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(54) **TREATMENT OF DISEASES CAUSED BY LJUNGAN VIRUS BY USING PLECONARIL**

BEHANDLUNG VON DURCH DAS LJUNGAN-VIRUS AUSGELÖSTEN ERKRANKUNGEN DURCH VERWENDUNG VON PLECONARIL

METHODE DE TRAITEMENT A L'AIDE DE PLECONARIL DE MALADIES INDUITES PAR LE VIRUS LJUNGAN

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Description

[0001] The invention relates to the treatment of diseases caused by viral infection. The disease may be caused by viral infection in most tissues or cell types. For example, the disease may be in muscle tissues, neural cells, or endocrine glands caused by a Ljungan virus infection. The invention also relates to the use of pleconaril or a derivative thereof effective against a Ljungan virus for the preparation of a medicament for the treatment of a disease. The disease may be caused by viral infection in most tissues or cell types. For example, the disease may be in muscle tissues, neural cells, or endocrine glands caused by a Ljungan virus infection.

BACKGROUND

[0002] Rodents are well-known reservoirs and vectors for viruses causing disease in humans. Puumala virus causing Nephropathia Epidemica (Myhrman, Nordisk Medicinsk Tidskrift, 7, 739-794, 1934; and Niklasson et al., Lancet, 1, 1012-3, 1984) is one example of an important human pathogen carried by bank voles. It has been demonstrated that the incidence rate of human Nephropathia Epidemica correlates with the vole population density during the previous year (Niklasson et al., Am. J. Trop. Med. Hyg., 53, 134-40, 1995). More recently, statistical evidence suggests that type 1 diabetes in humans also tracks the 3- to 4-year population density cycles of the bank vole with a similar time lag (Niklasson et al., Emerg. Infect. Dis., 4, 187-93, 1998). It was also observed that a high frequency of bank voles trapped in the wild and kept in the laboratory for studies of stereotypic behavior (Schoenecker et al., Appl. Anim. Behav. Sci., 68, 349-357, 2000) develop polydipsia and glucosuria at a high frequency.

[0003] Ljungan virus, belonging to the Picornavirus family, is carried by small rodents and causes diseases in other animals, including humans. The first three isolates were disclosed in the International Patent Application WO 98/11133 and the partial sequence of each were also comprised therein. The full sequences of these three Ljungan viruses have recently been published. (Johnsson S. et al., Journal of Virology, Sep. 2002, p. 8920-8930)

LJUNGAN VIRUS DEFINITION

[0004] Ljungan virus is a virus carried by small rodents. Ljungan virus belongs to the Picornavirus family. Ljungan virus is serologically and genetically distantly related to other members of the Picornavirus family. Ljungan virus will most likely form a new genus in the Picornavirus family.

[0005] Genetically the Ljungan virus genome and the polyprotein encoded by them exhibit several exceptional features, such as the absence of a predicted maturation cleavage of VP0, a conserved sequence determinant in VP0 that is typically found in VP1 of other Picornaviruses, and a cluster of two unrelated 2A proteins. The 2A1 protein is related to the 2A protein of cardio, erbo and aphthoviruses and the 2A2 protein is related to the 2A protein of parechoviruses, kobuviruses and avian encephalomyelitis virus. (A.M. Lindberg and Susanna Johansson, Virus Research 85 (2002) 61-70).

[0006] Ljungan virus is characterized by a chronic or long lasting infection in its rodent host and reservoir.

[0007] Ljungan virus can replicate and cause disease in a very broad host spectrum of animal species as well as in humans.

[0008] Ljungan virus infects these different species of animals as well as humans and the infection does often result in a long lasting or chronic infection.

[0009] Ljungan virus replicates in a wide variety of tissue culture cells giving a chronic infection with discrete CPE (cytopathogenic effect) and low viral output (in the order of 1000 - 100 000 viral particles per ml supernatant).

