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Submission Number:	056115	
Application Number:	PCT/IB2020/056115	
Date of Receipt:	29 June 2020	
Receiving Office:	International Bureau of the World Intellectual Property Organization	
Your Reference:	FD00230PCTR	
Applicant:	GLIGOROV, Daniel	
Number of Applicants:	1	
Title:	A METHOD FOR ANTIVIRAL AND CYTOKINE STORM TREATMENT	
Documents Submitted:	FD00230PCTR-appb-000001.pdf (说明书.pdf)	284633
	FD00230PCTR-appb-000002.pdf (权利要求书.pdf)	133669
	FD00230PCTR-appb-000003.pdf (1.pdf)	33729
	FD00230PCTR-appb.xml	762
	FD00230PCTR-fees.xml	2301
	FD00230PCTR-requ.xml	5022
	FD00230PCTR-vlog.xml	423
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Timestamp of Receipt:	29 June 2020 13:30 UTC+2 (CEST)	
Official Digest of Submission:	FC:6F:40:DE:61:F7:67:1C:25:04:59:8D:D1:5E:B4:36:C9:93:3B:1E	

/Geneva, RO/IB/

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0	**For receiving Office use only**	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	**Form PCT/RO/101 PCT Request**	
0-4-1	Prepared Using	**ePCT-Filing** **Version 4.7.005 MT/FOP 20200617/1.1**
0-5	**Petition**	
	The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	**International Bureau of the World Intellectual Property Organization (RO/IB)**
0-7	**Applicant's or agent's file reference**	**FD00230PCTR**
I	**Title of Invention**	**A METHOD FOR ANTIVIRAL AND CYTOKINE STORM TREATMENT**
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IV-1-5(a)	E-mail authorization The receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority are authorized to use this e-mail address, if the Office or Authority so wishes, to send notifications issued in respect of this international application:	**exclusively in electronic form (no paper notifications will be sent)**	
V	**DESIGNATIONS**		
V-1	**The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.**		
VI-1	**Priority Claim**	**NONE**	
VII-1	**International Searching Authority Chosen**	**European Patent Office (EPO) (ISA/EP)**	
VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

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IX	Check list	Number of sheets	Electronic file(s) attached
IX-1	Request (including declaration sheets)	**4**	✓
IX-2	Description	**33**	✓
IX-3	Claims	**3**	✓
IX-4	Abstract	**1**	✓
IX-5	Drawings	**0**	-
IX-6a	Sequence listing part of the description (also to be used for the purposes of international search)	-	-
IX-7	TOTAL	**41**	
	Accompanying Items	Paper document(s) attached	Electronic file(s) attached
IX-8	Fee calculation sheet	-	✓
IX-20	**Figure of the drawings which should accompany the abstract**		
IX-21	**Language of filing of the international application**	**English**	
IX-22	**The receiving Office is requested to make this international application available to the Priority Document Access Service (DAS) (provided that an international application number and international filing date is accorded to this purported international application.)**	**Yes**	
X-1	**Signature of applicant, agent or common representative**	**/GLIGOROV,Daniel/**	
X-1-1	Name (LAST, First)	**GLIGOROV, Daniel**	
X-1-3	Capacity (if such capacity is not obvious from reading the request)		

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10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	**ISA/EP**
10-6	**Transmittal of search copy delayed until search fee is paid**	

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11-1	**Date of receipt of the record copy by the International Bureau**	

ABSTRACT

The present invention relates to a new application of Allostatin. The method for treating a viral infection or cytokine storm with Allostatin is described. In some embodiments, Allostatin is also used in prevention and treatment of cytokine storm caused by viral infection and other conditions. In some embodiments，the virus is viruse associated with respiratory infection or respiratory virus, for example, corona virus.

CLAIMS

1. A method for treating a viral infection, comprising administrating to a subject of an effective amount of a compound or the preparation thereof, wherein the compound comprises the general structural formula: X1 TrpGly Gln X2 or pharmaceutically acceptable salts, or ethers, or amides thereof, wherein X1 is absent or comprises no less than 1 amino acid, and X2 is absent or comprises no less than 1 amino acid.

2. The method of claim 1or 2, wherin the compound comprises up to 30 amino acid residues.

3. The method of any one of claims 1-2, wherein X1 is selected from the group consisting of 0 amino acid, His-Gly-Val-Ser-Gly-, His-Gly-Gly-Gly-, His-Val-Gly-Gly-, His-Gly-Gly-Gly-Gly, Gln-Gly-Gly-Gly-Gly and His-Gly-Gly-Gly-.

4. The method of any one of claims 1-4, wherein X2 is selected from the group consisting of 0 amino acid, -His-Gly-Thr-His-Gly-, -Gly-Gly-Thr-His-Gly-, -Pro-His-Val-Gly-Gly-, -Pro-His-Gly-Gly-Gly-, -Pro-His-Gly-Gly-Gly-Trp-Gly-, -Gly-Gly-Gly-Thr-His-Ser.

5. The method of any one of claims 1-5, wherein the compound comprises any one selected from the group consisting of His-Gly-Val-Ser-Gly-Trp-Gly-Gln-His-Gly-Thr-His-Gly (SEQ ID NO 1), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly (SEQ NO 2), His-Gly-Gly-Gly-Gly-Trp-Gly-Gln-Gly-Gly-Thr-His-Gly (SEQ ID NO 3), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Val-Gly-Gly (SEQ ID NO 4), His-Val-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly (SEQ NO 5), Gln-Gly-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 9), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 10), and His-Gly-Gly-Gly-Trp-Gly-Gln-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 11).

6. The method of any of claims 1-5, wherein the compound is a peptide.

7. The method of any one of claims 1-6, wherein the compound is a part of a chemical that is not a natural protein or peptide.

8. The method of any one of claims 1-7, wherein the subject infected with virus has fever.

9. The method of any one of claims 1-8, wherein the subject infected with virus has pneumonia.

10. The method of any one of claims 1-9, wherein the subject infected with virus has dyspnea.

11. The method of any one of claims 1-10, wherein the subject is infected with virus that led to systemic inflammatory response.

12. The method of any one of claims 1-11, wherein the subject is infected with virus that led to cytokine storm.

13. The method of any one of claims 1-12, wherin the virus is viruse associated with respiratory infection or respiratory virus.

14. The method of any one of claims 1-13,wherin the virus is selected from corona virus (including COVID19), cytomegalovirus, Epstein-Barr virus, influenza virus, or variola virus.

15. The method of any one of claims 1-14, wherein the compound improves or alleviates the symptoms selected from the group consisting of fever, fatigue, dyspnea, and Oxygen Saturation of Blood.

16. The method of claim 1, wherein the virus is selected fromhuman papillomavirus (HPV), herpes simplex virus (HSV), molluscum contagiosum virus (MCV) and varicella zoster virus (VZV).

17. A method to prevent or suppress cytokine storm comprising administrating to a subject of an effective amount of a compound or the preparation thereof, wherein the compound has the general structural formula: X1 TrpGly Gln X2 or pharmaceutically acceptable salts, or ethers, or amides thereof, wherein X1 is absent or comprises no less than 1 amino acid, and X2 is absent or comprises no less than 1 amino acid.

18. The method of claim 17, wherein the compound comprises up to 30 amino acid residues.

19. The method of claim 17 or 18, wherein X1 is selected from the group consisting of 0 amino acid, His-Gly-Val-Ser-Gly-, His-Gly-Gly-Gly-, His-Val-Gly-Gly-, His-Gly-Gly-Gly-Gly, Gln-Gly-Gly-Gly-Gly and His-Gly-Gly-Gly-.

