~~WHAT IS CLAIMED IS:~~

1. A method for stable integration and expression of a heterologous polynucleotide in a host cell, comprising inserting the heterologous polynucleotide into the genome of the host cell at a native chromosomal site located within or adjacent to a gene selected from the group consisting of ankyrin 2 gene (Ank2), cleavage and polyadenylation specific factor 4 gene (Cpsf4), C-Mos gene, and Nephrocystin-1/Mal gene.

2. The method of claim 1, wherein insertion of the heterologous polynucleotide is mediated by homologous recombination or by a hybrid recombinase.

3. The method of claim 1, wherein the host cell is a mammalian cell.

4. The method of claim 1, wherein the host cell is a Chinese hamster ovary (CHO) cell.

5. The method of claim 4, wherein the native chromosomal insertion site is at or close to positions 130-131 of SEQ ID NO: 1 for the Ank2 gene, positions 629-630 of SEQ ID NO: 2 for the Cpsf4 gene, positions 272-273 of SEQ ID NO: 3 for the C-Mos gene, positions 239-240 of SEQ ID NO: 4 for the Nephrocystin-1/Mal gene.

6. The method of claim 1, wherein the heterologous polynucleotide encodes a polypeptide.

7. The method of claim 6, wherein the polypeptide is a therapeutic protein or an industrial protein.

8. A recombinant polynucleotide for stably integrating a heterologous polynucleotide sequence into the genome of a mammalian cell, comprising:

a first homology arm, the heterologous polynucleotide sequence, and a second homology arm;

wherein the first and second homology arms are substantially identical to the 5'- and 3'- sequences, respectively, that flank a native chromosomal insertion site located within or adjacent to a gene selected from the group consisting of ankyrin 2 gene (Ank2), cleavage and polyadenylation specific factor 4 gene (Cpsf4), C-Mos gene, and Nephrocystin-1/Mal gene.

9. The polynucleotide of claim 8, wherein the native chromosomal insertion site supports stable integration of a foreign gene.

10. The polynucleotide of claim 8, wherein the heterologous polynucleotide sequence encodes a polypeptide.

11. The polynucleotide of claim 8, wherein the polypeptide is a therapeutic protein or an industrial protein.

12. The polynucleotide of claim 8, wherein the heterologous polynucleotide sequence comprises a site-specific recombination sequence (chromosomal landing pad).

13. The polynucleotide of claim 12, wherein the site-specific recombination sequence is a recognition sequence recognized by a phage integrase.

14. The polynucleotide of claim 13, wherein the phage integrase is phiC-31 integrase.

15. The polynucleotide of claim 13, wherein the recognition sequence is an attP site or an attB site recognized by the phage integrase.

16. The polynucleotide of claim 8, wherein the mammalian cell is a Chinese hamster ovary (CHO) cell.

17. The polynucleotide of claim 16, wherein the native chromosomal insertion site is at or close to positions 130-131 of SEQ ID NO: 1 for the Ank2 gene, positions 629-630 of SEQ ID NO: 2 for the Cpsf4 gene, positions 272-273 of SEQ ID NO: 3 for the C-Mos gene, positions 239-240 of SEQ ID NO: 4 for the Nephrocystin-1/Mal gene.

18. A vector comprising the recombinant polynucleotide of claim 8.

19. An engineered mammalian cell, comprising a heterologous polynucleotide which is stably integrated into its genome at one or more native chromosomal insertion sites located within or adjacent to a gene selected from the group consisting of ankyrin 2 gene (Ank2), cleavage and polyadenylation specific factor 4 gene (Cpsf4), C-Mos gene and Nephrocystin-1/Mal gene.

~~20. The cell of claim 19, wherein the native chromosomal insertion site supports~~ stable integration of a foreign gene.

21. The cell of claim 19, wherein the heterologous polynucleotide encodes a polypeptide.

22. The cell of claim 21, wherein the polypeptide is a therapeutic protein or an industrial protein.

23. The cell of claim 19, wherein the heterologous polynucleotide comprises a site-specific recombination sequence (chromosomal landing pad).

24. The cell of claim 23, wherein the site-specific recombination sequence is a recognition sequence recognized by a phage integrase.

