Dandekar (2005) Nat. Rev. Immunol. 5(12): 917-927; Chen et al. (2020) Current Tropical Medicine Reports 3:1-4).

Tada et al. (2020), available at https://www.biorxiv.org/content/10.1101/2020.09.16.300319v1.full, disclose an "ACE2 microbody" in which the extracellular domain of catalytically inactive ACE2 is fused to Fc domain 3of the immunoglobulin heavy chain.

Hence, there is still a need for agents which can be used for the treatment and/or prevention of infections with coronaviruses, in particular with SARS-CoV-2.

SUMMARY

The present disclosure provides a fusion protein comprising a first part comprising a fragment of human ACE2 or a variant of said fragment, said human ACE2 having the amino acid sequence according to SEQ ID No. 1, and a second part comprising the Fc portion of human IgG4 or a variant of the Fc portion of human IgG4, said Fc portion of human IgG4 having the amino acid sequence according to SEQ ID No. 5, wherein the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 4.

The fragment of human ACE2 may consist of SEQ ID No. 2 or may be the extracellular domain of ACE2 consisting of SEQ ID No. 3.

In one example, the fusion protein has the amino acid sequence according to any one of SEQ ID Nos. 6 to 9.

In one aspect, the present disclosure provides a fusion protein comprising a first part comprising a fragment of human ACE2 consisting of the amino acid sequence according to SEQ ID No. 2 or a variant of said fragment, and a second part comprising the Fc portion of human IgG or a variant of the Fc portion of human IgG.

In one example, the IgG is IgG1 or IgG4.

In one example, the IgG is IgG4 and the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 4.

In one example, the IgG is IgG1 and the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 15.

In one example, the fusion protein has the amino acid sequence according to any one of SEQ ID Nos. 6, 8, 10 and 12.

In one example, the present disclosure provides a fusion protein comprising a first part comprising a fragment of human ACE2 or a variant of said fragment, said human ACE2 having the amino acid sequence according to SEQ ID No. 1, and a second part comprising the Fc portion of human IgG2 or IgG3 or a variant of the Fc portion of human IgG1, IgG2 or IgG3, wherein the fusion protein has reduced binding to FcγRIIIa compared to a fusion protein comprising the same first part and a second part comprising the Fc portion of wild-type human IgG1.

In one example, the fusion protein has essentially the same binding to FcRn compared to a fusion protein comprising the same first part and a second part comprising the Fc portion of wild-type human IgG1.

In one example, the variant of the Fc portion of human IgG1 comprises the amino acid substitutions L3A and L4A in the sequence according to SEQ ID No. 16.

In one example, the fragment of human ACE2 consists of the amino acid sequence according to SEQ ID No. 2 or is the extracellular domain of ACE2 consisting of the amino acid sequence according to SEQ ID No. 3.

In one example, the variant of the human ACE2 fragment is an enzymatically inactive variant of human ACE2 which may comprise a H374N and a H378N mutation, the numbering referring to SEQ ID No. 1.

The variant of the human ACE2 fragment may comprise an amino acid substitution at leucine 584, the numbering referring to SEQ ID No. 1 and/or at least one amino acid substitution at at least one residue selected from lysine 619, arginine 621, lysine 625, arginine 697, lysine 702, arginine 705, arginine 708, arginine 710 and arginine 716, the numbering referring to SEQ ID No. 1.

In one example the variant of the human ACE2 fragment comprises amino acid substitutions at lysine 619, arginine 621, lysine 625, arginine 697, lysine 702, arginine 705, arginine 708, arginine 710 and arginine 716, the numbering referring to SEQ ID No. 1.

In one example the variant of the human ACE2 fragment comprises a S645C mutation, the numbering referring to SEQ ID No. 1.

In further aspects, the present disclosure also relates to a nucleic acid molecule comprising a nucleic acid sequence encoding said fusion protein, an expression vector comprising said nucleic acid molecule and a host cell comprising said nucleic acid molecule or said expression vector.

Further, in another aspect, the present disclosure relates to a method for producing said fusion protein, comprising culturing said host cell in a suitable culture medium.

In yet another aspect, the present disclosure provides the fusion protein as described herein for use in therapy. In yet another aspect, the present disclosure provides a use of the fusion protein as described herein in the manufacture of a medicament for preventing and/or treating an infection with a coronavirus binding to ACE2.The present disclosure also relates to said fusion protein for medical use, in particular for use in preventing and/or treating an infection with a coronavirus binding to ACE2.

In one example, the coronavirus binding to ACE2 is selected from the group consisting of SARS, SARS-CoV-2 and NL-63, preferably is SARS-CoV-2.

Said fusion protein may be administered in combination with an anti-viral agent which may be selected from the group consisting of remdesivir, arbidol HCl, ritonavir, lopinavir, darunavir, ribavirin, chloroquin and derivatives thereof, nitazoxanide, camostat mesilate, tocilizumab, siltuximab, sarilumab and baricitinib phosphate.

