

Claims

1. An isolated antibody or antigen-binding fragment thereof capable of binding to IL-11 and inhibiting IL-11 mediated signaling, comprising
~~wherein said isolated antibody or antigen binding fragment thereof is capable of reducing blood loss during abnormal uterine bleeding.~~
2. ~~An isolated antibody or antigen binding fragment thereof capable of binding to IL-11 and inhibiting IL-11 mediated signaling,
 according to claim 1
 wherein said isolated antibody or antigen binding fragment thereof binds to human IL-11 with a dissociation constant (K_D) $\leq 1.0 \text{ E-}08 \text{ M}$, $\leq 1.0 \text{ E-}09 \text{ M}$, $\leq 5.0 \text{ E-}10 \text{ M}$, $\leq 1.0 \text{ E-}10 \text{ M}$, $\leq 5.0 \text{ E-}11 \text{ M}$, $\leq 2.5 \text{ E-}11 \text{ M}$ or $\leq 1.0 \text{ E-}11 \text{ M}$~~
3. ~~An isolated antibody or antigen binding fragment thereof capable of binding to IL-11 and inhibiting IL-11 mediated signaling,
 according to claim 1-2
 wherein said isolated antibody or antigen binding fragment thereof inhibits human IL-11 mediated signaling with an IC_{50} of $\leq 100 \text{ nM}$, $\leq 50 \text{ nM}$, $\leq 25 \text{ nM}$, $\leq 10 \text{ nM}$, $\leq 1 \text{ nM}$, $\leq 0.5 \text{ nM}$ or $\leq 0.1 \text{ nM}$.~~
4. ~~An isolated antibody or antigen binding fragment thereof capable of binding to IL-11 and inhibiting IL-11 mediated signaling,
 according to claim 1-3
 wherein said isolated antibody or antigen binding fragment thereof inhibits the interaction of IL-11 with IL-11Ra and
 wherein said isolated antibody or antigen binding fragment thereof inhibits the formation of IL-11/IL-11Ra/gp130 complex.~~
5. ~~An isolated antibody or antigen binding fragment thereof capable of binding to IL-11 and inhibiting IL-11 mediated signaling,
 according to claim 1-3
 wherein said isolated antibody or antigen binding fragment thereof inhibits the formation of IL-11/IL-11Ra/gp130 complex and
 wherein said isolated antibody or antigen binding fragment thereof does not inhibit the interaction of IL-11 with IL-11Ra.~~

- ~~6. The isolated antibody or antigen binding fragment thereof according to claims 1-3 wherein said isolated antibody or antigen binding fragment thereof is a bispecific antibody or antigen binding fragment thereof capable of binding to two different IL-11 epitopes.~~
- ~~7. The isolated antibody or antigen binding fragment thereof according to claims 6 wherein said isolated antibody or antigen binding fragment thereof inhibits the binding of IL-11 to IL-11Ra and wherein said isolated antibody or antigen binding fragment thereof inhibits the formation of IL-11/IL-11Ra/gp130 complex.~~
- ~~8. The isolated antibody or antigen binding fragment thereof according to claims 1-7 wherein said human IL-11 is of the sequence of SEQ ID NO: 1, aa 22-199; wherein said human IL-11Ra is of the sequence of SEQ ID NO: 3 and/or wherein said human gp130 is sequence SEQ ID 12.~~
- ~~9. The isolated antibody or antigen binding fragment thereof according to claims 1-3 wherein said isolated antibody or antigen binding fragment thereof does not bind to IL-2Ra.~~
- ~~10. The isolated antibody or antigen binding fragment thereof according to any one of claims 1-9 comprising~~
- ~~i) a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 33, an H-CDR2 comprising SEQ ID NO: 34, and an H-CDR3 comprising SEQ ID NO: 35 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 37, an L-CDR2 comprising SEQ ID NO: 38, and an L-CDR3 comprising SEQ ID NO:39; or~~
 - ~~ii) a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 43, an H-CDR2 comprising SEQ ID NO: 44, and an H-CDR3 comprising SEQ ID NO: 45 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 47, an L-CDR2 comprising SEQ ID NO: 48, and an L-CDR3 comprising SEQ ID NO:49; or~~
 - ~~iii) a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 55, an H-CDR2 comprising SEQ ID NO: 56, and an H-CDR3~~

comprising SEQ ID NO: 57 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 59, an L-CDR2 comprising SEQ ID NO: 60, and an L-CDR3 comprising SEQ ID NO:61; or