25. The cell of claim 24, wherein the phage integrase is phiC-31 integrase.

26. The cell of claim 24, wherein the recognition sequence is an attP site or an attB site recognized by the phage integrase.

27. The cell of claim 19, which is a Chinese hamster ovary (CHO) cell.

28. The cell of claim 27, wherein the heterologous polynucleotide is integrated at or close to positions 130-131 of SEQ ID NO: 1 for the Ank2 gene, positions 629-630 of SEQ ID NO: 2 for the Cpsf4 gene, positions 272-273 of SEQ ID NO: 3 for the C-Mos gene, positions 239-240 of SEQ ID NO: 4 for the Nephrocystin-1/Mal gene.

29. A method for stably integrating a heterologous polynucleotide into the genome of a mammalian cell, comprising:

(a) inserting a site-specific recombination sequence into the genome of the cell, wherein the insertion is at a native chromosomal insertion site located within or adjacent to a gene selected from the group consisting of ankyrin 2 gene (Ank2), cleavage and polyadenylation specific factor 4 gene (Cpsf4), C-Mos gene, and Nephrocystin-1/Mal gene.

(b) integrating by homologous recombination the heterologous polynucleotide into the genome of the cell at the inserted site-specific recombination sequence.

30. The method of claim 29, wherein the native chromosomal insertion site supports stable integration of a foreign gene.

31. The method of claim 29, wherein the site-specific recombination sequence is a first recognition sequence recognized by a phage integrase.

32. The method of claim 31, wherein the phage integrase is phiC-31 integrase.

33. The method of claim 31, wherein the first recognition sequence is an attP site or an attB site.

34. The method of claim 31, wherein the heterologous polynucleotide is attached to a second recognition sequence of the phage integrase which is cognate to the first recognition sequence.

35. The method of claim 34, wherein the second recognition sequence is an attB site or an attP site.

36. The method of claim 29, wherein the cell is a Chinese hamster ovary (CHO) cell.

37. The method of claim 36, wherein the site-specific recombination sequence is inserted into the genome at or close to positions 130-131 of SEQ ID NO: 1 for the Ank2 gene, positions 629-630 of SEQ ID NO: 2 for the Cpsf4 gene, positions 272-273 of SEQ ID NO: 3 for the C-Mos gene, positions 239-240 of SEQ ID NO: 4 for the Nephrocystin-1/Mal gene Mal gene.

38. The method of claim 29, wherein the heterologous polynucleotide comprises a target polypeptide-encoding sequence that is operably linked to a promoter sequence.

39. The method of claim 31, wherein the integration occurs in the presence of the phage integrase.

40. The method of claim 39, wherein the phage integrase is expressed from a vector introduced into the cell.

WHAT IS CLAIMED IS:

1. An *ex vivo* or *in vitro* method for stable integration and expression of a heterologous polynucleotide in a host cell, comprising inserting the heterologous polynucleotide into the genome of the host cell at a native chromosomal site located at or close to:

i. positions 629-630 of SEQ ID NO: 2 in CHO cells or a position corresponding to positions 629-630 of SEQ ID NO: 2 in other mammalian cells in the cleavage and polyadenylation specific factor 4 gene (Cpsf4),

ii. positions 272-273 of SEQ ID NO:3 in CHO cells or a position corresponding to positions 272-273 of SEQ ID NO:3 for the C-Mos gene; or

iii. positions 239-240 of SEQ ID NO:4 in CHO cells or a position corresponding to positions 239-240 of SEQ ID NO:4 in the Nephrocystin-1/Mal gene.

2. The method of claim 1, wherein insertion of the heterologous polynucleotide is mediated by homologous recombination or by a hybrid recombinase.