20. The method of any one of claims 17-19, wherein X2 is selected from the group consisting of 0 amino acid, -His-Gly-Thr-His-Gly-, -Gly-Gly-Thr-His-Gly-, -Pro-His-Val-Gly-Gly-, -Pro-His-Gly-Gly-Gly-, -Pro-His-Gly-Gly-Gly-Trp-Gly-, -Gly-Gly-Gly-Thr-His-Ser.

21. The method of any one of claims 17-20, wherein the compound is selected from the group consisting of His-Gly-Val-Ser-Gly-Trp-Gly-Gln-His-Gly-Thr-His-Gly (SEQ ID NO 1), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly (SEQ NO 2), His-Gly-Gly-Gly-Gly-Trp-Gly-Gln-Gly-Gly-Thr-His-Gly (SEQ ID NO 3),

His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Val-Gly-Gly (SEQ ID NO 4),

His-Val-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly (SEQ NO 5),

Gln-Gly-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 9),

His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 10), and

His-Gly-Gly-Gly-Trp-Gly-Gln-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 11).

22. The method of any one of claims 17-21, wherein the compound is a peptide.

23. The method of any one of claims 17-22, wherein the compound is a part of a chemical that is not is a natural protein or peptide.

24. The method of any one of claims 17-23, wherein the subject is suffering from a disease that leads to cytokine storm.

25. The method of any one of claims 17-24, wherein the compound improves or alleviates the symptoms selected from the group consisting of fever, fatigue, dyspnea, and Oxygen Saturation of Blood.

26. The method of any one of claims 17-25, wherein the disease a viral infection disease.

27. The method of any one of claims 1-26,wherein the compound kills virus inside and outside of cells of the subject.

A method for antiviral and cytokine storm treatment

FIELD OF THE INVENTION

The invention relates to the field of immunotherapy and new application of Allostatin. The priority area of application of the invention is the treatment of virosis of humans and other warm-blooded animals and the prevention and suppression of cytokine storm.

BACKGROUND OF THE INVENTION

For at least 300 years the immune system has been targeted to improve human health.As is well known in recent years, themodulationandexploitingofimmunesystemhave great potential in the treatment of malignancy and infectious disease. Studies on the activity of vaccines, the role ofnew checkpoint molecules, new pathways for stimulationof innate responses, and even the genetic determinants ofresponse will all inform both basic immune mechanismsand have applications in the generation of effective immunityto pathogens. (Samantha L. Bucktrout, etc., Recent advances in immunotherapies: frominfection and autoimmunity, to cancer, andback again, Genome Medicine, 2018).

Alloferon is a group of bioactive, slightly cationic peptides, with immunomodulatory properties.It is isolated from infected insects. In vitro experiments reveal that the syntheticversion of Alloferon has stimulatory activities on natural killerlymphocytes, whereas in vivo trials indicate induction of IFNproduction in mice after treatments with synthetic Alloferon.Additional in vivo experiments in mice indicate that Alloferon hasantiviral and antitumor capabilities (Sergey Chernysh, Antiviral and antitumor peptides from insects, PNAS, 2002).At present, aninjectable formulation of Alloferon has been registered in Russia as an antiviral drug.

Recently, a new family of peptides, named Allostatin was developed (WO2005/068491).Allostatinis a group of compounds relates to linear peptides which structure is presents by the following formula: X1 TrpGly Gln X2, wherein X1 is absent or comprises no less than 1 amino acid, and X2 is absent or comprises no less than 1 amino acid.It’s clear that the characters of Allostatin are not the same as that of Alloferon. For example, in vitro experiments have shown that depending on the concentration in culture media, Alloferonmay both inhibit (at high

concentrations) and stimulate (at low concentrations) proliferation of tumor cells. In contract, Allostatin, at both high and low concentrations, exhibits a reduced growth-stimulating activity and enhanced antiproliferative and cytotoxic activities towards tumor cells. It's already known that, Allostatin is capable of activating cytotoxic effect of NK cells, as well as increasing and maintaining the population of NK and T lymphocytes producing IFNγ and increasing their sensitivity to the activating signals of IL-2 and IL-12. However, it's hard to say whether and how Allostatin may work clinically. It's also not easy to tell, with all these non-specific immune activation functions above, for which disease and in which means and dosing regimen could Allostatin play a role in the treatment.

At present, the antitumor characters of Allostatin have been relatively carefully studied, other potential effects of Allostatin are to be carefully explored.

SUMMARY OF THE INVENTION

In this invention, the antiviral and anti-cytokine storm application of Allostatin is developed. Thus, provided in the present invention is a method for treating a viral infection, comprising administrating to a subject of an effective amount of a compound or the preparation thereof, wherein the compound comprises the general structural formula: X1 TrpGly Gln X2 or pharmaceutically acceptable salts, or ethers, or amides thereof, wherein X1 is absent or comprises no less than 1 amino acid, and X2 is absent or comprises no less than 1 amino acid. In some embodiments, the compound comprises up to 30 amino acid residues. In some embodiments, X1 is selected from the group consisting of 0 amino acid, His-Gly-Val-Ser-Gly-, His-Gly-Gly-Gly-, His-Val-Gly-Gly-, His-Gly-Gly-Gly-Gly, Gln-Gly-Gly-Gly-Gly and His-Gly-Gly-Gly-. In some embodiments, X2 is selected from the group consisting of 0 amino acid, -His-Gly-Thr-His-Gly-, -Gly-Gly-Thr-His-Gly-, -Pro-His-Val-Gly-Gly-, -Pro-His-Gly-Gly-Gly-, -Pro-His-Gly-Gly-Gly-Trp-Gly-, -Gly-Gly-Gly-Thr-His-Ser. In some embodiments,the compound comprises any one selected from the group consisting of His-Gly-Val-Ser-Gly-Trp-Gly-Gln-His-Gly-Thr-His-Gly (SEQ ID NO 1), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly (SEQ NO 2), His-Gly-Gly-Gly-Gly-Trp-Gly-Gln-Gly-Gly-Thr-His-Gly (SEQ ID NO 3), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Val-Gly-Gly (SEQ ID NO 4), His-Val-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly (SEQ NO 5),

Gln-Gly-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 9), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 10), and His-Gly-Gly-Gly-Trp-Gly-Gln-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 11). In some embodiments,the compound is a peptide. In some embodiments, the compound is a part of a chemical that is not a natural protein or peptide.

According to the method, in some embodiments, the subject treated with is infected with virus that led to rash, wart, or lesion on skin or mucosa.In some embodiments, the subject is infected with virus that led to inflammatory response of skin or mucosa.In some embodiments, the virus is selected from human papillomavirus (HPV), herpes simplex virus (HSV), molluscum contagiosum virus (MCV) and varicella zoster virus (VZV). In some embodiments, the compound or the preparation thereof is applied topically. In some embodiments, the compound or the preparation thereof is applied externally. In some embodiments, the compound or the preparation thereof is applied cutaneously. In some embodiments, the compound or the preparation thereof is applied to the mucosa. In some embodiments, the compound or the preparation thereof is applied directly to the lesions.