[0010] Data generated by virus cultivation under laboratory conditions show that Ljungan virus grows/replicates in a number of cell lines that originate from different tissues and different species, e.g. Vero monkey kidney; Vero E6 monkey kidney; MA-104 monkey kidney; CV-1 monkey kidney; GMK monkey kidney; A-549 human lung; Hela human cervical tissue; BHK 21 hamster kidney; RD human muscle; and L-cells mouse skin.

[0011] In living animals and humans Ljungan virus replicates in muscle tissue including heart tissue, in neural cell including the brain, in endocrine glands including the beta cells of the pancreas, the thyroid gland, the supra renal gland.

[0012] Data generated by detection of virus by Ljungan virus specific immunohistochemistry test, thin section electron microscopy and by PCR in humans, bank voles, lemmings, laboratory mice rabbits, guinea pigs, arctic foxes, and moose show that Ljungan virus has been found in endocrine and exocrine pancreas tissue, in endothelial cells of vessels, cells in the brain (including nerve tissue), cells of the liver, cells of the placenta and the umbilical cord, muscle tissue, heart tissue, tissue of the thyroid gland. Conclusion is that Ljungan virus can grow in most cell types of the body and therefore infect all organs of the body.

[0013] *The only group of viruses that partly interferes with this definition are viruses in the cardio virus genus.*

Similarities

[0014] Cardioviruses belong to the picornavirus family.

[0015] Cardiovirus have rodents as their natural reservoir.

[0016] Cadioviruses can cause disease in a wide variety of animal species.

[0017] Cardiovirus can infect and cause disease in the same organs as Ljungan virus. *Differences*

[0018] Cardiovirus and Ljungan virus are genetically distantly related.

[0019] The double 2 A of Ljungan virus is absent in cardiovirus.

[0020] Cardiovirus is not related to Ljungan virus by serology.

[0021] Cardiovirus cause an acute disease (not long lasting or chronic) when it affects its non-rodent victims.

[0022] Cardiovirus is easy to cultivate in tissue culture without adaptation while Ljungan virus is often impossible to cultivate without blind passage in tissue culture or first passage in suckling mice and after several passages in suckling mice adaptation in tissue culture.

[0023] Cardioviruses do not infect humans (only rare case reports in the literature).

[0024] We will most likely find new variants of Ljungan virus in different continents. They will all be carried by small rodents and they will all cause the same disease syndromes in humans.

HOW TO DISCOVER/ISOLATE NEW STRAINS OF LJUNGAN VIRUS

[0025] The source for virus isolation/discovery can be selected/identified in different ways.

A. You may look for a wild rodent such as a mouse, rat or a vole with signs and symptoms similar to the diseases linked with Ljungan virus in humans (e.g. diabetes or myocarditis).

B. You may screen large numbers of wild rodents by PCR using several different primer combinations targeting the conserved region of the Ljungan virus genome.

C. You may screen a large number of wild rodents using specific antisera. Antisera are collected from patients with the disease in humans linked with Ljungan virus that are living in the same geographic area as the rodents. Ljungan virus infected rodents are identified by immunostaining (e.g. immunohistochemistry) of formalin fixed organs. A portion of the same organ that is tested by immunohistochemistry is kept without fixation in a minus 70°C freezer. The unfixed material is used for virus isolation if the immunohistochemistry turns out to be positive.

[0026] Tissue, from which virus isolation attempt will be made, is grinded and diluted in sterile saline or PBS. One-day old suckling mice are injected with 2-4 microliters of the tissue suspension intracerebrally.

[0027] When suckling mice are used for virus isolation, in general all the mice die within a week of inoculation if a virus is present. However, Ljungan virus is different in that you have to wait10 days to 3 weeks before signs of symptoms in the baby mice develop. Signs and symptoms are very discrete such as slow weight increase and altered mobility. Only 5-10% of the animals develop symptoms. This is very unusual and would in most cases result in a negative interpretation of the isolation attempt.

[0028] Only the brain tissue from suckling mice with signs and symptoms are used for passage in new one-day old suckling mice.

[0029] When passed, the brains from sick suckling mice are grinded and diluted in sterile saline or PBS. One-day old suckling mice are injected with 2-4 microliters of the tissue suspension intracerebrally.

