CLAIMS

1. Use of a first inducer and a second inducer in the manufacture of a medicament for regulating expression of a transgene in a primate subject, in which the primate subject comprises at least one cell comprising an exogenous nucleotide sequence comprising an inducible promoter operably linked to a transgene, in which the inducible promoter comprises a PBREM enhancer, in which:

(a) a first inducer is to be administered to the subject at a first time point, in which the first inducer is artemisinin or a derivative thereof or a flavonoid compound, and in which the inducer is to be administered in an amount that is sufficient to express a measurable level of the transgene in the subject; and

(b) a second inducer is to be administered to the subject at least at a second time point to continue expression of the transgene at a predetermined level for a predetermined time or to modulate expression of the transgene to a predetermined level, and

in which the second inducer is artemisinin; derivative of artemisinin; a flavonoid compound, e.g. flavone, chrysin, baicalein, or galangin; 1,4-Bis[2-(3,5-dichloropyridyloxy)]benzene (TCPOBOP); phenobarbital (PB); 6-(4Chlorophenyl)imidazo[2,1-b][1,3]thiazole-5-carbaldehyde-O-(3,4-dichlorobenzyl)oxime (CITCO); Acetaminophen; Buprenorphine; Phenytoin; Carbamazepine; Valproic Acid; Chlorpromazine; Efavirenz; Nevirapine; Rilpivirine; Etravirine; Diazepam; Cyclophosphamid; Ifosfamide; Cerivastatin; Simvastatin; lovastatin; substituted sulphonamides; Thiazolidin-4-one; Estradiol; Estrone and analogues; 17α-ethinyl-3;17ß-estradiol (EE2); Dehydroepiandrost erone (DHEA); 5ß-pregnane-3,20-dione; Diethylstilbestrol; Gingko *biloba* extract; Galangin; chrysin; baicalein; Diallyl sulphide; Ellagic acid; Resveratrol; Squalestatin-1; Bilobalide; Triclocarban; Triclosan; Dichlorodiphenyltrichloroethane (DDT); Dieldrin; Methoxychlor; Metofluthrin; Permethrin; Pyrethrins; Sulfoxaflor; Diethylhexyl phthalate (DEHP); Cyproconazole; Fluconazole; Propiconazole; FL81; Tri-p-methylphenyl phosphate (TMPP); UM104; or UM145.

2. Use according to Claim 1, in which the expression of the transgene increases for a predetermined time after each administration.

3. Use according to Claim 1 or 2, in which the first and second inducer are the same, optionally in which:

(i) the first and second inducer are artemisinin, a derivative of artemisinin, or a flavonoid compound; or

(ii) the first inducer and second inducer are artemisinin; or

(iii) the first inducer and second inducer are a derivative of artemisinin; or

(iv) the first inducer and second inducer are a flavonoid compound, optionally in which the flavonoid compound is flavone.

4. Use according to Claim 1 or 2, in which the first and second inducer are different, optionally in which:

(i) the first inducer is artemisinin, and the second inducer is an artemisinin derivative or a flavonoid compound;

(ii) the first inducer is a first artemisinin derivative, and the second inducer is artemisinin, a second artemisinin derivative, or a flavonoid compound; or

(iii) the first inducer is a flavonoid compound and the second inducer is artemisinin or a derivative of artemisinin.

5. Use according to any preceding claim, in which:

(i) the artemisinin derivative is a compound of Formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (I-I), (I-J), (I-K), (I-L), (I-M), (I-M'), (I-N), (I-N'), (I-O) or (I-O');

(ii) the artemisinin derivative is artesunate, dihydroartemisinin (DHA), artesunate or artemether, optionally in which the artemisinin derivative is artesunate or dihydroartemisinin, more optionally in which the artemisinin derivative is artesunate; and/or

(iii) the flavonoid compound is flavone, baicalein, chrysin, galangin, $(OH)_4$ flavone, 6-hydroxyluteolin, acacetin, acerosin, alnetin, apigenin, apiin, artocarpetin, balcalein, beta-sitosterol, biochamin A, cannaflavin A, cannflavin A, cannflavin B, cannflavin C, catechin, catechin-3-gallate, cerrosillin, chrysoeriol, chrysoeriol, cirsilineol, cirsiliol, cirsimaritin, corymbosin, cupressuflavone, cyanidine, daidzein, datiscetin, delphinidine,

digidrokempferol, dihydroquercetin, diosmetin, diosmin, echioidinin, epicatechin, epicatechin-3-gallate, epigallocatechin, epigallocatechin-3-gallate, eriodiktiol, eupatilin, eupatorin, fisetin, fizetin, flavonol, formononetin, fortunelin, gallocatechin, gallocatechin-3-gallate, gardenin D, genistein, genistin, genkwanin, geraldol, geraldone, glycitein, glycitin, gomoeriodiktiol, gossypetin, hesperetin, hinokiflavone, hispidulin, hymenoxin, hypolaetin, isoquercetin, isorhamnetin, isorhamnetin, isoscutellarein, isovitexin, jaceosidin, kaempferol, kaempferol, kampferide, largonidin, luteolin, luteolin, malvidine, mikanin, morin, myricetin, myricetin, naringenin, negletein, neodiosmin, nepetin, nevadensin, nobiletin, nodifloretin, norartocarpetin, norwogonin, onopordin, orientin, oroxylin a, pachipodol, pectolinarigenin, pedalitin, peonidin, petunidin, pilloin, pratol, primetin, primuletin, pruentin, quercetagetin, quercetin, ramnazin, rhoifolin, robinetin, rutin, scaposin, scutellarein, serpyllin, sinensetin, sorbifolin, sudachitin, tangeretin, tangeritin, taxifolin, tectochrysin, tithonine, tricetin, tricin, velutin, vitexin, wightin, wogonin, xanthomicrol, zapotin, zapotinin, 6,7,4'-trishydroxy isoflavone, or 7,3'4'-trihydroxy isoflavone; optionally in which the flavonoid compound is flavone.

6. Use according to any preceding claim, in which:

(i) the first and second inducer are to be administered at about the same amount; or

(ii) the first inducer and the second inducer are to be administered at different amounts, optionally in which:

(a) the second inducer is to be administered at a lower amount relative to the amount of the first inducer, preferably the second inducer is to be administered in amount about 1/2, 1/3, 1/4, 1/5, 1/6, 1/7, 1/8, 1/9, 1/10, 1/15, 1/20, 1/25, 1/30, 1/35, 1/40, 1/45, 1/50, 1/55, 1/60, 1/65, 1/70, 1/75, 1/80, 1/85, 1/90, 1/95, 1/100, 1/125, 1/150, 1/175, 1/200, 1/500, 1/1000 or even less of the amount of first the inducer, more preferably the second inducer is to be administered in amount about 1/2, 1/4, 1/5, 1/8, 1/10, 1/20, 1/40, 1/80 or less of the amount of the first inducer; or

(iii) the second inducer is to be administered at a higher amount relative to the amount of the first inducer, optionally in which the amount of inducer to be administered at the second time point is at least about 25%, 50%, about 75%, about 1-fold, about 1.2-folds, about 1.25-folds, about 1.3-folds, about 1.5-folds, about 1.75-folds, about 2-folds, about

2.25-folds, about 2.5-folds, about 2.5-folds, about 2.75-folds, about 3-folds, 4-fold, 5-fold, 6-folds, 7-fold, 8-fold, 9-folds, 10-folds or higher than the amount of the first inducer.

7. Use according to any preceding claim, in which:

(i) the first and second inducer are to be administered independently at a dose from about 0.5 mg/kg to about 150mg/kg;

(ii) the first inducer is to be administered at a dose from about 1 mg/kg to about 100 mg/kg;

(iii) the first inducer is to be administered at a dose of about 80mg/kg, about 70mg/kg, about 60mg/kg, about 50mg/kg, about 40mg/kg, about 30mg/kg, about 20mg/kg, about 10mg/kg, about 6mg/kg, about 5mg/kg, or about 1mg/kg;

(iv) the second inducer is to be administered at a dose from about 1 mg/kg to about 100 mg/kg; and/or

(v) the second inducer is to be administered at a dose of 80mg/kg, about 70mg/kg, about 60mg/kg, about 50mg/kg, about 40mg/kg, about 30mg/kg, about 20mg/kg, about 10mg/kg, about 6mg/kg, about 5mg/kg, or about 1mg/kg.