According to the method, in some embodiments, the subject is infected with virus that led to cytokine storm.In some embodiments, the subject is infected with virus that led to systemic inflammatory response. In some embodiments, the virus is selected from corona virus, cytomegalovirus, Epstein-Barr virus, influenza virus, or variola virus. In some embodiments, the virus is avian H5N1 influenza virus, severe acute respiratory syndrome coronavirus (SARS-CoV), or SARS-COV-2 virus. In some embodiments, the compound or the preparation thereof is applied subcutaneously.In some embodiments, the compound or the preparation thereof is applied intravenously. In some embodiments, the compound or the preparation thereof is injected or infiltrated into the tissues comprising the virus infected cells.

According to the method, the compound or the preparation thereof is also applied concomitantly with IFN-γ, IL-2, and/or IL12 in the treatment of viral infection.

The present invention also provides a method to prevent or suppress cytokine storm comprising administrating to a subject of an effective amount of a compound or the preparation thereof, wherein the compound has the general structural formula: X1 TrpGly Gln X2 or pharmaceutically acceptable salts, or ethers, or amides thereof, wherein X1 is absent or comprises no less than 1 amino acid, and

X2 is absent or comprises no less than 1 amino acid. In some embodiments, the compound comprises up to 30 amino acid residues. In some embodiments, X1 is selected from the group consisting of 0 amino acid, His-Gly-Val-Ser-Gly-, His-Gly-Gly-Gly-, His-Val-Gly-Gly-, His-Gly-Gly-Gly-Gly, Gln-Gly-Gly-Gly-Gly and His-Gly-Gly-Gly-. In some embodiments, X2 is selected from the group consisting of 0 amino acid, -His-Gly-Thr-His-Gly-, -Gly-Gly-Thr-His-Gly-, -Pro-His-Val-Gly-Gly-, -Pro-His-Gly-Gly-Gly-, -Pro-His-Gly-Gly-Gly-Trp-Gly-, -Gly-Gly-Gly-Thr-His-Ser. In some embodiments, the compound is selected from the group consisting of His-Gly-Val-Ser-Gly-Trp-Gly-Gln-His-Gly-Thr-His-Gly (SEQ ID NO 1), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly (SEQ NO 2), His-Gly-Gly-Gly-Gly-Trp-Gly-Gln-Gly-Gly-Thr-His-Gly (SEQ ID NO 3), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Val-Gly-Gly (SEQ ID NO 4), His-Val-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly (SEQ NO 5), Gln-Gly-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 9), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 10), and His-Gly-Gly-Gly-Trp-Gly-Gln-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 11). In some embodiments, the compound is a peptide. In some embodiments, the compound is a part of a chemical that is not is a natural protein or peptide.

According to the method to prevent or suppress cytokine storm,in some embodiments, the subject is infected with virus that causes cytokine storm. In some embodiments, the virus is selected from the group comprising corona virus, cytomegalovirus, Epstein-Barr virus, influenza virus, and variola virus.In some embodiments, the subject is suffering graft-versus-host disease, group A streptococcus infection, multiple sclerosis, pancreatitis or multiple organ dysfunction syndrome. In some embodiments, the compound or the preparation thereof is applied subcutaneously. In some embodiments, the compound or the preparation thereof is applied intravenously.

DETAIL DESCRIPTION OF THE INVENTION

Infections caused by herpes simplex virus 1 (HSV-1), HSV-2, varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human papillomaviruses (HPVs), and molluscum contagiosum virus (MCV) are common, and their incidence continues to grow despite a

wide range of available and experimental therapies (Jashin J. Wu, etc., Advances in Antiviral Therapy, Dermatologic Clinics, 2005).Besides, coronaviruses are pathogens with a serious impact on human and animal health. Coronaviruses mostly cause enteric or respiratory disease, which can be severe and life threatening, e.g., in the case of the zoonotic coronaviruses causing severe acute respiratory syndrome (SARS), coronavirus disease 2019 (COVID-19), and Middle East Respiratory Syndrome (MERS) in humans. Despite the economic and societal impact of such coronavirus infections, and the likelihood of future outbreaks of additional pathogenic coronaviruses, our options to prevent or treat coronavirus infections remain very limited (Adriaan H de Wilde, Host Factors in Coronavirus Replication, Curr Top Microbiol Immunol. 2018).At present, it is known that the modulation and exploiting of immune system can be a promising method for treating such infectious diseases.

Allostatin was generated in 2004, and its antitumor characters have been relatively carefully explored. Allostatin is reported to have antiproliferative and immunomodulatory activity to tumor cells both in vivo and in vitro (WO2005/068491). However, as a cytokine-like effector, the antiviral activities and other application in diseases treatment of Allostatin have been poorly researched. In the following examples in this article, the authors tested Allostatinboth onthepatients and in vitro, and the results support the application of Allostatin in virus infection treatment and the suppression and prevention of cytokine storm.

It’s known that current therapies for viral infections of the skin can reduce or suppress symptoms, but there is no known cure and no available method to reduce the frequency of outbreaks after antiviral drug cessation (Jashin J. Wu, etc., Advances in Antiviral Therapy, Dermatologic Clinics, 2005). While in the exemplary examples in this invention, Allostatin is applied on the surface of patients’ skin with a proper dosage and frequencies, showing a better efficacy than existing therapies. As shown in example 1, it was obvious that the efficacy difference between Acyclovirand Allomedin(a product containing Allostatin as the only active ingredient) groups was dominated at the beginning and the development stage of the symptoms (when the virus is active) rather than the end stage.

Besides, as is known, a new coronavirus named SARS-CoV-2 was identified as the causative agent of a several acute respiratory infection named COVID-19. COVID-19 can be confirmed based on the patient's history, clinical manifestations, imaging characteristics, and laboratory tests. Chest

CT examination plays an important role in the initial diagnosis of the novel coronavirus pneumonia. Multiple patchy ground glass opacities in bilateral multiple lobular with periphery distribution are typical chest CT imaging features of the COVID-19 pneumonia (Xu et al., Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2, *Eur J Nucl Med Mol Imaging.*, 2020).SARS-CoV-2 showed phylogenetic similarities to both SARS-CoV and MERS-CoV viruses, and some of the clinical features are shared between COVID-19 and previously identified beta-coronavirus infections, however there are still many unresolved questions regarding the pathogenesis of this disease(Coperchini et al. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system, Cytokine & Growth Factor Reviews, June 2020). Despide of this, in example 2 and 3, the signsof cytokine storm, high uncontrolled hyperthermia, aches, difficulty in breath, in patients infected with COVID-19 in some way went away after been given one injection of allostatin (1 mg, subcutaneously).

The facts above demonstrated the antiviral effect of Allostatin.Thus, provided in this invention isa method for treating a viral infectionor for suppressing or preventing cytokine storm in a proper way.In some embodiments, the method is for treating a virosis, comprisingadministrating to a subject of an effective amount of a compound or the preparation thereof, wherein the compound comprises the general structural formula: X1 TrpGly Gln X2 or pharmaceutically acceptable salts, or ethers, or amides thereof, wherein X1 is absent or comprises no less than 1 amino acid, and X2 is absent or comprises no less than 1 amino acid. In some embodiments, the compound comprises up to 30 amino acid residues. In some embodiments, X1 is selected from the group consisting of 0 amino acid, His-Gly-Val-Ser-Gly-, His-Gly-Gly-Gly-, His-Val-Gly-Gly-, His-Gly-Gly-Gly-Gly, Gln-Gly-Gly-Gly-Gly and His-Gly-Gly-Gly-. In some embodiments, X2 is selected from the group consisting of 0 amino acid, -His-Gly-Thr-His-Gly-, -Gly-Gly-Thr-His-Gly-, -Pro-His-Val-Gly-Gly-, -Pro-His-Gly-Gly-Gly-, -Pro-His-Gly-Gly-Gly-Trp-Gly-, -Gly-Gly-Gly-Thr-His-Ser. In some embodiments, the compound comprises any one selected from the group consisting of His-Gly-Val-Ser-Gly-Trp-Gly-Gln-His-Gly-Thr-His-Gly (SEQ ID NO 1), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly (SEQ NO 2), His-Gly-Gly-Gly-Gly-Trp-Gly-Gln-Gly-Gly-Thr-His-Gly (SEQ ID NO 3), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Val-Gly-Gly (SEQ ID NO 4),

His-Val-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly (SEQ NO 5), Gln-Gly-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 9), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 10), and His-Gly-Gly-Gly-Trp-Gly-Gln-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 11). In some embodiments, the compound is a peptide. In some embodiments, the compound is a part of a chemical that is not a natural protein or peptide.

