(12) STANDARD PATENT (11) Application No. AU 2018254529 B2
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Therapeutic genome editing in Wiskott-Aldrich syndrome and X-linked thrombocytopenia

(51) International Patent Classification(s)
A61K 35/28 (2015.01) ***A61K 48/00*** (2006.01)

(21) Application No: **2018254529** (22) Date of Filing: **2018.04.19**

(87) WIPO No: **WO18/195360**

(30) Priority Data

(31) Number	(32) Date	(33) Country
62/488,249	**2017.04.21**	**US**

(43) Publication Date: **2018.10.25**
(44) Accepted Journal Date: **2024.03.28**

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(56) Related Art
WANG ET AL., NUCLEIC ACID RESEARCH, vol. 45, no. 5, 29 November 2016 (2016-11-29), pages 1 - 12, XP055546039

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

CORRECTED VERSION

(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
25 October 2018 (25.10.2018)

WIPO | PCT

(10) **International Publication Number**
WO 2018/195360 A8

(51) **International Patent Classification:**
A61K 35/28 (2015.01) *A61K 48/00* (2006.01)

(21) **International Application Number:**
PCT/US2018/028442

(22) **International Filing Date:**
19 April 2018 (19.04.2018)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
62/488,249 21 April 2017 (21.04.2017) US

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH,

(54) **Title:** THERAPEUTIC GENOME EDITING IN WISKOTT-ALDRICH SYNDROME AND X-LINKED THROMBOCYTOPENIA

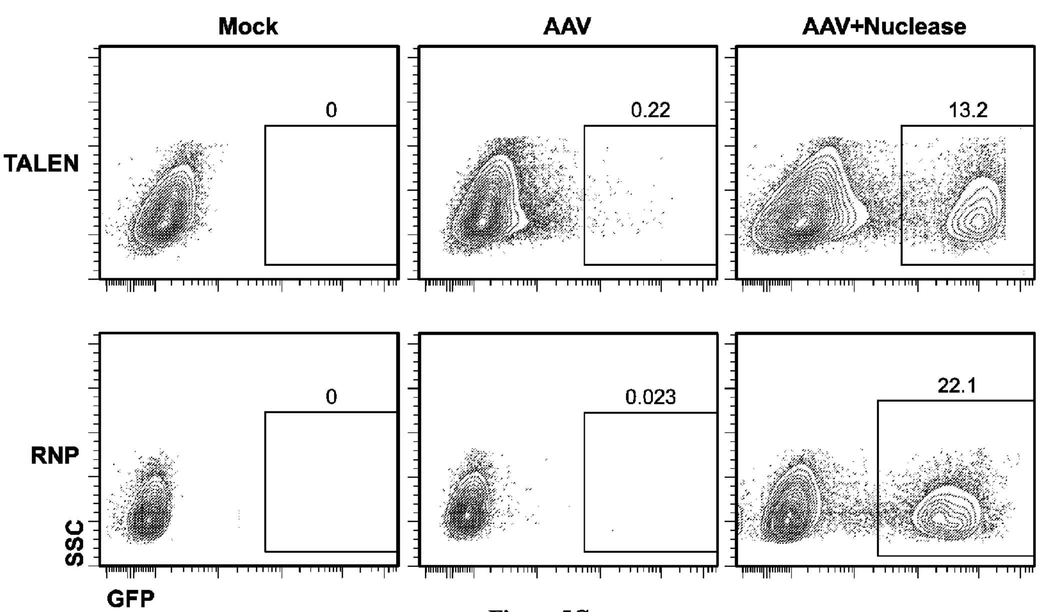

Figure 5C

(57) **Abstract:** Described herein are systems and methods for treating, inhibiting, or ameliorating X- linked disorders including Wiskott-Aldrich Syndrome (WAS) and X-linked thrombocytopenia (XLT) in subjects that have been identified or selected as being ones that would benefit from a therapy to treat, inhibit, or ameliorate WAS or XLT. The systems include nuclease and vector donor constructs configured for co-delivery to modify endogenous *WAS* locus.

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

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*

(48) Date of publication of this corrected version:
13 June 2019 (13.06.2019)

(15) Information about Correction:
see Notice of 13 June 2019 (13.06.2019)

Therapeutic Genome Editing in Wiskott-Aldrich Syndrome and X-Linked Thrombocytopenia

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of priority to U.S. Provisional Patent Application No. 62/488,249, filed April 21, 2017. The entire disclosure of the aforementioned application is expressly incorporated by reference in its entirety.

REFERENCE TO SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 2018-04-19 Sequence Listing –SCRI.149WO.txt, created April 19, which is 158 kb in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

FIELD

[0003] Alternatives herein relate generally to gene editing in primary human hematopoietic stem cells. More particularly, alternatives herein relate to nucleic acids and vectors that are configured to provide efficient homology directed repair of genes, and methods of repairing genetic deficiencies, such as X-linked recessive disorders.

BACKGROUND

[0004] Wiskott-Aldrich syndrome (WAS) is an inherited primary immunodeficiency caused by mutations in the *WAS* gene, which encodes a protein that regulates the actin cytoskeleton leading to altered signaling function and/or development in multiple hematopoietic cell lineages. WAS is an X-linked recessive disease, affecting approximately one in 250,000 males. The disease is characterized by eczema, thrombocytopenia, and immune deficiency. WAS is caused by a mutation in the *WAS* gene, resulting in mutated or absent forms of the WAS protein (WASp).

[0005] X-linked thrombocytopenia (XLT) is an inherited clotting disorder related to WAS. XLT primarily affects the circulatory system by reducing the platelet counts in the blood, and also reducing the platelet size compared to normal or healthy individuals, which compromises the clotting process. XLT is caused by a mutation in the *WAS* gene, resulting in decreased, absent, or altered WASp.

[0006] WASp is an activator of the actin nucleator Arp2/3 complex *in vitro* and is expressed exclusively in hematopoietic cells. WASp is believed to serve as a key integrator between surface receptors and the cytoskeleton of leukocytes.

[0007] Currently, therapies for individuals with WAS or XLT focus on the symptoms. The only available curative therapy for WAS or XLT is allogeneic stem cell transplantation. Viral-based gene replacement is also being explored in several current clinical trials but the need for more therapies for WAS and XLT is manifest.

SUMMARY

[0008] Some alternatives relate to therapeutic approaches designed to correct or repair the endogenous *WAS* locus in autologous hematopoietic stem cells. Some alternatives include compositions and methods, which comprise transcription activator-like effector nucleases (TALENs) and clustered regularly interspaced short palindromic repeats (CRISPR)/Cas that are configured to edit the *WAS* locus in primary human hematopoietic cells. Some alternatives also relate to co-delivery of a nuclease and an AAV donor for modifying endogenous *WAS* locus in primary human hematopoietic cells.

[0009] Some alternatives concern a nucleic acid for homology directed repair (HDR) of the Wiskott-Aldrich Syndrome (WAS) gene. In some alternatives, the nucleic acid comprises a first sequence encoding a *WAS* gene, a second sequence encoding one or more guide RNA cleavage sites, and a third sequence encoding one or more nuclease binding sites. In some alternatives, the *WAS* gene comprises the nucleic acid sequence set forth in SEQ ID NO: 4. In some alternatives, the second sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 17. In some alternatives, the one or more nuclease binding sites comprises a forward and reverse transcription activator-like effector nuclease (TALEN) binding site. In some alternatives, the one or more nuclease binding sites is a clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) binding site. In some alternatives, the nucleic acid further comprises one or more enhancer elements. In some alternatives, the nucleic acid further comprises homology arm sequences. In some alternatives, the nucleic acid further comprises a nucleic acid sequence encoding a promoter.

[0010] Some alternatives relate to a vector for promoting HDR of WAS protein (WASp) expression in a cell. In some alternatives, the vector comprises a first sequence encoding a *WAS* gene, a second sequence encoding one or more guide RNA cleavage sites, and a third sequence encoding one or more nuclease binding sites. In some alternatives, the *WAS* gene comprises the nucleic acid sequence set forth in SEQ ID NO: 4. In some alternatives, the second sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 17. In some alternatives, the one or more nuclease binding sites comprises a forward and reverse transcription activator-like effector nuclease (TALEN) binding site. In some alternatives, the one or more nucleic binding sites is a clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) binding site. In some alternatives, the vector further comprises one or more enhancer elements. In some alternatives, the vector is an adeno-associated viral vector (AAV). In some alternatives, the vector is a self-complementary AAV (scAAV). In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a hematopoietic stem cell (HSC). In some alternatives, the cell is a $CD34^+$ HSC.

[0011] Some alternatives relate to a system for promoting HDR of WAS protein (WASp) expression in a cell. In some alternatives, the system comprises a vector and a nucleic acid encoding a nuclease. In some alternatives, the nuclease is a TALEN nuclease. In some alternatives, the nuclease is a Cas nuclease. In some alternatives, the vector and nucleic acid are configured for co-delivery to the cell. In some alternatives, co-delivery to the cell modifies endogenous *WAS* locus. In some alternatives, the cell is a primary human hematopoietic cell.

[0012] Some alternatives relate to a cell for expressing a WASp. In some alternatives, the cell comprises a nucleic acid. In some alternatives, the nucleic acid comprises a first sequence encoding a WAS gene, a second sequence encoding a promoter, a third sequence encoding one or more guide RNA cleavage sites, and a fourth sequence encoding one or more nuclease binding sites. In some alternatives, the nucleic acid is in a vector. In some alternatives, the vector is an AAV. In some alternatives, the vector is a scAAV. In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a HSC. In some alternatives, the cell is a $CD34^+$ HSC.

[0013] Some alternatives relate to methods of promoting HDR of a WAS gene in a subject in need thereof (e.g., a subject identified or selected as one that would receive a benefit from HDR of a WAS gene, such as a subject having XLT). In some alternatives, the method comprises administering to a subject in need thereof a cell as described herein or a vector as described herein and administering to the subject a nuclease. In some alternatives, the nuclease is a TALEN nuclease. In some alternatives, the nuclease is a Cas nuclease. In some alternatives, the nuclease is co-administered to the subject with the cell or with the vector. In some alternatives, the cell is from the subject. In some alternatives, the cell is genetically modified by introducing a nucleic acid as described herein or a vector as described herein into the cell. In some alternatives, the administering is performed by adoptive cell transfer. In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a HSC. In some alternatives, the cell is a $CD34^+$ HSC. In some alternatives, the subject is male. In some alternatives, the subject is identified or selected as one that is suffering from Wiskott-Aldrich syndrome (WAS). In some alternatives, the subject is identified or selected as one that is suffering from X-linked thrombocytopenia (XLT).

[0014] Some alternatives provided herein relate to a method of treating, inhibiting, or ameliorating WAS and/or XLT or disease symptoms associated with WAS and/or XLT in a subject in need thereof. In some alternatives, the method comprises administering to a subject a cell as described herein or a vector as described herein, administering to the subject a nuclease, and optionally identifying or selecting the subject as one that would benefit from receiving a therapy for WAS and/or XLT or disease symptoms associated with WAS and/or XLT and/or, optionally measuring an improvement in the progression of WAS and/or XLT or an improvement in a disease symptom associated with

WAS and/or XLT in said subject. In some alternatives, the nuclease is a TALEN nuclease. In some alternatives, the nuclease is a CRISPR/Cas nuclease. In some alternatives, the nuclease is co-administered to the subject with the cell or with the vector. In some alternatives, the cell is from the subject. In some alternatives, the cell is genetically modified by introducing a nucleic acid as described herein or a vector as described herein into the cell. In some alternatives, the administering is performed by adoptive cell transfer. In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a HSC. In some alternatives, the cell is a $CD34^{-}$ HSC In some alternatives, the subject is male. In some alternatives, the method improves thrombocytopenia. In some alternatives, the method increases platelet counts. In some alternatives, the subject is identified or selected as one that is suffering from Wiskott-Aldrich syndrome (WAS). In some alternatives, the subject is identified or selected as one that is suffering from X-linked thrombocytopenia (XLT).

[0015] In a first aspect, a nucleic acid for homology directed repair (HDR) of Wiskott-Aldrich Syndrome (WAS) gene is provided, the nucleic acid comprising: a first sequence encoding a WAS gene; a second sequence encoding one or more guide RNA cleavage sites; and a third sequence encoding one or more nuclease binding sites. In some alternatives, the WAS gene comprises the nucleic acid sequence set forth in SEQ ID NO: 4. In some alternatives, the second sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 17. In some alternatives, the one or more nuclease binding sites comprises a forward and reverse transcription activator-like effector nuclease (TALEN) binding site. In some alternatives, the one or more nucleic binding sites is a clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) binding site. In some alternatives, the nucleic acid further comprises one or more enhancer elements. In some alternatives, the nucleic acid further comprises homology arm sequences. In some alternatives, the nucleic acid further comprises a nucleic acid sequence encoding a promoter.

[0016] In a second aspect, a vector for promoting HDR of WAS protein (WASp) expression in a cell is provided, the vector comprising: a first sequence encoding a WAS gene; a second sequence encoding one or more guide RNA cleavage sites; and a third sequence encoding one or more nuclease binding sites. In some alternatives, the WAS gene comprises the nucleic acid sequence set forth in SEQ ID NO: 4. In some alternatives, the second sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 17. In some alternatives, the one or more nuclease binding sites comprises a forward and reverse transcription activator-like effector nuclease (TALEN) binding site. In some alternatives, the one or more nucleic binding sites is a clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) binding site. In some alternatives, the vector further comprises one or more enhancer elements. In some alternatives, the vector is an adeno-associated viral vector (AAV). In some alternatives, the vector is a self-complementary AAV (scAAV). In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a hematopoietic stem cell (HSC). In some alternatives, the cell is a CD34+ HSC.

[0017] In a third aspect, a system for promoting HDR of WAS protein (WASp) expression in a cell is provided, the system comprising a vector of any one of the alternatives herein and a nucleic acid encoding a nuclease. In some alternatives, the nuclease is a TALEN nuclease. In some alternatives, the nuclease is a Cas nuclease. In some alternatives, the vector and nucleic acid are configured for co-delivery to the cell. In some alternatives, co-delivery to the cell modifies endogenous WAS locus. In some alternatives, the cell is a primary human hematopoietic cell.

[0018] In a fourth aspect, a cell for expressing a WASp is provided, the cell comprising:a nucleic acid, which comprises: a first sequence encoding a WAS gene; a second sequence encoding a promoter; a third sequence encoding one or more guide RNA cleavage sites; anda fourth sequence encoding one or more nuclease binding sites. In some alternatives, the nucleic acid is in a vector. In some alternatives, the vector is an AAV. In some alternatives, the AAV is a scAAV. In some alternatives, cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a HSC. In some alternatives, the cell is a CD34+ HSC.

[0019] In a fifth aspect, a method of promoting HDR of a WAS gene in a subject in need thereof, the method comprising: administering to a subject the cell or a vector of any one of the alternatives herein; and administering to the subject a nuclease. The cell comprises: a nucleic acid, which comprises: a first sequence encoding a WAS gene; a second sequence encoding a promoter; a third sequence encoding one or more guide RNA cleavage sites; anda fourth sequence encoding one or more nuclease binding sites. The vector comprises: a first sequence encoding a WAS gene; a second sequence encoding one or more guide RNA cleavage sites; and a third sequence encoding one or more nuclease binding sites. In some alternatives, the WAS gene comprises the nucleic acid sequence set forth in SEQ ID NO: 4. In some alternatives, the second sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 17. In some alternatives, the one or more nuclease binding sites comprises a forward and reverse transcription activator-like effector nuclease (TALEN) binding site. In some alternatives, the one or more nucleic binding sites is a clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) binding site. In some alternatives, the vector further comprises one or more enhancer elements. In some alternatives, the vector is an adeno-associated viral vector (AAV). In some alternatives, the vector is a self-complementary AAV (scAAV). In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a hematopoietic stem cell (HSC). In some alternatives, the cell is a CD34+ HSC. In some alternatives, the nucleic acid is in a vector. In some alternatives, the vector is an AAV. In some alternatives, the AAV is a scAAV. In some alternatives, cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a HSC. In some alternatives, the cell is a CD34+ HSC In some alternatives, the nuclease is a TALEN nuclease. In some alternatives, the nuclease is a Cas nuclease. In some alternatives, the nuclease is co-administered to the subject with the cell or with the vector. In some alternatives, the cell is from the subject and, wherein the cell is genetically modified by introducing the nucleic acid or the vector of any one of the alternatives described herein into the cell. In some alternatives, the administering is performed by adoptive cell transfer. In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a HSC. In some alternatives, the cell is a CD34+ HSC. In some alternatives, the subject is male. In some alternatives, the subject is suffering from Wiskott-

Aldrich syndrome (WAS). In some alternatives, the subject is suffering from X-linked thrombocytopenia (XLT).

[0020] In a sixth aspect, a method of treating, inhibiting, or ameliorating WAS and/or XLT or disease symptoms associated with WAS and/or XLT in a subject in need thereof, the method comprising: administering to a subject the cell or a vector of any one of the alternatives described herein; administering to the subject a nuclease; andoptionally identifying the subject as one that would benefit from receiving a therapy for WAS and/or XLT or disease symptoms associated with WAS and/or XLT and/or, optionally measuring an improvement in the progression of WAS and/or XLT or an improvement in a disease symptom associated with WAS and/or XLT in said subject. The cell comprises: a nucleic acid, which comprises: a first sequence encoding a WAS gene; a second sequence encoding a promoter; a third sequence encoding one or more guide RNA cleavage sites; anda fourth sequence encoding one or more nuclease binding sites. The vector comprises: a first sequence encoding a WAS gene; a second sequence encoding one or more guide RNA cleavage sites; and a third sequence encoding one or more nuclease binding sites. In some alternatives, the WAS gene comprises the nucleic acid sequence set forth in SEQ ID NO: 4. In some alternatives, the second sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 17. In some alternatives, the one or more nuclease binding sites comprises a forward and reverse transcription activator-like effector nuclease (TALEN) binding site. In some alternatives, the one or more nucleic binding sites is a clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) binding site. In some alternatives, the vector further comprises one or more enhancer elements. In some alternatives, the vector is an adeno-associated viral vector (AAV). In some alternatives, the vector is a self-complementary AAV (scAAV). In some alternatives, the nuclease is a TALEN nuclease. the nuclease is a CRISPR/Cas nuclease. the nuclease is co-administered to the subject with the cell or with the vector. the cell is from the subject, wherein the cell is genetically modified by introducing the nucleic acid or the vector of any one of the alternatives described herein into the cell. In some alternatives, the administering is performed by adoptive cell transfer. In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a HSC. In some

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alternatives, the cell is a HSC. In some alternatives, the cell is a CD34+ HSC. In some alternatives, the subject is male. In some alternatives, the method improves thrombocytopenia. In some alternatives, the method increases platelet counts.

[0020A] Another aspect of the disclosure provides a system for promoting homology directed repair (HDR) of a Wiskott-Aldrich Syndrome (WAS) gene in a cell, the system comprising: (i) a vector comprising: a first polynucleotide encoding a WAS gene or portion thereof; a second polynucleotide encoding a guide RNA cleavage site or a transcription activator-like effector nuclease (TALEN) cleavage site, and a third polynucleotide encoding a nuclease binding site; (ii) a nuclease or a nucleic acid encoding the nuclease, wherein the nuclease is capable of cleaving a target locus in order to promote insertion of the first polynucleotide within a first coding exon of the WAS gene in the cell genome, wherein the nuclease is selected from a transcription activator-like effector nuclease (TALEN), or a Cas nuclease; and (iii) a guide RNA (gRNA) comprising a nucleotide sequence selected from any one of SEQ ID NOs:31-34.

[0020B] A further aspect provides an *in vitro* or *ex vivo* method of promoting homology directed repair (HDR) of a WAS gene in a cell, the method comprising introducing the above-defined system into a cell to obtain a modified cell.

[0020C] A further aspect provides a modified cell prepared by the above-defined method.

[0020D] A further aspect provides a pharmaceutical composition comprising the above-defined modified cell and a pharmaceutically acceptable excipient.

[0020E] A further aspect provides the use of the above-defined modified cell in the manufacture of a medicament for treating, inhibiting, or ameliorating WAS or X-linked thrombocytopenia (XLT) in a subject.

[0020F] A further aspect provides a method of treating, inhibiting, or ameliorating WAS or X-linked thrombocytopenia (XLT) in a subject in need thereof, the method comprising administering the above-defined modified cell or pharmaceutical composition to the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] **Figures 1A and 1B** depict the assessment of cleavage efficiency of TALENs and guide RNAs in primary T cells. **Figure 1A** shows a schematic of the WAS locus with guides and TALENs annotated. Shown are the location of the WAS TALENs (TALEN #1 (T1) and TALEN #2 (T2)) and guide RNA (G1, G2, G3, and G4) cleavage sites within the human *WAS* gene. Scheme not drawn to scale. **Figure 1B** depicts the disruption of the WAS locus with TALENs and CRISPR guides. Shown is the percentage of NHEJ events in primary human T cells detected using the T7 assay, 5 days post-transfection with TALEN mRNAs (T1, T2) or with Cas9 mRNA co-delivered with scAAV expressing gRNAs (G1-4). N = 3, represents the number of independent experiments. TALEN #1 and G1 were selected for all further experiments.

[0022] **Figure 2** depicts human primary T cell editing with TALENs and rationally designed AAV donor templates. **Figure 2A** shows a schematic representation of the *WAS* locus and AAV donor templates used in targeting with WAS TALENs. Small boxes represent TALEN forward (T-for) and reverse (T-rev) binding sites. Homology arms are also depicted. X represents mutation of the T preceding the TALEN binding site designed to abolish cleavage by TALEN in #1244 vector. The #1262 vector has the entire region between the exon 1 up to the reverse TALEN binding site deleted. **Figure 2B** depicts a timeline of gene editing procedure beginning with bead stimulation of primary T cells. AAVs were added at 20% of culture volume. **Figures 2C** and **2D** depict time course of GFP expression indicative of HDR (**Figure 2C**) and cell viability (**Figure 2D**). **Figure 2E** shows cells that were also transfected with TALENs and transduced with an AAV vector with an MND promoter driven blue fluorescent protein (BFP) without any homology arms. Fluorescence from this vector at day 15 is indicative of random integration of the vector. Fluorescence from this vector at Day 15 is indicative of random integration of the vector. **Figure 2F** shows representative FACS plots with GFP expression at day 15 post co-delivery of TALEN mRNA and AAV donor templates. **Figure 2G** provides additional representative

FACS plots showing GFP expression at Day 15. N = 3 and represents the number of independent experiments performed using cells from three different donors. **Figure 2H** shows results from a test for nuclease specificity utilizing AAV without homology arms. Primary T cells transfected with TALENs and transduced with an AAV vector with an MND promoter driven blue fluorescent protein (BFP) without any homology arms. Fluorescence from this vector at day 15 is indicative of random integration. n=3 and represents the number of independent experiments performed using cells from 3 different donors. Data are presented as mean ± SEM. **Figure 2I** shows representative FACS plots with GFP expression at day 15 post co-delivery of TALEN mRNA and AAV donor templates. N = 3 and represents the number of independent experiments performed using cells from three different donors.

[0023] **Figure 3** depicts human primary T cell editing with CRISPR and AAV donors. **Figure 3A** shows a schematic of editing of the WAS locus using CRISPR in primary T cells. Schematic illustration of the scAAV guide RNA vector (G), donor template DT (PAM mutated) and AAV vector containing both guide and donor sequences (DTG). PAM site was mutated in both DT and DTG templates to abolish cleavage by the guide Shown is a schematic illustration of the scAAV guide RNA vector (#1189 (G)), donor template (#1201 (PAM mutated)), and AAV vector containing both guide and donor sequences (#1215 (DTG)). Both the PAM mutated donor template and the DTG AAVs have the PAM site mutated to abolish cleavage by guide. **Figures 3B** and **3C** provide graphs showing time course of % GFP+ cells (**Figure 3B**) and cell viability (**Figure 3C**). 10% and 20% represent the % culture volume #1215 AAV added. All other AAVs were added at 10% of culture volume. **Figure 3D** provides graphs depicting BFP expression when Cas9, guide and MND.BFP vector with no homology arms were delivered. 20% represent the % of culture volume AAVs were added at. AAVs were added at 10% of culture volume unless otherwise specified. **Figure 3E** provides FACS plots showing GFP expression at Day 15. N = 3 and represents the number of independent experiments performed using cells from three donors. **Figure 3F** Bar graphs showing time course of GFP expression. %HR is reported as %GFP at day 15. n=3 and represents the number of independent experiments performed using cells from 3 different donors. Data are presented as mean ± SEM. 20% represent the % culture volume #1215 AAV added. All other AAVs were added at 10% of culture volume. %HR is reported as %GFP at day 15. n=3 and represents the number of independent experiments performed using cells from 3 different donors. Data are presented as mean ± SEM. **Figure 3G** shows results from a test for nuclease specificity utilizing AAV without homology arms. Bar graphs depict BFP expression when Cas9, guide and MND.BFP vector with no homology arms were delivered. n=3 and represents the number of independent experiments performed using cells from 3 different donors. Data are presented as mean ± SEM. **Figure 3H** provides representative FACS plots showing GFP expression at day 15.

[0024] **Figure 4** depicts the editing mobilized adult $CD34^+$ cells using co-delivery of TALEN and AAV. **Figure 4A** depicts a timeline of gene editing procedure for human mobilized adult $CD34^+$ cells. **Figures 4B** and **4C** depicts time course of GFP expression indicative of HDR (**Figure 4B**) and viability (**Figure 4C**). **Figure 4D** depicts representative FACS plots showing GFP expression at Day 5.

[0025] **Figure 5A-G** depicts the editing mobilized adult $CD34^+$ cells using co-delivery of TALEN mRNA or CRISPR guide delivered as RNP and AAV donor and shows disruption of the WAS locus in human $CD34^+$ cells using TALENs or RNP. Mobilized human $CD34^+$ cells were cultured in SCGM media supplemented with TPO, SCF, FLT3L (100 ng/mL) and IL3 (60 ng/mL) for 48 hours, followed by electroporation using Neon electroporation system with either 1ug of each TALEN monomer or Ribonucleoprotein complex (RNP) of Cas9 protein and single guide RNA mixed in 1:1.2 ratio. The sgRNA was purchased from Trilink BioTechnologies and has chemically modified nucleotides at the three terminal positions at 5′ and 3′ ends. The cells were cultured for 5 days and genomic DNA was extracted. The region surrounding the cut site for WAS TALEN and guide was amplified and cloned into pJET cloning vector. Colony sequencing was performed to quantify % cleavage at the cut site by analyzing the indels. N=3 and represents the number of independent experiments performed using cells from three donors. **Figure 5A** shows disruption of the WAS locus in human $CD34^+$ cells using TALENs or RNP. Mobilized human $CD34^+$ cells were cultured in SCGM media supplemented with TPO, SCF, FLT3L (100 ng/mL) and IL3 (60 ng/mL) for 48 hours, followed by electroporation using Neon electroporation system with either 1ug of each TALEN monomer mRNA or Ribonucleoprotein complex (RNP) of Cas9 protein and single guide RNA mixed in 1:1.2 ratio. The sgRNA was purchased from Trilink BioTechnologies and has chemically modified nucleotides at the three terminal positions at 5′ and 3′ ends. The cells were cultured for 5 days and genomic DNA was extracted. The region surrounding the cut site for WAS TALEN and guide was amplified and cloned into pJET cloning vector. Colony sequencing was performed to quantify % cleavage at the cut site by analyzing the indels. N=3 and represents the number of independent experiments performed using cells from three donors. **Figure 5B** shows results from HDR editing of the WAS locus in $CD34^+$ HSCs using co-delivery of TALEN mRNA or RNP and AAV donor template. **Figure 5C** shows FACS plots depicting GFP expression from Mock, AAV or AAV plus TALEN treated CD34+ cells (top row) or AAV+RNP treated cells (bottom row) 5 days post editing. **Figure 5D** shows the cell viability of the edited cells. Bar graphs represent viability of mock and edited cells 2 days post editing. N=8 for RNP, n=12 for TALEN and represents >4 independent donors. **Figure 5E** shows colony forming unit (CFU) assay for TALEN edited $CD34^+$ cells and **Figure 5F** shows the results from a CFU assay for RNP edited $CD34^+$ cells. Briefly, 500 cells from edited or untreated (mock) were plated in duplicate in Methocult H4034 media (Stemcell Technologies), incubated at 37℃ for 12-14 days and colonies enumerated based on their morphology and GFP expression. CFU-E: Colony forming unit erythroid, M: Macrophage, GM: Granulocyte, macrophage, G: Granulocyte, GEMM: Granulocyte, erythroid, macrophage, megakaryocyte, BFU-E: Burst forming unit erythroid. n=3 experiments and 2 donors. Data are presented as mean ± SEM. **Figure 5G** shows results from a digital droplet PCR assay or flow cytometry staining for determining HDR.

