between Long COVID and autoimmunity. In this regard, a SARS-CoV-2 triggered autoimmune response was suggested as possible key factor for severity and longevity (Long-COVID) of the disease (Khamsi R 2021, Nature *590*(7844):*29-31*.).

Any new compounds and compositions may theoretically find use in many clinically relevant applications within a short time frame, including mitigating and curing symptoms caused by *Coronaviridae* in patients.

Accordingly, it is an object of the present invention to provide new molecules for the use in therapy of a subject suffering from an infection with a virus from the family *Coronaviridae*.

Furthermore, it is another object of the present invention to provide a method for preventing infection of somatic cells with a virus from the *Coronaviridae* family.

It is also an object of the present invention to provide a pharmaceutical composition and a kit which may be used against such viral infections.

It is a further object of the present invention to provide a use of novel molecules for preventing infection of somatic cells with a virus from the *Coronaviridae* family.

In view of the recently recognized relevance of microthrombosis in the course of COVID-19 disease, it is also an object to provide new molecules which are effective against infection with a virus from the family *Coronaviridae* and at the same time show anticoagulatory effects.

It is further an object of the present invention to provide affinity molecules which are directed against novel target sites within the *Coronaviridae* replication machinery.

Summary ~~of the Invention~~

The aforementioned objects are solved by the aspects of the present ~~invention~~disclosure as specified hereinafter.

~~According to~~In the first aspect, ~~of~~ the present ~~invention~~disclosure refers to~~,~~ a use of an aptamer ~~is provided~~ in the manufacture of a medicament for ~~use in therapy of a subject by~~ treating, curing or preventing further progression of infection with a virus from the *Coronaviridae* family, wherein the aptamer comprises a nucleic acid sequence of SEQ ID No. 1

(GGT TGG TGT GGT TGG) and/or a nucleic acid sequence being at least 80% identical to SEQ ID No. 1.

In a preferred ~~embodiment~~example of the first aspect of the ~~invention~~disclosure, the subject is a mammal, preferably the subject is a human.

In one preferred ~~embodiment~~example of the first aspect of the ~~invention~~disclosure, the infection is caused by a virus from the genus *Betacoronavirus*, preferably from the subgenus *Sarbecovirus* or *Merbecovirus*, more preferably by a virus selected from the group comprising MERS-CoV, SARS-CoV and SARS-CoV-2.

In another preferred ~~embodiment~~example of the first aspect of the ~~invention~~disclosure, the infection is caused by a virus from the subgenus *Sarbecovirus*, preferably from the species *Severe acute respiratory syndrome-related coronavirus*, even more preferably one of SARS-CoV and SARS-CoV-2

In a specifically preferred ~~embodiment~~example of the first aspect of the ~~invention~~disclosure, the infection is caused by SARS-CoV-2.

In one preferred ~~embodiment~~example of the first aspect of the ~~invention~~disclosure, the aptamer has anticoagulant activity, preferably the aptamer is able to prolong coagulation time measured as partial thromboplastin time (PTT or alternatively aPTT) of human calibration plasma to 60 seconds or more at an aptamer concentration of 0.03 mg/ml and/or the aptamer is able to lower the prothrombin time (Quick value) of human calibration plasma to 40% or less at an aptamer concentration of 0.03 mg/ml.

In another preferred ~~embodiment~~example of the first aspect of the ~~invention~~disclosure, the aptamer selectively interacts with or binds to human thrombin, preferably the K_D value for binding of the aptamer to human thrombin is 1µM or less.

In a preferred ~~embodiment~~example of the first aspect of the present ~~invention~~disclosure, the aptamer interferes with the infection of somatic cells by selectively interacting with the Spike (S) glycoprotein, preferably with the Receptor-binding domain (RBD) of the Spike (S) glycoprotein, of the virus, more preferably by preventing or interfering with the interaction of the Spike glycoprotein of the virus and the angiotensin-converting enzyme 2 (ACE2) or the dipeptidyl peptidase 4 (DPP4), even more preferably the ACE2, of a subject host cell.

In a more preferred ~~embodiment~~example of the previous ~~embodiment~~example of the first aspect of the present ~~invention~~disclosure, the Receptor-binding domain of the Spike glycoprotein has a sequence of SEQ ID NO: 2

(SARS-CoV-2 Spike RBD) or SEQ ID NO: 3 (SARS-CoV Spike RBD) or SEQ ID NO: 4 (MERS-CoV Spike RBD), preferably wherein the Receptor-binding domain of the Spike glycoprotein has a sequence of SEQ ID NO: 2 or SEQ ID NO: 3, preferably wherein the Spike glycoprotein has a sequence of SEQ ID NO: 2.