According to the method, in some embodiments, the subject treated with is infected with virus that led to rash, wart, or lesion on skin or mucosa. In some embodiments, the subject is infected with virus that led to inflammatory response of skin or mucosa. In some embodiments, the virus is selected from human papillomavirus (HPV), herpes simplex virus (HSV), molluscum contagiosum virus (MCV) and varicella zoster virus (VZV). Example 1 proves the antiviral efficacy of Allostatin when it's applied to the lesions on the skin or on the mucosa, thus, in some embodiments, the compound or the preparation thereof is applied topically. In some embodiments, the compound or the preparation thereof is applied externally. In some embodiments, the compound or the preparation thereof is applied cutaneously. In some embodiments, the compound or the preparation thereof is applied to the mucosa. In some embodiments, the compound or the preparation thereof is applied directly to the lesions.

According to the method, in some embodiments, the subject is infected with virus that led to cytokine storm. In some embodiments, the subject is infected with virus that led to systemic inflammatory response. In some embodiments, the virus is selected from corona virus, cytomegalovirus, Epstein-Barr virus, influenza virus, or variola virus. In some embodiments, the virus is avian H5N1 influenza virus, severe acute respiratory syndrome coronavirus (SARS-CoV), or SARS-COV-2 virus. According to Example 2,both subcutaneous injection and intravenous injection of Allostatin results in relieve in symptoms of patients infected with viruses that led to inflammatory response or rash, wart or lesion in skin or mucosa. Thus, in some embodiments, the compound or the preparation thereof is applied subcutaneously. In some embodiments, the compound or the preparation thereof is applied intravenously. In some embodiments, the compound or the preparation thereof is injected or infiltrated into the tissues comprising the virus infected cells.

According to the method, the compound or the preparation thereof is also applied concomitantly

with IFN-γ, IL-2, and/or IL12 in the treatment of viral infection.

Besides, the data in Table 1 shows that absolute majority of patients with skin herpes and genitalia mucous tunic herpes (labial and genital herpes, correspondingly) whose symptoms were scarcely improved when treated with conventional medications were effectively treated by Allomedin.And according to Table 2 and 3, compared to the standard acyclovir treatment, Allomedin rapidly eliminates inflammation symptoms like itch, burning, oedemaand the duration of the symptoms decreased about 10 times. Thus the provided method in some embodiments, Allostatin or the preparation thereof is utilized in treating patients who scarcely response to the traditional medications. And in some specific embodiments, comparing to that of conventional treatment, the duration of symptoms decreases about 10 times when patients are treated with Allostatin or the preparation thereof.

In Example 3,Allostatin is tested both in vitro on cytokine storm models and in clinical treatment of patients having systemic inflammatory response or the signs of cytokine storm. The result clearly shows the effectiveness of Allostatinapplication in preventing and suppressing cytokine storm in both infectious diseases and non-infectious diseases. The term cytokine storm refers to the general concept of an excessive or uncontrolled releaseof proinflammatory cytokines.The use of theterm in infectious disease research began in early 2000 in reportson cytomegalovirus, Epstein-Barr virus-associated hemophagocyticlymphohistiocytosis, group A streptococcus, influenza virus, variola virus, and severe acuterespiratory syndrome coronavirus (SARS-CoV). The termappears to have first been applied in the context of avian H5N1influenza virus infection in 2005, after which it began toappear more frequently in the scientific literature (Tisoncik et al., Into the Eye of the Cytokine Storm, Microbiology and Molecular Biology Reviews).Cytokine storms are associated with a wide variety of infectiousand noninfectious diseases and have even been the unfortunateconsequence of attempts at therapeutic intervention. Previousreviews have centered on the advent of the concept or itsrole in graft-versus-host disease, multiple sclerosis, pancreatitis, or multiple organ dysfunction syndrome (Tisoncik et al., Into the Eye of the Cytokine Storm, Microbiology and Molecular Biology Reviews).

Accordingly, provided in this invention is alsoa method to prevent or suppress cytokine storm comprising administrating to a subject of an effective amount of a compound or the preparation

thereof, wherein the compound has the general structural formula: X1 TrpGly Gln X2 or pharmaceutically acceptable salts, or ethers, or amides thereof, wherein X1 is absent or comprises no less than 1 amino acid, and X2 is absent or comprises no less than 1 amino acid. In some embodiments, the compound comprises up to 30 amino acid residues. In some embodiments, X1 is selected from the group consisting of 0 amino acid, His-Gly-Val-Ser-Gly-, His-Gly-Gly-Gly-, His-Val-Gly-Gly-, His-Gly-Gly-Gly-Gly, Gln-Gly-Gly-Gly-Gly and His-Gly-Gly-Gly-. In some embodiments, X2 is selected from the group consisting of 0 amino acid, -His-Gly-Thr-His-Gly-, -Gly-Gly-Thr-His-Gly-, -Pro-His-Val-Gly-Gly-, -Pro-His-Gly-Gly-Gly-, -Pro-His-Gly-Gly-Gly-Trp-Gly-, -Gly-Gly-Gly-Thr-His-Ser. In some embodiments, the compound is selected from the group consisting of His-Gly-Val-Ser-Gly-Trp-Gly-Gln-His-Gly-Thr-His-Gly (SEQ ID NO 1), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly(SEQ NO 2), His-Gly-Gly-Gly-Gly-Trp-Gly-Gln-Gly-Gly-Thr-His-Gly (SEQ ID NO 3), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Val-Gly-Gly (SEQ ID NO 4), His-Val-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly (SEQ NO 5), Gln-Gly-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 9), His-Gly-Gly-Gly-Trp-Gly-Gln-Pro-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 10), and His-Gly-Gly-Gly-Trp-Gly-Gln-His-Gly-Gly-Gly-Trp-Gly (SEQ ID NO 11). In some embodiments, the compound is a peptide. In some embodiments, the compound is a part of a chemical that is not is a natural protein or peptide.

According to the method to prevent or suppress cytokine storm, in some embodiments, the subject is infected with virus that causes cytokine storm. In some embodiments, the virus is selected from the group comprising corona virus, cytomegalovirus, Epstein-Barr virus, influenza virus, and variola virus. In some embodiments, the subject is suffering graft-versus-host disease, group A streptococcus infection, multiple sclerosis, pancreatitis or multiple organ dysfunction syndrome. In some embodiments, the compound or the preparation thereof is applied subcutaneously. In some embodiments, the compound or the preparation thereof is applied intravenously.