[0026] **Figure 6** shows editing of the WAS locus in $CD34^+$ HSCs using co-delivery of TALEN mRNA/RNP and AAV donor template. Adult mobilized human $CD34^+$ cells that were cultured in SCGM media as described in **Figure 5**, followed by electroporation using Neon electroporation system with either TALEN mRNA or RNP complex. AAV vector carrying the donor template was added immediately after electroporation. Controls included un-manipulated cells (mock) and cells transduced with AAV only without transfection of a nuclease (AAV). **Figure 6A** shows Graphs showing %GFP at day 5 indicative of HDR. **Figure 6B** shows viability of edited cells 2 days post editing. N=7 for TALEN and N=3 for RNP and represent independent donors. **Figures 6C** and **6D** show edited and mock cells that were plated one day post editing onto Methocult media for colony formation unit (CFU) assay. Briefly, 500 cells were plated in duplicate in

Methocult H4034 media (Stemcell Technologies, incubated at 37°C for 12-14 days and colonies enumerated based on their morphology and GFP expression. **Figure 6C** shows data from a TALEN experiment and **Figure 6D** from an RNP experiment. CFU-E: Colony forming unit erythroid, M: Macrophage, GM: Granulocyte, macrophage, G: Granulocyte, GEMM: Granulocyte, erythroid, macrophage, megakaryocyte, BFU-E: Burst forming unit erythroid.

[0027] **Figure 7** shows engraftment of edited human $CD34^+$ cells into immune deficient NSG mice. 2 million human $CD34^+$ cells untreated, AAV treated or treated with AAV and RNP were injected into immune deficient NSG mice preconditioned with 25mg/kg busulfan. The mice were sacrificed 10 weeks post-transplant and BM was harvested. **Figure 7A** depicts total engraftment of edited cells as defined by expression of human CD45 marker. **Figure 7B** illustrates %GFP+ cells within the engrafted cells. **Figure 7C** depicts FACS plots from representative mice.

[0028] **Figure 8** shows the design of AAV vectors expressing cDNA for human codon optimized WAS gene. AAV vectors with 0.6kb homology arms flanking either a promoter-less GFP (top) or WAS cDNA (bottom) followed by a shorter WPRE, designated WPRE3 followed by SV40 polyadenylation signal.

[0029] **Figure 9A** shows data representative of assays for cell viability and %HR in input cells used for engraftment in NSG mice. Adult mobilized human $CD34^+$ cells were cultured in SCGM media as previously described with the exception that IL-6 (100ng/ml) was added instead of IL-3. The cells were electroporated with 1 μg of RNP complex and AAV at an MOI of 62. Data are presented as mean ± SEM. N=5 and represents independent experiments using multiple donors.

[0030] **Figure 9B** shows the data representing the engraftment of edited cells in bone marrow of transplanted NSG mice. Six to 10-week old NSG mice were treated with 25 or 35 mg/kg of BUSULFEX (Henry Schein Inc.) via intraperitoneal injection, diluted 1:1 in phosphate-buffered saline. Twenty-four hours later, 2 x 10^6 mock or gene edited hematopoietic stem cells (cultured as described in Fig 5A) in phosphate-buffered saline were delivered via retro-orbital injection. Animals were euthanized 10 to 16 weeks post-transplant, bone marrow and spleens were harvested and analyzed for human cell engraftment. Dot plot depicts total engraftment of edited cells as defined by expression of human CD45 marker in BM of sacrificed mice. Dots represent individual mice. Data are presented as mean ± SEM.

[0031] **Figure 9C** shows data that represent the engraftment of edited cells in bone marrow of NSG mice 16 weeks post transplantation. Representative flow plots of cells harvested from the bone marrow of NSG mice 16 weeks following transplant. On left, bone marrow harvested from mouse transplanted with untreated cells. On right, bone marrow harvested from mouse transplanted with cells treated with AAV plus RNP. Top row, from left to right: hCD45:mCD45 chimerism, human CD45-gated $CD33^+$ and $CD19^+$ staining. Bottom row, from left to right: GFP expression among $hCD45^+$, $CD33^+$ and $CD19^+$ cells.

[0032] **Figure 9D** shows data that represent the engraftment of edited cells in spleens of transplanted mice. Graph depicts total engraftment of edited cells at 10-16 weeks as defined by expression of human CD45 marker in spleens of sacrificed mice. Dots represent individual mice. Data are presented as mean ± SEM.

[0033] **Figure 9E** shows data that represent the engraftment of edited cells in spleens of NSG Mice. Representative flow plots of cells harvested from the spleens of NSG mice 16 weeks following transplant. On left, spleen harvested from mouse transplanted with untreated cells. On right, spleen harvested from mouse transplanted with cells treated with AAV plus RNP. Top row, from left to right: hCD45:mCD45 chimerism, Human CD45-gated $CD33^+$ and $CD19^+$ staining. Bottom row, from left to right: GFP expression among $hCD45^+$, $CD33^+$ and $CD19^+$ cells. **Figure 9F** shows data that represent the engraftment of GFP^+ cells in NSG mice. HDR-editing rate (%GFP^+) among $hCD45^+$ cells recovered from the bone marrow and spleens of NSG mice sacrificed at 10-16 weeks. Data are presented as mean ± SEM.

[0034] **Figure 10A** shows data that represent the engraftment of edited cells in bone marrow of NSGW41 mice 16 weeks post transplantation. On right, bone marrow harvested from mouse transplanted with cells treated with AAV plus RNP. Top row, from left to right: hCD45:mCD45 chimerism, human CD45-gated $CD33^+$ and $CD19^+$ staining. Bottom row, from left to right: GFP expression among $hCD45^+$, $CD33^+$ and $CD19^+$ cells.

[0035] **Figure 10B** shows data that represent the engraftment of edited cells in spleens of NSGW41 mice 16 weeks post transplantation. On left, spleen harvested from mouse transplanted with untreated cells. On right, spleen harvested from mouse transplanted with cells treated with AAV plus RNP. Top row, from left to right: hCD45:mCD45 chimerism, Human CD45-gated $CD33^+$ and $CD19^+$ staining. Bottom row, from left to right: GFP expression among $hCD45^+$, $CD33^+$ and $CD19^+$ cells.

[0036] **Figure 11A** shows data that represent the design of AAV vectors expressing GFP or cDNA for codon optimized WAS gene from endogenous WAS promoter. AAV vectors with 0.6kb homology arms flanking either a promoter-less GFP (top) or WAS cDNA (bottom) followed by a shorter WPRE, designated WPRE3 followed by SV40 polyadenylation signal are shown.

[0037] **Figure 11B** shows data that represent the digital droplet PCR to determine editing rates in WAS targeted promoter-less GFP construct. In-out droplet digital PCR was performed as previously described. Droplets were analyzed on the QX200 Droplet Digital PCR System (Bio-Rad) using QuantaSoft software (Bio-Rad). All experiments were performed on female donors. The ddPCR rates were about half of HR rates by FACS suggesting that only one X chromosome was being targeted, n=3 and represents three independent experiments and donors. Data are presented as mean ± SEM.

[0038] **Figure 11C** shows data that represent the digital droplet PCR to determine editing rates with WAS targeted promoter-less coWAS expressing AAV vectors.

DETAILED DESCRIPTION

[0039] In the following detailed description, reference is made to the accompanying drawings, which form a part hereof. In the drawings, similar symbols typically identify similar components, unless context dictates otherwise. The illustrative alternatives described in the detailed description, drawings, and claims are not meant to be limiting. Other alternatives may be utilized, and other changes may be made, without departing from the spirit or scope of the subject matter presented herein. It will be readily understood that the aspects of the present disclosure, as generally described herein, and illustrated in the Figures, can be arranged, substituted, combined, separated, and designed in a wide variety of different configurations, all of which are explicitly contemplated herein.

Definitions

[0040] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the present disclosure belongs. *See, e.g.* Singleton et al., Dictionary of Microbiology and Molecular Biology 2nd ed., J. Wiley & Sons (New York, NY 1994); Sambrook et al., Molecular Cloning, A Laboratory Manual, Cold Springs Harbor Press (Cold Springs Harbor, NY 1989). For purposes of the present disclosure, the following terms are defined below.

[0041] The articles "a" and "an" are used herein to refer to one or to more than one (for example, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0042] By "about" is meant a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that varies by as much as 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1% to a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight, or length.

[0043] As used in this specification, whether in a transitional phrase or in the body of the claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least." When used in the context of a process, the term "comprising" means that the process comprises at least the recited steps, but may include additional steps. When used in the context of a compound, composition or device, the term "comprising" means that the compound, composition or device comprises at least the recited features or components, but may also include additional features or components.

[0044] As used herein, a "subject" or a "patient" as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, an animal that is the object of treatment, observation or experiment. "Animal" comprises cold- and warm-blooded vertebrates and invertebrates such as fish, shellfish, reptiles and, in particular, mammals. "Mammal" comprises, without limitation, mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, horses, primates, such as monkeys, chimpanzees, and apes, and, in particular, humans. In some alternatives, the subject is human.

[0045] Some alternatives disclosed herein relate to selecting a subject or patient in need. In some alternatives, a patient is selected who is in need of treatment, amelioration, inhibition, progression, or improvement in disease symptoms or who is in need of curative therapy. In some alternatives, a patient is selected who has symptoms of Wiskott-Aldrich Syndrome (WAS) or X-linked thrombocytopenia (XLT), or who has been diagnosed with WAS or XLT. Such identification or selection of said subjects or patients in need can be made through clinical and/or diagnostic evaluation.

[0046] As used herein, the term “treatment” as described herein, has their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, an intervention made in response to a disease, disorder or physiological condition manifested by a subject, particularly a subject suffering from an X-linked disorder, such as WAS or XLT. The aim of treatment may include, but is not limited to, one or more of the alleviation or prevention of symptoms, slowing or stopping the progression or worsening of a disease, disorder, or condition, curative treatment of the disease, disorder, or condition, and the remission of the disease, disorder, or condition. In some alternatives, “treatment” refers to both treatment of the underlying disease or treatment of the disease symptoms. For example, in some alternatives, treatments reduce, alleviate, ameliorate, or eradicate the symptom(s) of the disease and/or provide curative therapy of the disease.

[0047] “Adoptive cellular therapy” or “adoptive cell transfer,” as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, transfer of cells, most commonly immune-derived cells, back into the same patient or into a new recipient host with the goal of transferring the immunologic functionality and characteristics into the new host. In some alternatives, adoptive cellular therapy or adoptive cell transfer comprises administering cells for promoting homology directed repair of a *WAS* gene in a subject.

[0048] As used herein, the terms “nucleic acid” and “polynucleotide” are interchangeable and refer to any nucleic acid, whether composed of phosphodiester linkages or modified linkages such as phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphoramidate, bridged phosphoramidate, bridged methylene phosphonate, phosphorothioate, methylphosphonate, phosphorodithioate, bridged phosphorothioate or sulfone linkages, and combinations of such linkages. The terms “nucleic acid" and "polynucleotide" also specifically include nucleic acids composed of bases other than the five biologically occurring bases (adenine, guanine, thymine, cytosine and uracil).

[0049] As used herein, the term "fusion" or "fused" as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a first nucleic acid linked to a second nucleic acid by a phosphodiester bond, so that a coding sequence at the 3' end of the first nucleic acid is in frame with a coding sequence at the 5' end of the second nucleic acid, and by extension can further refer to a first polypeptide linked by a peptide bond to a second polypeptide at the C-terminus of the first polypeptide. As such, a "fused" (or "fusion of a") nucleic acid or peptide as used herein refers to a configuration of molecules, and does not necessarily involve performing the act of joining two molecules together. By way of example, the fusion of a first nucleic acid to a second nucleic acid can encode a single polypeptide in which a first polypeptide sequence (encoded by the first nucleic acid) is fused to a second polypeptide sequence (encoded by the second nucleic acid). In some alternatives, the molecule comprising the fused nucleic acids is referred to as a fusion nucleic acid.

[0050] As used herein, the term "vector" as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a polynucleotide construct, typically a plasmid or a virus, used to transmit genetic material to a host cell. Vectors can be, for example, viruses, plasmids, cosmids, or phage. A vector as used herein can be composed of either DNA or RNA. In some alternatives, a vector is composed of DNA. An "expression vector" is a vector that is capable of directing the expression of a protein encoded by one or more genes carried by the vector when it is present in the appropriate environment. Vectors are preferably capable of autonomous replication. Typically, an expression vector comprises a transcription promoter, a gene, and a transcription terminator. Gene expression is usually placed under the control of a promoter, and a gene is said to be "operably linked to" the promoter.

[0051] As used herein "AAV system" or "AAV expression system" as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, nucleic acids for expressing at least one transcript-encoding nucleic acid, and which are disposed on one or more AAV vectors. As used herein, "activity-dependent expression" (and variations of this root term) refers to nucleic acid expression that will be induced upon a change in a particular type of activity of a cell containing the nucleic acid, for example depolarization of the cell. In some alternatives, the cell is a neuron, and depolarization of the neuron in response to a stimulus induces "activity-dependent" nucleic acid expression. In some alternatives, an AAV vector includes a sequence as set forth in SEQ ID NOs: 5, 6, 7, 8, 9, 9,10, 11,12, 13,14,15, 21, 22, 23, or 26.

[0052] As used herein, the term "operably linked" is used to describe the connection between regulatory elements and a gene or its coding region. Typically, gene expression is placed under the control of one or more regulatory elements, for example, without limitation, constitutive or inducible promoters, tissue-specific regulatory elements, and enhancers. A gene or coding region is said to be "operably linked to" or "operatively linked to" or "operably associated with" the regulatory elements, meaning that the gene or coding region is controlled or influenced by the regulatory element. For instance, a promoter is operably linked to a coding sequence if the promoter effects transcription or expression of the coding sequence.

[0053] As used herein "upstream" as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, positions 5' of a location on a polynucleotide, and positions toward the N-terminus of a location on a polypeptide. As used herein "downstream" refers to positions 3' of a location on nucleotide, and positions toward the C-terminus of a location on a polypeptide.

[0054] The term "construct," as used herein, as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a recombinant nucleic acid that has been generated for the purpose of the expression of a specific nucleotide sequence(s), or that is to be used in the construction of other recombinant nucleotide sequences.

[0055] As used herein, the term "promoter" is a nucleotide sequence that permits binding of RNA polymerase and directs the transcription of a gene. Typically, a promoter is located in the 5' non-coding region of a gene, proximal to the transcriptional start site of the gene. Sequence elements within promoters that function in the initiation of transcription are often characterized by consensus nucleotide sequences. Examples of promoters include, but are not limited to, promoters from bacteria, yeast, plants, viruses, and mammals (including humans). A promoter can be inducible, repressible, and/or constitutive. Inducible promoters initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, such as a change in temperature. In some alternatives, the promoter described herein can be a U6 promoter or an MND promoter.

[0056] As used herein, the term “enhancer” refers to a type of regulatory element that can modulate the efficiency of transcription, regardless of the distance or orientation of the enhancer relative to the start site of transcription.

[0057] As used herein, the term “variant” as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a polynucleotide (or polypeptide) having a sequence substantially similar to a reference polynucleotide (or polypeptide). In the case of a polynucleotide, a variant can have deletions, substitutions, or additions of one or more nucleotides at the 5’ end, 3’ end, and/or one or more internal sites in comparison to the reference polynucleotide. Similarities and/or differences in sequences between a variant and the reference polynucleotide can be detected using conventional techniques known in the art, for example polymerase chain reaction (PCR) and hybridization techniques. Variant polynucleotides also include synthetically derived polynucleotides, such as those generated, for example, by using site-directed mutagenesis. Generally, a variant of a polynucleotide, including, but not limited to, a DNA, can have at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to the reference polynucleotide as determined by sequence alignment programs known by skilled artisans, or an amount within a range defined by any two of the aforementioned values. In the case of a polypeptide, a variant can have deletions, substitutions, or additions of one or more amino acids in comparison to the reference polypeptide. Similarities and/or differences in sequences between a variant and the reference polypeptide can be detected using conventional techniques known in the art, for example Western blot. Generally, a variant of a polypeptide, can have at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to the reference polypeptide as determined by sequence alignment programs known by skilled artisans, or an amount within a range defined by any two of the aforementioned values.

[0058] As used herein, the term "transfection" as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, introduction of a nucleic acid into a host cell, such as by contacting the cell with a recombinant AAV vector as described herein. As used herein, "transient transfection" refers to the introduction of exogenous nucleic acid(s) into a host cell by a method that does not generally result in the integration of the exogenous nucleic into the genome of the transiently transfected host cell. In some alternatives, the nucleic acid is RNA. In some alternatives, the nucleic acid is DNA. In some alternatives, when the nucleic acid is RNA, the nucleic acid does not generally integrate in the genome of the transiently transfected cell. In some alternatives, when the nucleic acid is DNA, the nucleic acid can integrate in the genome of the transiently transfected cell.

[0059] By the term "host cell" as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, a cell that is introduced with Cas9-mRNA/AAV-guide RNA according to the present alternatives, as well as, cells that are provided with the systems herein. Host cells can be prokaryotic cells or eukaryotic cells. Examples of prokaryotic host cells include, but are not limited to *E. coli*, nitrogen fixing bacteria, *Staphylococcus aureus*, *Staphylococcus albus*, *Lactobacillus acidophilus, Bacillus anthracis, Bacillus subtilis, Bacillus thuringiensis, Clostridium tetani, Clostridium botulinum, Streptococcus mutans, Streptococcus pneumoniae, mycoplasmas*, and *cyanobacteria.* Examples of eukaryotic host cells include, but are not limited to, protozoa, fungi, algae, plant, insect, amphibian, avian and mammalian cells. In some alternatives, a system for editing at least one target gene in a cell is provided, wherein the cell is a eukaryotic cell. In some alternatives, the cell is a mammalian cell. In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is not a transformed cell. In some alternatives, the cell is a primary lymphocyte. In some alternatives, the cell is a primary lymphocyte, a $CD34^+$ stem cell, a hepatocyte, a cardiomyocyte, a neuron, a glial cell, a muscle cell or an intestinal cell.

[0060] "T cell precursors" as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, lymphoid precursor cells that can migrate to the thymus and become T cell precursors, which do not express a T cell receptor. All T cells originate from hematopoietic stem cells in the bone marrow. Hematopoietic progenitors (lymphoid progenitor cells) from hematopoietic stem cells populate the thymus and expand by cell division to generate a large population of immature thymocytes. The earliest thymocytes express neither CD4 nor CD8, and are therefore classed as double-negative ($CD4^{-}CD8^{-}$) cells. As they progress through their development, they become double-positive thymocytes ($CD4^{+}CD8^{+}$), and finally mature to *single-positive* ($CD4^{+}CD8^{-}$ or $CD4^{-}CD8^{+}$) thymocytes that are then released from the thymus to peripheral tissues.

[0061] "Hematopoietic stem cells" or "HSC" as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, precursor cells that can give rise to myeloid cells such as, for example, macrophages, monocytes, macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells and lymphoid lineages (such as, for example, T-cells, B-cells, NK-cells). HSCs have a heterogeneous population in which three classes of stem cells exist, which are distinguished by their ratio of lymphoid to myeloid progeny in the blood (L/M). In some alternatives, the cells provided are HSC cells. In some alternatives, the cell is a primary lymphocyte or a $CD34^{+}$ stem cell.

[0062] As used herein, "autologous" refers to the donor and recipient of the stem cells being the same, for example, the patient or subject is the source of the cells.

[0063] "Primary human cells" as described herein, are directly cultured from their source organ tissue or blood cells. Compared to immortalized cell lines, primary human cells provide enhanced replication of *in vivo*. In some alternatives, the cells provided are primary human cells.

[0064] As used herein, the term "co-delivery" as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, delivery of two or more separate chemical entities, whether in vitro or in vivo. Co-delivery refers to the simultaneous delivery of separate agents; to the simultaneous delivery of a mixture of agents; as well as to the delivery of one agent followed by delivery of a second agent or additional agents. In all cases, agents that are co-delivered are intended to work in conjunction with each other. In some alternatives, for example, co-delivery comprises delivery of an mRNA of interest and an AAV vector.

[0065] The term "endonuclease" as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, enzymes that cleave the phosphodiester bond within a polynucleotide chain. The polynucleotide may be double-stranded DNA (dsDNA), single-stranded DNA (ssDNA), RNA, double-stranded hybrids of DNA and RNA, and synthetic DNA (for example, containing bases other than A, C, G, and T). An endonuclease may cut a polynucleotide symmetrically, leaving "blunt" ends, or in positions that are not directly opposing, creating overhangs, which may be referred to as "sticky ends." The methods and compositions described herein may be applied to cleavage sites generated by endonucleases. In some alternatives of the system, the system can further provide nucleic acids that encode an endonuclease, including zinc finger nucleases (ZFNs), TAL effector nucleases (TALENs), meganucleases (such as MegaTALs), and CRISPR/Cas9 or a fusion protein comprising a domain of an endonuclease, for example, Cas9, TALEN, or MegaTAL, or one or more portion thereof. These examples are not meant to be limiting and other endonucleases and alternatives of the system and methods comprising other endonucleases and variants and modifications of these exemplary alternatives are possible without undue experimentation.

[0066] The term "transcription activator-like (TAL) effector nuclease" (TALEN) as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, anuclease comprising a TAL-effector domain fused to a nuclease domain. TAL-effector DNA binding domains may be engineered to bind to a desired target and fused to a nuclease domain, such as the Fokl nuclease domain, to derive a TAL effector domain-nuclease fusion protein. The methods and systems described herein may be applied to cleavage sites generated by TAL effector nucleases. In some alternatives of the systems provided herein, the systems can further comprise a TALEN nuclease or a vector or nucleic acid encoding a TALEN nuclease. In some alternatives of the methods provided herein, the method can further comprise providing a nuclease, such as a TALEN nuclease.

[0067] CRISPRs (clustered regularly interspaced short palindromic repeats) are segments of prokaryotic DNA containing short repetitions of base sequences. Each repetition is followed by short segments of "spacer DNA" from previous exposures to a bacterial virus or plasmid.

[0068] Cas9 (CRISPR associated protein 9) is an RNA-guided DNA endonuclease enzyme associated with the CRISPR adaptive immunity system in *Streptococcus pyogenes*, among other bacteria. *S. pyogenes* utilizes Cas9 to memorize and later interrogate and cleave foreign DNA, such as invading bacteriophage DNA or plasmid DNA. Cas9 performs this interrogation by unwinding foreign DNA and checking for complementarity to the 20 base pair spacer region of the guide RNA. If the DNA substrate is complementary to the guide RNA, Cas9 cleaves the invading DNA.

[0069] The CRISPR/Cas system as described herein, is used for gene editing (adding, disrupting, or changing the sequence of specific genes) and gene regulation. By delivering the Cas9 protein, a derivative, or fragment thereof and appropriate guide RNAs into a cell, the organism's genome can be cut at any desired location. It can be possible to use CRISPR to build RNA-guided genes capable of altering the genomes of entire populations. The basic components of CRISPR/Cas9 system comprise a target gene, a guide RNA, and a Cas9 endonuclease, derivative, or fragment thereof. An important aspect of applying CRISPR/Cas9 for gene editing is the need for a system to deliver the guide RNAs efficiently to a wide variety of cell types. This could for example involve delivery of an *in vitro* generated guide RNA as a nucleic acid (the guide RNA generated by *in vitro* transcription or chemical synthesis). In some alternatives the nucleic acid encoding the guide RNA is rendered nuclease resistant by incorporation of modified bases, such as 2'O-methyl bases. In some alternatives, the CRISPR/Cas9 system described herein, whereby the polynucleotide encoding the Cas9 nuclease or a derivative or functional fragment thereof (for example, a 20 nucleic acid sequence of an mRNA vector with Cas9) is provided with a poly(T) or poly(A) tail of a desired length and prepared in accordance with the teachings described herein, for example, is provided with a guide RNA that comprises one or more modified bases, such as any one or more of the modified bases described herein.

[0070] Exemplary guide RNAs useful with the alternatives described herein, which may contain one or more of the modified bases set forth herein. In some alternatives, the modified guide RNA includes the sequences provided in SEQ ID NO: 10. Furthermore, an important system for expressing guide RNAs in this context is based on the use of adeno-associated virus (AAV) vectors because AAV vectors are able to transduce a wide range of primary cells. AAV vectors do not cause infection and are not known to integrate into the genome. Therefore, the use of AAV vectors has the benefits of being both safe and efficacious.

[0071] The term "complementary to" means that the complementary sequence is homologous to all or one or more portions of a reference polynucleotide sequence. For illustration, the nucleotide sequence "CAT" corresponds to a reference sequence "CAT" and is complementary to a reference sequence "GTA."

[0072] As used herein, "homology-directed repair" (HDR) as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, DNA repair that takes place in cells, for example, during repair of a double-stranded break (DSB) in DNA. HDR requires nucleotide sequence homology and uses a donor polynucleotide to repair the sequence where the DSB (e.g., within a target DNA sequence) occurred. The donor polynucleotide generally has the requisite sequence homology with the sequence flanking the DSB so that the donor polynucleotide can serve as a suitable template for repair. HDR results in the transfer of genetic information from, for example, the donor polynucleotide to the DNA target sequence. HDR may result in alteration of the DNA target sequence (e.g., insertion, deletion, mutation) if the donor polynucleotide sequence differs from the DNA target sequence and part or all of the donor polynucleotide is incorporated into the DNA target sequence. In some alternatives, an entire donor polynucleotide, a portion of the donor polynucleotide, or a copy of the donor polynucleotide is integrated at the site of the DNA target sequence.

[0073] As used herein, a "guide" as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, any polynucleotide that site-specifically guides a nuclease to a target nucleic acid sequence. In some alternatives, a guide comprises RNA, DNA, or combinations of RNA and DNA.

[0074] A "genomic region" is a segment of a chromosome in the genome of a host cell that is present on either side of the target nucleic acid sequence site or, alternatively, also comprises a portion of the target site. The homology arms of the donor polynucleotide have sufficient homology to undergo homologous recombination with the corresponding genomic regions. In some alternatives, the homology arms of the donor polynucleotide share significant sequence homology to the genomic region immediately flanking the target site; it is recognized that the homology arms can be designed to have sufficient homology to genomic regions farther from the target site.

[0075] As used herein, "non-homologous end joining" (NHEJ) as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, repair of a DSB in DNA by direct ligation of one end of the break to the other end of the break without a requirement for a donor polynucleotide. NHEJ is a DNA repair pathway available to cells to repair DNA without the use of a repair template. NHEJ in the absence of a donor polynucleotide often results in nucleotides being randomly inserted or deleted at the site of the DSB.

[0076] As used herein "cleavage site" refers to a sequence that mediates the separation of a first polypeptide that would otherwise be in cis to a second polypeptide. Accordingly, for simplicity, "cleavage," "cleavage site," and the like as used herein refer to the separation of any two polypeptides that are encoded by a single polynucleotide in *cis*. Thus, "cleavage" and "cleavage site," can, but do not necessarily refer to proteolytic sites and events, and can also refer to other mechanisms for mediating the separation of polypeptides, for example ribosomal skipping.

[0077] As used herein, the term "label" refers to a detectable molecule. A number of suitable labels comprise polypeptides. As such, as used herein, a "label nucleic acid" refers to a nucleic acid encoding a label. In some alternatives, the AAV vector systems comprise a label polynucleotide. Thus, in some alternatives, a promoter (such as an MND promoter) is operatively linked to a label polynucleotide, such that the AAV vectors described herein comprise a reporter. Example labels that are suitable in accordance with alternatives herein include, but are not limited to, green fluorescent protein (GFP), including, for example, *Aequoria victoria* GFP, *Renilla muelleri* GFP, *Renilla reniformis* GFP, *Renilla ptilosarcus*, blue fluorescent protein (BFP), yellow fluorescent protein (YFP), red fluorescent protein (RFP), cyan fluorescent protein (CFP), or orange fluorescent proteins (OFP). Additional reporter genes include, but are not limited to neomycin, phosphoro-transferase, chloramphenicol acetyl transferase, thymidine kinase, luciferase, β-glucuronidase, aminoglycoside, phosphotransferase, hygromycin B, xanthine-guanine phosphoribosyl, luciferases (e.g., renilla, firefly, etc.), DHFR/methotrexate, β-galactosidase, alkaline phosphatase, turbo and tagRFP, and nuclear targeted versions of any of the aforementioned reporter genes. In some alternatives, the polypeptide of interest comprises the label itself, for example when production of label in active cells is desired. In some alternatives, an AAV construct provided herein comprises a U6 promoter driven guide RNA cassette or an MND promoter driven GFP cassette, or both, and wherein the MND promoter driven GFP cassette provides for tracking of AAV transduction efficiency.

[0078] The term “gene expression” as described herein, have their plain and ordinary meaning when read in light of the specification, and may include but is not limited to, for example, biosynthesis of a gene product. For example, in the case of a structural gene, gene expression involves transcription of the structural gene into mRNA and the translation of mRNA into one or more polypeptides.

[0079] A “polypeptide” is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than 10 amino acid residues are commonly referred to as “peptides.” A polypeptide can be considered as a protein.

[0080] A “protein” is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptide components, such as carbohydrate groups. Carbohydrates and other non-peptide substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures; substituents such as carbohydrate groups are generally not specified, but may be present nonetheless. In some alternatives, a system for editing at least one target gene in a cell is provided, wherein the method comprises a first nucleic acid sequence encoding a CRISPR guide RNA, wherein the CRISPR guide RNA is complimentary to at least one target gene in a cell and, wherein said first nucleic acid sequence is present in a vector; said system also comprising a second nucleic acid sequence encoding a Cas9 protein, a third nucleic acid sequence encoding a first adenoviral protein and a fourth nucleic acid sequence encoding a second adenoviral protein. In some alternatives, the CRISPR guide sequence is defined by SEQ ID NO: 3, 5, 6, 7 and 8. In some alternatives, the CRISPR guide sequence is defined by SEQ ID NO: 31,32,33,34.

