CLAIMS

1. An expression vector comprising

a) a kill switch comprising a first site-specific recombination sequence and a second site-specific recombination sequence;

b) a regulatable element operably linked to a nucleic acid sequence encoding a therapeutic molecule, wherein activity of the regulatable element is regulated by a regulator compound; and

c) a constitutive promoter operably linked to a nucleic acid sequence encoding a regulator compound-binding polypeptide which is capable of binding a regulator compound, wherein upon binding the regulator compound, the regulator compound-binding polypeptide regulates expression of the therapeutic molecule,

wherein activation of the kill switch by recombination between the first site-specific recombination sequence and the second site-specific recombination sequence silences expression of the nucleic acid encoding the therapeutic molecule from the vector.

2. The expression vector of claim 1, wherein the first site-specific recombination sequence is positioned upstream of the nucleic acid sequence encoding the therapeutic molecule and the second site-specific recombination sequence is positioned downstream of the nucleic acid sequence encoding the therapeutic molecule, and/or wherein the first site-specific recombination sequence and the second site-specific recombination sequence are loxP sites.

~~3. The expression vector of claim 1 or claim 2, wherein the first site-specific recombination sequence and the second site-specific recombination sequence are loxP sites.~~

3. The expression vector of claim 1 or 2, wherein upon binding of the regulator compound, the regulator compound-binding polypeptide:

a) promotes expression of the therapeutic molecule, or

b) represses expression of the therapeutic molecule.

~~4. The expression vector of any one of claims 1 to 3, wherein upon binding of the regulator compound, the regulator compound-binding polypeptide promotes expression of the therapeutic molecule.~~

~~5. The expression vector of any one of claims 1 to 3, wherein upon binding of the regulator compound, the regulator compound-binding polypeptide represses expression of the therapeutic molecule.~~

~~6.~~4. The expression vector of any one of claims 1 to ~~5~~3, wherein one or more or all of the following apply:

a) the regulator compound-binding polypeptide comprises one or more of a reverse tetracycline-controlled transactivator (rtTA), a tetracycline-controlled transactivator or a cysteine metabolism repressor (CymR);

b) the regulator compound is tetracycline, cumate, progesterone, a glucocorticoid, estrogen, or mifepristone;

c) the regulatable element comprises one or more of a tetracycline responsive element (TRE), a cumate operator (CuO), an ecdysone response element (EcRE), estrogen response element (ERE), a glucocorticoid response element (GRE), a progesterone response element (PRE), a heat shock sequence element (HSE), or a light inducible promoter;

d) the constitutive promoter is a composite human CMV-EF1-HTLV promoter;

e) the therapeutic molecule inhibits angiogenesis;

f) wherein the therapeutic molecule:

- comprises endostatin, angiostatin, or a fusion of endostatin and angiostatin;
- is a binding protein;
- comprises an antigen binding site of an antibody;
- is selected from the group consisting of is ranibizumab, bevacizumab, and aflibercept;
- inhibits inflammation; or,
- is interleukin 10 (IL-10), interleukin 1 receptor antagonist (IL-1RA); or a fusion of IL-10 and IL-1RA;

g) the vector further comprises a transcription blocker between the constitutive promoter and the regulatable promoter;

h) the vector is a viral vector.

7. The expression vector of any one of claims 1 to 6, wherein the regulator compound is tetracycline, cumate, progesterone, a glucocorticoid, estrogen, or mifepristone.

8. The expression vector of any one of claims 1 to 7, wherein the regulatable element comprises one or more of a tetracycline responsive element (TRE), a cumate operator (CuO), an ecdysone response element (EcRE), estrogen response element (ERE), a glucocorticoid response element (GRE), a progesterone response element (PRE), a heat shock sequence element (HSE), or a light inducible promoter.

9. The expression vector of any one of claims 1 to 8, wherein the constitutive promoter is a composite human CMV-EF1-HTLV promoter.

10. The expression vector of any one of claims 1 to 9, wherein the therapeutic molecule inhibits angiogenesis.

11. The expression vector of any one of claims 1 to 9, wherein the therapeutic molecule:

- comprises endostatin, angiostatin, or a fusion of endostatin and angiostatin;
- is a binding protein;
- comprises an antigen binding site of an antibody;
- is selected from the group consisting of is ranibizumab, bevacizumab, and aflibercept;
- inhibits inflammation; or,
- is interleukin 10 (IL-10), interleukin 1 receptor antagonist (IL-1RA); or a fusion of IL-10 and IL-1RA.

12. The expression vector of any one of claims 1 to 11, wherein the vector further comprises a transcription blocker between the constitutive promoter and the regulatable promoter.

13. The expression vector of any one of claims 1 to 12, which is a viral vector.

~~14.~~5. The expression vector of ~~claim 13~~any one of claims 1 to 4, wherein the ~~viral~~ vector is an adeno-associated virus (AAV) vector.