[0030] Several such passages may be necessary before disease develops earlier (8-12 days) and in the majority of mice.

[0031] After several passages in suckling mice Ljungan virus is inoculated into tissue culture such as Vero cells for amplification and identification.

[0032] Ljungan virus must be adapted to cell culture by passages of the cells. No or very discrete cytopathogenic effect is seen. The cells (not the tissue culture fluid) are passed weekly into new tissue culture bottles at a rate of 1 to 5. After 3-6 such blind passages the cells are stained using antibodies directed to the isolate. These antisera can be made by immunising adult mice with the suckling mouse brain suspension of a suspected isolate and/or by using human serum from patients with the disease caused by Ljungan virus living in the same geographic region as the animals used as source for virus isolation.

DESCRIPTION OF THE INVENTION

[0033] The present invention is directed to a method of prophylactic and/or therapeutic treatment of a mammal for a disease that is caused by a Ljungan virus infection, comprising administration to said mammal of an antivirally effective amount of an antiviral compound effective against the Ljungan virus to eliminate or inhibit proliferation of said virus in

said mammal and at the same time prevent and/or treat said disease in said mammal.

[0034] Preferably the mammal is selected from the group consisting of humans, horses, cattle, pigs, cats, dogs and rodents such as rats and mice.

[0035] The disease caused by Ljungan virus infection may be caused by the infection of a tissue or cell type. As indicated above, it is known that Ljungan virus is capable of growth in most cell types of the body and can therefore infect all organs of the body.

[0036] In a preferred embodiment of the invention the Ljungan virus infection is in at least one of muscle tissues, neural cells and endocrine glands of the mammal, and the infection may also be in an organ, such as the liver.

[0037] In another embodiment the muscle tissue is heart tissue, the neural cells are brain cells, the endocrine glands are beta cells of pancreas, thyroid gland and/or supra renal gland.

[0038] In yet another embodiment the disease is selected from the group consisting of Myocarditis, Cardiomyopathia, Guillain Barre Syndrome, and Diabetes Mellitus, Multiple Sclerosis, Chronic Fatigue Syndrome, Myasthenia Gravis, Amyothrophic Lateral Sclerosis, Dermatomyositis, Polymyositis, Spontaneous Abortion, Intrauterine Death, Preeclampsia, Sudden Infant Death Syndrome, Bell's (facial) paralysis, Addison's disease, and Pernicious anemia.

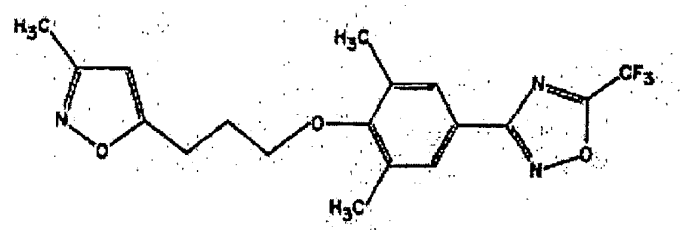
[0039] Preferably the antiviral compound is selected from compounds effective against a picornavirus.

[0040] All antiviral compounds effective against a picornavirus are at least partly also effective against Ljungan virus infection and are thus at least to some extent useful in the present invention.

[0041] At present the most preferred compound is Pleconaril or a derivative thereof.

[0042] Pleconaril: (3-[3,5-dimethyl-4-[[3-(3-methyl-5-isoxazolyl)propyl]oxy] phenyl]-5-(trifluoromethyl)-1,2,4-oxadiazole) (ViroPharma Inc.; Picovir®).

[0043] The structural formula of Pleconaril is:



[0044] Compounds comprising Pleconaril and derivatives thereof are shown in US patent 5,464,848, the European equivalent EP 0566199, and are claimed to have effect on picornaviral infections.

[0045] Other derivatives of Pleconaril claimed to have antiviral effects against picornavirus are disclosed e.g. in US patent 4, 945,164.