X-Linked Disorders

[0081] Some alternatives provided herein relate to treating, ameliorating, inhibiting, or improving an X-linked disorder. In some alternatives, the disorder is Wiskott-Aldrich Syndrome (WAS). WAS is a severe X-linked genetic disorder with an incidence of around 1 in 250,000 live male births. WAS is a result of mutation in the *WAS* gene. WAS is characterized by opportunistic viral and bacterial infections due to abnormal lymphocyte function, thrombocytopenia with small platelets, eczema, and increased risk of autoimmune disorders and malignancies. In some alternatives, the disorder is X-linked thrombocytopenia (XLT). XLT also results from mutations in the *WAS* gene leading primarily to thrombocytopenia and bleeding.

[0082] Hematopoietic cell transplantation (HCT) is the only widely available approach that can provide curative therapy for WAS. Overall, transplant survival has increased over the last two decades, with improvements in transplant care, donor matching, and earlier treatment. However, outcomes for patients without a human leukocyte antigen (HLA) matched donor, particularly older subjects, remain suboptimal. In addition, patients with mixed chimerism exhibit an increased risk of autoimmunity and low myeloid chimerism predicts persistent thrombocytopenia. Further, optimal conditioning regiments that limit HCT-related morbidity, as well as the late effects following conditions remain unclear.

[0083] The challenge of finding suitable donors and other significant complications associated with HCT have prompted efforts to develop alternative gene therapy (GT) strategies for WAS. Pioneering GT trials using integrating viral vectors, based on use of gamma-retroviral (RV) or self-inactivating lentiviral vectors (LV) have been carried out in Europe. Boztug et al. first reported on two patients treated by RV GT. Boztug et al. *N Engl J Med*, **2010**, *363(20)*, 1918-1927; incorporated by reference herein in its entirety. Both patients showed a reduced frequency and severity of infections and disappearance of bleeding episodes and autoimmune manifestations. In a subsequent follow on trial using hematopoietic stem cell gene therapy, a total of 10 patients were treated. Nine patients showed successful immune reconstitution with platelet counts greater than 80,0000 cells/μL in eight of nine subjects. Braun et al. *Sci Transl Med*, **2014**, *12(6)*, 227; incorporated by reference herein in its entirety. Strikingly, severe adverse events with insertional mutagenesis leading to leukemia occurred in seven patients.

[0084] Based on these adverse events, self-inactivating LV (SIN-LV) encoding WAS cDNA under the control of the native proximal *WAS* gene promoter were developed. Trials using this LV have opened in Europe and in the United States. Aiuti et al. reported on initial results in three patients treated in Italy. Aiuti et al. *Science*, **2013**, *341*, 6148; incorporated by reference herein in its entirety. Long-term engraftment with gene-modified cells was observed in all three patients in the range of 25-50% of the total peripheral blood cells. WASp expression was detected in a vector containing hematopoietic cells with approximate endogenous expression levels in T cells. A subset of immunological abnormalities was corrected. Thrombocytopenia improved, but unlike the results of the WAS RV trial, platelet counts were not corrected. In contrast to the RV trial, clonal analysis indicated no evidence of clonal expansion for greater than three years.

[0085] A French/UK group published the outcome of seven WAS patients who underwent GT using the identical LV. Abina et al. *JAMA*, **2015**, *313*, 1550-1563; incorporated by reference herein in its entirety. However, similar to data from Aiuti et al., thrombocytopenia improved but platelet counts were not corrected. In summary, to date WAS LV trials have shown sustained viral marking and WASp expression in multiple hematopoietic lineages with partial clinical improvement. However, LV therapy has failed to rescue thrombocytopenia. Further, the long-term response to immunization and infections challenge and risk for autoimmunity remain to be determined.

[0086] Thus, provided herein are systems and methods for the introduction of an intact WAS cDNA under control of the endogenous promoter and enhancer in hematopoietic stem cells (HSCs). In some alternatives, the systems and methods described herein rescue immunologic and functional defects in WAS and XLT and provide a curative therapy. As discussed above, *WAS* gene replacement using viral-based gene therapy has been used to partially correct this disease, current viral vector approaches have led to increased risk for malignancy (when using gamma-retroviral vectors) or have failed to correct all hematopoietic deficits, including, most notably, the failure to correct thrombocytopenia. However, the systems and methods provided herein for gene editing of the endogenous *WAS* gene lead to improved long-term disease correction.

[0087] Accordingly, the systems and methods described herein provide several unique opportunities for treatment of WAS and XLT. For example, some alternatives described herein relate to editing a gene product, for example, at the *WAS* locus. In some alternatives, the edited gene product remains under control of the endogenous promoter and enhancer elements. In some alternatives, the editing rates are performed at high efficiency in a cell, such as a hematopoietic stem cell. Accordingly, provided herein are systems and methods for achieving high efficiency editing. Also provided are systems and methods for engrafting edited cells. In some alternatives, the methods and systems provided herein include use of autologous stem cells. In comparison to prior treatments that use marrow transplantation of stem cells from an allogeneic donor, *WAS* gene editing as described herein uses autologous stem cells. Thus, there is no risk for graft versus host disease, a major problem and risk with transplants. In some alternatives, the methods and systems provided herein use the endogenous gene promoter/enhancer to control gene expression. In comparison to viral gene replacement therapy as used in previous treatments, the gene editing systems and methods described herein use an endogenous gene promoter/enhancer to control gene expression, which leads to endogenous levels of WASp in all relevant cell lineages. Gene editing also eliminates the risk for viral vector mutagenesis that is present in all gene replacement strategies and was observed as a serious adverse event in nearly all WAS patients treated with gamma-retroviral vectors. Gene editing also leads to more appropriate levels of WAS protein expression in comparison to current LV vector therapy. The published trials in WAS LV therapy utilized a vector containing the WAS minimal promoter, which partially rescued function in some cell types but did not rescue platelet production most likely because the minimal promoter was not sufficiently robust in platelet progenitor cells.

[0088] Furthermore, in all current therapies for WAS (transplant and LV gene therapy) conditioning regimens are being used. Conditioning is also required for successful application of gene editing in order to achieve a clinically relevant level of engraftment of edited HSC. In some alternatives, engraftment of 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65% 70%, or 70% of edited cells or an amount within a range defined by any two of the aforementioned values will lead to clinical benefit. In some alternatives, treosulfan/fludarabine conditioning is used.

[0089] Some alternatives provided herein relate to unique nuclease reagents based upon either a TALEN or CRISPR/Cas9 platform in parallel with AAV based delivery of novel HDR repair templates. In some alternatives, the combination of a nuclease and an AAV vector achieves high rates of HDR at the *WAS* locus in human T cells and $CD34^+$ HSCs, leading to sustained gene expression *in vitro* and *in vivo* following engraftment in immunodeficient mice. In some alternatives, the methods and systems provided herein permit introduction of corrective cDNAs into the *WAS* locus in autologous cells from control subjects of subjects with WAS or XLT, thereby permitting lineage and developmental specific regulation of the functional gene product *in vitro* and *in vivo*. In some alternatives, the methods and systems provided herein permit long-term sustained cell lineage appropriate therapeutic WASp expression without adverse events within the host genome.

[0090] In some alternatives, the systems and methods described herein minimize the risk of mutagenesis by targeting integration of a therapeutic cassette into the *WAS* locus. In some alternatives, the systems described herein include an AAV donor template for integrating an expression cassette into the first exon of *WAS* by homology directed repair. Also provided herein are nuclease platforms targeting the *WAS* locus, including TALENs and CRISPR/Cas9.

[0091] Some alternatives concern methods for using adult mobilized $CD34^+$ cells and co-delivery of either TALEN mRNA or Cas9/gRNA ribonucleoprotein complexes (RNPs) and an AAV donor for targeted integration of a promoter-driven fluorescent marker. In some alternatives, the methods provided herein achieve efficient homology directed repair rates across multiple donors at an efficiency of 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or greater, or an efficiency within a range defined by any two of the aforementioned values for TALEN and an efficiency of 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80%, or greater, or an efficiency within a range defined by any two of the aforementioned values for RNP. In some alternatives, the highest levels of cell viability is observed using RNP/AAV co-delivery. In some alternatives, edited HSC retain their potential to give rise to multiple lineages in colony forming unit assays. In some alternatives, the systems provided herein provide long-term engraftment and differentiation potential in immune-deficient mice. In some alternatives, AAV vectors carrying WAS cDNA restore expression in WAS deficient cells. In some alternatives, the systems and methods described herein provide therapeutic correction of the disease or a disease symptom in patients.

Homology Directed Repair

[0092] Homology directed repair (HDR), refers to the process of repairing DNA damage using a homologous nucleic acid (e.g., a sister chromatid or an exogenous nucleic acid). In a normal cell, HDR typically involves a series of steps such as recognition of the break, stabilization of the break, resection, stabilization of single stranded DNA, formation of a DNA crossover intermediate, resolution of the crossover intermediate, and ligation. As described herein, HDR can be used to alter a target sequence and correct (e.g., repair or edit) a mutation in the genome. While not wishing to be bound by theory, it is believed that alteration of the target sequence occurs by HDR with a donor template or template nucleic acid. For example, the donor template or the template nucleic acid provides for alteration of the target position.

[0093] Some alternatives provided herein relate to methods and systems for homology directed repair of the gene associated with a disorder. In some alternatives, the gene is a *WAS* gene. In some alternatives, the method comprises HDR of the *WAS* gene in human hematopoietic cells. In some alternatives, the disorder is an X-linked disorder. In some alternatives, the disorder is WAS. In some alternatives, the disorder is XLT. In some alternatives, the method and systems include nuclease-based HDR of the *WAS* gene. In some alternatives, the nuclease based HDR comprises a TALEN based nuclease. In some alternatives, the nuclease based HDR comprises a CRISPR/Cas based nuclease.

TALEN

[0094] Transcription activator-like (TAL) effector-DNA modifying enzyme (TALEN) is a restriction enzyme that can be engineered to cut specific sequences of DNA. TALENs are made by fusing a TAL-effector domain to a DNA cleavage domain.

[0095] In some alternatives, the *WAS* locus used in targeting with WAS TALENs is co-delivered with an AAV donor.

[0096] In some alternatives the WAS TALEN forward sequence is defined by SEQ ID NO: 27 or SEQ ID NO: 29. In some alternatives, the WAS TALEN reverse sequence is defined by SEQ ID NO: 28 or SEQ ID NO: 30. In some alternatives, the AAV donor comprises a GFP cassette under control of an MND promoter. In some alternatives, the AAV donor has a 1 kb homology arm flanking an MND promoter driven GFP cassette (SEQ ID

NO: 35). In some alternatives, the AAV donor comprises one or more nucleotide mutations to abolish cleavage by TALENs. In some alternatives, the nucleotide mutation is a mutation of the T preceding the TALEN binding site (SEQ ID NO: 36). In some alternatives, the AAV donor comprises deletion of the entire region between exon 1 up to the reverse TALEN binding site (SEQ ID NO: 37).

[0097] Some alternatives provided herein relate to a TALEN nuclease for use in HDR of a gene of interest. In some alternatives, the TALEN binds to a TALEN binding site in a gene of interest. In some alternatives, the gene of interest is a *WAS* gene (SEQ ID NO: 4). In some alternatives, a *WAS* TALEN binds to native WAS sequence (SEQ ID NO: 4). The *WAS* locus used in targeting with WAS TALENs comprises the following components from 5' to 3': upstream homology arm (SEQ ID NO: 11); exon 1, including a guide RNA (SEQ ID NO: 19); T-for (TALEN forward binding site; SEQ ID NO: 15); cleavage site (SEQ ID NO: 17); T-rev (TALEN reverse binding site; SEQ ID NO: 16); exon 2 (SEQ ID NO: 18); and downstream homology arm (SEQ ID NOs: 12, 13, or 14).

[0098] In some alternatives, the *WAS* locus used in targeting with WAS TALENs is co-delivered with an AAV donor. In some alternatives the WAS TALEN forward sequence is defined by SEQ ID NO: 1 or SEQ ID NO: 24. In some alternatives, the WAS TALEN reverse sequence is defined by SEQ ID NO: 2 or SEQ ID NO: 25. In some alternatives, the AAV donor comprises a GFP cassette under control of an MND promoter. In some alternatives, the AAV donor has a 1 kb homology arm flanking an MND promoter driven GFP cassette (SEQ ID NO: 5). In some alternatives, the AAV donor comprises one or more nucleotide mutations to abolish cleavage by TALENs. In some alternatives, the nucleotide mutation is a mutation of the T preceding the TALEN binding site (SEQ ID NO: 6). In some alternatives, the AAV donor comprises deletion of the entire region between exon 1 up to the reverse TALEN binding site (SEQ ID NO: 7).

[0099] In some alternatives the WAS TALEN forward sequence is defined by SEQ ID NO: 27 or SEQ ID NO: 29. In some alternatives, the WAS TALEN reverse sequence is defined by SEQ ID NO: 28 or SEQ ID NO: 30. In some alternatives, the AAV donor comprises a GFP cassette under control of an MND promoter. In some alternatives, the AAV donor has a 1 kb homology arm flanking an MND promoter driven GFP cassette (SEQ ID NO: 35). In some alternatives, the AAV donor comprises one or more nucleotide mutations to abolish cleavage by TALENs. In some alternatives, the nucleotide mutation is a mutation of the T preceding the TALEN binding site (SEQ ID NO: 36). In some alternatives, the AAV donor comprises deletion of the entire region between exon 1 up to the reverse TALEN binding site (SEQ ID NO: 37).

CRISPR/Cas

[0100] Some alternatives provided herein relate to a Cas nuclease for use in HDR of a gene of interest. In some alternatives, the Cas nuclease is a Cas9 nuclease. Cas9 is an RNA-guided DNA endonuclease enzyme associated with the CRISPR (Clustered Regularly Interspersed Palindromic Repeats) adaptive immunity system in *Streptococcus pyogenes*, among other bacteria. *S. pyogenes* utilizes Cas9 to memorize and later interrogate and cleave foreign DNA, such as invading bacteriophage DNA or plasmid DNA. Cas9 performs this interrogation by unwinding foreign DNA and checking for if it is complementary to the 20 base pair spacer region of the guide RNA. If the DNA substrate is complementary to the guide RNA, Cas9 cleaves the invading DNA.

[0101] In some alternatives, the Cas nuclease is delivered in a complex with a single guide RNA as a ribonucleoprotein complex (RNP). In some alternatives, the CRISPR guide sequence is defined by SEQ ID NO: 3. In some alternatives, the RNP is co-delivered with an AAV donor. In some alternatives, the AAV donor is a self-complementary AAV (scAAV). In some alternatives, the AAV donor comprises a GFP cassette under control of an MND promoter wherein a protospacer adjacent motif (PAM) site is deleted (SEQ ID NO: 5). In some alternatives, the AAV donor comprises a U6 promoter driven guide RNA cassette (SEQ ID NO: 8). In some alternatives, the AAV donor comprises both the donor and guide sequences (SEQ ID NO: 9). In some alternatives, the AAV donor is an scAAV done including guide sequences, and includes a sequence defined by SEQ ID NO: 21, SEQ ID NO: 22, or SEQ ID NO: 23.

[0102] In some alternatives, the Cas nuclease is delivered in a complex with a single guide RNA as a ribonucleoprotein complex (RNP). In some alternatives, the CRISPR guide sequence is defined by SEQ ID NO: 31,32,33,34. In some alternatives, the RNP is co-delivered with an AAV donor. In some alternatives, the AAV donor is a self-complementary AAV (scAAV). In some alternatives, the AAV donor comprises a GFP cassette under control of an MND promoter wherein a protospacer adjacent motif (PAM) site is deleted (SEQ ID

NO: 9). In some alternatives, the AAV donor comprises a U6 promoter driven guide RNA cassette (SEQ ID NO: 38). In some alternatives, the AAV donor comprises both the donor and guide sequences (SEQ ID NO: 39).

Cells

[0103] Some alternatives provided herein relate to co-delivery of a nuclease, such as a TALEN or Cas nuclease, and an AAV donor template to modify endogenous *WAS* locus in a cell. In some alternatives, the cell is a mammalian cell. In some alternatives, the cell is a human cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is a lymphocyte. In some alternatives, the cell is not a transformed cell. In some alternatives, the cell is a primary lymphocyte. In some alternatives, the cell is a lymphocyte precursor cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a hematopoietic cell. In some alternatives, the cell is a $CD34^{+}$ cell. In some alternatives, the cell is a primary human hematopoietic cell.

[0104] In some alternatives, the cell is transformed by co-delivery of a nuclease, such as a TALEN nuclease or Cas nuclease, and an AAV donor template to modify endogenous *WAS* locus in a cell. In some alternatives, a method of editing a *WAS* gene in a cell is provided, wherein the method comprises introducing into a cell a first vector that comprises a first nucleic acid sequence encoding a guide RNA, such as a TALEN guide RNA or a CRISPR guide RNA, wherein the guide RNA is complimentary to at least one target gene in said cell, and introducing into said cell a second nucleic acid sequence encoding a nuclease, such as a TALEN nuclease or a Cas nuclease, a derivative, or fragment thereof. In some alternatives, a cell is provided, wherein the cell is manufactured by the said methods.

Methods of Treating, Inhibiting, or Ameliorating WAS or XLT in a Subject in Need

[0105] Some alternatives provided herein related to methods of promoting HDR of a *WAS* gene in a subject in need thereof. In some alternatives, the method comprises selecting or identifying a subject in need thereof. A selected or identified subject in need thereof is a subject that presents with symptoms of an X-linked disorder, such as WAS or

XLT, or a subject that has been diagnosed with an X-linked disorder, such WAS or XLT. Such evaluations can be made clinically or by diagnostic test.

[0106] In some alternatives, the method comprises adoptive cellular therapy or adoptive cell transfer of treated cells to a subject in need. In some alternatives, adoptive cellular therapy or adoptive cell transfer comprises administering cells for promoting homology directed repair of a *WAS* gene in a subject. In some alternatives, the method comprises obtaining cells from the subject in need thereof. In some alternatives, the cells from the subject in need are primary human hematopoietic cells. In some alternatives, the cells are transformed by co-delivery of a nuclease, such as a TALEN nuclease or a Cas nuclease, and an AAV donor, which modifies the endogenous *WAS* locus in the cell. In some alternatives, the method comprises expanding the transformed cells. In some alternatives, the method comprises selecting transformed cells that have successful modification of the *WAS* locus in the cell. In some alternatives, the transformed cells are administered to the patient.

[0107] In some alternatives, administration of the transformed cells to the patient comprises administration of autologous cells to the patient. In some alternatives, administration of the transformed cells to the patient treats, inhibits, or ameliorates symptoms of WAS and/or XLT. In some alternatives, administration of the transformed cells to the patient treats WAS and/or XLT. In some alternatives, the method improves thrombocytopenia. In some alternatives, the method increases platelet counts.

[0108] In some alternatives, an amount of treated cells is administered to the composition. In some alternatives, the amount of cells administered is 1×10^4, 2×10^4, 3×10^4, 4×10^4, 5×10^4, 6×10^4, 7×10^4, 8×10^4, 9×10^4, 1×10^5, 2×10^5, 3×10^5, 4×10^5, 5×10^5, 6×10^5, 7×10^5, 8×10^5, 9×10^5, 1×10^6, 2×10^6, 3×10^6, 4×10^6, 5×10^6, 6×10^6, 7×10^6, 8×10^6, 9×10^6, 1×10^7, 2×10^7, 3×10^7, 4×10^7, 5×10^7, 6×10^7, 7×10^7, 8×10^7, 9×10^7, 1×10^8, 2×10^8, 3×10^8, 4×10^8, 5×10^8, 6×10^8, 7×10^8, 8×10^8, 9×10^8, or 1×10^9 cells, or greater, or an amount within a range defined by any two of the aforementioned values.

[0109] In some alternatives, the treated cells are administered to a subject as a co-therapy with an additional therapy that is used to treat the symptoms of the disorder or used to treat the disorder. In some alternatives, the additional therapy includes immunoglobulin therapy, an antibiotic therapy, corticosteroid therapy, or transfusion therapy.

Pharmaceutical Compositions and Administration

[0110] Cells prepared by the systems or methods provided herein can be administered directly to a patient for targeted homology directed repair of a *WAS* locus and for therapeutic or prophylactic applications, for example, for treating, inhibiting, or ameliorating an X-linked disorder, such as WAS or XLT. In some alternatives, cells are prepared by the systems provided herein. In some alternatives, a composition is provided, wherein the composition comprises the cell. In some alternatives, the compositions described herein, can be used in methods of treating, preventing, ameliorating, or inhibiting an X-linked disorder, such as WAS or XLT or ameliorating a disease condition or symptom associated with an X-linked disorder, such as WAS or XLT.

[0111] The compositions comprising the cells are administered in any suitable manner, and in some alternatives with pharmaceutically acceptable carriers. Suitable methods of administering such compositions comprising the cells are available and well known to those of skill in the art, and, although more than one route can be used to administer a particular composition, a particular route can often provide a more immediate and more effective reaction than another route.

[0112] Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as, by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions that are available (see, e.g., Remington's Pharmaceutical Sciences).

[0113] Formulations suitable for parenteral administration, such as, for example, by intravenous, intramuscular, intradermal, and subcutaneous routes, include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The disclosed compositions can be administered, for example, by intravenous infusion, orally, topically, intraperitoneally, intravesically or intrathecally. The formulations of compounds can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials. Injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0114] In some alternatives, one or more of parenteral, subcutaneous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal routes of administration are contemplated. In some alternatives, the composition to be administered can be formulated for delivery via one or more of the above noted routes.

ADDITIONAL ALTERNATIVES

[0115] Additional alternatives are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims. The examples provided below demonstrate genome editing tools that possess a high degree of specificity, providing the foundation for site-specific modification of the *WAS* locus for therapeutics.

Alternative 1

Cleavage Efficiency of TALENs in Primary T Cells

[0116] This alternative demonstrates methods for determining the cleavage efficiency of the systems described herein.

[0117] A panel of candidate guide RNAs (delivered as self-complementary AAV (scAAV) and Cas9 as mRNA) or TALEN mRNAs were prepared and tested in T cells. **Figure 1A** depicts the location of the WAS TALENs (TALEN #1 and TALEN #2) and guide RNAs, termed G1, G2, G3, and G4 within the human *WAS* gene.

[0118] Primary human T cells were cultured in T cell growth medium supplemented with IL-2 (50 ng/mL), IL-7 (5 ng/mL), and IL-15 (5 ng/mL) and stimulated using CD3/CD28 beads (Dynabeads, Life Technologies) for 48 hours. Beads were removed and cells rested overnight followed by electroporation using Neon Transfection system with either TALEN mRNA (1 μg of each RNA monomer) or co-delivery of 1 μg of Cas9 mRNA and scAAV carrying guide RNA. Cells were cultured for 5 more days and genomic DNA was extracted. The region surrounding the cut site was amplified and purified using PCR purification kit. 200 ng of purified PCR product was incubated with T7 endonuclease (NEB), analyzed on a gel and percent disruption quantified using Licor Image Studio Lite software.

[0119] **Figure 1B** depicts the percentage of non-homologous end joining (NHEJ) events in primary human T cells detected using the T7 assay, 5 days post-transfection with TALEN mRNAs (T1, T2) or with Cas9 mRNA co-delivered with scAAV expressing gRNAs (G1-4). n=2, represents the number of independent experiments. TALEN T1 and Guide G1 were used in the following examples.

[0120] Primary human T cells were cultured in T cell growth medium supplemented with IL-2 (50ng/ml) , IL-7 (5ng/ml), and IL-15 (5 ng/ml) and stimulated using CD3/CD28 beads (Dynabeads, Life Technologies) for 48 hours. Beads were removed and cells rested overnight followed by electroporation using Neon Transfection system with either TALEN mRNA (1μg of each RNA monomer) or co-delivery of 1μg of Cas9 mRNA and scAAV carrying guide RNA. Cells were cultured for 5 more days and the genomic DNA was extracted. The region surrounding the cut site was amplified and purified using PCR purification kit. 200 ng of purified PCR product was incubated with T7 endonuclease (NEB), analyzed on a gel and percent disruption quantified using Licor Image Studio Lite software. TALEN T1 and Guide G1 were used in experiments in subsequent figures.

Alternative 2

Editing of Human Primary T Cells With TALEN and AAV Co-Delivery

[0121] This alternative demonstrates methods for editing primary T Cells with TALEN and AAV as described in some alternatives herein.

[0122] A *WAS* gene was prepared using the TALEN T1 and Guide G1 as described in Example 1, and as shown in **Figure 2A**. **Figure 2A** depicts the *WAS* locus and AAV donor templates used in targeting with WAS TALENs. The *WAS* locus shows the TALEN binding sites, represented by T-f (TALEN forward) and T-r (TALEN reverse). Homology arms are also shown. The three AAV vectors are represented as vectors #1201, #1244, and #1262. AAV vector #1201 has 1 kb of homology arms flanking an MND promoter driven green fluorescent protein (GFP) cassette. AAV vector #1244 has couple nucleotide mutations (represented by X) to abolish cleavage by TALENs. AAV vector #1262 has the entire region between the exon 1 up to the reverse TALEN binding site deleted.

[0123] As shown in **Figure 2A** small red boxes represent TALEN forward (T-for) and reverse (T-rev) binding sites. Homology arms are depicted in white. DT AAV vector has 1 kb of homology arms flanking an MND promoter driven green fluorescent protein (GFP) cassette. DT-M AAV donor has couple nucleotide mutations (represented by X) to abolish cleavage by TALENs. The #DT-D vector has the entire region between the exon 1 up to the reverse TALEN binding site deleted.

[0124] **Figure 2B** depicts the timescale for the experimental method. Primary human T cells were cultured in T cell growth medium supplemented with IL-2 (50 ng/mL), IL-7 (5 ng/mL), and IL-15 (5 ng/mL) and stimulated using CD3/CD28 beads (Dynabeads, Life Technologies) for 48 hours. Primary human T cells were cultured in T cell growth medium supplemented with IL-2 (50ng/ml) , IL-7 (5ng/ml), and IL-15 (5 ng/ml) and stimulated using CD3/CD28 beads (Dynabeads, Life Technologies) for 48 hours. Beads were removed and cells rested overnight followed by electroporation with the nuclease TALEN mRNA using Neon Transfection system. AAV donors were added 2-4 hrs. post transfection at 20% of culture volume.. Cells were analyzed for GFP expression on Days 2, 8 and 15. Day 15 GFP is indicative of homology directed repair (HDR). **Figure 2C** depicts the %GFP at days 2, 8, and 15 at the indicated conditions (+/- mRNA and the various AAV vectors). Primary human CD3+ T cells were cultured and bead stimulated. Cells were then transfected with TALEN mRNA and AAV donors added two hours later at 20% of culture volume. Cells were analyzed for GFP expression on Days 2, 8 and 15. GFP expression at day 15 is indicative of homology directed repair (HDR). n=3 and represents the number of independent experiments performed using cells from 3 different donors. Data are presented as mean ± SEM. GFP expression at day 15 is indicative of homology directed repair (HDR). n=3 and represents the number of independent experiments performed using cells from 3 different donors. Data are presented as mean ± SEM. **Figure 2D** shows the cell viability under each condition. **Figure 2E** are the results from a test for nuclease specificity utilizing AAV without homology arms. Primary T cells transfected with TALENs and transduced with an AAV vector with an MND promoter driven blue fluorescent protein (BFP) without any homology arms. Fluorescence from this vector at day 15 is indicative of random integration. n=3 and represents the number of independent experiments performed using cells from 3 different donors. Data are presented as mean ± SEM. **Figure 2F** shows representative FACS plots with GFP expression at day 15 post co-delivery of TALEN mRNA and AAV donor templates. **Figure 2G** provides additional representative FACS plots showing GFP expression at Day 15. N = 3 and represents the number of independent experiments performed using cells from three different donors. Shown in Figure 2H are the results from a test for nuclease specificity utilizing AAV without homology arms. Primary T cells transfected with TALENs and transduced with an AAV vector with an MND promoter driven blue fluorescent protein (BFP) without any homology arms. Fluorescence from this vector at day 15 is indicative of random integration. n=3 and represents the number of independent experiments performed using cells from 3 different donors. Data are presented as mean ± SEM. Fig.2I shows representative FACS plots showing GFP expression at day 15. n=3 and represents the number of independent experiments performed using cells from 3 different donors.

Alternative 3

Editing of Human Primary T Cells With CRISPR and AAV Co-Delivery

[0125] This alternative demonstrates methods for editing primary T Cells with CRISPR and AAV as described in some alternatives herein.

[0126] **Figure 3A** depicts the scAAV guide RNA vector (#1189), donor template (#1201), and AAV vector containing both guide and donor sequences (#1215). Both #1201 and #1215 AAVs have the PAM site mutated to abolish cleavage by guide.

