

Claims

1. A protein binder that binds to human iRhom2, and inhibits and/or reduces TACE/ADAM17 activity when bound to human iRhom2, the protein binder further inhibits or reduces TNF α shedding.
2. The protein binder according to claim 1, which is a monoclonal antibody, or a target-binding fragment or derivative thereof retaining target binding capacities, or an antibody mimetic.
3. The protein binder according to claim 1 or 2, wherein the inhibition or reduction of TACE/ADAM17 activity is caused by interference with iRhom2-mediated TACE/ADAM17 activation.
4. The protein binder according to any one of the aforementioned claims, wherein the human iRhom2 to which the protein binder binds comprises
 - a) the amino acid sequence set forth in SEQ ID NO 16, or
 - b) an amino acid sequence that has at least 80 % sequence identity with SEQ ID NO 16, with the proviso that said sequence maintains iRhom2 activity.
5. The protein binder according to any one of the aforementioned claims, which binds to the juxtamembrane domain adjacent to the transmembrane domain 1 (TMD1) of human iRhom2, which juxtamembrane domain comprises amino acid residues 431 – 459 of SEQ ID NO 16.
6. The protein binder according to any one of the aforementioned claims, which binds to an amino acid sequence of human iRhom2 comprising
 - a) at least the amino acid sequence set forth in SEQ ID NO 3, or
 - b) an amino acid sequence that has at least 90 % sequence identity with SEQ ID NO 3.

7. The protein binder according to any one of the aforementioned claims, which binds to one or more amino acid sequences of human iRhom2 each comprising one or more amino acids within the amino acid sequence set forth in SEQ ID NO 3
8. The protein binder according to any one of the aforementioned claims, which binds to at least one amino acid residue selected from the group consisting of A431, Q432, H433, V434, T435, T436, Q437, L438, V439, L440, R441, N442, K443, G444, V445, Y446, E447, S448, V449, K450, Y451, I452, Q453, Q454, E455, N456, F457, W458, V459, wherein the numbering of the amino acid residues refers to the amino acid sequence set forth in SEQ ID NO 16 (human iRhom2).
9. The protein binder according to any one of the aforementioned claims, which is not cross reactive with human iRhom1, or the juxtamembrane domain adjacent to the transmembrane domain 1 (TMD1) thereof.
10. The protein binder according to any one of the aforementioned claims, which is an antibody in at least one of the formats selected from the group consisting of: IgG, scFv, Fab, (Fab)₂
11. The protein binder according to any one of the aforementioned claims, which protein binder
 - a) comprises a set of heavy chain/light chain complementarity determining regions (CDR) comprised in the heavy chain/light variable region sequence pair set forth in SEQ ID NOs 33 and 40
 - b) comprises a set of heavy chain/light chain complementarity determining regions (CDR) comprising the following sequences
 - HC CDR1 (SEQ ID NO 34 or 37)
 - HC CDR2 (SEQ ID NO 35 or 38)
 - HC CDR3 (SEQ ID NO 36 or 39)
 - LC CDR1 (SEQ ID NO 41 or 44)

- LC CDR2 (SEQ ID NO 42 or 45), and
- LC CDR3 (SEQ ID NO 43 or 46)

c) comprises the heavy chain/light chain complementarity determining regions (CDR) of b), with the proviso that at least one of the CDRs has up to 3 amino acid substitutions relative to the respective SEQ ID NO 34 – 39 or 41 – 46, and/or

d) comprises the heavy chain/light chain complementarity determining regions (CDR) of b) or c), with the proviso that at least one of the CDRs has a sequence identity of $\geq 66\%$ to the respective SEQ ID NO 34 – 39 or 41 – 46,

wherein the CDRs are embedded in a suitable protein framework so as to be capable to bind to human iRhom2 with sufficient binding affinity and to inhibit or reduce TACE/ADAM17 activity.

12. The protein binder according to any one of the aforementioned claims, wherein the framework is a human VH/VL framework.

13. The protein binder according to any one of the aforementioned claims, which comprises

a) the heavy chain/light chain variable domains (VD)

- HC VD (SEQ ID NO 33), and
- LC VD (SEQ ID NO 40)

b) the heavy chain/light chain variable domains (VD) of a), with the proviso that

- the HCVD has a sequence identity of $\geq 80\%$ to the respective SEQ ID NO 33, and/or
- the LCDVD has a sequence identity of $\geq 80\%$ to the respective SEQ ID NO 40,

c) the heavy chain/light chain variable domains (VD) of a) or b), with the proviso that at least one of the HCVD or LCVD has up to 10 amino acid substitutions relative to the respective SEQ ID NO 33 and/or 40.

said protein binder still being capable to bind to human iRhom2 with sufficient binding affinity and to inhibit or reduce TACE/ADAM17 activity.

14. The protein binder according to any one of the aforementioned claims, which protein binder has at least one of

- target binding affinity of ≥ 50 % to iRhom2, and measured by SPR, compared to that of the protein binder according to any one of the aforementioned claims, and/or
- ≥ 50 % of the inhibiting or reducing effect on TACE/ADAM17 activity of the protein binder according to any one of the aforementioned claims.

15. A protein binder that binds to essentially the same, or the same, epitope on iRhom2 as the protein binder according to any one of the aforementioned claims.

16. The protein binder according to any one of claims 10 - 15, which is a monoclonal antibody, or a target-binding fragment or derivative thereof retaining target binding capacities, or an antibody mimetic.

17. A protein binder according to any one of claims 1 – 15 for use in the treatment of a human or animal subject

- being diagnosed for,
- suffering from or
- being at risk of developing

an inflammatory condition, or for the prevention of such condition.

18. A pharmaceutical composition comprising the protein binder according to any one of claims 1 – 15, and optionally one or more pharmaceutically acceptable excipients.

19. A combination comprising (i) the protein binder according to any one of claims 1 – 15 or the pharmaceutical composition according to claim ~~26~~18 and (ii) one or more therapeutically active compounds.

20. A therapeutic kit of parts comprising:

- a) the composition according to any one of claims 1 – 15, the pharmaceutical composition according to claim ~~23~~18 or the combination according to claim 19,
- b) an apparatus for administering the composition, composition or combination, and
- c) instructions for use.