTGTTCGAGAACACCGAGCGCACCACCGAGTTCTGGAAGCAGTACGTG
GACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGA
GTGCTGGTGCCCCTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCC
GCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTG
GCCGAGAACCAGAAGAGCTGCGAGCCCGCCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAG
CAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCGAGGCCGAGACCATCC
TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGCCAAG
CCCGGCCAGTTCCCCTGGCAGGTGGTGCTGAACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAA
CGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGC
ACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCCACCACAACTAC
AACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCTGGTGCTGAACAG
CTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACG
TGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGCAGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCCTG
GTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCA
CGAGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCT
TCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTG
AGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGAAAGATGGATTTCCAAGGTTAATT
CATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCCCCCCTGCAGATCTGAGCCGAATTCCTGCAGCCCGG
GGGATCAGCCTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGA
CCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGG
TGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCA
TGCTGGGGATGCGGTGGGCTCTATGGCTTCTGAGGCGGAAAGAACCAGCTGGGGA**CCGGTGGATCTCGATA**
GCAGGCATGCTGGGGAGAGATCG

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

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGGAGGCTGCTGGTGAATATTA
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATAT
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAAT
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*
TTGAGTAAGATGGAAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTC
TAATCTCCCTAGGCAAGGTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCA
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC
CTTCACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA***AAGAGGTAAGGGTTTAAGGGATGG*
*TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTCAGGTTGG***GCT**
AGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGC
TACCTGCTGAGCGCCGAGTGCACCGTGTTCCTGGACCACGAGAACGCCAACAAGATCCTGAACCGCCCCAA
GCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGT
GCAGCTTCGAGGAGGCCCGCGAGGTGTTCGAGAACACCGAGCGCACCACCGAGTTCTGGAAGCAGTACGTG
GACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGA
GTGCTGGTGCCCCTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCC
GCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTG

GCCGAGAACCAGAAGAGCTGCGAGCCCGCCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAG
CAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCGAGGCCGAGACCATCC
TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGCCAAG
CCCGGCCAGTTCCCCTGGCAGGTGGTGCTGAACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAA
CGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGC
ACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCCACCACAACTAC
AACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCTGGTGCTGAACAG
CTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACG
TGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGCAGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCCTG
GTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCA
CGAGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCT
TCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTG
AGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGAAAGATGGATTTCCAAGGTTAATT
CATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCCCCCTGCAAATAAAAGATCTTTATTTTCATTAGAT
CTGTGTGTTGGTTTTTTGTGTG

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

AATTCACGCGTGGATCTGAATTCAATTCACGCGTGGTACGGCCGCGGGGGGGAGGCTGCTGGTGAATATTA
ACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATAT
TAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAAT
ATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATG*
TTGAGTAAGATGGAAAACTACTGATGACCCTTGCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCG
*GGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**GTCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTC
TAATCTCCCTAGGCAAGGTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCA
GAATCAGCAGGTTTGGAGTCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCC
CTTCACCAGGAGAAGCCGTC**ACACAGATCCACAAGCTCCTGGCTAGA***AAGAGGTAAGGGTTTAAGGGATGG*
*TTGGTTGGTGGGGTATTAATGTTTAATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTCAGGTTGG***GCT**
AGCCCACCATGCAGCGCGTGAACATGATCATGGCCGAGAGCCCCGGCCTGATCACCATCTGCCTGCTGGGC
TACCTGCTGAGCGCCGAGTGCACCGTGTTCCTGGACCACGAGAACGCCAACAAGATCCTGAACCGCCCCAA
GCGCTACAACAGCGGCAAGCTGGAGGAGTTCGTGCAGGGCAACCTGGAGCGCGAGTGCATGGAGGAGAAGT
GCAGCTTCGAGGAGGCCCGCGAGGTGTTCGAGAACACCGAGCGCACCACCGAGTTCTGGAAGCAGTACGTG
GACGGCGACCAGTGCGAGAGCAACCCCTGCCTGAACGGCGGCAGCTGCAAGGACGACATCAACAGCTACGA
GTGCTGGTGCCCCTTCGGCTTCGAGGGCAAGAACTGCGAGCTGGACGTGACCTGCAACATCAAGAACGGCC
GCTGCGAGCAGTTCTGCAAGAACAGCGCCGACAACAAGGTGGTGTGCAGCTGCACCGAGGGCTACCGCCTG
GCCGAGAACCAGAAGAGCTGCGAGCCCGCCGTGCCCTTCCCCTGCGGCCGCGTGAGCGTGAGCCAGACCAG
CAAGCTGACCCGCGCCGAGGCCGTGTTCCCCGACGTGGACTACGTGAACAGCACCGAGGCCGAGACCATCC
TGGACAACATCACCCAGAGCACCCAGAGCTTCAACGACTTCACCCGCGTGGTGGGCGGCGAGGACGCCAAG
CCCGGCCAGTTCCCCTGGCAGGTGGTGCTGAACGGCAAGGTGGACGCCTTCTGCGGCGGCAGCATCGTGAA
CGAGAAGTGGATCGTGACCGCCGCCCACTGCGTGGAGACCGGCGTGAAGATCACCGTGGTGGCCGGCGAGC
ACAACATCGAGGAGACCGAGCACACCGAGCAGAAGCGCAACGTGATCCGCATCATCCCCCACCACAACTAC
AACGCCGCCATCAACAAGTACAACCACGACATCGCCCTGCTGGAGCTGGACGAGCCCCTGGTGCTGAACAG
CTACGTGACCCCCATCTGCATCGCCGACAAGGAGTACACCAACATCTTCCTGAAGTTCGGCAGCGGCTACG
TGAGCGGCTGGGGCCGCGTGTTCCACAAGGGCCGCAGCGCCCTGGTGCTGCAGTACCTGCGCGTGCCCCTG
GTGGACCGCGCCACCTGCCTGCTGAGCACCAAGTTCACCATCTACAACAACATGTTCTGCGCCGGCTTCCA
CGAGGGCGGCCGCGACAGCTGCCAGGGCGACAGCGGCGGCCCCCACGTGACCGAGGTGGAGGGCACCAGCT
TCCTGACCGGCATCATCAGCTGGGGCGAGGAGTGCGCCATGAAGGGCAAGTACGGCATCTACACCAAGGTG
AGCCGCTACGTGAACTGGATCAAGGAGAAGACCAAGCTGACCTAATGAAAGATGGATTTCCAAGGTTAATT
CATTGGAATTGAAAATTAACAGCCCCCCCCCCCCCCCCCCTGCAAATAAAAGATCTTTATTTTCATTAGAT
CTGTGTGTTGGTTTTTTGTGTG**CCGGTGGATCTCGATAGCAGGCATGCTGGGGAGAGATCG**