8. Use according to any of Claims 1 to 4, in which:

(i) the first inducer is to be administered at a dose of about 80 mg/kg or less and the second inducer is to be administered at a dose of about 20mg/kg or less at the second or subsequent time point; or

(ii) the first inducer is to be administered at a dose of about 40 mg/kg and the second inducer is to be administered at a dose of about 80mg/kg or less at the second or subsequent time point; or

(iii) the first inducer is to be administered at a dose of about 20mg/kg and the second inducer is to be administered at a dose of about 80 mg/kg, 40mg/kg, 20mg/kg, 10 mg/kg, 6 mg/kg or 1 mg/kg at the second or subsequent time point; or

(iv) the first inducer is to be administered at a dose of about 10 mg/kg and the second inducer is to be administered at a dose of about 80mg/kg or less at the second or subsequent time point; or

(v) the first inducer is to be administered at a dose of about 6 mg/kg and the second inducer is to be administered at a dose of about 80mg/kg or less at the second or subsequent time point; or

(vi) the first inducer is to be administered at a dose of about 1 mg/kg and the second inducer is to be administered at a dose of about 80mg/kg or less at the second or subsequent time point; or

(vii) the second inducer is to be administered at a dose of about 80 mg/kg and the first inducer is to be administered at a dose of about 80 mg/kg or less; or

(viii) the second inducer is to be administered at a dose of about 40 mg/kg and the first inducer is to be administered at a dose of about 80 mg/kg or less; or

(ix) the second inducer is to be administered at a dose of about 20 mg/kg and the first inducer is to be administered at a dose of about 80 mg/kg or less; or

(x) the second inducer is to be administered at a dose of about 10 mg/kg and the first inducer is to be administered at a dose of about 80 mg/kg or less; or

(xi) the second inducer is to be administered at a dose of about 6 mg/kg and the first inducer is to be administered at a dose of about 80 mg/kg or less; or

(xii) the second inducer is to be administered at a dose of about 1 mg/kg and the first inducer is to be administered at a dose of about 80 mg/kg or less.

9. Use according to any preceding claim, in which:

(i) the expression of the transgene goes down to a background expression level within one week of administering the inducer;

(ii) the second inducer is to be administered when it is determined that the level of expression of the transgene is decreased to 75% or less of the level of expression of the transgene attained after induction with the first inducer;

(iii) the second inducer is to be administered when it is determined that the level of expression of the transgene is decreased to 50% or less of the level of expression of the transgene after the first inducer;

(iv) the second inducer is to be administered when it is determined that the level of expression of the transgene is decreased to 25% or less of the level of expression of the transgene after the first inducer;

(v) the second inducer is to be administered when it is determined that the level of expression of the transgene is decreased to a background level of expression of the transgene; and/or

(vi) in which:

(c) a second inducer is to be further administered to the subject at least at a second time point to continue expression of the transgene at a predetermined level for a predetermined time or to modulate expression of the transgene to a predetermined level, optionally, a third inducer in which the third inducer is same or different from the first and/or second inducer; and

(d) optionally in which step (c) is to be repeated one or more times, and where the inducer at each administration is same or different from the inducer immediately prior to administration.

10. Use according to any preceding claim, in which:

(i) the time between administrations is at least 12 hours, at least 24 hours, 48 hours, 72 hours, 1 week, 10 days, 2 weeks, 3 weeks, or 4 weeks;

(ii) the time between administrations is at least 24 hours, 48 hours, or 72 hours;

(iii) the time between administrations is no more than 2 months, 3 months, 4 months, 5 months, or 6 months;

(iv) the time between administrations is no more than 2 months;

(v) the time between administrations is 1-2 days, 3-4 days, 5-7 days, 5-10 days, 7-10 days, 7-14 days, 10-14 days, 10-20 days, 14-21 days, 14-28 days, 21-28 days, or 21-34 days; and/or

(vi) the time between administrations is about a day, e.g., about 24 hours.

11. Use according to any preceding claim, in which:

(i) the use further comprises a step of determining the expression level of the transgene after the inducer is administered;

(ii) the use further comprises a step of determining the expression level of the transgene prior to the inducer being administered; and/or

(iii) in which the exogenous nucleotide sequence is to be further administered to the subject prior to the first or second inducer being administered;

12. Use according to any preceding claim for therapy, optionally for gene therapy.

13. Use according to any preceding claim, in which:

(i) the exogenous nucleotide sequence comprising the inducible promoter operably linked to a transgene is a viral vector; and/or

(ii) the exogenous nucleotide sequence comprising the inducible promoter operably linked to a transgene is adeno-associated viral (AAV), lentiviral, adenoviral, herpes viral, or hepatitis viral vector; and/or

(iii) the exogenous nucleotide sequence comprising the inducible promoter operably linked to a transgene is an AAV vector, e.g., an AAV gene therapy vector.

14. Use according to any preceding claim, in which:

(i) the inducers independently of other administrations are to be administered orally or intraperitoneally;

(ii) at least one of the inducers is to be administered orally, optionally in which:

(a) the second inducer is to be administered orally; or

(b) the first inducer is to be administered orally;

(iii) at least one of the inducers is to be administered intraperitoneally, optionally in which:

(a) the second inducer is to be administered intraperitoneally; or

(b) the first inducer is to be administered intraperitoneally.

15. Use according to any preceding claim, in which the first induction increases the transgene expression level to a maximum at about 24 hrs and declines thereafter, and in which the second induction and/or successive inductions has similar induction profile as seen with the first induction, for at least about 1 month, or at least about 2 months, or at least about 3 months, or at least about 5 months, or at least about six months, or longer, optionally in which:

(i) the transgene expression level at about 24 hrs after the first induction, or second induction, or successive inductions is at least about 200-fold higher than that of prior to the inducer being administered for the first time, or, the second time, or, any number of successive administrations; or

(ii) the first induction, the second induction, and/or, the successive inductions are not complete until about 160 hours after the inducer is administered; or

(iii) the dose of the inducer in successive administrations is reduced from its prior administration; or

(iv) the dose of the inducer in successive administrations remains same; or

(v) the dose of the inducer ranges from about 1mg/kg to about 80mg/kg; or

(vi) the inducers are to be administered orally; or

(vii) the inducers are to be administered intraperitoneally.

16. Use of an inducer in the manufacture of a medicament for regulating expression of a transgene in a primate subject, in which an inducer is to be administered to a primate subject, in which the inducer is artemisinin, an artemisinin derivative or a flavonoid compound, in which the primate subject comprises at least one cell comprising an exogenous nucleotide sequence comprising an inducible promoter operably linked to a transgene, in which the inducible promoter comprises a PBREM enhancer, in which the inducer is to be administered in an amount that is sufficient to express a measurable level of the transgene in the subject.

17. Use according to Claim 16, in which a plurality of doses of the inducer is to be administered, optionally in which:

(i) the time between administrations is at least 12 hours, at least 24 hours, 48 hours, 72 hours, 1 week, 10 days, 2 weeks, 3 weeks, or 4 weeks;

(ii) the time between administrations is at least 24 hours, 48 hours, or 72 hours;

(iii) the time between administrations is no more than 2 months, 3 months, 4 months, 5 months, or 6 months;

(iv) the time between administrations is no more than 2 months;

(v) the time between administrations is 1-3 days, 5-7 days, 5-10 days, 7-10 days, 7-14 days, 10-14 days, 10-20 days, 14-21 days, 14-28 days, 21-28 days, or 21-34 days;

(vi) the time between administrations is about 1 day;

(vii) the transgene expression level at about 24 hrs after an induction is at least about 200-fold higher than that of prior to the inducer being administered for the first time or any number of prior administrations;

(viii) an induction is not complete until about 160 hours after the inducer is administered;

(ix) the transgene expression level increases to a maximum at about 24 hrs after the first administration and declines thereafter and a second induction, and/or successive inductions, has similar induction profile as seen with the first induction, for at least about 1 month, or at least about 2 months, or at least about 3 months, or at least about 5 months, or at least about six months, or longer;

(x) the dose in successive administrations is reduced from a prior administration; and/or

(xi) the dose in successive administrations remains the same.