EXAMPLES

Example 1. The clinical efficacy of Allomedinin the treatment of Herpes simplex virus (HSV) infections

Allomedin® is registered as a cosmetic product, containing Allostatin (a peptide with the sequence: His-Gly-Val-Ser-Gly-Trp-Gly-Gln-His-Gly-Thr-His-Gly (SEQ ID No. 1))and additional compounds commonly used in dermatological and cosmetic products: carbopolgel (base), Allantoin, phenoxyethanol, ethylhexylglycerin, sodium hydroxide.Allomedin®isin the form of hydrogel and is designed to apply on face and mucosa to help keeping a good appearance. The patients using Allomedin®daily were clinically evaluated in specialized clinics, hospitals and medical centers as follows:

1.Russian medical academy of postgraduate education, St. Petersburg (dermatology and cosmetology department, stomatology department)

2.St. Petersburg city center for prevention of infectious diseases

3.Pasteur research institute, St. Petersburg

4.Center for preventive Medicine, St. Petersburg

5.Center of clinical immunology, St. Petersburg

6.Republican clinical hospital for infectious diseases

7.First St. Petersburg medical university (department of otorhinolaryngology)

8. District antenatal clinic №1, St. Petersburg

9.District antenatal clinic №2, St. Petersburg

10.Medical university, Petrozavodsk

Allostatin treatmentfor skin herpes and genitalia mucous herpesClinical data characterizing Allomedin therapeutic efficacy in patients infected with *Herpes simplex* virus include 104 patients (81 females, 23 males) experiencing relapsing herpes of different location more than 4 years before the study. The recorded medical history of these patients showed little improvement of the symptoms when treated with conventional medications.Age of the patients was varied from 18 to 60 years.

Allomedin was applied onto the surface of herpetic lesions 2 to 3 times a day during 3 to 5 days.In each application, the affected area was gelled by Allomedin. Patientsweredeterminedtohavepositive responses when anyone of the following happened:

1) the symptoms relieved, e.g. the area of the herpetic lesion narrowed, the number of herpetic lesions decreased, the duration of symptoms decreased, and/orreduced itching, pain,

swelling, and/or oedema,etc.;

2) the frequency of relapses decreased;
3) the symptoms in following relapses were milder; or
4) the relapse stopped;

Results were independently collected from different medical facilities listed above and summarized in Table 1.

Table 1. Allomedin clinical efficacy in the therapy of herpes relapses with reference to thelesion's

Location	Therapeutic efficacy evaluation		
	Patientsnumber	Positive responses	
		N	%
Skin	27	26	96.3
Vagina or urethra mucous tunic	44	41	93.1
Mouth mucous tunic	33	20	66.6

Data of Table 1 demonstrate that absolute majority of patients with skin herpes and genitalia mucous tunic herpes (labial and genital herpes, correspondingly) can be effectively treated by Allomedin.

Comparison of the efficacies of Allostatin (Allomedin) and Acyclovir onherpes:

Clinical studies of Allomedin efficacy in labial and genital herpes demonstrated also extraordinary fast relief of herpes symptoms elimination compared to the treatment with Acyclovir, a standard antiviral medication, according to the labeled instructions.

Symptom of patients were recorded from the treatment of Allomedin or Acyclovir and till the end of a relapse. Patients were interviewed in each visit and their subjective feelings were recorded in their medical history. Data of patients subjective feelings were summarized in Tables 2 and3 which illustrated the fact thatAllomedin rapidly eliminates inflammation symptoms like itch, burning, oedema so that duration of the symptoms decreased about **10 times** compared to the standard acyclovir treatment. Besides, it was obvious that the efficacy difference between the Acyclovir and Allomedin groups was dominated at the beginning and the development stage of the symptoms (when the virus is active) rather than the end stage. This demonstrated the antiviral effect of Allostatin.

Table 2. Efficacy comparison of Allomedin and acyclovir in the reduction ofcold sores symptoms(labial herpes) (data from the Center of clinical immunology, St. Petersburg).

Index	The index rate, hours	
	Acyclovir	Allomedin
Itchiness and burning duration	60 - 84	4-8
50% decrease in the size of the oedema zone	84 -108	8-12
Total relapse duration	168 - 192	72 - 96

Table 3. Efficacy comparison of Allomedin and acyclovir in the elimination of genital herpessymptoms (data from the Pasteur research institute, St. Petersburg).

Indices and stages	Symptoms duration, hours	
	Acyclovir	Allomedin
Itch	84,3 ± 9,4	13,6 ± 3,7
Burning	93,2 ± 12,8	14,0 ± 2,2
Vesicular-erosive stage	96,2 ± 12,8	54,6 ± 10,2
Scab stage	114,1 ± 20,8	98,0 ± 12,8

Example 2. The clinical efficacy of Allostatin in the treatment of Corvid-19

A35 years old man got COVID-19 like symptoms as follows: hard to breath and weakness,but no fever. Computed Tomography (CT) of the chest organs was typical for COVID-19 associated bilateral pneumonia with the defeat of at least 50% of the pulmonary parenchyma. CT2 (moderate). Besides, all other family members of the man were infected and were tested positive for COVID19.

After the conclusion of CT, the man was treated with 1mgAllostatin®subcutaneously for once, and no other treatments were administered.

As a result, in 1-2 hours after the injection, the symptoms relieved, breathing returned to normal and the man felt better.

Example 3. Cytokine storm prevention and suppression by Allostatin

<u>In vitro tests</u>

Table 4. In vitro Test of Allostatin in suppressing excessive cytokine production

	Control	Allostatin	UVB	UVB + Allostatin
IL-1α pg/ml	19.1 ± 3.2	26.7 ± 2.4	109.3 ± 1.7	32.4 ± 4.3
IL-1β pg/ml	12.8 ± 1.3	12.6 ± 0.7	48.08 ± 3.1	19.7 ± 1.2
IL-6 pg/ml	2643.5 ± 72.1	4457.1 ± 204.3	16572.3 ± 712.4*	5932.7 ± 431.5*
IL-18 pg/ml	4.8 ± 0.9	11.6 ± 2.4	73.1 ± 21.7*	16.3 ± 1.3*
* - P < 0.001				

Human keratinocytes in medium (RPMI 1640 with 10% FBS) were exposed to UVB (110 J/m^2), then add with 2 mcg/ml of Allostatin. Medium supernatants were measured by ELISA 24h later for IL-1 α/β, IL-6 and IL-18. Results are representative of three independent experiments. Treatment with allostatin led to a statistically significant decrease in the production of pro-inflammatory cytokines.

Production of IL-6 by human keratinocytes after ultraviolet treatment positive correlate with degree of p38MAPK phosphorylation.

Table 5. Comparison of Allostatin and p38MAPK inhibitor in suppressing excessive IL-6 production

	Control	UVB	UVB + Allostatin	UVB + p38MAPK inhibitor*
IL-6 (pg/ml)	2563.7 ± 120.4	16781.9 ± 308.6**	5588.1 ± 275.3**	2584.7 ± 153.2**
share of p-p38 in cells, %	10	70	4	-

* - pyridinyl imidazole

** - P < 0.001

Clinical trials

To determine the effect of Allostatin in treatment of hyperthermia, a sign of cytokine storm, a clinical study was conducted within 15 patients.

All patients experienced hyperthermia within the range between 37.5 and 39.3℃. Average temperature measured across the group was 38.5℃.

With exception of one patient suspected of COVID19 who received Allostatin 2 hours after he experienced temperature higher than normal, Allostatin was administered at least 6 hours after the start of hyperthermia. In cases of Pneumonia patients, Allostatin was administered 3 days later.

