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(54) Title: COMPOSITIONS AND METHODS FOR TREATING INFECTIOUS DISEASES

(57) Abstract: Compositions and methods for treating infectious diseases are provided. Accordingly, there is provided a method of preventing an infectious disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of an ADNF polypeptide; and a vaccine to an infectious disease. Also provided are methods of treating Acute Respiratory Distress Syndrome (ARDS) and Corona virus infection.

WO 2021/209992 A1

COMPOSITIONS AND METHODS FOR TREATING INFECTIOUS DISEASES

RELATED APPLICATION/S

This application claims the benefit of priority of US Provisional Patent Application No. 63/011,579 filed on April 17, 2020, the contents of which are incorporated herein by reference in their entirety.

SEQUENCE LISTING STATEMENT

The ASCII file, entitled 86648SequenceListing.txt, created on 12 April 2021, comprising 22,692 bytes, submitted concurrently with the filing of this application is incorporated herein by reference.

FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to compositions and methods for treating infectious diseases.

Acute Respiratory Distress Syndrome (ARDS) is a devastating disease characterized by the breakage of the blood-air barrier inducing alveolar flooding and inflammation. ARDS affects over a quarter million patients, causing over four million hospital-days per year. The mechanical cause of ARDS is fluid leaked from the smallest blood vessels in the lungs into alveoli where blood is oxygenated. Normally, a protective membrane keeps this fluid in the vessels. Severe illness or injury, however, can cause damage to the membrane, leading to the fluid leakage of ARDS. The accumulation of fluids leads to a reduced level of oxygen in the bloodstream, thereby depriving the organs of the oxygen they need to function.

One of the underlying causes of ARDS is a Corona virus infection. The worldwide viral pandemic termed COVID-19, caused by the new Corona virus, SAR-CoV-2, is associated with significant morbidity and mortality with collateral effects on culture and economics. The rapid increase in number of confirmed cases and seriously ill patients makes prevention, control as well as finding an efficient and easily accessible medical therapy of outmost importance.

From studying the clinical characteristics of the severely ill COVID-19 patients, the dominant clinical picture is one of a hyper-inflammation immune response (also known as ‘cytokine storm’) and ARDS.

Activity-dependent neuroprotective protein (also referred to as ADNP or ADNF III) is essential for brain formation and function. ADNP was shown to function in key cellular activities

including embryogenesis, autophagy, dendritic spine plasticity, axonal transport, alternative RNA-splicing, wnt signaling, autism-linked protein translation and chromatin remodeling. De novo mutations in ADNP lead to the autistic ADNP syndrome [Van Dijck A, et al. Biological psychiatry 2019, 85(4): 287-297; Helsmoortel C, et al. Nature genetics 2014, 46(4): 380-384] and somatic ADNP mutations may drive Alzheimer's disease (AD) tauopathy (Ivashko-Pachima Y, G et al. Molecular psychiatry 2019). Furthermore, a decrease in blood ADNP expression was linked to increased inflammation [Braitch M, et al. Neuroimmunomodulation 2010, 17(2): 120-125] and reduced cognitive functions [Malishkevich A, et al. Journal of Alzheimer's disease: JAD 2016, 50(1): 249-260]. ADNP is found in the nucleus being part of the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex, which constitutes a major part of the chromatin remodeling complexes [Eubanks CG, et al. Expert review of proteomics 2017, 14(10): 905-915]. In mature neurons, ADNP is found in the cytoplasm [Mandel S, et al. J Mol Neurosci 2008, 35(2): 127-141] in association with microtubules through interaction with the microtubule end binding proteins, EB1 and EB3 [Oz S, et al. Molecular psychiatry 2014, 19(10): 1115-1124]. In turn, EB1/EB3 interaction with ADNP have been linked to dendritic spine formation [Oz S, et al. Molecular psychiatry 2014, 19(10): 1115-1124; Hacohen-Kleiman G, et al. The Journal of clinical investigation 2018, 128(11): 4956-4969], axonal transport [Amram N, et al. Molecular psychiatry 2016; 21(10): 1467-1476], enhancement of Tau-microtubule binding [Ivashko-Pachima Y, et al. Molecular psychiatry 2017, 22(9): 1335-1344; Grigg I, et al. Translational psychiatry 2020, 10(1): 228; Ivashko-Pachima Y, et al. Molecular psychiatry 2019] and protection against tau hyperphosphorylation/tauopathy [Grigg I, et al. Translational psychiatry 2020, 10(1): 228; Ivashko-Pachima Y, et al. Molecular psychiatry 2019; Vulih-Shultzman I, et al. The Journal of pharmacology and experimental therapeutics 2007, 323(2): 438-449].

ADNP polypeptides, including a proline-rich 8-amino acid polypeptide known as NAP [NAPVSIPQ (SEQ ID NO: 2), also known as Davunetide or CP201] and uses thereof in neuroprotection and treating multiple disorders are the subject of patents and patent applications including International Application Publication No. WO1/92333, WO98/35042, WOOO/27875, WO00/53217, WO01/12654, WO2004/080957, WO2006/099739, WO2007/096859, WO2008/084483, WO2011/021186, WO2009/026687, WO2011/083461, WO2011/099011, WO2013/171595, WO2017/130190, WO2004/060309, WO2003/022226 and WO2010/075635; and U.S. Patent Nos. US5767240, US6174862 and US6613740; herein each incorporated by reference in their entirety.

SUMMARY OF THE INVENTION

According to an aspect of some embodiments of the present invention there is provided a method of preventing an infectious disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an ADNF polypeptide, wherein the ADNF polypeptide is capable of binding EB1 and/or EB3; and a vaccine to an infectious disease, thereby preventing the infectious disease in the subject.

According to an aspect of some embodiments of the present invention there is provided an ADNF polypeptide, wherein the ADNF polypeptide is capable of binding EB1 and/or EB3; and a vaccine to an infectious disease, for use in preventing the infectious disease in a subject in need thereof.

According to some embodiments of the invention, the polypeptide and the vaccine are provided to the subject sequentially.

According to an aspect of some embodiments of the present invention there is provided an article of manufacture comprising as active ingredients an ADNF polypeptide, wherein the ADNF polypeptide is capable of binding EB1 and/or EB3; and a vaccine to an infectious disease.

According to some embodiments of the invention, the polypeptide and the vaccine are provided in a co-formulation.

According to some embodiments of the invention, the polypeptide and the vaccine are provided in separate formulations.

According to some embodiments of the invention, the infectious disease is associated with a viral infection.

According to an aspect of some embodiments of the present invention there is provided a method of treating Acute Respiratory Distress Syndrome (ARDS) in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an ADNF polypeptide, wherein the ADNF polypeptide is capable of binding EB1 and/or EB3, thereby treating the ARDS in the subject.

According to an aspect of some embodiments of the present invention there is provided an ADNF polypeptide, wherein the ADNF polypeptide is capable of binding EB1 and/or EB, for use in treating Acute Respiratory Distress Syndrome (ARDS) in a subject a subject in need thereof.

According to some embodiments of the invention, the method further comprising administering to the subject a therapeutically effective amount of a therapeutic agent for ARDS.

According to some embodiments of the invention, the polypeptide for use further comprising a therapeutic agent for ARDS.

According to an aspect of some embodiments of the present invention there is provided a method of treating an infectious disease associated with Corona virus infection in a subject in need thereof the method comprising administering to the subject a therapeutically effective amount of an ADNF polypeptide, wherein the ADNF polypeptide is capable of binding EB1 and/or EB3, thereby treating the infectious disease associated with the Corona virus infection in the subject.

According to an aspect of some embodiments of the present invention there is provided an ADNF polypeptide, wherein the ADNF polypeptide is capable of binding EB1 and/or EB3, for use in treating an infectious disease associated with Corona virus infection in a subject in need thereof.

According to some embodiments of the invention, the method further comprising administering to the subject a therapeutically effective amount of a therapeutic agent for an infectious disease associated with Corona virus infection.

According to some embodiments of the invention, the polypeptide for use further comprising a therapeutic agent for an infectious disease associated with Corona virus infection.

According to an aspect of some embodiments of the present invention there is provided an article of manufacture comprising as active ingredients an ADNF polypeptide, wherein the ADNF polypeptide is capable of binding EB1 and/or EB3; and a therapeutic agent for Acute Respiratory Distress Syndrome (ARDS).

According to some embodiments of the invention, the polypeptide and the therapeutic agent are provided in a co-formulation.

According to some embodiments of the invention, the polypeptide and the therapeutic agent are provided in separate formulations.

According to some embodiments of the invention, the therapeutic agent is selected from the group consisting of anti-inflammatory agent, antibiotic and vaccine.

According to some embodiments of the invention, the therapeutic agent is selected from the group consisting of hydroxychloroquine, chloroquine, Remdesivir, Zinc Sulfate, vasoactive intenstinal peptide (VIP), Aviptadil, phentolamine, tocilizumab, Sarilumab, Situximab, Janus kinase (JAK) inhibitor, nemonoxacin, linezolid and azithromycin.

According to some embodiments of the invention, the polypeptide and the therapeutic agent are provided to the subject sequentially.

According to some embodiments of the invention, the ARDS is associated with a viral infection.

According to some embodiments of the invention, the viral infection is a respiratory viral infection.

According to some embodiments of the invention, the respiratory viral infection is selected from the group consisting of a Corona virus infection, a respiratory syncytial virus (RSV) infection, an influenza virus infection, a parainfluenza virus infection, an adenovirus infection and a rhinovirus infection.

According to some embodiments of the invention, the viral infection is a Corona virus infection.

According to some embodiments of the invention, the Corona virus is SAR-CoV-2, Middle East respiratory syndrome Coronavirus (MERS-CoV) or severe acute respiratory syndrome Coronavirus (SARS-CoV).

According to some embodiments of the invention, the Corona virus is SAR-CoV-2.

According to some embodiments of the invention, the subject has a blood level of a pro-inflammatory cytokine above a predetermined threshold.

According to some embodiments of the invention, the subject is immunodeficient.

According to some embodiments of the invention, the subject is diagnosed with a syndrome selected from the group consisting of ADNP syndrome, fragile X syndrome, Syngap-1 syndrome, Phelan McDermid syndrome and Rett syndrome.

According to some embodiments of the invention, the ADNF polypeptide has a neurotrophic/neuroprotective activity in an in vitro cortical neuron culture assay.

According to some embodiments of the invention, the ADNF polypeptide comprises an SH3 binding domain.

According to some embodiments of the invention, the ADNF polypeptide is an ADNF III polypeptide.

According to some embodiments of the invention, the polypeptide comprises an amino acid sequence selected form the group consisting of 2-22.

According to some embodiments of the invention, the polypeptide comprises an amino acid sequence selected form the group consisting of 2-20.

According to some embodiments of the invention, the polypeptide comprises SEQ ID NO: 2.

According to some embodiments of the invention, the polypeptide has the formula $(R^1)_x$-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-$(R^2)_y$ (SEQ ID NO: 49), or an analogue thereof, in which R^1 is an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected from the group consisting of naturally occurring amino acids and amino

acid analogs; R^2 is an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected from the group consisting of naturally occurring amino acids and amino acid analogs; and x and y are independently selected and are equal to zero or one.

According to some embodiments of the invention, the polypeptide comprises at least one D-amino acid.

According to some embodiments of the invention, the polypeptide is less than 50 amino acids in length.

According to some embodiments of the invention, the polypeptide is less than 20 amino acids in length.

According to some embodiments of the invention, the polypeptide is attached to a cell penetrating or stabilizing moiety.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to compositions and methods for treating infectious diseases.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

Acute Respiratory Distress Syndrome (ARDS) is a devastating disease characterized by the breakage of the blood-air barrier inducing alveolar flooding and inflammation. One of the underlying causes of ARDS is a Corona virus infection.