3. The method of claim 1, wherein the host cell is a mammalian cell.

4. The method of claim 1, wherein the host cell is a Chinese hamster ovary (CHO) cell.

5. The method of claim 1, wherein the heterologous polynucleotide encodes a polypeptide.

6. The method of claim 5, wherein the polypeptide is selected from the group consisting of factor VIII, factor IX, β-globin, low-density lipoprotein receptor, adenosine deaminase, purine nucleoside phosphorylase, sphingomyelinase, glucocerebrosidase, cystic fibrosis transmembrane conductance regulator, α-antitrypsin, CD-18, ornithine transcarbamylase, argininosuccinate synthetase, phenylalanine hydroxylase, branched-chain α-ketoacid dehydrogenase, fumarylacetoacetate hydrolase, glucose 6-phosphatase, α-L-fucosidase, β-glucuronidase, α-L-iduronidase, galactose 1-phosphate uridyltransferase, interleukins, cytokines, small peptides, Herceptin®, polypeptide antigens from bacterial or

viral pathogens (e.g., E. coli, P. aeruginosa, S. aureus, malaria, HIV, rabies virus, HBV, and cytomegalovirus), lactoferrin, thioredoxin, beta-casein vaccines, insulin, erythropoietin, tissue plasminogen activator (tPA), urokinase, streptokinase, neutropoesis stimulating protein, filgastim, granulocyte colony stimulating factor (G-CSF)), thrombopoietin (TPO), growth hormone, hemoglobin, insulinotropin, imiglucerase, sarbramostim, endothelian, soluble CD4, ciliary neurite transforming factor (CNTF), granulocyte macrophage colony stimulating factor (GM-CSF), brain-derived neurite factor (BDNF), parathyroid hormone(PTH)-like hormone, insulinotrophic hormone, insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), acidic fibroblast growth factor, basic fibroblast growth factor, transforming growth factor β, neurite growth factor (NGF), interferons (IFN) (e.g., IFN- α2b, IFN- α2a, IFN-αNI , IFN-plb, IFN-γ), interleukins (e.g., IL-1, IL-2, IL-8), tumor necrosis factor (TNF) (e.g., TNF-α, TNF-β), transforming growth factor- α and -β, catalase, calcitonin, arginase, phenylalanine ammonia lyase, L-asparaginase, pepsin, uricase, trypsin, chymotrypsin, elastase, carboxypeptidase, lactase, sucrase, intrinsic factor, vasoactive intestinal peptide (VIP), calcitonin, Ob gene product, cholecystokinin (CCK), serotonin, glucagon, adrenergic receptors, serotonin receptors, low-density lipoprotein receptor, CD-I8, sarcoglycans fumarylacetoacetate hydrolase (FAH), antiviral proteins, collagens, and dystrophin.

7. A recombinant polynucleotide for stably integrating a heterologous polynucleotide sequence into the genome of a mammalian cell, comprising:

a first homology arm, the heterologous polynucleotide sequence, and a second homology arm;

wherein the first and second homology arms are substantially identical to the 5'- and 3'- sequences, respectively, that flank a native chromosomal insertion site located at or close to:

i. positions 629-630 of SEQ ID NO:2 in CHO cells or a position corresponding to positions 629-630 of SEQ ID NO:2 in other mammalian cells in the cleavage and polyadenylation specific factor 4 gene (Cpsf4);

ii. positions 272-273 of SEQ ID NO:3 in CHO cells or a position corresponding to positions 272-273 of SEQ ID NO:3 for the C-Mos gene; or

iii. positions 239-240 of SEQ ID NO:4 in CHO cells or a position corresponding to positions 239-240 of SEQ ID NO:4 in the Nephrocystin-1/Mal gene.

8. The polynucleotide of claim 7, wherein the native chromosomal insertion site supports stable integration of a foreign gene.

