

What is claimed is:

1. A non-human animal embryonic stem (ES) cell comprising an immunoglobulin locus that comprises an unrearranged immunoglobulin variable gene sequence comprising a substitution of at least one non-histidine codon with a histidine codon or an insertion of at least one histidine codon,
wherein the substituted or inserted histidine codon is not encoded by a corresponding wild-type gene segment.
2. The non-human animal ES cell of claim 1, wherein the non-human animal ES cell comprises a first and a second immunoglobulin variable locus, wherein at least the first or the second immunoglobulin variable locus comprises an unrearranged immunoglobulin variable gene sequence comprising the insertion of the at least one histidine codon or the substitution of the at least one non-histidine codon with a histidine codon.
3. The non-human animal ES cell of claim 2, wherein both the first and the second immunoglobulin variable locus each comprise an unrearranged immunoglobulin variable gene sequence comprising the substitution of the at least one non-histidine codon with a histidine codon or the insertion of the at least one histidine codon.
4. The non-human animal ES cell of claim 2, wherein the first immunoglobulin variable locus comprises at least a functional portion of an unrearranged immunoglobulin heavy chain variable gene sequence (unrearranged V, D, J segments).
5. The non-human animal ES cell of claim 4, wherein the unrearranged immunoglobulin heavy chain variable gene sequence comprises at least a portion of a human immunoglobulin heavy chain gene sequence (unrearranged V, D, J segments).
6. The non-human animal ES cell of claim 4, wherein the unrearranged immunoglobulin heavy chain variable gene sequence is a human immunoglobulin heavy chain gene sequence comprising unrearranged V segments, a synthetic D segment that comprises a linker, and a human J segment.

7. The non-human animal ES cell of claim 6, wherein the synthetic D segment comprises at least one histidine codon.
8. The non-human animal ES cell of claim 2, wherein the second immunoglobulin variable locus comprises at least a functional portion of an unrearranged immunoglobulin light chain variable gene sequence (unrearranged V, J segments).
9. The non-human animal ES cell of claim 2, wherein the second immunoglobulin variable locus comprises a rearranged immunoglobulin light chain variable gene sequence (rearranged VJ sequence).
10. The non-human animal ES cell of claim 1, wherein the substitution of the at least one non-histidine codon with a histidine codon and/or the insertion of the at least one histidine codon is in a nucleic acid sequence that encodes an immunoglobulin variable domain and the inserted or substituted histidine is in a region selected from an N-terminal region of an immunoglobulin chain, a loop 4 region of an immunoglobulin chain, a CDR1 of an immunoglobulin heavy chain, a CDR2 of an immunoglobulin heavy chain, a CDR3 of an immunoglobulin heavy chain, a CDR1 of an immunoglobulin light chain, a CDR2 of an immunoglobulin light chain, a CDR3 of an immunoglobulin light chain, and a combination thereof.
11. The non-human animal ES cell of claim 2, wherein at least one of the first immunoglobulin variable locus or the second immunoglobulin variable locus is operably linked to an endogenous non-human immunoglobulin constant region nucleic acid sequence at an endogenous non-human immunoglobulin locus.
12. The non-human animal ES cell of claim 5, wherein the unrearranged immunoglobulin heavy chain variable gene sequence (unrearranged human V, D, J segments) is operably linked to an endogenous non-human immunoglobulin heavy chain constant region nucleic acid sequence.
13. The non-human animal ES cell of claim 12, wherein the endogenous non-human immunoglobulin heavy chain constant region nucleic acid sequence is at an endogenous non-human immunoglobulin locus.

14. The non-human animal ES cell of claim 8, wherein the unrearranged immunoglobulin light chain variable gene sequence (unrearranged V, J segments) is operably linked to an endogenous non-human immunoglobulin light chain constant region nucleic acid sequence.

15. The non-human animal of ES cell of claim 14, wherein the endogenous non-human immunoglobulin light chain constant region nucleic acid sequence is at an endogenous non-human immunoglobulin locus.

16. The non-human animal ES cell of claim 1, comprising at least a portion of a human unrearranged immunoglobulin heavy chain variable region nucleic acid sequence (unrearranged V, D, J segments) operably linked to an immunoglobulin heavy chain constant region gene sequence, wherein one or more of the V, D, and J segments comprise at least one substitution of a non-histidine codon with a histidine codon, or at least one histidine codon insertion, wherein the histidine codon substituted or inserted into the one or more of the V, D and J segments of the human unrearranged immunoglobulin heavy chain variable region nucleic acid sequence is not encoded by a corresponding human germline gene segment; and
at least a portion of a human unrearranged immunoglobulin light chain variable region nucleic acid sequence (unrearranged V, J segments) operably linked to an immunoglobulin light chain constant region gene sequence, wherein one or more of the V and J segments comprise at least one substitution of a non-histidine codon with a histidine codon, or at least one histidine codon insertion, wherein the histidine codon substituted or inserted into one or more of the V and J segments of the human unrearranged immunoglobulin light chain variable region nucleic acid sequence is not encoded by a corresponding human germline gene segment; and

wherein a non-human animal generated with the non-human animal ES cell expresses an immunoglobulin heavy chain variable domain and/or an immunoglobulin light chain variable domain that comprises a histidine derived from the at least one histidine codon substituted or inserted into the one or more of the V, D and J segments of the human unrearranged immunoglobulin heavy chain variable region nucleic acid sequence and/or one or more of the V and J segments of the human unrearranged immunoglobulin light chain variable region nucleic acid sequence, respectively.