[0127] Primary human CD3 T cells were cultured as described in Example 1 and transfected with 1 µg of Cas9 mRNA followed by transduction with either vector #1189 and #1201 or #1215 AAV vectors. **Figure 3B** shows the %GFP at days 2, 8, and 15, and **Figure 3C** shows the cell viability at days 2, 8, and 15 under the specified conditions. 10% and 20% represent the % of culture volume #1215 AAV was added at. All other AAVs were added at 10% of culture volume. **Figure 3D** depicts BFP expression when Cas9, guide and MND.BFP vector with no homology arms were delivered. **Figure 3E** shows representative FACS plots showing GFP expression at Day 15. N = 3 and represents the number of independent experiments performed using cells from 3 donors. **Figure 3F**shows the %GFP at days 2, 8, and 15, and **Figure 3G** depicts BFP expression when Cas9, guide and MND.BFP vector with no homology arms were delivered. **Figure 3H** shows representative FACS plots showing GFP expression at day 15. N = 3 and represents the number of independent experiments performed using cells from 3 donors.

[0128] Examples 2 and 3 show that using the T7 endonuclease assay, frequencies of 85% and 73% were achieved with TALENs and CRISPR/Cas systems, respectively. These examples also show methods that result in 70% homology directed repair (HDR) in T cells when the nucleases were co-delivered with an AAV donor template.

Alternative 4

Editing of Mobilized Adult CD34+ Cells With TALEN and AAV Co-Delivery

[0129] This alternative demonstrates methods for editing mobilized adult $CD34^+$ cells using co-delivery of TALEN and AAV as described in some alternatives herein.

[0130] $CD34^+$ cells were transfected as described in Example 2 with TALEN and AAV. **Figure 4A** shows the timeline for the experimental conditions, where the cells were analyzed at days 2, 5, and 8 with flow cytometry. **Figure 4B** shows the %GFP at days 2 and 5, and the cell viability is depicted in **Figure 4C**. **Figure 4D** shows representative FACS plots showing GFP expression at day 5.

[0131] This alternative demonstrates that the co-delivery of TALEN and AAV induces HDR in adult human mobilized $CD34^+$ cells.

Alternative 5

Off-Target Cleavage with TALEN

[0132] This alternative provides potential off-target cleavage sites for TALENs.

[0133] T cells were transfected with 1 µg of forward and reverse *WAS* TALEN. Five days post-transfection, genomic DNA was extracted, endogenous *WAS* locus and predicted off target loci were amplified and colony sequenced. Off-targets were predicted using Prognos software. As shown in Table 1 below, potential off-target cleavage sites for TALENs identified using the Prognos software were amplified and sequenced, with no evidence of off-target cleavage observed at any of the predicted loci.

Ranking	TALEN Score	Orientation	Mismatches	Chr Name	Genomic Region	Closest Gene	% Cleavage
1	100	L-17-R	0_0	ChrX	Intron	WAS	94% (32/34)
2	60.25	R-26-L	6_2	Chr6	Intergenic	LRFN2	0% (0/30)

3	59.44	R-25-L	6_3	Chr18	Intron	DLGAP1	0% (0/30)
4	59.18	R-30-L	5_3	Chr12	Exon	MAGOHB	0% (0/30)
5	56.42	R-30-R	5_3	Chr7	Intergenic	INHBA	0% (0/30)
6	56.15	L-13-R	6_3	Chr1	Intergenic	SIKE1	0% (0/30)
7	55.97	R-16-L	6_3	Chr8	Intergenic	ANGPT1	0% (0/30)
8	55.74	R-15-R	5_3	Chr2	Intron	RALB	0% (0/30)
12	55.18	R-11-L	5_4	Chr3	Intergenic	MIR548A3	0% (0/30)

Alternative 6

Disruption of *WAS* Locus in Human CD34+ Cells Using TALENS or RNP

[0134] This alternative demonstrates the disruption of human $CD34^+$ cells using TALEN or a ribonucleoprotein complex (RNP).

[0135] Mobilized human $CD34^+$ cells were cultured in stem cell growth medium (SCGM) supplemented with thrombopoietin (TPO), stem cell factor (SCF), Fms-related tyrosine kinase 3 ligand (FLT-3L) (100 ng/mL) and IL-3 (60 ng/mL) for 48 hours, followed by electroporation using Neon electroporation system with either 1 μg of each TALEN monomer or ribonucleoprotein complex (RNP) of Cas9 protein and single guide RNA (sgRNA) mixed in 1:1.2 ratio. The sgRNA was purchased from Trilink BioTechnologies and has chemically modified nucleotides at the three terminal positions at 5′ and 3′ ends. The cells were cultured for 5 days and genomic DNA was extracted. The region surrounding the cut site for WAS TALEN and guide was amplified and cloned into pJET cloning vector. Colony sequencing was performed to quantify % cleavage at the cut site by analyzing the indels. **Figure 5A** depicts the % cleavage of the *WAS* locus in the $CD34^+$ cells for both TALEN and RNP. N=3 and represents the number of independent experiments performed using cells from three donors.

[0136] As shown in Figure 5A, adult human mobilized $CD34^+$ cells were cultured in SCGM media supplemented with TPO, SCF, FLT3L (100ng/ml) and IL-3 (60ng/ml) for 48 hours, followed by electroporation using Neon electroporation system with either 1μg of each TALEN monomer or Ribonucleoprotein complex (RNP) of Cas9 protein and single guide RNA mixed in 1:1.2 ratio. The sgRNA was purchased from Trilink Biotechnologies and has chemically modified nucleotides at the three terminal positions at 5′ and 3′ ends. The cells were cultured for 5 days and genomic DNA was extracted. The region surrounding the cut site for WAS TALEN and guide was amplified and cloned into pJET cloning vector. Colony sequencing was performed to quantify % cleavage at the cut site by analyzing the indels. N=3 and represents the number of independent experiments performed using cells from 3 donors.

[0137] As shown in Figure 5B, adult mobilized human CD34^{+} cells were cultured in SCGM media as described in Figure 5A, followed by electroporation using Neon electroporation system with either TALEN mRNA or RNP complex (2μg). AAV vector (MOI ranging from 62-300) carrying the donor template was added immediately after electroporation. Controls included un-manipulated cells (mock) and cells transduced with AAV only without transfection of a nuclease (AAV). Bar graphs depict %GFP at day 5, indicative of HDR. n=8 for RNP, n=15 for TALEN, and represents >4 donors.

[0138] Shown in **Figure 5C,** are FACS plots depicting GFP expression from Mock, AAV or AAV plus TALEN treated CD34+ cells (top row) or AAV+RNP treated cells (bottom row) 5 days post editing.

[0139] Shown in **Figure 5D,** bar graphs represent viability of mock and edited cells 2 days post editing. N=8 for RNP, n=12 for TALEN and represents >4 independent donors.

[0140] Shown in **Figure 5E**, are results from a CFU assay for TALEN edited CD34+ cells. TALEN edited and mock cells were plated one day post editing onto Methocult media for colony formation unit (CFU) assay. Briefly, 500 cells were plated in duplicate in Methocult H4034 media (Stemcell Technologies), incubated at 37℃ for 12-14 days and colonies enumerated based on their morphology and GFP expression. CFU-E: Colony forming unit erythroid, M: Macrophage, GM: Granulocyte, macrophage, G: Granulocyte, GEMM: Granulocyte, erythroid, macrophage, megakaryocyte, BFU-E: Burst forming unit erythroid. n=3 independent donors. Data are presented as mean ± SEM.

[0141] Shown in **Figure 5F**, are results from a CFU assay for RNP edited CD34+ cells. RNP edited and mock cells were plated one day post editing onto Methocult media for colony formation unit (CFU) assay. Briefly, 500 cells were plated in duplicate in Methocult H4034 media (Stemcell Technologies), incubated at 37℃ for 12-14 days and colonies enumerated based on their morphology and GFP expression. CFU-E: Colony forming unit erythroid, M: Macrophage, GM: Granulocyte, macrophage, G: Granulocyte, GEMM: Granulocyte, erythroid, macrophage, megakaryocyte, BFU-E: Burst forming unit erythroid. n=3 experiments and 2 donors. Data are presented as mean ± SEM.

[0142] Shown in **Figure 5G** are results from the digital droplet PCR assay for determining HDR. Genomic DNA was isolated from hematopoietic stem and progenitor cells (HSPCs) using a DNeasy Blood and Tissue kit (Qiagen). To assess editing rates, "in-out" droplet digital PCR was performed with the forward primer binding within the AAV insert and the reverse primer binding the WAS locus outside the region of homology. A control amplicon of similar size was generated for the ActB gene to serve as a control. All reactions were performed in duplicate. The PCR reactions were partitioned into droplets using a QX200 Droplet Generator (Bio-Rad). Amplification was performed using ddPCR Supermix for Probes without UTP (Bio-Rad), 900nM of primers, 250nM of Probe, 50 ng of genomic DNA, and 1% DMSO. Droplets were analyzed on the QX200 Droplet Digital PCR System (Bio-Rad) using QuantaSoft software (Bio-Rad). Data are presented as mean ± SEM .

Alternative 7

Editing of the *WAS* Locus in CD34+ HSCs with TALEN mRNA/RNP and AAV Co-Delivery

[0143] This alternative demonstrates editing of the *WAS* locus in $CD34^+$ hematopoietic stem cells using co-delivery of TALEN mRNA or RNP and an AAV donor template.

[0144] Adult mobilized human $CD34^+$ cells were cultured in SCGM media as described in Example 6, followed by electroporation using Neon electroporation system with either TALEN mRNA or RNP complex. AAV vector carrying the donor template was added immediately after electroporation. Controls included un-manipulated cells (mock) and cells transduced with AAV only without transfection of a nuclease (AAV). **Figure 6A** shows % GFP at day 5 indicative of HDR. **Figure 6B** shows the viability of edited cells two days post editing. N=7 for TALEN and N=3 for RNP and represent independent donors. Edited and mock cells were plated one day post editing onto Methocult media for colony formation unit (CFU) assay. Briefly, 500 cells were plated in duplicate in Methocult H4034 media (Stemcell Technologies, incubated at 37°C for 12-14 days and colonies enumerated based on their morphology and GFP expression. **Figure 6C** shows data from TALEN and **Figure 6D** shows data from RNP. CFU-E: Colony forming unit erythroid, M: Macrophage, GM: Granulocyte, macrophage, G: Granulocyte, GEMM: Granulocyte, erythroid, macrophage, megakaryocyte, BFU-E: Burst forming unit erythroid.

Alternative 8

Engraftment of Edited Human CD34+ Cells into Immune Deficient NSG Mice

[0145] This alternative demonstrates the use of the edited cells in immune deficient mice.

[0146] Two million human $CD34^+$ cells that were either untreated, AAV treated, or treated with AAV and RNP were injected into immune deficient non-obese diabetic (NOD) severe combined immunodeficiency (scid) gamma (NSG) mice preconditioned with 25 mg/kg busulfan. The mice were sacrificed 10 weeks post-transplant and bone marrow was harvested. **Figure 7A** depicts total engraftment of edited cells as defined by expression of human CD45 marker. **Figure 7B** Illustrates %GFP+ cells within the engrafted cells. **Figure 7C** shows FACS plots from representative mice.

Alternative 9

Percent HR in cells for engraftment

[0147] Shown in **Figure 9A** is the cell viability and %HR in input cells used for engraftment in NSG mice. Adult mobilized human CD34+ cells were cultured in SCGM media as previously described with the exception that IL-6 (100ng/ml) was added instead of IL-3. The cells were electroporated with 1 μg of RNP complex and AAV at an MOI of 62. Data are presented as mean ± SEM. N=5 and represents independent experiments. Figure 9B shows the results from engraftment of edited cells in bone marrow of transplanted NSG mice. Six to 10 week old NSG mice were treated with 25 or 35 mg/kg of BUSULFEX (Henry Schein Inc.) via intraperitoneal injection, diluted 1:1 in phosphate-buffered saline. Twenty-four hours later, 2×10^6 mock or gene edited hematopoietic stem cells (cultured as described in Figure 9A) in phosphate-buffered saline were delivered via retro-orbital injection. Animals were euthanized 10 to 16 weeks post-transplant, bone marrow and spleens were harvested and analyzed for human cell engraftment. Dot plot depicts total engraftment of edited cells as defined by expression of human CD45 marker in BM of sacrificed mice. Dots represent individual mice. Data are presented as mean ± SEM. **Figure 9C** shows the result of engraftment of edited Cells in bone marrow of NSG mice 16 weeks post transplantation. Representative flow plots of cells harvested from the bone marrow of NSG mice 16 weeks following cell transplantation. On left panel shows the data of bone marrow harvested from mouse transplanted with untreated cells. On right, bone marrow harvested from mouse transplanted with cells treated with AAV plus RNP. On the top row of the figure, from left to right: hCD45:mCD45 chimerism, human CD45-gated CD33+ and CD19+ staining. Bottom row, from left to right: GFP expression among hCD45+, CD33+ and CD19+ cells. Figure 9D Engraftment of edited cells in spleens of transplanted mice. Graph depicts total engraftment of edited cells at 10-16 weeks as defined by expression of human CD45 marker in spleens of sacrificed mice. Dots represent individual mice. **Figure 9E** shows results from engraftment of edited cells in spleens of NSG Mice. Representative flow plots of cells harvested from the spleens of NSG mice 16 weeks following cell transplantation are shown. On left, bone marrow harvested from mouse transplanted with untreated cells. On right, bone marrow harvested from mouse transplanted with cells treated with AAV plus RNP. Top row, from left to right: hCD45:mCD45 chimerism, Human CD45-gated CD33+ and CD19+ staining. Bottom row, from left to right: GFP expression among hCD45+, CD33+ and CD19+ cells. Figure 9F Engraftment of GFP+ cells in NSG mice. HDR-editing rate (%GFP+) among hCD45+ cells recovered from the bone marrow and spleens of NSG mice sacrificed at 10-16 weeks. Mean ± SEM shown on graph.

Alternative 10
Engraftment of edited cells in NSGW41 mice

[0148] Shown in **Figure 10A** are the results from engraftment of edited cells in bone marrows of NSGW41 mice. Representative flow plots of cells harvested from the bone marrows of NSGW41 mice 16 weeks following cell transplantation. On left, bone marrow harvested from mouse transplanted with untreated cells. On right, bone marrow harvested from mouse transplanted with cells treated with AAV plus RNP. Top row, from left to right: hCD45:mCD45 chimerism, Human CD45-gated $CD33^+$ and $CD19^+$ staining. Bottom row, from left to right: GFP expression among $hCD45^+$, $CD33^+$ and $CD19^+$ cells.

[0149] Shown in **Figure 10B** are the results from engraftment of edited cells in spleens of NSGW41 mice. Representative flow plots of cells harvested from the spleens of NSGW41 mice 16 weeks following cell transplantation. On left, bone marrow harvested from mouse transplanted with untreated cells. On right, bone marrow harvested from mouse transplanted with cells treated with AAV plus RNP. Top row, from left to right: hCD45:mCD45 chimerism, Human CD45-gated $CD33^+$ and $CD19^+$ staining. Bottom row, from left to right: GFP expression among $hCD45^+$, $CD33^+$ and $CD19^+$ cells .

Alternative 11
Engraftment of edited cells in NSGW41 mice

[0150] **Figure 11A** shows the design of AAV vectors expressing cDNA for GFP or codon optimized WAS gene from the endogenous promoter. AAV vectors with 0.6kb homology arms flanking either a promoterless GFP (top) or WAS cDNA (bottom) followed by a shorter WPRE, designated WPRE3 followed by SV40 polyadenylation signal. As shown in **Figure 11B** is the results from the digital droplet PCR to determine editing rates in WAS targeted promoterless GFP construct. In-out droplet digital PCR was performed as previously described. Droplets were analyzed on the QX200 Droplet Digital PCR System (Bio-Rad) using QuantaSoft software (Bio-Rad). All experiments were performed on female donors. The ddPCR rates were about half of HR rates by FACS suggesting that only one X chromosome was being targeted, n=3 and represents three independent experiments and donors. Data are presented as mean ± SEM. As shown in **Figure 11C** is the results from the digital droplet PCR to determine editing rates with WAS targeted promoterless coWAS expressing AAV vectors.

More Alternatives

[0151] Further aspects of the disclosure are realized in the following numbered alternatives.

[0152] In some alternatives, a nucleic acid for homology directed repair (HDR) of Wiskott-Aldrich Syndrome (WAS) gene is provided, the nucleic acid comprising: a first sequence encoding a *WAS* gene; a second sequence encoding one or more guide RNA-cleavage sites; and a third sequence encoding one or more nuclease-binding sites. In some alternatives, the *WAS* gene comprises the nucleic acid sequence set forth in SEQ ID NO: 4. In some alternatives, the second sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 17. In some alternatives, the one or more nuclease binding sites comprises a forward and reverse transcription activator-like effector nuclease (TALEN) binding site. In some alternatives, the one or more nucleic binding sites is a clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) binding site. In some alternatives, the nucleic acid further comprises one or more enhancer elements. In some alternatives, the nucleic acid further comprises homology arm sequences. In some alternatives, the nucleic acid further comprises nucleic acid sequence encoding a promoter.

[0153] In some alternatives, a vector for promoting HDR of WAS protein (WASp) expression in a cell is provided, the vector comprising: a first sequence encoding a *WAS* gene; a second sequence encoding one or more guide RNA-cleavage sites; and a third sequence encoding one or more nuclease-binding sites. In some alternatives, the *WAS* gene comprises the nucleic acid sequence set forth in SEQ ID NO: 4. In some alternatives, the second sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 17. In some alternatives, the one or more nuclease binding sites comprises a forward and reverse transcription activator-like effector nuclease (TALEN) binding site. In some alternatives, the one or more nucleic binding sites is a clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) binding site. In some alternatives, the vector further comprises one or more enhancer elements. In some alternatives, the vector is an adeno-associated viral vector (AAV). In some alternatives, the vector is a self-complementary AAV (scAAV). In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a hematopoietic stem cell (HSC). In some alternatives, the cell is a $CD34^+$ HSC.

[0154] In some alternatives, a system for promoting HDR of WAS protein (WASp) expression in a cell is provided, where're the system comprises a vector of any one of the alternatives herein and a nucleic acid encoding a nuclease. In some alternatives, the vector comprises a first sequence encoding a *WAS* gene; a second sequence encoding one or more guide RNA-cleavage sites; and a third sequence encoding one or more nuclease-binding sites. In some alternatives, the *WAS* gene comprises the nucleic acid sequence set forth in SEQ ID NO: 4. In some alternatives, the second sequence comprises the nucleic acid sequence set forth in SEQ ID NO: 17. In some alternatives, the one or more nuclease binding sites comprises a forward and reverse transcription activator-like effector nuclease (TALEN) binding site. In some alternatives, the one or more nucleic binding sites is a clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) binding site. In some alternatives, the vector further comprises one or more enhancer elements. In some alternatives, the vector is an adeno-associated viral vector (AAV). In some alternatives, the vector is a self-complementary AAV (scAAV). In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a hematopoietic stem cell (HSC). In some alternatives, the cell is a $CD34^+$ HSC. In some alternatives of the system, the nuclease is a TALEN nuclease. In some alternatives of the system, the nuclease is a Cas nuclease. In some alternatives of the system, the vector and nucleic acid are configured for co-delivery to the cell. In some alternatives of the system, co-delivery to the cell modifies endogenous *WAS* locus. In some alternatives of the system, the cell is a primary human hematopoietic cell.

[0155] In some alternatives, a cell for expressing a WASp is provided, the cell comprising: a nucleic acid, which comprises: a first sequence encoding a WAS gene; a second sequence encoding a promoter; a third sequence encoding one or more guide RNA cleavage sites; and a fourth sequence encoding one or more nuclease binding sites. In some alternatives, the nucleic acid is in a vector. In some alternatives, the vector are an AAV. In some alternatives, the AAV are a scAAV. In some alternatives, the cell are a human cell. In some alternatives, the cell are a primary cell. In some alternatives, the cell are an autologous cell. In some alternatives, the cell are a T cell. In some alternatives, the cell are a HSC. In some alternatives, the cell are a $CD34^+$ HSC.

[0156] In some alternatives, a method of promoting HDR of a WAS gene in a subject in need thereof is provided, the method comprising: administering to a subject the cell of any one of alternatives provided herein or a vector of any one of the alternatives provided herein, and administering to the subject a nuclease. In some alternatives, the nuclease is a TALEN nuclease. In some alternatives, the nuclease is a Cas nuclease. In some alternatives, the nuclease is co-administered to the subject with the cell or with the vector. In some alternatives, the cell is from the subject and, wherein the cell is genetically modified by introducing the nucleic acid of any one of alternatives of any one of the alternatives herein or the vector of any one of the alternatives herein into the cell. In some alternatives, the administering is performed by adoptive cell transfer. In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a HSC. In some alternatives, the cell is a $CD34^+$ HSC. In some alternatives, the subject is male. In some alternatives, the subject is suffering from Wiskott-Aldrich syndrome (WAS). In some alternatives, the subject is suffering from X-linked thrombocytopenia (XLT).

[0157] In some alternatives, a method of treating, inhibiting, or ameliorating WAS and/or XLT or disease symptoms associated with WAS and/or XLT in a subject in need thereof is provided, the method comprising: administering to a subject the cell of any one of the alternatives herein or a vector of any one of the alternatives herein; administering to the subject a nuclease; and optionally identifying the subject as one that would benefit from receiving a therapy for WAS and/or XLT or disease symptoms associated with WAS and/or XLT and/or, optionally measuring an improvement in the progression of WAS and/or XLT or an improvement in a disease symptom associated with WAS and/or XLT in said subject. In some alternatives, the nuclease is a TALEN nuclease. In some alternatives, the nuclease is a CRISPR/Cas nuclease. In some alternatives, the nuclease is co-administered to the subject with the cell or with the vector. In some alternatives, the cell is from the subject, wherein the cell is genetically modified by introducing the nucleic acid of any one of alternatives 1-8 or the vector of any one of the alternatives herein into the cell. In some alternatives, the administering is performed by adoptive cell transfer. In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a HSC. In some alternatives, the cell is a $CD34^+$ HSC. In some alternatives, the subject is male. In some alternatives, the method improves thrombocytopenia. In some alternatives, the method increases platelet counts.

[0158] In some alternatives, a nucleic acid for homology directed repair (HDR) of Wiskott-Aldrich Syndrome (WAS) gene is provided, the nucleic acid comprising: a first sequence encoding a WAS gene, a second sequence encoding one or more guide RNA cleavage sites; and a third sequence encoding one or more nuclease binding sites. In some alternatives, the one or more nuclease binding sites comprises a forward and reverse transcription activator-like effector nuclease (TALEN) binding site. In some alternatives, the one or more nucleic binding sites is a clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) binding site. In some alternatives, the nucleic acid further comprises one or more enhancer elements. n some alternatives, the nucleic acid further compriseshomology arm sequences. n some alternatives, the nucleic acid further comprisesa nucleic acid sequence encoding a promoter.

[0159] In some alternatives, a vector for promoting HDR of WAS protein (WASp) expression in a cell is provided, the vector comprising a first sequence encoding a WAS gene, a second sequence encoding one or more guide RNA cleavage sites; and a third sequence encoding one or more nuclease binding sites. In some alternatives, the one or more nuclease binding sites comprises a forward and reverse transcription activator-like effector nuclease (TALEN) binding site. In some alternatives, the one or more nucleic binding sites is a clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) binding site. In some alternatives, the vector further comprises one or more enhancer elements. In some alternatives, the vector is an adeno-associated viral vector (AAV). In some alternatives, the vector is a self-complementary AAV (scAAV). In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a hematopoietic stem cell (HSC). In some alternatives, the cell is a CD34+ HSC.

[0160] IN some alternatives, a system for promoting HDR of WAS protein (WASp) expression in a cell is provided, the system comprising a vector of any one of the alternatives herein and a nucleic acid encoding a nuclease. In some alternatives, the nuclease is a TALEN nuclease. In some alternatives, the nuclease is a Cas nuclease. In some alternatives, the vector and nucleic acid are configured for co-delivery to the cell. In some alternatives, co-delivery to the cell modifies endogenous WAS locus. In some alternatives, the cell is a primary human hematopoietic cell.

[0161] In some alternatives, a cell for expressing a WASp is provided, the cell comprising: a nucleic acid, which comprises a first sequence encoding a WAS gene, a second sequence encoding a promoter, a third sequence encoding one or more guide RNA cleavage sites; and a fourth sequence encoding one or more nuclease binding sites. In some alternatives, the nucleic acid is in a vector. In some alternatives, the vector is an AAV. In some alternatives, the AAV is a scAAV. In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a HSC. In some alternatives, the cell is a CD34+ HSC.

[0162] In some alternatives a method of promoting HDR of a WAS gene in a subject in need thereof, the method comprising: administering to a subject the cell or a vector of any one of the alternatives herein; and administering to the subject a nuclease. In some alternatives, the nuclease is a TALEN nuclease. In some alternatives, the nuclease is a Cas nuclease. In some alternatives, the nuclease is co-administered to the subject with the cell or with the vector. In some alternatives, the cell is from the subject and, wherein the cell is genetically modified by introducing the nucleic acid or the vector of any one of the alternatives herein into the cell. In some alternatives, the administering is performed by adoptive cell transfer. In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a HSC. In some alternatives, the cell is a CD34+ HSC. In some alternatives, the subject is male. In some alternatives, the subject is suffering from Wiskott-Aldrich syndrome (WAS). In some alternatives, the subject is suffering from X-linked thrombocytopenia (XLT).

[0163] In some alternatives, a method of treating, inhibiting, or ameliorating WAS and/or XLT or disease symptoms associated with WAS and/or XLT in a subject in need thereof is provided, the method comprising: administering to a subject the cell or a vector of any one of the alternatives herein, administering to the subject a nuclease; and optionally identifying the subject as one that would benefit from receiving a therapy for WAS and/or XLT or disease symptoms associated with WAS and/or XLT and/or, optionally measuring an improvement in the progression of WAS and/or XLT or an improvement in a disease symptom associated with WAS and/or XLT in said subject. In some alternatives, the nuclease is a TALEN nuclease. In some alternatives, the nuclease is a CRISPR/Cas nuclease. In some alternatives, the nuclease is co-administered to the subject with the cell or with the vector. In some alternatives, the cell is from the subject, wherein the cell is genetically modified by introducing the nucleic acid or the vector of any one of the alternatives into the cell. In some alternatives, the administering is performed by adoptive cell transfer. In some alternatives, the cell is a human cell. In some alternatives, the cell is a primary cell. In some alternatives, the cell is an autologous cell. In some alternatives, the cell is a T cell. In some alternatives, the cell is a HSC. In some alternatives, the cell is a CD34+ HSC. In some alternatives, the subject is male. In some alternatives, the method improves thrombocytopenia. In some alternatives, the method increases platelet counts.

[0164] It is to be understood that the description, specific examples and data, while indicating exemplary alternatives, are given by way of illustration and are not intended to limit the various alternatives of the present disclosure. Various changes and modifications within the present disclosure will become apparent to the skilled artisan from the description and data contained herein, and thus are considered part of the various alternatives of this disclosure.