Activity-dependent neuroprotective protein (also referred to as ADNP or ADNF III) is essential for brain formation and function. ADNP was shown to function in key cellular activities including embryogenesis, autophagy, dendritic spine plasticity, axonal transport, alternative RNA-splicing, wnt signaling, autism-linked protein translation and chromatin remodeling. ADNP

polypeptides, including a proline-rich 8-amino acid polypeptide known as NAP [NAPVSIPQ (SEQ ID NO: 2), also known as Davunetide or CP201] and uses thereof in neuroprotection and treating multiple disorders are the subject of patents and patent applications including International Application Publication No. WO1/92333, WO98/35042, WOOO/27875, WO00/53217, WO01/12654, WO2004/080957, WO2006/099739, WO2007/096859, WO2008/084483, WO2011/021186, WO2009/026687, WO2011/083461, WO2011/099011, WO2013/171595, WO2017/130190, WO2004/060309, WO2003/022226 and WO2010/075635; and U.S. Patent Nos. US5767240, US6174862 and US6613740.

Specific embodiments of the present teachings suggest the use of compositions comprising an ADNP polypeptide (e.g. NAP) in the treatment of ARDS in general and Corona virus infection in particular. In addition, other specific embodiments of the present teachings suggest the use of compositions comprising an ADNP polypeptide (e.g. NAP) to augment vaccination against infectious diseases.

Thus, according to an aspect of the present invention, there is provided a method of preventing an infectious disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB3; and a vaccine to an infectious disease, thereby preventing the infectious disease in the subject.

According to an additional or an alternative aspect of the present invention, there is provided an ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB3; and a vaccine to an infectious disease, for use in preventing the infectious disease in a subject in need thereof.

According to an additional or an alternative aspect of the present invention, there is provided a method of treating Acute Respiratory Distress Syndrome (ARDS) in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB3, thereby treating the ARDS in the subject.

According to an additional or an alternative aspect of the present invention, there is provided an ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB, for use in treating Acute Respiratory Distress Syndrome (ARDS) in a subject a subject in need thereof.

According to an additional or an alternative aspect of the present invention, there is provided a method of treating an infectious disease associated with Corona virus infection in a subject in need thereof the method comprising administering to the subject a therapeutically

effective amount of an ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB3, thereby treating the infectious disease associated with the Corona virus infection in the subject.

According to an additional or an alternative aspect of the present invention, there is provided an ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB3, for use in treating an infectious disease associated with Corona virus infection in a subject in need thereof.

As used herein, the term "treating" refers to abrogating, substantially inhibiting, slowing or reversing the progression of a pathology (disease, disorder or condition, e.g. ARDS, infectious disease e.g. caused by Corona virus infection), substantially ameliorating a symptom of a pathology and/or improving survival rate in a subject diagnosed with the pathology. Those of skill in the art will understand that various methodologies and assays can be used to assess the development of a pathology or reduction or regression of a pathology, as further disclosed herein.

As used herein, the term "preventing" refers to keeping a pathology from occurring in a subject that has not yet been diagnosed as having the pathology and/or preventing the manifestation of a symptom associated with the pathology before it occurs.

According to specific embodiments, the disease is ARDS.

According to specific embodiments, the ARDS is not in co-morbidity with other inflammatory diseases.

Acute Respiratory Distress Syndrome (ARDS) is a respiratory failure characterized by rapid onset of widespread inflammation in the lungs. Symptoms include shortness of breath, rapid breathing, and bluish skin coloration. The underlying mechanism involves diffuse injury to cells which form the barrier of the microscopic air sacs of the lungs, surfactant dysfunction, activation of the immune system, and dysfunction of the body's regulation of blood clotting. In effect, ARDS impairs the lungs' ability to exchange oxygen and carbon dioxide.

Methods of diagnosing ARDS are known in the art and include a PaO_2/FiO_2 ratio (ratio of partial pressure arterial oxygen and fraction of inspired oxygen) of less than 300 mm Hg despite a positive end-expiratory pressure (PEEP) of more than 5 cm H_2O.

Viral infection, sepsis, pancreatitis, trauma, pneumonia, and aspiration are non-limiting examples of underlying causes of ARDS.

According to specific embodiments, the ARDS is associated with an infectious disease.

As used herein, the term "associated with infectious disease" means that a pathogen infection leads to the ARDS.

According to specific embodiments, the disease is an infectious disease.

According to specific embodiments, the infectious disease is not in co-morbidity with other inflammatory diseases.

As used herein, the term “infection” or "infectious disease" refers to a disease induced by a pathogen. Non-limiting specific examples of pathogens include, viral pathogens, bacterial pathogens e.g., intracellular mycobacterial pathogens (such as, for example, Mycobacterium tuberculosis), intracellular bacterial pathogens (such as, for example, Listeria monocytogenes), intracellular protozoan pathogens (such as, for example, Leishmania and Trypanosoma), parasitic diseases, fungal diseases, prion diseases.

Methods of analyzing infection are well known in the art and are either based on serology, protein markers, or nucleic acid assays.

According to specific embodiments, the infectious disease is associated with a viral infection.

As used herein, the term “associated with a viral infection” means that a viral infection leads to the disease.

Specific types of viral pathogens causing infectious diseases treatable according to specific embodiments of the present invention include, but are not limited to, retroviruses, circoviruses, parvoviruses, papovaviruses, adenoviruses, herpesviruses, iridoviruses, poxviruses, hepadnaviruses, picornaviruses, caliciviruses, togaviruses, flaviviruses, reoviruses, orthomyxoviruses, paramyxoviruses, rhabdoviruses, bunyaviruses, coronaviruses, arenaviruses, and filoviruses.

Non-limiting examples of viral infections include human immunodeficiency virus (HIV)-induced acquired immunodeficiency syndrome (AIDS), coronavirus, influenza, rhinoviral infection, viral meningitis, Epstein-Barr virus (EBV) infection, hepatitis A, B or C virus infection, measles, papilloma virus infection/warts, cytomegalovirus (CMV) infection, Herpes simplex virus infection, yellow fever, Ebola virus infection, rabies, etc.

According to specific embodiments, the ARDS is associated with a viral infection.

According to specific embodiments, the viral infection is respiratory viral infection.

Non-limiting examples of respiratory viral infections associated with ARDS include a Corona virus infection, a respiratory syncytial virus (RSV) infection, an influenza virus infection, a parainfluenza virus infection, an adenovirus infection and a rhinovirus infection.

According to specific embodiments, the viral infection is a Corona virus infection.

According to specific embodiments, a clinical manifestation of Corona virus infection includes symptoms selected from the group consisting of inflammation in the lung, alveolar

damage, ARDS, fever, cough, shortness of breath, diarrhea, organ failure, pneumonia, cytokine storm, septic shock and/or blood clots.

As used herein, "Corona virus" refers to enveloped positive-stranded RNA viruses that belong to the family *Coronaviridae* and the order *Nidovirales.*

Examples of Corona viruses which are contemplated herein include, but are not limited to, 229E, NL63, OC43, and HKU1 with the first two classified as antigenic group 1 and the latter two belonging to group 2, typically leading to an upper respiratory tract infection manifested by common cold symptoms.

However, Corona viruses, which are zoonotic in origin, can evolve into a strain that can infect human beings leading to fatal illness. Thus particular examples of Corona viruses contemplated herein are SARS-CoV, Middle East respiratory syndrome Coronavirus (MERS-CoV), and the recently identified SAR-CoV-2 [causing 2019-nCoV (also referred to as "COVID-19")].

It would be appreciated that any Corona virus strain is contemplated herein even though SAR-CoV-2 is emphasized in a detailed manner.

According to specific embodiments, the Corona virus is SAR-CoV-2.

As used herein the phrase "subject in need thereof" refers to a mammalian male or female subject (e.g., human being). Veterinary uses are also contemplated. The subject may be of any age including neonatal, infant, juvenile, adolescent, adult and elderly adult.

According to some embodiments, the subject is under 18 years old.

According to some embodiments, the subject is over 60 years old.

According to specific embodiments, the subject is diagnosed with a pathology (e.g. ARDS, infectious disease e.g. Corona virus infection).

According to specific embodiments, the subject is at risk of developing a pathology (e.g. ARDS, infectious disease e.g. Corona virus infection).

According to some embodiments, the subject is immunodeficient.

According to specific embodiments, the subject does not have an inflammatory disease other than the ARDS or infectious disease (e.g. Corona virus infection).

According to specific embodiments, the subject suffers from autism spectrum disorder, neurodegenerative disease, cognitive deficit, mental disorder and/or cytoskeletal disorder.

According to specific embodiments, the subject suffers from a syndrome selected from the group consisting of ADNP syndrome, fragile X syndrome, Syngap-1 syndrome, Phelan McDermid syndrome and Rett syndrome.

According to specific embodiments, the subject suffers from ADNP syndrome.

According to specific embodiments, the subject has a blood level of a pro-inflammatory cytokine above a predetermined threshold.

Thus, according to specific embodiments, the method comprises determining a level of a pro-inflammatory cytokine in the blood of the subject.

Non-limiting examples of pro-inflammatory cytokines include IL-6, IL-1, TNFα, IFNγ, IL-12, IL-18, granulocyte-macrophage colony stimulating factor.

According to specific embodiments, the pro-inflammatory cytokine is IL-6.

As used herein the phrase "predetermined threshold" refers to a level of a pro-inflammatory cytokine that characterizes a blood sample obtained from a healthy subject. Such a level can be experimentally determined by comparing blood samples with normal levels of a pro-inflammatory cytokine (e.g., samples obtained from healthy subjects) to samples derived from subjects diagnosed with ARDS or infectious disease (e.g. Corona virus infection). Alternatively, such a level can be obtained from the scientific literature and from databases.

According to specific embodiments, the predetermined threshold is derived from a control sample. Several control samples can be used with specific embodiments of the present invention. Typically, the control sample contains a level of a pro-inflammatory cytokine comparable to a healthy blood sample.

Since biological characteristics depend on, amongst other things, species and age, it is preferable that the control sample is obtained from a subject of the same species, age, gender and from the same sub-population (e.g. smoker/nonsmoker).

According to specific embodiments, the increase above a predetermined threshold is statistically significant.

According to specific embodiments, the predetermined threshold is at least 1.5 fold, at least 2 fold, at least 3 fold, at least 5 fold, at least 10 fold, or at least 20 fold as compared the level of a pro-inflammatory cytokine in a control sample as measured using the same assay such as e.g. ELISA, flow cytometry.

According to specific embodiments, the predetermined threshold is at least 2 %, at least 5 %, at least 10 %, at least 20 %, at least 30 %, at least 40 %, at least 50 %, at least 60 %, at least 70 %, at least 80 %, at least 90 %, e.g., 100 %, at least 200 %, at least 300 %, at least 400 %, at least 500 %, at least 600 % as compared the level of a pro-inflammatory cytokine in a control sample.

The blood sample may be e.g. serum, plasma, or whole blood. The sample may be a venous sample, peripheral blood mononuclear cell sample or a peripheral blood sample.

Methods of determining blood level of cytokines are well known in the art and include e.g. ELISA, flow cytometry.

According to specific embodiments, the predetermined threshold is a blood level of a pro-inflammatory cytokine (e.g. IL-6) > 10 pg / ml, > 15 pg / ml, > 20 pg / ml or > 24 pg / ml.

According to specific embodiments, the predetermined threshold is a blood level of a pro-inflammatory cytokine that characterizes a cytokine storm.

