MICE EXPRESSING HUMANIZED FC ALPHA RECEPTORS

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/126,326, filed December 16, 2020, which is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] Mice are an essential *in vivo* model for preclinical testing of therapeutic agents due to their small size, well-characterized physiology, and relatively inexpensive maintenance compared to larger mammalian models (*e.g.*, primates). Mouse models are often used to assess the toxicity and pharmacokinetics of therapeutic agents prior to proceeding to human clinical studies. Despite these advantages, there are serious drawbacks to *in vivo* testing of antibodies and Fc fusion proteins as these therapeutic agents can behave differently in mice than they do in humans. This is especially true for testing IgA-based therapeutics in mice as they do not express an Fc receptor for binding IgA antibodies. Thus, mouse models have not been extensively characterized or used for predicting the safety, efficacy, and optimal dosing of IgA-based therapeutic agents. There is a need for new mouse models and methods that allow for precise pre-clinical testing of IgA-based therapeutic agents that are predictive of the properties of such therapeutic agents in human patients.

SUMMARY

[0003] Provided herein are methods and compositions related to mice that express a human or humanized Fcα receptor (FcαR) and methods and compositions related to the *in vivo* testing of therapeutic agents comprising a human IgA Fc in such mice (*e.g.*, the testing of the pharmacokinetic and/or pharmacodynamic properties and dosing regimens of such therapeutic agents). As described herein, mice are convenient animal models for testing therapeutic antibodies and Fc fusion proteins due to their small size, well-characterized physiology, and amenability to genetic modification. Unfortunately, agents comprising a human IgA Fc region (*e.g.*, IgA antibodies and Fcα fusion proteins) often exhibit very different pharmacokinetic and pharmacodynamic properties when administered to wild type mice compared to when administered to humans because such mice lack an FcαR. Thus, the

mice provided herein can serve as *in vivo* systems for the development, screening and testing of human IgA antibodies and Fcα fusion proteins for therapeutic use.

[0004] In certain aspects, provided herein is a mouse comprising in its genome an Fc alpha receptor (FcαR) locus positioned in the mouse leukocyte receptor complex (LRC), wherein the FcαR locus (such as human or humanized FcαR locus) comprises a nucleic acid sequence encoding a FcαR polypeptide comprising a human extracellular domain and a human or rodent cytoplasmic domain. In some embodiments, the mouse expresses the FcαR polypeptide on mouse neutrophils, monocytes, macrophages, eosinophils, and dendritic cells (e.g., plasmacytoid dendritic cells). In some embodiment, the neutrophils, monocytes, macrophages, eosinophils, and/or dendritic cells (e.g., plasmacytoid dendritic cells) are from the blood of the mouse. In some embodiment, the neutrophils, monocytes, macrophages, eosinophils, and dendritic cells (e.g., plasmacytoid dendritic cells) are from the spleen of the mouse.

[0005] In some aspects, provided herein is a mouse embryonic stem cell (ES cell) comprising in its genome an Fc alpha receptor (FcαR) locus positioned in the leukocyte receptor complex (LRC) of the mouse genome, wherein the FcαR locus comprises a nucleic acid sequence encoding an FcαR polypeptide comprising a human extracellular domain and a human or rodent cytoplasmic domain.

[0006] In some embodiments, the FcαR locus is positioned in an intergenic region between the gene loci for the Tthy1 protein and the Rdh13 protein. In some embodiments, the FcαR locus is positioned in an intergenic region between the gene loci for the Lilra5 protein and the Gp6 protein. In some embodiments, the FcαR locus is positioned in an intergenic region between the gene loci for the Pira6 protein and the Gp6 protein. In some embodiments, the FcαR locus is positioned in an intergenic region between the gene loci for the Pira6 protein and the Ncr1 protein. In some embodiments, the FcαR locus is positioned in an intergenic region between the coding nucleic acid sequences for the for the Pira6 protein and the Ncr1 protein. In some embodiments, the intergenic region is the 54kb region between the Pira6 and Ncr1 loci. In some embodiments, the FcαR locus is positioned between coordinates 4,303,905 – 4,312,280 on mouse chromosome 7 (+strand, GRCm38 assembly).