The record of patientssymptems, treatment and therapeutic effect of each patients are shown as below:

CASE 1

Condition: Hyperthermia

NAME OF PATIENT (initials if confidential): Sergey

GENDER: male

AGE: 55

NAME OF VIRAL INFECTION: flu-like syndrome

1. When did high fever start? 2005
2. What was the highest temperature you had? 38.5
3. How long did the fever last? first day
4. Did you experience any of these following symptoms?

- excessive sweating. - no
- exhaustion. - no
- flushed or red skin. - no
- muscle cramps, spasm, and pain. - yes
- headache or mild light-headedness. - yes
- nausea. - no

5. Did you seek a medical help and if yes, what diagnosis were given? - no
6. Did you take a laboratory test? - no

7. When did you receive Allostatin injection? - 6 hours after the onset of hyperthermia
8. Did fever reduce 1 hour after the first Allostatin injection? - fever stopped
9. How many Allostatin injections did you receive and in what time period? - 1 (one)
10. Besides Allostatine, did you receive any other medication for the treatment? - no
11. How long did it take for the symptoms of the viral infection to disappear? - after overnight
12. Were you tested for the existence of the virus after the treatment? If yes, when was this done? - no
13. How happy are you with the use of Allostatine in your treatment? - completely healthy
14. Will you recommend Allostatine in treatment of hyperthermia to others? - definitely yes
15. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. - diabetes
16. Did you have any surgery in the past 3 years? If yes, please specify - no

CASE 2

Condition: Hyperthermia

NAME OF PATIENT (initials if confidential): Fedor

GENDER: male

AGE: 12

NAME OF VIRAL INFECTION: flu-like syndrome

1. When did high fever start? June of 2020
2. What was the highest temperature you had? 39.4
3. How long did the fever last? One day
4. Did you experience any of these following symptoms?

- excessive sweating. – yes
- exhaustion. - yes

- flushed or red skin. - no
- muscle cramps, spasm, and pain. - yes
- headache or mild light-headedness. - yes
- nausea. - yes

5. Did you seek a medical help and if yes, what diagnosis were given? - no
6. Did you take a laboratory test? - no
7. When did you receive Allostatin injection? - 8 hours after the onset of hyperthermia
8. Did fever reduce 1 hour after the first Allostatin injection? - no fever.
9. How many Allostatin injections did you receive and in what time period? - 1 (one)
10. Besides Allostatine, did you receive any other medication for the treatment? - no
11. How long did it take for the symptoms of the viral infection to disappear? - overnight
12. Were you tested for the existence of the virus after the treatment? If yes, when was this done? - no
13. How happy are you with the use of Allostatine in your treatment? - (full recovery)
14. Will you recommend Allostatine in treatment of hyperthermia to others?-definitely yes
15. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. - no
16. Did you have any surgery in the past 3 years? If yes, please specify - no

CASE 3

Condition: Hyperthermia

NAME OF PATIENT (initials if confidential): Nina

GENDER: female

AGE: 9

NAME OF VIRAL INFECTION: flu-like syndrome

1. When did high fever start? June of 2020
2. What was the highest temperature you had? 39.2

3. How long did the fever last? A day
4. Did you experience any of these following symptoms?

- excessive sweating. - no
- exhaustion. - yes
- flushed or red skin. - no
- muscle cramps, spasm, and pain. - yes
- headache or mild light-headedness. - yes
- nausea. - yes

5. Did you seek a medical help and if yes, what diagnosis were given? - no
6. Did you take a laboratory test? - no
7. When did you receive Allostatin injection? - 9 hours after the onset of hyperthermia
8. Did fever reduce 1 hour after the first Allostatin injection? - the fever stopped
9. How many Allostatin injections did you receive and in what time period? - 1 (one)
10. Besides Allostatine, did you receive any other medication for the treatment? - no
11. How long did it take for the symptoms of the viral infection to disappear? - after overnight
12. Were you tested for the existence of the virus after the treatment? If yes, when was this done? - no
13. How happy are you with the use of Allostatine in your treatment? - completely healthy (full recovery)
14. Will you recommend Allostatine in treatment of hyperthermia to others?- definitely yes
15. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. - no
16. Did you have any surgery in the past 3 years? If yes, please specify - no

CASE 4

Condition: Hyperthermia

NAME OF PATIENT (initials if confidential): Tatiana

GENDER: female

AGE: 48

NAME OF VIRAL INFECTION: flu-like syndrome, pneumonia

1. When did high fever start? July of 2019
2. What was the highest temperature you had? 38.7
3. How long did the fever last? few day
4. Did you experience any of these following symptoms?

- excessive sweating. - yes
- exhaustion. - no
- flushed or red skin. - no
- muscle cramps, spasm, and pain. - yes
- headache or mild light-headedness. - yes
- nausea. - no

5. Did you seek a medical help and if yes, what diagnosis were given? - yes, pneumonia
6. Did you take a laboratory test? - yes
7. When did you receive Allostatin injection? - 3 days after the onset of hyperthermia
8. Did fever reduce 1 hour after the first Allostatin injection? yes
9. How many Allostatin injections did you receive and in what time period? - 3 (three times every other day)
10. Besides Allostatine, did you receive any other medication for the treatment? - yes; antibiotics
11. How long did it take for the symptoms of the viral infection to disappear? - after second injection relief came
12. Were you tested for the existence of the virus after the treatment? If yes, when was this done? - no

13. How happy are you with the use of Allostatine in your treatment? - full recovery

14. Will you recommend Allostatine in treatment of hyperthermia to others?- definitely yes

15. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. - no

16. Did you have any surgery in the past 3 years? If yes, please specify - no

CASE 5

Condition: Hyperthermia

NAME OF PATIENT (initials if confidential): Dmitry (!!!the described effect was repeated three times; below data for 2019, in other cases, there was a drop of hyperthermia - like Fedor's).

GENDER: male

AGE: 49

NAME OF VIRAL INFECTION: flu-like syndrome, systemic inflammatory reaction after severe sunburn

1. When did high fever start? 2010, 2013, august of 2019
2. What was the highest temperature you had? > 39
3. How long did the fever last? three day
4. Did you experience any of these following symptoms?

- excessive sweating. - yes
- exhaustion. - yes
- flushed or red skin. - yes
- muscle cramps, spasm, and pain. - yes
- headache or mild light-headedness. - yes
- nausea. - no

5. Did you seek a medical help and if yes, what diagnosis were given? - no
6. Did you take a laboratory test? - no

7. When did you receive Allostatin injection? - 2 days after the onset of hyperthermia
8. Did fever reduce 1 hour after the first Allostatin injection? Yes,
9. How many Allostatin injections did you receive and in what time period? - 2 (two)
10. Besides Allostatine, did you receive any other medication for the treatment? - no
11. How long did it take for the symptoms of the viral infection to disappear? - after second injection
12. Were you tested for the existence of the virus after the treatment? If yes, when was this done? - no
13. How happy are you with the use of Allostatine in your treatment? - symptom relief; decrease in body temperature
14. Will you recommend Allostatine in treatment of hyperthermia to others?- definitely yes
15. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. - diabetes
16. Did you have any surgery in the past 3 years? If yes, please specify - no

CASE 6

Condition: Hyperthermia

NAME OF PATIENT (initials if confidential): Pavel

GENDER: male

AGE: 34

NAME OF VIRAL INFECTION: flu-like syndrome

1. When did high fever start? 2018
2. What was the highest temperature you had? 38.8
3. How long did the fever last? first day
4. Did you experience any of these following symptoms?