[0165] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as, an acknowledgement or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

APPENDIX I

Sequence Identification Numbers, Identifying Descriptions, and Sequences

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<u>SEQ ID NO: 2 WAS TALEN reverse</u>
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<u>SEQ ID NO: 4 *WAS* gene sequence</u>
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SEQ ID NO: 10 Sequence of Full chemically modified guide #1
5' 2'OMe(G(ps)G(ps)U(ps)) AUG UUC UGC UGA ACC GCG UUU UAG AGC UAG AAA UAG CAA GUU AAA AUA AGG CUA GUC CGU UAU CAA CUU GAA AAA GUG GCA CCG AGU CGG UGC 2'OMe(U(ps)U(ps)U(ps)) U 3'

SEQ ID NO: 11 Upstream homology arm (common in #1201, #1262 and #1244)
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AC

SEQ ID NO: 12 Downstream homology arm for #1201
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SEQ ID NO: 13 Downstream homology arm #1244
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SEQ ID NO: 14 Downstream homology arm #1262
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ATATTCCATTGATCCTTGAACTCCAAATCTGTCCTTCTAAATCCACAGCACAGAC
CCCAGAGTTCCCA

SEQ ID NO: 15 WAS TALEN binding site on the genome (forward-TALEN)
CTCCTAGAATTTCCCGT

SEQ ID NO: 16 WAS TALEN binding site on the genome (reverse-TALEN)
AGGAAGATCTCAATGTCT

SEQ ID NO: 17 TALEN cleavage site (spacer sequence)
CATAATCCACCCTTCCC

SEQ ID NO: 18 WAS exon 2
ACGCTGGCCACTGCAGTTGTTCAGCTGTACCTGGCGCTGCCCCCTGGAGCTGAGC
ACTGGACCAAGGAGCATTGTGGGGCTGTGTGCTTCGTGAAGGATAACCCCCAGA
AGTCCTACTTCATCCGCCTTTACGGCCTTCAG

SEQ ID NO: 19 WAS exon 1 sequence

TCCTCTTCTTACCCTGCACCCAGAGCCTCGCCAGAGAAGACAAGGGCAGAAAGC
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SEQ ID NO: 20 pWNY.2xNLS.Cas9.mCherry
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SEQ ID NO: 21 1190 scAAV.U6.guideRNA2
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<u>SEQ ID NO: 25 WAS TALEN #2 Reverse</u>

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SEQ ID NO: 27 WAS TALEN#1forward RVD sequence

HD NG HD HD NG NI NN NI NI NG NG NG HD HD HD NN NG
| | | | | | | | | | | | | | | | |
C T C C T A G A A T T T C C C G T

SEQ ID NO: 28 WAS TALEN#1 reverse RVD sequence

NI NN NI HD NI NG NG NN NI NN NI NG HD NG NG HD HD NG
| | | | | | | | | | | | | | | | | I
A G A C A T T G A G A T C T T C C T

SEQ ID NO: 29 WAS TALEN#2 forward RVD sequence

HD NG NN NN HD NG NN HD NI NN HD NG HD NG NG HD HD NG
| | | | | | | | | | | | | | | | | I
C T G G C T G C A G C T C T T C C T

SEQ ID NO: 30 WAS TALEN#2 reverse RVD sequence

NN NN NG HD HD NG NG HD HD NG NN HD HD NG HD NI NG
| | | | | | | | | | | | | | | | |
G G T C C T T C C T G C C T C A T

SEQ ID NO: 31 WAS GUIDE#1 sequence

GGTATGTTCTGCTGAACCGC

SEQ ID NO: 32 WAS GUIDE#2 sequence

CAAAGAGTCGCTGGTTCTCG

SEQ ID NO: 33 WAS GUIDE#3 sequence

CAAGCATCTCAAAGAGTCGC

SEQ ID NO: .34 WAS GUIDE#4 sequence

ACCATGAGTGGGGGCCCAAT

SEQ ID NO: 35 pAAV.DT (#1201)
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SEQ ID NO: 36 pAAV.DT-M (#1244)

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SEQ ID NO: 37 pAAV.DT-D (#1262)

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SEQ ID NO: 39 pAAV.DTG(#1215)

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SEQ ID NO: 40 pAAV.ATG.GFP (#1374)

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SEQ ID NO: 41 pAAV.ATG.coWAS (#1380)

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CTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGC
CCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCCAGCTGGCGTAA
TAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGG
CGAATGGCGATTCCGTTGCAATGGCTGGCGGTAATATTGTTCTGGATATTACCAG
CAAGGCCGATAGTTTGAGTTCTTCTACTCAGGCAAGTGATGTTATTACTAATCAA
AGAAGTATTGCGACAACGGTTAATTTGCGTGATGGACAGACTCTTTTACTCGGTG
GCCTCACTGATTATAAAAACACTTCTCAGGATTCTGGCGTACCGTTCCTGTCTAA
AATCCCTTTAATCGGCCTCCTGTTTAGCTCCCGCTCTGATTCTAACGAGGAAAGC
ACGTTATACGTGCTCGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTA
AGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCC
CTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTT
CCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTAC
GGCACCTCGACCCCAAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCCAT
CGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGT
GGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGTCTATTCTTTTGA
TTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAA
CAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTTACAATTTAAATATTTG
CTTATACAATCTTCCTGTTTTTGGGGCTTTTCTGATTATCAACCGGGGTACATATG
ATTGACATGCTAGTTTTACGATTACCGTTCATCGATTCTCTTGTTTGCTCCAGACT
CTCAGGCAATGACCTGATAGCCTTTGTAGAGACCTCTCAAAAATAGCTACCCTCT
CCGGCATGAATTTATCAGCTAGAACGGTTGAATATCATATTGATGGTGATTTGAC
TGTCTCCGGCCTTTCTCACCCGTTTGAATCTTTACCTACACATTACTCAGGCATTG
CATTTAAAATATATGAGGGTTCTAAAAATTTTTATCCTTGCGTTGAAATAAAGGC
TTCTCCCGCAAAAGTATTACAGGGTCATAATGTTTTTGGTACAACCGATTTAGCT
TTATGCTCTGAGGCTTTATTGCTTAATTTTGCTAATTCTTTGCCTTGCCTGTATGAT
TTATTGGATGTTGGAATCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGT
ATTTCACACCGCATATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGT
TAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCT
GCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGT
CAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATA
CGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTG
GCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACAT
TCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATT
GAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTT
TGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAA
GATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAAC
AGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCA

CTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGA
GCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCA
GTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCT
GCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGA
GGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGC
CTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGAC
ACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCGAA
CTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAA
GTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATA
AATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAG
ATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTAT
GGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTG
GTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCATT
TTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAAT
CCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAA
GGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAA
ACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTT
CCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGT
AGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGC
TCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACC
GGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACG
GGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGA
TACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCG
GACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCT
TCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGA
CTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAAC
GCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACAT
GTTCTTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGT
GAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCG
AGGAAGCGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGA
TTCATTAATG

The claims defining the invention are as follows:

1. A system for promoting homology directed repair (HDR) of a Wiskott-Aldrich Syndrome (WAS) gene in a cell, the system comprising:

(i) a vector comprising:

a first polynucleotide encoding a WAS gene or portion thereof;

a second polynucleotide encoding a guide RNA cleavage site or a transcription activator-like effector nuclease (TALEN) cleavage site, and

a third polynucleotide encoding a nuclease binding site;

(ii) a nuclease or a nucleic acid encoding the nuclease, wherein the nuclease is capable of cleaving a target locus in order to promote insertion of the first polynucleotide within a first coding exon of the WAS gene in the cell genome, wherein the nuclease is selected from a transcription activator-like effector nuclease (TALEN), or a Cas nuclease; and

(iii) a guide RNA (gRNA) comprising a nucleotide sequence selected from any one of SEQ ID NOs:31-34.

2. The system of claim 1, wherein the first polynucleotide is a WAS cDNA.

3. The system of claim 2, wherein the WAS cDNA comprises a nucleotide sequence selected from SEQ ID NO:18 or 19.

4. The system of any one of claims 1-3, wherein the first polynucleotide is operably linked to a promoter.

5. The system of any one of claims 1-4, wherein the second polynucleotide comprises homology arm comprising a WAS gene genomic sequence.

6. The system of any one of claims 1-5, wherein the vector is an adeno-associated viral vector (AAV).

7. The system of any one of claims 1-6, wherein the vector is a self-complementary AAV (scAAV).

8. The system of any one of claims 1-7, wherein the nuclease is a Cas nuclease.

9. The system of any one of claims 1-8, wherein the gRNA comprises the nucleotide sequence of SEQ ID NO: 31.

10. The system of any one of claims 1-9, wherein the vector and the nuclease or the nucleic acid encoding the nuclease are configured for co-delivery to a cell.

11. The system of any one of claims 1-10, further comprising a cell, wherein the cell comprises the vector, the nuclease or the nucleic acid encoding the nuclease, and the gRNA.

12. The system of claim 11, wherein the cell is a T cell or a hematopoietic stem cell (HSC).

13. An *in vitro* or *ex vivo* method of promoting homology directed repair (HDR) of a WAS gene in a cell, the method comprising introducing the system of any one of claim 1-10 into a cell to obtain a modified cell.

14. The method of claim 13, further comprising administering the modified cell to subject having WAS or X-linked thrombocytopenia (XLT).

15. A modified cell prepared by the method of claim 13.

16. A pharmaceutical composition comprising the modified cell of claim 15 and a pharmaceutically acceptable excipient.

17. Use of the modified cell of claim 15 in the manufacture of a medicament for treating, inhibiting, or ameliorating WAS or X-linked thrombocytopenia (XLT) in a subject.

18. A method of treating, inhibiting, or ameliorating WAS or X-linked thrombocytopenia (XLT) in a subject in need thereof, the method comprising administering the modified cell of claim 15 or the pharmaceutical composition of claim 16 to the subject.

19. The method of claim 14 or 18, wherein the administering is performed by adoptive cell transfer.

20. The method of any one of claims 14, 18 and 19, wherein the cell is autologous to the subject.

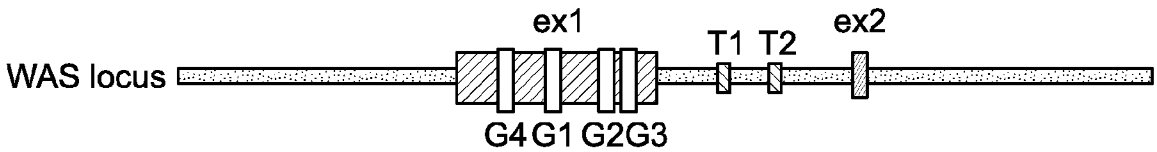


Figure 1A

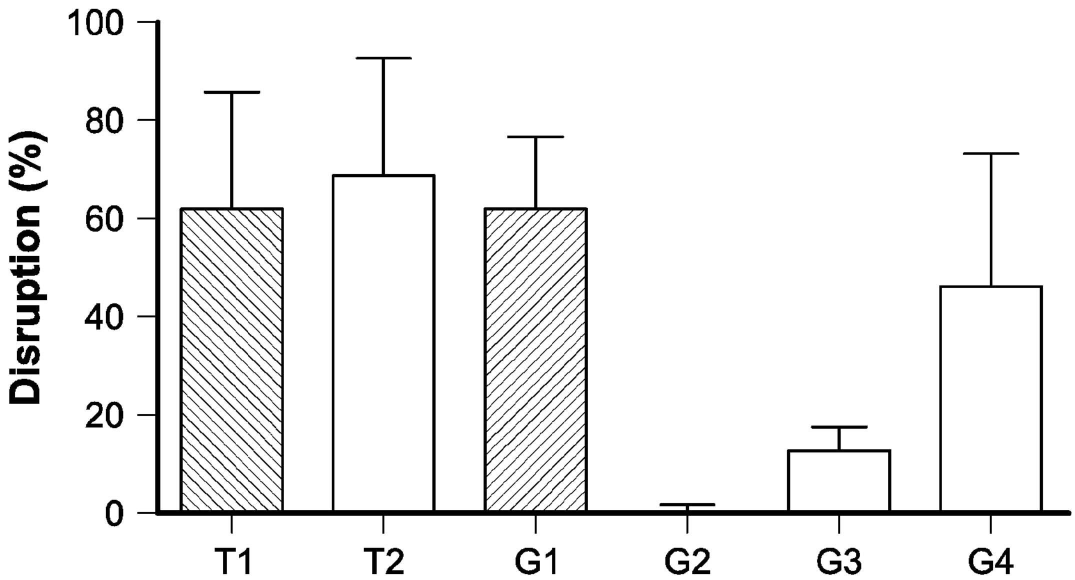


Figure 1B

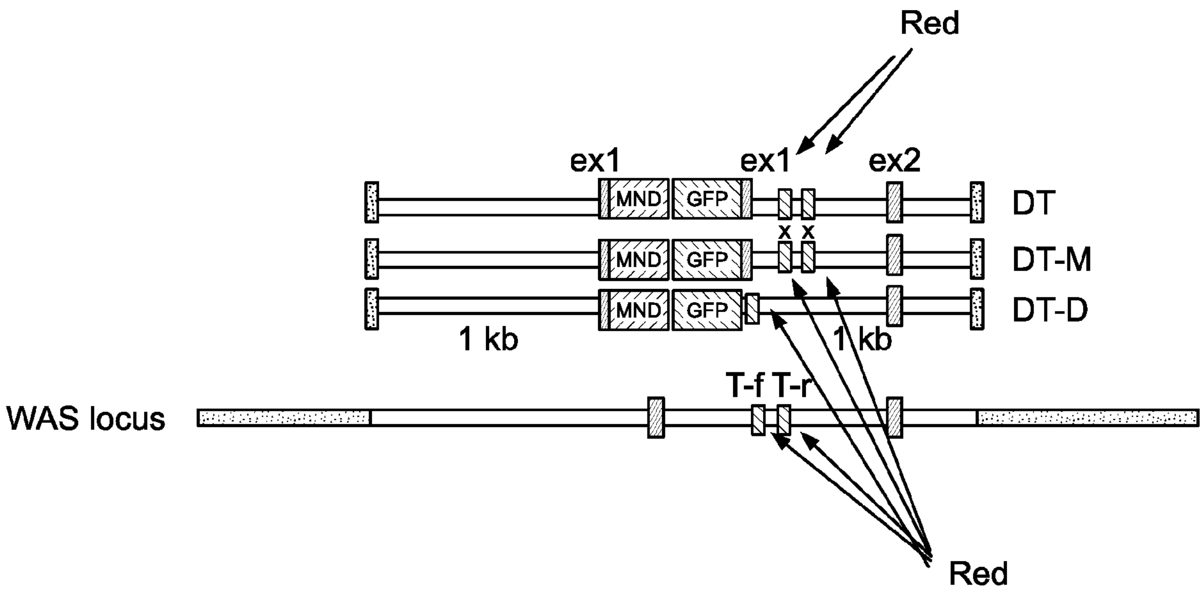


Figure 2A

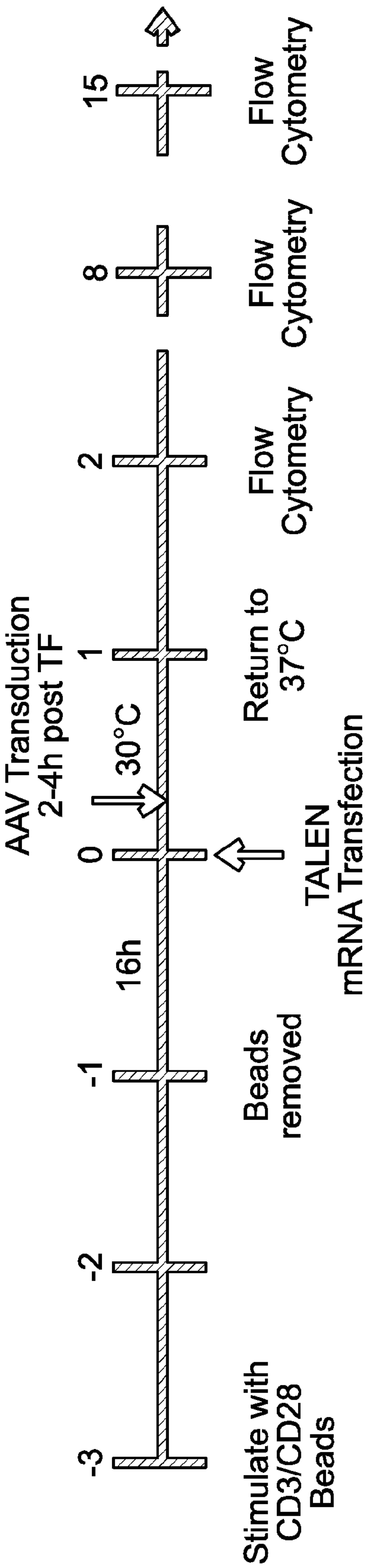

-3
-2
-1
0
1
2
8
15
16h
30°C
AAV Transduction
2-4h post TF
Stimulate with
CD3/CD28
Beads
Beads
removed
TALEN
mRNA Transfection
Return to
37°C
Flow
Cytometry
Flow
Cytometry
Flow
Cytometry

Figure 2B

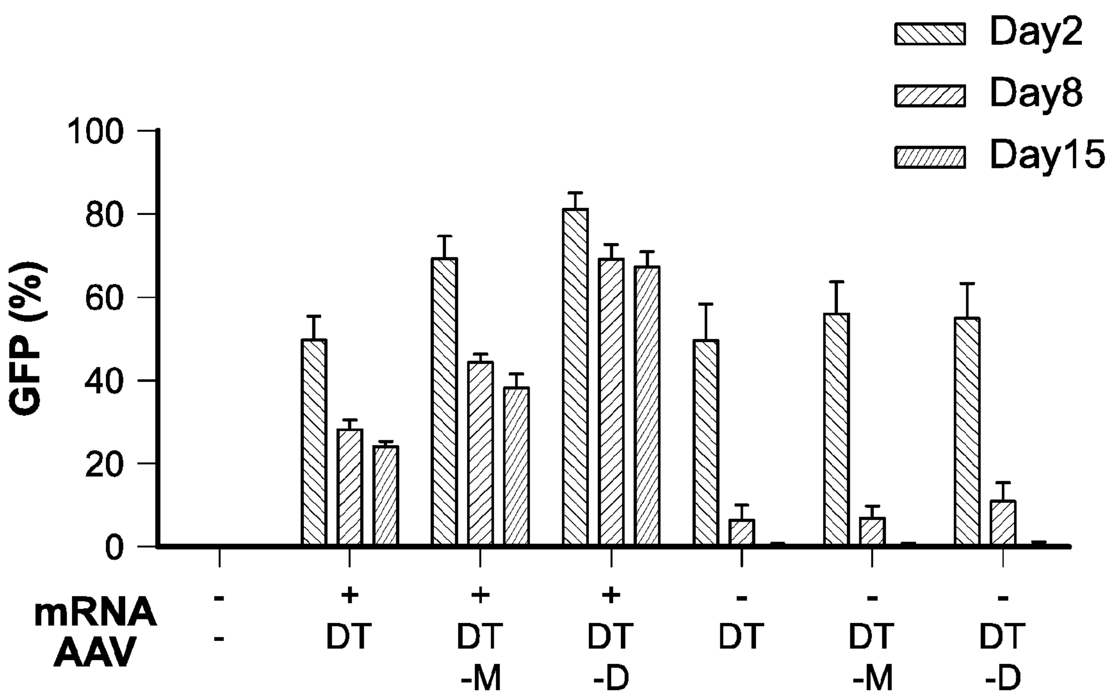

Day2
Day8
Day15
GFP (%)
100
80
60
40
20
0
mRNA
AAV
-
-
+
DT
+
DT
-M
+
DT
-D
-
DT
-
DT
-M
-
DT
-D

Figure 2C

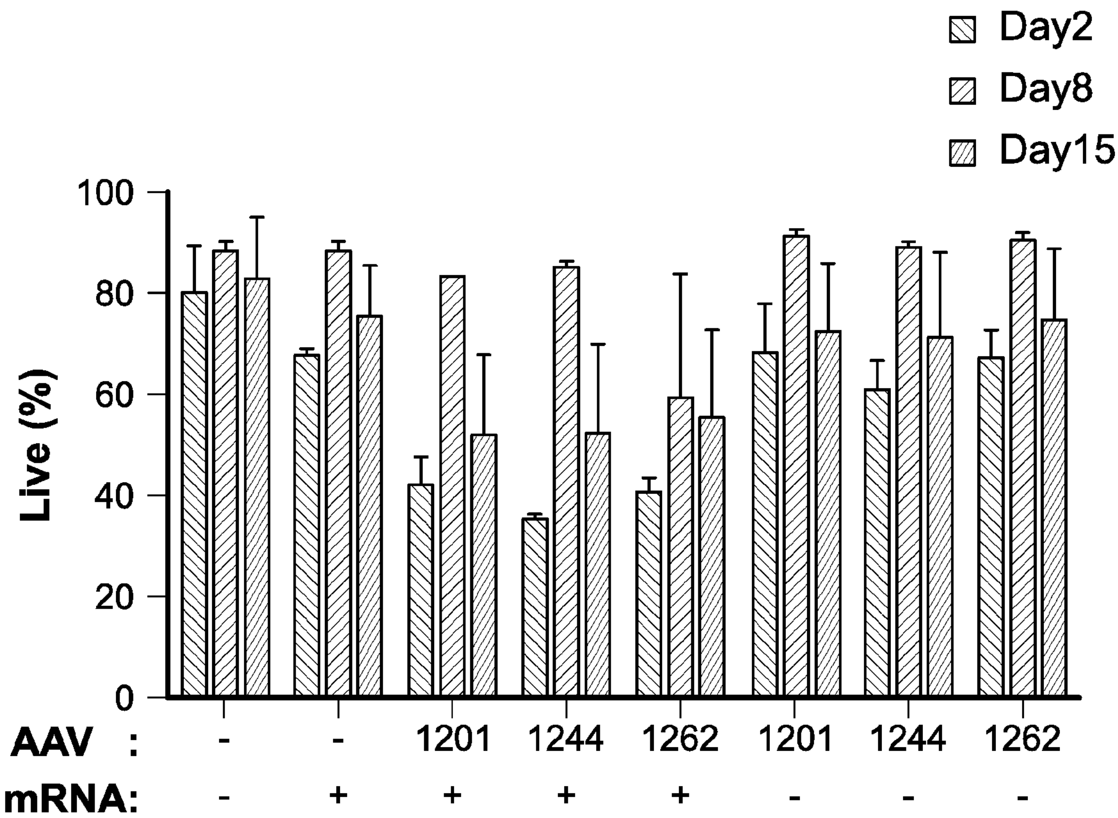

Day2
Day8
Day15
Live (%)
100
80
60
40
20
0
AAV :
-
-
1201
1244
1262
1201
1244
1262
mRNA:
-
+
+
+
+
-
-
-

Figure 2D

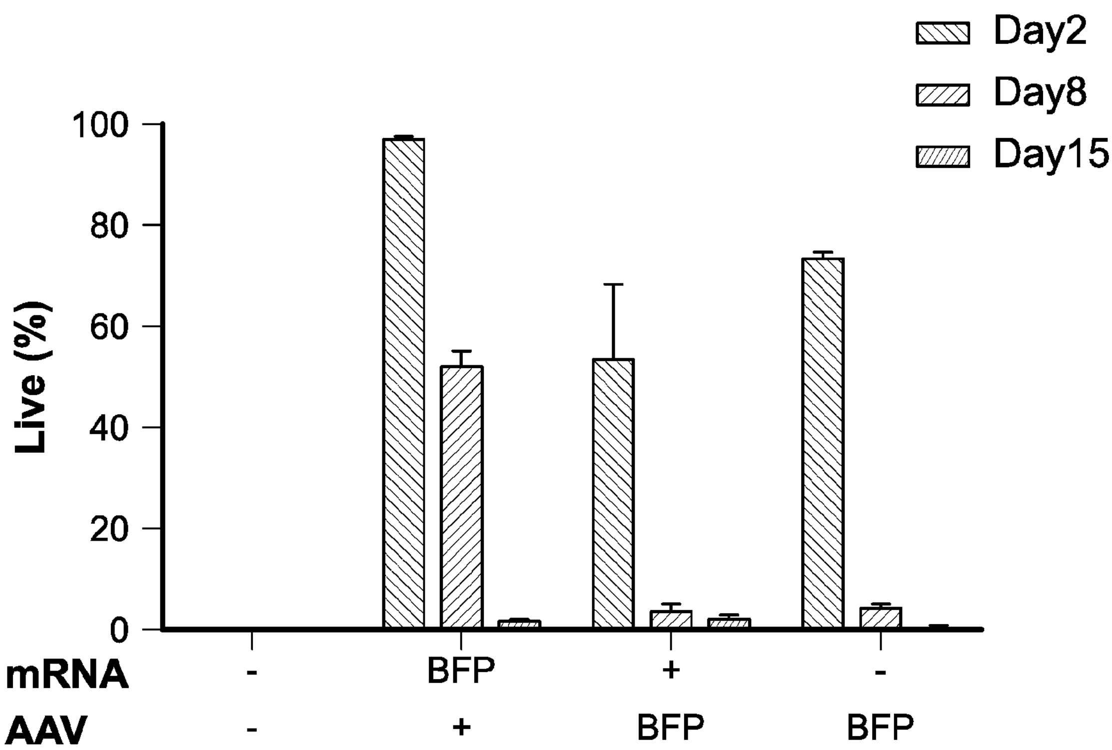


Figure 2E

8/49

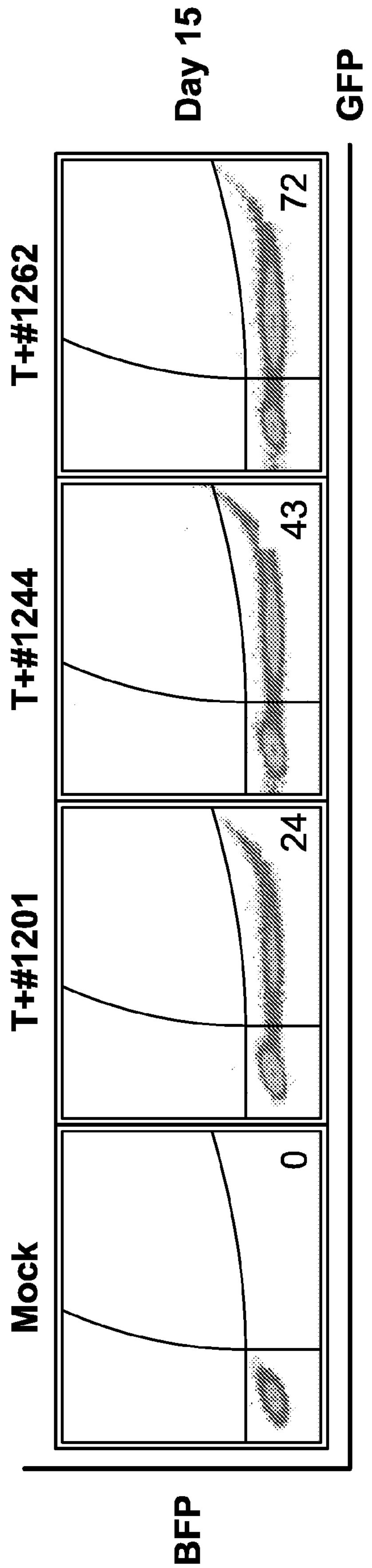


Figure 2F

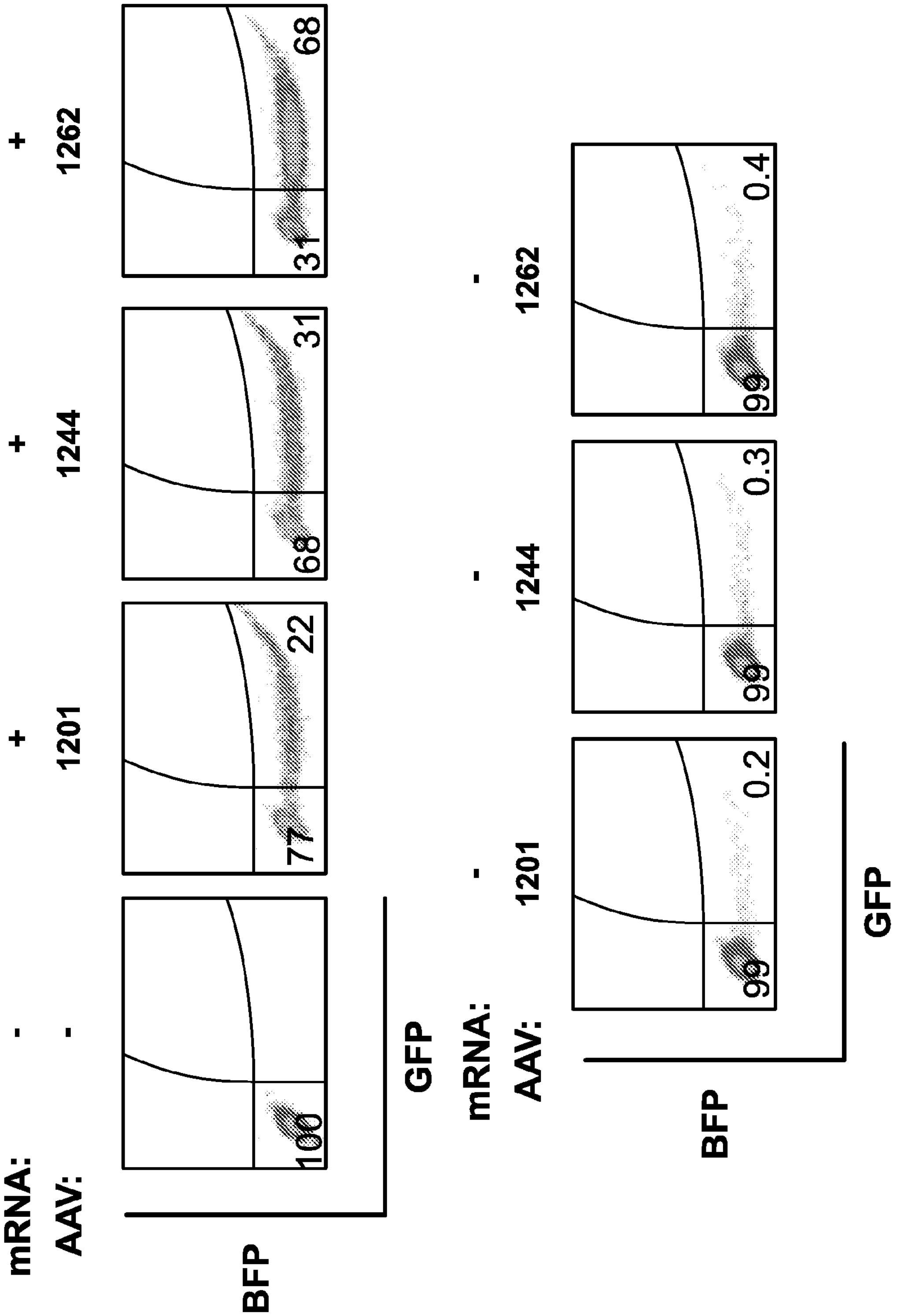

mRNA:
AAV:
-
-
+
1201
+
1244
+
1262
100
77
22
68
31
31
68
BFP
GFP
mRNA:
AAV:
-
1201
-
1244
-
1262
99
0.2
99
0.3
99
0.4
BFP
GFP