[0007] In some embodiments, the FcαR locus comprises a nucleic acid sequence encoding a human FcαR polypeptide. In some embodiments, the FcαR locus comprises human exons 1-5 of the human Fc alpha receptor gene. In some embodiments, the FcαR locus comprises a non-coding portion of rodent (non-mouse) FcαR exon 1, a coding portion of

human FcαR exons 1 and 2, human FcαR exons 3 and 4, and rodent (non-mouse) FcαR exon 5. In some embodiments, the human or humanized FcαR receptor locus comprises a genomic sequence found between coordinates 54,862,297 and 54,906,185 on human chromosome 19 (+ strand, GRCh38 assembly). In some embodiments, the FcαR locus further comprises a nucleic acid sequence present in a human KIR3DL2 gene. In some embodiments, the locus further comprises a nucleic acid sequence present in the 5'UTR of the human NCR1 gene.

[0008] In some embodiments, the mouse or mouse ES cell is heterozygous for the FcαR locus. In some embodiments, the mouse or mouse ES cell is homozygous for the FcαR locus.

[0009] In some embodiments, the mouse or mouse ES cell of any of the above aspects or embodiments further comprises in its genome a human or humanized Fc gamma receptor (FcγR) locus, a human or humanized IgH locus, a human or humanized Igκ locus, a human or humanized Igλ locus, a human or humanized FcRn locus, a human or humanized β2M locus, and/or a human or humanized FcεR1α locus. In some embodiments, the mouse or mouse ES cell is heterozygous for the human or humanized FcγR locus, the human or humanized IgH locus, the human or humanized Igκ locus, the human or humanized Igλ locus, the human or humanized FcRn locus, the human or humanized β2M locus, and/or the human or humanized FcεR1α locus. In some embodiments, the mouse or mouse ES cell is homozygous for the human or humanized FcγR locus, the human or humanized IgH locus, the human or humanized Igκ locus, the human or humanized Igλ locus, the human or humanized FcRn locus, the human or humanized β2M locus, and/or the human or humanized FcεR1α locus.

[0010] In some embodiments, the mouse or mouse ES cell comprising the FcαR locus of the various embodiments described herein comprises in its genome a human or humanized FcγR locus comprising a nucleic acid sequence encoding a human or humanized FcγR. In some embodiments, the human or humanized FcγR locus comprises a nucleic acid sequence encoding one or more low affinity FcγR selected from Fc gamma receptor 2a (FcγR2a), Fc gamma receptor 2b (FcγR2b), Fc gamma receptor 3a (FcγR3a), Fc gamma receptor 3b (FcγR3b), and/or Fc gamma receptor 2c (FcγR2c). In some embodiments, the human or humanized FcγR locus comprises a nucleic acid sequence encoding one or more FcγR selected from a human or humanized Fc gamma receptor 1 alpha (FcγR1a), Fc gamma receptor 2a (FcγR2a), Fc gamma receptor 2b (FcγR2b), Fc gamma receptor 3a (FcγR3a), Fc gamma receptor 3b (FcγR3b), and/or Fc gamma receptor 2c (FcγR2c). In some embodiments, the human or humanized FcγR comprises a human extracellular domain. In some

lox2372 cassette, a PI-SceI site, the 3' mouse homology arm, and a chloramphenicol-resistance cassette; final clone was selected based on CM/kanamycin resistance (**FIG. 2**). Various junctions in the final clone are depicted in **Table 2**.

Table 2

Junction	Sequence
Mouse 5' arm/ I-CeuI/ human sequence within intron 6 of the KIR3DL2 gene	CTACCCATGCTCTACCCTAGTACCCTTTCTTCAGCACTCCCCTCTCTGTG TCGCTACCTTAGGACCGTTATAGTTAG AGTCAAGAGGGTTGTGGATGTAGAAACTGTAAAGCACATTCACTGTGTAT (SEQ ID NO:23)
human/ AgeI/ *5' lox2372*	GGCCCGCCCGGCTCAGTCCCCACTGCTCAGCACTAGGCCGGCAGAATCTG ACCGGT *ATAACTTCGTATAAGGTATCCTATACGAAGTTAT* (SEQ ID NO:24)
3' lox2372/ PI-SceI/ mouse 3' arm	*ATAACTTCGTATAAGGTATCCTATACGAAGTTAT* CTCGAGATCTATGTCGGGTGCGGAGAAAGAGGTAATGAAATGGCAT ATGAATGCAGGTAAGGGGGAAACCTCACAGAATATCCAGAATTCTGTTAT (SEQ ID NO:25)