- excessive sweating. - no
- exhaustion. - yes

- flushed or red skin. - no
- muscle cramps, spasm, and pain. - yes
- headache or mild light-headedness. - yes
- nausea. - no

5. Did you seek a medical help and if yes, what diagnosis were given? - no
6. Did you take a laboratory test? - no
7. When did you receive Allostatin injection? - 12 hours after the onset of hyperthermia
8. Did fever reduce 1 hour after the first Allostatin injection? no fever
9. How many Allostatin injections did you receive and in what time period? - 1 (one)
10. Besides Allostatine, did you receive any other medication for the treatment? - no
11. How long did it take for the symptoms of the viral infection to disappear? - overnight
12. Were you tested for the existence of the virus after the treatment? If yes, when was this done? - no
13. How happy are you with the use of Allostatine in your treatment? - very happy
14. Will you recommend Allostatine in treatment of hyperthermia to others? - definitely yes
15. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. - no
16. Did you have any surgery in the past 3 years? If yes, please specify - no

CASE 7

Condition: Hyperthermia

NAME OF PATIENT (initials if confidential): Timofey

GENDER: male

AGE: 51

NAME OF VIRAL INFECTION: flu-like syndrome

1. When did high fever start? 2008

2. What was the highest temperature you had? 39
3. How long did the fever last? first day
4. Did you experience any of these following symptoms?

- excessive sweating. - no
- exhaustion. - yes
- flushed or red skin. - no
- muscle cramps, spasm, and pain. - no
- headache or mild light-headedness. - yes
- nausea. - no

5. Did you seek a medical help and if yes, what diagnosis were given? - no
6. Did you take a laboratory test? - no
7. When did you receive Allostatin injection? - 6 hours after the onset of hyperthermia
8. Did fever reduce 1 hour after the first Allostatin injection? Yes.
9. How many Allostatin injections did you receive and in what time period? - 1 (one)
10. Besides Allostatine, did you receive any other medication for the treatment? - no
11. How long did it take for the symptoms of the viral infection to disappear? - overnight
12. Were you tested for the existence of the virus after the treatment? If yes, when was this done? - no
13. How happy are you with the use of Allostatine in your treatment? - happy
14. Will you recommend Allostatine in treatment of hyperthermia to others?- definitely yes
15. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. - diabetes
16. Did you have any surgery in the past 3 years? If yes, please specify - no

CASE 8

Condition: Hyperthermia

NAME OF PATIENT (initials if confidential): Igor

GENDER: male

AGE: 48

NAME OF VIRAL INFECTION: flu-like syndrome

1. When did high fever start? March 2020
2. What was the highest temperature you had? 38.7
3. How long did the fever last? first day
4. Did you experience any of these following symptoms?

- excessive sweating. - no
- exhaustion. - no
- flushed or red skin. - no
- muscle cramps, spasm, and pain. - no
- headache or mild light-headedness. - yes
- nausea. - no

5. Did you seek a medical help and if yes, what diagnosis were given? - no
6. Did you take a laboratory test? - no
7. When did you receive Allostatin injection? - first day of hyperthermia
8. Did fever reduce 1 hour after the first Allostatin injection? no fever
9. How many Allostatin injections did you receive and in what time period? - 3
10. Besides Allostatine, did you receive any other medication for the treatment? - no
11. How long did it take for the symptoms of the viral infection to disappear? - after overnight
12. Were you tested for the existence of the virus after the treatment? If yes, when was this done? - no
13. How happy are you with the use of Allostatine in your treatment? - completely healthy
14. Will you recommend Allostatine in treatment of hyperthermia to others?- definitely yes
15. Do you suffer from any serious diseases, or conditions, including chronic diseases and

conditions? If yes, please specify. - no

16. Did you have any surgery in the past 3 years? If yes, please specify - no

CASE 9

Condition: Hyperthermia

NAME OF PATIENT (initials if confidential): Andrey

GENDER: male

AGE: 32

NAME OF VIRAL INFECTION: flu-like syndrome

1. When did high fever start? 2015
2. What was the highest temperature you had? High, 39
3. How long did the fever last? first day
4. Did you experience any of these following symptoms?

- excessive sweating. - no
- exhaustion. - yes
- flushed or red skin. - no
- muscle cramps, spasm, and pain. - no
- headache or mild light-headedness. - yes
- nausea. - yes

5. Did you seek a medical help and if yes, what diagnosis were given? - no
6. Did you take a laboratory test? - no
7. When did you receive Allostatin injection? - 6 hours after the onset of hyperthermia
8. Did fever reduce 1 hour after the first Allostatin injection? yes
9. How many Allostatin injections did you receive and in what time period? - 1 (one)
10. Besides Allostatine, did you receive any other medication for the treatment? - no
11. How long did it take for the symptoms of the viral infection to disappear? - after

overnight

12. Were you tested for the existence of the virus after the treatment? If yes, when was this done? - no

13. How happy are you with the use of Allostatine in your treatment? - happy

14. Will you recommend Allostatine in treatment of hyperthermia to others? - yes

15. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. - no

16. Did you have any surgery in the past 3 years? If yes, please specify - no

CASE 10

NAME OF PATIENT (initials if confidential): Lubov

GENDER: female

AGE: 34

NAME OF VIRAL INFECTION: flu-like syndrome

1. When did high fever start? In the evening (May, 2020)
2. What was the highest temperature you had? 37.6
3. How long did the fever last? first day
4. Did you experience any of these following symptoms?

- excessive sweating. - no
- exhaustion. - no
- flushed or red skin. - no
- muscle cramps, spasm, and pain. - no
- headache or mild light-headedness. - yes
- nausea. - no

5. Did you seek a medical help and if yes, what diagnosis were given? - no
6. Did you take a laboratory test? - no

7. When did you receive Allostatin injection? - 2 hours after the onset of hyperthermia
8. Did fever reduce 1 hour after the first Allostatin injection? yes
9. How many Allostatin injections did you receive and in what time period? - 1 (one)
10. Besides Allostatine, did you receive any other medication for the treatment? - no
11. How long did it take for the symptoms of the viral infection to disappear? - after injection and night, I felt absolutely good
12. Were you tested for the existence of the virus after the treatment? If yes, when was this done? - no
13. How happy are you with the use of Allostatine in your treatment? yes
14. Will you recommend Allostatine in treatment of hyperthermia to others? - definitely yes
15. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. - nothing
16. Did you have any surgery in the past 3 years? If yes, please specify - no

CASE 11

GENDER: female

AGE: 38

NAME OF VIRAL INFECTION: flu-like syndrome

1. When did high fever start? In the evening (February of 2020)
2. What was the highest temperature you had? 38++
3. How long did the fever last? first day
4. Did you experience any of these following symptoms?

a) excessive sweating. - no
b) exhaustion. - no
c) flushed or red skin. - no
d) muscle cramps, spasm, and pain. -yes
e) headache or mild light-headedness. - no
f) nausea. - no

5. Did you seek a medical help and if yes, what diagnosis were given? - no

6. Did you take a laboratory test? - no

7. When did you receive Allostatin injection? - 4 hours after the onset of hyperthermia

8. Please describe what happened 1 hours after you took the first Allostatin injection? - after 1 hour nothing happened because I went to sleep immediately

9. How many Allostatin injections did you receive and in what time period? - 1 (one)

10. Besides Allostatine, did you receive any other medication for the treatment? - no

11. How long did it take for the symptoms of the viral infection to disappear? - in the morning I felt good, 36.6 and without any flu-like syndrome

