(22) Date de dépôt/Filing Date: 1997/12/30
(41) Mise à la disp. pub./Open to Public Insp.: 1998/09/06
(45) Date de délivrance/Issue Date: 2011/08/02
(30) Priorité/Priority: 1997/03/06 (JP9-51612)

(51) Cl.Int./Int.Cl. A61K 38/21 (2006.01), A61K 47/26 (2006.01), A61K 47/42 (2006.01), C07K 14/57 (2006.01), A61K 38/00 (2006.01)

(72) Inventeurs/Inventors:
UCHINO, TOMiya, JP;
YAMADA, KATSUSHIGE, JP;
OKANO, FUMIYOSHI, JP;
SATOH, MASAHiro, JP;
KAWAKAMI, ISao, JP

(73) Propriétaire/Owner:
TORAY INDUSTRIES, INC., JP

(74) Agent: SMART & BIGGAR

(54) Titre : AGENT THERAPEUTIQUE ET TRAITEMENT DE LA DERMATITE INCURABLE CHEZ LE CHIEN
(54) Title: THERAPEUTIC AGENT AND TREATMENT FOR CANINE INTRACTABLE DERMATITIS

(57) Abrégé/Abstract:
Disclosed is a therapeutic agent for treating or preventing canine intractable dermatitis, comprising an effective amount of canine interferon-γ in admixture with a carrier, excipient or diluent suitable for administering to dogs. By using this therapeutic agent, canine skin diseases which are hardly cured by a therapeutic agent of prior art may be treated effectively without adverse side effects.
ABSTRACT

Disclosed is a therapeutic agent for treating or preventing canine intractable dermatitis, comprising an effective amount of canine interferon-γ in admixture with a carrier, excipient or diluent suitable for administering to dogs. By using this therapeutic agent, canine skin diseases which are hardly cured by a therapeutic agent of prior art may be treated effectively without adverse side effects.
THERAPEUTIC AGENT AND TREATMENT FOR
CANINE INTRACTABLE DERMATITIS

Technical Field

The present invention relates to a therapeutic agent for treating or preventing canine intractable dermatitis containing an effective amount of canine interferon-γ.

Background Art

Interferon-γ (hereinafter interferon is referred to as "IFN") is mainly produced by T-cells and is known to have three main functions, i.e., antiviral activity, anticell proliferation activity, and immunoregulation (see Reference 1 hereinunder). With the recent development in gene manipulation techniques, not only the human IFN genes but also animal IFN genes, such as bovine, equine, and feline, have been isolated, and concerning canines, IFN-α, β, and γ have been reported (see References 2 and 3). Compared with human or mouse IFN-γ, however, only a little knowledge has been obtained from in vitro and in vivo studies on canine IFN-γ, and there is no report using canine IFN-γ as a therapeutic agent for a certain canine disease.

With respect to humans, IFN-γ has already been put into practical use as a therapeutic agent for malignant tumors, and concerning skin diseases, Hanifin et al. (Reference 4) and Rheinhold et al. (References 5 and 6) reported its effectiveness on treating atopic dermatitis and steroid dependent asthma. There is doubt (Reference 7), however, regarding the use of human IFN-γ for human atopic dermatitis
because of the following reasons: for effectively treating human atopic dermatitis by human IFN-γ, daily administration for consecutive six weeks or more is necessary; IFN-γ has adverse effects such as fever and headache and gives the patients a rather large amount of stress while its effects are rather small; and IFN-γ formulations are expensive.

Concerning human dermatitis, diagnosis criteria have been established (Reference 8) and a genetic background is regarded as being an important criterion. In addition, human atopic dermatitis is known to be a type I allergic reaction, in which production of an excess amount of IgE in response to foods, animal scales, insect poisons, and the like deeply participates (Reference 9). However, there have not been any systematic studies done on canine atopic dermatitis. Therefore, the evaluation criteria are unclear and the relationship between the production of excess canine IgE and atopic dermatitis is not clear.

In general, canine skin diseases include eczema, urticaria, allergic dermatitis, traumatic dermatitis, mange, otitis externa, pruritic dermatitis, and the like. Conventionally, the following agents have been used for the above diseases: antihistamines (e.g. diphenhydramines), anti-phlogistics (e.g. dibucaine hydrochloride, etc.), insecticides and bacteriocides (e.g. malathion, benzalkonium chloride, etc.), and steroids (e.g. dexamethasone, etc.).

