WHAT IS CLAIMED IS:

1. A pre-implantation non-human host embryo comprising (1) in its germ line a disruption of a fertility gene, and (2) a donor pluripotent cell that comprises the fertility gene lacking a disruption, wherein the fertility gene is located on the X chromosome and wherein the disrupted fertility gene inhibits male fertility.

2. A pre-implantation non-human host embryo according to claim 1, wherein the donor pluripotent cell further comprises a genetic modification in its genome.

3. A pre-implantation non-human host embryo according to claim 1 or claim 2, wherein the pluripotent cell is a male pluripotent cell.

4. A pre-implantation non-human host embryo according to any one of claims 1 to 3, wherein the fertility gene modulates spermatogenesis.

5. A pre-implantation non-human host embryo according to any one of claims 1 to 4, wherein the fertility gene is *GILZ*.

6. A pre-implantation non-human host embryo according to any one of claims 1 to 5, wherein the pluripotent cell is a stem cell.

7. A pre-implantation non-human host embryo according to claim 6, wherein the stem cell is an embryonic stem (ES) cell.

8. A method of generating a non-human animal, the method comprising introducing the pre-implantation non-human host embryo according to any one of claims 1 to 7 into a pseudopregnant non-human animal and gestating the pre-implantation non-human host embryo under conditions suitable for development of the embryo, thereby generating a non-human animal.

9. A surrogate or foster non-human animal comprising a non-human host embryo according to any one of claims 1 to 7.

10. A method of generating a chimeric non-human animal, the method comprising introducing the pre-implantation non-human host embryo according to any one of claims 1 to 7 into a pseudopregnant non-human animal and gestating the pre-implantation non-human host embryo under conditions suitable for development of the embryo, thereby generating a chimeric non-human animal.

11. A method of producing a non-human host embryo that comprises a disruption of a fertility gene and a donor pluripotent cell that comprises the fertility gene lacking a disruption, the method comprising: crossing: 1) a first animal strain carrying a conditional infertility transgene that comprises a disruptable fertility gene ("conditional infertility strain"), wherein the fertility gene is located on the X chromosome, wherein disruption of the fertility gene inhibits male fertility and wherein the first animal strain is homozygous for the conditional infertility

transgene; with 2) a second animal strain carrying an infertility-activating transgene that comprises a gene that disrupts the disruptable fertility gene ("infertility-activating strain"), wherein a female member of the first animal strain is crossed with a male member of the second animal strain, thereby generating a transgenic non-human host embryo that comprises germ cells having a disrupted fertility gene; and 3) introducing into the transgenic non-human host embryo a donor pluripotent cell that comprises the fertility gene lacking a disruption.

12. A method of producing a non-human host embryo that comprises a disruption of a fertility gene and a donor pluripotent cell that comprises the fertility gene lacking a disruption, the method comprising: crossing: (1) a first breeding partner comprising a first disruptable transgene that comprises a disruptable fertility gene operably connected to a promoter and to first recombinase recognition sites, which mediate disruption of the disruptable fertility gene in the presence of a first recombinase, and a first disruptor transgene that comprises a coding sequence for a second recombinase operably linked to a promoter, wherein the second recombinase specifically recognizes second recombinase recognition sites, wherein disruption of the fertility gene of the first disruptable transgene inhibits male fertility and wherein the fertility gene is located on the X chromosome; with (2) a second breeding partner comprising a second disruptable transgene that comprises a disruptable fertility gene operably connected to a promoter and to second recombinase recognition sites, which mediate disruption of the disruptable fertility gene in the presence of the second recombinase, and a second disruptor transgene that comprises a coding sequence for the first recombinase operably linked to a promoter, wherein the first recombinase specifically recognizes the first recombinase recognition sites, wherein disruption of the fertility gene of the second disruptable transgene inhibits male fertility, wherein the fertility gene is located on the X chromosome, wherein the fertility genes of the first and second disruptable transgenes are the same or corresponding genes, wherein the first breeding partner is female and the second breeding partner is male, and wherein the first breeding partner is homozygous for the first disruptable and first disruptor transgenes and the second breeding partner is homozygous for the second disruptable and second disruptor transgenes, thereby generating a transgenic non-human host embryo that comprises germ cells having a disrupted fertility gene; and 3) introducing into the transgenic non-human host embryo a donor pluripotent cell that comprises the fertility gene lacking a disruption.

13. A method according to claim 12, wherein the first recombinase recognition sites are loxP sites, the second recombinase is Cre, the second recombinase recognition sites are Frt sites and the first recombinase is FLP.

14. A system for improving germ line transmission of a donor pluripotent cell, the system comprising:

a breeding pair of non-human animals, comprising: 1) a first breeding partner comprising a fertility gene that is disruptable by a fertility gene disruptor molecule ("a disruptable fertility gene"), wherein the disruptable fertility gene is operably connected to a promoter, wherein the fertility gene is located on the X chromosome and wherein disruption of the fertility gene inhibits male fertility and wherein the first breeding partner is homozygous for the disruptable fertility gene, and (2) a second breeding partner comprising a disruptor transgene that comprises a nucleotide sequence encoding the fertility gene disruptor molecule ("a disruptor nucleotide sequence"), wherein the disruptor nucleotide sequence is operably linked to a promoter, wherein the first breeding partner is female and the second breeding partner is male; and

a donor pluripotent cell that comprises the fertility gene lacking a disruption.