Figure 2G

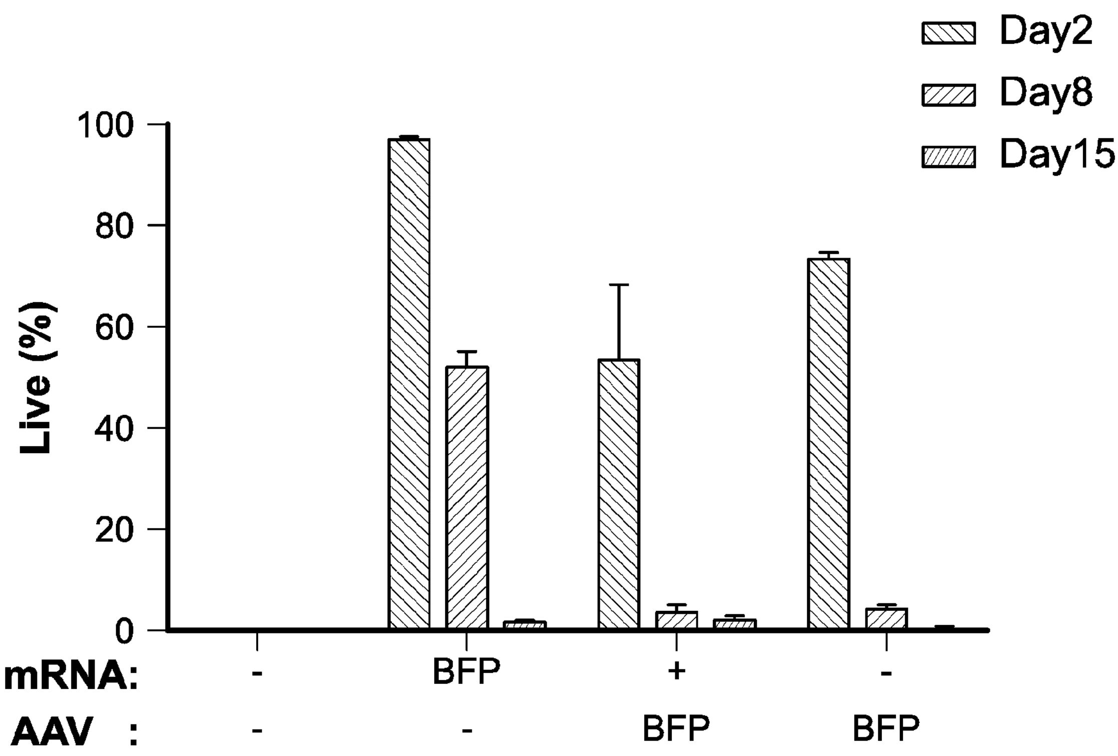


Figure 2H

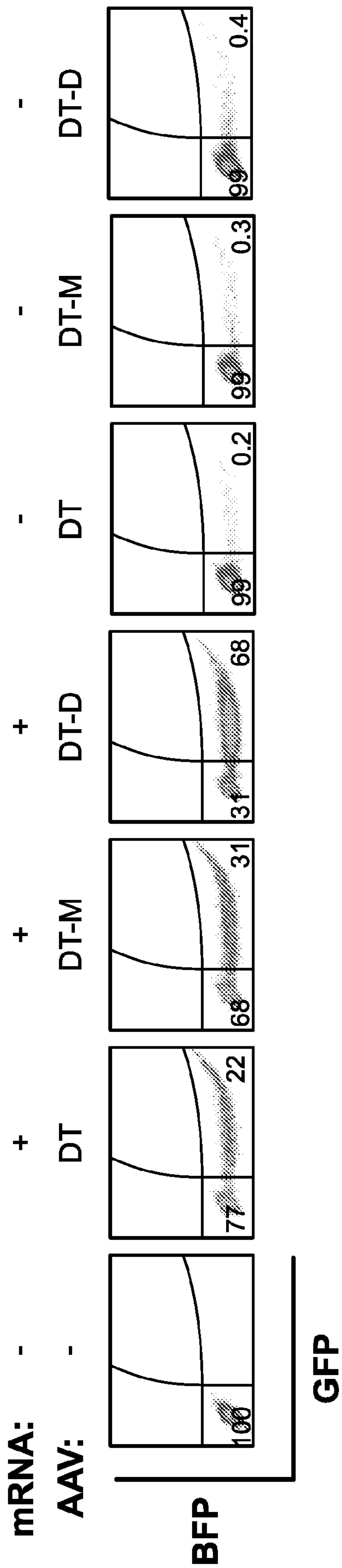

mRNA:
AAV:
-
-
+
DT
+
DT-M
+
DT-D
-
DT
-
DT-M
-
DT-D
100
77
22
68
31
31
68
99
0.2
99
0.3
99
0.4
BFP
GFP

Figure 2I

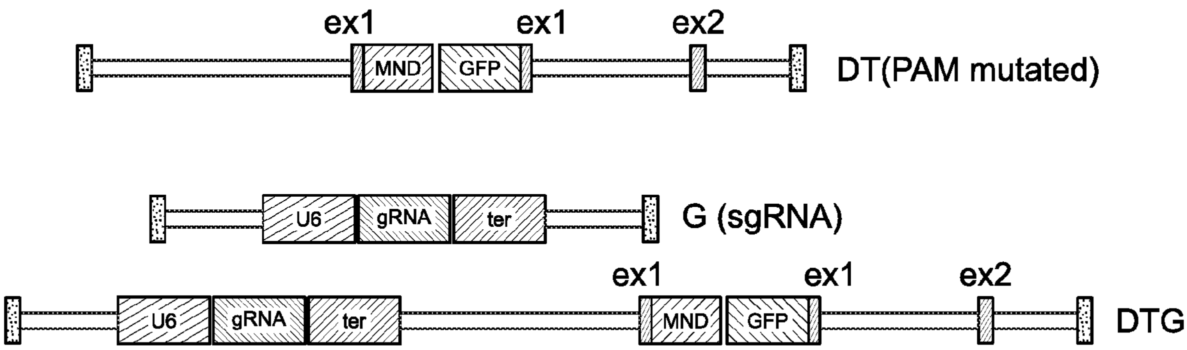

ex1
ex1
ex2
MND
GFP
DT(PAM mutated)
U6
gRNA
ter
G (sgRNA)
ex1
ex1
ex2
U6
gRNA
ter
MND
GFP
DTG

Figure 3A

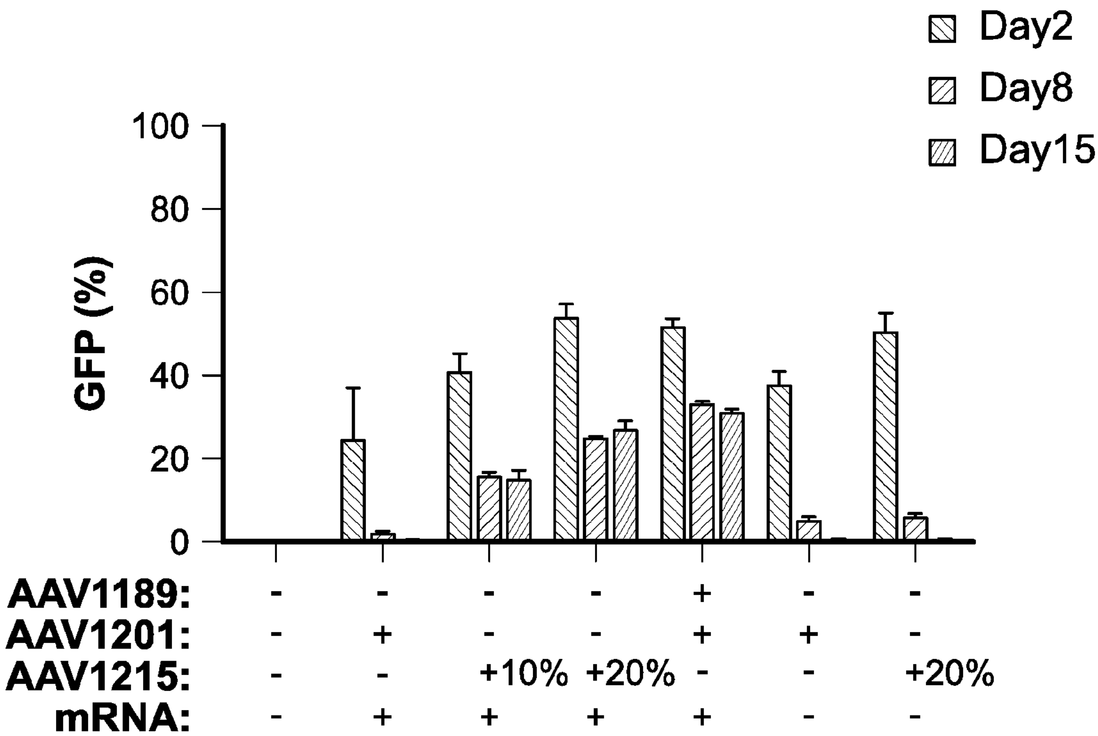

Day2
Day8
Day15
100
80
60
40
20
0
GFP (%)
AAV1189: - - - - + - -
AAV1201: - + - - + + -
AAV1215: - - +10% +20% - - +20%
mRNA: - + + + + - -

Figure 3B

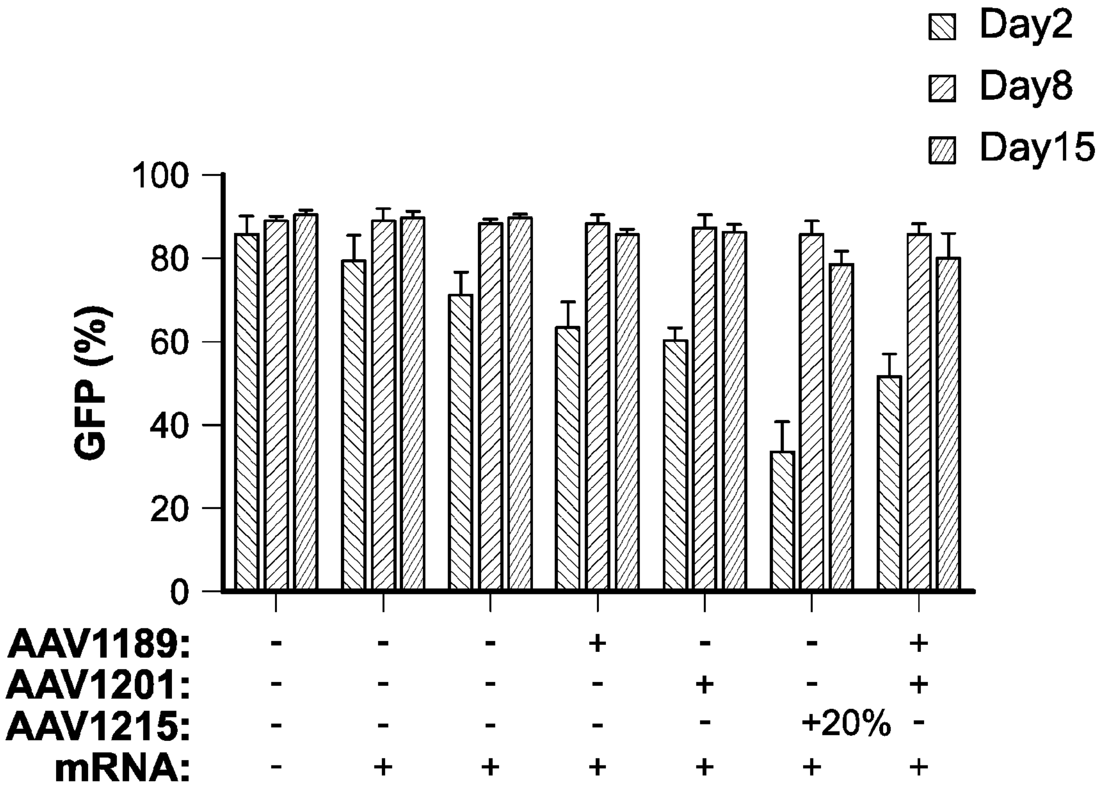

Day2
Day8
Day15
100
80
60
40
20
0
GFP (%)
AAV1189: - - - + - - +
AAV1201: - - - - + - +
AAV1215: - - - - - +20% -
mRNA: - + + + + + +

Figure 3C

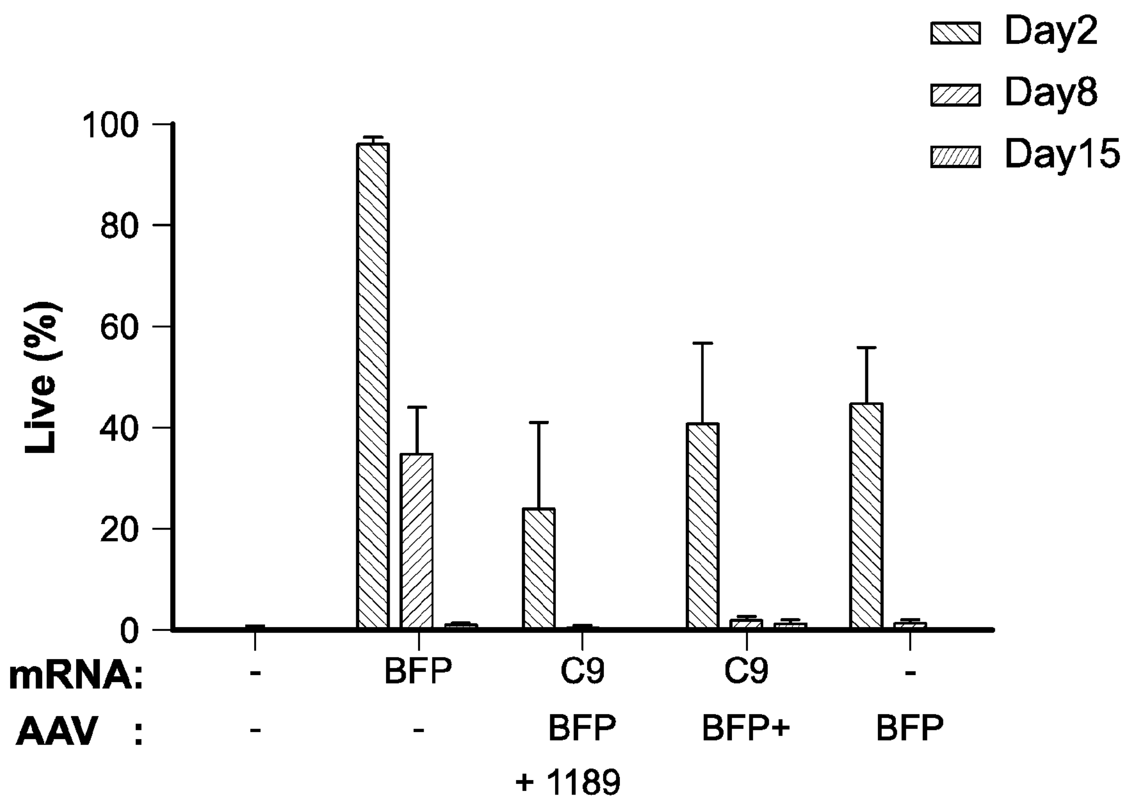

Day2
Day8
Day15
100
80
60
40
20
0
Live (%)
mRNA:
-
BFP
C9
C9
-
AAV :
-
-
BFP
BFP+
BFP
+ 1189

Figure 3D

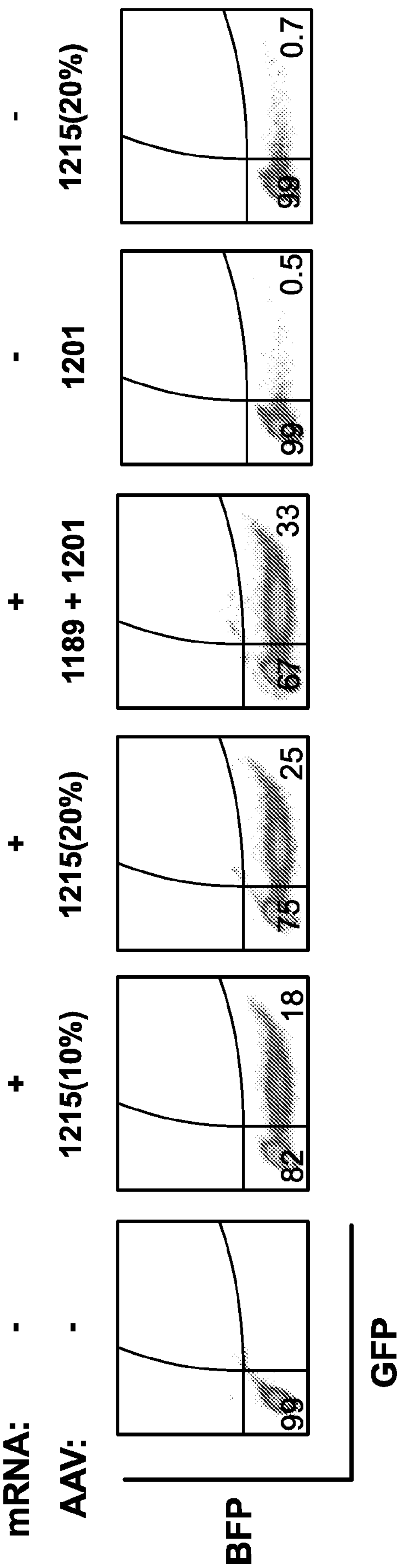

mRNA:
AAV:
-
-
+
1215(10%)
+
1215(20%)
+
1189 + 1201
-
1201
-
1215(20%)
99
82
18
75
25
67
33
99
0.5
99
0.7
BFP
GFP

Figure 3E

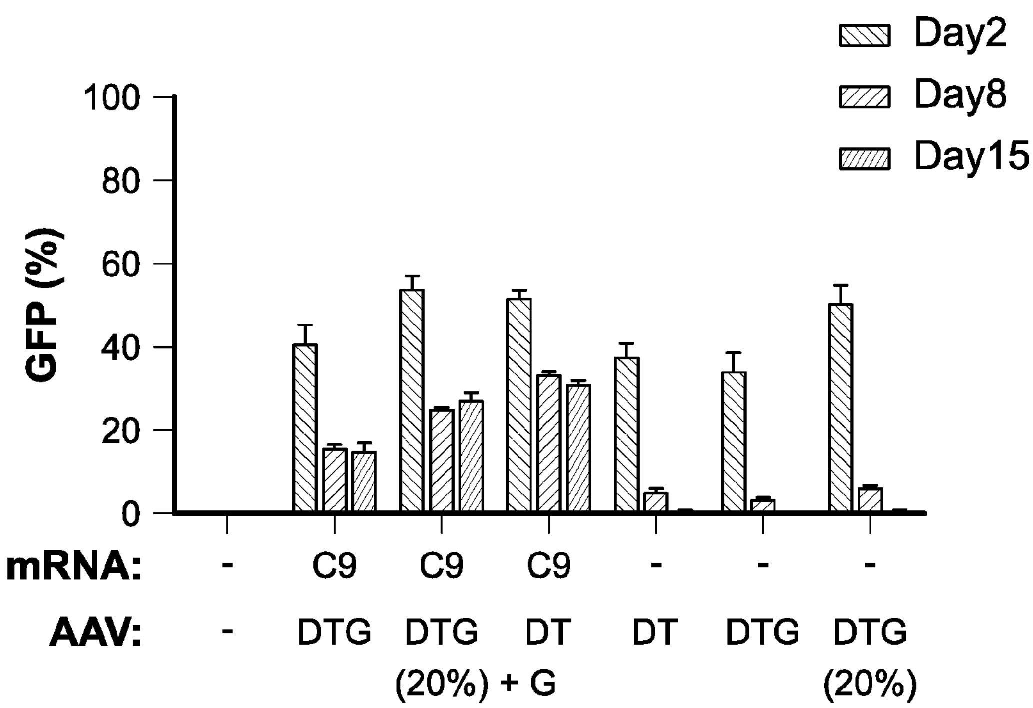

Day2
Day8
Day15
GFP (%)
100
80
60
40
20
0
mRNA:
-
C9
C9
C9
-
-
-
AAV:
-
DTG
DTG
(20%) + G
DT
DT
DTG
DTG
(20%)

Figure 3F

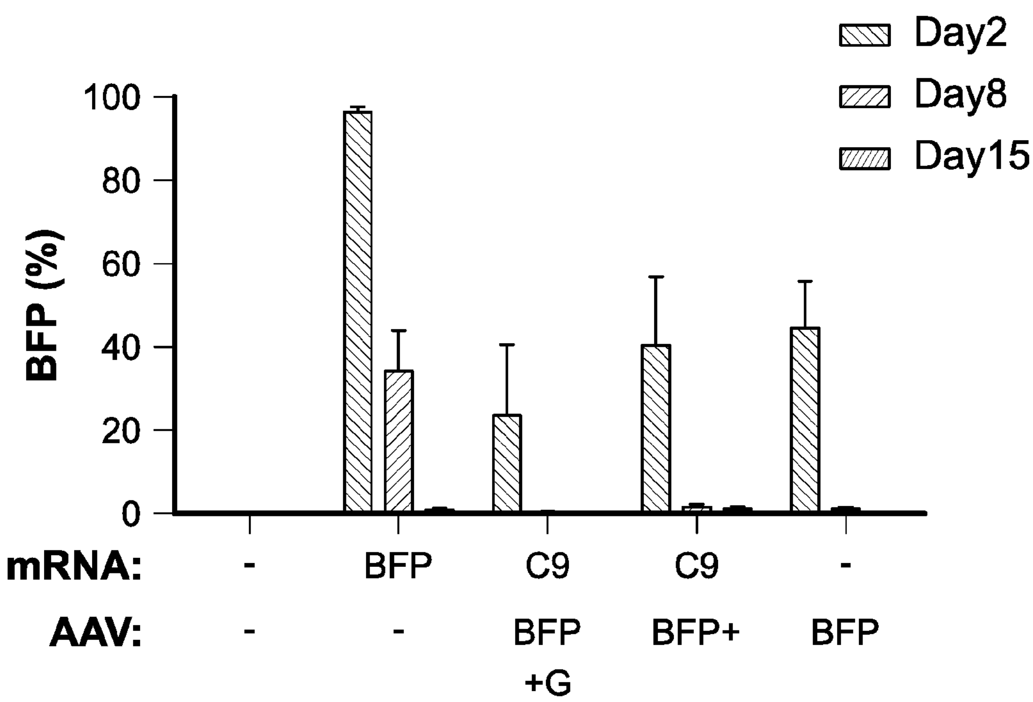

Day2
Day8
Day15
100
80
60
40
20
0
BFP (%)
mRNA:
-
BFP
C9
C9
-
AAV:
-
-
BFP
+G
BFP+
BFP

Figure 3G

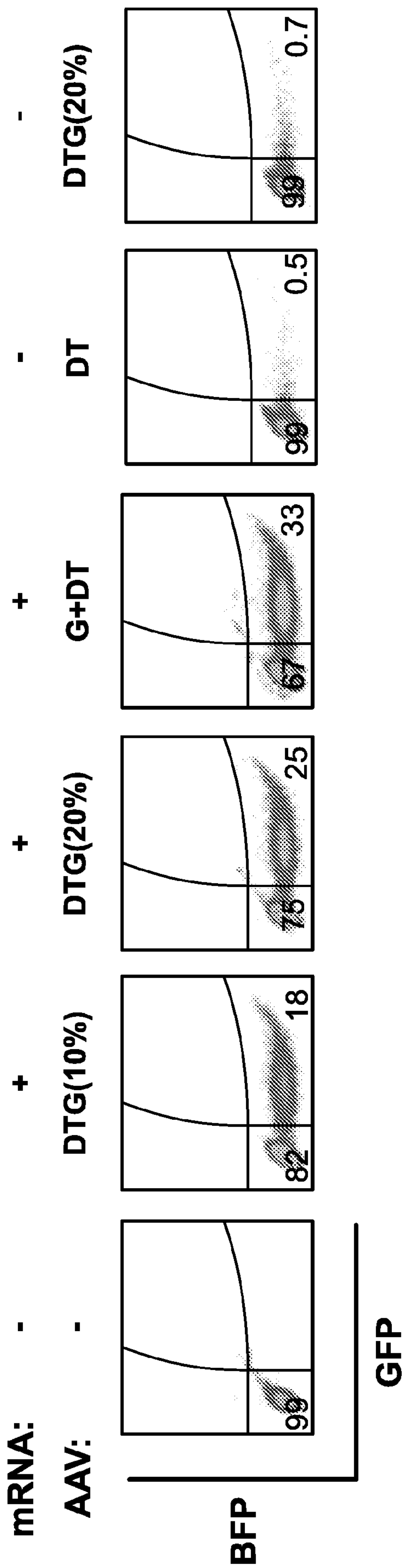

mRNA: - + + + - -
AAV: - DTG(10%) DTG(20%) G+DT DT DTG(20%)
99
82
18
75
25
67
33
99
0.5
99
0.7
BFP
GFP

Figure 3H

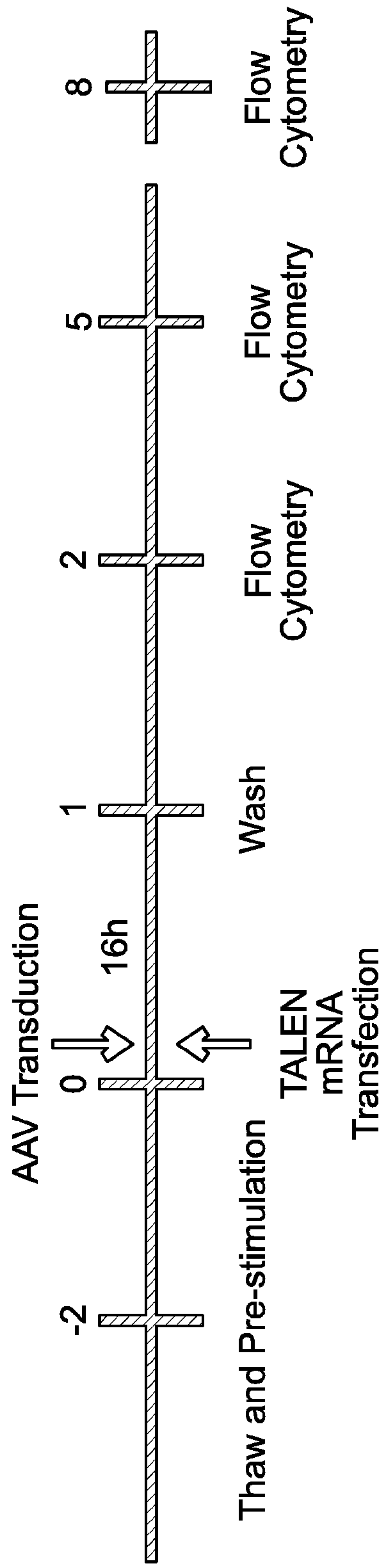

AAV Transduction
16h
-2
0
1
2
5
8
Thaw and Pre-stimulation
TALEN
mRNA
Transfection
Wash
Flow
Cytometry
Flow
Cytometry
Flow
Cytometry