Among therapeutic agents of the prior art used for treating canine skin diseases, however, there are disadvantages
in the use of non-steroidal agents as their effects are insufficient and their therapeutic effects are very low, and although steroidal agents have extremely strong pharmacological effects, they occasionally show adverse effects, such as enhancement of infection at diseased regions and increases in vascular-wall fragility, and by long-term administration, they may cause obesity or systematic adverse effects as a result of an effect on other organs.

In general, canine skin diseases cannot be cured as well as those of humans because of inferior housing conditions. Thus, frequently dogs are treated with repeated doses of the above therapeutic agents of the prior art. Treatment periods are thus extended, and occasionally, diseases are not completely cured even if treatment is continued for more than half a year. In some cases, treatment is extended for several years, resulting in great stress for the dog owner. Therefore, there is a demand for a therapeutic agent with an acute and sustained effect on canine intractable dermatitis that cannot completely be cured by long-term treatment using therapeutic agents of the prior art.

Accordingly, an object of the present invention is to provide an effective therapeutic agent for canine intractable dermatitis.

**Disclosure of the Invention**

Inventors of the present invention found that canine skin diseases, which could hardly be cured by the prior art, were remarkably improved by administering a canine IFN-γ
formulation. Therefore, the present invention provides a therapeutic agent for treating or preventing canine intractable dermatitis which comprises an effective amount of canine IFN-γ in admixture with a carrier, excipient or diluent suitable for administering to dogs.

One aspect of the invention relates to a therapeutic agent for treating or preventing canine dermatitis selected from the group consisting of allergic dermatitis, pemphigus, hypertrophic dermatitis, mycodermatitis, intractable drug eruption, acanthosis, chronic dermatosis and ulcerative dermatosis, comprising an effective amount of canine interferon-γ in admixture with a carrier, excipient or diluent.

Another aspect of the invention relates to a kit comprising the therapeutic agent as set forth herein and instructions which states that the therapeutic agent is used for treating or preventing canine dermatitis selected from the group consisting of allergic dermatitis, pemphigus, hypertrophic dermatitis, mycodermatitis, intractable drug eruption, acanthosis, chronic dermatosis and ulcerative dermatosis.

**Best Mode for Carrying Out the Invention**

For example, canine IFN-γ used according to the present invention is a polypeptide having an amino acid sequence shown by SEQ ID NO. from 1 to 6, however, the therapeutic agent of the present invention may employ a polypeptide which is not exactly the same as that of SEQ ID NOS. 1 to 6 as far as the polypeptide is within the spirit of the present invention. For example, even if the amino acid sequence has the replacement, insertion, or deletion of
one or more amino acid residues, the polypeptide is included in the present invention as long as it shows biological activity of the original IFN-γ as is shown in Reference 1. This is because in such a case, the polypeptide is regarded as canine IFN-γ having essentially the same effects as those having the amino acid sequence shown by SEQ ID NOS. 1 to 6.

Among the polypeptides having the amino acid sequences shown by SEQ ID NOS. 1 to 6, those of SEQ ID NOS. 2 to 6 are new.

Although canine IFN-γ may be produced by an isolation and purification process from natural biomaterials, by chemical synthesis, or by gene-recombinant techniques, the use of canine IFN-γ produced by gene-recombinant techniques is preferable from an economical point of view. The method for producing canine IFN-γ by gene recombinant techniques is not particularly limited. For example, canine IFN-γ can be produced by using host
cells or host animals into which a gene, coding for the whole or part of the amino acid sequence of canine IFN-γ shown in SEQ ID NO. from 1 to 6, has been transduced by an already established conventional method. For example, after proliferating Escherichia coli, into which cDNA of the whole or part of the base sequence of canine IFN-γ shown in SEQ ID NO. from 1 to 6 has been transduced, canine IFN-γ can be obtained from the bacterial cells or supernatants of the bacterial cultures by isolation and purification.

Furthermore, after infecting cultured insect cell line such as Spodoptera frugiperda cells and Bombyx mori cells or silkworms with Baculovirus, into which cDNA of the whole or part of the base sequence of canine IFN-γ shown in SEQ ID NO. from 1 to 6 has been transduced, canine IFN-γ can be obtained from the cultured cells, supernatants of cell cultures, or hemolymph of silk worms by isolation and purification. In the above cases, the base sequence of canine IFN-γ is not limited to that of SEQ ID NO. from 1 to 6, as long as it is translated into the amino acid sequence of SEQ ID NO. from 1 to 6. In addition, canine IFN-γ having similar effects to those of SEQ ID NO. from 1 to 6 can be produced by using cDNA having a base sequence coding for a polypeptide which is included in the spirit of the present invention, even if the amino
acid sequence has the replacement, insertion, or deletion of one or more amino acid residues.