15. A system according to claim 14, wherein the fertility gene disruptor is a recombinase and the disruptable fertility gene is operably connected to recombinase recognition sites that mediate disruption of the fertility gene in the presence of the recombinase.

16. A system according to claim 14, wherein the fertility gene disruptor is an inhibitory RNA molecule that inhibits the expression of the fertility gene, suitably by antisense suppression or RNA interference.

17. A system according to claim 14, wherein the fertility gene disruptor is an antibody that is immuno-interactive with a polypeptide product of the fertility gene.

18. A system according to any one of claims 14 to 17, wherein the disruptor nucleotide sequence is conditionally expressible.

19. A system according to claim 18, wherein the disruptor transgene comprises an expression-modulating element operably linked to the disruptor nucleotide sequence, wherein the element conditionally inhibits expression of the disruptor nucleotide sequence.

20. A system according to claim 19, wherein the expression-modulating element inhibits transcription of the disruptor nucleotide sequence under a first condition and disruption of the expression-modulating element permits or enhances transcription of the disruptor nucleotide sequence under a second condition.

21. A system according to claim 19 or claim 20, wherein the expression-modulating element comprises an inhibitor nucleotide sequence (*e.g.*, a transcription terminator) that inhibits expression of the disruptor nucleotide

sequence and that is operably linked to recombinase recognition sites, wherein the recombinase recognition sites mediate disruption of the inhibitor nucleotide sequence in the presence of a recombinase, and wherein the first breeding partner comprises an activator transgene that comprises a coding sequence for the recombinase, operably connected to a promoter.

22. A system according to claim 21, wherein the first breeding partner is homozygous for the activator transgene.

23. A system according to any one of claims 14 to 22, wherein the second breeding partner is homozygous for the disruptor transgene.

24. A system for improving germ line transmission of a donor pluripotent cell, the system comprising:

a breeding pair of non-human animals, comprising: (1) a first breeding partner comprising a first disruptable transgene that comprises a disruptable fertility gene operably connected to a promoter and to first recombinase recognition sites, which mediate disruption of the disruptable fertility gene in the presence of a first recombinase, and a first disruptor transgene that comprises a coding sequence for a second recombinase operably linked to a promoter, wherein the second recombinase specifically recognizes second recombinase recognition sites, wherein disruption of the fertility gene of the first disruptable transgene inhibits male fertility and wherein the fertility gene is located on the X chromosome, and (2) a second breeding partner comprising a second disruptable transgene that comprises the disruptable fertility gene operably connected to a promoter and to second recombinase recognition sites, which mediate disruption of the disruptable fertility gene in the presence of the second recombinase, and a second disruptor transgene that comprises a coding sequence for the first recombinase operably linked to a promoter, wherein the first recombinase specifically recognizes the first recombinase recognition sites, wherein disruption of the fertility gene of the second disruptable transgene inhibits male fertility, wherein the fertility gene is located on the X chromosome, wherein the fertility genes of the first and second disruptable transgenes are the same or corresponding genes, wherein the first breeding partner is female and the second breeding partner is male and wherein the first breeding partner is homozygous for the first disruptable and first disruptor transgenes and the second breeding partner is homozygous for the second disruptable and second disruptor transgenes; and

a donor pluripotent cell that comprises the fertility gene lacking a disruption.

25. A system according to claim 24, wherein the first recombinase recognition sites are loxP sites, the second recombinase is Cre, the second recombinase recognition sites are Frt sites and the first recombinase is FLP.

26. A method of producing a chimeric non-human animal, the method comprising (1) transplanting a pre-implantation non-human embryo that comprises in its germ line a disruption of a fertility gene and that further comprises a donor pluripotent cell, as defined in any one of claims 1 to 7, wherein the pluripotent cell comprises a genetic modification ; and (2) gestating the non-human host embryo of (1) under conditions suitable for development of the embryo, thereby generating a chimeric non-human animal with a disrupted fertility gene and the genetic modification in its germ line.

27. A method according to claim 26, wherein the chimeric non-human animal is a male chimeric non-human animal.

28. A method of producing a non-human animal that comprises a genetic modification in its genome, the method comprising breeding a male chimeric non-human animal produced according to the method of claim 27 with a cognate female non-human animal that comprises in its genome the fertility gene lacking a disruption therein, to produce a non-human animal that comprises the genetic modification when the male chimeric non-human animal comprises germ cells or gametes derived from the donor pluripotent cell.

29. A chimeric non-human animal that is derived from a pre-implantation non-human host embryo according to any one of claims 1 to 7.