9. The polynucleotide of claim 7, wherein the heterologous polynucleotide sequence encodes a polypeptide.

10. The polynucleotide of claim 7, wherein the polypeptide is selected from the group consisting of selected from the group consisting of factor VIII, factor IX, β-globin, low-density lipoprotein receptor, adenosine deaminase, purine nucleoside phosphorylase, sphingomyelinase, glucocerebrosidase, cystic fibrosis transmembrane conductance regulator, α-antitrypsin, CD- 18, ornithine transcarbamylase, argininosuccinate synthetase, phenylalanine hydroxylase, branched-chain α-ketoacid dehydrogenase, fumarylacetoacetate hydrolase, glucose 6-phosphatase, α-L-fucosidase, β-glucuronidase, α-L-iduronidase, galactose 1-phosphate uridyltransferase, interleukins, cytokines, small peptides, Herceptin®, polypeptide antigens from bacterial or viral pathogens (e.g., E. coli, P. aeruginosa, S. aureus, malaria, HIV, rabies virus, HBV, and cytomegalovirus), lactoferrin, thioredoxin, beta-casein vaccines, insulin, erythropoietin, tissue plasminogen activator (tPA), urokinase, streptokinase, neutropoesis stimulating protein, filgastim, granulocyte colony stimulating factor (G-CSF)), thrombopoietin (TPO), growth hormone, hemoglobin, insulinotropin, imiglucerase, sarbramostim, endothelian, soluble CD4, ciliary neurite transforming factor (CNTF), granulocyte macrophage colony stimulating factor (GM-CSF), brain-derived neurite factor (BDNF), parathyroid hormone(PTH)-like hormone, insulinotrophic hormone, insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), acidic fibroblast growth factor, basic fibroblast growth factor, transforming growth factor β, neurite growth factor (NGF), interferons (IFN) (e.g., IFN- α2b, IFN- α2a, IFN-αNI , IFN-plb, IFN-γ), interleukins (e.g., IL-1, IL-2, IL-8), tumor necrosis factor (TNF) (e.g., TNF-α, TNF-β), transforming growth factor-α and -β, catalase, calcitonin, arginase, phenylalanine ammonia lyase, L-asparaginase, pepsin, uricase, trypsin, chymotrypsin, elastase,

carboxypeptidase, lactase, sucrase, intrinsic factor, vasoactive intestinal peptide (VIP), calcitonin, Ob gene product, cholecystokinin (CCK), serotonin, glucagon, adrenergic receptors, serotonin receptors, low-density lipoprotein receptor, CD-I8, sarcoglycans fumarylacetoacetate hydrolase (FAH), antiviral proteins, collagens, and dystrophin.

11. The polynucleotide of claim 7, wherein the heterologous polynucleotide sequence comprises a site-specific recombination sequence (chromosomal landing pad).

12. The polynucleotide of claim 11, wherein the site-specific recombination sequence is a recognition sequence recognized by a phage integrase.

13. The polynucleotide of claim 12, wherein the phage integrase is phiC-31 integrase.

14. The polynucleotide of claim 12, wherein the recognition sequence is an attP site or an attB site recognized by the phage integrase.

15. The polynucleotide of claim 7, wherein the mammalian cell is a Chinese hamster ovary (CHO) cell.

16. A vector comprising the recombinant polynucleotide of claim 7.

17. An engineered mammalian cell, comprising a heterologous polynucleotide which is stably integrated into its genome at one or more native chromosomal insertion sites located at or close to:

i. positions 629-630 of SEQ ID NO:2 in CHO cells or a position corresponding to positions 629-630 of SEQ ID NO:2 in other mammalian cells in the cleavage and polyadenylation specific factor 4 gene (Cpsf4);

ii. positions 272-273 of SEQ ID NO:3 in CHO cells or a position corresponding to positions 272-273 of SEQ ID NO:3 for the C-Mos gene; or

iii. positions 239-240 of SEQ ID NO:4 in CHO cells or a position corresponding to positions 239-240 of SEQ ID NO:4 in the Nephrocystin-1/Mal gene.