Hence, according to specific embodiments, the subject has a cytokine storm.

According to other specific embodiments, the subject does not have a cytokine storm.

According to specific embodiments, the subject suffers from Multisystem Inflammatory Syndrome (MIS) associated with Corona virus infection.

As used herein, the term "activity-dependent neuroprotective factor (ADNF)" refers to ADNF III (also known as ADNP) and/or ADNF I.

As used herein, the term “ADNF polypeptide” refers to the amino acid sequence of human ADNF III and/or ADNF I, or a functional homolog thereof, having at least one of the activities of ADNF III or ADNF I, as further described hereinbelow. According to specific embodiments, the phrase "ADNF polypeptide" refers to a mixture of at least two distinct ADNF polypeptides. According to specific embodiments, the phrase "ADNF polypeptide" refers to a mixture of an ADNF III polypeptide and an ADNF I polypeptide.

As use herein, the phrase “a functional homolog” refers to a fragment, a naturally occurring or synthetically/recombinantly produced homolog, a non-human homolog, an allelic or polymorphic variant, an amino acid sequence comprising conservative and non-conservative amino acid substitutions deletions or additions, an analog, a lipophilic variant and/or a chemically modified variant, which maintains at least one of the activities of the full length protein, e.g. binding EB1 and/or EB3, binding an SH3 domain, neurotrophic/neuroprotective activity, as further described hereinbelow.

Non-limiting examples of ADNF polypeptides that can be used with specific embodiments of the invention are described in details in e.g. International Patent Application Publication Nos. WO1992/018140, WO9611948, WO 98/35042, WO 0027875, WO 00/53217, WO01/12654, WO 01/92333, WO 2004/080957, WO 2006/099739, WO2007/096859, 2008/08448, WO 2011/021186, WO/2009/026687, WO2010/075635, 2011/083461, WO 2011/099011, WO2013/171595, WO 2017/130190, WO 2004/060309, WO2003022226 and U.S. Patent Nos. US5767240, US6174862, US6613740 and US8586548; herein each incorporated by reference in their entirety; and further hereinbelow.

According to specific embodiments, ADNF is ADNF III.

"ADNF III", also known as ADNP (activity- dependent neuroprotective protein), refers to the polypeptide encoded by the *ADNP* gene (Gene ID 23394). According to specific embodiments, ADNF III is human ADNF III. Full length human ADNF III (ADNP) has a predicted molecular weight of 123,562.8 Da (>1000 amino acid residues) and a theoretical pi of about 6.97. The human ADNF III gene is localized to chromosome 20ql3.13-13.2, a region associated with cognitive function. Exemplary full-length amino acid and nucleic acid sequences of ADNF III can be found in WO 98/35042, WO 00/27875, US Patent Nos. 6,613,740 and 6,649,411. According to specific embodiments, ADNF III amino acid sequence comprises SEQ ID NO: 1.

The ADNF III polypeptide described herein possesses at least one of the activities of the full length ADNF III e.g. binding EB1 and/or EB3, binding an SH3 domain (i.e. comprises an SH3 binding domain), neurotrophic/neuroprotective activity as measured with in vitro cortical neuron culture assays.

Assays for testing binding are well known in the art and include, but not limited, to flow cytometry, BiaCore, bio-layer interferometry Blitz® assay, HPLC.

Assays for testing neurotrophic/neuroprotective activity are well known in the art and include, but not limited to, in vitro cortical neuron culture assays described by, e.g., Hill et ah, Brain Res. 603:222-233 (1993); Brenneman & Gozes, J. Clin. Invest. 97:2299-2307 (1996), Gozes et al, Proc. Natl. Acad. ScL USA 93, 427-432 (1996).

Non-limiting examples of ADNF III polypeptides that can be used with specific embodiments of the invention are provided in Table 1 hereinbelow.

According to specific embodiments, the ADNF III polypeptide comprises an amino acid sequence having at least 80 %, at least 81 %, at least 82 %, at least 83 %, at least 84 %, at least 85 %, at least 86 %, at least 87 %, at least 88 %, at least 89 %, at least 90 %, at least 91 %, at least 92 %, at least 93 %, at least 94 %, at least 95 %, at least 96 %, at least 97 %, at least 98 %, at least 99 % or 100 % identity or homology to SEQ ID NO: 1-22.

As used herein, "identity" or "sequence identity" refers to global identity, *i.e.*, an identity over the entire amino acid or nucleic acid sequences disclosed herein and not over portions thereof.

Sequence identity or homology can be determined using any protein or nucleic acid sequence alignment algorithm such as Blast, ClustalW, and MUSCLE.

According to specific embodiments, the ADNF III polypeptide may comprise conservative and non-conservative amino acid substitutions. Additional description on

conservative amino acid and non-conservative amino acid substitutions is further provided hereinbelow.

According to specific embodiments, the ADNF III polypeptide comprises an amino acid sequence selected form the group consisting of 2-22, each possibility represents a separate embodiment of the present invention.

According to specific embodiments, the ADNF III polypeptide comprises an amino acid sequence selected form the group consisting of 2-20.

According to specific embodiments, the ADNF III polypeptide comprises SEQ ID NO: 2.

According to specific embodiments, the ADNF III polypeptide has the formula $(R^1)_x$-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-$(R^2)_y$ (SEQ ID NO: 49), or an analogue thereof, in which R^1 is an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected from the group consisting of naturally occurring amino acids and amino acid analogs; R^2 is an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected from the group consisting of naturally occurring amino acids and amino acid analogs; and x and y are independently selected and are equal to zero or one.

According to specific embodiments, the R^1 and R^2 are independent of each other.

According to specific embodiments x and y are equal to zero.

According to specific embodiments, the ADNF III polypeptide consists of SEQ ID NO: 2.

According to specific embodiments, ADNF is ADNF I.

"ADNF I" refers to the activity dependent neurotrophic factor described in Gozes I, Brenneman DE. J Mol Neurosci. 1996 Winter; 7(4):235-44; Brenneman DE, Gozes I. J Clin Invest. 1996 May 15; 97(10):2299-307 and Brenneman DE, et al., J Pharmacol Exp Ther. 1998 May; 285(2):619-27, the contents of each are incorporated herein by reference in their entirety. According to specific embodiments, ADNF I is human ADNF I. Full length human ADNF I has a predicted molecular weight of about 14,000 Da with a pi of 8.3 ± 0.25. According to specific embodiments, ADNF I amino acid sequence comprises SEQ ID NO: 24 or 45.

The ADNF I polypeptide described herein possesses at least one of the activities of the full length ADNF I e.g. neurotrophic/neuroprotective activity as measured with in vitro cortical neuron culture assays, binding EB1 and EB3.

Non-limiting examples of ADNF I polypeptides that can be used with specific embodiments of the invention are provided in Table 1 hereinbelow.

According to specific embodiments, the ADNF I polypeptide comprises an amino acid

sequence having at least 80 %, at least 81 %, at least 82 %, at least 83 %, at least 84 %, at least 85 %, at least 86 %, at least 87 %, at least 88 %, at least 89 %, at least 90 %, at least 91 %, at least 92 %, at least 93 %, at least 94 %, at least 95 %, at least 96 %, at least 97 %, at least 98 %, at least 99 % or 100 % identity or homology to SEQ ID NO: 24-48.

According to specific embodiments, the ADNF I polypeptide may comprise conservative and non-conservative amino acid substitutions. Additional description on conservative amino acid and non-conservative amino acid substitutions is further provided hereinbelow.

According to specific embodiments, the ADNF I polypeptide comprises an amino acid sequence selected form the group consisting of 24-48, each possibility represents a separate embodiment of the invention.

According to specific embodiments, the ADNF I polypeptide comprises SEQ ID NO: 24.

According to specific embodiments, the ADNF I polypeptide has the formula $(R^1)_x$-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala-$(R^2)_y$ (SEQ ID NO: 50), or an analogue thereof, in which R^1 is an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected from the group consisting of naturally occurring amino acids and amino acid analogs; R^2 is an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected from the group consisting of naturally occurring amino acids and amino acid analogs; and x and y are independently selected and are equal to zero or one.

According to specific embodiments, the R^1 and R^2 are independent of each other.

According to specific embodiments x and y are equal to zero.

According to specific embodiments, the ADNF I polypeptide consists of SEQ ID NO: 24.

Table 1: list of possible ADNF polypeptides that can be used with specific embodiments of the invention.

SEQ ID NO:	ADNF III polypeptide		SEQ ID NO:	ADNF I polypeptide	
	Single letter aa code	Three letters aa code		Single letter aa code	Three letters aa code
1	Full length		24	SALLRSIPA	Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala
2	NAPVSIPQ	Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln	25	VAGGGSALLRSIPA	Val-Ala-Gly-Gly-Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala
3	SVRLGLGGNAPVSIPQQS	Ser-Val-Arg-Leu-Gly-Leu-Gly-Gly-Asn-Ala-Pro-Val-	26	VEEGIVLGGGSALLRSIPA	Val-Glu-Glu-Gly-Ile-Val-Leu-Gly-Gly-Gly-Ser-Ala-Leu-

		Ser-Ile-Pro-Gln-Gln-Ser			Leu-Arg-Ser-Ile-Pro-Ala
4	LGLGGNAPVSIPQQS	Leu-Gly-Leu-Gly-Gly-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-Gln-Ser	27	VLGGGCALLRCIPA	Val-Leu-Gly-Gly-Gly-Cys-Ala-Leu-Leu-Arg-Cys-Ile-Pro-Ala
5	LGGNAPVSIPQQS	Leu-Gly-Gly-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-Gln-Ser	28	ALLRSIPA	Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala
6	GGNAPVSIPQ	Gly-Gly-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln	29	GSALLRSIPA	Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala
7	Ac-NAPVSKIPQ	Ac-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln	30	SALLRS	Ser-Ala-Leu-Leu-Arg-Ser
8	NAPVSKIPQ	Asn-Ala-Pro-Val-Ser-Lys-Ile-Pro-Gln	31	GSALLRSIPA	Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala
9	NAPBSAIPQ	Asn-Ala-Pro-Asx-Ser-Ala-Ile-Pro-Gln	32	VAGGGSALLRSI	Val-Ala-Gly-Gly-Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile
10	NAPVSRIPQ	Asn-Ala-Pro-Val-Ser-Arg-Ile-Pro-Gln	33	VLGGGSALLR	Val-Leu-Gly-Gly-Gly-Ser-Ala-Leu-Leu-Arg
11	NAPVTRIPQ	Asn-Ala-Pro-Val-Thr-Arg-Ile-Pro-Gln	34	VLGGGSALL	Val-Leu-Gly-Gly-Gly-Ser-Ala-Leu-Leu
12	NAPVAAAAQ	Asn-Ala-Pro-Val-Ala-Ala-Ala-Ala-Gln	35	VAGGGSAL	Val-Ala-Gly-Gly-Gly-Ser-Ala-Leu
13	All d-amino acid NAPVSIPQ	All d-amino acid Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln	36	All d-amino acid SALLRSIPA	All d-amino acid Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala
14	AAPVSIPQ	Ala-Ala-Pro-Val-Ser-Ile-Pro-Gln	37	AALLRSIPA	Ala-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala
15	NAAVSIPQ	Asn-Ala-Ala-Val-Ser-Ile-Pro-Gln	38	SAALRSIPA	Ser-Ala-Ala-Leu-Arg-Ser-Ile-Pro-Ala
16	NAPASIPQ	Asn-Ala-Pro-Ala-Ser-Ile-Pro-Gln	39	SALARSIPA	Ser-Ala-Leu-Ala-Arg-Ser-Ile-Pro-Ala
17	NAPVAIPQ	Asn-Ala-Pro-Val-Ala-Ile-Pro-Gln	40	SALLASIPA	Ser-Ala-Leu-Leu-Ala-Ser-Ile-Pro-Ala
18	NAPVSAPQ	Asn-Ala-Pro-Val-Ser-Ala-Pro-Gln	41	SALLRAIPA	Ser-Ala-Leu-Leu-Arg-Ala-Ile-Pro-Ala
19	NAPVSIAQ	Asn-Ala-Pro-Val-Ser-Ile-Ala-Gln	42	SALLRSAPA	Ser-Ala-Leu-Leu-Arg-Ser-Ala-Pro-Ala
20	NAPVSIPA	Asn-Ala-Pro-Val-Ser-Ile-Pro-Ala	43	SALLRSIAA	Ser-Ala-Leu-Leu-Arg-Ser-Ile-Ala-Ala
21	SKIP	Ser-Lys-Ile-Pro	44	SALLRSIPAPAGASRLLLLTGEIDLP	Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala-Pro-Ala-Gly-Ala-Ser-Arg-Leu-Leu-Leu-Leu-Thr-