In one preferred ~~embodiment~~example of the present ~~invention~~disclosure, the aptamer is administered to the subject by systemic delivery or pulmonary delivery, preferably by pulmonary delivery, more preferably by inhalation.

~~According to~~In the second aspect, ~~of~~ the present ~~invention~~disclosure~~,~~ refers to a use of an aptamer ~~is provided~~ in the manufacture of a medicament for ~~use in therapy of a subject by~~ treating, curing or preventing disease symptoms associated with Long COVID in a patient having overcome an infection with a virus from the *Coronaviridae* family, wherein the aptamer comprises a nucleic acid sequence of SEQ ID No. 1 (GGT TGG TGT GGT TGG) and/or a nucleic acid sequence being at least 80% identical to SEQ ID No. 1.

In a preferred ~~embodiment~~example of the second aspect, the disease symptoms comprise one or more from the group comprising neurological symptoms, such as chronic fatigue syndrome, postural orthostatic tachycardia syndrome (PoTS), dysautonomia, tremor, attention deficit, anomic aphasia, neuropathy, transverse myelitis, acute necrotising myelitis, and Guillain-Barré syndrome, cardiovascular symptoms, such as myocardial inflammation, arrhythmia, tachycardia, bradycardia, hypertension, and atrioventricular (AV) block, dermatological symptoms, such as alopecia and eczema, or gastrointestinal diseases.

In another preferred ~~embodiment~~example of the second aspect of the present ~~invention~~disclosure, the aptamer is used to inhibit the interaction of autoantibodies specific for a G-protein coupled receptor with its target proteins.

In yet another preferred ~~embodiment~~example of the second aspect of the present ~~invention~~disclosure, the aptamer is for use in the treatment of a patient in which autoantibodies against G-protein coupled receptors can be detected.

In one preferred ~~embodiment~~example of the second aspect of the present ~~invention~~disclosure, the patient exhibits functional autoantibodies against G-protein coupled receptors, preferably functional autoantibodies specific for any one of the human G-protein coupled receptor adrenergic alpha-1 receptor, adrenergic beta-2 receptor, endothelin 1 ETA receptor, muscarinic M_2 receptor, angiotensin II AT1 receptor, MAS-receptor and/or the nociception receptor, more preferably for

any one of the adrenergic beta-2 receptor, muscarinic M_2 receptor, angiotensin II AT1 receptor, MAS-receptor, particularly preferably wherein the patient exhibits an antibody pattern comprising functional autoantibodies specific for each of the adrenergic beta-2 receptor, muscarinic M_2 receptor, angiotensin II AT1 receptor, and MAS-receptor.

~~According to~~In the third aspect~~,~~ ~~of~~ the present ~~invention~~disclosure~~,~~ refers to a method of preventing infection of somatic cells with a virus from the *Coronaviridae* family by using an aptamer is provided, wherein the method is carried out *in vitro/ex vivo* and wherein the aptamer comprises a nucleic acid sequence of SEQ ID No. 1 (GGT TGG TGT GGT TGG) and/or a nucleic acid sequence being at least 80% identical to SEQ ID No. 1.

In a preferred ~~embodiment~~example of the third aspect of the present ~~invention~~disclosure, the cell is a mammalian cell, preferably wherein the cell is a human cell.

~~According to~~ In the fourth aspect~~,~~ ~~of~~ the present ~~invention~~disclosure~~,~~ refers to an aptamer, as disclosed herein, and a pharmaceutically acceptable excipient, in the manufacture of a pharmaceutical composition ~~is provided~~ for treating, curing or preventing further progression of infection with a virus from the *Coronaviridae* family~~comprising an aptamer for use according to the first aspect of the present invention and at least one pharmaceutically acceptable excipient~~.

In a preferred ~~embodiment~~example of the fourth aspect of the present ~~invention~~disclosure, the pharmaceutical composition for use according to the first aspect is for administration to the subject by systemic delivery or pulmonary delivery, preferably by pulmonary delivery, more preferably by inhalation.

~~According to~~In the fifth aspect~~,~~ ~~of~~ the present ~~invention~~disclosure~~,~~ provides a kit ~~is provided~~ comprising at least one aptamer for use according to the first aspect of the present ~~invention~~disclosure and a container.

~~According to~~In the sixth aspect~~,~~ ~~of~~ the present ~~invention~~disclosure~~,~~ refers to the use of the aptamer as defined in the first aspect of the present ~~invention~~disclosure is provided for preventing infection of somatic cells with a virus from the *Coronaviridae* family, wherein the aptamer is used *in vitro/ex vivo*.