18. Use according to Claim 16 or 17, in which the inducer is artemisinin or an artemisinin derivative, optionally in which:

(i) the artemisinin derivative is a compound of Formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (I-I), (I-J), (I-K), (I-L), (I-M), (I-M'), (I-N), (I-N'), (I-O) or (I-O');

(ii) the derivative of artemisinin is artesunate, dihydroartemisinin, artesunate or artemether; optionally in which the derivative of artemisinin is artesunate or dihydroartemisinin.

19. Use according to Claim 16 or 17, in which the inducer is a flavonoid compound, optionally in which the flavonoid compound is flavone, baicalein, chrysin, galangin, $(OH)_4$ flavone, 6-hydroxyluteolin, acacetin, acerosin, alnetin, apigenin, apiin, artocarpetin, balcalein, beta-sitosterol, biochamin A, cannaflavin A, cannflavin A, cannflavin B, cannflavin C, catechin, catechin-3-gallate, cerrosillin, chrysoeriol, chrysoeriol, cirsilineol, cirsiliol, cirsimaritin, corymbosin, cupressuflavone, cyanidine, daidzein, datiscetin, delphinidine, digidrokempferol, dihydroquercetin, diosmetin, diosmin, echioidinin, epicatechin, epicatechin-3-gallate, epigallocatechin, epigallocatechin-3-gallate, eriodiktiol, eupatilin,

eupatorin, fisetin, fizetin, flavonol, formononetin, fortunelin, gallocatechin, gallocatechin-3-gallate, gardenin D, genistein, genistin, genkwanin, geraldol, geraldone, glycitein, glycitin, gomoeriodiktiol, gossypetin, hesperetin, hinokiflavone, hispidulin, hymenoxin, hypolaetin, isoquercetin, isorhamnetin, isorhamnetin, isoscutellarein, isovitexin, jaceosidin, kaempferol, kaempferol, kampferide, largonidin, luteolin, luteolin, malvidine, mikanin, morin, myricetin, myricetin, naringenin, negletein, neodiosmin, nepetin, nevadensin, nobiletin, nodifloretin, norartocarpetin, norwogonin, onopordin, orientin, oroxylin a, pachipodol, pectolinarigenin, pedalitin, peonidin, petunidin, pilloin, pratol, primetin, primuletin, pruentin, quercetagetin, quercetin, ramnazin, rhoifolin, robinetin, rutin, scaposin, scutellarein, serpyllin, sinensetin, sorbifolin, sudachitin, tangeretin, tangeritin, taxifolin, tectochrysin, tithonine, tricetin, tricin, velutin, vitexin, wightin, wogonin, xanthomicrol, zapotin, zapotinin, 6,7,4'-trishydroxy isoflavone, or 7,3'4'-trihydroxy isoflavone; optionally in which the flavonoid compound is flavone.

20. Use according to any of Claims 16 to 19, in which:

(i) each dose is independently from about 0.5 mg/kg to about 150mg/kg;

(ii) each dose is independently from about 1 mg/kg to about 100 mg/kg;

(iii) each dose is independently from about 1 mg/kg to about 80 mg/kg;

(iv) each dose is independently from about 1 mg/kg to about 40 mg/kg;

(v) each dose is independently from about 1 mg/kg to about 20 mg/kg;

(vi) each dose is independently from about 1 mg/kg to about 10 mg/kg;

(vii) each dose is independently about 80mg/kg, about 70mg/kg, about 60mg/kg, about 50mg/kg, about 40mg/kg, about 30mg/kg, about 20mg/kg, about 10mg/kg, about 6mg/kg, about 5mg/kg, or about 1mg/kg;

(viii) the exogenous nucleotide sequence is to be further administered to the subject prior to the inducer being administered for the first time;

(ix) a second inducer or, subsequent inducer is to be administered to the primate subject following the prior administration of an inducer to the primate subject, and optionally in which the inducer of the prior administration is to be administered in an amount that is sufficient to express a measurable level of the transgene in the subject, optionally in which:

(a) the inducer of the prior administration is different from the second or subsequent inducer administered to the subject; or

(b) the inducer of the prior administration is same as the second or, subsequent inducer administered to the subject but at a different dose;

(x) the method is a method of therapy, optionally in which the method of therapy is a method of gene therapy;

(xi) the exogenous nucleotide sequence comprising the inducible promoter operably linked to a transgene is a viral vector;

(xii) the exogenous nucleotide sequence comprising an inducible promoter operably linked to a transgene is adeno-associated viral (AAV), lentiviral, adenoviral, herpes viral, or hepatitis viral vector;

(xiii) the exogenous nucleotide sequence comprising an inducible promoter operably linked to a transgene is an AAV vector, e.g., an AAV gene therapy vector;

(xiv) each administration independently of other administrations is oral administration or intraperitoneal administration;

(xv) each administration is oral administration; and/or

(xvi) each administration is intraperitoneal administration.

21. Use according to any preceding claim, in which the transgene encodes an antibody or antigen binding portion an antibody, a coagulation factor, a cytokine, a hormone, a growth factor, a virus protein, a cell receptor ligand, a chimeric antigen receptor (CAR) or a CRISPR-Cas nuclease, optionally in which:

(i) the transgene encodes an antibody or an antigen binding portion thereof, optionally in which the antibody is an anti-PD1 antibody, anti-HER2 antibody, anti-PCSK9 antibody, anti-VEGFR2 antibody, anti-IL17 antibody, anti-Aβ3-42 antibody, anti-Sema3A antibody, anti-4-1BB (CD137) antibody, anti-5'-nucleotidase antibody, anti-5T4 antibody, anti-activin receptor-like kinase 1 antibody, anti-ACVR2B antibody, anti-adenocarcinoma antigen antibody, anti-amyloid antibody, anti-Ang-2 antibody, anti-angiopoietin 2 antibody, anti-angiopoietin 2 antibody, anti-angiopoietin 3 antibody, anti-anthrax toxin antibody, anti-AOC3 (VAP-1) antibody, anti-AXL antibody, anti-BAFF-R antibody, anti-B-cell activating factor (BAFF) antibody, anti-B-cell maturation

antigen (BCMA) antibody, anti-B-lymphoma cell antibody, anti-C242 antigen antibody, anti-C5 antibody, anti-C5a receptor (C5a) antibody, anti-CA-125 antibody, anti-calcitonin antibody, anti-calcitonin gene-related peptide alpha antibody, anti-calcitonin gene-related peptide beta antibody, anti-calcitonin gene-related peptide receptor (CGRP) antibody, anti-CanAg (a glycoform of MUC1) antibody, anti-carbonic anhydrase 9 (CA-IX) antibody, anti-Carcinoembryonic antigen (CEA) antibody, anti-Carcinoembryonic antigen (CEA)-related antigen antibody, anti-cardiac myosin antibody, anti-CCL11 antibody, anti-CCR2 antibody, anti-CCR4 antibody, anti-CCR5 antibody, anti-CCR5 antibody, anti-CD11 antibody, antibody, anti-CD123 antibody, anti-CD125 antibody, anti-CD134 antibody, anti-CD134 antibody, anti-CD147 antibody, anti-CD15 antibody, anti-CD152 antibody, anti-CD154 antibody, anti-CD18 antibody, anti-CD19 antibody, anti-CD2 antibody, anti-CD20 antibody, anti-CD20 antibody, anti-CD20 antibody, anti-CD200 antibody, anti-CD22 antibody, anti-CD23 antibody, anti-CD25 antibody, anti-CD27 antibody, anti-CD276 antibody, anti-CD278 antibody, antibody, anti-CD279 antibody, anti-CD28 antibody, anti-CD3 antibody, anti-CD3 antibody, anti-CD3 antibody, anti-CD3 antibody, anti-CD3 antibody, anti-CD30 antibody, anti-CD319 antibody, anti-CD33 antibody, anti-CD37 antibody, anti-CD38 antibody, anti-CD3E antibody, anti-CD3E antibody, anti-CD4 antibody, anti-CD40 antibody, anti-CD41 antibody, anti-CD44 antibody, anti-CD45 antibody, anti-CD5 antibody, anti-CD51 antibody, anti-CD52 antibody, anti-CD56 antibody, anti-CD6 antibody, anti-CD70 antibody, anti-CD74 antibody, anti-CD79B antibody, anti-CD80 antibody, anti-CEACAM5 antibody, anti-Claudin 18 Isoform 2 antibody, anti-clumping factor A antibody, anti-cMet antibody, anti-c-Met antibody, anti-coagulation factor III antibody, anti-complement C5a antibody, anti-complement component 1s (C1s) antibody, anti-Complement factor D (CFD) antibody, anti-connective tissue growth factor (CTGF) antibody, anti-CSF1 antibody, antibody, anti-CSF1R antibody, anti-CSF2 antibody, anti-CTLA-4 antibody, anti-CXCL10 (IP-10) antibody, anti-CXCR4 (CD184) antibody, anti-dabigatran antibody, anti-dendritic cell-associated lectin 2 antibody, anti-DLL3 antibody, anti-DLL4 antibody, anti-DPP4 antibody, anti-DR5 antibody, anti-EGFL7 antibody, anti-EGFR antibody, anti-EGFR antibody, anti-EGFR antibody, anti-EGFR extracellular domain III antibody, anti-endoglin antibody, anti-endotoxin antibody, anti-EpCAM antibody, anti-EPHA3 antibody, anti-ephrin receptor A3 antibody, anti-episialin antibody, anti-ERBB1 antibody, anti-ERBB3 (HER3) antibody, anti-FAP

