

WHAT IS CLAIMED IS:

1. A genetically modified rodent, whose genome comprises a modified rodent *Acvr1* gene within an endogenous rodent *Acvr1* locus, wherein the modified rodent *Acvr1* gene comprises
 - a. a substantially human *ACVR1* exon 7 in sense orientation flanked by a first pair of site-specific recombinase recognition sites (SRRS'), ~~wherein the substantially human *ACVR1* exon 7 encodes the same amino acids as a human *ACVR1* exon 7~~; and
 - b. an altered rodent *Acvr1* exon 7 encoding R258G in antisense orientation, flanked by a second pair of SRRS' that are different from the first pair of SRRS';

wherein the substantially human *ACVR1* exon 7 (i) encodes the same amino acids as a human *ACVR1* exon 7, but differs from the human *ACVR1* exon 7 by at least one nucleotide; and (ii) has a reduced sequence identity to the altered rodent *Acvr1* exon 7 as compared to the human *ACVR1* exon 7; and

wherein the first and second SRRS' are oriented so that a recombinase can invert the mutant rodent *Acvr1* exon 7 into sense orientation, delete the substantially human *ACVR1* exon 7, and allow an altered *Acvr1* allele comprising the altered rodent *Acvr1* exon 7 to be expressed.
- ~~2. The genetically modified rodent of claim 1, wherein the substantially human *ACVR1* exon 7 differs from the human *ACVR1* exon 7 by at least one nucleotide and has a reduced sequence identity with the altered rodent *Acvr1* exon 7 as compared to the sequence identity between the human *ACVR1* exon 7 and the altered rodent *Acvr1* exon 7.~~
- ~~3.~~2. The genetically modified rodent of claim 1, wherein the gene encoding the recombinase is in the genome of the genetically modified rodent, and the activity of the recombinase is inducible.
- ~~4.~~3. The genetically modified rodent ~~according to any one of claims 1-3~~of claim 1 or 2, wherein the recombinase is Cre.

5.4. The genetically modified rodent of claim 43, wherein the Cre is fused to a ligand binding domain of an estrogen receptor (ER) such that the activity of the Cre is induced by ligand binding to the ER.

6.5. The genetically modified rodent of claim 54, wherein the ligand binding domain of the ER comprises T2 mutations.

7.6. The genetically modified rodent of claim 4 or 5 or 6, wherein the ligand is tamoxifen.

8.7. The genetically modified rodent of any one of claims 1-76, wherein the genetically modified rodent is homozygous for the modified *Acvr1* gene.

9.8. A mutant rodent derived from the genetically modified rodent of any of claims 1-87, wherein the mutant rodent has a genome comprising an altered *Acvr1* allele which comprises the altered exon 7 in sense orientation, and wherein the altered *Acvr1* allele is expressed in the mutant rodent resulting in ectopic bone formation.

10.9. The rodent according to any of the preceding claims, selected from a mouse or a rat.

11.10. A nucleic acid, comprising a modified rodent *Acvr1* gene, wherein the modified rodent *Acvr1* gene comprises

a. a substantially human *ACVR1* exon 7 in sense orientation flanked by a first pair of site-specific recombinase recognition sites (SRRS'), ~~wherein the substantially human *ACVR1* exon 7 encodes the same amino acids as a human *ACVR1* exon 7~~; and

b. an altered rodent *Acvr1* exon 7 encoding R258G in antisense orientation, flanked by a second pair of SRRS' that are different from the first pair of SRRS';

wherein the substantially human *ACVR1* exon 7 (i) encodes the same amino acids as a human *ACVR1* exon 7, but differs from the human *ACVR1* exon 7 by at least one nucleotide; and (ii) has a reduced sequence identity to the altered rodent *Acvr1* exon 7 as compared to the human *ACVR1* exon 7; and -

wherein the first and second SRRS' are oriented so that a recombinase can invert the mutant rodent *Acvr1* exon 7 into sense orientation, delete the substantially human *ACVR1* exon 7.

~~12.~~ ~~The nucleic acid of claim 11, wherein the substantially human *ACVR1* exon 7 differs from the human *ACVR1* exon 7 by at least one nucleotide and has a reduced sequence identity with the altered rodent *Acvr1* exon 7 as compared to the sequence identity between the human *ACVR1* exon 7 and the altered rodent *Acvr1* exon 7.~~

~~13.~~11. The nucleic acid of claim ~~11~~10, wherein the activity of the recombinase is inducible.