The method for isolating and purifying canine IFN-γ produced by gene-recombinant techniques is not particularly limited, and conventional protein purification methods can be employed. For example, with the antiviral activity of canine IFN-γ as an index, canine IFN-γ can be purified and isolated by combining the following methods for desalting or concentration: chromatography employing silica gel carriers, ion exchange carriers, gel filtration carriers, chelate carriers, pigment ligand carriers, or the like; ultrafiltration; gel filtration; dialysis; salting out; and the like. In the above procedure, the antiviral activity of canine IFN-γ can be measured according to the CPE method of reference 10 using vesicular stomatitis virus (VSV) as the virus and canine MDCK (ATCC CCL-34) as the sensitive cells.

In the present invention, canine intractable dermatitis is defined as a group of skin diseases which are not remarkably improved by treatment with therapeutic agents of the prior art for canine skin diseases for at least more than half a year, or which recur after the symptoms had once been reduced; examples of the therapeutic agents of the prior art for treating canine skin disease are as follows: exodermatic bacteriocidic disinfectants, antihistamines, steroid hormones, analgesics, antipruritics, astringents, anti-inflammatory agents, and agents for parasitic skin
diseases. Frequently, canine intractable dermatitis is not remarkably improved by steroid hormones, or even if the symptoms are reduced, they recur soon after discontinuing the administration. Canine intractable dermatitis includes allergic dermatitis, pemphigus, hypertrophic dermatitis, mycodermatitis, atopic dermatitis, intractable drug eruption, and the like.

In addition to canine IFN-γ, a therapeutic agent for canine intractable dermatitis used in the present invention may optionally contain other components. Components added to the agent are mainly determined depending on the route of administration. When the agent is used as a solid, for example, fillers such as lactose, binders such as carboxymethyl cellulose and gelatin, coloring agents, and coating agents may be employed; such an agent that is in a solid form may be suitable for oral administration. In addition, the agent can be a formulation which is applied externally to the lesions, such as a cream, a lotion, a latex, and the like, by adding carriers or excipients, such as white petrolatum, cellulose derivatives, surfactants, polyethylene glycol, silicone, or olive oil. When the agent is administered as a liquid, it may contain generally used physiologically acceptable solvents, emulsifiers, and stabilizers. Examples of solvents are water, PBS, and isotonic physiological saline; examples of emulsifiers are polyoxyethylene surfactants, fatty acid surfactants, and silicone; and examples of stabilizers are proteins, such as canine serum albumin and gelatin, polyols, such as polyethylene glycol and ethylene glycol, and
saccharides, such as sorbitol and trehalose. Although the administration route of the therapeutic agent of the present invention is not particularly limited, stronger therapeutic effects can be expected by injection. Any injection method including intravenous administration, intramuscular administration, subcutaneous administration, intraperitoneal administration, and intrapleural administration can be employed, however subcutaneous administration is preferable because its procedure is simple and a lower amount of stress is caused to the patient dogs.

Although treatment dose is appropriately determined according to the size of the individual, the route of administration, the symptoms, and the like, a dosage sufficient for reducing the symptoms of canine intractable dermatitis is generally administered. For example, administration of 0.002 to 1.0 MU/kg of canine IFN-γ per day reveals sufficient effects, and preferably, 0.005 to 0.5 MU/kg, especially preferably 0.01 to 0.4 MU/kg from the effectiveness and economical point of view. In the above, kg is the unit of the patient dog weight and U is the unit number determined by the antiviral activity of IFN-γ measured according to the CPE method of Reference 10 using vesicular stomatitis virus (VSV) as the virus and canine MDCK (ATCC CCL-34) as the sensitive cells as follows: the amount of IFN-γ that can decrease the cytopathic effect of VSV against canine MDCK (ATCC CCL-34) by 50% is defined as one unit.

In addition, the frequency of administration is also determined depending on the size of the individual, the route
of administration, the symptoms, and the like, however, it is generally thought that by administration of once or twice a week, the symptoms are remarkably reduced at the second week after the beginning of the treatment. Although it is possible to alter the frequency or number of administration while observing the treatment course, administration of twice to ten times every other day or seven days is preferable from the point of view of amount of stress to the dog owners and the therapeutic effect.