					Gly-Glu-Ile-Asp-Leu-Pro
22	Ac-SKIP-NH2	Ac-Ser-Lys-Ile-Pro-NH2	45	VLGGGSALLRSIPA	Val-Leu-Gly-Gly-Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala
			46	LGGGSALLRSIPA	Leu-Gly-Gly-Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala
			47	GGGSALLRSIPA	Gly-Gly-Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala
			48	GGSALLRSIPA	Gly-Gly-Ser-Ala-Leu-Leu-Arg-Ser-Ile-Pro-Ala

As used herein, the term “polypeptide”, "peptide" or “amino acid sequence”, which are interchangeably used herein, encompasses native peptides (either degradation products, synthetically synthesized peptides or recombinant peptides) and peptidomimetics (typically, synthetically synthesized peptides), as well as peptoids and semipeptoids which are peptide analogs, which may have, for example, modifications rendering the peptides more stable while in a body or more capable of penetrating into cells. Such modifications include, but are not limited to N terminus modification, C terminus modification, peptide bond modification, backbone modifications, and residue modification. Methods for preparing peptidomimetic compounds are well known in the art and are specified, for example, in Quantitative Drug Design, C.A. Ramsden Gd., Chapter 17.2, F. Choplin Pergamon Press (1992), which is incorporated by reference as if fully set forth herein. Further details in this respect are provided hereinunder.

Peptide bonds (-CO-NH-) within the peptide may be substituted, for example, by N-methylated amide bonds (-N(CH3)-CO-), ester bonds (-C(=O)-O-), ketomethylene bonds (-CO-CH2-), sulfinylmethylene bonds (-S(=O)-CH2-), α-aza bonds (-NH-N(R)-CO-), wherein R is any alkyl (e.g., methyl), amine bonds (-CH2-NH-), sulfide bonds (-CH2-S-), ethylene bonds (-CH2-CH2-), hydroxyethylene bonds (-CH(OH)-CH2-), thioamide bonds (-CS-NH-), olefinic double bonds (-CH=CH-), fluorinated olefinic double bonds (-CF=CH-), retro amide bonds (-NH-CO-), peptide derivatives (-N(R)-CH2-CO-), wherein R is the "normal" side chain, naturally present on the carbon atom.

These modifications can occur at any of the bonds along the peptide chain and even at several (2-3) bonds at the same time.

Natural aromatic amino acids, Trp, Tyr and Phe, may be substituted by non-natural aromatic amino acids such as 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic),

naphthylalanine, ring-methylated derivatives of Phe, halogenated derivatives of Phe or O-methyl-Tyr.

The polypeptides of some embodiments of the invention may also include one or more modified amino acids or one or more non-amino acid monomers (e.g. fatty acids, complex carbohydrates etc).

The term "amino acid" or "amino acids" is understood to include the 20 naturally occurring amino acids; those amino acids often modified post-translationally in vivo, including, for example, hydroxyproline, phosphoserine and phosphothreonine; and other unusual amino acids including, but not limited to, 2-aminoadipic acid, hydroxylysine, isodesmosine, nor-valine, nor-leucine and ornithine. Furthermore, the term "amino acid" includes both D- and L-amino acids.

According to specific embodiments, the polypeptide comprises at least one D-amino acid.

According to specific embodiments, the polypeptide comprises at least two, at least three, at least 4, at least 5, at least 6, at least 8 D-amino acids.

According to specific embodiments, all the polypeptide amino acids are D-amino acids.

Tables 2 and 3 below list naturally occurring amino acids (Table 2), and non-conventional or modified amino acids (e.g., synthetic, Table 3) which can be used with some embodiments of the invention.

Table 2

Amino Acid	*Three-Letter Abbreviation*	*One-letter Symbol*
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic Acid	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V
Any amino acid as above	Xaa	X

Table 3

Non-conventional amino acid	***Code***	***Non-conventional amino acid***	***Code***
ornithine	Orn	hydroxyproline	Hyp
α-aminobutyric acid	Abu	aminonorbornyl-carboxylate	Norb
D-alanine	Dala	aminocyclopropane-carboxylate	Cpro
D-arginine	Darg	N-(3-guanidinopropyl)glycine	Narg
D-asparagine	Dasn	N-(carbamylmethyl)glycine	Nasn
D-aspartic acid	Dasp	N-(carboxymethyl)glycine	Nasp
D-cysteine	Dcys	N-(thiomethyl)glycine	Ncys
D-glutamine	Dgln	N-(2-carbamylethyl)glycine	Ngln
D-glutamic acid	Dglu	N-(2-carboxyethyl)glycine	Nglu
D-histidine	Dhis	N-(imidazolylethyl)glycine	Nhis
D-isoleucine	Dile	N-(1-methylpropyl)glycine	Nile
D-leucine	Dleu	N-(2-methylpropyl)glycine	Nleu
D-lysine	Dlys	N-(4-aminobutyl)glycine	Nlys
D-methionine	Dmet	N-(2-methylthioethyl)glycine	Nmet
D-ornithine	Dorn	N-(3-aminopropyl)glycine	Norn
D-phenylalanine	Dphe	N-benzylglycine	Nphe
D-proline	Dpro	N-(hydroxymethyl)glycine	Nser
D-serine	Dser	N-(1-hydroxyethyl)glycine	Nthr
D-threonine	Dthr	N-(3-indolylethyl) glycine	Nhtrp
D-tryptophan	Dtrp	N-(*p*-hydroxyphenyl)glycine	Ntyr
D-tyrosine	Dtyr	N-(1-methylethyl)glycine	Nval
D-valine	Dval	N-methylglycine	Nmgly
D-N-methylalanine	Dnmala	L-N-methylalanine	Nmala
D-N-methylarginine	Dnmarg	L-N-methylarginine	Nmarg
D-N-methylasparagine	Dnmasn	L-N-methylasparagine	Nmasn
D-N-methylasparatate	Dnmasp	L-N-methylaspartic acid	Nmasp
D-N-methylcysteine	Dnmcys	L-N-methylcysteine	Nmcys
D-N-methylglutamine	Dnmgln	L-N-methylglutamine	Nmgln
D-N-methylglutamate	Dnmglu	L-N-methylglutamic acid	Nmglu
D-N-methylhistidine	Dnmhis	L-N-methylhistidine	Nmhis
D-N-methylisoleucine	Dnmile	L-N-methylisolleucine	Nmile
D-N-methylleucine	Dnmleu	L-N-methylleucine	Nmleu
D-N-methyllysine	Dnmlys	L-N-methyllysine	Nmlys
D-N-methylmethionine	Dnmmet	L-N-methylmethionine	Nmmet
D-N-methylornithine	Dnmorn	L-N-methylornithine	Nmorn
D-N-methylphenylalanine	Dnmphe	L-N-methylphenylalanine	Nmphe
D-N-methylproline	Dnmpro	L-N-methylproline	Nmpro
D-N-methylserine	Dnmser	L-N-methylserine	Nmser
D-N-methylthreonine	Dnmthr	L-N-methylthreonine	Nmthr
D-N-methyltryptophan	Dnmtrp	L-N-methyltryptophan	Nmtrp
D-N-methyltyrosine	Dnmtyr	L-N-methyltyrosine	Nmtyr
D-N-methylvaline	Dnmval	L-N-methylvaline	Nmval
L-norleucine	Nle	L-N-methylnorleucine	Nmnle
L-norvaline	Nva	L-N-methylnorvaline	Nmnva
L-ethylglycine	Etg	L-N-methyl-ethylglycine	Nmetg
L-t-butylglycine	Tbug	L-N-methyl-t-butylglycine	Nmtbug
L-homophenylalanine	Hphe	L-N-methyl-homophenylalanine	Nmhphe

α-naphthylalanine	Anap	N-methyl-α-naphthylalanine	Nmanap
penicillamine	Pen	N-methylpenicillamine	Nmpen
γ-aminobutyric acid	Gabu	N-methyl-γ-aminobutyrate	Nmgabu
cyclohexylalanine	Chexa	N-methyl-cyclohexylalanine	Nmchexa
cyclopentylalanine	Cpen	N-methyl-cyclopentylalanine	Nmcpen
α-amino-α-methylbutyrate	Aabu	N-methyl-α-amino-α-methylbutyrate	Nmaabu
α-aminoisobutyric acid	Aib	N-methyl-α-aminoisobutyrate	Nmaib
D-α-methylarginine	Dmarg	L-α-methylarginine	Marg
D-α-methylasparagine	Dmasn	L-α-methylasparagine	Masn
D-α-methylaspartate	Dmasp	L-α-methylaspartate	Masp
D-α-methylcysteine	Dmcys	L-α-methylcysteine	Mcys
D-α-methylglutamine	Dmgln	L-α-methylglutamine	Mgln
D-α-methyl glutamic acid	Dmglu	L-α-methylglutamate	Mglu
D-α-methylhistidine	Dmhis	L-α-methylhistidine	Mhis
D-α-methylisoleucine	Dmile	L-α-methylisoleucine	Mile
D-α-methylleucine	Dmleu	L-α-methylleucine	Mleu
D-α-methyllysine	Dmlys	L-α-methyllysine	Mlys
D-α-methylmethionine	Dmmet	L-α-methylmethionine	Mmet
D-α-methylornithine	Dmorn	L-α-methylornithine	Morn
D-α-methylphenylalanine	Dmphe	L-α-methylphenylalanine	Mphe
D-α-methylproline	Dmpro	L-α-methylproline	Mpro
D-α-methylserine	Dmser	L-α-methylserine	Mser
D-α-methylthreonine	Dmthr	L-α-methylthreonine	Mthr
D-α-methyltryptophan	Dmtrp	L-α-methyltryptophan	Mtrp
D-α-methyltyrosine	Dmtyr	L-α-methyltyrosine	Mtyr
D-α-methylvaline	Dmval	L-α-methylvaline	Mval
N-cyclobutylglycine	Ncbut	L-α-methylnorvaline	Mnva
N-cycloheptylglycine	Nchep	L-α-methylethylglycine	Metg
N-cyclohexylglycine	Nchex	L-α-methyl-*t*-butylglycine	Mtbug
N-cyclodecylglycine	Ncdec	L-α-methyl-homophenylalanine	Mhphe
N-cyclododecylglycine	Ncdod	α-methyl-α-naphthylalanine	Manap
N-cyclooctylglycine	Ncoct	α-methylpenicillamine	Mpen
N-cyclopropylglycine	Ncpro	α-methyl-γ-aminobutyrate	Mgabu
N-cycloundecylglycine	Ncund	α-methyl-cyclohexylalanine	Mchexa
N-(2-aminoethyl)glycine	Naeg	α-methyl-cyclopentylalanine	Mcpen
N-(2,2-diphenylethyl)glycine	Nbhm	N-(N-(2,2-diphenylethyl) carbamylmethyl-glycine	Nnbhm
N-(3,3-diphenylpropyl)glycine	Nbhe	N-(N-(3,3-diphenylpropyl) carbamylmethyl-glycine	Nnbhe
1-carboxy-1-(2,2-diphenyl ethylamino)cyclopropane	Nmbc	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid	Tic
phosphoserine	pSer	phosphothreonine	pThr
phosphotyrosine	pTyr	O-methyl-tyrosine	
2-aminoadipic acid		hydroxylysine	

The amino acids of the polypeptides of some embodiments of the present invention may be substituted either conservatively or non-conservatively.