(gene) (FAP) antibody, anti-FCGRT antibody, anti-FGF 23 antibody, anti-FGFR2 antibody, anti-FGFR2 antibody, anti-fibrin II antibody, anti-fibronectin extra domain-B antibody, anti-folate hydrolase antibody, anti-folate receptor 1 antibody, anti-folate receptor alpha antibody, anti-Frizzled receptor antibody, anti-FVIX antibody, anti-FVX antibody, anti-GD2 ganglioside antibody, anti-GD3 ganglioside antibody, anti-GDF-8 antibody, anti-gelatinase B antibody, anti-glucagon receptor (GCGR) antibody, anti-Glutamate carboxypeptidase II antibody, anti-glypican 3 antibody, anti-GMCSF antibody, anti-GPNMB antibody, anti-GPRC5D antibody, antibody, anti-growth differentiation factor 8 antibody, anti-GUCY2C antibody, anti-Hepatocyte growth factor (HGF) antibody, anti-HER1 antibody, anti-HER1 antibody, anti-HER1 antibody, anti-HER2/neu antibody, anti-HGFR antibody, anti-histone complex antibody, anti-HLA-DR antibody, anti-Hsp90 antibody, anti-human scatter factor receptor kinase antibody, anti-ICAM-1 (CD54) antibody, anti-IFN receptor antibody, anti-IFN-α antibody, anti-IFN-α/β receptor antibody, anti-IFN-γ antibody, anti-IgE antibody, anti-IgE Fc region antibody, anti-IGF-1 receptor (CD221) antibody, anti-IGF-2 antibody, anti-IGHE antibody, anti-IL-1 antibody, anti-IL-12 antibody, anti-IL-13 antibody, anti-IL-17A antibody, anti-IL-17AF antibody, anti-IL-17F antibody, anti-IL-1α antibody, anti-IL-1β antibody, anti-IL-2 antibody, anti-IL-20 antibody, anti-IL-22 antibody, anti-IL-23 antibody, anti-IL-23 antibody, anti-IL-23 antibody, anti-IL-23 antibody, anti-IL-23 antibody, anti-IL-23A antibody, anti-IL-3 receptor antibody, anti-IL-31 receptor A antibody, anti-IL-4 antibody, anti-IL-4Rα antibody, anti-IL-5 antibody, anti-IL-6 antibody, anti-IL-6 receptor antibody, anti-IL-9 antibody, anti-inducible T-cell co-stimulatory ligand (ICOSL) antibody, anti-integrin α4 antibody, anti-integrin β7 antibody, anti-integrin α4 β7 antibody, anti-integrin α4 β7 antibody, anti-integrin α5β1 antibody, anti-integrin αIIbβ3 antibody, anti-integrin αvβ3 antibody, anti-Interleukin 36 receptor (IL1RL2/IL1RAP) antibody, anti-ITGA2 (CD49b) antibody, anti-ITGB2 (CD18) antibody, anti-kallikrein antibody, anti-KIR2D antibody, anti-LAG3 antibody, anti-Lewis-Y antigen antibody, anti-LFA-1 (CD11a) antibody, anti-LINGO-1 antibody, anti-lipoteichoic acid antibody, anti-LIV-1 antibody, anti-LOXL2 antibody, anti-LRRC15 antibody, anti-L-selectin (CD62L) antibody, anti-lymphotoxin alpha (LTA) antibody, anti-LYPD3 antibody, anti-macrophage colony stimulating factor (MCSF) antibody, anti-macrophage migration inhibitory factor (MIF) antibody, anti-MASP-2 antibody, anti-MCP-1 antibody, anti-melanoma cell adhesion molecule (MCAM)

antibody, anti-mesothelin antibody, anti-MS4A1 antibody, antibody, anti-MST1R antibody, anti-MUC1 antibody, anti-MUC5AC antibody, anti-mucosal addressin cell adhesion molecule antibody, anti-myelin-associated glycoprotein antibody, anti-myostatin antibody, anti-NCA-90 (granulocyte antigen) antibody, anti-nectin-4 antibody, anti-nerve growth factor (NGF) antibody, anti-NGNA ganglioside antibody, anti-NKG2A antibody, anti-NOGO-A antibody, anti-Notch 1 antibody, anti-Notch receptor antibody, anti-NRP1 antibody, anti-OX-40 antibody, anti-oxLDL antibody, anti-PCDC1 antibody, anti-PCDP1 antibody, anti-PDGFRA antibody, anti-PDGFRB antibody, anti-PD-L1 antibody, anti-phosphate-sodium co-transporter antibody, anti-phosphatidylserine antibody, anti-PTK7 antibody, anti-RANKL antibody, anti-repulsive guidance molecule A (RGMA) antibody, anti-RHD (gene) (RHD) antibody, anti-Rhesus factor antibody, anti-Rhesus factor antibody, anti-root plate-specific spondin 3 antibody, anti-ROR1 antibody, anti-RTN4 antibody, anti-sclerostin antibody, anti-sclerostin (SOST) antibody, anti-SDC1 antibody, anti-selectin P antibody, anti-serum amyloid A protein antibody, anti-serum amyloid P component antibody, anti-SLAMF7 antibody, anti-SLITRK6 antibody, anti-SOST antibody, anti-sphingosine-1-phosphate antibody, anti-STEAP1 antibody, anti-TAG-72 antibody, anti-TAG-72 antibody, anti-tau protein antibody, anti-T-cell receptor antibody, anti-TEM1 antibody, anti-tenascin C antibody, anti-TGF-β antibody, anti-TGF-β1 antibody, anti-TGF-β2 antibody, anti-thymic stromal lymphopoietin (TSLP) antibody, anti-TIGIT antibody, anti-tissue factor pathway inhibitor (TFPI) antibody, anti-TNF antibody, anti-TNF antibody, anti-TNF-α antibody, anti-TNF-α antibody, anti-TRAIL-R1 antibody, anti-TRAIL-R2 antibody, anti-TROP-2 antibody, anti-tumor antigen CTAA16.88 antibody, anti-tumor necrosis factor receptor (TNFR) antibody, anti-tumor necrosis factor related activation protein (TRAP) antibody, anti-Tumor-associated glycoprotein 72 (TAG-72) antibody, anti-TWEAK receptor antibody, anti-TYRP1 (glycoprotein 75) antibody, anti-vascular endothelial growth factor A (VEGFA) antibody, anti-VEGFA antibody, anti-VEGFR-1 antibody, anti-vimentin antibody, anti-VISTA (protein) (VSIR) antibody, anti-VWF antibody, anti-α-fetoprotein antibody, anti-A-synuclein antibody or anti-β-amyloid antibody. optionally in which the antibody is selected from the group consisting of an anti-TNFα, anti-PD1 antibody, anti-HER2 antibody, anti-PCSK9 antibody, anti-VEGFR2 antibody, anti-IL17 antibody, anti-Aβ3-42 antibody, and anti-Sema3A antibody; or