Figure 14

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

CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTT
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CGGCCGCGGTACCGTCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGG
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TCAGCTTGGCAGGGATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCTTCACCAGGAGAAGCCG
TCACACAGATCCACAAGCTCCTGAAGAGGTAAGGGTTTAAGGGATGGTTGGTTGGTGGGGTATTAATGTTT
AATTACCTGGAGCACCTGCCTGAAATCACTTTTTTTCAGGTTGGCTAGTATGCAGATCGAGCTGTCCACCT
GCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGCGCCACCCGGCGGTACTACCTGGGCGCCGTGGAGCTG
TCCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCGTGGACGCCCGGTTCCCCCCCAGAGTGCCCAA
GAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCCTGTTCGTGGAGTTCACCGACCACCTGTTCA
ATATCGCCAAGCCCAGGCCCCCCTGGATGGGCCTGCTGGGCCCCACCATCCAGGCCGAGGTGTACGACACC
GTGGTGATCACCCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAA
GGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAAGAAGATGACAAGGTGTTCCCTG
GCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGGCCCCATGGCCTCCGACCCCCTGTGCCTG
ACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGCCTGATCGGCGCTCTGCTCGT
CTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAGTTCATCCTGCTGTTCGCCGTGT
TCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCAGGACCGGGACGCCGCCTCTGCC
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CCGGAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACACCCGAGGTGCACAGCATCTTTCTGGAAG
GGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAGCCCTATCACCTTCCTGACCGCC
CAGACACTGCTGATGGACCTGGGCCAGTTCCTGCTGTTTTGCCACATCAGCTCTCACCAGCACGACGGCAT
GGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCCAGCTGCGGATGAAGAACAACGAGGAAGCCG
AGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGGTGCGGTTCGACGACGACAACAGCCCCAGC
TTCATCCAGATCAGAAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTGCACTATATCGCCGCCGAGGAAGA
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GCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTTCATGGCCTACACCGACGAGACATTCAAGACC
CGGGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGCGAAGTGGGCGACACACTGCT
GATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTACCCCCACGGCATCACCGACGTGCGGCCCC
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AAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACCCCAGATGCCTGACCCGGTACTA
CAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGACCTCTGCTGATCTGCTACAAAG
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CATCATGGACACCCTGCCTGGCCTGGTGATGGCCCAGGACCAGAGAATCCGGTGGTATCTGCTGTCCATGG
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AAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTCGAGACAGTGGAGATGCTGCCCAGCAAGGCCGGCAT
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ACAAGTGCCAGACCCCACTGGGCATGGCCTCTGGCCACATCCGGGACTTCCAGATCACCGCCTCCGGCCAG
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GCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCTATGATCATCCACGGCATTAAGACCCAGGGCGCCA
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CAACATCTTCAACCCCCCCATCATTGCCCGGTACATCCGGCTGCACCCCACCCACTACAGCATTAGATCCA
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TTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCC
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TATATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAA
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GGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAG

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

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CTCTAATCTCCCTAGGCAAGGTTCATATTTGTGTAGGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAA
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CCCCTTCACCAGGAGAAGCCGTCACACAGATCCACAAGCTCCTGAAGAGGTAAGGGTTTAAGGGATGGTTG
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TACCTGGGCGCCGTGGAGCTGTCCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCGTGGACGCCCG
GTTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCCTGTTCGTGG
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CAGGCCGAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGC
CGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAAG
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TCATCCTGCTGTTCGCCGTGTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCAG
GACCGGGACGCCGCCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGAAGCCT
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TGCACAGCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAGC
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CTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCTTGCCCCGAGGAACCCCAGCTGCGGA
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AGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGCCGGAAGTACAAGAAAGTGCGGTTCATGGCCTAC
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CGAAGTGGGCGACACACTGCTGATCATCTTCAAGAACCAGGCTAGCCGGCCCTACAACATCTACCCCCACG
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CAGATGCCTGACCCGGTACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGAC
CTCTGCTGATCTGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGCGACAAGCGGAACGTG
ATCCTGTTCAGCGTGTTCGATGAGAACCGGTCCTGGTATCTGACCGAGAACATCCAGCGGTTTCTGCCCAA
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CCGACCAGGAAGAGATCGATTACGACGACACCATCAGCGTGGAGATGAAGAAAGAGGATTTCGATATCTAC
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SEQ ID NO.19: SV40polyA

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

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

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SEQ ID NO.39: **Flank**-3xSERP-**Flank**-*TTRe*
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SEQ ID NO.40: **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**

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

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

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TCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTCATATTTGTGTA
GGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGG
ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCTTCACCAGGAGAAGCCGTC**CTAGT**

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

GCGGCCGCGGTACGCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA
CAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA
AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG
CAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATGTTGAGTAAGATGGAAAACTACTGATGACCCTT*
*GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**G
TCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTCATATTTGTGTA

GGTTACTTATTCTCCTTTTGTTGACTAAGTCAATAATCAGAATCAGCAGGTTTGGAGTCAGCTTGGCAGGG
ATCAGCAGCCTGGGTTGGAAGGAGGGGGTATAAAAGCCCCTTCACCAGGAGAAGCCGTC**CTAGTATGCAGA**
TCGAGCTGTCCACCTGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGCGCCACCCGGCGGTACTACCTG
GGCGCCGTGGAGCTGTCCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCCGTGGACGCCCGGTTCCC
CCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAGAAAACCCTGTTCGTGGAGTTCA
CCGACCACCTGTTCAATATCGCCAAGCCCAGGCCCCCCTGGATGGGCCTGCTGGGCCCCACCATCCAGGCC
GAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGCCGTGGG
CGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGCCAGCGGGAGAAAGAAGATG
ACAAGGTGTTCCCTGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAAGAAAACGGCCCCATGGCCTCC
GACCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGCCTGAT
CGGCGCTCTGCTCGTCTGCCGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAGTTCATCC
TGCTGTTCGCCGTGTTCGACGAGGGCAAGAGCTGGCACAGCGAGACAAAGAACAGCCTGATGCAGGACCGG
GACGCCGCCTCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGAAGCCTGCCCGG
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GCATCTTTCTGGAAGGGCACACCTTTCTGGTCCGGAACCACCGGCAGGCCAGCCTGGAAATCAGCCCTATC
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CAGCGGCATCAAGCACAACATCTTCAACCCCCCCATCATTGCCCGGTACATCCGGCTGCACCCCACCCACT
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ATGGAAAGCAAGGCCATCAGCGACGCCCAGATCACAGCCAGCAGCTACTTCACCAACATGTTCGCCACCTG
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CTTTCAGAACGGCAAGGTGAAAGTGTTCCAGGGCAACCAGGACTCCTTCACCCCCGTGGTGAACTCCCTGG
ACCCCCCCCTGCTGACCCGCTACCTGAGAATCCACCCCCAGTCTTGGGTGCACCAGATCGCCCTCAGGATG
GAAGTCCTGGGATGTGAGGCCCAGGATCTGTACTGATGA

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

GCGGCCGCGGTACGCGGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCAAA
CAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA
AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG
CAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATGTTGAGTAAGATGGAAAACTACTGATGACCCTT*
*GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**G
TCTGTCTGCACATTTCGTAGAGCGAGTGTTCCGATACTCTAATCTCCCTAGGCAAGGTTCATATTTGTGTA
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GAAGTCCTGGGATGTGAGGCCCAGGATCTGTACTGATGAGGATCC

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

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AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG
CAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATGTTGAGTAAGATGGAAAACTACTGATGACCCTT*
*GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**G
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SEQ ID NO.46: **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-**Flank**-**coFVIIIdeltaB**-**Flank**-SV40pA-**Flank**

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AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG
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TTTCAGGTTCAGGGGGAGGTGTGGGAGGTTTTTTAAA**CTCGAGATCCACGGCCGC**

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

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CAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA
AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG
CAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATGTTGAGTAAGATGGAAAACTACTGATGACCCTT*
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SEQ ID NO.48: **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-**Flank**-coFVIIIdeltaB-**Flank**- SyntpA-**Flank**

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CAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAGCA
AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG
CAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATGTTGAGTAAGATGGAAAACTACTGATGACCCTT*
*GCAGAGACAGAGTATTAGGACATGTTTGAACAGGGGCCGGGCGATCAGCAGGTAG***CTCTAGAGGATCCCC**G
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SEQ ID NO.49: **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-*MVM*-**Flank**

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AACAGGGGCTAAGTCCAC**C**GGGGGAGGCTGCTGGTGAATATTAACCAAGGTCACCCCAGTTATCGGAGGAG
CAAACAGGGGCTAAGTCCAC**GGTACC***CACTGGGAGGATGTTGAGTAAGATGGAAAACTACTGATGACCCTT*
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SEQ ID NO.50: **Flank**-3xSERP-**Flank**-*TTRe*-**Flank**-TTRm-*MVM*-**Flank**-
coFVIIIdeltaB

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

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

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

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

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

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SEQ ID NO.56: Synt.pA

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

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SEQ ID NO.58: 3xSERP-**Flank**-*TTRe*-**Flank**-TTRm