- 5 iv) a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 65, an H-CDR2 comprising SEQ ID NO: 66, and an H-CDR3 comprising SEQ ID NO: 67 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 69, an L-CDR2 comprising SEQ ID NO: 70, and an L-CDR3 comprising SEQ ID NO:71; or
- 10 v) a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 83, an H-CDR2 comprising SEQ ID NO: 84, and an H-CDR3 comprising SEQ ID NO: 85 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 87, an L-CDR2 comprising SEQ ID NO: 88, and an L-CDR3 comprising SEQ ID NO:89; or
- 15 vi) a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 107, an H-CDR2 comprising SEQ ID NO: 108, and an H-CDR3 comprising SEQ ID NO: 109 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 111, an L-CDR2 comprising SEQ ID NO: 112, and an L-CDR3 comprising SEQ ID NO:113; or
- 20 vii) a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 121, an H-CDR2 comprising SEQ ID NO: 122, and an H-CDR3 comprising SEQ ID NO: 123 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 125, an L-CDR2 comprising SEQ ID NO: 126, and an L-CDR3 comprising SEQ ID NO:127; or
- 25 viii) a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 137, an H-CDR2 comprising SEQ ID NO: 138, and an H-CDR3 comprising SEQ ID NO: 139 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 141, an L-CDR2 comprising SEQ ID NO: 142, and an L-CDR3 comprising SEQ ID NO:143; or
- 30 ix) a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 149, an H-CDR2 comprising SEQ ID NO: 150, and an H-CDR3 comprising SEQ ID NO: 151 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 153, an L-CDR2 comprising SEQ ID NO: 154, and an L-CDR3 comprising SEQ ID NO:155; or

- 5 x) a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 161, an H-CDR2 comprising SEQ ID NO: 162, and an H-CDR3 comprising SEQ ID NO: 163 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 165, an L-CDR2 comprising SEQ ID NO: 166, and an L-CDR3 comprising SEQ ID NO: 167; or
- 10 xi) a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 173, an H-CDR2 comprising SEQ ID NO: 174, and an H-CDR3 comprising SEQ ID NO: 175 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 177, an L-CDR2 comprising SEQ ID NO: 178, and an L-CDR3 comprising SEQ ID NO: 179; or
- 15 xii) a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 185, an H-CDR2 comprising SEQ ID NO: 186, and an H-CDR3 comprising SEQ ID NO: 187 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 189, an L-CDR2 comprising SEQ ID NO: 190, and an L-CDR3 comprising SEQ ID NO: 191.
- 11.2.** _____ The isolated antibody or antigen-binding fragment thereof according to ~~any one of~~ claims 1 –10 comprising
- 20 xiii) a variable heavy chain domain comprising SEQ ID NO: 32 and a variable light chain domain comprising SEQ ID NO: 36; or
- xiv) a variable heavy chain domain comprising SEQ ID NO: 42 and a variable light chain domain comprising SEQ ID NO: 46; or
- xv) a variable heavy chain domain comprising SEQ ID NO: 54 and a variable light chain domain comprising SEQ ID NO: 58; or
- 25 xvi) a variable heavy chain domain comprising SEQ ID NO: 64 and a variable light chain domain comprising SEQ ID NO: 68; or
- xvii) a variable heavy chain domain comprising SEQ ID NO: 82 and a variable light chain domain comprising SEQ ID NO: 86; or
- xviii) a variable heavy chain domain comprising SEQ ID NO: 106 and a variable light chain domain comprising SEQ ID NO: 110; or
- 30 xix) a variable heavy chain domain comprising SEQ ID NO: 120 and a variable light chain domain comprising SEQ ID NO: 124; or

- xx) a variable heavy chain domain comprising SEQ ID NO: 136 and a variable light chain domain comprising SEQ ID NO: 140; or
- xxi) a variable heavy chain domain comprising SEQ ID NO: 148 and a variable light chain domain comprising SEQ ID NO: 152; or
- 5 xxii) a variable heavy chain domain comprising SEQ ID NO: 160 and a variable light chain domain comprising SEQ ID NO: 164; or
- xxiii) a variable heavy chain domain comprising SEQ ID NO: 172 and a variable light chain domain comprising SEQ ID NO: 176; or
- xxiv) a variable heavy chain domain comprising SEQ ID NO: 184 and a variable light chain domain comprising SEQ ID NO: 188.

~~12.3.~~ 12.3. The isolated antibody
 according to ~~any one of claims 1-11~~ claim 1 or 2,
 which is an IgG antibody, in particular an IgG1 or an IgG4 antibody.