30. A non-human animal produced according to the method of claim 29.

31. A method of producing a non-human host embryo that comprises a disruption of a fertility gene, the method comprising: crossing: 1) a first animal strain carrying a conditional infertility transgene that comprises a disruptable fertility gene ("conditional infertility strain"), wherein the fertility gene is located on the X chromosome, and wherein disruption of the fertility gene inhibits male fertility wherein the first animal strain is homozygous for the conditional infertility transgene; with 2) a second animal strain carrying an infertility-activating transgene that comprises a gene that disrupts the disruptable fertility gene ("infertility-activating strain"), wherein a female member of the first animal strain is crossed with a male member of the second animal strain, thereby generating a transgenic non-human host embryo that comprises germ cells having a disrupted fertility gene.

32. A method of producing a non-human host embryo that comprises a disruption of a fertility gene, the method comprising: crossing: (1) a first breeding partner comprising a first disruptable transgene that comprises a disruptable

fertility gene operably connected to a promoter and to first recombinase recognition sites, which mediate disruption of the disruptable fertility gene in the presence of a first recombinase, and a first disruptor transgene that comprises a coding sequence for a second recombinase operably linked to a promoter, wherein the second recombinase specifically recognizes second recombinase recognition sites, wherein disruption of the fertility gene of the first disruptable transgene inhibits male fertility and wherein the fertility gene is located on the X chromosome; with (2) a second breeding partner comprising a second disruptable transgene that comprises a disruptable fertility gene operably connected to a promoter and to second recombinase recognition sites, which mediate disruption of the disruptable fertility gene in the presence of the second recombinase, and a second disruptor transgene that comprises a coding sequence for the first recombinase operably linked to a promoter, wherein the first recombinase specifically recognizes the first recombinase recognition sites, wherein disruption of the fertility gene of the second disruptable transgene inhibits male fertility, wherein the fertility gene is located on the X chromosome, wherein the fertility genes of the first and second disruptable transgenes are the same or corresponding genes, wherein the first breeding partner is female and the second breeding partner is male and wherein the first breeding partner is homozygous for the first disruptable and first disruptor transgenes and the second breeding partner is homozygous for the second disruptable and second disruptor transgenes, thereby generating a transgenic non-human host embryo that comprises germ cells having a disrupted fertility gene.

33. A method according to claim 32, wherein the first recombinase recognition sites are loxP sites, the second recombinase is Cre, the second recombinase recognition sites are Frt sites and the first recombinase is FLP.

34. A method according to any one of claims 31 to 33, further comprising cryopreserving the transgenic non-human host embryo.

35. A system for improving germ line transmission of a donor pluripotent cell, the system comprising:

a breeding pair of non-human animals, comprising: 1) a first breeding partner comprising a fertility gene that is disruptable by a fertility gene disruptor molecule ("a disruptable fertility gene"), wherein the disruptable fertility gene is operably connected to a promoter, wherein the fertility gene is located on the X chromosome, wherein disruption of the fertility gene inhibits male fertility and wherein the first breeding partner is homozygous for the disruptable fertility gene, and (2) a second breeding partner comprising a disruptor transgene that comprises a nucleotide sequence encoding the fertility gene disruptor molecule ("a disruptor nucleotide

sequence"), wherein the disruptor nucleotide sequence is operably linked to a promoter, wherein the first breeding partner is female and the second breeding partner is male.

36. A system for producing a non-human host embryo that comprises a disruption of a fertility gene, the system comprising: a breeding pair of non-human animals, comprising: (1) a first breeding partner comprising a first disruptable transgene that comprises a disruptable fertility gene operably connected to a promoter and to first recombinase recognition sites, which mediate disruption of the disruptable fertility gene in the presence of a first recombinase, and a first disruptor transgene that comprises a coding sequence for a second recombinase operably linked to a promoter, wherein the second recombinase specifically recognizes second recombinase recognition sites, wherein disruption of the fertility gene of the first disruptable transgene inhibits male fertility and wherein the fertility gene is located on the X chromosome, and (2) a second breeding partner comprising a second disruptable transgene that comprises a disruptable fertility gene operably connected to a promoter and to second recombinase recognition sites, which mediate disruption of the disruptable fertility gene in the presence of the second recombinase, and a second disruptor transgene that comprises a coding sequence for the first recombinase operably linked to a promoter, wherein the first recombinase specifically recognizes the first recombinase recognition sites, wherein disruption of the fertility gene of the second disruptable transgene inhibits male fertility and wherein the fertility gene is located on the X chromosome, wherein the fertility genes of the first and second disruptable transgenes are the same or corresponding genes, wherein the first breeding partner is female and the second breeding partner is male and wherein the first breeding partner is homozygous for the first disruptable and first disruptor transgenes and the second breeding partner is homozygous for the second disruptable and second disruptor transgenes.

37. A system according to claim 36, wherein the first recombinase recognition sites are loxP sites, the second recombinase is Cre, the second recombinase recognition sites are Frt sites and the first recombinase is FLP.