6. Use of an effective amount of the vector of any one of claims 1 to 5 in the preparation of a medicament for treating an ocular disorder in a subject.

7. Use of an effective amount of an expression vector in the preparation of a medicament for treating an ocular inflammatory disorder in a subject, wherein the expression vector comprises a kill switch and a nucleic acid encoding a therapeutic molecule, wherein activation of the kill switch silences expression of the therapeutic molecule.

8. The use of claim 7, wherein the expression vector further comprises a regulatable element operably linked to the nucleic acid encoding the therapeutic molecule, wherein the activity of the regulatable element is regulated by administration of a regulator compound to the subject.

9. The use of claim 8, wherein:

a) a second expression vector is administered which comprises a constitutive promoter operably linked to a nucleic acid sequence encoding a regulator compound-binding polypeptide which is capable of binding a regulator compound, wherein upon binding the regulator compound, the regulator compound-binding polypeptide regulates expression of the therapeutic molecule from the first expression vector; or

b) the expression vector further comprises a constitutive promoter operably linked to a nucleic acid sequence encoding a regulator compound-binding polypeptide which binds the regulator compound, wherein upon binding the regulator compound, the regulator compound-binding polypeptide regulates expression of the therapeutic molecule,

wherein upon binding the regulator compound, the regulator compound-binding polypeptide promotes expression of the therapeutic molecule or represses expression of the therapeutic molecule.

10. The use of any one of claims 7 to 9, wherein:

a) activation of the kill switch excises:

- one or more promoters; and/or,

- the nucleic acid encoding the therapeutic molecule, and/or

b) the kill switch comprises site-specific recombination sequences which flank:

- one or more promoters; and/or
- the nucleic acid encoding a therapeutic molecule.

11. The use of claim 6, wherein the ocular disorder is diabetic retinopathy, cystoid macular oedema, clinically significant macular oedema, uveitis, iritis, giant cell arteritis, vasculitis, pars planitis, corneal transplant rejection, intraocular inflammation, lamellar corneal transplant rejection, uveal melanoma or retinoblastoma.

12. The use of claim 6, wherein the ocular disorder is macular degeneration, diabetic retinopathy, cystoid macular oedema, clinically significant macular oedema, central retinal vein occlusion, branch retinal vein occlusion or ocular neovascularisation.

13. The use of claim 7, wherein the ocular inflammatory disorder is uveitis, intraocular inflammation, iritis, giant cell arteritis, vasculitis, pars planitis, retinitis pigmentosa, corneal transplant rejection, or lamellar corneal transplant rejection.

14. The use of any one of claims 6 to 13, which comprises intravitreal or subretinal administration of the expression vector, and/or the use comprises activating the kill switch by administering a site-specific recombinase or a nucleic acid encoding a site-specific recombinase, wherein the site-specific recombinase catalyses the recombination between a first site-specific recombination sequence and a second site-specific recombination sequence, thereby silencing expression of the therapeutic molecule.

15. The use of any one of claims 6 to 14, wherein one or more or all of the following apply:

a) the use comprises administering the regulator compound to the eye topically;

b) the regulator compound is a small molecule;

c) the regulator compound is tetracycline or cumate; and

d) the regulator compound is administered in eye drops.

16. Use of an effective amount of an expression vector in the preparation of a medicament for treating an ocular disorder in a subject, the expression vector comprising a kill switch comprising a first site-specific recombination sequence and a second site-specific recombination sequence, a nucleic acid encoding a therapeutic molecule, a regulatable promoter operably linked to the nucleic acid encoding the therapeutic molecule and a constitutive promoter operably linked to a nucleic acid sequence encoding a regulator compound-binding polypeptide, wherein the activity of the regulatable promoter is regulated by the regulator compound-binding polypeptide following administration of a regulator compound to the subject and wherein, activation of the kill switch by recombination between the first site-specific recombination sequence and the second site-specific recombination sequence silences expression of the therapeutic molecule.

~~15. A method of treating an ocular disorder in a subject, the method comprising administering an effective amount of the vector of any one of claims 1 to 14.~~

~~16. A method of treating an ocular inflammatory disorder in a subject, the method comprising administering an effective amount of an expression vector which comprises a kill switch and a nucleic acid encoding a therapeutic molecule, wherein activation of the kill switch silences expression of the therapeutic molecule.~~

~~17. The method of claim 16, wherein the expression vector further comprises a regulatable element operably linked to the nucleic acid encoding the therapeutic molecule, wherein the activity of the regulatable element is regulated by administration of a regulator compound to the subject.~~

~~18. The method of claim 17, further comprising administering a second expression vector which comprises a constitutive promoter operably linked to a nucleic acid sequence encoding a regulator compound-binding polypeptide which is capable of binding a regulator compound, wherein upon binding the regulator compound, the regulator compound-binding polypeptide regulates expression of the therapeutic molecule from the first expression vector.~~

~~19. The method of claim 17, wherein the expression vector further comprises a constitutive promoter operably linked to a nucleic acid sequence encoding a regulator~~

compound-binding polypeptide which binds the regulator compound, wherein upon binding the regulator compound, the regulator compound-binding polypeptide regulates expression of the therapeutic molecule.