The term “conservative substitution” as used herein, refers to the replacement of an amino acid present in the native sequence in the peptide with a naturally or non-naturally occurring amino or a peptidomimetics having similar steric properties. Where the side-chain of the native amino acid to be replaced is either polar or hydrophobic, the conservative substitution should be with a naturally occurring amino acid, a non-naturally occurring amino acid or with a peptidomimetic moiety which is also polar or hydrophobic (in addition to having the same steric properties as the side-chain of the replaced amino acid).

As naturally occurring amino acids are typically grouped according to their properties, conservative substitutions by naturally occurring amino acids can be easily determined bearing in mind the fact that in accordance with the invention replacement of charged amino acids by sterically similar non-charged amino acids are considered as conservative substitutions.

For producing conservative substitutions by non-naturally occurring amino acids it is also possible to use amino acid analogs (synthetic amino acids) well known in the art. A peptidomimetic of the naturally occurring amino acid is well documented in the literature known to the skilled practitioner.

When affecting conservative substitutions the substituting amino acid should have the same or a similar functional group in the side chain as the original amino acid.

Conservative substitution tables providing functionally similar amino acids are well known in the art. Guidance concerning which amino acid changes are likely to be phenotypically silent can also be found in Bowie et al., 1990, Science 247: 1306 1310.

The phrase "non-conservative substitutions" as used herein refers to replacement of the amino acid as present in the parent sequence by another naturally or non-naturally occurring amino acid, having different electrochemical and/or steric properties. Thus, the side chain of the substituting amino acid can be significantly larger (or smaller) than the side chain of the native amino acid being substituted and/or can have functional groups with significantly different electronic properties than the amino acid being substituted. Examples of non-conservative substitutions of this type include the substitution of phenylalanine or cycohexylmethyl glycine for alanine, isoleucine for glycine, or -NH-CH[(-CH_2)$_5$-COOH]-CO- for aspartic acid. Those non-conservative substitutions which fall under the scope of the present invention are those which still constitute a peptide having neuroprotective properties.

The polypeptides of some embodiments of the invention are preferably utilized in a linear form, although it will be appreciated that in cases where cyclicization does not severely interfere with peptide characteristics, cyclic forms of the peptide can also be utilized.

Since according to specific embodiments, the present polypeptides are utilized in therapeutics which require the peptides to be in soluble form, the polypeptides of some embodiments of the invention include one or more non-natural or natural polar amino acids, including but not limited to serine and threonine which are capable of increasing peptide solubility due to their hydroxyl-containing side chain.

According to specific embodiments, the polypeptide is less than 100, less than 50, less than 20 or less than 10 amino acids in length.

According to specific embodiments, the polypeptide is 4-100, 4-50, 4-40, 4-20, 4-15, 4-10, 4-8 or 8 amino acids in length, each possibility represents a separate embodiment of the present invention.

According to specific embodiments, the polypeptide is at least 4, at least 5, at least 6, at least 7, at least 8 amino acids in length.

According to specific embodiments, the polypeptide is attached, directly or through a spacer or a linker, to a cell penetrating and/or stabilizing moiety. Such moieties are well known in the art and are further described in details hereinbelow.

According to specific embodiments, the N and/or C termini of the polypeptides of some embodiments of the present invention may be protected by functional groups (i.e. end-capping moieties). Examples of such functional groups can be found, for example, in Green *et al.*, "Protective Groups in Organic Chemistry", (Wiley, 2.sup.nd ed. 1991), Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996); and Green and Wuts, "Protecting Groups in Organic Synthesis", John Wiley and Sons, Chapters 5 and 7, 1991, the teachings of which are incorporated herein by reference. Preferred protecting groups are those that increase stability of the polypeptide and/or facilitate transport of the compound attached thereto into a cell, for example, by reducing the hydrophilicity and increasing the lipophilicity of the compounds.

According to specific embodiments, the end-capping comprises an N terminus end-capping.

Representative examples of N-terminus end-capping moieties include, but are not limited to, formyl, acetyl (also denoted herein as “Ac”), stearyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (also denoted herein as "Cbz"), tert-butoxycarbonyl (also denote d herein as "Boc"), trimethylsilyl (also denoted "TMS"), 2-trimethylsilyl-ethanesulfonyl (also denoted

"SES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (also denoted herein as "Fmoc"), and nitro-veratryloxycarbonyl ("NVOC").

According to specific embodiments, the N terminus end-capping comprises an Acetyl.

According to specific embodiments, the N terminus end-capping comprises a stearyl (see e.g. Gozes I, et al. Proc Natl Acad Sci U S A. 1996 Jan 9; 93(1): 427-32).

According to specific embodiments, the end-capping comprises a C terminus end-capping.

Representative examples of C-terminus end-capping moieties are typically moieties that lead to acylation of the carboxy group at the C-terminus and include, but are not limited to, benzyl and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers, allyl ethers, monomethoxytrityl and dimethoxytrityl. Alternatively the –COOH group of the C-terminus end-capping may be modified to an amide group.

According to specific embodiments, the C terminus end-capping comprises an Amide.

Other end-capping modifications of peptides include replacement of the amine and/or carboxyl with a different moiety, such as hydroxyl, thiol, halide, alkyl, aryl, alkoxy, aryloxy and the like.

According to other specific embodiments of the invention, the polypeptide is attached to a non-proteinaceous moiety.

According to specific embodiments, the polypeptide and the attached non-proteinaceous moiety are covalently attached, directly or through a spacer or a linker.

The phrase “non-proteinaceous moiety” as used herein refers to a molecule not including peptide bonded amino acids that is attached to the above-described polypeptide. According to a specific embodiment the non-proteinaceous is a non-toxic moiety. Exemplary non-proteinaceous moieties which may be used according to the present teachings include, but are not limited to a drug, a chemical, a small molecule, a polynucleotide, a detectable moiety, polyethylene glycol (PEG), Polyvinyl pyrrolidone (PVP), poly(styrene comaleic anhydride) (SMA), and divinyl ether and maleic anhydride copolymer (DIVEMA). According to specific embodiments of the invention, the non-proteinaceous moiety comprises polyethylene glycol (PEG).

Such a molecule is highly stable (resistant to in-vivo proteolytic activity probably due to steric hindrance conferred by the non-proteinaceous moiety) and may be produced using common solid phase synthesis methods which are inexpensive and highly efficient, as further described hereinbelow. However, it will be appreciated that recombinant techniques may still be used, whereby the recombinant peptide product is subjected to in-vitro modification (e.g., PEGylation as further described hereinbelow).

Bioconjugation of the peptide amino acid sequence with PEG (*i.e.*, PEGylation) can be effected using PEG derivatives such as N-hydroxysuccinimide (NHS) esters of PEG carboxylic acids, monomethoxyPEG$_2$-NHS, succinimidyl ester of carboxymethylated PEG (SCM-PEG), benzotriazole carbonate derivatives of PEG, glycidyl ethers of PEG, PEG p-nitrophenyl carbonates (PEG-NPC, such as methoxy PEG-NPC), PEG aldehydes, PEG-orthopyridyl-disulfide, carbonyldimidazol-activated PEGs, PEG-thiol, PEG-maleimide. Such PEG derivatives are commercially available at various molecular weights [See, e.g., Catalog, Polyethylene Glycol and Derivatives, 2000 (Shearwater Polymers, Inc., Huntsvlle, Ala.)]. If desired, many of the above derivatives are available in a monofunctional monomethoxyPEG (mPEG) form. In general, the PEG added to the peptide of some embodiments of the present invention should range from a molecular weight (MW) of several hundred Daltons to about 100 kDa (e.g., between 3-30 kDa). Larger MW PEG may be used, but may result in some loss of yield of PEGylated polypeptides. The purity of larger PEG molecules should be also watched, as it may be difficult to obtain larger MW PEG of purity as high as that obtainable for lower MW PEG. It is preferable to use PEG of at least 85 % purity, and more preferably of at least 90 % purity, 95 % purity, or higher. PEGylation of molecules is further discussed in, e.g., Hermanson, Bioconjugate Techniques, Academic Press San Diego, Calif. (1996), at Chapter 15 and in Zalipsky et al., "Succinimidyl Carbonates of Polyethylene Glycol," in Dunn and Ottenbrite, eds., Polymeric Drugs and Drug Delivery Systems, American Chemical Society, Washington, D.C. (1991).

Conveniently, PEG can be attached to a chosen position in the peptide by site-specific mutagenesis as long as the activity of the conjugate is retained. A target for PEGylation could be any Cysteine residue at the N-terminus or the C-terminus of the peptide sequence. Additionally or alternatively, other Cysteine residues can be added to the peptide amino acid sequence (e.g., at the N-terminus or the C-terminus) to thereby serve as a target for PEGylation. Computational analysis may be effected to select a preferred position for mutagenesis without compromising the activity.

Various conjugation chemistries of activated PEG such as PEG-maleimide, PEG-vinylsulfone (VS), PEG-acrylate (AC), PEG-orthopyridyl disulfide can be employed. Methods of preparing activated PEG molecules are known in the arts. For example, PEG-VS can be prepared under argon by reacting a dichloromethane (DCM) solution of the PEG-OH with NaH and then with di-vinylsulfone (molar ratios: OH 1: NaH 5: divinyl sulfone 50, at 0.2 gram PEG/mL DCM). PEG-AC is made under argon by reacting a DCM solution of the PEG-OH with acryloyl chloride and triethylamine (molar ratios: OH 1: acryloyl chloride 1.5: triethylamine 2, at

0.2 gram PEG/mL DCM). Such chemical groups can be attached to linearized, 2-arm, 4-arm, or 8-arm PEG molecules.

Resultant conjugated molecules (e.g., PEGylated or PVP-conjugated peptide) are separated, purified and qualified using e.g., high-performance liquid chromatography (HPLC) as well as biological assays.

The polypeptides and compositions of matter of the present invention may be attached (either covalently or non-covalently) to a penetrating moiety.

According to other specific embodiments, the polypeptide is not attached to a heterologous penetrating moiety. Thus, for Example, the ADNF polypeptide NAP (SEQ ID NO: 2) is bioavailable by endocytosis (see e.g. Ivashko-Pachima Y, Gozes I.J Mol Neurosci. 2020 Jul;70(7):993-998), thus being a cell penetrating peptide by itself.

As used herein the phrase "penetrating moiety" refers to an agent which enhances translocation of any of the attached polypeptide or composition of matter comprising same across a cell membrane.

According to one embodiment, the penetrating moiety is a peptide and is attached to the polypeptide (either directly or non-directly) via a peptide bond.

Typically, peptide penetrating moieties have an amino acid composition containing either a high relative abundance of positively charged amino acids such as lysine or arginine, or have sequences that contain an alternating pattern of polar/charged amino acids and non-polar, hydrophobic amino acids.