Figure 4A

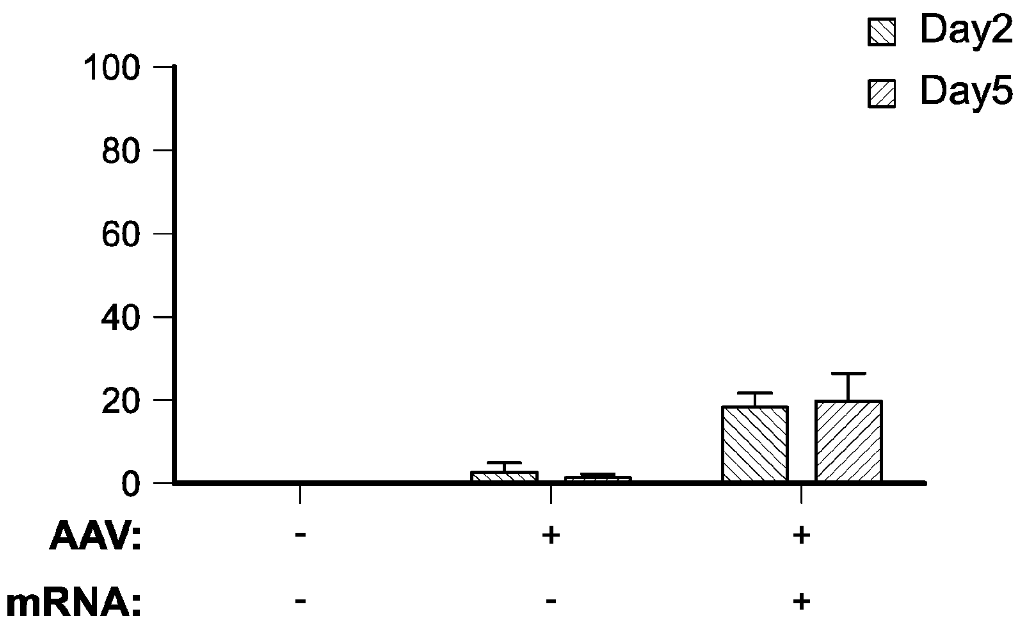


Figure 4B

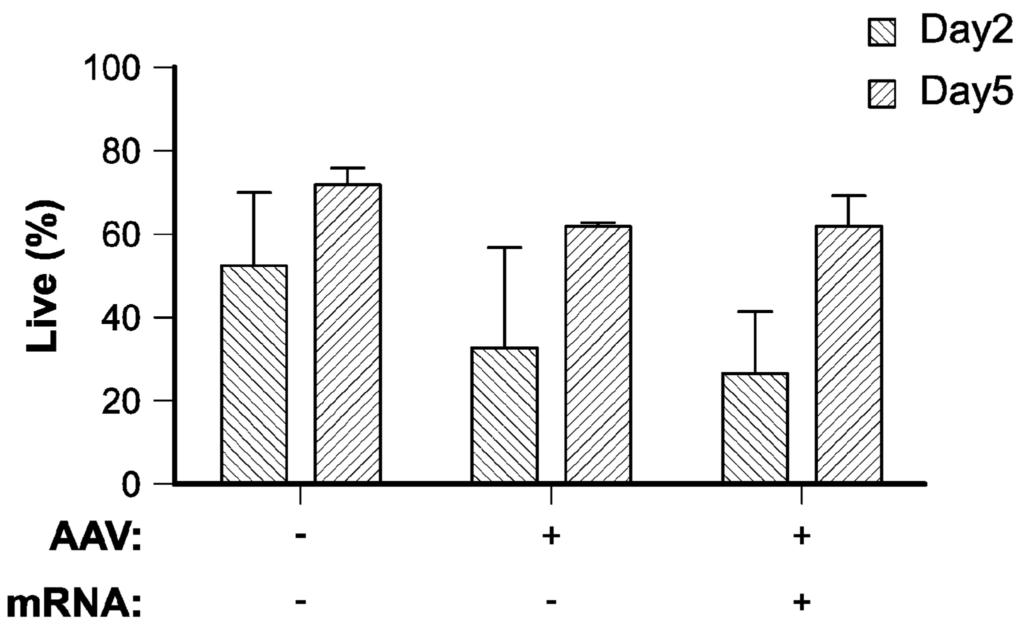


Figure 4C

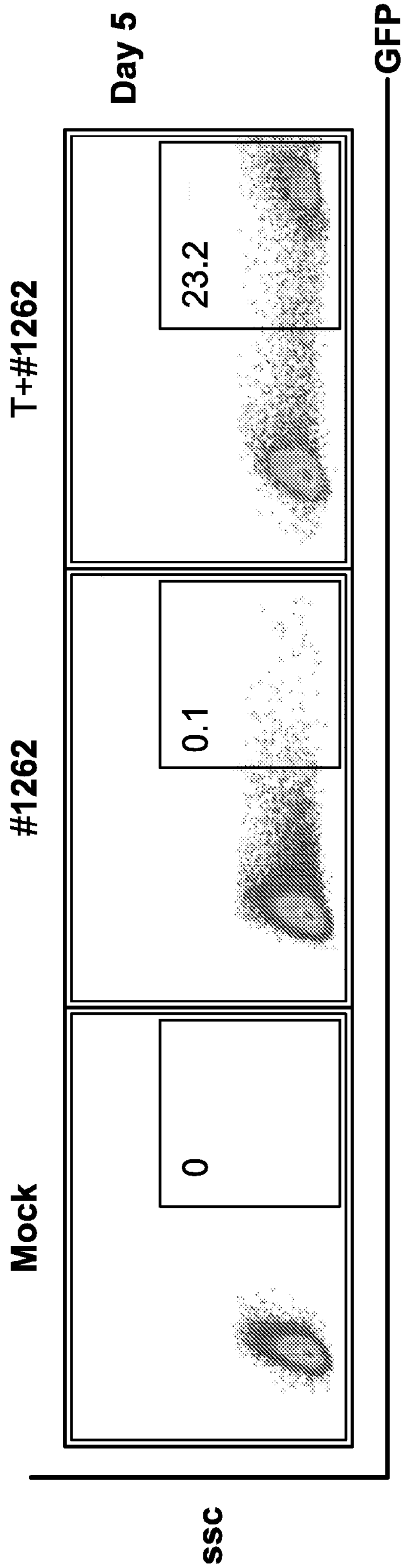


Figure 4D

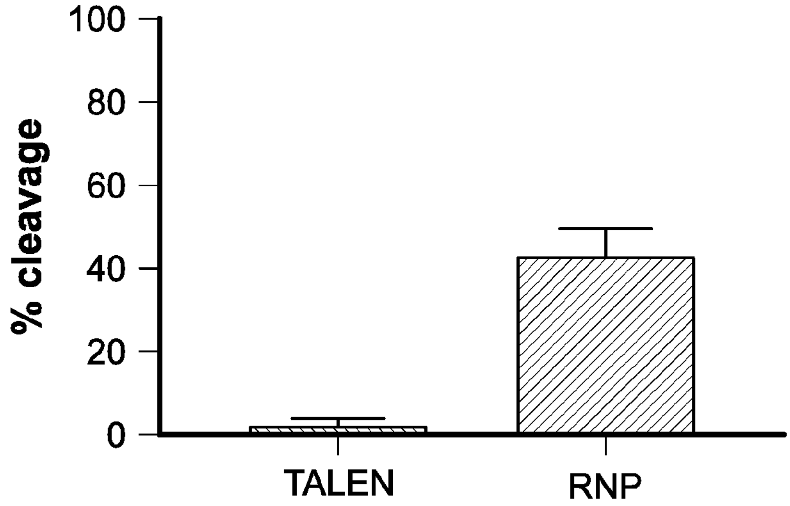


Figure 5A

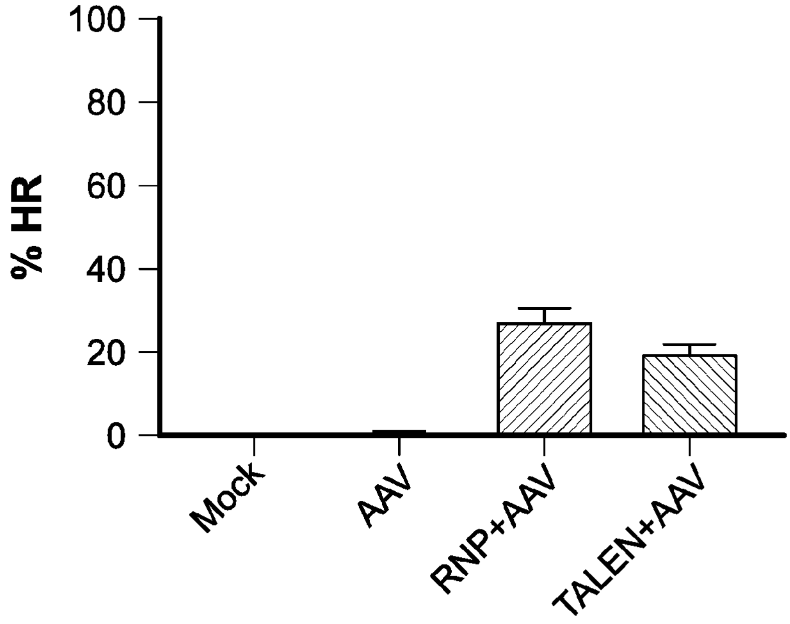


Figure 5B

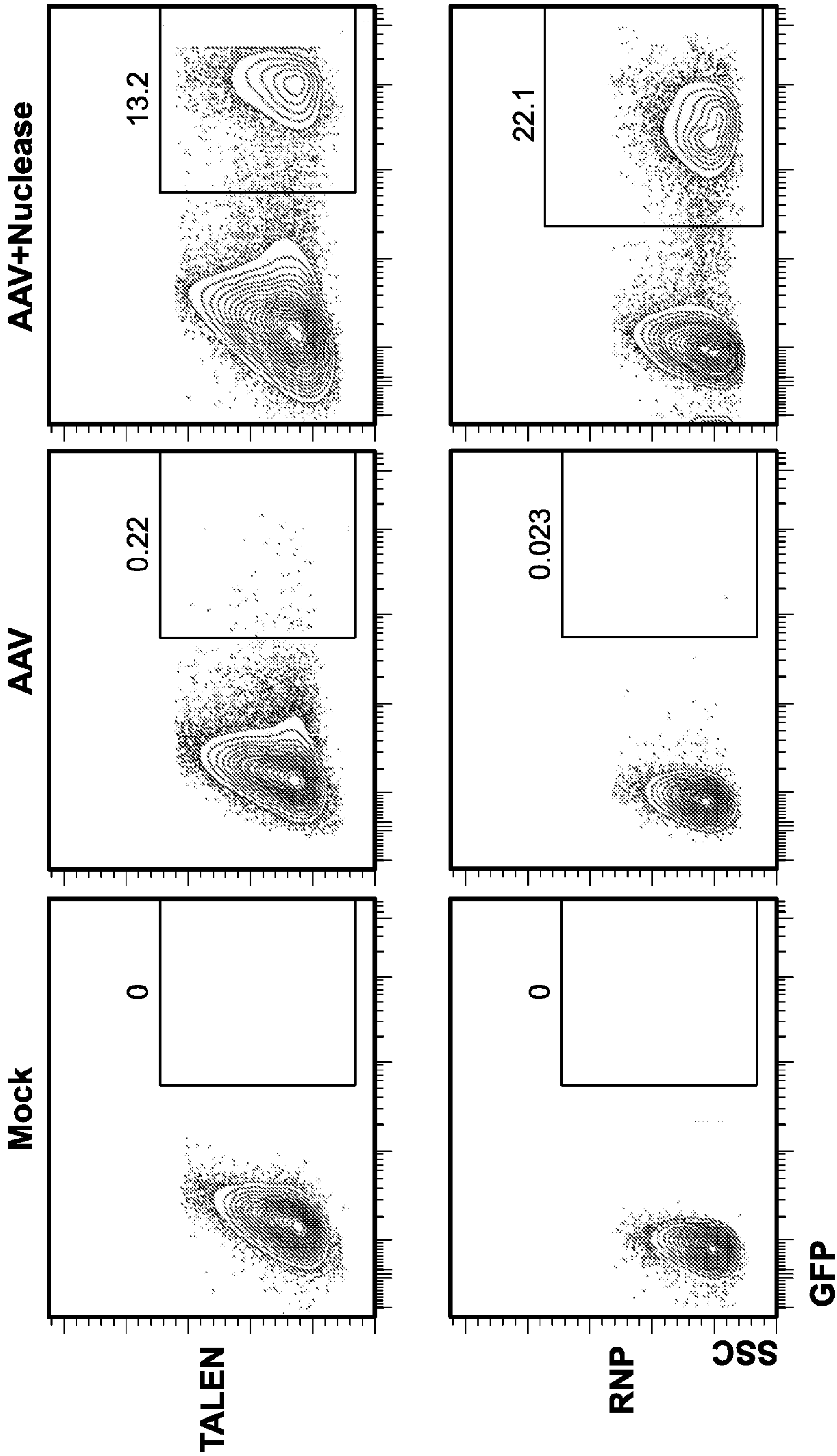


Figure 5C

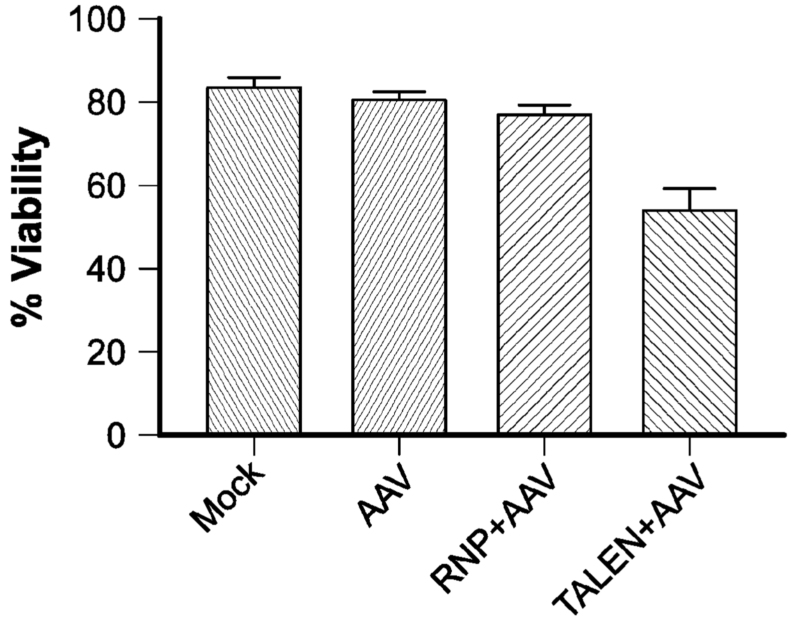


Figure 5D

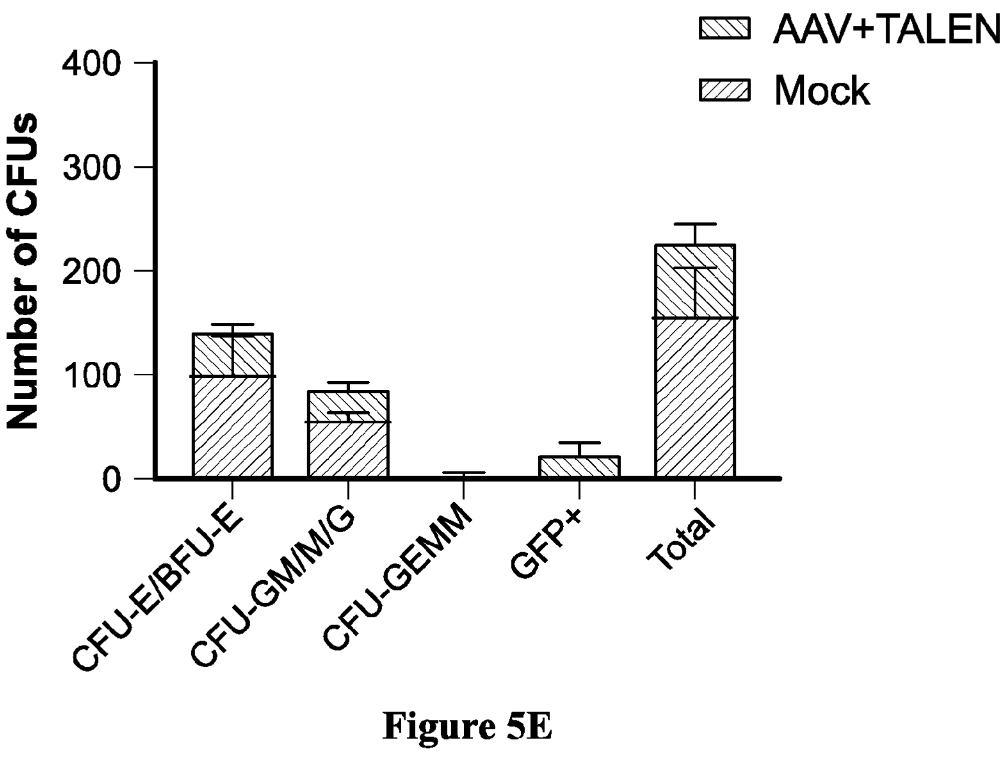

AAV+TALEN
Mock
Number of CFUs
400
300
200
100
0
CFU-E/BFU-E
CFU-GM/M/G
CFU-GEMM
GFP+
Total

Figure 5E

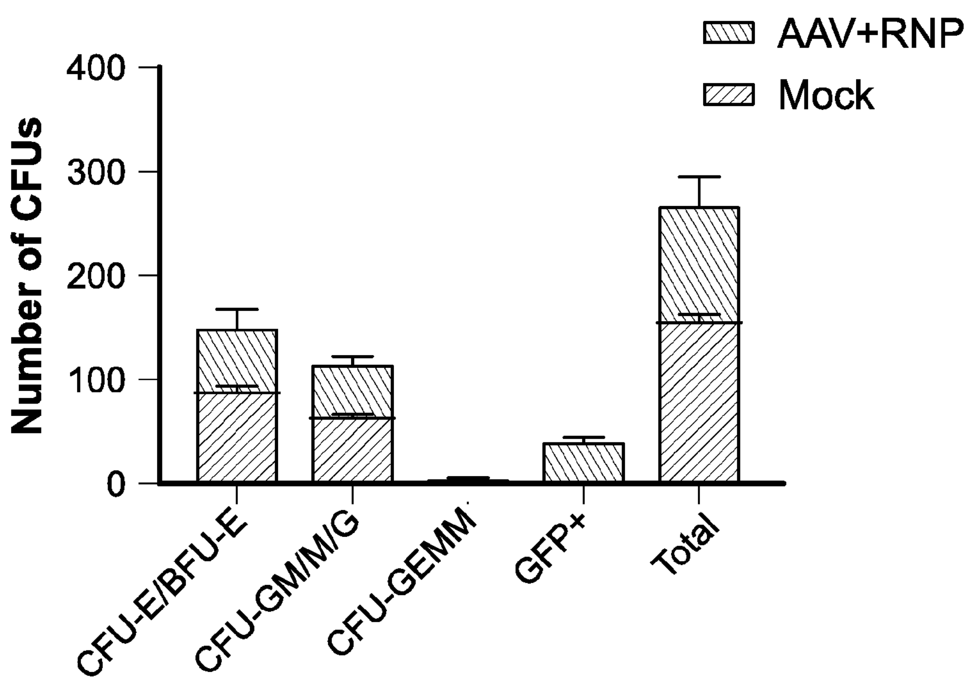

AAV+RNP
Mock
Number of CFUs
400
300
200
100
0
CFU-E/BFU-E
CFU-GM/M/G
CFU-GEMM
GFP+
Total

Figure 5F

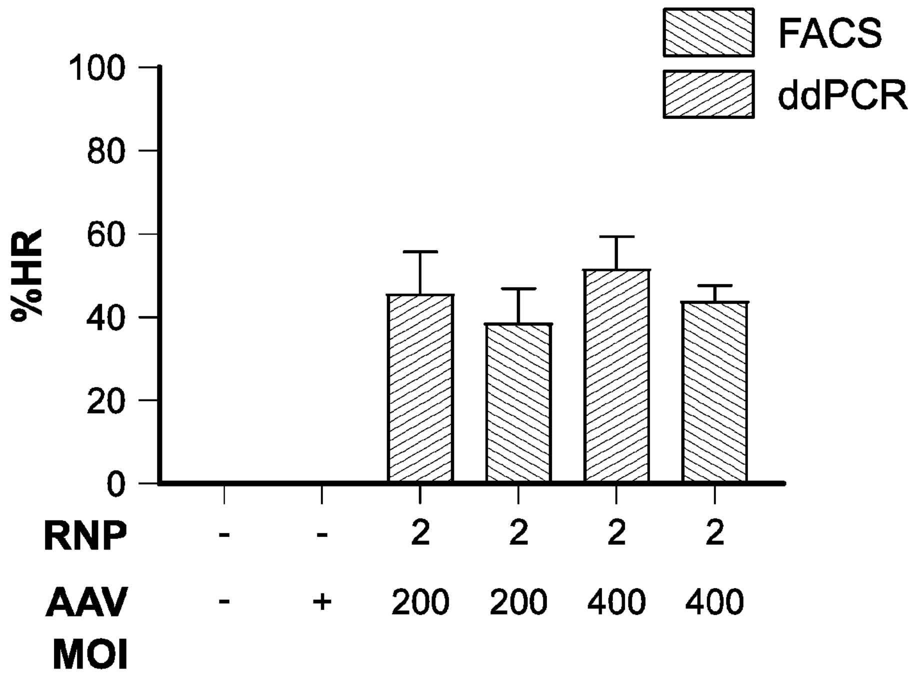


Figure 5G

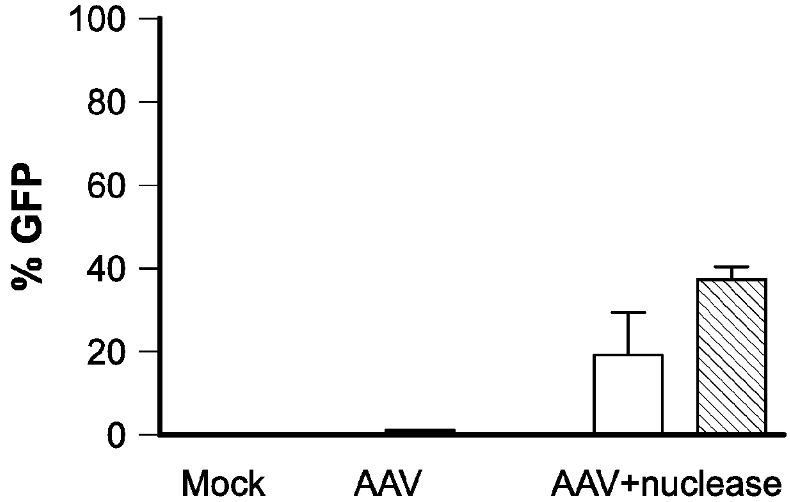


Figure 6A

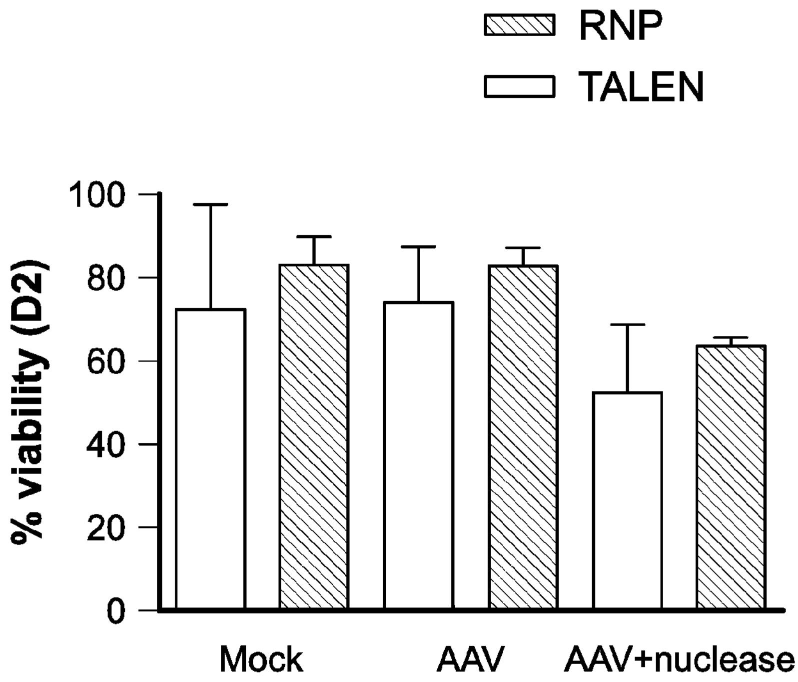


Figure 6B

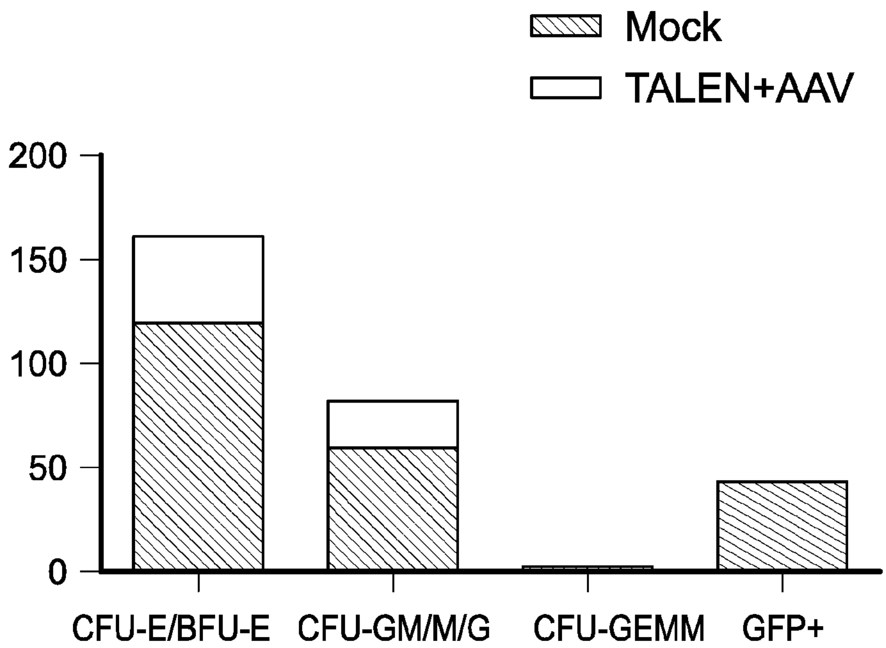


Figure 6C

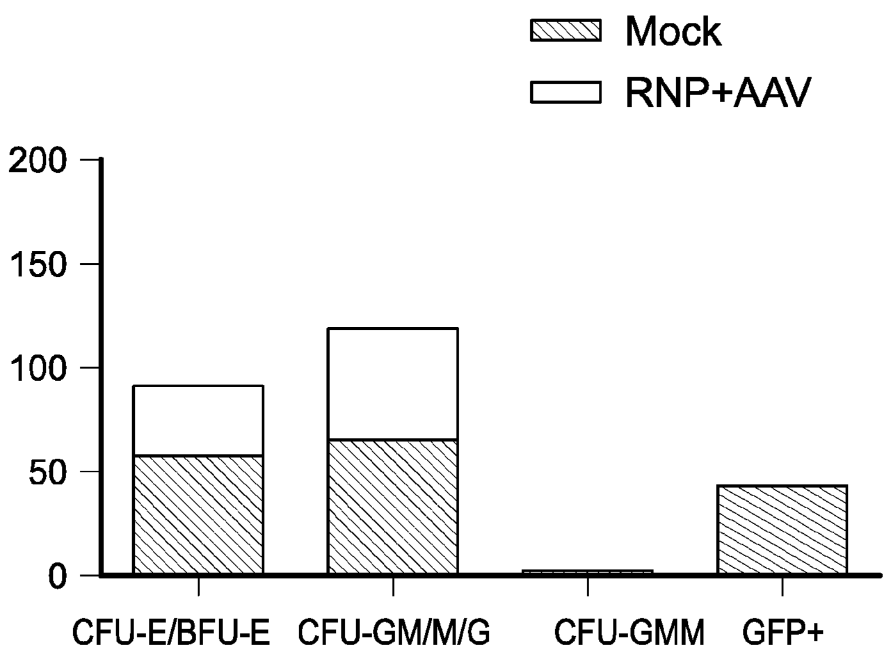


Figure 6D

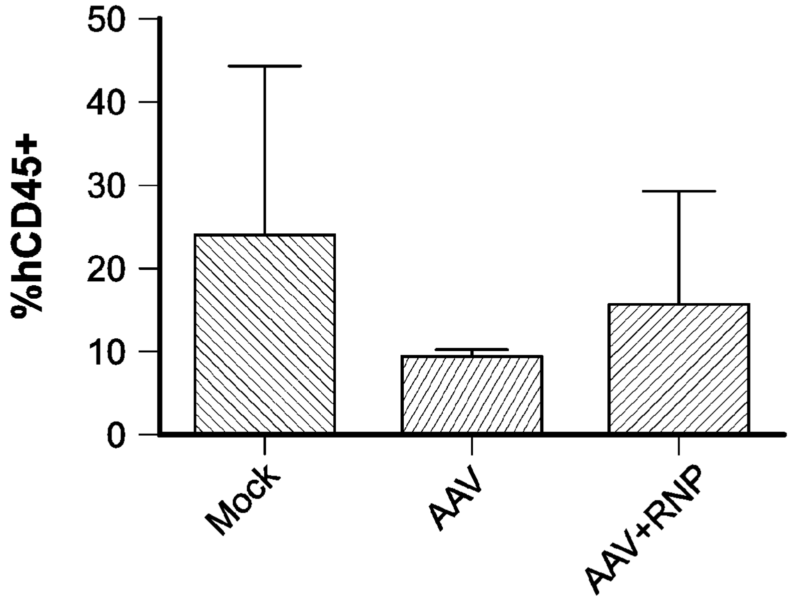


Figure 7A

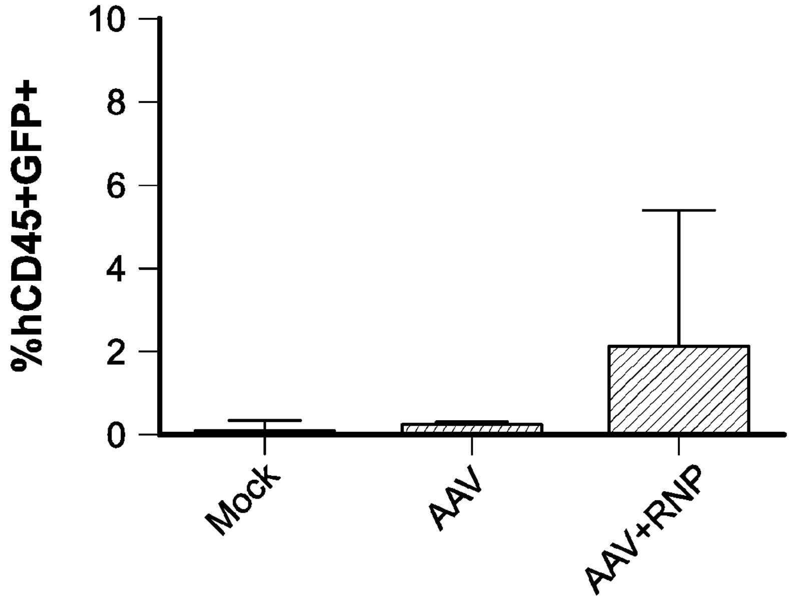
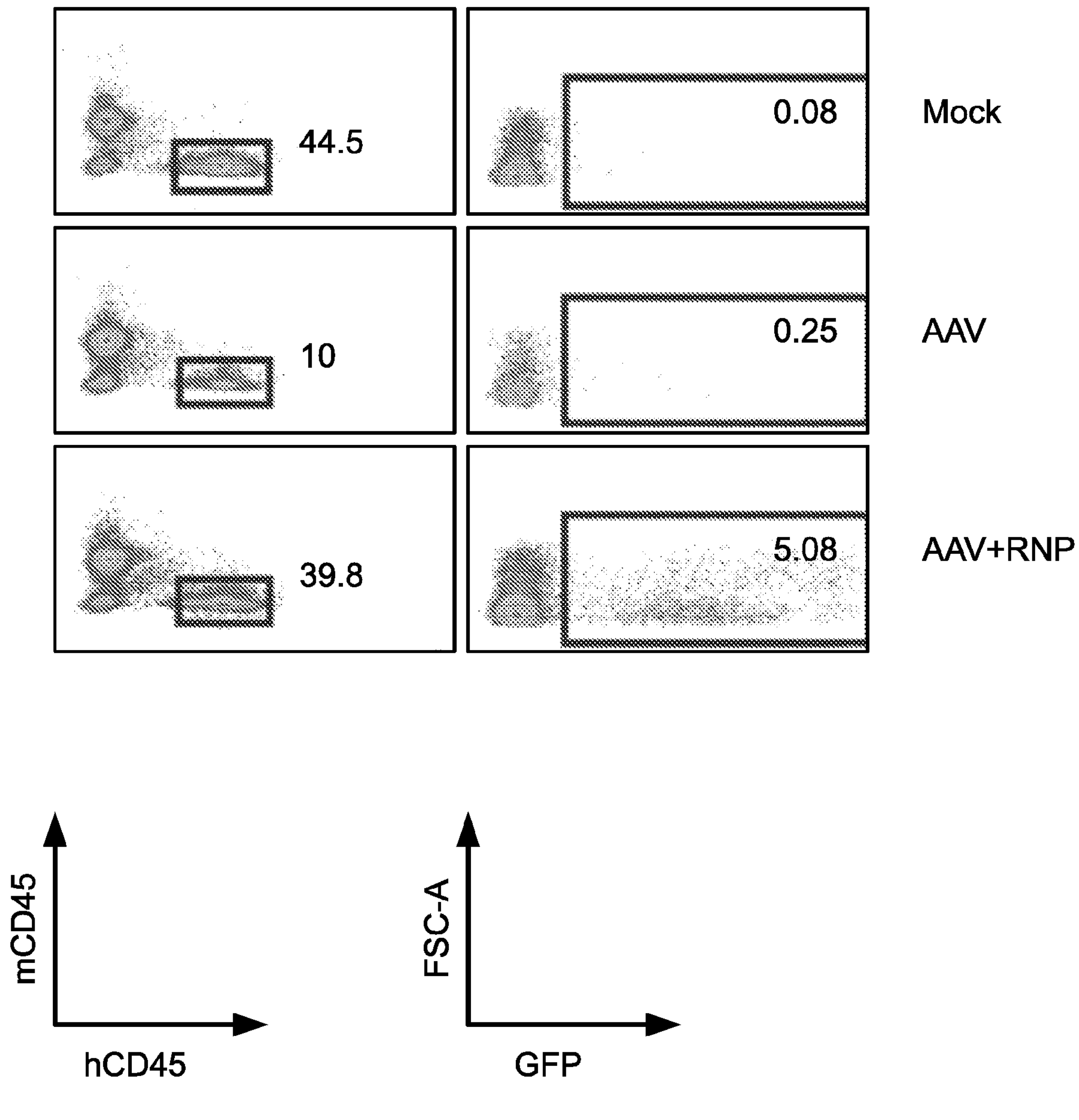


