

### **Summary of invention**

In one aspect, the present disclosure refers to a humanized antibody that specifically binds to IL-1R3 or a fragment or derivative thereof that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity, comprising a heavy chain variable region (VH) and a light chain variable region (VL) comprising the respective CDR1, CDR2 and CDR3 regions of SEQ ID NO: 69, 86, 103, 120, 137 and 154; 70, 87, 104, 121, 138 and 155; 71, 88, 105, 122, 139 and 156; 72, 89, 106, 123, 140 and 157; 73, 90, 107, 124, 141 and 158; 74, 91, 108, 125, 142 and 159; 75, 92, 109, 126, 143 and 160; 76, 93, 110, 127, 144 and 161; 77, 94, 111, 128, 145 and 162; 78, 95, 112, 129, 146 and 163; 79, 96, 113, 130, 147 and 164; 80, 97, 114, 131, 148 and 165; 81, 98, 115, 132, 149 and 166; 82, 99, 116, 133, 150 and 167; 83, 100, 117, 134, 151 and 168; 84, 101, 118, 135, 152 and 169; 85, 102, 119, 136, 153 and 170; 79, 96, 113, 130, 147 and 175; or 71, 88, 105, 122, 139 and 156; wherein the humanized antibody or a fragment or derivative thereof inhibits IL-1R3 induced NFkB activity. In another aspect, the present disclosure refers to the humanized antibody according to any of the previous claims for the use in therapy. In another aspect, the present disclosure also refers to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody as disclosed herein. In yet another aspect, the present disclosure refers to the pharmaceutical composition as disclosed herein for the use in therapy. In a further aspect, the present disclosure refers to the use of the humanized antibody as disclosed herein, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating cancer.

The present disclosure relates to a humanized IgG1<sub>LALA</sub> antibody that specifically binds to IL-1R3 or a fragment or derivative thereof or a polypeptide that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity. Said antibody inhibits IL-1R3 induced NFkB activity. It also inhibits IL-1alpha, IL-1beta, IL-33, and/or IL-36 stimulated NFkB activity.

The disclosure further relates to an antibody according to the invention for the use in treating a IL-1R3 mediated disease.

The disclosure further encompasses a method of treating an IL-1R3 mediated disease in a patient, comprising administering to a patient a pharmaceutically effective amount of said antibody.

The present disclosure also comprises a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of said antibody.

## **Definitions**

The term “rabbit” according to the invention means an animal of the members of the taxonomic order Lagomorpha, which includes the families (hares and rabbits) and Ochotonidae (pikas), preferably of genus *Oryctolagus*.

The term "antibody" encompasses the various forms of antibody structures including, but not being limited to, whole antibodies and antibody fragments as long as it shows the properties according to the invention.

The term “rabbit monoclonal antibody” according to the invention means a monoclonal antibody produced by immunizing a rabbit and isolated from a antigen producing cell of said rabbit as well as such an antibody which is further modified, preferably a humanized antibody, a chimeric antibody, a fragment thereof, or a further genetically engineered and recombinant produced antibody as long as the characteristic properties according to the invention are retained. Preferably the antibody is from a B cell or a rabbit hybridoma cell of said rabbit.