By way of non-limiting example, cell penetrating peptide (CPP) sequences may be used in order to enhance intracellular penetration; however, the disclosure is not so limited, and any suitable penetrating agent may be used, as known by those of skill in the art.

Cell-Penetrating Peptides (CPPs) are short peptides (≤40 amino acids), with the ability to gain access to the interior of almost any cell. They are highly cationic and usually rich in arginine and lysine amino acids. They have the exceptional property of carrying into the cells a wide variety of covalently and noncovalently conjugated cargoes such as proteins, oligonucleotides, and even 200 nm liposomes. Therefore, according to additional exemplary embodiment CPPs can be used to transport Livin polynucleotide or polypeptide to the interior of cells.

TAT (transcription activator from HIV-1), pAntp (also named penetratin, Drosophila antennapedia homeodomain transcription factor) and VP22 (from Herpes Simplex virus) are non-limiting examples of CPPs that can enter cells in a non-toxic and efficient manner and may be suitable for use with some embodiments of the invention. Protocols for producing CPPs-

cargos conjugates and for infecting cells with such conjugates can be found, for example L Theodore et al. [The Journal of Neuroscience, (1995) 15(11): 7158-7167], Fawell S, et al. [Proc Natl Acad Sci USA, (1994) 91:664–668], and Jing Bian et al. [Circulation Research. (2007) 100: 1626-1633].

According to another exemplary embodiment the polypeptide may be incorporated into a particulated delivery vehicle, e.g., a liposome, or a nano- or microparticle. For example, a Livin cDNA may be encapsulated in or attached to a delivery vehicle by any of the known methods in the art [Liposome Technology, Vol. II, Incorporation of Drugs, Proteins, and Genetic Material, CRC Press; Monkkonen, J. *et al.*, 1994, J. Drug Target, 2:299-308; Monkkonen, J. *et al.*, 1993, Calcif. Tissue Int., 53:139-145; Lasic D D., Liposomes Technology Inc., Elsevier, 1993, 63-105. (chapter 3); Winterhalter M, Lasic D D, Chem Phys Lipids, 1993 September;64(1-3):35-43].

Liposomes include any synthetic (i.e., not naturally occurring) structure composed of lipid bilayers, which enclose a volume. Liposomes include emulsions, foams, micelles, insoluble monolayers, liquid crystals, phospholipid dispersions, lamellar layers and the like. Liposomes can be of different sizes, may contain a low or a high pH and may be of different charge.

According to specific embodiments, the polypeptide is attached to a lipophilic molecule, ion chelator and/or femtomolar-acting humanin derivative named colivelin.

The polypeptides of some embodiments of the invention may be synthesized by any techniques that are known to those skilled in the art of peptide synthesis, such as, but not limited to, solid phase and recombinant techniques.

For solid phase peptide synthesis, a summary of the many techniques may be found in J. M. Stewart and J. D. Young, Solid Phase Peptide Synthesis, W. H. Freeman Co. (San Francisco), 1963 and J. Meienhofer, Hormonal Proteins and Peptides, vol. 2, p. 46, Academic Press (New York), 1973. For classical solution synthesis see G. Schroder and K. Lupke, The Peptides, vol. 1, Academic Press (New York), 1965.

In general, these methods comprise the sequential addition of one or more amino acids or suitably protected amino acids to a growing peptide chain. Normally, either the amino or carboxyl group of the first amino acid is protected by a suitable protecting group. The protected or derivatized amino acid can then either be attached to an inert solid support or utilized in solution by adding the next amino acid in the sequence having the complimentary (amino or carboxyl) group suitably protected, under conditions suitable for forming the amide linkage. The protecting group is then removed from this newly added amino acid residue and the next amino acid (suitably protected) is then added, and so forth. After all the desired amino acids have been

linked in the proper sequence, any remaining protecting groups (and any solid support) are removed sequentially or concurrently, to afford the final peptide compound. By simple modification of this general procedure, it is possible to add more than one amino acid at a time to a growing chain, for example, by coupling (under conditions which do not racemize chiral centers) a protected tripeptide with a properly protected dipeptide to form, after deprotection, a pentapeptide and so forth. Further description of peptide synthesis is disclosed in U.S. Pat. No. 6,472,505.

Large scale peptide synthesis is described by Andersson Biopolymers 2000;55(3):227-50.

Specific embodiments of the present invention contemplates the use of a combined treatment/prophylaxis comprising the polypeptide and a therapeutic agent other than the polypeptides disclosed herein.

Hence, according to specific embodiments, the polypeptides disclosed herein are provided to the individual with additional active agents to achieve an improved therapeutic or preventive effect as compared to treatment with each agent by itself. Thus, the polypeptide can be administered alone or with other established or experimental therapeutic regimen to treat or prevent ARDS or infectious disease e.g. Corona virus infection, such as, but not limited to, mechanical ventilation, neuromuscular blockers, extracorporeal membrane oxygenation (ECMO), anti-viral drug, anti-fungal drug, anti-bacterial drug, immune-globulin treatment, glucocorticoid therapy, vaccine. In such therapy, measures (e.g., dosing and selection of the complementary agent) are taken to adverse side effects which may be associated with combination therapies.

Thus, according to specific embodiments, the method disclosed herein further comprises administering to the subject a therapeutically effective amount of a therapeutic agent for ARDS.

According to specific embodiments, the method disclosed herein further comprises administering to the subject a therapeutically effective amount of a therapeutic agent for an infectious disease.

According to specific embodiments, the method disclosed herein further comprises administering to the subject a therapeutically effective amount of a therapeutic agent for an infectious disease associated with Corona virus infection.

According to specific embodiments, the method disclosed herein further comprises administering to the subject a therapeutically effective amount of a vaccine.

Further, according to an additional or an alternative aspect of the present invention there is provided an article of manufacture comprising a packaging material packaging as active ingredients an ADNF polypeptide; and a vaccine to an infectious disease.

According to an additional or an alternative aspect of the present invention there is provided an article of manufacture comprising a packaging material packaging as active ingredients an ADNF polypeptide; and a therapeutic agent for Acute Respiratory Distress Syndrome (ARDS).

According to an additional or an alternative aspect of the present invention there is provided an article of manufacture comprising a packaging material packaging as active ingredients an ADNF polypeptide; and a therapeutic agent for an infectious disease associated with Corona virus infection.

According to specific embodiments, the article of manufacture is identified for the treatment and/or prevention of a pathology (e.g. ARDS, infectious disease e.g. Corona virus infection).

According to specific embodiments, the polypeptide and the therapeutic agent (e.g. vaccine) are packaged in separate containers (i.e. in separate formulations).

According to specific embodiments, the polypeptide and the therapeutic agent (e.g. vaccine)are packaged in a co-formulation.

As used herein, the term "therapeutic agent" refers to an agent other than the polypeptide disclosed herein capable of treating and/or preventing a pathology (e.g. ARDS, infectious disease e.g. Corona virus infection).

Non-limiting Examples of therapeutic agents that may be used with specific embodiments of the invention include small molecules, antibodies, polypeptides, vaccines.

According to specific embodiments, the therapeutic agent is selected from the group consisting of anti-inflammatory agent, antibiotic and vaccine.

Non-limiting Examples of therapeutic agents that can be used with specific embodiments include hydroxychloroquine, chloroquine, Remdesivir, Zinc Sulfate, vasoactive intenstinal peptide (VIP), Aviptadil, phentolamine, tocilizumab, Sarilumab, Situximab, Janus kinase (JAK) inhibitor, antibiotic such as nemonoxacin, linezolid and azithromycin; or any analog or derivative thereof.

According to specific embodiments, the therapeutic agent comprises hydroxychloroquine, Zinc Sulfate and Azithromycin.

According to specific embodiments, the therapeutic agent comprises Aviptadil and phentolamine.

According to specific embodiments, the therapeutic agent is a vaccine to an infectious disease.

Selection of the vaccine to be used depends on the infectious disease to be prevented and/or treated and is well within the capability of those skilled in the art.

Non-limiting examples of vaccines include inactivated vaccines, live attenuated vaccines, viral vector vaccines, polypeptide vaccines and RNA vaccines.

According to specific embodiments, the vaccine has a relatively low efficacy (e.g. less than 70 %, less than 60 %, less than 50 % efficacy).

Non-limiting examples of vaccines include a malaria vaccine (e.g. RTS,S, known by the brand name Mosquirix), Influenza vaccine (e.g. inactivated or live attenuated), Corona virus vaccine (see non-limiting examples hereinbelow), Ebola vaccine (e.g. rVSV-ZEBOV, Zabdeno/Mvabea), tuberculosis vaccine [e.g. bacilli Calmette-Guérin (BCG)].

Non-limiting Examples of Corona virus vaccines that can be used with specific embodiments of the invention include the Pfizer–BioNTech vaccine BNT162b2, the Moderna vaccine mRNA-1273, Sputnik V, the Oxford–AstraZeneca vaccine AZD12220, Convidecia, the Johnson & Johnson vaccine, BBIBP-CorV, CoronaVac, Covaxin, WIBP-CorV, CoviVac, EpiVacCorona and RBD-Dimer.

According to specific embodiments, the polypeptide and the therapeutic agent are provided to the subject concomitantly.

According to specific embodiments, the polypeptide and the therapeutic agent are provided to the subject sequentially.

For Example, according to specific embodiments, the polypeptide is administered following first, second or multiple administrations of the therapeutic agent.

According to another specific embodiments, polypeptide is administered prior to administration of the therapeutic agent (e.g. vaccine).

According to specific embodiments, the combination therapy has an additive effect.

According to specific embodiments, the combination therapy has a synergistic effect.

The polypeptides and/or therapeutic agents described herein can be provided to the subject *per se*, or as part of a pharmaceutical composition where it is mixed with a pharmaceutically acceptable carrier.

As used herein a "pharmaceutical composition" refers to a preparation of one or more of the active ingredients described herein with other chemical components such as physiologically suitable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

Herein the term "active ingredient" refers to the polypeptide or therapeutic agent accountable for the biological effect.

Hereinafter, the phrases "physiologically acceptable carrier" and "pharmaceutically acceptable carrier" which may be interchangeably used refer to a carrier or a diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound. An adjuvant is included under these phrases.

Herein the term "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of an active ingredient. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

Techniques for formulation and administration of drugs may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition, which is incorporated herein by reference.

Suitable routes of administration may, for example, include oral, topical, intra-dermal, rectal, transmucosal, especially transnasal, intestinal or parenteral delivery, including intramuscular, subcutaneous and intramedullary injections as well as intrathecal, direct intraventricular, intracardiac, e.g., into the right or left ventricular cavity, into the common coronary artery, intravenous, intraperitoneal, intranasal, intrapulmonary or intraocular injections.

According to specific embodiments, the active ingredients are provided in a systemic manner.

According to specific embodiments, the route of administration is intranasal or intrapulmonary administration.

According to specific embodiments, the polypeptide is formulated for nasal administration as described in WO16/073,199, the contents of which are fully incorporated herein by reference.

According to other specific embodiments, the route of administration is into the skin. Methods of administering an active agent into a skin are known in the art and include, for example, intradermal injections, gels, liquid sprays and patches which comprise the active agent and which are applied on the outer surface of the skin.

According to some embodiments of the invention, administration of the active agent into the skin of the subject is performed topically (on the skin).

According to some embodiments of the invention, administration of the active agent into the skin of the subject is performed non-invasively, e.g., using a gel, a liquid spray or a patch (e.g. reservoir type patch and matrix type patch) comprising the active ingredient, which are applied onto the skin of the subject.