~~14.~~12. The nucleic acid of ~~any one of claims 11-13~~claim 10 or 11, wherein the recombinase is Cre.

~~15.~~13. The nucleic acid of claim ~~14~~12, wherein the Cre is fused to a ligand binding domain of an estrogen receptor (ER) such that the activity of Cre is induced by ligand binding to the ER.

~~16.~~14. The nucleic acid of claim ~~15~~13, wherein the ligand binding domain of the ER comprises T2 mutations.

~~17.~~15. The nucleic acid of claim ~~13 or 14~~15 or 16, wherein the ligand is tamoxifen.

~~18.~~16. The nucleic acid of any one of claims ~~11-17~~10-15, wherein the rodent is a mouse or a rat.

~~19.~~17. A rodent genome comprising the nucleic acid of claim ~~11 or 12~~10.

~~20.~~18. The rodent genome of claim ~~19~~17, further comprising a gene encoding the recombinase that recognizes the SRRS' and inverts the altered exon.

~~21.~~19. The rodent genome of claim ~~20~~18, wherein the activity of the recombinase is inducible.

~~22.~~20. The rodent genome of claim ~~21~~19, wherein the recombinase is Cre.

~~23.21.~~ The rodent genome of claim ~~2220~~, wherein the Cre is fused to a ligand binding domain of an estrogen receptor (ER) such that the activity of the Cre is induced by ligand binding to the ER.

~~24.22.~~ The rodent genome of claim ~~2321~~, wherein the ligand binding domain of the ER comprises T2 mutations.

~~25.23.~~ The rodent genome of claim ~~23 or 24~~~~21 or 22~~, wherein the ligand is tamoxifen.

~~26.24.~~ The rodent genome of any one of claims ~~19-25~~~~17-23~~, wherein the rodent genome is homozygous for ~~for~~ the modified *Acvr1* gene.

~~27.25.~~ The rodent genome of any one of claims ~~19-26~~~~17-24~~, wherein the rodent is a mouse or a rat.

~~28.26.~~ An isolated rodent tissue or cell comprising the rodent genome of any one of claims ~~19-27~~~~17-25~~.

~~29.27.~~ The isolated rodent tissue or cell of claim ~~28~~~~26~~, wherein the rodent is a mouse or a rat.

~~30.28.~~ The isolated rodent tissue or cell of claim ~~28 or 29~~~~26 or 27~~, wherein the rodent cell is an embryonic stem cell.

~~31.29.~~ A nucleic acid construct for targeted modification of an *Acvr1* gene in a rodent genome, comprising:

a. a substantially human *ACVR1* exon 7 in sense orientation flanked by a first pair of site-specific recombinase recognition sites (SRRS'), ~~wherein the substantially human *ACVR1* exon 7 encodes the same amino acids as a human *ACVR1* exon 7~~; and

b. an altered rodent *Acvr1* exon 7 encoding R258G in antisense orientation, flanked by a second pair of SRRS' that are different from the first pair of SRRS';

wherein the substantially human *ACVR1* exon 7 (i) encodes the same amino acids as a human *ACVR1* exon 7, but differs from the human *ACVR1* exon 7 by at least one

nucleotide; and (ii) has a reduced sequence identity to the altered rodent *Acvr1* exon 7 as compared to the human *ACVR1* exon 7; and -

wherein the first and second SRRS' are oriented so that a recombinase can invert the mutant rodent *Acvr1* exon 7 into sense orientation, delete the substantially human *ACVR1* exon 7, and allow an altered *Acvr1* allele comprising the altered rodent *Acvr1* exon 7 to be expressed.

~~32. The nucleic acid construct of claim 31, wherein the substantially human *ACVR1* exon 7 differs from the human *ACVR1* exon 7 by at least one nucleotide and has a reduced sequence identity with the altered rodent *Acvr1* exon 7 as compared to the sequence identity between the human *ACVR1* exon 7 and the altered rodent *Acvr1* exon 7.~~

~~33.~~30. The nucleic acid construct of claim ~~31~~29, wherein the first and second pairs of SRRS are Lox2372 and LoxP or vice versa.