The therapeutic agent of the present invention may further contain one or more other agents of the prior art for treating canine skin diseases. Such other known agents may be, for example, antihistamines (diphenhydramines), antiphlogistics (dibucaine hydrochloride, etc.), insecticides and bacteriocides (malathion, benzalkonium chloride, etc.), steroids (dexamethasone, etc.), and the like.

As is above-mentioned in detail, the present invention provides a therapeutic agent for canine intractable dermatitis having canine IFN-γ as the active ingredient. According to the therapeutic agent of the present invention, canine skin diseases which are hardly cured by therapeutic agents of the prior art for canine dermatitis can be treated effectively without adverse effects.

For practical use, the therapeutic agent may be put in a commercial package. Such a commercial package usually contains a written matter which states that the therapeutic agent can or should be used for treating or preventing canine skin diseases.
EXAMPLES

The present invention is illustrated in more detail with reference to the following examples, though the present invention is not limited to these examples.

EXAMPLE 1  Measurement of antiviral activity of canine IFN-γ

Basically, antiviral activity of canine IFN-γ was measured according to the method described in Reference 10 using canine MDCK (ATCC CCL-34) cells and VSV. In other words, a diluted solution of a sample containing canine IFN-γ was added to the canine MDCK (ATCC CCL-34) cells, which had been cultured on a 96-well microplate at 37°C until they reached a confluent state, and then the cells were further incubated at 37°C for 20 to 24 hours to induce antiviral activity. The cells were mixed with VSV and cultured for 24 hours at 37°C, the living canine MDCK cells that adhered to the microplate were stained by crystal violet solution containing 20% formalin. The amount of crystal violet on the microplate was obtained by measuring the absorbance at 570 nm so as to evaluate the amount of canine IFN-γ at which 50% of cells were alive. The thus-obtained amount of canine IFN-γ was defined as one unit (1 U) of antiviral activity.

EXAMPLE 2  Canine IFN-γ production by Escherichia coli having DNA coding for canine IFN-γ

In accordance with a conventional method, cDNA of canine IFN-γ shown by SEQ ID NO. 5 was inserted in pET8c, which is a manifestation vector of Escherichia coli, and then
**Escherichia coli** HBl01 were transformed by a conventional method. The thus-obtained transformants were inoculated into an LB medium containing 100 \( \mu g/ml \) of ampicillin. The transformants were cultured at 37°C until the OD\(_{600}\) reached approximately 0.7, were mixed with isopropyl-\( \beta \)-D-thiogalactopyranoside (IPTG) to make a final concentration of 0.5 nM, and then were cultured for further 1.5 hours. The thus-obtained 11 L of culture medium was centrifuged at 12,000 rpm for 5 min. to separate the supernatant, the residue was suspended in 60 ml of 10 mM Tris-Cl (pH 7.5), and bacterial cells were completely disrupted by sonication on ice. The resultant was centrifuged at 20,000 rpm for 30 min. and the supernatant was recovered to obtain 54 ml of a soluble protein fraction. This fraction had not less than \( 10^6 \) U/ml of antiviral activity.

**EXAMPLE 3** Canine IFN-\( \gamma \) production by **Bombyx mori** cells or silk worms both having DNA coding for canine IFN-\( \gamma \)

In accordance with a conventional method, cDNA of canine IFN-\( \gamma \) shown by SEQ ID NO. 1 was transduced into a vector pBM030 (Reference 11) to obtain a recombinant plasmid pBM\( \gamma \). Recombinant Baculoviruses were prepared in accordance with the method of Reference 11. In other words, both DNA of **Bombyx mori** nuclear polyhedrosis virus BmNPV T3 strain (Reference 11) and DNA of the recombinant plasmid pBM\( \gamma \) were used to be co-transfected into **Bombyx mori** cells, Bm-N cells by
a calcium phosphate method, and then recombinant Baculoviruses rBNVγ having DNA coding for canine IFN-γ was cloned by limiting dilution method with the following fact as an index: microscopically, when viral infection was observed and when polyhedrine particles were not being formed. Each 0.5 ml of the thus-obtained recombinant virus solution was added to approximately 3 x 10^6 Bm-N cells cultured in a TC-100 medium containing 10% FBS in a 25 cm^2 tissue culture flask. After 30 min., the medium was replaced with 5 ml of fresh TC-100 medium containing 10% FBS and cultured at 27°C for 3 days. The centrifuged supernatant of the medium was collected and revealed to have an antiviral activity of 10^4 U/ml.