(ii) the transgene encodes an antibody or an antigen binding portion thereof, and in which the antibody is selected from the group consisting 3F8, Abagovomab, Abciximab, Abituzumab, Abrezekimab, Abrilumab, Actoxumab, Adalimumab, Adecatumumab, Aducanumab, Afasevikumab, Afelimomab, Alacizumab pegol, Alemtuzumab, Alirocumab, Altumomab pentetate, Amatuximab, Amivantamab, Anatumomab mafenatox, Andecaliximab, Anetumab ravtansine, Anifrolumab, Ansuvimab, Anrukinzumab, (IMA-638), Apolizumab, Aprutumab ixadotin, Arcitumomab, Ascrinvacumab, Aselizumab, Atezolizumab, Atidortoxumab, Atinumab, Atoltivimab, Atoltivimab/maftivimab/odesivimab, Atorolimumab, Avelumab, Azintuxizumab vedotin, Bamlanivimab, Bapineuzumab, Basiliximab, Bavituximab, BCD-100, Bebtelovimab, Bectumomab, Bedinvetmab, Begelomab, Belantamab mafodotin, Belimumab, Bemarituzumab, Benralizumab, Berlimatoxumab, Bermekimab, Bersanlimab, Bertilimumab, Besilesomab, Bevacizumab, Bezlotoxumab, Biciromab, Bimagrumab, Bimekizumab, Birtamimab, Bivatuzumab, Bleselumab, Blinatumomab, Blontuvetmab, Blosozumab, Bococizumab, Brazikumab, Brentuximab vedotin, Briakinumab, Brodalumab, Brolucizumab, Brontictuzumab, Burosumab, Cabiralizumab, Camidanlumab tesirine, Camrelizumab, Canakinumab, Cantuzumab mertansine, Cantuzumab ravtansine, Caplacizumab, Casirivimab, Capromab, Carlumab, Carotuximab, Catumaxomab, cBR96-doxorubicin immunoconjugate, Cedelizumab, Cemiplimab, Cergutuzumab amunaleukin, Certolizumab pegol, Cetrelimab, Cetuximab, Cibisatamab, Cilgavimab, Cirmtuzumab, Citatuzumab bogatox, Cixutumumab, Clazakizumab, Clenoliximab, Clivatuzumab tetraxetan, Codrituzumab, Cofetuzumab pelidotin, Coltuximab ravtansine, Conatumumab, Concizumab, Cosfroviximab, Crenezumab, Crizanlizumab, Crotedumab, CR6261, Cusatuzumab, Dacetuzumab, Daclizumab, Dalotuzumab, Dapirolizumab pegol, Daratumumab, Dectrekumab, Demcizumab, Denintuzumab mafodotin, Denosumab, Depatuxizumab mafodotin, Derlotuximab biotin, Detumomab, Dezamizumab, Dinutuximab, Dinutuximab beta, Diridavumab, Domagrozumab, Donanemab, Dorlimomab aritox, Dostarlimab, Drozitumab, DS-8201, Duligotuzumab, Dupilumab, Durvalumab, Dusigitumab, Duvortuxizumab, Ecromeximab, Eculizumab, Edobacomab, Edrecolomab, Efalizumab, Efungumab, Eldelumab, Elezanumab, Elgemtumab, Elotuzumab, Elsilimomab, Emactuzumab, Emapalumab, Emibetuzumab, Emicizumab, Enapotamab vedotin, Enavatuzumab, Enfortumab vedotin, Enlimomab pegol, Enoblituzumab, Enokizumab,

Enoticumab, Ensituximab, Epcoritamab, Epitumomab cituxetan, Epratuzumab, Eptinezumab, Erenumab, Erlizumab, Ertumaxomab, Etaracizumab, Etesevimab, Etigilimab, Etrolizumab, Evinacumab, Evolocumab, Exbivirumab, Fanolesomab, Faralimomab, Faricimab, Farletuzumab, Fasinumab, FBTA05, Felvizumab, Fezakinumab, Fibatuzumab, Ficlatuzumab, Figitumumab, Firivumab, Flanvotumab, Fletikumab, Flotetuzumab, Fontolizumab, Foralumab, Foravirumab, Fremanezumab, Fresolimumab, Frovocimab, Frunevetmab, Fulranumab, Futuximab, Galcanezumab, Galiximab, Gancotamab, Ganitumab, Gantenerumab, Gatipotuzumab, Gavilimomab, Gedivumab, Gemtuzumab ozogamicin, Gevokizumab, Gilvetmab, Gimsilumab, Girentuximab, Glembatumumab vedotin, Glofitamab, Golimumab, Gomiliximab, Gosuranemab, Guselkumab, Ianalumab, Ibalizumab, Sintilimab, Ibritumomab tiuxetan, Icrucumab, Idarucizumab, Ifabotuzumab, Igovomab, Iladatuzumab vedotin, Imalumab, Imaprelimab, Imciromab, Imdevimab, Imgatuzumab, Inclacumab, Indatuximab ravtansine, Indusatumab vedotin, Inebilizumab, Infliximab, Intetumumab, Inolimomab, Inotuzumab ozogamicin, Ipilimumab, Iomab-B, Iratumumab, Isatuximab, Iscalimab, Istiratumab, Itolizumab, Ixekizumab, Keliximab, Labetuzumab, Lacnotuzumab, Ladiratuzumab vedotin, Lampalizumab, Lanadelumab, Landogrozumab, Laprituximab emtansine, Larcaviximab, Lebrikizumab, Lecanemab, Lemalesomab, Lendalizumab, Lenvervimab, Lenzilumab, Lerdelimumab, Leronlimab, Lesofavumab, Letolizumab, Lexatumumab, Libivirumab, Lifastuzumab vedotin, Ligelizumab, Loncastuximab tesirine, Losatuxizumab vedotin, Lilotomab satetraxetan, Lintuzumab, Lirilumab, Lodelcizumab, Lokivetmab, Lorvotuzumab mertansine, Lucatumumab, Lulizumab pegol, Lumiliximab, Lumretuzumab, Lupartumab, Lupartumab amadotin, Lutikizumab, Maftivimab, Mapatumumab, Margetuximab, Marstacimab, Maslimomab, Mavrilimumab, Matuzumab, Mepolizumab, Metelimumab, Milatuzumab, Minretumomab, Mirikizumab, Mirvetuximab soravtansine, Mitumomab, Modotuximab, Mogamulizumab, Monalizumab, Morolimumab, Mosunetuzumab, Motavizumab, Moxetumomab pasudotox, Muromonab-CD3, Nacolomab tafenatox, Namilumab, Naptumomab estafenatox, Naratuximab emtansine, Narnatumab, Natalizumab, Navicixizumab, Navivumab, Naxitamab, Nebacumab, Necitumumab, Nemolizumab, NEOD001, Nerelimomab, Nesvacumab, Netakimab, Nimotuzumab, Nirsevimab, Nivolumab, Nofetumomab merpentan, Obiltoxaximab, Obinutuzumab, Ocaratuzumab, Ocrelizumab, Odesivimab, Odulimomab, Ofatumumab, Olaratumab, Oleclumab,