~~13.4.~~ 13.4. The isolated antibody
 according to any one of claims 1-~~39~~ comprising

- xxv) a heavy chain comprising SEQ ID NO: 40 and a light chain comprising SEQ ID NO: 41; or
- xxvi) a heavy chain comprising SEQ ID NO: 90 and a light chain comprising SEQ ID NO: 91; or
- 20 xxvii) a heavy chain comprising SEQ ID NO: 92 and a light chain comprising SEQ ID NO: 33; or
- xxviii) a heavy chain comprising SEQ ID NO: 116 and a light chain comprising SEQ ID NO: 117; or
- xxix) a heavy chain comprising SEQ ID NO: 130 and a light chain comprising SEQ ID NO: 131; or
- 25 xxx) a heavy chain comprising SEQ ID NO: 146 and a light chain comprising SEQ ID NO: 147; or
- xxxi) a heavy chain comprising SEQ ID NO: 158 and a light chain comprising SEQ ID NO: 159; or

xxxii) a heavy chain comprising SEQ ID NO: 170 and a light chain comprising SEQ ID NO: 171; or

xxxiii) a heavy chain comprising SEQ ID NO: 182 and a light chain comprising SEQ ID NO: 183; or

5 xxxiv) a heavy chain comprising SEQ ID NO: 192 and a light chain comprising SEQ ID NO: 193; or

xxxv) a heavy chain comprising SEQ ID NO: 194 and a light chain comprising SEQ ID NO: 195; or

10 xxxvi) a heavy chain comprising SEQ ID NO: 196 and a light chain comprising SEQ ID NO: 197.

15 5. An isolated antibody or antigen-binding fragment thereof capable of binding to IL-11 and inhibiting IL-11 mediated signaling wherein said isolated antibody or antigen-binding fragment thereof is a bispecific antibody or antigen-binding fragment thereof capable of binding to two different IL-11 epitopes comprising

~~14. The isolated bispecific antibody or antigen-binding fragment thereof according to claim 6 or 7 comprising~~

20 xxxvii) a first chain comprising a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 33, an H-CDR2 comprising SEQ ID NO: 34, and an H-CDR3 comprising SEQ ID NO: 35 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 37, an L-CDR2 comprising SEQ ID NO: 38, and an L-CDR3 comprising SEQ ID NO: 39 and a second chain comprising a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 55, an H-CDR2 comprising SEQ ID NO: 56, and an H-CDR3 comprising SEQ ID NO: 57 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 59, an L-CDR2 comprising SEQ ID NO: 60, and an L-CDR3 comprising SEQ ID NO: 61; or

30 xxxviii) a first chain comprising a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 121, an H-CDR2 comprising SEQ ID NO: 122, and an H-CDR3 comprising SEQ ID NO: 123 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 125, an L-

CDR2 comprising SEQ ID NO: 126, and an L-CDR3 comprising SEQ ID NO:127 and

a second chain comprising a heavy chain antigen-binding region that comprises an H-CDR1 comprising SEQ ID NO: 107, an H-CDR2 comprising SEQ ID NO: 108, and an H-CDR3 comprising SEQ ID NO: 109 and a light chain antigen-binding region that comprises an L-CDR1 comprising SEQ ID NO: 111, an L-CDR2 comprising SEQ ID NO: 112, and an L-CDR3 comprising SEQ ID NO:113.

15.6. The isolated bispecific antibody or antigen-binding fragment thereof according to claim ~~6, 7 or 14~~ 5 comprising

xxxix) a first chain comprising a variable heavy chain domain comprising SEQ ID NO: 32 and a variable light chain domain comprising SEQ ID NO: 36 and a second chain comprising a variable heavy chain domain comprising SEQ ID NO: 54 and a variable light chain domain comprising SEQ ID NO: 58; or

xl) a first chain comprising a variable heavy chain domain comprising SEQ ID NO: 120 and a variable light chain domain comprising SEQ ID NO: 124 and a second chain comprising a variable heavy chain domain comprising SEQ ID NO: 106 and a variable light chain domain comprising SEQ ID NO: 110.

16.7. The isolated bispecific antibody according to claim ~~6, 7, 14 or 15~~ 5 or 6 comprising

xli) a first chain comprising SEQ ID NO: 74 and a second chain comprising SEQ ID NO: 75; or

xlii) a first chain comprising SEQ ID NO: 132 and a second chain comprising SEQ ID NO: 133.

17.8. The antigen-binding fragment according to any one of claims ~~1, 2, 5, or 6-11 or 14-15~~, which is an scFv, Fab, Fab' fragment or a F(ab')₂ fragment.

18.9. The isolated antibody or antigen-binding fragment according to any one of claims ~~1-8~~ 1-6, which is a monoclonal antibody or antigen-binding fragment.

19.10. The isolated antibody or antigen-binding fragment

according to any one of claims 1-~~18~~,
which is a human, humanized or chimeric antibody or antigen-binding fragment.