[0032] The MAID20277 targeting vector was electroporated into mouse embryonic stem (ES) cells comprising human low affinity Fcγ receptors. The genetic modification of low affinity Fcγ receptor locus is described in U.S. Patent No. 8,658,154, and depicted schematically in **FIG. 3**. Targeted homologous recombination resulted in deletion of ~8.4 kb of mouse sequence (GRCm38 coordinates chr7:4,303,905 – 4,312,280) and insertion of ~44 kb of human sequence including the FCAR gene. Successful integration was confirmed by a modification of allele (MOA) assay as described, e.g., in Valenzuela et al, supra. Primers (forward (F) and reverse (R) primers) and probes used for the MOA assay for detecting presence of human FCAR sequences and the loss of mouse LRC sequences are depicted in **Table 3** below, and their locations are designated in **FIG 1A**. The antibody resistance cassette was subsequently removed by transient expression of CRE recombinase in the ES cell clone, **FIG. 1B**.

TABLE 3

Description (probe and F and R primers)	Sequence	Loss of Allele (LOA) or Gain of Allele (GOA)	SEQ ID NO
GOA 1 Probe	ACCCAGAAGGGCCCTCCAAGC	GOA	5
F	GGTGTCTGCCCATGAAATGAG		6

Example 1.2: Phenotype Analysis of Genetically Engineering of Mice Comprising Human or Humanized FcαR

[00309] Mice described in Example 1.1 above, comprising human FCAR and low affinity FCGR genes were analyzed for FcαR expression. All mice were housed and bred in the specific pathogen-free conditions. Mice were sacrificed, and spleens and blood were harvested. Blood was collected into BD microtainer tubes with EDTA (Cat # 365973). Red blood cells from spleen and blood preparations were lysed with ACK lysis buffer (ThermoFisher, Cat. # A1049201), followed by washing with complete RPMI medium.

[00310] Both spleen and blood cells were incubated with Live Dead Aqua (ThermoFisher) for exclusion of non-viable cells. Prior to staining, cells were incubated with anti-mouse CD16/32 (2.4G2; BD) on ice for 10 minutes. Cells were then stained with fluorochrome conjugated anti-human CD89 (BioLegend, Clone No. A59) and the following anti-mouse antibodies; CD45 (BioLegend, Clone No. 30-F11), B220 (BioLegend, Clone No. RA3-6B2), CD11c (BioLegend, Clone No. N418), Ly6G (BioLegend, Clone No. 1A8), Ly6C (BioLegend, Clone No. HK1.4), SiglecF (BD Biosciences Clone No. E50-2440), NKp46 (BioLegend, Clone No. 29A1.4), CD11b (BioLegend, Clone No. M1/70), F4/80 (BD Biosciences Clone No. T45-2342), and NK1.1 (BioLegend, Clone No. PK136) for 30 min on ice.

[00311] Lymphocyte and myeloid cell populations were identified by flow cytometry on the BD Symphony A3 instrument (BD Biosciences). First, viable single cells were gated on CD45+. The following subsets were then identified: B cells (B220+), cDCs (CD11c++), pDCs (CD11cint, Ly6C+ B220+), PMN Ly6G+ Ly6C+), eosinophils (Ly6G-, SiglecF+CD11b+), macrophages/monocytes (Ly6G-, SiglecF-, F4/80+ CD11b+), and NK cells (Ly6G-, SiglecF-, F4/80- CD11b-, NK1.1+). Expression of CD89 (FcαR) was determined on each cell type.

[00312] The mice genetically engineered with the MAID20278 cassette exhibited a gain of hFcαR on splenic and blood neutrophils, eosinophils, some blood monocytes/macrophages, and splenic plasmacytoid dendritic cells. No hFcαR expression was observed in splenic monocytes or macrophages (**FIGs. 4A-4B**).

Incorporation by Reference

[0033] All publications, patents, and patent applications mentioned herein are hereby incorporated by reference in their entirety as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Equivalents

[00313] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

SEQUENCE LISTING

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<120> MICE EXPRESSING HUMANIZED FC ALPHA RECEPTORS

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<141> 2021-12-15

<150> 63/126,326
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attctgttat 130

What is claimed is:

1. A mouse comprising in its genome an Fc alpha receptor (FcαR) locus positioned in the mouse leukocyte receptor complex (LRC), wherein the FcαR locus comprises a nucleic acid sequence encoding a FcαR polypeptide comprising a human extracellular domain and a human or rodent cytoplasmic domain.