[0046] There are numerous antiviral compounds effective against picornaviruses disclosed in the prior art with several different modes of actions. Such compounds are for example

[0047] Compounds that inhibit the proteolytic activity of picornaviral proteases disclosed in the patent application WO 9222570;

[0048] 2-(4-pyridylaminomethyl)benzimidazole derivatives with in vitro and in vivo antipicornavirus activities disclosed in EP 0252507 B1.

[0049] Benzisoxazole derivatives for treatment of picornavirus infection disclosed in WO 0250045.

[0050] All the mentioned references are incorporated herein by reference.

[0051] Candidate compounds can be tested by use of animal models or in vitro infected cell or tissue cultures in a way known to a man skilled in the art, e.g as shown in the Examples below.

[0052] Another aspect of the invention is directed to the use of an antiviral compound effective against a Ljungan virus for the preparation of a medicament for the treatment of a disease in a mammal that is caused by a Ljungan virus infection.

[0053] Preferably the mammal is selected from the group consisting of humans, horses, cattle, pigs, cats, dogs and rodents such as rats and mice.

[0054] The disease caused by Ljungan virus infection may be caused by the infection of any tissue or cell type. As indicated above, it is known that Ljungan virus is capable of growth in most cell types of the body and can therefore infect all organs of the body.

[0055] In a preferred embodiment of the invention the Ljungan virus infection is in at least one of muscle tissues, neural cells and endocrine glands of the mammal, but the infection may also be in an organ, such as the liver.

[0056] In an other embodiment of this aspect of the invention the muscle tissue is heart tissue, the neural cells are brain cells, the endocrine glands are beta cells of pancreas, thyroid gland and/or supra renal gland.

[0057] In yet another embodiment the disease is selected from the group consisting of Myocarditis, Cardiomyopathia,

Guillain Barré Syndrome, and Diabetes Mellitus, Multiple Sclerosis, Chronic Fatigue Syndrome, Myasthenia Gravis, Amyothrophic Lateral Sclerosis, Dermatomyositis, Polymyositis, Spontaneous Abortion, Intrauterine Death, Preeclampsia, Sudden Infant Death Syndrome, Bell's (facial) paralysis, Addison's disease, and Pernicious anemia.

[0058] In a preferred embodiment the antiviral compound is selected from compounds effective against a picornavirus.

[0059] In a presently preferred embodiment the antiviral compound is Pleconaril or a derivative thereof.

MEDICAMENT

[0060] While it is possible that an antiviral compound may be administered as the neat chemical, it is preferable to present the active ingredient as a pharmaceutical formulation or as a medicament.

[0061] A suitable medicament or pharmaceutical formulation useful in the present invention comprises an antiviral compound together with one or more pharmaceutically acceptable carriers and, optionally, other therapeutic and/or prophylactic ingredients. The carrier (s) must be acceptable in the sense that it should be compatible with the other active or inactive ingredients of the formulation and not deleterious to the recipient thereof.

[0062] The antiviral compounds used in the invention may also be used in combination with other anti-viral agents or other pharmaceuticals used in the treatment of viral infections.

[0063] Representative examples of other active ingredients include immunomodulators, immunostimulants, such as various interleukins, cytokines and antibody preparations, antibiotics and anti-inflammatory agents.

[0064] Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including intramuscular, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

THERAPY

Antiviral compound

[0065] An antiviral compound effective against Ljungan virus is in many cases the only active ingredient needed for termination of Ljungan virus infection and thereby reverse the disease in muscle tissues, neural cells, or endocrine glands that is caused by a Ljungan virus infection.

Interferon

[0066] It is very likely that Ljungan virus is interferon sensitive. It can be expected that interferon can have an effect if given before the infection or very early in the course of infection. It is very likely that interferon can be used in combination with other therapeutic measures to terminate a chronic infection. The combination can be immunoglobulins, vaccination and antiviral compounds. This can be evaluated in an animal model.