Olendalizumab, Olokizumab, Omalizumab, Omburtamab, OMS721, Onartuzumab, Ontuxizumab, Onvatilimab, Opicinumab, Oportuzumab monatox, Oregovomab, Orticumab, Otelixizumab, Otilimab, Otlertuzumab, Oxelumab, Ozanezumab, Ozoralizumab, Pagibaximab, Palivizumab, Pamrevlumab, Panitumumab, Pankomab, Panobacumab, Parsatuzumab, Pascolizumab, Pasotuxizumab, Pateclizumab, Patritumab, PDR001, Pembrolizumab, Pemtumomab, Perakizumab, Pertuzumab, Pexelizumab, Pidilizumab, Pinatuzumab vedotin, Pintumomab, Placulumab, Pozelimab, Prezalumab, Plozalizumab, Pogalizumab, Polatuzumab vedotin, Ponezumab, Porgaviximab, Prasinezumab, Prezalizumab, Priliximab, Pritoxaximab, Pritumumab, PRO 140, Quilizumab, Racotumomab, Radretumab, Rafivirumab, Ralpancizumab, Ramucirumab, Ranevetmab, Ranibizumab, Raxibacumab, Ravagalimab, Ravulizumab, Refanezumab, Regavirumab, Regdanvimab, Relatlimab, Remtolumab, Reslizumab, Retifanlimab, Rilotumumab, Rinucumab, Risankizumab, Rituximab, Rivabazumab pegol, Robatumumab, Rmab, Roledumab, Romilkimab, Romosozumab, Rontalizumab, Rosmantuzumab, Rovalpituzumab tesirine, Rovelizumab, Rozanolixizumab, Ruplizumab, SA237, Sacituzumab govitecan, Samalizumab, Samrotamab vedotin, Sarilumab, Satralizumab, Satumomab pendetide, Secukinumab, Selicrelumab, Seribantumab, Setoxaximab, Setrusumab, Sevirumab, Sibrotuzumab, SGN-CD19A, SHP647, Sifalimumab, Siltuximab, Simtuzumab, Siplizumab, Sirtratumab vedotin, Sirukumab, Sofituzumab vedotin, Solanezumab, Solitomab, Sonepcizumab[104], Sontuzumab, Sotrovimab, Spartalizumab, Spesolimab[107], Stamulumab, Sulesomab, Suptavumab, Sutimlimab, Suvizumab, Suvratoxumab, Tabalumab, Tacatuzumab tetraxetan, Tadocizumab, Tafasitamab, Talacotuzumab, Talizumab, Talquetamab, Tamtuvetmab, Tanezumab, Taplitumomab paptox, Tarextumab, Tavolimab, Teclistamab, Tefibazumab, Telimomab aritox, Telisotuzumab, Telisotuzumab vedotin, Tenatumomab, Teneliximab, Teplizumab, Tepoditamab, Teprotumumab, Tesidolumab, Tetulomab, Tezepelumab, TGN1412, Tibulizumab, Tildrakizumab, Tigatuzumab, Timigutuzumab, Timolumab, tiragolumab, Tiragotumab, Tislelizumab, Tisotumab vedotin, Tixagevimab, TNX-650, Tocilizumab, Tomuzotuximab, Toralizumab, Tosatoxumab, Tositumomab, Tovetumab, Tralokinumab[115], Trastuzumab, Trastuzumab duocarmazine, Trastuzumab emtansine, TRBS07[117], Tregalizumab, Tremelimumab[118], Trevogrumab, Tucotuzumab celmoleukin, Tuvirumab, Ublituximab[120], Ulocuplumab, Urelumab, Urtoxazumab, Ustekinumab, Utomilumab,

Vadastuximab talirine, Vanalimab, Vandortuzumab vedotin, Vantictumab, Vanucizumab, Vapaliximab, Varisacumab, Varlilumab, Vatelizumab, Vedolizumab, Veltuzumab, Vepalimomab, Vesencumab, Vilobelimab, Visilizumab, Vobarilizumab, Volociximab, Vonlerolizumab, Vopratelimab, Vorsetuzumab mafodotin, Votumumab, Vunakizumab, Xentuzumab, XMAB-5574, Zalutumumab, Zanolimumab, Zatuximab, Zenocutuzumab, Ziralimumab, Zolbetuximab, and Zolimomab aritox; or

(iii) the transgene encodes a coagulation factor, optionally in which the coagulation factor is Factor VIII, Factor IX, Factor VII, Factor X, or Factor XI, preferably the coagulation factor is Factor VIII or Factor IX; or

(iv) the transgene encodes a hormone, optionally in which the hormone is selected from the group consisting of selected from erythropoietin (EPO), parathyroid hormone (PTH), adiponectin, adrenaline (or epinephrine), adrenocorticotropic hormone (ACTH or corticotropin), adropin, aldosterone, amylin (or islet amyloid polypeptide), androstenedione, angiotensin, angiotensinogen, antidiuretic hormone (or vasopressin), anti-müllerian hormone (or müllerian-inhibiting factor/hormone), arginine vasopressin), atrial natriuretic peptide (ANP or atriopeptin), brain natriuretic peptide, calcitonin, calcitriol, cholecystokinin (CCK), corticotropin-releasing hormone, cortisol, cortistatin, dehydroepiandrosterone, dihydrotestosterone, dopamine, endothelin, enkephalin, estradiol, estriol, estrone, follicle-stimulating hormone (FSH), galanin, gastric inhibitory polypeptide, gastrin, ghrelin, glucagon, glucagon-like peptide-1, gonadotropin-releasing hormone, growth hormone, growth hormone-releasing hormone, guanylin, hepcidin, human chorionic gonadotropin, human placental lactogen, inhibin, insulin, insulin-like growth factor (or somatomedin), leptin, leukotrienes, lipotropin, luteinizing hormone (LH), melanocyte stimulating hormone (MSH), melatonin, motilin, noradrenaline (or norepinephrine), orexin, osteocalcin, oxytocin (or pitocin), pancreatic polypeptide, pituitary adenylate cyclase-activating peptide, progesterone, prolactin (or leuteotropic hormone), prolactin-releasing hormone, prostacyclin, prostaglandins, relaxin, renin, secretin, somatostatin (or growth hormone–inhibiting hormone or growth hormone release–inhibiting hormone or somatotropin release–inhibiting factor or somatotropin release–inhibiting hormone), testosterone, thrombopoietin, thromboxane, thyroid-stimulating hormone (TSH or thyrotropin), thyrotropin-releasing hormone (TRH), thyroxine, triiodothyronine, uroguanylin, vasoactive intestinal peptide (VIP), or

vasopressin, more optionally in which the hormone is erythropoietin (EPO) and parathyroid hormone (PTH); or

(v) the transgene encodes a growth factor, optionally in which the growth factor is tumor necrosis factor-alpha (TNF-α), adrenomedullin (AM), angiopoietin (Ang), autocrine motility factor, bone morphogenetic protein (BMP), ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), colony-stimulating factor (e.g., macrophage colony-stimulating factor (M-CSF), granulocyte colony-stimulating factor (G-CSF), or granulocyte macrophage colony-stimulating factor (GM-CSF)), epidermal growth factor (EGF), ephrin (e.g., ephrin A1, ephrin A2, ephrin A3, ephrin A4, ephrin A5, ephrin B1, ephrin B2, or ephrin B3), erythropoietin (EPO), fibroblast growth factor (e.g., FGF1, FGF2, FGF3, FGF4, FGF5, FGF6, FGF7, FGF8, FGF9, FGF10, FGF11, FGF12, FGF13, FGF14, FGF15, FGF16, FGF17, FGF18, FGF19, FGF20, FGF21, FGF22 or FGF23), glial cell line-derived neurotrophic factor (GDNF), neurturin, persephin, artemin, growth differentiation factor-9 (GDF9), hepatocyte growth factor (HGF), hepatoma-derived growth factor (HDGF), insulin-like growth factor (e.g., IGF-1 or IGF-2), interleukin (e.g., IL-1, IL-2, IL-3, IL-4, IL-5, IL-6 or IL-7), keratinocyte growth factor (KGF), migration-stimulating factor (MSF), macrophage-stimulating protein (MSP), myostatin (GDF-8), neuregulin (e.g., NRG1, NRG3, NRG3 or NRG4), neurotrophin (e.g., brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3) or neurotrophin-4 (NT-4)), placental growth factor (PGF), platelet-derived growth factor (PDGF), renalase (RNLS), T-cell growth factor (TCGF), thrombopoietin (TPO), transforming growth factor (e.g., TGF-α or TGF-β), or vascular endothelial growth factor (VEGF); or

(vi) the transgene encodes a CRISPR-Cas nuclease, optionally selected from the group consisting of Cas9, Cas12, Cas Phi, CasX, and CasRx; or

(vii) the transgene encodes a cytokine, optionally in which the cytokine is interleukin-lα (IL-lα), interleukin-1/3 (IL-1/3), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-8 (IL-8/CXCL8), interleukin-10 (IL-10), interleukin-12 (IL-12), interleukin- 13 (IL-13), interleukin-15 (IL-15), interleukin-17 (IL-17), interleukin-18 (IL-18), interleukin-37 (IL-37), interleukin-38 (IL-38), tumor necrosis factor-α (TNF-α), interferon-α (INF-α), interferon-b (INF-b), interferon-γ (INF-γ), granulocyte- monocyte colony stimulating

factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), monocyte chemoattractant protein- 1 (MCP-1/CCL2), macrophage inflammatory protein l-ct (MCP-1/CCL3), macrophage inflammatory protein-1/3, RANTES (CCL5), Eotaxin (CCL11), variable endothelial growth factor (VEGF), endothelial growth factor (EGF), or fibroblast growth factor (FGF). In some embodiments, the transgene encodes IL-2. In some embodiments, the transgene encodes IL-37. In some embodiments, the transgene encodes IL-38; or

(viii) the transgene encodes a virus protein, optionally selected from the group consisting of viral envelop protein, viral nucleocapsid protein, viral membrane protein, REP, CAP, REV, VSV-G and RD114.