17. The non-human animal ES cell of claim 16, wherein the human unrearranged immunoglobulin heavy chain variable region nucleic acid sequence is operably linked to a non-human immunoglobulin heavy chain constant region nucleic acid sequence.
18. The non-human animal ES cell of claim 17, wherein the human unrearranged immunoglobulin heavy chain variable region nucleic acid sequence operably linked to the non-human immunoglobulin heavy chain constant region nucleic acid sequence is at an endogenous non-human immunoglobulin heavy chain locus.
19. The non-human animal ES cell of claim 16, wherein the human unrearranged immunoglobulin light chain variable region nucleic acid sequence is operably linked to a non-human immunoglobulin light chain constant region nucleic acid sequence.
20. The non-human animal ES cell of claim 19, wherein the human unrearranged immunoglobulin light chain variable region nucleic acid sequence operably linked to the non-human immunoglobulin light chain constant region nucleic acid sequence is at an endogenous non-human immunoglobulin locus.
21. The non-human animal ES cell of claim 1, comprising
at least a portion of a human unrearranged immunoglobulin heavy chain variable region nucleic acid sequence (unrearranged V, D, J segments) operably linked to an immunoglobulin heavy chain constant region gene sequence, wherein one or more of the unrearranged V, D, and J segments comprise at least one substitution of a non-histidine codon with a histidine codon, or at least one histidine codon insertion, wherein the histidine codon substituted or inserted into the one or more of the unrearranged V, D and J segments of the human unrearranged immunoglobulin heavy chain variable region nucleic acid sequence is not encoded by a corresponding human germline gene segment; and
a human rearranged immunoglobulin light chain variable region nucleic acid sequence (rearranged VJ sequence) operably linked to an immunoglobulin light chain constant region gene sequence, wherein the rearranged VJ sequence comprises at least one substitution of a non-histidine codon with a histidine codon, or at least one histidine codon insertion, wherein the histidine codon substituted or inserted the rearranged VJ sequence is not encoded by a corresponding human germline gene segment; and

wherein a non-human animal generated by the non-human animal ES cell expresses an immunoglobulin heavy chain variable domain and/or an immunoglobulin light chain variable domain that comprises a histidine derived from the at least one histidine codon substituted or inserted into the one or more of the unrearranged V, D and J segments of the human unrearranged immunoglobulin heavy chain variable region nucleic acid sequence and/or the rearranged VJ sequence, respectively.

22. The non-human animal ES cell of claim 21, wherein the human unrearranged immunoglobulin heavy chain variable region nucleic acid sequence is operably linked to a non-human immunoglobulin heavy chain constant region sequence.

23. The non-human animal ES cell of claim 22, wherein the human unrearranged immunoglobulin heavy chain variable region nucleic acid sequence operably linked to the non-human immunoglobulin heavy chain constant region sequence is at an endogenous non-human immunoglobulin heavy chain locus.

24. The non-human animal ES cell of claim 23, wherein the human rearranged immunoglobulin light chain variable region nucleic acid sequence is operably linked to a non-human immunoglobulin light chain constant region sequence.

25. A non-human animal embryonic stem (ES) cell comprising at an endogenous immunoglobulin light chain locus an unrearranged immunoglobulin variable gene sequence comprising unrearranged VL and JL gene segments and, in a complementarity determining region 3 (CDR3) encoding sequence, a substitution of a non-histidine codon with a histidine codon or an insertion of a histidine codon,

wherein the histidine codon is not encoded by a corresponding germline gene segment in a wild-type non-human animal ES cell,

and wherein the unrearranged immunoglobulin variable gene sequence comprises no more than two unrearranged VL gene segments and one or more JL gene segments.

26. The non-human animal ES cell of claim 25, wherein each of the no more than two human VL gene segments comprises in a CDR3 encoding sequence a substitution of a non-histidine codon with a histidine codon or an insertion of a histidine codon.

27. The non-human animal ES cell of claim 25, wherein the unrearranged VL and JL gene segments are human VL and JL gene segments.
28. The non-human animal ES cell of claim 25, wherein the unrearranged VL and JL gene segments are human Vk and Jk gene segments.
29. The non-human animal ES cell of claim 25, wherein the unrearranged immunoglobulin variable region gene sequence is operably linked to a non-human immunoglobulin light chain constant region nucleic acid sequence at the endogenous immunoglobulin light chain locus.
30. The non-human animal ES cell of any one of the preceding claims, wherein the non-human animal ES cell is a mammalian ES cell.
31. The non-human animal ES cell of any one of the preceding claims, wherein the non-human animal ES cell is a rodent ES cell.
32. The non-human animal ES cell of any one of the preceding claims, wherein the non-human animal ES cell is a rat ES cell.
33. The non-human animal ES cell of any one of claims 1-31, wherein the non-human animal ES cell is a mouse ES cell.