Antibody

[0067] Data from picornavirus infection suggests that specific antibodies can be used in the treatment of severe and chronic infections. It can be used by it self or in combination with other therapeutic measures. Antibodies to Ljungan virus can be as polyclonal antibodies prepared from immune humans or animals or as human monoclonal antibodies or as "humanized" monoclonal antibodies originating from an animal system such as mice. The Ljungan virus antibodies can be used in combination with antiviral compounds and possibly interferon.

DETERMINATION OF PRESENCE OF LJUNGAN VIRUS

[0068] The presence of Ljungan virus can be determined using any standard procedure including immunohistochemistry using antibody molecules having affinity for Ljungan virus or by using a labeled nucleic acid probe capable of specifically hybridising to Ljungan virus nucleic acid. Alternatively the presence of Ljungan virus can be determined by detecting the presence of anti-Ljungan virus antibodies using a suitable test. Suitable techniques for determining the

presence of Ljungan virus or anti-Ljungan virus antibodies are described in the examples below. Determination of the presence of Ljungan virus RNA by Polymerase Chain Reaction (PCR) is also described in the examples below.

EXAMPLES

Tissue culture, Antiviral compound

[0069] Ljungan virus was first tested in tissue culture of Vero cells in combination with Pleconaril. 1,6 micrograms of active substance per ml of the tissue culture medium were used. This dose was used in all experiment below where it says "with Pleconaril".

[0070] 10 000 000 tissue culture infectious doses (TCID) of Ljungan virus treated with Pleconaril give full cytopathogenic effect (CPE) in 4 days while the control culture with no Pleconaril show full CPE in 3 days.

[0071] 100 TCID of Ljungan virus is fully inhibited if the cells were treated with Pleconaril. For a control picornavirus known not to be sensitive to Pleconaril no inhibition of any amount of the virus can be detected. 10 000 000 (TCID) of a picornavirus known to be sensitive to Pleconaril were inhibited (no CPE).

[0072] This means that Ljungan virus is semi-sensitive" or "semi-resistant" to Pleconaril.

Diabetic Bank voles, Antiviral compound

[0073] Bank voles with diabetes were randomised into 2 groups one treated with Pleconaril and one not receiving any treatment. Treated animals were given 100 mg Pleconaril per kg body weight per day seven days. The drug was administered orally in the drinking water. All animals were subjected to a glucose tolerance test the day before the treatment and again 15 days later. Glucose tolerance test was performed by administrating 2 grams of glucose per kg BW intraperitoneally. The blood glucose levels were measured after 60 min.

[0074] In the treated group 2 out of six animals improved and had blood glucose levels decreasing more than 200 mg per dl while this was not seen in any of the six control animals.

[0075] This shows for the first time that a chronic disease, in this case diabetes, can be reversed by oral ingestion of an antiviral compound.

Encephalitis in arctic fox

[0076] The arctic fox in Sweden is a species close to being extinct. The reason for this is unknown. Nordens Ark has a breeding program for arctic foxes with the aim to save the species. However, several animals in captivity have developed encephalitis and died. Nordens Ark has lost almost all their animals. The encephalitis is a slow progressing disease often starting with stereotypic behaviour followed by visual problem, loss of smell and loss of muscle coordination. The condition is slowly progressing over several months leading to the deaths of the animal. No spontaneous recovery has been seen in any of the arctic foxes observed.

[0077] Ljungan virus was isolated from the brain of one arctic fox suffering from encephalitis. Ljungan virus RNA was also detected by PCR in the brain and the heart of the same individual. Ljungan virus could also be detected in the brain and the heart by immunohistochemistry.

[0078] One arctic fox with severe encephalitis was treated with 50 mg/kg of Pleconaril twice daily for 7 days.

[0079] The clinical condition of the fox improved after the treatment in a way never seen in any of the untreated animals. However, after several months signs and symptoms of encephalitis came back. It could not be determined if this was because of re-infection or partial therapy failure.

[0080] This is the first time a chronic progressing central neural disease can be treated by an antiviral compound with significant and long lasting improvement.