~~34.~~31. The nucleic acid construct of claim ~~31~~29, wherein the recombinase is Cre.

~~35.~~32. The nucleic acid construct of claim ~~34~~31, wherein the Cre is fused to an estrogen receptor (ER) such that the activity of the Cre is induced by ligand binding to the ER.

~~36.~~33. The nucleic acid construct of claim ~~35~~32, wherein the ER comprises T2 mutations.

~~37.~~34. The nucleic acid construct of claim ~~35~~32, wherein the ligand is tamoxifen.

~~38.~~35. The nucleic acid construct according to any one of claim ~~31-37~~29-34, wherein the rodent is selected from a mouse or a rat.

~~39.~~36. A method of making a genetically modified rodent, comprising modifying a rodent genome to comprise a modified rodent *Acvr1* gene within an endogenous rodent *Acvr1* locus, wherein the modified rodent *Acvr1* gene comprises

a. a substantially human *ACVR1* exon 7 in sense orientation flanked by a first pair of site-specific recombinase recognition sites (SRRS'), ~~wherein the substantially human *ACVR1* exon 7 encodes the same amino acids as a human *ACVR1* exon 7; and~~

b. an altered rodent *Acvr1* exon 7 encoding R258G in antisense orientation, flanked by a second pair of SRRS' that are different from the first pair of SRRS';

wherein the substantially human *ACVR1* exon 7 (i) encodes the same amino acids as a human *ACVR1* exon 7, but differs from the human *ACVR1* exon 7 by at least one nucleotide; and (ii) has a reduced sequence identity to the altered rodent *Acvr1* exon 7 as compared to the human *ACVR1* exon 7; —

wherein the first and second SRRS' are oriented so that a recombinase can invert the altered rodent *Acvr1* exon 7 into sense orientation, delete the substantially human *ACVR1* exon 7, and allow an altered *Acvr1* allele comprising the altered rodent *Acvr1* exon 7 to be expressed; —

~~40. The method of claim 39,~~ wherein the rodent genome is modified by a process comprising:

~~a.i.~~ i. introducing a nucleic acid construct into a rodent embryonic stem (ES) cell, wherein the nucleic acid construct comprises:

the substantially human *ACVR1* exon 7 in sense orientation flanked by the first pair of SRRS', and

the altered rodent *Acvr1* exon 7 encoding R258G in antisense orientation, flanked by the second pair of SRRS';

wherein the nucleic acid construct targets the endogenous rodent *Acvr1* locus resulting in the modified rodent *Acvr1* gene within the endogenous rodent *Acvr1* locus;

~~b.~~ ii. obtaining a genetically modified rodent ES cell whose genome comprises the modified rodent *Acvr1* gene; and

~~c.~~ iii. making a genetically modified rodent by using the genetically modified rodent ES cell from ~~b.ii.~~ ii.

41.37. The method of claim ~~39 or 40~~36, wherein the genetically modified rodent is homozygous for the modified *Acvr1* gene.

42.38. The method of claim ~~40 or 41~~36 or 37, wherein the rodent ES cell further comprises a gene encoding the recombinase.

43.39. The method of any one of claims ~~39-42~~36-38, wherein the activity of the recombinase is inducible.

44.40. The method according to any one of claims ~~39-43~~36-39, wherein the recombinase is Cre.

45.41. The method of claim ~~44~~40, wherein the Cre is fused to a ligand binding domain of an estrogen receptor (ER) such that the activity of the Cre is induced by ligand binding to the ER.

46.42. The method of claim ~~45~~41, wherein the ligand binding domain of the ER comprises T2 mutations.

47.43. The method of claim ~~45 or 46~~41 or 42, wherein the ligand is tamoxifen.

48.44. The method of any one of claims ~~43-47~~39-43, further comprising inducing the activity of the recombinase in a cell or tissue of the rodent, wherein the recombinase inverts the altered exon 7, deleting the substantially human exon 7, thereby allowing an altered *Acvr1* allele comprising the altered exon 7 to be expressed in the cell or tissue.