~~According to~~In the seventh aspect~~,~~ ~~of~~ the present ~~invention~~disclosure~~,~~ provides affinity molecules ~~are provided~~ that specifically bind to a peptide of amino acid sequence Leu-Tyr-Arg-Asn-Arg-Asp-Val (LYRNRDV; SEQ ID NO: 9) and/or His-Arg-Phe-Tyr-Arg-Leu-Ala-Asn (HRFYRLAN; SEQ ID NO: 10) of the RNA-dependent RNA polymerase of the Severe acute respiratory syndrome coronavirus 2.

In a preferred ~~embodiment~~example of the seventh aspect of the present ~~invention~~disclosure, the affinity molecule is a small molecule having a molecular weight of at most 900 Daltons, more preferably the affinity

molecule is a small molecule from any one small molecule collection from the group comprising the University of Cincinnati Compound Collection, the DiscoveryProbe™ Bioactive Compound Library Plus from ApexBio Technology LLC, and the SARS-CoV-2 Screening Library from Cayman Chemical.

In another preferred ~~embodiment~~example of the seventh aspect of the present ~~invention~~disclosure, the affinity molecule is a peptide-based compound, more preferably an antibody or a binding fragment thereof.

In one preferred ~~embodiment~~example of the seventh aspect of the present ~~invention~~disclosure, the affinity molecule is an aptamer or oligonucleotide.

In an eighth aspect, ~~of~~ the present ~~invention~~disclosure~~,~~ provides a use of the affinity molecule of the seventh aspect ~~is provided for use~~ as a medicament.

In a ninth aspect, ~~of~~ the present ~~invention~~disclosure~~,~~ provides a use of the affinity molecule of the seventh aspect ~~is provided~~ in the manufacture of a medicament for ~~use in therapy of a subject by~~ treating, curing or preventing further progression of infection with a virus from the *Coronaviridae* family.

Description of Figures

Figure 1 shows NMR-analysis of quadruplex formation of BC 007 in presence of peptide No. 4 (a 6 aa peptide-sequence of SEQ ID NO: 5; **YRLFRK**) from the spike protein of SARS-CoV-2; upper spectrum: 1H-NMR spectrum of a 1: 1 mixture of BC007 and peptide No. 4 with the sequence YRLFRK; middle spectrum: the spectrum of peptide No. 4 of SEQ ID NO: 5 in pure water; bottom spectrum: spectrum of the quadruplex structure of BC007 in the presence of KCl.

Figure 2 shows the same spectra of Figure 1, wherein the view is zoomed into the range between 8.5-6.0 ppm; middle und bottom: pure substances show rather sharp signals, which are broadened and shifted in their position in the upper spectrum due to the interaction of the two substances with each other.

Figure 3 shows inhibition of SARS-CoV-2 replication by BC 007 in cell culture based on antiviral dose-response effects of BC 007 in VeroFM and Calu-3 cells.

Claims

1. Use of an ~~A~~aptamer in the manufacture of a medicament for ~~use in therapy of a subject by~~ treating, curing or preventing further progression of infection with a virus from the *Coronaviridae* family, wherein the aptamer comprises a nucleic acid sequence of SEQ ID No. 1 (GGT TGG TGT GGT TGG) and/or a nucleic acid sequence being at least 80% identical to SEQ ID No. 1.

2. The use according to claim 1, wherein the infection is caused by a virus from the genus *Betacoronavirus*, preferably from the subgenus *Sarbecovirus* or *Merbecovirus*, more preferably by a virus selected from the group comprising MERS-CoV, SARS-CoV and SARS-CoV-2, particularly preferably wherein the infection is caused by SARS-CoV-2.

3. The use according to any of the preceding claims, wherein the aptamer has anticoagulant activity, preferably wherein the aptamer is able to prolong coagulation time measured as partial thromboplastin time (PTT) of human calibration plasma to 60 seconds or more at an aptamer concentration of 0.03 mg/ml and/or wherein the aptamer is able to lower the prothrombin time (Quick value) of human calibration plasma to 40% or less at an aptamer concentration of 0.03 mg/ml.

4. The use according to any one of the preceding claims, wherein the aptamer interferes with the infection of somatic cells by selectively interacting with the Spike (S) glycoprotein of the virus, preferably by preventing or interfering with the interaction of the Spike glycoprotein of the virus and the angiotensin-converting enzyme 2 (ACE2) or the dipeptidyl peptidase 4 (DPP4), more preferably the ACE2 of a subject host cell.

5. The use according to claim 4, wherein the Receptor-binding domain of the Spike glycoprotein has a sequence of SEQ ID NO: 2 (SARS-CoV-2 Spike RBD) or SEQ ID NO: 3 (SARS-CoV Spike RBD) or SEQ ID NO: 4 (MERS-CoV Spike RBD), preferably wherein the Receptor-binding domain of the Spike glycoprotein has a sequence of SEQ ID NO: 2 or SEQ ID NO: 3, preferably wherein the Spike glycoprotein has a sequence of SEQ ID NO: 2.