## Claims

1. Humanized antibody that specifically binds to IL-1R3 or a fragment or derivative thereof that contains at least a portion of said antibody that is sufficient to confer IL-1R3 binding specificity, comprising a heavy chain variable region (VH) and a light chain variable region (VL) comprising the respective CDR1, CDR2 and CDR3 regions of SEQ ID NO: 69, 86, 103, 120, 137 and 154; 70, 87, 104, 121, 138 and 155; 71, 88, 105, 122, 139 and 156; 72, 89, 106, 123, 140 and 157; 73, 90, 107, 124, 141 and 158; 74, 91, 108, 125, 142 and 159; 75, 92, 109, 126, 143 and 160; 76, 93, 110, 127, 144 and 161; 77, 94, 111, 128, 145 and 162; 78, 95, 112, 129, 146 and 163; 79, 96, 113, 130, 147 and 164; 80, 97, 114, 131, 148 and 165; 81, 98, 115, 132, 149 and 166; 82, 99, 116, 133, 150 and 167; 83, 100, 117, 134, 151 and 168; 84, 101, 118, 135, 152 and 169; 85, 102, 119, 136, 153 and 170; 79, 96, 113, 130, 147 and 175; or 71, 88, 105, 122, 139 and 156; wherein the humanized antibody or a fragment or derivative thereof inhibits IL-1R3 induced NFkB activity.
2. The humanized antibody that specifically binds to IL-1R3 or a fragment or derivative thereof according to claim 1, wherein the antibody comprises a heavy chain variable (VH) region that is at least 90 % identical to a VH region selected from the group consisting of VH regions of SEQ ID NO: 1 to 34 and 173.
3. The humanized antibody that specifically binds to IL-1R3 or a fragment or derivative thereof according to claim 1, wherein the antibody comprises a light chain variable (VL) region that is at least 90% identical to a VL region selected from the group consisting of VL regions of SEQ ID NO: 35 to 68 and SEQ ID NO:174.
4. The humanized antibody that specifically binds to IL-1R3 or a fragment or derivative thereof according to claim 1, wherein the antibody comprises a heavy chain variable region (VH) comprising an amino acid sequence selected from the group of SEQ ID NO: 1 to 34 and 173.
5. The humanized antibody that specifically binds to IL-1R3 or a fragment or derivative thereof according to claim 1, wherein the antibody comprises a light chain variable region (VL) comprising an amino acid sequence selected from the group of SEQ ID NO: 35 to 68 and 174.

6. The humanized antibody according to any of the previous claims, wherein said antibody inhibits IL-1 $\alpha$ , IL-1 $\beta$ , IL-33, and/or IL-36 stimulated NF $\kappa$ B activity.
7. The humanized antibody according to any of the previous claims, wherein said antibody inhibits NF $\kappa$ B activity stimulated by a complex selected from the group consisting of IL-1 $\beta$ /IL-1R1/IL-1RAcP, IL-1 $\alpha$ /IL-1R1/IL-1RAcP IL-33/ST2/IL-1RAcP, and/or IL-36/IL-36R/IL-1RAcP.
8. The humanized antibody according to any of the previous claims, wherein said antibody inhibits in a concentration of 10  $\mu$ g/ml NF $\kappa$ B expression in A549-NF $\kappa$ B-RE-Luc cell lysates stimulated with 0.1 ng/ml human IL-1 $\alpha$ , human IL-1 $\beta$ , IL-33 and/or IL-36, for 50% or more, preferably for 60% or more, preferably for 70% or more, preferably for 80% or more, preferably for 90% and more, and more preferably for 95% or more, related to the same assay without said antibody according to the invention.
9. The humanized antibody according to any of the previous claims, wherein said antibody inhibits IL-1 $\alpha$ , IL-1 $\beta$ , IL-33, and/or IL-36, respectively, stimulated luciferase activity in HEK293T/17 cells transfected with luciferase under control of NF- $\kappa$ B reporter gene.
10. The humanized antibody according to any of the previous claims, wherein said antibody comprises at least amino acid substitutions at L234A and L235A of the human IgG1 Fc region or S228P and L235E of the human IgG4 Fc region.
11. The humanized antibody according to any of the previous claims for the use in therapy.
12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody according to any one of claims 1-10.
13. The pharmaceutical composition according to claim 12 for the use in therapy.
14. Use of the humanized antibody according to any one of claims 1-10, or the pharmaceutical composition according to claim 13 in the manufacture of a medicament for treating cancer.
15. The use according to claim 14, where in the cancer is selected from the group consisting of lung cancer, non-small cell lung (NSCL) cancer, bronchioloalviolar cell lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma,

uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, gastric cancer, colon cancer, breast cancer, or uterine cancer.

16. The use according to claim 14 or 15, wherein the medicament is to be used in combination with one or more cytotoxic, cytostatic or targeted anti-cancer compounds.