Silk worms in the second day of their fifth instar were injected with 50 µl/worm of the liquid of the recombinant Baculovirus rBNVγ having DNA coding for canine IFN-γ, fed a commercially available artificial feed (Kanebo Silk Elegance Co.) at 25°C for 4 days, then the abdomen of ten of these silk worms was cut open to collect their hemolymph into an Eppendorf tube cooled on ice, the resulting hemolymph was centrifuged, and the thus-obtained supernatant was sterilized by filtration using a 0.22 µm filter, resulting in a measured antiviral activity of 10^7 U/ml.

EXAMPLE 4 Preparation of canine IFN-γ

A 20 mM phosphate buffer (pH 7.0) was used to obtain a two-fold dilution of 50 ml of the soluble protein fraction obtained in EXAMPLE 2, and then it was added to a column
packed with 20 ml of silica gel which was equilibrated with the same buffer; the column was washed with a sufficient amount of 20 mM phosphate buffer (pH 7.0). The absorbed components were eluted with 20 mM phosphate buffer (pH 7.0) containing 3 M ammonium chloride and 5% polyethylene glycol to collect a 45 ml eluate. The thus-obtained eluate contained approximately 30 mg of protein and the yield of protein was approximately 30%. After dialyzing 40 ml of the eluate twice with a 10-times volume of 20 mM phosphate buffer (pH 7.0), the resultant was added to a column packed with 10 ml of SP Sepharose™ FF and the column was washed with 100 ml of 20 mM phosphate buffer (pH 7.0). The absorbed components were eluted by a NaCl concentration gradient to collect eluted fractions containing canine IFN-γ. The thus-obtained eluate fraction contained approximately 15 mg of protein and the purity of the canine IFN-γ was approximately 30%. The eluate was further applied to re-chromatography according to a similar method, and the thus-obtained eluate was desalted by a conventional method using a gel filtration column packed with 80 ml of Sephadex™ G-25 to obtain 10 ml of a purified canine IFN-γ fraction. From analysis using SDS-PAGE, it was revealed that this fraction contained 5 mg of protein and the purity of the canine IFN-γ was not less than 80%.

About 2 mg of canine IFN-γ having more than 85% purity was obtained from 100 ml of silk worm hemolymph

* Trade-mark
obtained in Example 3, in which recombinant Baculoviruses were inactivated.

EXAMPLE 5 Production of a canine IFN-γ formulation

A physiological saline for injection, low-molecular gelatin for injection (Nitta Gelatin Inc.), and sorbitol were added to the purified canine IFN-γ solution obtained in EXAMPLE 4 to make a final gelatin concentration of 0.5% and a final sorbitol concentration of 30%. The resultant was then treated with POSIDYNE® (Poll Filtron Co.) to remove pyrogens, and 1 ml of filtrate was each added to glass vials sterilized by dry heat at 250°C for 2 hours. A canine IFN-γ formulation, with each vial containing 0.1 MU to 2.5 MU of canine IFN-γ, was then obtained by lyophilizing aseptically. This canine IFN-γ formulation was stable in the dark at room temperature and highly soluble in water or physiological saline.

EXAMPLE 6 Treatment of canine intractable dermatitis by canine IFN-γ

Dogs that had been treated for 0.5 to 7 years without showing a

* Trade-mark

14
remarkable reduction in symptoms of skin diseases by therapeutic agents of the prior art or with repeated recurrences were employed for this study. The subjects of this study included those that had the complication of mycosis supposedly due to adverse effects from steroid hormones. The canine IFN-γ formulation prepared in EXAMPLE 5 was dissolved in 1 ml of physiological saline for injection and administered subcutaneously to the subjects; the therapeutic effects were evaluated by observing the clinical symptoms of skin diseases and adverse effects. Table 1 shows the dose per administration and administration schedule. The severity of canine skin diseases was evaluated as follows: 6 parameters, i.e., erythema, papule, eczema, lichen, excoriation, and scale, were scored as 0 (none), 1 (weak), 2 (moderate), and 3 (severe); the total scores of the parameters were defined as the total clinical severity. The therapeutic effects were evaluated from the severity of the clinical symptoms. The therapeutic effects are shown in Table 1 concerned with the canine IFN-γ formulation prepared from Escherichia coli and in Table 3 concerned with that from silk worms.

