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SUMMARY

It has been found that anti-IGF-1R antibodies with abolished FcRn-binding can be used for the treatment of IGF-1R-related disorders in the eye (vascular eye diseases).

One aspect as reported herein is an anti-IGF-1R antibody that specifically binds to human IGF-1R and that has abolished FcRn binding.

One aspect as reported herein is an anti-IGF-1R antibody as defined herein for use in inhibiting IGF-1R in the eye.

~~One aspect a~~As reported herein is the use of an anti-IGF-1R antibody with abolished human neonatal Fc-receptor (FcRn) binding for inhibition of IGF-1R in the eye.

~~One aspect a~~As reported herein is the use of an anti-IGF-1R antibody with abolished human neonatal Fc-receptor (FcRn) binding for the treatment of vascular eye diseases.

In one embodiment the anti-IGF-1R antibody has no (remaining) detectable FcRn binding using a surface plasmon resonance based determination method.

In one embodiment the anti-IGF-1R antibody binds to human FcRn with a K_D-value of more than 1.7 μM at pH 6, i.e. with low affinity.

I253A/H310A/H435A or H310A/H433A/Y436A or L251D/L314D/L432D in the first as well as in the second Fc-region polypeptide (numbering according to Kabat EU index numbering system), or which comprise the mutations I253A/H310A/H435A in the first Fc-region polypeptide and the mutations H310A/H433A/Y436A in the second Fc-region polypeptide (numbering according to Kabat EU index numbering system).

In one embodiment of all aspects the second Fc-region polypeptide further comprises the mutations Y349C, T366S, L368A and Y407V („hole“) and the first Fc-region polypeptide further comprises the mutations S354C and T366W („knob“).

In one embodiment of all aspects the Fc-region polypeptides are of the human IgG1 subclass. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutations L234A and L235A. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutation P329G.

In one embodiment of all aspects the Fc-region polypeptides are of the human IgG4 subclass. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutations S228P and L235E. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutation P329G.

~~One aspect a~~As reported herein is method of treatment of patient suffering from ocular vascular diseases by administering an anti-IGF-1R antibody as reported herein to a patient in the need of such treatment.

In one embodiment the anti-IGF-1R antibody has no (remaining) detectable FcRn binding using a surface plasmon resonance based determination method.

In one embodiment the anti-IGF-1R antibody binds to human FcRn with a K_D-value of more than 1.7 µM at pH 6, i.e. with low affinity.

In one embodiment of all aspects the antibody has the same or a shorter retention time on an FcRn affinity chromatography column as an antibody comprising an Fc-region with the mutations I253A/H310A/H435A or H310A/H433A/Y436A or L251D/L314D/L432D or combinations thereof (numbering according to Kabat EU index numbering system).

In one embodiment of all aspects the second Fc-region polypeptide further comprises the mutations Y349C, T366S, L368A and Y407V („hole") and the first Fc-region polypeptide further comprises the mutations S354C and T366W („knob").

In one embodiment of all aspects the Fc-region polypeptides are of the human IgG1 subclass. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutations L234A and L235A. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutation P329G.

In one embodiment of all aspects the Fc-region polypeptides are of the human IgG4 subclass. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutations S228P and L235E. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutation P329G.

~~One aspect a~~As reported herein is an anti-IGF-1R antibody with abolished human neonatal Fc-receptor (FcRn) binding for intravitreal application. One aspect as reported herein is an anti-IGF-1R antibody as defined herein for intravitreal application.

~~One aspect a~~As reported herein is an anti-IGF-1R antibody with abolished human neonatal Fc-receptor (FcRn) binding for the treatment of vascular eye diseases. One aspect as reported herein is an anti-IGF-1R antibody as defined herein for the treatment of vascular eye diseases.

In one embodiment the anti-IGF-1R antibody has no (remaining) detectable FcRn binding using a surface plasmon resonance based determination method.

In one embodiment the anti-IGF-1R antibody binds to human FcRn with a K_D-value of more than 1.7 µM at pH 6, i.e. with low affinity.

In one embodiment of all aspects the antibody has the same or a shorter retention time on an FcRn affinity chromatography column as an antibody comprising an Fc-region with the mutations I253A/H310A/H435A or H310A/H433A/Y436A or L251D/L314D/L432D or combinations thereof (numbering according to Kabat EU index numbering system).

In one embodiment of all aspects the antibody has a retention time on an FcRn affinity chromatography column of three minutes or less.

In one embodiment the FcRn affinity column has the column dimensions of 50 mm x 5 mm, the bed height is 5 cm and the loading is 50 µg antibody. In one

In one embodiment of all aspects the second Fc-region polypeptide further comprises the mutations Y349C, T366S, L368A and Y407V („hole") and the first Fc-region polypeptide further comprises the mutations S354C and T366W („knob").

In one embodiment of all aspects the Fc-region polypeptides are of the human IgG1 subclass. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutations L234A and L235A. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutation P329G.

In one embodiment of all aspects the Fc-region polypeptides are of the human IgG4 subclass. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutations S228P and L235E. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutation P329G.

~~One aspect a~~As reported herein is a pharmaceutical formulation comprising an anti-IGF-1R antibody with abolished human neonatal Fc-receptor (FcRn) binding and optionally a pharmaceutically acceptable carrier. One aspect as reported herein is a pharmaceutical formulation comprising an anti-IGF-1R antibody as defined herein and optionally a pharmaceutically acceptable carrier. Another aspect is reported herein is a pharmaceutical formulation comprising an anti-IGF-1R antibody as defined herein.

