



US007572441B2

(12) **United States Patent**
Epshtein et al.

(10) **Patent No.:** **US 7,572,441 B2**
(45) **Date of Patent:** **Aug. 11, 2009**

(54) **MEDIA AND METHOD FOR TREATING
PATHOLOGICAL SYNDROME**

7,087,726 B2 * 8/2006 Chuntharapai et al. . 530/388.23
2003/0099636 A1 * 5/2003 Epshtein et al. 424/130.1
2008/0025985 A1 1/2008 Ilich et al.

(75) Inventors: **Oleg Ilich Epshtein**, B Razeni per. d. 4
RV 41, Moscow 103064 (RU); **Goldberg**
Evgeny Danilovich, Tomsk (RU);
Alexandr Mikhailovich Dygay, Tomsk
(RU)

FOREIGN PATENT DOCUMENTS

RU 98109384 A 3/2000
RU WO 01/97842 A1 * 12/2001
SU 1331508 A1 8/1987
SU 1730144 A1 4/1992
WO WO 01/97842 * 12/2001

(73) Assignee: **Oleg Ilich Epshtein**, Moscow (RU)

OTHER PUBLICATIONS

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 49 days.

International Search Report from International Application No. PCT/
RU02/00369, filed Aug. 2, 2002, mailed on Dec. 26, 2002.

(21) Appl. No.: **10/522,652**

Frimel, G., ed., "Immunological Methods," Moscow, Medicina Pub-
lishing House, 1987, pp. 9-33.

(22) PCT Filed: **Aug. 2, 2002**

Jeger, J., Ed., "Clinical Immunology and Allergology" (Russian
translation), Meditsina, Moscow, 1990, vol. 3, pp. 479-482.

(86) PCT No.: **PCT/RU02/00369**

Register of Pharmaceuticals of Russia, Encyclopedia of Pharmaceu-
ticals (in Russian), Moscow, 2000, pp. 358-359.

§ 371 (c)(1),
(2), (4) Date: **Jan. 22, 2005**

Schwabe, W., "German Homoeopathic Pharmacopoeia
(Homoeopathisches Arzneibuch)," Stuttgart, Translation of the 5th
Supplement (1991) to the 1978 edition.

(87) PCT Pub. No.: **WO2005/000350**

* cited by examiner

PCT Pub. Date: **Jan. 6, 2005**

Primary Examiner—Ilia Ouspenski

(74) *Attorney, Agent, or Firm*—Kaplan Gilman & Pergament
LLP

(65) **Prior Publication Data**

US 2006/0024307 A1 Feb. 2, 2006

(57) **ABSTRACT**

(51) **Int. Cl.**
A61K 39/395 (2006.01)
C07K 16/24 (2006.01)

A medicament based on antibodies contains an activated form
of monoclonal, polyclonal, or natural antibodies to interferon
in low or ultra-low doses prepared by multiple consecutive
dilutions and exposure to external factors, preferably in
accordance with homeopathic technology. In order to obtain
antibodies, human or heterologous interferon alpha, beta, or
gamma, including recombinant interferon, is used; a mixture
of various, mostly centimal, homeopathic dilutions being
employed. A method of treating a pathologic syndrome,
whose formation is affected by interferon, consists in the use
of activated forms of antibodies to interferon alpha, beta, or
gamma in low or ultra-low doses obtained by multiple con-
secutive dilutions and exposure to external factors.

(52) **U.S. Cl.** **424/130.1**; 424/141.1; 424/158.1;
530/387.1; 530/388.1; 530/388.23

(58) **Field of Classification Search** None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,629,286 A 5/1997 Brewitt
5,683,712 A * 11/1997 Cavazza 424/449
6,136,309 A 10/2000 Novick et al.

5 Claims, No Drawings

1

MEDIA AND METHOD FOR TREATING PATHOLOGICAL SYNDROME

FIELD OF THE INVENTION

The preset invention relates to the field of medicine and can be used for the treatment and prevention of acute and chronic infectious diseases, mostly of viral etiology, and for producing an immunomodulating effect.

BACKGROUND OF THE INVENTION

It is a well-known practice to use antibodies for the treatment of pathologic syndromes (SU 1331598 A, A 61 K 39/00, 1984; SU 1730144 A1, C 12 N 7/00, 1992).