Figure 7B



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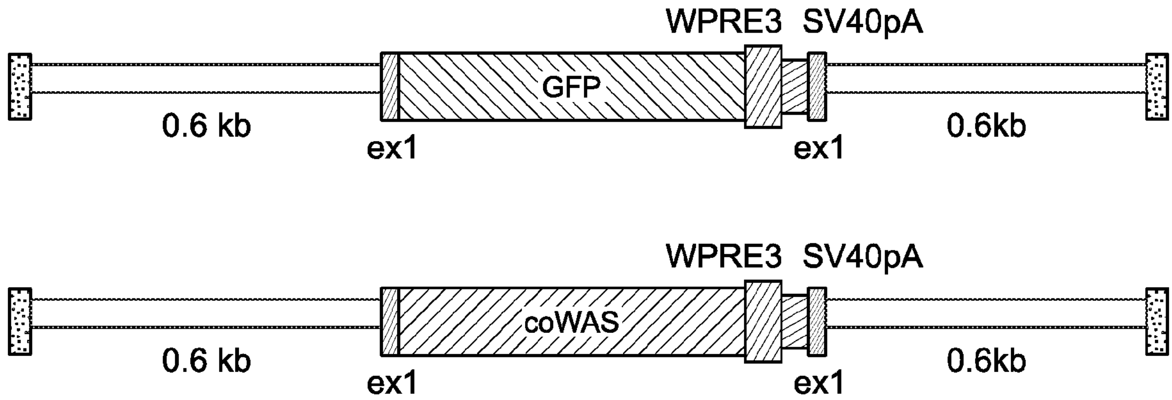
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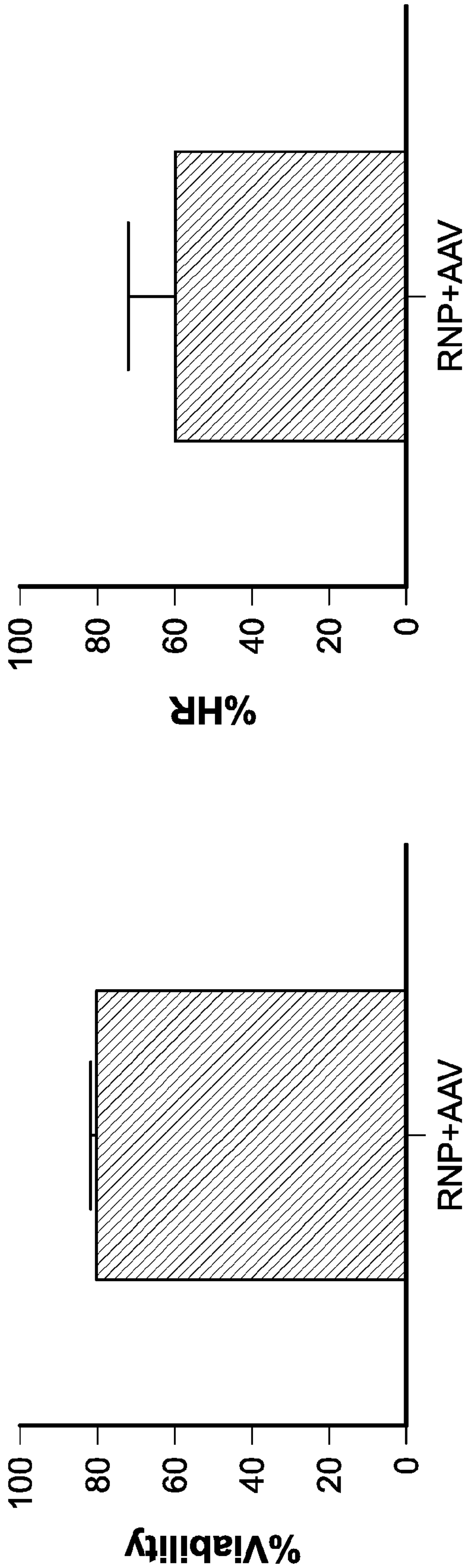

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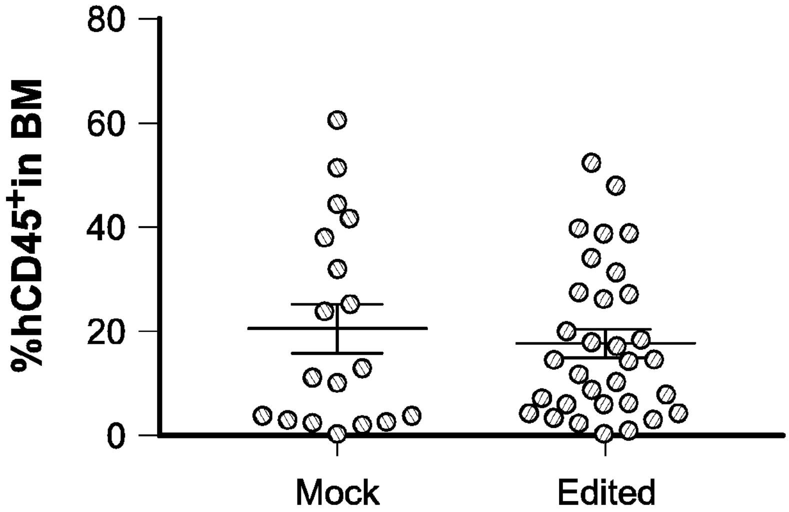

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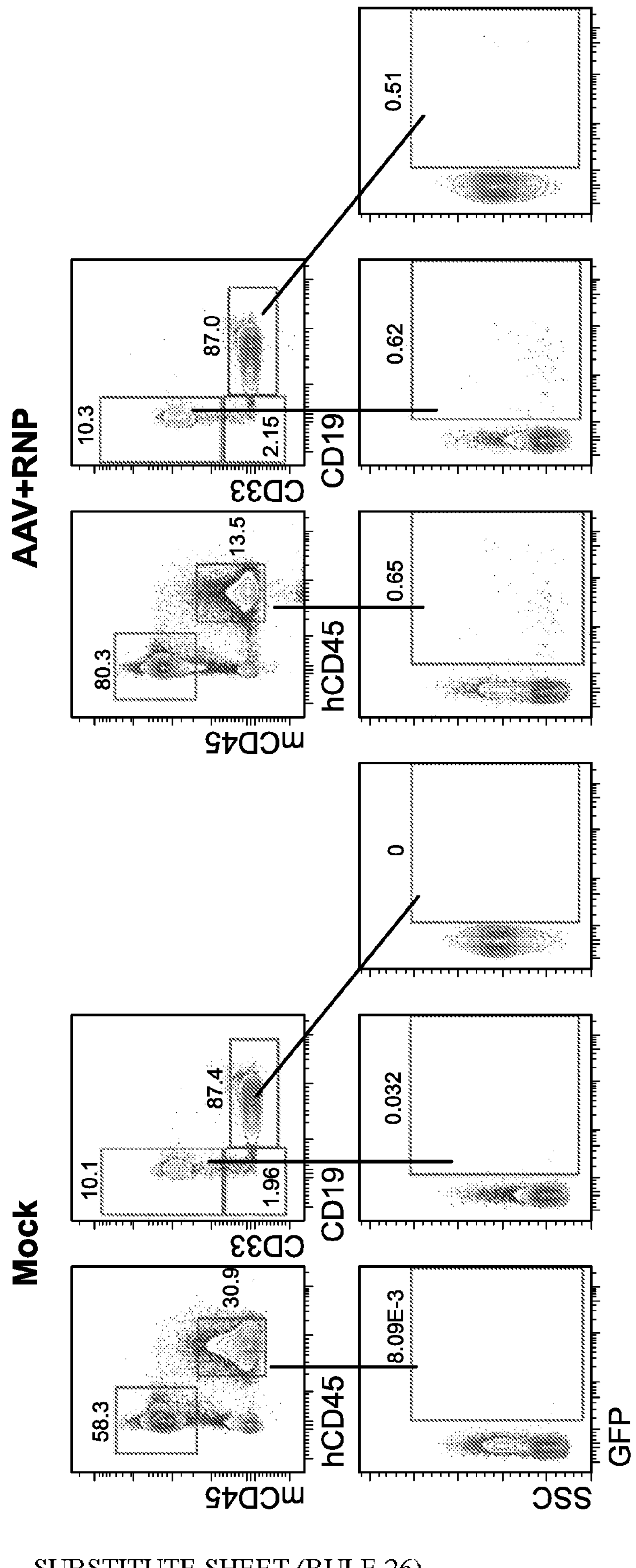
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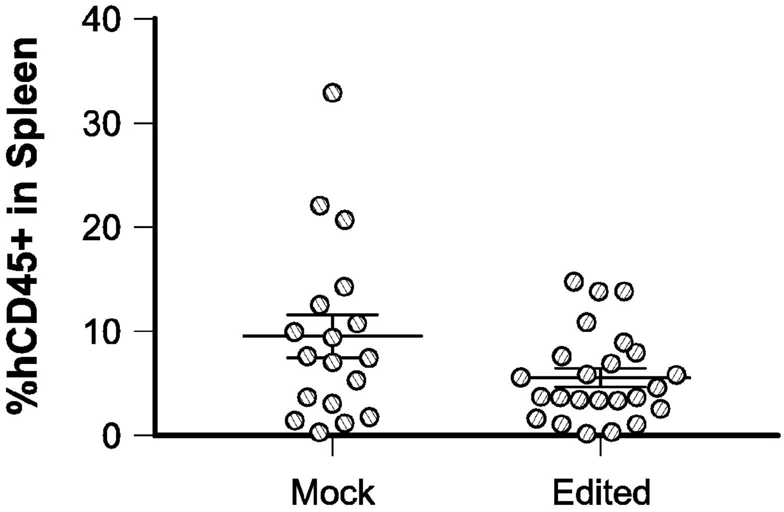
Figure 9C



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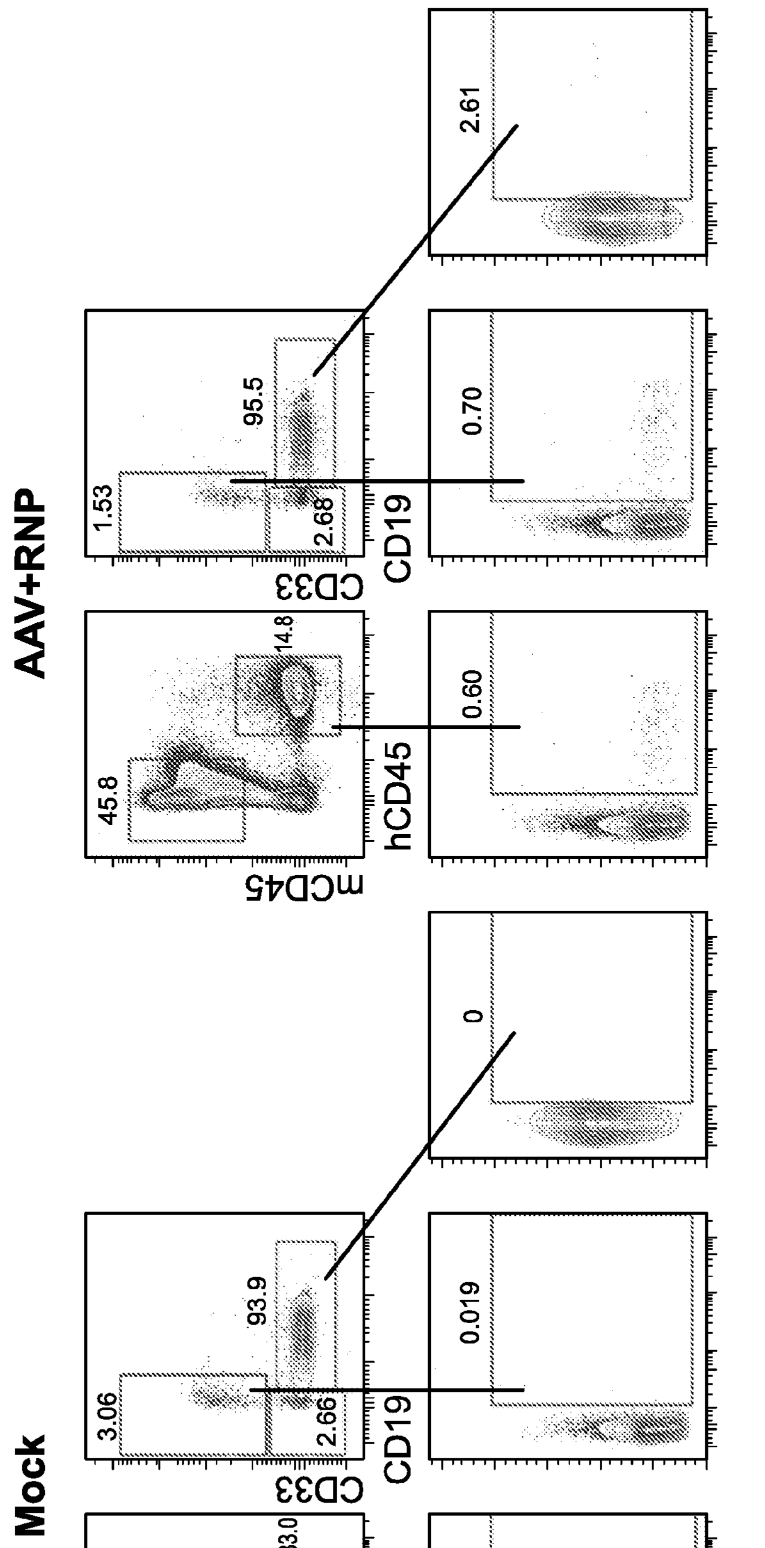
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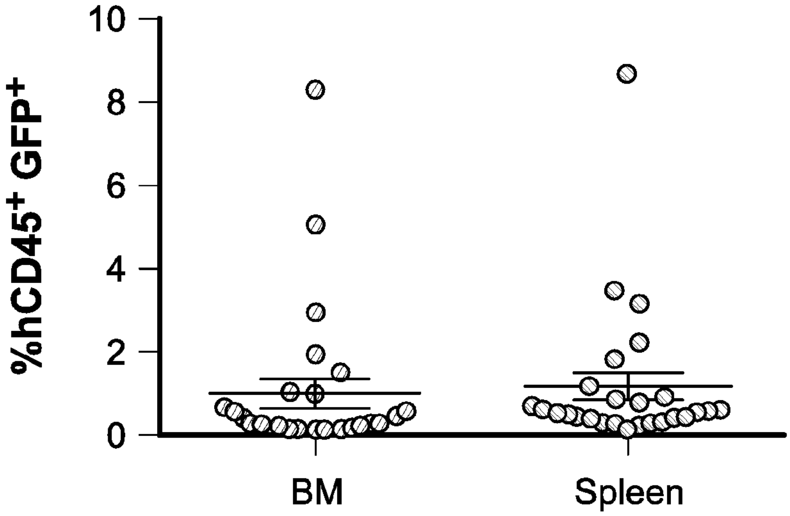
Figure 9E



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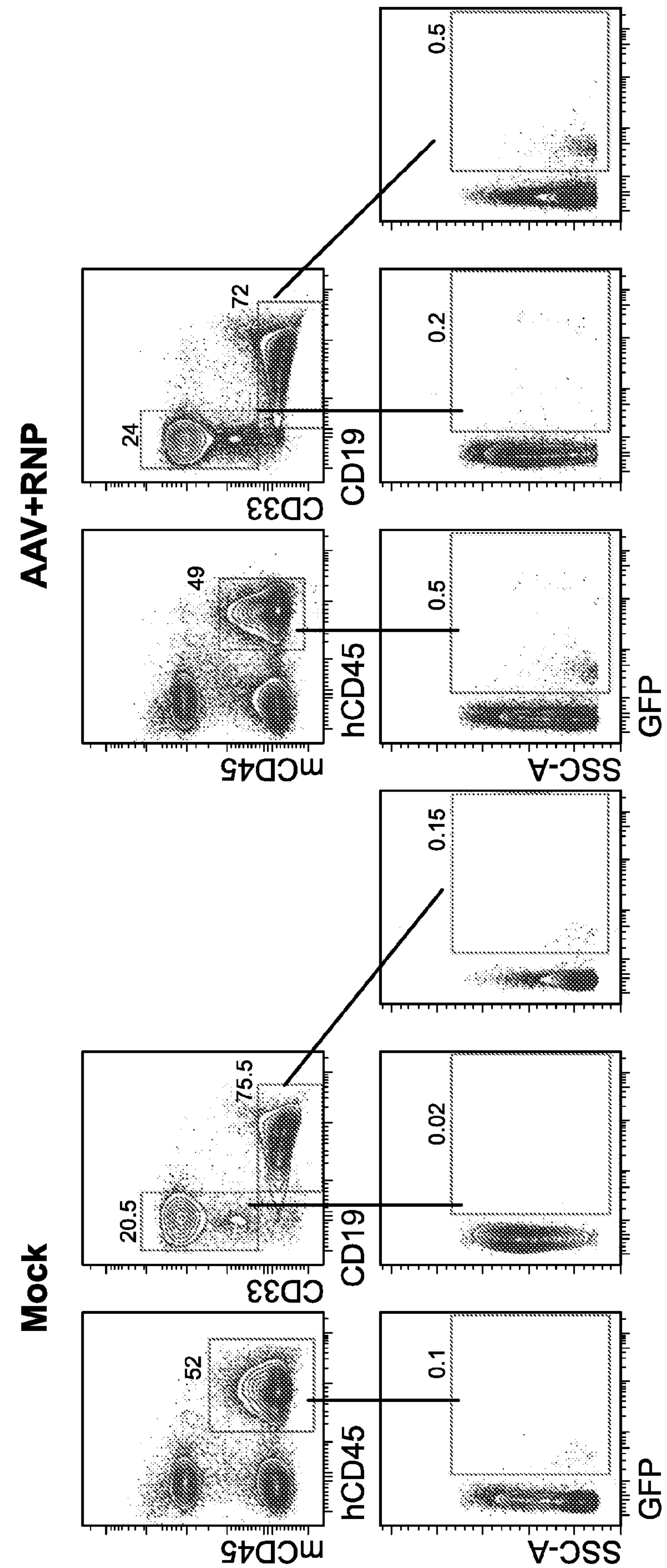
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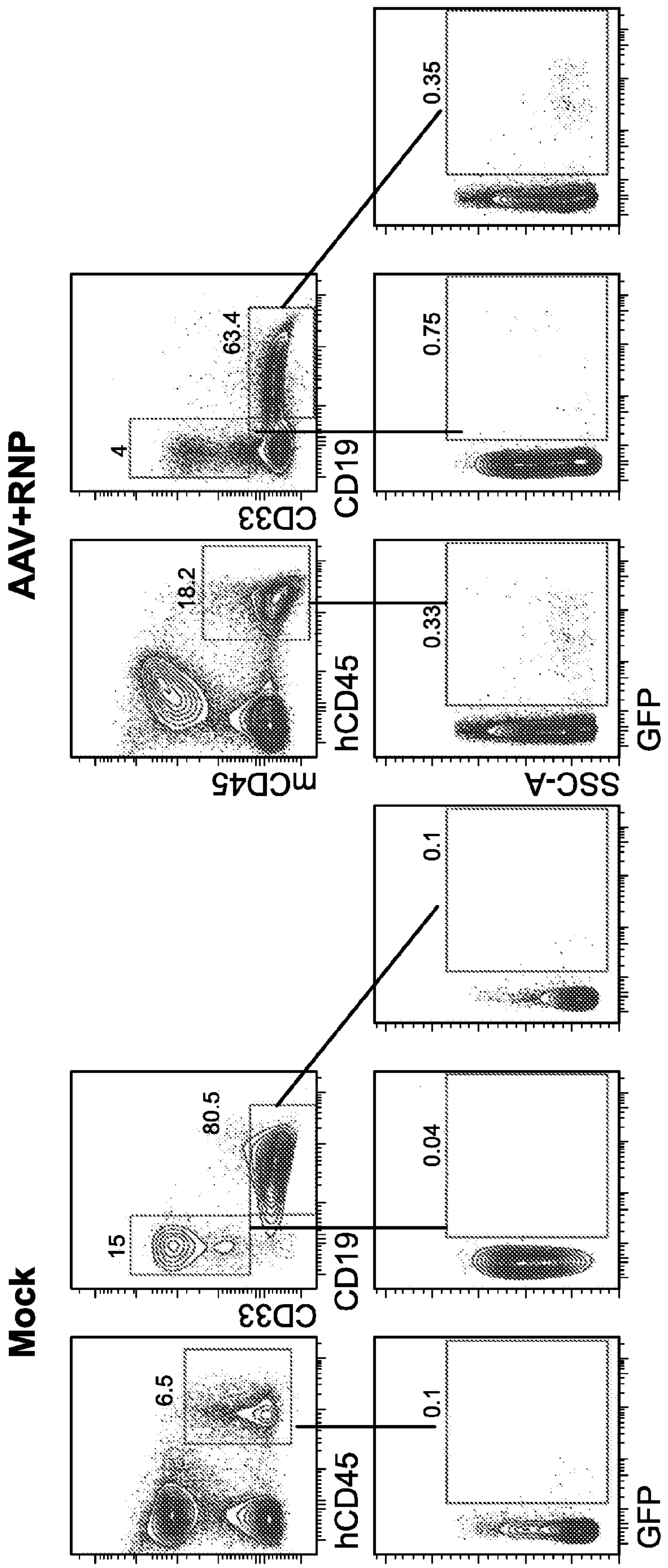
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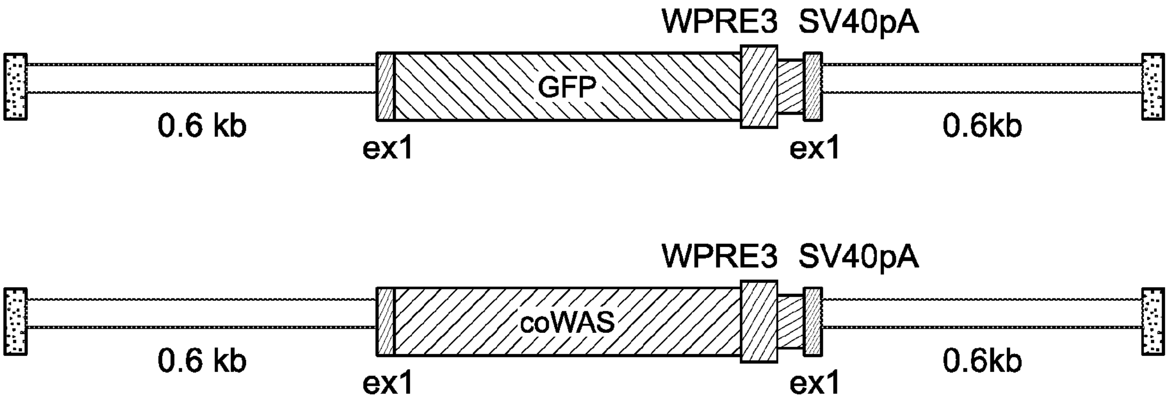
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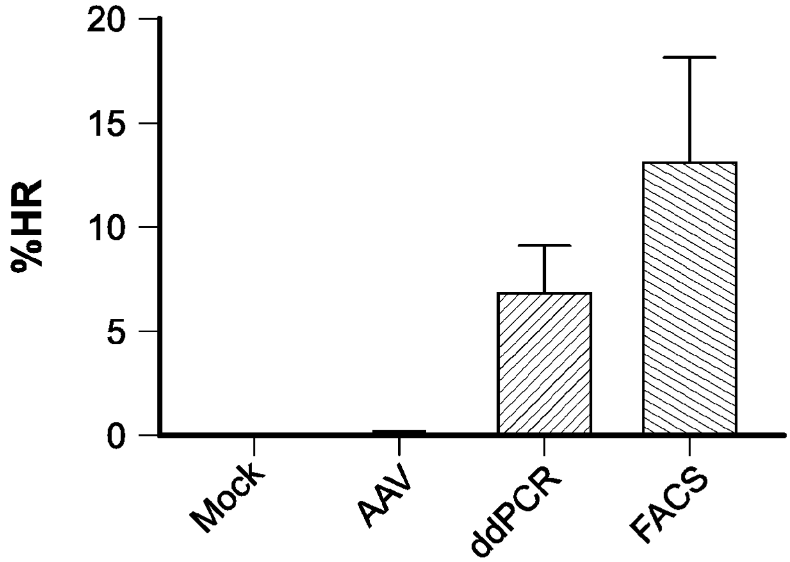

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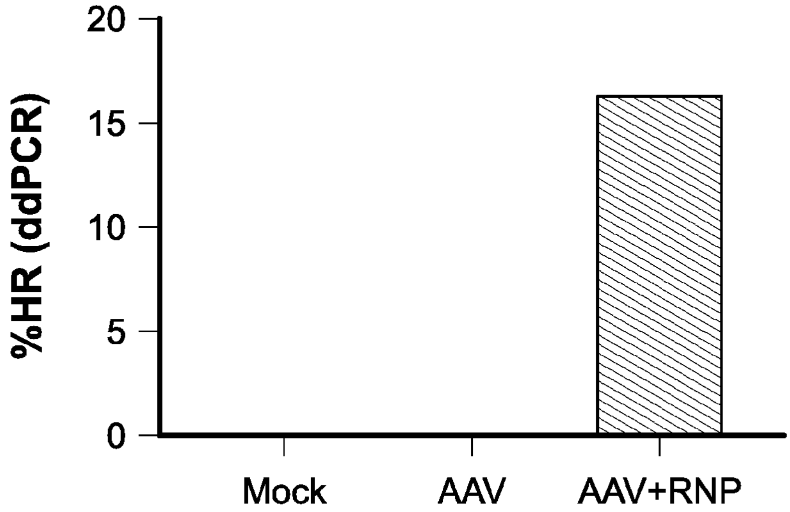

Figure 11C

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<220>

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<210> 11
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<220>
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<220>
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(reverse-TALEN)

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<220>
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