One aspect as reported herein is an anti-IGF-1R antibody as defined herein for use as a medicament.

One aspect as reported herein is an anti-IGF-1R antibody as defined herein for use in treating vascular eye diseases.

One aspect as reported herein is an anti-IGF-1R antibody as defined herein for use in a method of treatment.

One aspect as reported herein is an anti-IGF-1R antibody as defined herein for use in a method of treating an individual having a vascular eye disease comprising administering to the individual an effective amount of the anti-IGF-1R antibody as defined herein.

One aspect as reported herein is an anti-IGF-1R antibody as defined herein for use in a method of inhibiting angiogenesis in an individual comprising administering to the individual an effective of the anti-IGF-1R antibody as defined herein to inhibit IGF-1R signaling.

One aspect as reported herein is use of an anti-IGF-1R antibody as defined herein in the manufacture of a medicament.

In one embodiment the anti-IGF-1R antibody has no (remaining) detectable FcRn binding using a surface plasmon resonance based determination method.

In one embodiment the anti-IGF-1R antibody binds to human FcRn with a K_D-value of more than 1.7 µM at pH 6, i.e. with low affinity.

In one embodiment of all aspects the antibody has the same or a shorter retention time on an FcRn affinity chromatography column as an antibody comprising an Fc-region with the mutations I253A/H310A/H435A or H310A/H433A/Y436A or L251D/L314D/L432D or combinations thereof (numbering according to Kabat EU index numbering system).

In one embodiment of all aspects the antibody has a retention time on an FcRn affinity chromatography column of three minutes or less.

In one embodiment the FcRn affinity column has the column dimensions of 50 mm x 5 mm, the bed height is 5 cm and the loading is 50 µg antibody. In one embodiment the equilibration buffer is 20 mM MES, with 150 mM NaCl, adjusted to pH 5.5, the elution buffer is 20 mM Tris/HCl, with 150 mM NaCl, adjusted to

In one embodiment of all aspects the Fc-region polypeptides are of the human IgG1 subclass. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutations L234A and L235A. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutation P329G.

In one embodiment of all aspects the Fc-region polypeptides are of the human IgG4 subclass. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutations S228P and L235E. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutation P329G.

~~One aspect a~~As reported herein is an anti-IGF-1R antibody with abolished human neonatal Fc-receptor (FcRn) binding.

In one embodiment the anti-IGF-1R antibody has no (remaining) detectable FcRn binding using a surface plasmon resonance based determination method.

In one embodiment the anti-IGF-1R antibody binds to human FcRn with a K_D-value of more than 1.7 µM at pH 6, i.e. with low affinity.

In one embodiment of all aspects the antibody has the same or a shorter retention time on an FcRn affinity chromatography column as an antibody comprising an Fc-region with the mutations I253A/H310A/H435A or H310A/H433A/Y436A or L251D/L314D/L432D or combinations thereof (numbering according to Kabat EU index numbering system).

In one embodiment of all aspects the antibody has a retention time on an FcRn affinity chromatography column of three minutes or less.

In one embodiment the FcRn affinity column has the column dimensions of 50 mm x 5 mm, the bed height is 5 cm and the loading is 50 µg antibody. In one embodiment the equilibration buffer is 20 mM MES, with 150 mM NaCl, adjusted to pH 5.5, the elution buffer is 20 mM Tris/HCl, with 150 mM NaCl, adjusted to pH 8.8 and the elution is by applying 7.5 CV equilibration buffer, from 0 % to 100 % elution buffer in 30 CV, and thereafter 10 CV elution buffer.

In one embodiment the anti-IGF-1R antibody does not bind to a human FcRn column due to single or multiple point mutations in the CH2 and/or CH3 domain of the anti-IGF-1R antibody. In one embodiment the antibody has a comparable, i.e.

region polypeptide further comprise the mutations L234A and L235A. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutation P329G.

In one embodiment of all aspects the Fc-region polypeptides are of the human IgG4 subclass. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutations S228P and L235E. In one embodiment the first Fc-region polypeptide and the second Fc-region polypeptide further comprise the mutation P329G.

~~One aspect a~~As reported herein is a nucleic acid encoding the anti-IGF-1R antibody as reported herein.

~~One aspect a~~As reported herein is a host cell comprising the nucleic acid encoding the anti-IGF-1R antibody as reported herein.

~~One aspect a~~As reported herein is a method for producing the anti-IGF-1R antibody as reported herein comprising culturing the host cell comprising the nucleic acid encoding the anti-IGF-1R antibody as reported herein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Antibodies engineered with respect to their ability to bind FcRn display prolonged (YTE) or shortened (AAA) in vivo half-lives, enhanced (YTE) or reduced FcRn binding (AAA) compared to the reference wild-type (wt) antibody in SPR analysis as well as enhanced or reduced retention time in FcRn column chromatography; a) PK data after single i.v. bolus application of 10 mg/kg into huFcRn transgenic male C57BL/6J mice +/- 276: AUC data for wild-type IgG as well as YTE and AAA Fc-modified IgGs; b) BIAcore sensorgram; c) FcRn affinity column elution; wild-type anti-IGF-1R antibody (reference), YTE-mutant of anti-IGF-1R antibody, AAA-mutant of anti-IGF-1R antibody.

Figure 2: Comparison of serum concentrations after intravenous application of antibodies IGF-1R 0033, 0035 and 0045.

Figure 3: Comparison of eye lysate concentration after intravitreal and intravenous application of antibody IGF-1R 0033.

Figure 4: Comparison of eye lysate concentration after intravitreal and intravenous application of antibody IGF-1R 0035.