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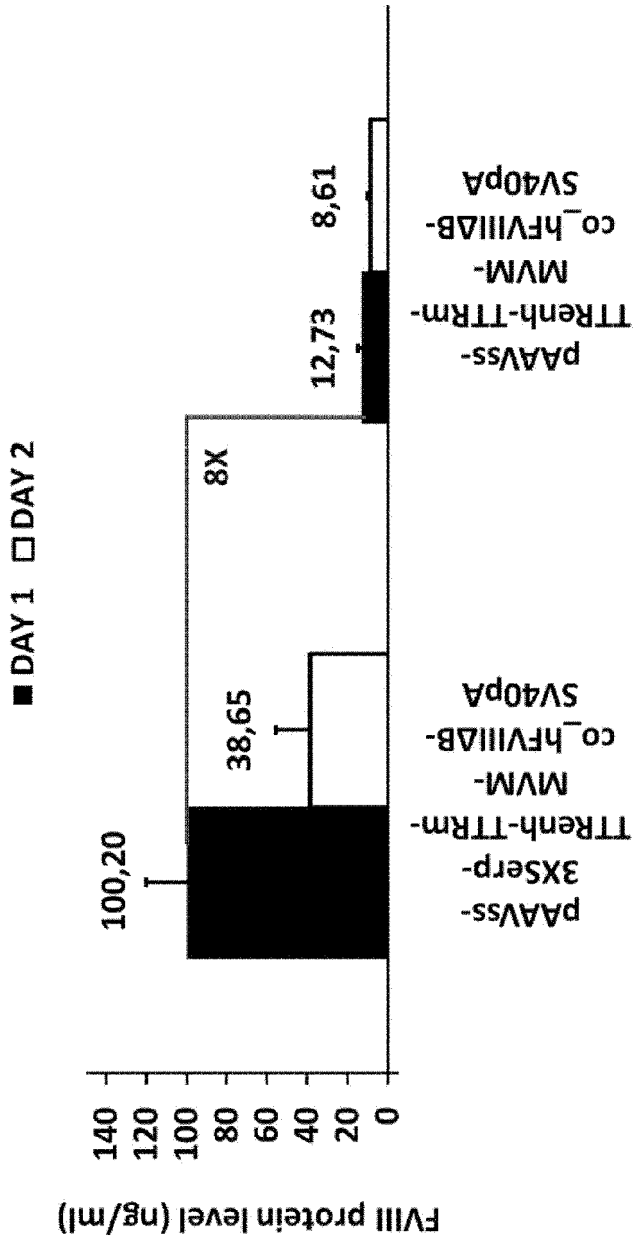
Figure 15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40
60
80
100
120
140
DAY 1
DAY 2
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38,65
8X
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8,61
pAAVss-
3XSerp-
TTRenh-TTRm-
MVM-
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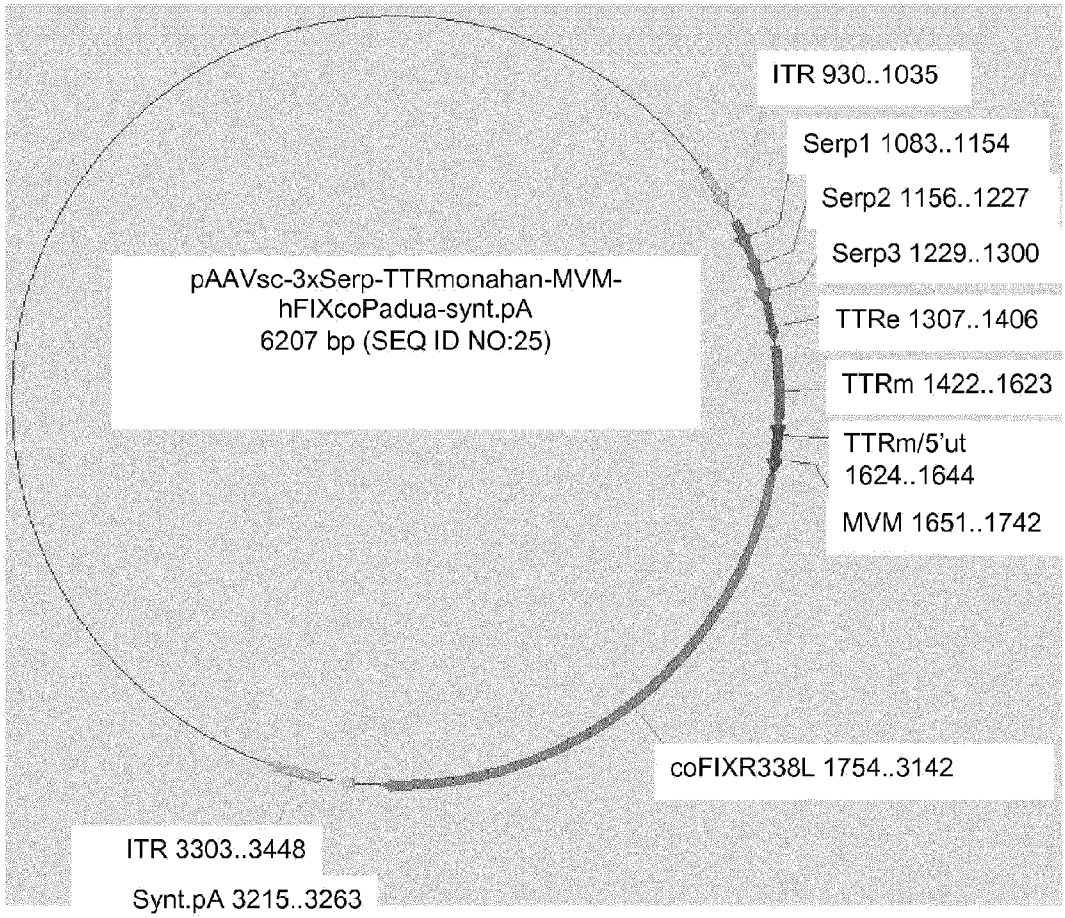
MVM-
co_hFVIIIΔB-
SV40pA

Figure 16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Serp2 1156..1227
Serp3 1229..1300
TTRe 1307..1406
TTRm 1422..1623
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Figure 17