49.45. The method according to any one of claims ~~40-48~~36-44, wherein the rodent is selected from a mouse or a rat.

50.46. A method of breeding, comprising breeding a first rodent whose genome comprises a modified rodent *Acvr1* gene with a second mouse, resulting in a progeny rodent whose genome comprises the modified rodent *Acvr1* gene, wherein the modified rodent *Acvr1* gene comprises:

a. a substantially human *ACVR1* exon 7 in sense orientation flanked by a first pair of site-specific recombinase recognition sites (SRRS'), ~~wherein the substantially human *ACVR1* exon 7 encodes the same amino acids as a human *ACVR1* exon 7~~; and

b. an altered rodent *Acvr1* exon 7 encoding R258G in antisense orientation, flanked by a second pair of SRRS' that are different from the first pair of SRRS';

wherein the substantially human *ACVR1* exon 7 (i) encodes the same amino acids as a human *ACVR1* exon 7, but differs from the human *ACVR1* exon 7 by at least one nucleotide; and (ii) has a reduced sequence identity to the altered rodent *Acvr1* exon 7 as compared to the human *ACVR1* exon 7; and -

wherein the first and second SRRS' are oriented so that a recombinase can invert the altered rodent *Acvr1* exon 7 into sense orientation, delete the substantially human *ACVR1* exon 7, and allow an altered *Acvr1* allele comprising the altered rodent *Acvr1* exon 7 to be expressed.

~~51.47.~~ The method of claim ~~5046~~, wherein the first rodent is homozygous for the modified rodent *Acvr1* gene.

~~52.48.~~ The method of claim ~~50 or 5146 or 47~~, wherein the second rodent comprises an inducible recombinase.

~~53.49.~~ The method of claim ~~5248~~, wherein the inducible recombinase is an inducible Cre recombinase.

~~54.50.~~ The method of claim ~~5349~~, wherein the inducible Cre recombinase comprises a tamoxifen-inducible Cre-ER^{T2} recombinase.

~~55.51.~~ The method of any one of claims ~~52-5448-50~~, further comprising inducing the inducible recombinase in a cell or tissue in the progeny rodent, such that the induced recombinase inverts the altered rodent *Acvr1* exon 7 into sense orientation and delete the substantially human *ACVR1* exon 7 in the cell or tissue, thereby producing an altered *Acvr1* allele comprising the altered rodent *Acvr1* exon 7.

~~56.52.~~ The method of any one of claims ~~50-55~~46-51, wherein the rodent is a mouse or a rat.

~~57.~~ ~~A progeny rodent produced according to the method of any one of claims 50-56.~~

~~58.53.~~ A method of testing a candidate therapeutic compound for treating ectopic bone formation, comprising:

providing a genetically modified rodent according to any one of claims 1-~~8~~7 and ~~109~~;

inducing the activity of the recombinase in the rodent to allow an altered *Acvr1* allele comprising the altered rodent *Acvr1* exon 7 to be expressed;

administering the candidate compound to the rodent; and

determining whether the candidate compound inhibits the development of ectopic bone formation in the rodent.

~~59.54.~~ The method of claim ~~58~~53, wherein the candidate compound is administered to the rodent before, during, or after the induction of the recombinase activity.

~~60.55.~~ The method of claim ~~58~~53, wherein the candidate compound is a small molecule chemical compound.

~~61.56.~~ The method of claim ~~58~~53, wherein the candidate compound is a nucleic acid.

~~62.57.~~ The method of claim ~~58~~53, wherein the candidate compound is an antibody or antigen-binding fragment thereof.

~~63.58.~~ The method of claim ~~62~~57, wherein the antibody or antigen-binding fragment thereof is an antibody or antigen-binding fragment thereof against activin receptor 1.

~~64.59.~~ The method of claim ~~62~~57, wherein the antibody or antigen-binding fragment thereof is an antibody or antigen-binding fragment thereof against activin receptor type 2A.

~~65.60.~~ The method of claim ~~62~~57, wherein the antibody or antigen-binding fragment thereof is an antibody or antigen-binding fragment thereof against activin receptor type 2B.

~~66-61.~~ The method of claim ~~62~~57, wherein the antibody or antigen-binding fragment thereof is an antibody or antigen-binding fragment thereof against activin A.

~~67-62.~~ The method according to any one of claims ~~58-66~~53-61, wherein the rodent is a mouse or a rat.