Myocarditis, Humans

[0081] Serology. Antibodies to Ljungan virus have been measured by indirect immunofluorescence tests. Four out of 5 patients with lethal myocarditis were Ljungan virus positive and only one out of 15 matched controls.

[0082] Heart tissue from patients dying from myocarditis has been tested for presence of Ljungan virus RNA by PCR in parallel with matched controls by PCR. Four out of 6 patients with myocarditis were Ljungan virus positive and none of 10 controls were found positive.

[0083] Heart tissue from patients dying from myocarditis has been tested for the presence of Ljungan virus by immunohistochemistry (IHC) in parallel with matched controls. Six out of 9 patients with myocarditis were Ljungan virus positive and one of 10 controls was found positive.

[0084] This indicates that prophylactic and/or therapeutic treatment with an antiviral compound effective against Ljun-

gan virus of patients with myocarditis and a Ljungan virus infection will be effective against myocarditis in addition to the viral infection.

Cardiomyopathy, Humans

[0085] Five patients with severe cardiomyopathy undergoing heart transplantation have been tested for presence of Ljungan virus in their heart by IHC. They were found to be Ljungan virus positive.

[0086] This indicates that prophylactic and/or therapeutic treatment with an antiviral compound effective against Ljungan virus of patients with cardiomyopathy and a Ljungan virus infection will be effective against cardiomyopathy in addition to the viral infection.

Type 1 Diabetes, Humans

[0087] Serology. Antibodies to Ljungan virus have been measured by indirect immunofluorescence test. 19 out of 58 (33%) patients with recent onset of type 1 diabetes were Ljungan virus positive and only 2 out of 34 (6%) of the matched controls.

[0088] Serum from patients with recent onset of type 1 diabetes have been tested for presence of Ljungan virus RNA by PCR. Two out of 30 were found positive.

[0089] Muscle tissue from patients with type 1 diabetes has been tested for presence of Ljungan virus by immunohistochemistry (IHC) in parallel with matched controls. Ten out of 12 patients with diabetes were positive and one of 10 controls were found Ljungan virus positive.

[0090] It is likely that that prophylactic and/or therapeutic treatment with an antiviral compound effective against Ljungan virus of patients with type 1 diabetes and a Ljungan virus infection will be effective against type 1 diabetes in addition to the viral infection. Cf. Diabetic Bank voles

Sudden Infant Death, Humans

[0091] Heart tissue from patients dying from sudden infant deaths (SID) has been tested for presence of Ljungan virus by immunhistochemistry. Six out of 8 patients with SID were Ljungan virus positive.

[0092] This indicates that prophylactic treatment, of the newborn or perhaps the pregnant mother, with an antiviral compound effective against Ljungan virus may reduce the risk of sudden infant death.

Multipe Sclerosis, Humans

[0093] Cerebrospinal fluid from patients with multiple sclerosis (MS) has been tested for presence of Ljungan virus RNA by PCR. Three out of 10 were found positive.

[0094] Brain tissue from 2 patients with multiple sclerosis has been tested for presence of Ljungan virus by immunohistochemistry and both were found positive.

[0095] This indicates that prophylactic and/or therapeutic treatment with an antiviral compound effective against Ljungan virus of patients with MS and a Ljungan virus infection will be effective against MS in addition to the viral infection.

Claims

1. Use of pleconaril or a derivative thereof effective against a Ljungan virus for the preparation of a medicament for the treatment of a disease in a mammal that is caused by a Ljungan virus infection.

2. Use according to claim 1, wherein the mammal is selected from the group consisting of humans, horses, cattle, pigs, cats, dogs and rodents.

3. Use according to claim 1, wherein the Ljungan virus infection is in at least one of muscle tissues, neural cells and endocrine glands of the mammal.

4. Use according to claim 3, wherein the muscle tissue is heart tissue, the neural cells are brain cells, the endocrine glands are beta cells of pancreas, thyroid gland and/or supra renal gland.