22. Use according to any preceding claim, in which the transgene is detrimental to the cell or to the subject when constitutively expressed.

23. Use according to any preceding claim, in which the subject is a non-human primate.

24. Use according to any of Claims 1 to 22, in which the subject is a human.

25. Use according to any preceding claim, in which the cell comprising the cell comprising the exogenous nucleotide sequence is a liver cell.

26. A first and at least a second inducer for use in a method of regulating expression of a transgene in a primate subject, in which:

(a) a first inducer is to be administered to the subject at a first time point, in which the primate subject comprises at least one cell comprising an exogenous nucleotide sequence comprising an inducible promoter operably linked to a transgene, in which the inducible promoter comprises a PBREM enhancer, in which the first inducer is artemisinin, a derivative of artemisinin or a flavonoid compound, and in which the first dose comprises an amount of the inducer that is sufficient to express a measurable level of the transgene in the subject; and

(b) a second inducer is to be administered to the subject at least at a second time point to continue expression of the transgene at a predetermined level for a predetermined time or to modulate expression of the transgene to a predetermined level, and

in which the second inducer is artemisinin; derivative of artemisinin; a flavonoid compound, e.g. flavone, chrysin, baicalein, or galangin; 1,4-Bis[2-(3,5-

dichloropyridyloxy)]benzene (TCPOBOP); phenobarbital (PB); 6-(4Chlorophenyl)imidazo[2,1-b][1,3]thiazole-5-carbaldehyde-O-(3,4-dichlorobenzyl)oxime (CITCO); Acetaminophen; Buprenorphine; Phenytoin; Carbamazepine; Valproic Acid; Chlorpromazine; Efavirenz; Nevirapine; Rilpivirine; Etravirine; Diazepam; Cyclophosphamid; Ifosfamide; Cerivastatin; Simvastatin; lovastatin; substituted sulphonamides; Thiazolidin-4-one; Estradiol; Estrone and analogues; 17α-ethinyl-3;17ß-estradiol (EE2); Dehydroepiandrost erone (DHEA); 5ß-pregnane-3,20-dione; Diethylstilbestrol; Gingko *biloba* extract; Galangin; chrysin; baicalein; Diallyl sulphide; Ellagic acid; Resveratrol; Squalestatin-1; Bilobalide; Triclocarban; Triclosan; Dichlorodiphenyltrichloroethane (DDT); Dieldrin; Methoxychlor; Metofluthrin; Permethrin; Pyrethrins; Sulfoxaflor; Diethylhexyl phthalate (DEHP); Cyproconazole; Fluconazole; Propiconazole; FL81; Tri-p-methylphenyl phosphate (TMPP); UM104; or UM145.

27. A first and at least a second inducer for use according to Claim 26, in which the use is according to any of Claims 1 to 25.

28. A first and at least a second inducer for use according to Claim 26 or 27, which is a method of therapy, suitably a method of gene therapy.

29. A first and at least a second inducer for use according to Claim 26, 27 or 28, in which the exogenous nucleotide sequence comprising an inducible promoter operably linked to a transgene is an AAV gene therapy vector.

30. Artemisinin or a derivative of artemisinin, for use as an inducer in a method of regulating expression of a transgene in a primate subject, in which the primate subject comprises at least one cell comprising an exogenous nucleotide sequence comprising an inducible promoter operably linked to a transgene, in which the inducible promoter comprises a PBREM enhancer, in which the inducer is to be administered to the subject at a dose which comprises an amount of the inducer that is sufficient to express a therapeutically effective level of the transgene in the subject.

31. Artemisinin or a derivative of artemisinin for use according to Claim 30, in which:

(i) the method is a method of therapy, suitably a method of gene therapy;

(ii) the artemisinin derivative is a compound as defined in Claim 2, optionally in which the artemisinin derivative is of Formula (I), (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (I-I), (I-J), (I-K), (I-L), (I-M), (I-M'), (I-N), (I-N'), (I-O) or (I-O');

(iii) the derivative of artemisinin is artesunate, dihydroartemisinin, artesunate, or artemether;

(iv) artemisinin or a derivative of artemisinin is to be administered to the primate subject following the prior administration of an inducer to the primate subject, optionally in which the inducer of the prior administration was a different inducer, or in which the inducer of the prior administration was the same inducer but at a different dose;

(v) the exogenous nucleotide sequence comprising an inducible promoter operably linked to a transgene is an AAV gene therapy vector;

(vi) the method comprises prior administration of the exogenous nucleotide sequence to the subject prior to the inducer being administered.

(vii) the artemisinin or a derivative of artemisinin is to be administered at a dose of from about 0.1mg/kg to 80mg/kg, from about 0.1mg/kg to about 70mg/kg, from about 0.1mg/kg to about 60mg/kg, from about 0.1mg/kg to about 50mg/kg, from about 0.1mg/kg to about 40mg/kg, from about 0.1mg/kg to about 30mg/kg, from about 0.1mg/kg to about 20mg/kg, from about 0.1mg/kg to about 10mg/kg, from about 0.1mg/kg to about 6mg/kg, from about 0.1mg/kg to about 5mg/kg, or from about 0.1mg/kg to about 1mg/kg; and/or

(vii) the inducer comprising artemisinin or a derivative of artemisinin is to be administered orally, optionally in which the composition comprises artesunate.

32. A flavonoid compound, for use as an inducer in a method of regulating expression of a transgene in a primate subject, in which the primate subject comprises at least one cell comprising an exogenous nucleotide sequence comprising an inducible promoter operably linked to a transgene, in which the inducible promoter comprises a PBREM enhancer, in which the inducer is to be administered to the subject at a dose which comprises an amount of the inducer that is sufficient to express a therapeutically effective level of the transgene in the subject.

33. Flavonoid compound for use according to Claim 32, in which:

(i) the method is a method of therapy, suitably a method of gene therapy;

(ii) the flavonoid compound is flavone, baicalein, chrysin, galangin, $(OH)_4$ flavone, 6-hydroxyluteolin, acacetin, acerosin, alnetin, apigenin, apiin, artocarpetin, balcalein, beta-sitosterol, biochamin A, cannaflavin A, cannflavin A, cannflavin B, cannflavin C, catechin, catechin-3-gallate, cerrosillin, chrysoeriol, chrysoeriol, cirsilineol, cirsiliol, cirsimaritin, corymbosin, cupressuflavone, cyanidine, daidzein, datiscetin, delphinidine, digidrokempferol, dihydroquercetin, diosmetin, diosmin, echioidinin, epicatechin, epicatechin-3-gallate, epigallocatechin, epigallocatechin-3-gallate, eriodiktiol, eupatilin, eupatorin, fisetin, fizetin, flavonol, formononetin, fortunelin, gallocatechin, gallocatechin-3-gallate, gardenin D, genistein, genistin, genkwanin, geraldol, geraldone, glycitein, glycitin, gomoeriodiktiol, gossypetin, hesperetin, hinokiflavone, hispidulin, hymenoxin, hypolaetin, isoquercetin, isorhamnetin, isorhamnetin, isoscutellarein, isovitexin, jaceosidin, kaempferol, kaempferol, kampferide, largonidin, luteolin, luteolin, malvidine, mikanin, morin, myricetin, myricetin, naringenin, negletein, neodiosmin, nepetin, nevadensin, nobiletin, nodifloretin, norartocarpetin, norwogonin, onopordin, orientin, oroxylin a, pachipodol, pectolinarigenin, pedalitin, peonidin, petunidin, pilloin, pratol, primetin, primuletin, pruentin, quercetagetin, quercetin, ramnazin, rhoifolin, robinetin, rutin, scaposin, scutellarein, serpyllin, sinensetin, sorbifolin, sudachitin, tangeretin, tangeritin, taxifolin, tectochrysin, tithonine, tricetin, tricin, velutin, vitexin, wightin, wogonin, xanthomicrol, zapotin, zapotinin, 6,7,4'-trishydroxy isoflavone, or 7,3'4'-trihydroxy isoflavone;