Pharmaceutical preparations (sera, immunoglobulins) based on antibodies employed in therapeutic doses are also well known (see, for instance, Register of Pharmaceuticals in Russia, Encyclopedia of Pharmaceuticals (in Russian), Moscow, 2000, pp. 358-359).

However, the use of such preparations may be accompanied by undesired side effects caused by the injection of substantial doses of foreign proteins into the body.

A method of the treatment of a pathologic syndrome (whose development is affected by various forms of interferon) by the administration of interferon has been described (see, for instance, J. Jeger, Ed., Clinical Immunology and Allergology (Russian translation), Meditsina, Moscow, 1990, Vol. 3, pp. 479-482).

DESCRIPTION OF THE INVENTION

The present invention is directed at obtaining an efficient and safe preparation with immunotropic activity and no tolerance formation by using activated forms of antibodies.

The formulated objective is attained by making an agent containing an activated (potentised) form of monoclonal, polyclonal, or natural antibodies to interferon in low or ultra-low doses prepared by multiple consecutive dilutions and by exposure to external impact, mostly following homeopathic technology.

After the activation (potentiation) of antibodies to interferon the ultra-diluted solutions (or pharmaceutical carriers impregnated with the activated antibodies) retain their biological (pharmaceutical) activity manifested in modification of molecular-cellular and systemic effects mediated by interferon or its receptors. Unlike the action of physiologic (non-activated) forms of antibodies to interferon there is no suppression of the activity of interferon.

The antibodies are obtained with the use of human or heterologous interferon alpha, beta, or gamma, including recombinant interferon.

The agent prepared according to the present invention is a new immunotropic pharmacologic preparation possessing pronounced specific pharmacologic activity, free of side effects, retention of therapeutic action, environmental purity, and low manufacturing costs. In contrast to non-activated forms of antibodies used, among other forms, in small doses, the homeopathically activated (potentised) antibodies to interferon feature an action that does not suppress the activity of endogenous interferon; the activated antibodies act more often synergistically (unidirectionally) with interferon and enhance, among other things, the induction of various forms of endogenous interferon.

It is preferred to use mixtures of different, mostly centimal, homeopathic dilutions.

2

The method of treating a pathologic syndrome, whose formation mechanisms are affected by interferon, consists in that activated forms of ultra-low doses of antibodies to interferon alpha, beta, or gamma prepared by multiple consecutive dilutions and exposure to external impact are used.

EMBODIMENTS OF THE INVENTION

The new medicament is mainly prepared in the following manner.

Recombinant interferon gamma expressed in the *Escherichia coli* culture is purified by electrophoresis to at least 97% of the active substance and used as an immunogen in hybridoma technology for obtaining monoclonal antibodies. The latter are affinity purified by chromatography on Protein A.

The method of preparation of monoclonal antibodies is described, for instance, in the book edited by G. Frimel, Ed., Immunological Methods, Moscow, Meditsina, 1987, pp. 9-33.

The isolated antibodies to the recombinant human interferon gamma are subjected to consecutive multiple dilutions and to the impact of an external mechanical factor until ultra-low or low doses are obtained, for example, by the homeopathic potentisation procedure (see W. Schwabe, Homöopathisches Arzneibuch, Stuttgart, 1978). This procedure gives rise to a uniform decrease in the concentration through consecutive dilutions of 1 volumetric part of the initial matter (antibodies) in 9 volumetric parts (for decimal dilution, D) or in 99 volumetric parts (for centimal dilution, C) of a neutral solvent with multiple vertical shaking of each solution; preferably, different containers for each subsequent dilution are used. Finally, this procedure gives the required dose (potency).

The external treatment in the course of concentration reduction can also be executed by exposure to ultrasonic, electromagnetic, or other physical factors.

The resultant medicines are used mostly in the dosage forms and dilutions adopted in the homeopathic practice: as alcoholic and aqueous solutions or as tablets (granules) prepared by impregnating the carrier contained in the dosage form by the potentised solution to saturation; also, the potentised solution can be added directly to a liquid dosage form.