2. The mouse of claim 1, wherein the FcαR locus is positioned in an intergenic region between the gene loci for the Tthy1 protein and the Rdh13 protein.

3. The mouse of claim 1 or 2, wherein the FcαR locus is positioned in an intergenic region between the gene loci for the Lilra5 protein and the Gp6 protein.

4. The mouse of any one of claims 1-3, wherein the FcαR locus is positioned in an intergenic region between the gene loci for the Pira6 protein and the Ncr1 protein, such as between coding nucleic acid sequences for the Pira6 protein and the Ncr1 protein.

5. The mouse of claim 4, wherein the intergenic region is the 54kb region between the Pira6 and Ncr1 loci.

6. The mouse of any one of claims 1-5, wherein the FcαR locus is positioned between coordinates 4,303,905 – 4,312,280 on mouse chromosome 7 (+strand, GRCm38 assembly).

7. The mouse of any one of claims 1-6, wherein the FcαR locus comprises a nucleic acid sequence encoding a human FcαR polypeptide.

8. The mouse of any one of claims 1-7, wherein the FcαR locus comprises human exons 1-5 of the human Fc alpha receptor gene.

9. The mouse of any one of claims 1-6, wherein the FcαR locus comprises a non-coding portion of non-mouse rodent FcαR exon 1, a coding portion of human FcαR exons 1 and 2, human FcαR exons 3 and 4, and non-mouse rodent FcαR exon 5.

10. The mouse of claim 7 or 8, wherein the human or humanized FcαR receptor locus comprises a genomic sequence found between coordinates 54,862,297 and 54,906,185 on human chromosome 19 (+ strand, GRCh38 assembly).

11. The mouse of claim 7 or 8, wherein the FcαR locus further comprises a nucleic acid sequence present in a human KIR3DL2 gene, and/or nucleic acid sequence present in the 5'UTR of the human NCR1 gene.

12. The mouse of any one of claims 1-11, wherein the mouse expresses the FcαR polypeptide on mouse neutrophils, monocytes, macrophages, eosinophils, and dendritic cells (e.g., plasmacytoid dendritic cells).

13. The mouse of any one of claims 1-12, wherein the mouse is heterozygous or homozygous for the FcαR locus.

14. The mouse of any one of claims 1-13, further comprising in its genome a human or humanized Fc gamma receptor (FcγR) locus, a human or humanized IgH locus, a human or humanized Igκ locus, a human or humanized Igλ locus, a human or humanized FcRn locus, a human or humanized β2M locus, and/or a human or humanized FcεR1α locus.

15. A mouse embryonic stem cell (ES cell) comprising in its genome an Fc alpha receptor (FcαR) locus positioned in the leukocyte receptor complex (LRC) of the mouse genome, wherein the FcαR locus comprises a nucleic acid sequence encoding a FcαR polypeptide comprising a human extracellular domain and a human or rodent cytoplasmic domain.

16. The mouse ES cell of claim 15, wherein the FcαR locus is positioned in an intergenic region between the gene loci for the Tthy1 protein and the Rdh13 protein.

17. The mouse ES cell of claim 15 or 16, wherein the FcαR locus is positioned in an intergenic region between the gene loci for the Lilra5 protein and the Gp6 protein.

18. The mouse ES cell of any one of claims 15-17, wherein the Fc alpha receptor (FcαR) locus is positioned in an intergenic region between the gene loci for the Pira6 protein and the Ncr1 protein, such as between the coding nucleic acid sequences for the Pira6 protein and the Ncr1 protein.

19. The mouse ES cell of claim 18 wherein the intergenic region is the 54kb region between the Pira6 and Ncr1 loci.

20. The mouse ES cell of any one of claims 15-19 wherein the FcαR locus is positioned between coordinates 4,303,905 – 4,312,280 on mouse chromosome 7 (+strand, GRCm38 assembly).

21. The mouse ES cell of any one of claims 15-20, wherein the FcαR locus comprises a nucleic acid sequence encoding a human FcαR polypeptide.

22. The mouse ES cell of anyone claims 15-21, wherein the FcαR locus comprises human exons 1-5 of the human Fc alpha receptor gene.