6. Use of an ~~A~~aptamer in the manufacture of a medicament for ~~use in therapy of a subject by~~ treating, curing or preventing disease symptoms associated with long COVID in a patient having overcome an infection with a virus from the *Coronaviridae* family, wherein the aptamer

comprises a nucleic acid sequence of SEQ ID No. 1 (GGT TGG TGT GGT TGG) and/or a nucleic acid sequence being at least 80% identical to SEQ ID No. 1.

7. The use according to claim 6, wherein the disease symptoms comprise one or more from the group comprising neurological symptoms, such as chronic fatigue syndrome, postural orthostatic tachycardia syndrome (PoTS), dysautonomia, tremor, attention deficit, anomic aphasia, neuropathy, transverse myelitis, acute necrotising myelitis, and Guillain-Barré syndrome, cardiovascular symptoms, such as myocardial inflammation, arrhythmia, tachycardia, bradycardia, hypertension, and atrioventricular (AV) block, dermatological symptoms, such as alopecia and eczema, or gastrointestinal diseases.

8. The use according to any of claims 6 or 7, wherein the aptamer is used to inhibit the interaction of autoantibodies specific for a G-protein coupled receptor with its target proteins.

9. The use according to any of claims 6 to 8, wherein the aptamer is for use in the treatment of a patient in which autoantibodies against G-protein coupled receptors can be detected.

10. The use according to any of claims 6 to 9, wherein the patient exhibits functional autoantibodies against G-protein coupled receptors, preferably functional autoantibodies specific for any one of the human G-protein coupled receptor adrenergic alpha-1 receptor, adrenergic beta-2 receptor, endothelin 1 ETA receptor, muscarinic M_2 receptor, angiotensin II AT1 receptor, MAS-receptor and/or the nociception receptor, more preferably for any one of the adrenergic beta-2 receptor, muscarinic M_2 receptor, angiotensin II AT1 receptor, MAS-receptor, particularly preferably wherein the patient exhibits an antibody pattern comprising functional autoantibodies specific for each of the adrenergic beta-2 receptor, muscarinic M_2 receptor, angiotensin II AT1 receptor, and MAS-receptor.

11. A method of preventing infection of somatic cells with a virus from the *Coronaviridae* family by using an aptamer, wherein the method is carried out *in vitro/ex vivo* and wherein the aptamer comprises a nucleic acid sequence of SEQ ID No. 1 (GGT TGG TGT GGT TGG) and/or a nucleic acid sequence being at least 80% identical to SEQ ID No. 1.

12. Use of an aptamer, as defined in any of claims 1 to 10, and a pharmaceutically acceptable excipient, in the manufacture of a ~~P~~pharmaceutical composition for treating, curing or preventing further progression of infection with a virus from the *Coronaviridae* family, or for treating, curing or preventing disease symptoms associated with long COVID in a patient

having overcome an infection with a virus from the Coronaviridae family ~~comprising an aptamer for use according to any of claims 1 to 10 and at least one pharmaceutically acceptable excipient~~.

13. Kit comprising at least one aptamer for use according to any of claims 1 to 10 and a container.

14. Use of the aptamer as defined in claim 1 for preventing infection of somatic cells with a virus from the *Coronaviridae* family, wherein the aptamer is used *in vitro/ex vivo*.

15. Affinity molecule that specifically binds to a peptide of amino acid sequence Leu-Tyr-Arg-Asn-Arg-Asp-Val (LYRNRDV; SEQ ID NO: 9) and/or His-Arg-Phe-Tyr-Arg-Leu-Ala-Asn (HRFYRLAN; SEQ ID NO: 10) within the RNA-dependent RNA polymerase of the Severe acute respiratory syndrome coronavirus 2 (SEQ ID NO: 8).

16. Affinity molecule according to claim 15, wherein the affinity molecule is a small molecule having a molecular weight of at most 900 Daltons, preferably wherein the affinity molecule is a small molecule from any one small molecule collection from the group comprising the University of Cincinnati Compound Collection, the DiscoveryProbe™ Bioactive Compound Library Plus from ApexBio Technology LLC, and the SARS-CoV-2 Screening Library from Cayman Chemical.

17. Affinity molecule according to claim 15, wherein the affinity molecule is a peptide-based compound, preferably an antibody or a binding fragment thereof.

18. Affinity molecule according to claim 15, wherein the affinity molecule is an aptamer or oligonucleotide.

19. Affinity molecule according to any of claims 15 to 18 for use as a medicament.

20. Use of an ~~A~~affinity molecule according to any of claims 15 to 18 in the manufacture of a medicament for ~~use in therapy of a subject by~~ treating, curing or preventing further progression of infection with a virus from the *Coronaviridae* family.