EXAMPLE 1

In studies of the action of antibodies to interferon on the humoral immune response we immunized mice by ram erythrocytes (thymus-dependent corpuscular antigen). After that, the mice received per os a preparation containing homeopathically potentised polyclonal sheep antibodies to murine interferon alpha (a-IFN) in a mixture of C12+C30 dilutions within a period of 5 days. On the first day of the 5-day course the mice also received single intraperitoneal injections of cyclophosphamide ($\frac{1}{2}$ of the maximal tolerable dose). Five days later an evaluation of the humoral immune response parameters showed that the administration of potentised antibodies to a-IFN favored the growth of the functional activity of antibody-forming cells in the spleen and an increase in the titres of hemagglutinins in the blood serum, which was particularly important against the background of immunosuppression. Thus, the claimed agent stimulates the humoral immune response.

EXAMPLE 2

In studies of the action of activated forms of ultra-low doses of antibodies to interferon on the manifestation of the

3

delayed-type hypersensitivity reaction (DHR) of mice we immunized the animals by subcutaneous injection of ram erythrocytes (RE); the challenging dose of RE was injected into the cushion of the rear paw at the end of a 10 days' course of peroral administration of a preparation containing homeopathically potentised monoclonal antibodies (AB) to the murine interferon beta (β -IFN) in a mixture of C12+C30+C200 dilutions in an amount of 0.2 ml.

Simultaneously, we injected saline into the contralateral paw in the same volume. The intensity of the response was assessed 24 hours later from the reaction index (RI), which was calculated individually for each animal from the formula:

$$RI(\%) = (P_o - P_c) / P_c \times 100$$

where P_o is the weight of the test paw, P_c is the weight of the control paw.

Table 1 presents the experimental data.

TABLE 1

Effect of Potentised AB to β -IFN on the Intensity of the DHR		
Indices	Test groups	
	RE	AB to β -IFN + RE
DHR RI	28.00 \pm 2.34	36.60 \pm 2.00 $P_{c1} = 0.026$

It follows that AB to β -IFN activate the function of T-effectors, which is manifested in the enhancement of the delayed-type hypersensitivity reaction in response to sensitization by ram erythrocytes.

EXAMPLE 3

In studies of the action of activated forms of ultra-low doses of antibodies to interferon on the phagocytal activity of neutrophils in the peritoneal exudate we evaluated the phagocytal activity of neutrophils 24 hours after the end of a 10 days' course of subcutaneous administration of natural antibodies (AB) to interferon gamma (γ -IFN) in a C60 homeopathic dilution in an amount of 0.1 ml.

The phagocytal activity was evaluated from the capacity of these cells to absorb daily culture of *St. aureus*, Strain 209 (the concentration of the suspension of the microorganisms was 100×10^6 /ml. We took account of the neutrophils that had absorbed the microorganisms (the phagocytal index, PI) and the average number of staphylococci absorbed by one cell (the phagocytal number, PN).

TABLE 2

Effect of AB to γ -IFN on the Phagocytal Activity of Neutrophils		
Indices	Test groups	
	RE	AB to γ -IFN
PI, %	8.80 \pm 1.36*	29.20 \pm 3.20 $P_{c1} = 0.0004$
PN	7.61 \pm 1.24	8.78 \pm 2.33

These results indicate that AB to γ -IFN stimulate phagocytosis substantially as compared with the control (RE immu-

4

nization) because of an increase in the proportion of neutrophils capable of absorbing staphylococci.

EXAMPLE 4

5 Patient K. (female), aged 62, had been suffering from repeated fits of fever accompanied by eruptions on the chest and pain along the intercostal nerves. Diagnosis: 'relapsing herpes zoster'. The generally adopted therapy (antiviral agents, analgetics) did not bring stable results. As a result of everyday intake of potentised monoclonal antibodies to the human interferon gamma (C1000, 1 tablet, twice a day), the fever and pain syndrome were arrested on the third day. On the seventh day of the treatment the eruptions virtually disappeared. Recommendation: a preventive intake of the remedy, 1 tablet every other day. No relapses of herpes have been noted within a year.