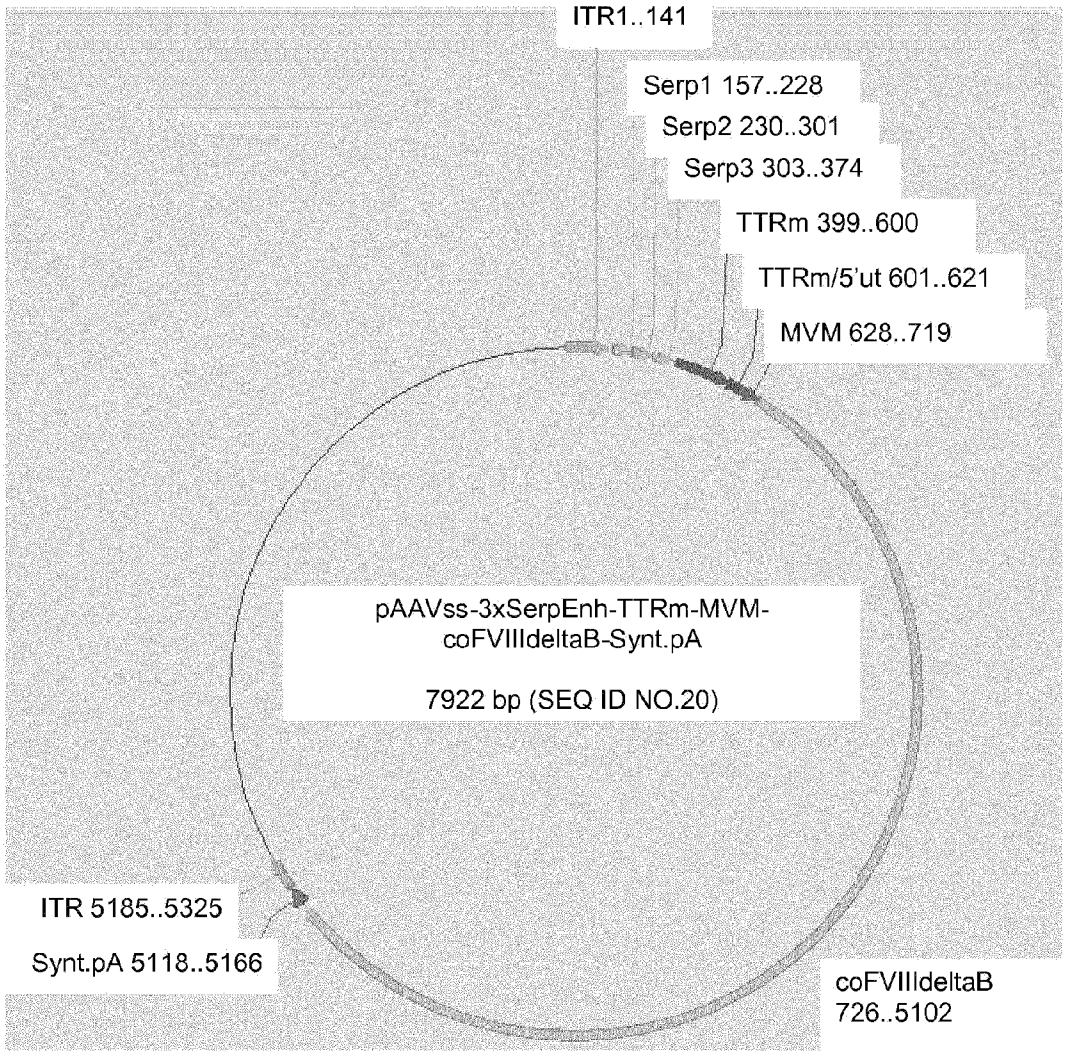
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Figure 18

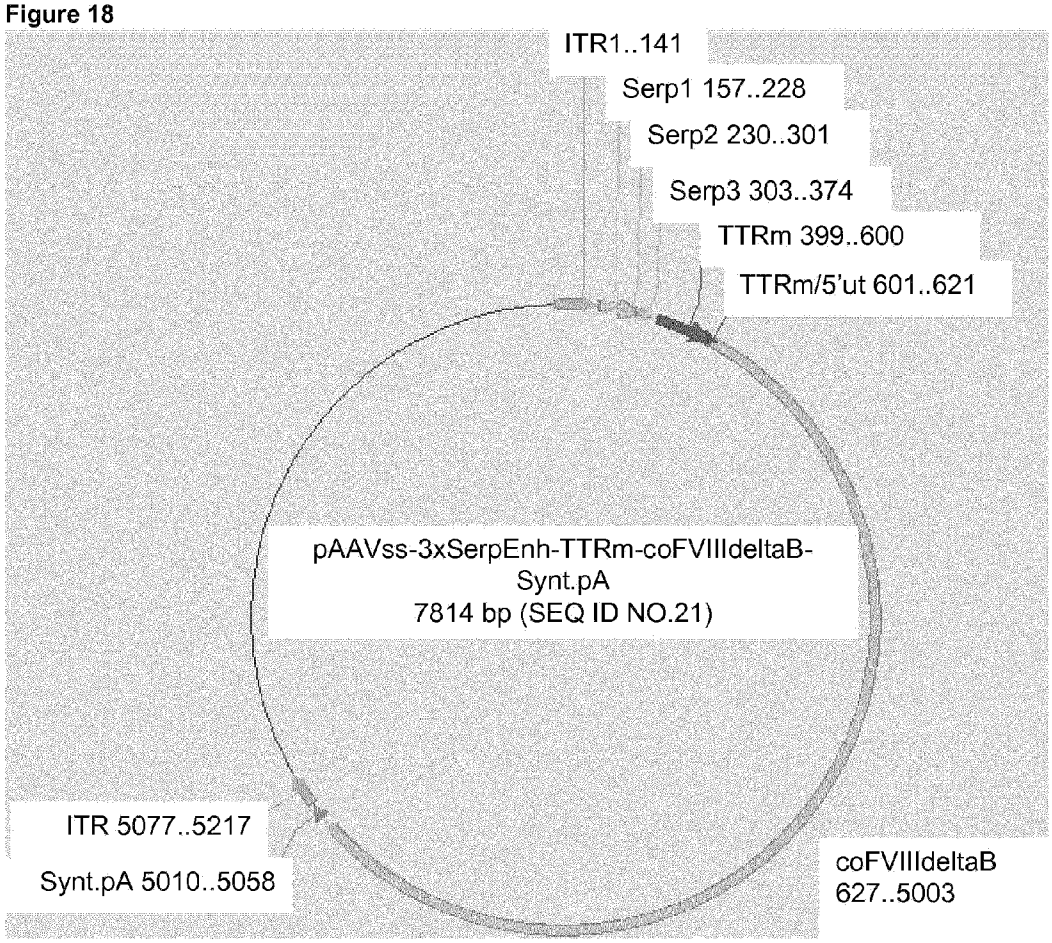
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Figure 19