5. Use according to claim 4, wherein the disease is selected from the group consisting of Myocarditis, Cardiomyopathia, Guillain Barre Syndrome, and Diabetes Mellitus, Multiple Sclerosis, Chronic Fatigue Syndrome, Myasthenia Gravis,

Amyothrophic Lateral Sclerosis, Dermatomyositis, Polymyositis, Spontaneous Abortion, Intrauterine Death, Pre-eclampsia, Sudden Infant Death Syndrome, Bell's (facial) paralysis, Addison's disease, and Pernicious anemia.

6. The use according to any one of the preceding claims, wherein the medicament additionally comprises an anti-Ljungan virus antibody.

7. The use according to any one of the preceding claims, wherein the medicament additionally comprises interferon.

Patentansprüche

1. Verwendung von Pleconaril oder einem gegen ein Ljungan-Virus wirksamen Derivat davon zur Herstellung eines Medikaments zur Behandlung einer Krankheit bei einem Säuger, die von einer Ljungan-Virus-Infektion hervorgerufen wird.

2. Verwendung nach Anspruch 1, wobei der Säuger ausgewählt ist aus der Gruppe bestehend aus Menschen, Pferden, Rindern, Schweinen, Katzen, Hunden und Nagern.

3. Verwendung nach Anspruch 1, wobei die Ljungan-Virus-Infektion in wenigstens einem von Muskelgeweben, Nervenzellen und endokrinen Drüsen des Säugers vorliegt.

4. Verwendung nach Anspruch 3, wobei das Muskelgewebe Herzgewebe ist, die Nervenzellen Hirnzellen sind, und die endokrinen Drüsen Beta-Zellen des Pankreas, Schilddrüse und/oder Nebenniere sind.

5. Verwendung nach Anspruch 4, wobei die Krankheit ausgewählt ist aus der Gruppe bestehend aus Myokarditis, Kardiomyopathie, Guillain-Barre-Syndrom, und Diabetes mellitus, Multipler Sklerose, Chronischem Erschöpfungssyndrom, Myasthenia gravis, Amyotropher Lateralsklerose, Dermatomyositis, Polymyositis, Spontanabort, intrauterinem Fruchttod, Präeklampsie, plötzlichem Kindstod, Bell's (Fazialis)parese, Addison-Krankheit und perniziöser Anämie.

6. Verwendung nach einem der vorhergehenden Ansprüche, wobei das Medikament zusätzlich einen Antikörper gegen Ljungan-Virus umfasst.

7. Verwendung nach einem der vorhergehenden Ansprüche, wobei das Medikament zusätzlich Interferon umfasst.

Revendications

1. Utilisation de pleconaril ou de son dérivé efficace contre un virus Ljungan pour la préparation d'un médicament destiné au traitement d'une maladie chez un mammifère qui est provoquée par l'infection par le virus Ljungan.

2. Utilisation selon la revendication 1, dans laquelle le mammifère est choisi dans le groupe consistant en humains, chevaux, bétail, cochons, chats, chiens et rongeurs.

3. utilisation selon la revendication 1, dans laquelle l'infection par le virus Ljungan est dans au moins l'un des tissus musculaires, des cellules neurales et des glandes endocrines du mammifère.

4. Utilisation selon la revendication 3, dans laquelle le tissu musculaire est le tissu du coeur, les cellules neurales sont des cellules du cerveau, les glandes endocrines sont les cellules bêta du pancréas, de la glande thyroïde et/ou de la glande surrénale.

5. Utilisation selon la revendication 4, dans laquelle la maladie est choisie dans le groupe consistant en myocardite, cardiomyopathie, syndrome de Guillain Barré et diabète sucré, sclérose en plaques, syndrome de fatigue chronique, myasthenia gravis, sclérose latérale amyothrophe, dermatomyosite, polymyosite, avortement spontané, mort intra-utérine, pré-éclampsie, syndrome de la mort subite du nourrisson, paralysie faciale de Bell, maladie d'Addison et anémie pernicieuse.

6. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle le médicament comprend, de plus,

un anticorps du virus anti-Ljungan.

7. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle le médicament comprend, de plus, de l'interféron.

REFERENCES CITED IN THE DESCRIPTION

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