In yet another aspect, the present disclosure provides a use of the fusion protein as described herein in the manufacture of a medicament for treating hypertension (including high blood pressure), congestive heart failure, chronic heart failure, acute heart failure, contractile heart failure, myocardial infarction, arteriosclerosis, kidney failure, renal failure, Acute Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI), chronic obstructive pulmonary disease (COPD), pulmonary hypertension, renal fibrosis, chronic renal failure, acute renal failure, acute kidney injury, inflammatory bowel disease and multi-organ dysfunction syndrome. The present disclosure also relates to said fusion protein for use in treating hypertension (including high blood pressure), congestive heart failure, chronic heart failure, acute heart failure, contractile heart failure, myocardial infarction, arteriosclerosis,

kidney failure, renal failure, Acute Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI), chronic obstructive pulmonary disease (COPD), pulmonary hypertension, renal fibrosis, chronic renal failure, acute renal failure, acute kidney injury, inflammatory bowel disease and multi-organ dysfunction syndrome.

In yet another aspect, the present disclosure also relates to a pharmaceutical composition comprising said fusion protein and a pharmaceutically acceptable carrier or excipient. The pharmaceutical composition may further comprise an anti-viral agent.

CLAIMS

1. A fusion protein comprising a first part comprising a fragment of human ACE2 consisting of the amino acid sequence according to SEQ ID No. 2 or a variant of said fragment, and a second part comprising the Fc portion of human IgG or a variant of the Fc portion of human IgG, wherein the IgG is IgG1 and the first part and the second part are linked by the amino acid sequence according to SEQ ID No. 15.

2. The fusion protein according to claim 1, having the amino acid sequence according to SEQ ID No. 10 or 12.

3. The fusion protein according to claim 1 or 2 wherein the variant of the human ACE2 fragment is an enzymatically inactive variant of human ACE2.

4. The fusion protein according to claim 3, wherein the enzymatically inactive variant of human ACE2 comprises a H374N and a H378N mutation, the numbering referring to SEQ ID No. 1.

5. The fusion protein according to any one of claims 1 to 4, wherein the variant of the human ACE2 fragment comprises an amino acid substitution at leucine 584, the numbering referring to SEQ ID No. 1.

6. The fusion protein according to any one of claims 1 to 5, wherein the variant of the human ACE2 fragment comprises at least one amino acid substitution at at least one residue selected from lysine 619, arginine 621, lysine 625, arginine 697, lysine 702, arginine 705, arginine 708, arginine 710 and arginine 716, the numbering referring to SEQ ID No. 1.

7. The fusion protein according to any one of claims 1 to 6, wherein the variant of the human ACE2 fragment comprises amino acid substitutions at lysine 619, arginine 621, lysine 625, arginine 697, lysine 702, arginine 705, arginine 708, arginine 710 and arginine 716, the numbering referring to SEQ ID No. 1.

8. The fusion protein according to any one of claims 1 to 7, wherein the variant of the human ACE2 fragment comprises a S645C mutation, the numbering referring to SEQ ID No. 1.

9. A nucleic acid molecule comprising a nucleic acid sequence encoding the fusion protein according to any one of claims 1 to 8.

10. An expression vector comprising the nucleic acid molecule according to claim 9.

11. A host cell comprising the nucleic acid molecule according to claim 9 or the expression vector according to claim 10.

12. A method for producing the fusion protein according to any one of claims 1 to 8, comprising culturing the host cell according to claim 11 in a suitable culture medium.

13. The fusion protein according to any one of claims 1 to 8 for use in therapy.

14. Use of the fusion protein according to any one of claims 1 to 8 in the manufacture of a medicament for preventing and/or treating an infection with a coronavirus binding to ACE2.

15. The use according to claim 14, wherein the coronavirus binding to ACE2 is selected from the group consisting of SARS, SARS-CoV-2 and NL63, preferably it is SARS-CoV-2.

16. The use according to claim 14 or 15, wherein the fusion protein is to be administered in combination with an anti-viral agent.

17. The use according to claim 16, wherein the anti-viral agent is selected from the group consisting of remdesivir, arbidol HCl, ritonavir, lopinavir, darunavir, ribavirin, chloroquin and derivatives thereof, nitazoxanide, camostat mesilate, tocilizumab, siltuximab, sarilumab and baricitinib phosphate.

18. Use of the fusion protein according to any one of claims 1 to 8 in the manufacture of a medicament for treating hypertension (including high blood pressure), congestive heart failure, chronic heart failure, acute heart failure, contractile heart failure, myocardial infarction, arteriosclerosis, kidney failure, renal failure, Acute Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI), chronic obstructive pulmonary disease (COPD), pulmonary hypertension, renal fibrosis, chronic renal failure, acute renal failure, acute kidney injury, inflammatory bowel disease and multi-organ dysfunction syndrome.

19. A pharmaceutical composition comprising an effective amount of the fusion protein according to any one of claims 1 to 8 and a pharmaceutically acceptable carrier or excipient.

20. The pharmaceutical composition according to claim 19, further comprising an anti-viral agent.