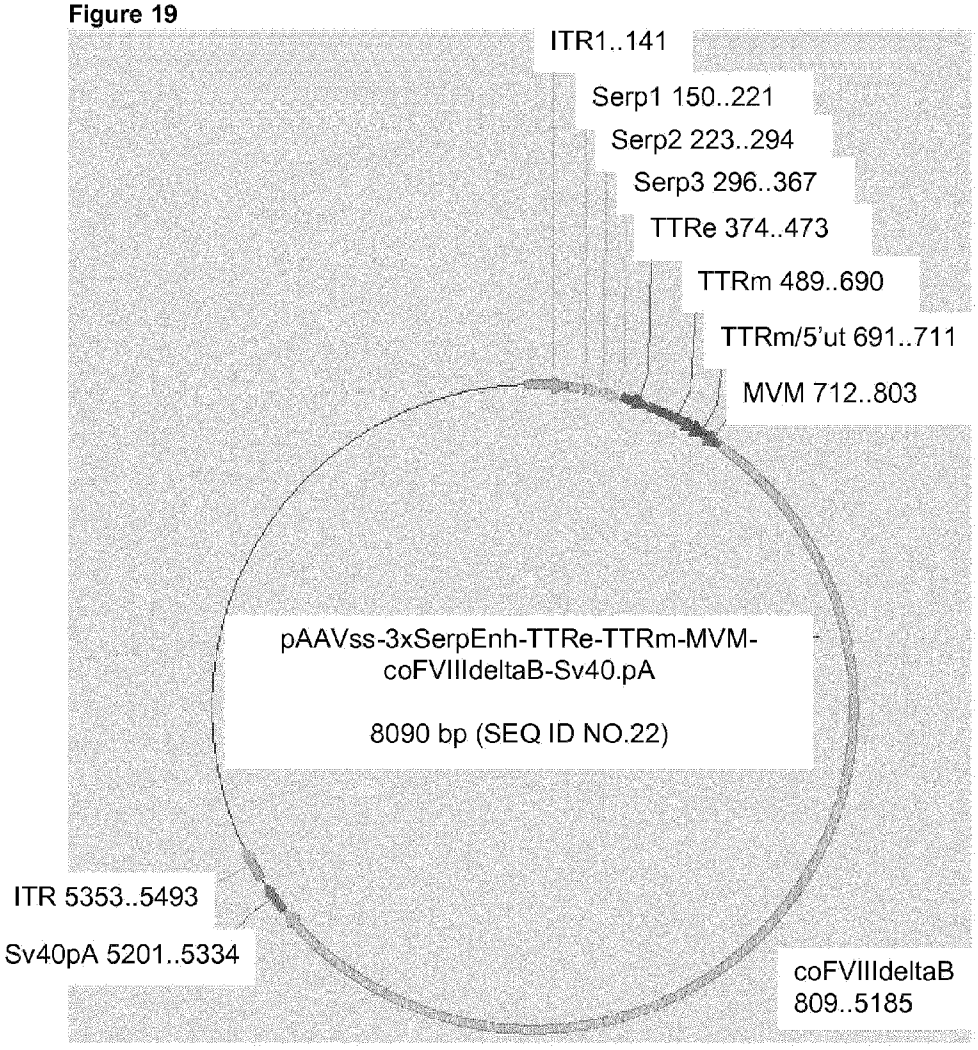
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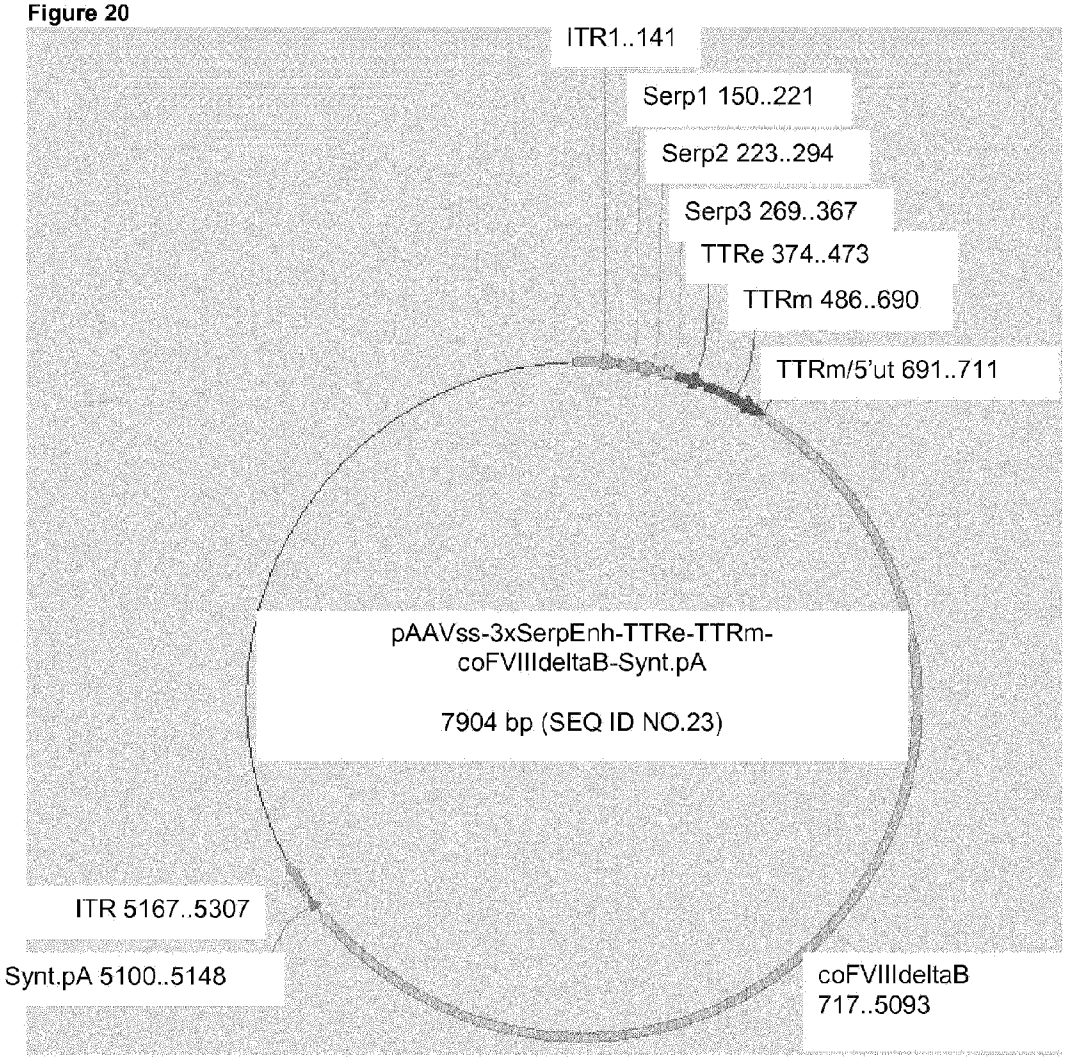
Figure 20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Serp1 150..221
Serp2 223..294
Serp3 269..367