20. The method of claim 18 or claim 19, wherein upon binding the regulator compound, the regulator compound-binding polypeptide promotes expression of the therapeutic molecule.

21. The method of claim 18 or claim 19, wherein upon binding the regulator compound, the regulator compound-binding polypeptide represses expression of the therapeutic molecule.

22. The method of any one of claim 15 to 21, wherein activation of the kill switch excises:

- one or more promoters; and/or,
- the nucleic acid encoding the therapeutic molecule.

23. The method of any one of claim 15 to 22, wherein the kill switch comprises site-specific recombination sequences which flank:

- one or more promoters; and/or
- the nucleic acid encoding a therapeutic molecule.

24. The method of any one of claim 16 to 23, the method comprising administering an expression vector defined by any one of claims 1 to 14.

25. The method of any one of claims 15, wherein the ocular disorder is diabetic retinopathy, cystoid macular oedema, clinically significant macular oedema, uveitis, iritis, giant cell arteritis, vasculitis, pars planitis, corneal transplant rejection, intraocular inflammation, lamellar corneal transplant rejection, uveal melanoma or retinoblastoma.

26. The method of any one of claims 15, wherein the ocular disorder is macular degeneration, diabetic retinopathy, cystoid macular oedema, clinically significant macular oedema, central retinal vein occlusion, branch retinal vein occlusion or ocular neovascularisation.

27. The method of claim 16, wherein the ocular inflammatory disorder is uveitis, intraocular inflammation, iritis, giant cell arteritis, vasculitis, pars planitis, retinitis pigmentosa, corneal transplant rejection, or lamellar corneal transplant rejection.

28. The method of any one of claims 15 to 27, which comprises intravitreal or subretinal administration of the expression vector.

29. The method of any one of claims 15 or 17 to 28, which comprises administering the regulator compound to the eye topically.

30. The method of any one of claims 15 or 17 to 29, wherein the regulator compound is a small molecule.

31. The method of any one of claims 15 or 17 to 30, wherein the regulator compound is tetracycline or cumate.

32. The method of any one of claims 15 or 17 to 31, wherein the regulator compound is administered in eye drops.

33. The method of any one of claims 15 to 32, further comprising activating the kill switch by administering a site-specific recombinase or a nucleic acid encoding a site-specific recombinase, wherein the site-specific recombinase catalyses the recombination between a first site-specific recombination sequence and a second site-specific recombination sequence, thereby silencing expression of the therapeutic molecule.

34. A method of treating an ocular disorder in a subject, the method comprising administering an effective amount of an expression vector, the expression vector comprising a kill switch comprising a first site-specific recombination sequence and a second site-specific recombination sequence, a nucleic acid encoding a therapeutic molecule, a regulatable promoter operably linked to the nucleic acid encoding the therapeutic molecule and a constitutive promoter operably linked to a nucleic acid sequence encoding a regulator compound-binding polypeptide, wherein the activity of the regulatable promoter is regulated by the regulator compound-binding polypeptide following administration of a regulator compound to the subject and wherein, activation of the kill switch by recombination between the first site-specific recombination

~~sequence and the second site-specific recombination sequence silences expression of the therapeutic molecule~~.

~~35.~~17. The expression vector of any one of claims 1 to ~~14 or the method of any one of claims 15 to 34~~5, or the use of any one of claims 6 to 16, wherein the therapeutic molecule is a nucleic acid or polypeptide.

~~36. The expression vector of any one of claims 1 to 14 or the method of any one of claims 15 to 34, wherein the therapeutic molecule is a polypeptide.~~

~~37.~~18. A pharmaceutical composition comprising the expression vector defined by any one of claims 1 to ~~14~~5 or 17.

~~38.~~19. A kit comprising the expression vector of any one of claims 1 to ~~14~~5 or 17 and an eye drop formulation comprising a regulator compound.

~~39. The kit of claim 38, further comprising a recombinase or an expression vector comprising a nucleic acid sequence encoding a recombinase.~~

~~40.~~20. The kit of claim ~~38 or claim 39~~19, comprising a recombinase or an expression vector comprising a nucleic acid sequence encoding a recombinase and/or

- ~~The expression vector of any one of claims 1 to 14,~~
- an eye drop formulation comprising tetracycline, and
- a Cre recombinase or an expression vector comprising a nucleic acid sequence encoding a Cre recombinase.