(iii) the flavonoid compound is flavone;

(iv) the flavonoid compound is to be administered to the primate subject following the prior administration of an inducer to the primate subject, optionally in which the inducer of the prior administration was a different inducer, or in which the inducer of the prior administration was the same inducer but at a different dose;

(v) the exogenous nucleotide sequence comprising an inducible promoter operably linked to a transgene is an AAV gene therapy vector;

(vi) the method comprises prior administration of the exogenous nucleotide sequence to the subject prior to the inducer being administered.

(vii) the flavonoid compound is to be administered at a dose of from about 0.1mg/kg to 80mg/kg, from about 0.1mg/kg to about 70mg/kg, from about 0.1mg/kg to about 60mg/kg, from about 0.1mg/kg to about 50mg/kg, from about 0.1mg/kg to about 40mg/kg, from about 0.1mg/kg to about 30mg/kg, from about 0.1mg/kg to about 20mg/kg, from about 0.1mg/kg to about 10mg/kg, from about 0.1mg/kg to about 6mg/kg, from about 0.1mg/kg to about 5mg/kg, or from about 0.1mg/kg to about 1mg/kg;

(vii) the flavonoid compound is to be administered orally; and/or

(ix) the flavonoid compound is to be administered intraperitoneally.

34. Use of a first inducer, a second inducer and a third inducer in the manufacture of a medicament for regulating expression of a transgene in the liver of a subject, in which:

a dose of a first inducer is to be administered to the subject at least a first time point;

a second dose of a second inducer is to be administered to the subject at least a second time point, in which the second inducer can be the same as or different than the first inducer; and

a third dose of a third inducer is to be administered to the subject at least a third time point, in which the third inducer can be the same as or different than the first inducer and the second inducer;

in which the subject comprises at least one liver cell comprising an exogenous nucleotide sequence comprising a synthetic inducible promoter operably linked to a transgene;

in which the synthetic inducible promoter comprises at least one PBREM enhancer; and

in which the transgene is detrimental to the liver cell or to the subject when constitutively expressed.

35. Use according to Claim 34, in which:

(i) the first inducer is selected from the group consisting of artemisinin; derivative of artemisinin; a flavonoid compound, e.g. flavone, chrysin, baicalein, or galangin; 1,4-Bis[2-(3,5-dichloropyridyloxy)]benzene (TCPOBOP); phenobarbital (PB); 6-(4Chlorophenyl)imidazo[2,1-b][1,3]thiazole-5-carbaldehyde-O-(3,4-dichlorobenzyl)oxime (CITCO); Acetaminophen; Buprenorphine; Phenytoin; Carbamazepine; Valproic Acid; Chlorpromazine; Efavirenz; Nevirapine; Rilpivirine;

Etravirine; Diazepam; Cyclophosphamid; Ifosfamide; Cerivastatin; Simvastatin; lovastatin; substituted sulphonamides; Thiazolidin-4-one; Estradiol; Estrone and analogues; 17α-ethinyl-3;17ß-estradiol (EE2); Dehydroepiandrost erone (DHEA); 5ß-pregnane-3,20-dione; Diethylstilbestrol; Gingko *biloba* extract; Galangin; chrysin; baicalein; Diallyl sulphide; Ellagic acid; Resveratrol; Squalestatin-1; Bilobalide; Triclocarban; Triclosan; Dichlorodiphenyltrichloroethane (DDT); Dieldrin; Methoxychlor; Metofluthrin; Permethrin; Pyrethrins; Sulfoxaflor; Diethylhexyl phthalate (DEHP); Cyproconazole; Fluconazole; Propiconazole; FL81; Tri-p-methylphenyl phosphate (TMPP); UM104; or UM145;

(ii) the second inducer is selected from the group consisting of artemisinin; derivative of artemisinin; a flavonoid compound, e.g. flavone, chrysin, baicalein, or galangin; 1,4-Bis[2-(3,5-dichloropyridyloxy)]benzene (TCPOBOP); phenobarbital (PB); 6-(4Chlorophenyl)imidazo[2,1-b][1,3]thiazole-5-carbaldehyde-O-(3,4-dichlorobenzyl)oxime (CITCO); Acetaminophen; Buprenorphine; Phenytoin; Carbamazepine; Valproic Acid; Chlorpromazine; Efavirenz; Nevirapine; Rilpivirine; Etravirine; Diazepam; Cyclophosphamid; Ifosfamide; Cerivastatin; Simvastatin; lovastatin; substituted sulphonamides; Thiazolidin-4-one; Estradiol; Estrone and analogues; 17α-ethinyl-3;17ß-estradiol (EE2); Dehydroepiandrost erone (DHEA); 5ß-pregnane-3,20-dione; Diethylstilbestrol; Gingko biloba extract; Galangin; chrysin; baicalein; Diallyl sulphide; Ellagic acid; Resveratrol; Squalestatin-1; Bilobalide; Triclocarban; Triclosan; Dichlorodiphenyltrichloroethane (DDT); Dieldrin; Methoxychlor; Metofluthrin; Permethrin; Pyrethrins; Sulfoxaflor; Diethylhexyl phthalate (DEHP); Cyproconazole; Fluconazole; Propiconazole; FL81; Tri-p-methylphenyl phosphate (TMPP); UM104; or UM145;

(iii) the third inducer is selected from the group consisting of artemisinin; derivative of artemisinin; a flavonoid compound, e.g. flavone, chrysin, baicalein, or galangin; 1,4-Bis[2-(3,5-dichloropyridyloxy)]benzene (TCPOBOP); phenobarbital (PB); 6-(4Chlorophenyl)imidazo[2,1-b][1,3]thiazole-5-carbaldehyde-O-(3,4-dichlorobenzyl)oxime (CITCO); Acetaminophen; Buprenorphine; Phenytoin; Carbamazepine; Valproic Acid; Chlorpromazine; Efavirenz; Nevirapine; Rilpivirine; Etravirine; Diazepam; Cyclophosphamid; Ifosfamide; Cerivastatin; Simvastatin; lovastatin; substituted sulphonamides; Thiazolidin-4-one; Estradiol; Estrone and analogues; 17α-ethinyl-3;17ß-estradiol (EE2); Dehydroepiandrost erone (DHEA); 5ß-

pregnane-3,20-dione; Diethylstilbestrol; Gingko *biloba* extract; Galangin; chrysin; baicalein; Diallyl sulphide; Ellagic acid; Resveratrol; Squalestatin-1; Bilobalide; Triclocarban; Triclosan; Dichlorodiphenyltrichloroethane (DDT); Dieldrin; Methoxychlor; Metofluthrin; Permethrin; Pyrethrins; Sulfoxaflor; Diethylhexyl phthalate (DEHP); Cyproconazole; Fluconazole; Propiconazole; FL81; Tri-p-methylphenyl phosphate (TMPP); UM104; or UM145.

36. Use according to any preceding claim, in which the first inducer is artemisinin, or a derivative thereof.

37. Use according to any of Claims 1 to 35, in which first inducer is a flavonoid compound.

38. Use according to any of Claims 1 to 36, in which the second inducer or third inducer is artemisinin or, derivative thereof.

39. Use according to any of Claims 1 to 36, in which the second inducer is flavonoid compound.