TTRe 374..473
TTRm 486..690
TTRm/5'ut 691..711
pAAVss-3xSerpEnh-TTRe-TTRm-
coFVIIIdeltaB-Synt.pA
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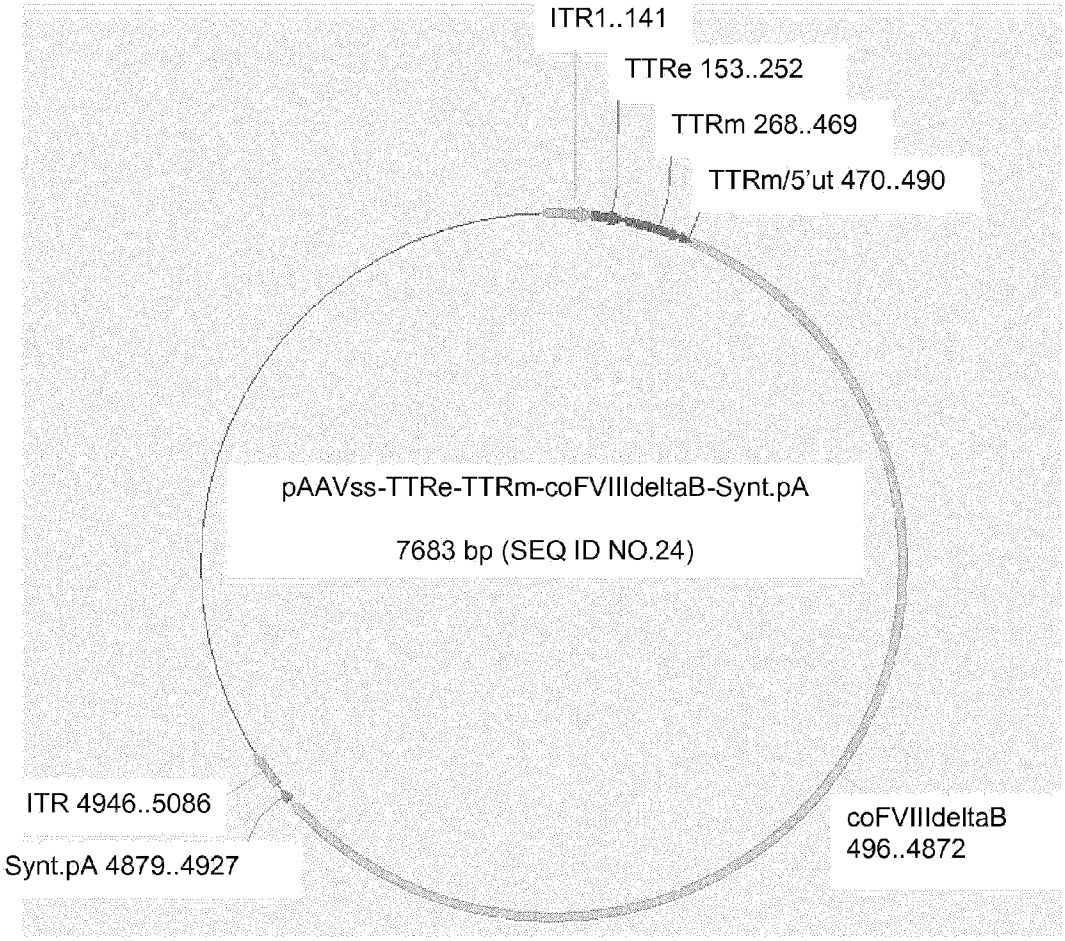
Synt.pA 5100..5148
coFVIIIdeltaB
717..5093