18. The cell of claim 17, wherein the native chromosomal insertion site supports stable integration of a foreign gene.

19. The cell of claim 17, wherein the heterologous polynucleotide encodes a polypeptide.

20. The cell of claim 19, wherein the polypeptide is selected from the group consisting of selected from the group consisting of factor VIII, factor IX, β-globin, low-density lipoprotein receptor, adenosine deaminase, purine nucleoside phosphorylase, sphingomyelinase, glucocerebrosidase, cystic fibrosis transmembrane conductance regulator, α-antitrypsin, CD- 18, ornithine transcarbamylase, argininosuccinate synthetase, phenylalanine hydroxylase, branched-chain α-ketoacid dehydrogenase, fumarylacetoacetate hydrolase, glucose 6-phosphatase, α-L-fucosidase, β-glucuronidase, α-L-iduronidase, galactose 1-phosphate uridyltransferase, interleukins, cytokines, small peptides, Herceptin®, polypeptide antigens from bacterial or viral pathogens (*e.g.*, E. coli, P. aeruginosa, S. aureus, malaria, HIV, rabies virus, HBV, and cytomegalovirus), lactoferrin, thioredoxin, beta-casein vaccines, insulin, erythropoietin, tissue plasminogen activator (tPA), urokinase, streptokinase, neutropoesis stimulating protein, filgastim, granulocyte colony stimulating factor (G-CSF)), thrombopoietin (TPO), growth hormone, hemoglobin, insulinotropin, imiglucerase, sarbramostim, endothelian, soluble CD4, ciliary neurite transforming factor (CNTF), granulocyte macrophage colony stimulating factor (GM-CSF), brain-derived neurite factor (BDNF), parathyroid hormone(PTH)-like hormone, insulinotrophic hormone, insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), acidic fibroblast growth factor, basic fibroblast growth factor, transforming growth factor β, neurite growth factor (NGF), interferons (IFN) (*e.g.*, IFN- α2b, IFN- α2a, IFN-αNI , IFN-plb, IFN-γ), interleukins (*e.g.*, IL-1, IL-2, IL-8), tumor necrosis factor (TNF) (*e.g.*, TNF-α, TNF-β), transforming growth factor-α and -β, catalase, calcitonin, arginase, phenylalanine ammonia lyase, L-asparaginase, pepsin, uricase, trypsin, chymotrypsin, elastase, carboxypeptidase, lactase, sucrase, intrinsic factor, vasoactive intestinal peptide (VIP), calcitonin, Ob gene product, cholecystokinin (CCK), serotonin, glucagon, adrenergic receptors, serotonin receptors, low-density lipoprotein receptor, CD-I8, sarcoglycans fumarylacetoacetate hydrolase (FAH), antiviral proteins, collagens, and dystrophin.

21. The cell of claim 17, wherein the heterologous polynucleotide comprises a site-specific recombination sequence (chromosomal landing pad).

22. The cell of claim 21, wherein the site-specific recombination sequence is a recognition sequence recognized by a phage integrase.

23. The cell of claim 22, wherein the phage integrase is phiC-31 integrase.

24. The cell of claim 22, wherein the recognition sequence is an attP site or an attB site recognized by the phage integrase.

25. The cell of claim 17, which is a Chinese hamster ovary (CHO) cell.

26. An *ex vivo* or *in vitro* method for stably integrating a heterologous polynucleotide into the genome of a mammalian cell, comprising:

(a) inserting a site-specific recombination sequence into the genome of the cell, wherein the insertion is at a native chromosomal insertion site located at or close to

i. positions 629-630 of SEQ ID NO:2 in CHO cells or a position corresponding to positions 629-630 of SEQ ID NO:2 in other mammalian cells in the cleavage and polyadenylation specific factor 4 gene (Cpsf4);

ii. positions 272-273 of SEQ ID NO:3 in CHO cells or a position corresponding to positions 272-273 of SEQ ID NO:3 for the C-Mos gene; or

iii. positions 239-240 of SEQ ID NO:4 in CHO cells or a position corresponding to positions 239-240 of SEQ ID NO:4 in the Nephrocystin-1/Mal gene; and

(b) integrating by homologous recombination the heterologous polynucleotide into the genome of the cell at the inserted site-specific recombination sequence.

27. The method of claim 26, wherein the native chromosomal insertion site supports stable integration of a foreign gene.

28. The method of claim 26, wherein the site-specific recombination sequence is a first recognition sequence recognized by a phage integrase.

29. The method of claim 28, wherein the phage integrase is phiC-31 integrase.

30. The method of claim 28, wherein the first recognition sequence is an attP site or an attB site.

31. The method of claim 28, wherein the heterologous polynucleotide is attached to a second recognition sequence of the phage integrase which is cognate to the first recognition sequence.

32. The method of claim 31, wherein the second recognition sequence is an attB site or an attP site.

33. The method of claim 26, wherein the cell is a Chinese hamster ovary (CHO) cell.

34. The method of claim 26, wherein the heterologous polynucleotide comprises a target polypeptide-encoding sequence that is operably linked to a promoter sequence.

35. The method of claim 26, wherein the integration occurs in the presence of the phage integrase.

36. The method of claim 35, wherein the phage integrase is expressed from a vector introduced into the cell.