It should be noted that in order to increase delivery of the active agent into the skin, the active agent can be formulated with various vehicles designed to increase delivery to the epidermis or the dermis layers. Such vehicles include, but are not limited to liposomes, dendrimers, noisome, transfersome, microemulsion and solid lipid nanoparticles.

According to some embodiments of the invention, administering is performed by an intradermal injection.

Conventional approaches for drug delivery to the central nervous system (CNS) include: neurosurgical strategies (e.g., intrahippocampal (IH), intracranial (IC), intracerebral injection, intracerebroventricular injection (ICV) or infusion or intrathecal administration); molecular manipulation of the agent (e.g., production of a chimeric fusion protein that comprises a transport peptide that has an affinity for an endothelial cell surface molecule in combination with an agent that is itself incapable of crossing the BBB) in an attempt to exploit one of the endogenous transport pathways of the BBB; pharmacological strategies designed to increase the lipid solubility of an agent (e.g., conjugation of water-soluble agents to lipid or cholesterol carriers); and the transitory disruption of the integrity of the BBB by hyperosmotic disruption (resulting from the infusion of a mannitol solution into the carotid artery or the use of a biologically active agent such as an angiotensin peptide). However, each of these strategies has limitations, such as the inherent risks associated with an invasive surgical procedure, a size limitation imposed by a limitation inherent in the endogenous transport systems, potentially undesirable biological side effects associated with the systemic administration of a chimeric molecule comprised of a carrier motif that could be active outside of the CNS, and the possible risk of brain damage within regions of the brain where the BBB is disrupted, which renders it a suboptimal delivery method.

Alternately, one may administer the pharmaceutical composition in a local rather than systemic manner, for example, via injection of the pharmaceutical composition directly into a tissue region of a patient.

Pharmaceutical compositions of some embodiments of the invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with some embodiments of the invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the

active ingredients into preparations which, can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the active ingredients of the pharmaceutical composition may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological salt buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the pharmaceutical composition can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the pharmaceutical composition to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for oral ingestion by a patient. Pharmacological preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carbomethylcellulose; and/or physiologically acceptable polymers such as polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

According to specific embodiments, the pharmaceutical composition is formulated for oral administration.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical compositions which can be used orally, include push-fit capsules made of gelatin as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active ingredients in admixture with filler such as lactose, binders such as starches, lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active ingredients may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition,

stabilizers may be added. All formulations for oral administration should be in dosages suitable for the chosen route of administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

According to specific embodiments, the pharmaceutical composition is formulated for inhalation (e.g. intranasal or intrapulmonary).

For administration by inhalation, the active ingredients for use according to some embodiments of the invention are conveniently delivered in the form of an aerosol spray presentation from a pressurized pack or a nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichloro-tetrafluoroethane or carbon dioxide. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in a dispenser may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The pharmaceutical composition described herein may be formulated for parenteral administration, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multidose containers with optionally, an added preservative. The compositions may be suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical compositions for parenteral administration include aqueous solutions of the active preparation in water-soluble form. Additionally, suspensions of the active ingredients may be prepared as appropriate oily or water based injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acids esters such as ethyl oleate, triglycerides or liposomes. Aqueous injection suspensions may contain substances, which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the active ingredients to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water based solution, before use.

The pharmaceutical composition of some embodiments of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, using, e.g., conventional suppository bases such as cocoa butter or other glycerides.

The pharmaceutical composition of some embodiments of the invention may also be formulated for sustained-release to provide elevated serum half-life. Such sustained release systems are well known to those of skill in the art and include e.g. microcapsules and nanoparticles. According to specific embodiments, the ProLease biodegradable microsphere delivery system for proteins and peptides (Tracy, 1998, Biotechnol. Prog. 14, 108; Johnson et al., 1996, Nature Med. 2, 795; Herbert et al., 1998, Pharmaceut. Res. 15, 357) a dry powder composed of biodegradable polymeric microspheres containing the protein in a polymer matrix that can be compounded as a dry formulation with or without other agents.

Pharmaceutical compositions suitable for use in context of some embodiments of the invention include compositions wherein the active ingredients are contained in an amount effective to achieve the intended purpose. More specifically, a therapeutically effective amount means an amount of active ingredients effective to prevent, alleviate or ameliorate symptoms of a disorder (e.g., ARDS, infectious diseases e.g. Corona virus infection) or prolong the survival of the subject being treated.

Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

For any preparation used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from in vitro and cell culture assays. For example, a dose can be formulated in animal models to achieve a desired concentration or titer. Such information can be used to more accurately determine useful doses in humans.

Toxicity and therapeutic efficacy of the active ingredients described herein can be determined by standard pharmaceutical procedures in vitro, in cell cultures or experimental animals. The data obtained from these in vitro and cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1).

For complete toxicity assessment of the ADNF polypeptide of SEQ ID NO: 2 see Gozes I. Front Neurol. 2020 Nov 24; 11: 608444, the contents of which are fully incorporated herein by reference.

Dosage amount and interval may be adjusted individually to provide that the levels of the active ingredient are sufficient to induce or suppress the biological effect (minimal effective concentration, MEC). The MEC will vary for each preparation, but can be estimated from in

vitro data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. Detection assays can be used to determine plasma concentrations.

A non-limiting example of an animal model for SAR-CoV-2 is the transgenic mouse expressing human ACE2 (see e.g, Bao et al. (2020) Nature 583: 830-833.

The doses determined in the mouse animal model can be converted for the treatment other species such as human and other animals diagnosed with the disease. Conversion Table approved by the FDA is shown in Reagan-Shaw S., et al., FASEB J. 22:659-661 (2007).

The human equivalent dose is calculated as follows: HED (mg/kg) = Animal dose (mg/kg) multiplied by (Animal K_m/human K_m).

Depending on the severity and responsiveness of the condition to be treated, dosing can be of a single or a plurality of administrations, with course of treatment lasting from several days to several weeks or until cure is effected or diminution of the disease state is achieved.

According to specific embodiments, the polypeptide is administered once or twice a day.

The amount of a composition to be administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, etc.

According to some embodiments of the invention, the polypeptide is provided at an amount ranging from 0.0001 mg/kg to 10,000 mg/kg including any intermediate subranges and values therebetween, e.g. 0.001 mg/kg, 0.1 mg/kg, 1 mg/kg, 5 mg/kg, 15 mg/kg, 50 mg/kg or 500 mg/kg per dose. According to specific embodiments, the polypeptide is provided in an amount ranging from 0.05 – 0.1 mg/kg e.g. 0.08 mg/kg.

According to specific embodiments, the polypeptide is provided in an amount ranging from 0.1 – 1 mg/kg e.g. 0.4 mg/kg given e.g. subcutaneously.

According to specific embodiments, the polypeptide is provided in an amount ranging from 0.05 – 0.5 mg/kg e.g. 0.2 mg/kg (15 mg to a 70 kg subject) or 0.07 mg/kg (5 mg to a 70 kg subject) e.g. intranasaly.

According to specific embodiments, Hydroxychloroquine is administered to a 75 kg patient in a dose of 1-1000 mg including any intermediate subranges and values therebetween, e.g. 200 mg e.g. twice a day for 5 days.

According to specific embodiments, Azithromycin is administered to a 75 kg patient in a dose of 1-1000 mg including any intermediate subranges and values therebetween, e.g. 500 mg e.g. once a day for 5 days.

According to specific embodiments, Zinc sulfate is administered to a 75 kg patient in a dose of 1-1000 mg including any intermediate subranges and values therebetween, e.g. 220 mg e.g. once a day for 5 days.

Compositions of some embodiments of the invention may, if desired, be presented in a pack or dispenser device, such as an FDA approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accommodated by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions or human or veterinary administration. Such notice, for example, may be of labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. Compositions comprising a preparation of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition, as is further detailed above.

As used herein the term “about” refers to ± 10 %.

The terms "comprises", "comprising", "includes", "including", “having” and their conjugates mean "including but not limited to".

The term “consisting of” means “including and limited to”.

The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from

3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

When reference is made to particular sequence listings, such reference is to be understood to also encompass sequences that substantially correspond to its complementary sequence as including minor sequence variations, resulting from, e.g., sequencing errors, cloning errors, or other alterations resulting in base substitution, base deletion or base addition, provided that the frequency of such variations is less than 1 in 50 nucleotides, alternatively, less than 1 in 100 nucleotides, alternatively, less than 1 in 200 nucleotides, alternatively, less than 1 in 500 nucleotides, alternatively, less than 1 in 1000 nucleotides, alternatively, less than 1 in 5,000 nucleotides, alternatively, less than 1 in 10,000 nucleotides.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions illustrate some embodiments of the invention in a non limiting fashion.

Generally, the nomenclature used herein and the laboratory procedures utilized in the present invention include molecular, biochemical, microbiological and recombinant DNA techniques. Such techniques are thoroughly explained in the literature. See, for example, "Molecular Cloning: A laboratory Manual" Sambrook et al., (1989); "Current Protocols in Molecular Biology" Volumes I-III Ausubel, R. M., ed. (1994); Ausubel et al., "Current Protocols in Molecular Biology", John Wiley and Sons, Baltimore, Maryland (1989); Perbal, "A Practical Guide to Molecular Cloning", John Wiley & Sons, New York (1988); Watson et al., "Recombinant DNA", Scientific American Books, New York; Birren et al. (eds) "Genome Analysis: A Laboratory Manual Series", Vols. 1-4, Cold Spring Harbor Laboratory Press, New York (1998); methodologies as set forth in U.S. Pat. Nos. 4,666,828; 4,683,202; 4,801,531; 5,192,659 and 5,272,057; "Cell Biology: A Laboratory Handbook", Volumes I-III Cellis, J. E., ed. (1994); "Culture of Animal Cells - A Manual of Basic Technique" by Freshney, Wiley-Liss, N. Y. (1994), Third Edition; "Current Protocols in Immunology" Volumes I-III Coligan J. E., ed. (1994); Stites et al. (eds), "Basic and Clinical Immunology" (8th Edition), Appleton & Lange, Norwalk, CT (1994); Mishell and Shiigi (eds), "Selected Methods in Cellular Immunology", W. H. Freeman and Co., New York (1980); available immunoassays are extensively described in the patent and scientific literature, see, for example, U.S. Pat. Nos. 3,791,932; 3,839,153; 3,850,752; 3,850,578; 3,853,987; 3,867,517; 3,879,262; 3,901,654; 3,935,074; 3,984,533; 3,996,345; 4,034,074; 4,098,876; 4,879,219; 5,011,771 and 5,281,521; "Oligonucleotide Synthesis" Gait, M. J., ed. (1984); “Nucleic Acid Hybridization" Hames, B. D., and Higgins S. J., eds. (1985); "Transcription and Translation" Hames, B. D., and Higgins S. J., eds. (1984); "Animal Cell Culture" Freshney, R. I., ed. (1986); "Immobilized Cells and Enzymes" IRL Press, (1986); "A Practical Guide to Molecular Cloning" Perbal, B., (1984) and "Methods in Enzymology" Vol. 1-317, Academic Press; "PCR Protocols: A Guide To Methods And Applications", Academic Press, San Diego, CA (1990); Marshak et al., "Strategies for Protein Purification and Characterization - A Laboratory Course Manual" CSHL Press (1996); all of which are incorporated by reference as if fully set forth herein. Other general references are provided throughout this document. The procedures therein are believed to be well known in the art and are provided for the convenience of the reader. All the information contained therein is incorporated herein by reference.