EXAMPLE 5

20 Patient Sh. (male), aged 5, had been regularly examined because of relapsing infections of the upper respiratory tract (rhinolarngotracheitis lasting 10 days every 2 months). The assessment of his immune status revealed the lowering of the count of CD4 lymphocytes, neutrophils, and interferon gamma in the peripheral blood. Prescription: potentised polyclonal (immune) antibodies to the recombinant human interferon gamma in a mixture of D24+C30+C200 dilutions, 1 tablet every day. Within a period of four months the child had no relapses of acute respiratory infection; his parents say that the child became more active and regained weight. The second evaluation of the immune status 6 months after the beginning of the treatment indicated the normalization of the indices of the cellular and humoral immunity.

EXAMPLE 6

35 Patient P. (male), aged 34, complained of rhinitis, pain in the nasopharynx, and subfebrile condition. Diagnosis: acute viral respiratory infection. The intranasal administration of drops of a potentised C12 aqueous solution of monoclonal antibodies to recombinant human interferon gamma (3 times a day) normalized patient's condition within 2 days. A new examination revealed no catarrhal phenomena.

EXAMPLE 7

40 Patient S. (male), aged 32, was hospitalized in the infectious unit on the second day of the disease with the diagnosis "influenza with a grave course". Later on, the diagnosis was confirmed virologically. The condition on entry was grave, hyperthermia (up to 41.6° C.), mental confusion, heavy breathing, dry cough. Auscultation revealed vesicular breathing in the lungs. Prescription: monoclonal antibodies to the human interferon gamma in mixed C12+C30+C200 potences, 1 ml of an aqueous solution subcutaneously every 2 hours. Within 6 hours the body temperature fell to 37.4° C., the general condition became satisfactory. During subsequent 3 days the patient received the preparation twice a day, parenterally (1 ml of an aqueous solution). On the fourth day of the therapy the condition was satisfactory, the body temperature was 36.4° C.; the patient noted general weakness. The patient was discharged in a satisfactory condition on the fifth day after hospitalization.

EXAMPLE 8

65 Patient U. (male), aged 27, appealed to the urologist with complaints about unpleasant sensations, itch, pain in the ure-

5

thra, frequent micturate urges, mucosal discharge of one-month duration. A detailed inquiry also revealed pain in the ankles and muco-purulent discharge from the eyes. A visual examination detected hyperemia, edema, and adhesion of the urethral lips. Laboratory immunofluorescence studies of the urethral discharge detected *Chlamidia trachomatis*. Prescription: a mixture of polyclonal antibodies to the human interferons alpha and gamma in a C1000 homeopathic dilution, 1 tablet every day over a period of 2 weeks. On the fifth day of the treatment the patient noted a pronounced improvement of the symptoms and the lessening of the discharge from the urethra and eyes. At the end of therapy the immunofluorescent analysis of the prostatic secretion for *Chlamidia trachomatis* gave a negative result. Recommendation: administration of the preparation every other day over a period of two weeks. The second examination showed that the patient had no complaints; no signs of the frontal urethritis were found.

6

The invention claimed is:

1. A medicament for treating a disease of viral etiology comprising a homeopathically potentised form of at least one monoclonal, polyclonal, or natural antibody to gamma interferon wherein said homeopathically potentised form does not suppress the activity of the interferon.
2. The medicament of claim 1, wherein said gamma interferon is human gamma interferon.
3. The medicament of claim 1, wherein said gamma interferon is a recombinant gamma interferon.
4. The medicament of claim 1, wherein said homeopathically potentised form of monoclonal, polyclonal or natural antibody comprises at least one homeopathic dilution.
5. The medicament according to claim 4, wherein said at least one homeopathic dilution comprises one or more centesimal homeopathic dilutions.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,572,441 B2
APPLICATION NO. : 10/522652
DATED : August 11, 2009
INVENTOR(S) : Epshtein et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

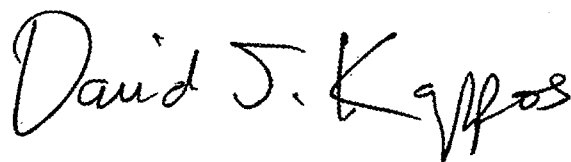
On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b)
by 328 days.

Signed and Sealed this

Seventh Day of September, 2010

A handwritten signature in black ink that reads "David J. Kappos". The signature is written in a cursive, flowing style.

David J. Kappos
Director of the United States Patent and Trademark Office