~~20.~~ ~~An isolated antibody or antigen-binding fragment thereof that competes with the isolated antibody or antigen-binding fragment according to any one of claims 1-19 for binding to IL-11.~~

~~21.~~ 11. An antibody conjugate, comprising the isolated antibody or antigen binding fragment according to any one of claims 1 - 120.

~~22.~~ 12. An isolated nucleic acid sequence that encodes the antibody or antigen-binding fragment according to any one of claims 1 to 120.

~~23.~~ 13. A vector comprising a nucleic acid sequence according to claim 122.

~~24.~~ 14. An isolated cell expressing the antibody or antigen-binding fragment according to any one of claims 1 to 120 and/or comprising the nucleic acid according to claim 122 or the vector according to claim 123.

~~25.~~ 15. The isolated cell according to claim 124, wherein said cell is a prokaryotic or a eukaryotic cell.

~~26.~~ 16. A method of producing the isolated antibody or antigen-binding fragment according to any one of claims 1 to 120 comprising culturing of the cell according to any one of claims 124 or 125 and optionally purification of the antibody or antigen-binding fragment.

~~27.~~ 17. A pharmaceutical composition comprising the isolated antibody or antigen-binding fragment according to any one of claims 1 to 120 or the antibody conjugate according to claim 121 and optionally one or more pharmaceutically acceptable excipients.

~~28.~~ 18. An isolated antibody or antigen-binding fragment according to any one of claims 1 to 120 or the conjugate according to claim 121 or the pharmaceutical composition according to claim 127 for use in the treatment or prophylaxis of a disease.

~~29.~~ ~~An isolated antibody or antigen-binding fragment according to any one of claims 1 to 20 or the antibody conjugate according to claim 21 for use as a diagnostic agent.~~

~~30.~~ 19. An isolated antibody or antigen-binding fragment according to any one of claims 1 to 120 or the conjugate according to claim 121 or the pharmaceutical composition according to claim 127 for use in the for treatment or prevention of abnormal uterine bleeding (AUB),

dysmenorrhea, leiomyoma, or endometriosis.

~~31. The isolated antibody or antigen binding fragment according to any one of claims 1 to 20 or the conjugate according to claim 21 or the pharmaceutical composition according to claim 27 for use in the treatment or prevention of abnormal uterine bleeding (AUB);~~
~~dysmenorrhea, leiomyoma, or endometriosis~~
~~according to claim 30~~
~~wherein abnormal uterine bleeding is heavy menstrual bleeding, prolonged bleeding or altered bleeding pattern.~~

~~32. The isolated antibody or antigen binding fragment according to any one of claims 1 to 20 or the conjugate according to claim 21 or the pharmaceutical composition according to claim 27 for use in the treatment or prevention of abnormal uterine bleeding (AUB);~~
~~dysmenorrhea, leiomyoma, or endometriosis~~
~~according to claim 30 or 31~~
~~wherein abnormal uterine bleeding is heavy menstrual bleeding and~~
~~wherein heavy menstrual bleeding is secondary to leiomyoma or endometriosis.~~

~~33. The isolated antibody or antigen binding fragment according to any one of claims 1 to 20 or the conjugate according to claim 21 or the pharmaceutical composition according to claim 27 for use in the treatment or prevention of abnormal uterine bleeding (AUB);~~
~~dysmenorrhea, leiomyoma, or endometriosis~~
~~according to any of claims 30—31~~
~~wherein abnormal uterine bleeding is associated with dysmenorrhea.~~

~~34. The isolated antibody or antigen binding fragment according to any one of claims 1 to 20 or the conjugate according to claim 21 or the pharmaceutical composition according to claim 27 for use in the treatment or prevention of abnormal uterine bleeding (AUB);~~
~~dysmenorrhea, leiomyoma, or endometriosis~~
~~according to any of claims 30—33~~
~~wherein abnormal uterine bleeding is associated with dysmenorrhea secondary to leiomyoma or endometriosis.~~

~~35. Use of an isolated antibody or antigen-binding fragment according to any one of claims 1 to 20 or the conjugate according to claim 21 or the pharmaceutical composition according to claim 27 for inhibition or modulation of menstruation.~~

~~36. An isolated antibody or antigen-binding fragment according to any one of claims 1 to 20 or the conjugate according to claim 21 or the pharmaceutical composition according to claim 27 for use in simultaneous, separate, or sequential combination with one or more further therapeutically active compounds.~~

~~37.~~20. A kit comprising the isolated antibody or antigen-binding fragment according to any one of claims 1 to 1~~2~~0 or the conjugate according to claim 1~~2~~1 or the pharmaceutical composition according to claim 1~~2~~7 and instructions for use.