Figure 21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TTRe 153..252
TTRm 268..469
TTRm/5'ut 470..490
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Synt.pA 4879..4927
coFVIIIdeltaB
496..4872

Figure 22

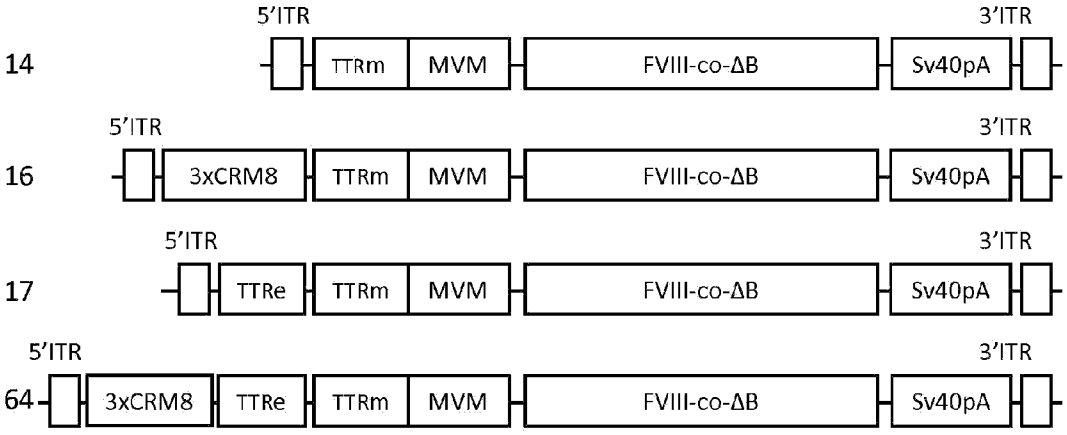

Figure 23

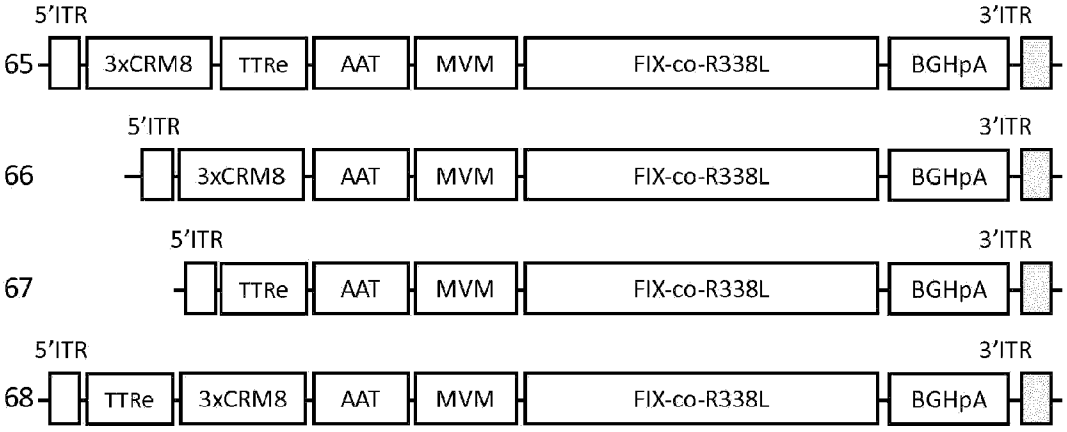

Figure 24

SEQ ID NO:64: AAT promoter

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

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SEQ ID NO:67: pAAVsc-TTRe-AAT-FIX-co-R338L-BGHpA

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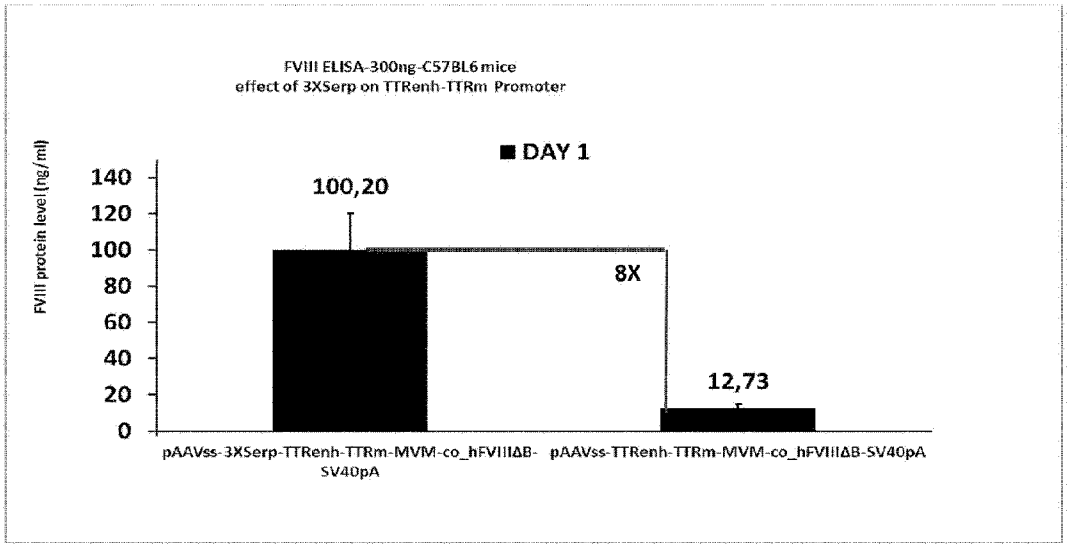
Figure 25a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effect of 3XSerp on TTRenh-TTRm Promoter
FVIII protein level (ng/ml)
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100
80
60
40
20
0
100,20
8X
12,73
pAAVss-3XSerp-TTRenh-TTRm-MVM-co_hFVIIIΔB-SV40pA
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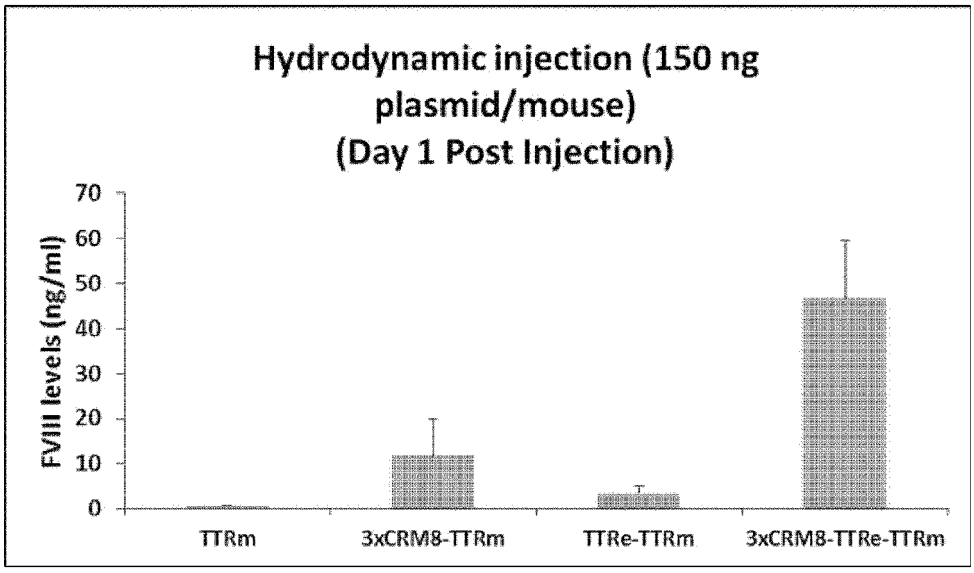
Figure 25b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(Day 1 Post Injection)
FVIII levels (ng/ml)
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TTRe-TTRm
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