12. Were you tested for the existence of the virus after the treatment? If yes, when was this done? - no

13. How happy are you with the use of Allostatine in your treatment? - completely healthy (full recovery)

14. Will you recommend Allostatine in treatment of hyperthermia to others? - definitely yes

15. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. - no

16. Did you have any surgery in the past 3 years? If yes, please specify - no

CASE 12

GENDER: female

AGE: 64

NAME OF VIRAL INFECTION: flu-like syndrome

1. When did high fever start? Middle of the day (May of 2020)
2. What was the highest temperature you had? 38
3. How long did the fever last? first day
4. Did you experience any of these following symptoms?

g) excessive sweating. - yes

h) exhaustion. - no

i) flushed or red skin. - no

j) muscle cramps, spasm, and pain. - yes

k) headache or mild light-headedness. - yes

l) nausea. - no

5. Did you seek a medical help and if yes, what diagnosis were given? - no

6. Did you take a laboratory test? - no

7. When did you receive Allostatin injection? - 2 hours after the onset of hyperthermia

8. Please describe what happened 1 hours after you took the first Allostatin injection? - after 1 hour I felt better and in the evening, I had 36.5

9. How many Allostatin injections did you receive and in what time period? - 1 (one)

10. Besides Allostatine, did you receive any other medication for the treatment? - no

11. How long did it take for the symptoms of the viral infection to disappear? - next morning after injection I felt better, had 36.6, but continuer to felt flu-like syndrome. After 2 days after injection I felt absolutely healthy

12. Were you tested for the existence of the virus after the treatment? If yes, when was this done? - no

13. How happy are you with the use of Allostatine in your treatment? - achieved full recovery

14. Will you recommend Allostatine in treatment of hyperthermia to others? - definitely yes

15. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. - cancer in remission

16. Did you have any surgery in the past 3 years? If yes, please specify - no

CASE 13

GENDER: male

AGE: 35

NAME OF VIRAL INFECTION: COVID19-like syndrome, pneumonia

1. When did high fever start? HAVE NO FEVER

2. What was the highest temperature you had? 36.8

3. How long did the fever last? 0

4. Did you experience any of these following symptoms?

m) excessive sweating. - yes

n) exhaustion. - no

o) flushed or red skin. - no

p) muscle cramps, spasm, and pain. - NO

q) headache or mild light-headedness. - NO

r) nausea. – no

MY SYMPTOMS WAS - hard to breath, weakness, no temperature

5. Did you seek a medical help and if yes, what diagnosis were given? - yes, Conclusion based on the results of Computed Tomography of the chest organs: CT picture is typical for COVID-19 associated bilateral pneumonia with the defeat of at least 50% of the pulmonary parenchyma. CT2 (moderate).

6. Did you take a laboratory test? - NO

7. When did you receive Allostatin injection? - once, after receipt of the Conclusion

8. Please describe what happened 1 hours after you took the first Allostatin injection? - I just felt better

9. How many Allostatin injections did you receive and in what time period? - 1 (ONE TIME)

10. Besides Allostatine, did you receive any other medication for the treatment? - NO

11. How long did it take for the symptoms of the viral infection to disappear? - Relief came after first injection in 1-2 hours. This evening I felt better after injections. I started breathe normally.

12. Were you tested for the existence of the virus after the treatment? If yes, when was this done? - yes. After one day while I made injections specialists come to my home and gave the COVID test. But results were negative.

13. How happy are you with the use of Allostatine in your treatment? - full recovery

14. Will you recommend Allostatine in treatment of viral infections hyperthermia to others? -

definitely yes

15. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. - no

16. Did you have any surgery in the past 3 years? If yes, please specify - no

CASE 14:

NAME OF THE PATIENT OR INITIALS: ENK

GENDER: female

AGE: 48

NAME OF VIRAL INFECTION: COVID19 LIKE

1. When was the first time you started experiencing symptoms of the viral infection? 13.05.2020

2. Did you experience the following symptoms?

a) Most common symptoms: Fever, dry cough, tiredness? – Tiredness

b) Less common symptoms: Aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, a rash on skin, or discoloration of fingers or toes

c) Serious symptoms:

Difficulty breathing or shortness of breath, chest pain or pressure, loss of speech or movement/ No

3. Did you seek a medical help?/No.

4. Did you take a laboratory test for the viral infection? If yes, what is the name of the viral infection? No.

5. When did you receive Allostatin injection? -On the 1st day, before injection temperature was about 37.5°C.

6. Please describe what happened 1 hours after you took the first Allostatin injection? Temperature dropped to 36.5°C.

7. How many Allostatin injections did you receive and in what time period?/

2 injection

8. Besides Allostatine, did you receive any other medication for the treatment? No.

9. How long did it take for the symptoms of the viral infection to disappear? In 2 days

10. Were you tested for the existence of the virus after the treatment? If yes, when was this done? /No. There were contacts with the coronavirus in the family

11. How happy are you with the use of Allostatine in your treatment?/ I was pleased and happy.

12. Will you recommend Allostatine in treatment of viral infections to others? Absolutely yes.

13. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. /No

14. Did you have any surgery in the past 3 years? If yes, please specify/No

CASE 15:

NAME OF THE PATIENT OR INITIALS: OVV

GENDER: male

AGE: 17

NAME OF VIRAL INFECTION: COVID19 LIKE

1. When was the first time you started experiencing symptoms of the viral infection? -02.02.2020

2. Did you experience the following symptoms?

a) Most common symptoms: Fever, dry cough, tiredness? –Yes. All this symptoms.

b) Less common symptoms: Aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, a rash on skin, or discoloration of fingers or toes

c) Serious symptoms:

Difficulty breathing or shortness of breath, chest pain or pressure, loss of speech or movement/ No

3. Did you seek a medical help?/ Yes.

4. Did you take a laboratory test for the viral infection? If yes, what is the name of the viral infection?/ No.

5. When did you receive Allostatin injection? - On the fifth day, but before injection

temperature was about 38.5°C.

6. Please describe what happened 1 hours after you took the first Allostatin injection? Temperature dropped to 37°C and headache decreased.

7. How many Allostatin injections did you receive and in what time period? /

Only 1 injection

8. Besides Allostatine, did you receive any other medication for the treatment?/ No.

9. How long did it take for the symptoms of the viral infection to disappear? Half a day (after I slept a night)

10. Were you tested for the existence of the virus after the treatment? If yes, when was this done? /No.

11. How happy are you with the use of Allostatine in your treatment? -I was pleased and excited.

12. Will you recommend Allostatine in treatment of viral infections to others? Absolutely yes.

13. Do you suffer from any serious diseases, or conditions, including chronic diseases and conditions? If yes, please specify. /No.

14. Did you have any surgery in the past 3 years? If yes, please specify /No.

The two tables below is the conclusion of the information of patients above.

Table 6 demonstrates the reduction of temperature after administration of Allostatine regardless of the condition:

	After 1 hour	After 4 hours	After 8 hours
Less or equal to 36.5 ℃	20%	66%	100%
Improvement in Symptoms	20%	100%	

Table 7 presents the recovery time of the patients treated with Allostatine based on the conditions:

	Common Flu	Pneumonia	COVID19
No of patients	10	2	3
Dosage	1 injection	3 injections	3 injections
Gap between	-	1 day	1 day

injections			
Full Recovery from all symptom's (longest time)	8 hours	3 days	2 days