EXAMPLE 1

AN ADNP POLYPEPTIDE INHIBITS IN-VITRO SECRETION OF PRO-INFLAMMATORY CYTOKINES FROM PBMCs OBTAINED FROM COVID-19 PATIENTS

The ability of the ADNP polypeptide NAP [having an amino acid sequence NAPVSIPQ (SEQ ID NO: 2)] to inhibit *in-vitro* the release of the pro-inflammatory cytokines (e.g. IL-6, IL-1β and TNFα) from PBMCs and monocytes/macrophages obtained from COVID19 patients as compared to PBMCs obtained from aged-sex matched healthy patients is analyzed by ELISA. Monocytes are isolated from PBMCs using a monocyte isolation kit. Monocyte derived macrophages are obtained following 7 days incubation of the monocytes. Further, the signaling proteins involved in this inhibition are determined using e.g. signaling protein inhibitors, Western Blot, intracellular flow cytometry, confocal microscopy and qRT-PCR.

EXAMPLE 2

AN ADNP POLYPEPTIDE AS TREATMENT FOR COVID-19

The lungs are the organs most affected by SAR-CoV-2 [causing 2019-nCoV (also referred to as "COVID-19")], because the virus accesses host cells via the enzyme ACE2, which is most abundant in the alveolar cells of the lungs. COVID-19 induced pneumonia may rapidly progress to acute respiratory distress syndrome (ARDS) causing respiratory failure, septic shock, or multi-organ failure.

The therapeutic effect of the ADNP polypeptide NAP [having an amino acid sequence NAPVSIPQ (SEQ ID NO: 2)] is evaluated in-vitro or in-vivo as a single agent or in combination with anti-viral and/or anti-bacterial drug or in combination with a COVID-19 vaccine.

Non-limiting examples of in-vitro models include human airway epithelial cells, Vero E6 cells, Caco-2 cells or Calu-3 cells infected with COVID-19.

A non-limiting example of an in-vivo model for COVID-19 includes the transgenic mouse expressing human ACE2 (see e.g, Bao et al. (2020) Nature 583: 830-833.

Mice are monitored daily for weight loss and survival.

Blood levels of pro-inflammatory cytokines (e.g. IL-6, IL-1β, TNFα) are determined on e.g. day 2, 5 and 10.

Lung tissue histopathology in is examined on e.g. day 2 and 10.

Alternatively or additionally, the therapeutic effect of the ADNP polypeptide NAP [having an amino acid sequence NAPVSIPQ (SEQ ID NO: 2)] is evaluated in a clinical trials in

human patients as a single agent or in combination with anti-viral and/or anti-bacterial drug or in combination with a COVID-19 vaccine.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

In addition, any priority document(s) of this application is/are hereby incorporated herein by reference in its/their entirety.

WHAT IS CLAIMED IS:

1. A method of preventing an infectious disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB3; and a vaccine to an infectious disease, thereby preventing the infectious disease in the subject.

2. An ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB3; and a vaccine to an infectious disease, for use in preventing the infectious disease in a subject in need thereof.

3. The method of claim 1 or the polypeptide and vaccine for use of claim 2, wherein said polypeptide and said vaccine are provided to said subject sequentially.

4. An article of manufacture comprising as active ingredients an ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB3; and a vaccine to an infectious disease.

5. The article of manufacture of claim 4, wherein said polypeptide and said vaccine are provided in a co-formulation.

6. The article of manufacture of claim 4, wherein said polypeptide and said vaccine are provided in separate formulations.

7. The method, polypeptide and vaccine for use or the article of manufacture of any one of claims 1-6, wherein said infectious disease is associated with a viral infection.

8. A method of treating Acute Respiratory Distress Syndrome (ARDS) in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB3, thereby treating the ARDS in the subject.

9. An ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB, for use in treating Acute Respiratory Distress Syndrome (ARDS) in a subject a subject in need thereof.

10. The method of claim 8, further comprising administering to the subject a therapeutically effective amount of a therapeutic agent for ARDS.

11. The polypeptide for use of claim 9, further comprising a therapeutic agent for ARDS.

12. A method of treating an infectious disease associated with Corona virus infection in a subject in need thereof the method comprising administering to the subject a therapeutically effective amount of an ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB3, thereby treating the infectious disease associated with the Corona virus infection in the subject.

13. An ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB3, for use in treating an infectious disease associated with Corona virus infection in a subject in need thereof.

14. The method of claim 12, further comprising administering to the subject a therapeutically effective amount of a therapeutic agent for an infectious disease associated with Corona virus infection.

15. The polypeptide for use of claim 13, further comprising a therapeutic agent for an infectious disease associated with Corona virus infection.

16. An article of manufacture comprising as active ingredients an ADNF polypeptide, wherein said ADNF polypeptide is capable of binding EB1 and/or EB3; and a therapeutic agent for Acute Respiratory Distress Syndrome (ARDS).

17. The article of manufacture of claim 16, wherein said polypeptide and said therapeutic agent are provided in a co-formulation.

18. The article of manufacture of claim 16, wherein said polypeptide and said therapeutic agent are provided in separate formulations.

19. The method, the polypeptide for use or the article of manufacture of any one of claims 10-11, 14-15 and 16-18, wherein said therapeutic agent is selected from the group consisting of anti-inflammatory agent, antibiotic and vaccine.

20. The method, the polypeptide for use or the article of manufacture of any one of claims 10-11, 14-15 and 16-18, wherein said therapeutic agent is selected from the group consisting of hydroxychloroquine, chloroquine, Remdesivir, Zinc Sulfate, vasoactive intenstinal peptide (VIP), Aviptadil, phentolamine, tocilizumab, Sarilumab, Situximab, Janus kinase (JAK) inhibitor, nemonoxacin, linezolid and azithromycin.

21. The method or the polypeptide for use of any one of claims 10-11, 14-15 and 19-20, wherein said polypeptide and said therapeutic agent are provided to said subject sequentially.

22. The method, the polypeptide for use or the article of manufacture of any one of claims 8-11 and 16-21, wherein said ARDS is associated with a viral infection.

23. The method, the polypeptide for use, the article of manufacture polypeptide and vaccine for use of any one of claims 7 and 22, wherein said viral infection is a respiratory viral infection.

24. The method, the polypeptide for use, the article of manufacture or the polypeptide and vaccine for use of claim 23, wherein said respiratory viral infection is selected from the group consisting of a Corona virus infection, a respiratory syncytial virus (RSV) infection, an influenza virus infection, a parainfluenza virus infection, an adenovirus infection and a rhinovirus infection.

25. The method, the polypeptide for use, the article of manufacture or the polypeptide and vaccine for use of any one of claims 7 and 22-23, wherein said viral infection is a Corona virus infection.

26. The method, the polypeptide for use, the article of manufacture or the polypeptide and vaccine for use of any one of claims 12-15 and 24-25, wherein said Corona virus is SAR-CoV-2, Middle East respiratory syndrome Coronavirus (MERS-CoV) or severe acute respiratory syndrome Coronavirus (SARS-CoV).

27. The method, the polypeptide for use, the article of manufacture or the polypeptide and vaccine for use of any one of claims 12-15 and 24-25, wherein said Corona virus is SAR-CoV-2.

28. The method, the polypeptide for use or the polypeptide and vaccine for use of any one of claims 1-3, 7-15 and 19-27, wherein said subject has a blood level of a pro-inflammatory cytokine above a predetermined threshold.

29. The method, the polypeptide for use or the polypeptide and vaccine for use of any one of claims 1-3, 7-15 and 19-28, wherein said subject is immunodeficient.

30. The method, the polypeptide for use or the polypeptide and vaccine for use of any one of claims 1-3, 7-15 and 19-29, wherein said subject is diagnosed with a syndrome selected from the group consisting of ADNP syndrome, fragile X syndrome, Syngap-1 syndrome, Phelan McDermid syndrome and Rett syndrome.

31. The method, the polypeptide for use, the polypeptide and vaccine for use or the article of manufacture of any one of claims 1-30, wherein said ADNF polypeptide has a neurotrophic/neuroprotective activity in an in vitro cortical neuron culture assay.

32. The method, the polypeptide for use, the polypeptide and vaccine for use or the article of manufacture of any one of claims 1-31, wherein said ADNF polypeptide comprises an SH3 binding domain.

33. The method, the polypeptide for use, the polypeptide and vaccine for use or the article of manufacture of any one of claims 1-32, wherein said ADNF polypeptide is an ADNF III polypeptide.

34. The method, the polypeptide for use, the polypeptide and vaccine for use or the article of manufacture of claim 33, wherein said polypeptide comprises an amino acid sequence selected form the group consisting of 2-22.

35. The method, the polypeptide for use, the polypeptide and vaccine for use or the article of manufacture of claim 33, wherein said polypeptide comprises an amino acid sequence selected form the group consisting of 2-20.

36. The method, the polypeptide for use, the polypeptide and vaccine for use or the article of manufacture of claim 33 wherein said polypeptide comprises SEQ ID NO: 2.

37. The method, the polypeptide for use, the polypeptide and vaccine for use or the article of manufacture of claim 33, wherein said polypeptide has the formula $(R^1)_x$-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-$(R^2)_y$ (SEQ ID NO: 49), or an analogue thereof, in which R^1 is an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected from the group consisting of naturally occurring amino acids and amino acid analogs; R^2 is an amino acid sequence comprising from 1 to about 40 amino acids wherein each amino acid is independently selected from the group consisting of naturally occurring amino acids and amino acid analogs; and x and y are independently selected and are equal to zero or one.

38. The method, the polypeptide for use, the polypeptide and vaccine for use or the article of manufacture of any one of claims 1-37, wherein said polypeptide comprises at least one D-amino acid.

39. The method, the polypeptide for use, the polypeptide and vaccine for use or the article of manufacture of any one of claims 1-38, wherein said polypeptide is less than 50 amino acids in length.

40. The method, the polypeptide for use, the polypeptide and vaccine for use or the article of manufacture of any one of claims 1-38, wherein said polypeptide is less than 20 amino acids in length.

41. The method, the polypeptide for use, the polypeptide and vaccine for use or the article of manufacture of any one of claims 1-40, wherein said polypeptide is attached to a cell penetrating or stabilizing moiety.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2021/050421

A. CLASSIFICATION OF SUBJECT MATTER
IPC (20210101) A61K 38/17, A61P 11/00, A61K 39/215
CPC (20130101) A61K 38/1709, A61P 11/00, A61K 39/215
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC (20210101) A61K 38/17, A61P 11/00, A61K 39/215
CPC (20130101) A61K 38/1709, A61P 11/00, A61K 39/215

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Databases consulted: PATENTSCOPE, THOMSON INNOVATION, Esp@cenet, Google Patents, CAPLUS, BIOSIS, EMBASE, Google Scholar
Search terms used: ADNP ADNF peptide infection infectious "activity-dependent neuroprotective protein" ADNP "activity-dependent neuroprotective fragment" ADNF EB1 EB3 "acute respiratory distress syndrome" ARDS vaccine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018117613 A1 Jeong et al. 28 Jun 2018 (2018/06/28) Whole document	1-41

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 Jul 2021	29 Jul 2021

Name and mailing address of the ISA:	Authorized officer
Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Email address: pctoffice@justice.gov.il	POUNY Yehonathan Telephone No. 972-73-3927124

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2021/050421

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

a. [X] forming part of the international application as filed:

[X] in the form of an Annex C/ST.25 text file.

[ ] on paper or in the form of an image file.

b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

[ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

[ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2021/050421

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
WO 2018117613 A1	28 Jun 2018	WO 2018117613 A1	28 Jun 2018
		AR 110549 A1	10 Apr 2019
		CN 110312532 A	08 Oct 2019
		EP 3556399 A1	23 Oct 2019
		JP 2020501611 A	23 Jan 2020
		KR 20180071193 A	27 Jun 2018
		TW 201825123 A	16 Jul 2018
		US 2019352335 A1	21 Nov 2019