23. The mouse ES cell of any one of claims 15-20, wherein the FcαR locus comprises a non-coding portion of non-mouse rodent FcαR exon 1, a coding portion of human FcαR exons 1 and 2, human FcαR exons 3 and 4, and non-mouse rodent FcαR exon 5.

24. The mouse ES cell of claim 21 or 22, wherein the human or humanized FcαR receptor locus comprises a genomic sequence found between coordinates 54,862,297 and 54,906,185 on human chromosome 19 (+ strand, GRCh38 assembly).

25. The mouse ES cell of claim 21 or 22, wherein the FcαR locus further comprises a nucleic acid sequence present in a human KIR3DL2 gene, and/or a nucleic acid sequence present in the 5' UTR of the human NCR1 gene.

26. The mouse ES cell of any one of claims 15-25, wherein the ES cell is heterozygous or homozygous for the FcαR locus.

27. The mouse ES cell of any one of claims 15-26, further comprising in its genome a human or humanized Fc gamma receptor (FcγR) locus, a human or humanized IgH locus, a human or humanized Igκ locus, a human or humanized Igλ locus, a human or humanized FcRn locus, a human or humanized β2M locus, and/or a human or humanized FcεR1α locus.

28. A method of testing a human IgA antibody or an Fcα fusion polypeptide comprising administering the IgA antibody or Fcα fusion polypeptide to a mouse of any one of claims 1 to 14.

29. The method of claim 28 further comprising measuring one or more pharmacokinetic properties of the administered human IgA antibody or Fcα fusion polypeptide, optionally wherein the one or more pharmacokinetic properties are selected from one or more of area under the plasma concentration versus time (AUC), in vivo recovery (IVR), clearance rate (CL), mean residence time (MRT), agent half-life (t½), and/or volume of distribution at steady state (Vss).

30. The method of any one of claims 28 or 29 further comprising measuring the therapeutic efficacy of the administered human antibody or Fcα fusion polypeptide.

31. The method of any one of claims 28-30 further comprising administering a plurality of doses of the human antibody or Fcα fusion polypeptide and determining a therapeutic efficacy, safety, and/or tolerability of each dose of the human antibody or Fcα fusion polypeptide.

32. The method of any one of claims 28-31 further comprising measuring one or more Fc receptor mediated responses in the mouse, optionally wherein the one or more Fc receptor mediated response is an antibody-dependent cell-mediated cytotoxicity (ADCC) response.

33. The method of any one of claims 28-32, wherein the human antibody binds to a target cell in the mouse, and further comprising measuring antibody-dependent cell-mediated cytotoxicity (ADCC) of natural killer (NK) cells against the target cell and comparing the amount of ADCC to a control, wherein increased target cell killing indicates the agent has increased ability to mediate ADCC.

34. The method of any one of claims 28-33, further comprising measuring the immune response generated by the mouse against the human antibody.

35. A method of modifying a mouse genome, the method comprising:

inserting an Fc alpha receptor (FcαR) locus into the leukocyte receptor complex (LRC) of a mouse genome, thereby modifying the mouse genome, wherein the FcαR locus comprises a nucleic acid sequence encoding an FcαR polypeptide comprising a human extracellular domain and a human or rodent cytoplasmic domain.

36. The method of claim 35, wherein the FcαR locus comprises a nucleic acid sequence encoding a human FcαR polypeptide.

37. The method of claim 35 or 36, wherein the FcαR locus is positioned in an intergenic region between the gene loci for the Tthy1 protein and the Rdh13 protein.

38. The method of any one of claims 35-37, wherein the FcαR locus is positioned in an intergenic region between the gene loci for the Lilra5 protein and the Gp6 protein.

39. The method of any one of claims 35-38, wherein the FcαR locus is positioned in an intergenic region between the gene loci for the Pira6 protein and the Ncr1 protein, such as between the coding nucleic acid sequences for the Pira6 protein and the Ncr1 protein.

40. The method of claim 39, wherein the intergenic region is the 54kb region between the Pira6 and Ncr1 loci.

41. The method of any one of claims 35-40, wherein the FcαR locus is between coordinates 4,303,905 – 4,312,280 on mouse chromosome 7 (+strand, GRCm38 assembly).

42. A method of making a mouse comprising an Fc alpha receptor (FcαR) locus, the method comprising:

generating a mouse ES cell of any one of claims 15-27; and

generating a mouse from said ES cell.