As is apparent from Tables 1 and 3, in each of the dogs employed for this study, the clinical severity of the skin diseases was remarkably reduced, indicating that canine IFN-γ is extremely effective in the treatment of skin diseases. In addition, the symptoms of these five dogs shown in Table 1 had not been notably reduced by steroid hormone therapy, which is thought to be the most
effective among therapeutic agents of the prior art, or had recurred soon after discontinuing the administration of steroid hormones, however, the symptoms were rapidly cured by a once or twice administration of canine IFN-γ of the present invention. Furthermore, there were no clinically meaningful adverse effects observed in any the five dogs.

EXAMPLE 7  Treatment of canine intractable dermatitis by canine IFN-γ in combination with other therapeutic agents

Similarly to EXAMPLE 6, dogs that had been treated for at least half a year without showing remarkable reduction in symptoms of skin diseases by therapeutic agents of the prior art or with repeated recurrences were employed for this study. Tests and therapeutic-effect evaluation were carried out according to similar methods described in EXAMPLE 6, except that the therapeutic agents shown in Table 2 were used in combination with the canine IFN-γ formulation prepared in EXAMPLE 5. From the results shown in Table 2, it is understood that canine IFN-γ rapidly reduces the clinical symptoms due to canine intractable dermatitis and is effective, even when it is used in combination with therapeutic agents of the prior art. In addition, there is a trend that canine IFN-γ exhibits sufficient therapeutic effects at smaller dose as compared with EXAMPLE 6 when it is used in combination with therapeutic agents of the prior art.
Furthermore, adverse effects because of the combined therapy are not particularly observed.
<table>
<thead>
<tr>
<th>Test dog No.</th>
<th>Day of administration 1)</th>
<th>Dose of dog IFN-γ (MU/kg)</th>
<th>Severity of clinical symptoms 2)</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Erythema Papule Eczema Lichen Excoriation Scale Total clinical severity</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0.400</td>
<td>3 3 2 2 1 1</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.400</td>
<td>3 1 1 0 1 1</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.400</td>
<td>1 0 1 0 1 1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.400</td>
<td>0 0 0 0 0 0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>0.400</td>
<td>0 0 0 0 0 0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>0.400</td>
<td>0 0 0 0 0 0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0.007</td>
<td>3 3 2 1 2 2</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.007</td>
<td>1 1 1 1 1 1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>0.007</td>
<td>0 0 0 0 0 0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0.003</td>
<td>3 2 2 2 1 1</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.003</td>
<td>2 2 1 1 0 0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.003</td>
<td>2 1 1 1 0 0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>0.003</td>
<td>1 1 0 0 0 0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>0.003</td>
<td>1 1 0 1 0 0</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0.008</td>
<td>3 2 3 2 2 2</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.030</td>
<td>2 2 1 2 2 1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>0.016</td>
<td>2 2 1 1 1 1</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>0.008</td>
<td>1 1 0 0 1 1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>0.004</td>
<td>1 1 0 1 0 1</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0.007</td>
<td>3 3 2 1 2 1</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.004</td>
<td>3 3 1 1 2 1</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0.004</td>
<td>1 1 1 0 1 0</td>
<td>4</td>
</tr>
</tbody>
</table>

1) Day of administration: defined such that the initial day of administration is day 0.  
2) Severity of clinical symptoms: 0 (none), 1 (weak), 2 (moderate), and 3 (severe).
### Table 2 Therapeutic effects of dog IFN-γ on dog intractable dermatitis (combination with conventional therapeutic agent(s))

<table>
<thead>
<tr>
<th>Test Dog No.</th>
<th>Day of administration 1</th>
<th>Dose of dog IFN-γ (IU/kg)</th>
<th>Erythema</th>
<th>Papule</th>
<th>Eczema</th>
<th>Lichen</th>
<th>Excoriation</th>
<th>Scale</th>
<th>Total clinical severity</th>
<th>Evaluation</th>
<th>Combined agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0</td>
<td>0.100</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>Effective</td>
<td>Predonine (4mg/dog)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.100</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.100</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>0.100</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0.040</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>Very effective</td>
<td>Predonine (4mg/dog), Lincomycin (50mg/dog)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.040</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.040</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0.007</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>12</td>
<td>Very effective</td>
<td>Predonine (2.5mg/dog)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.007</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>0.007</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>0.007</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Predonine (2.5mg/dog)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>0.004</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0.010</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>Effective</td>
<td>Predonine (4mg/dog), Lincomycin (50mg/dog)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.010</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.010</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>0.005</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>0.002</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>Predonine (2.5mg/dog)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>0.002</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>Predonine (2.5mg/dog)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0.010</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>Effective</td>
<td>Predonine (10mg/dog)</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>0.010</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>Predonine (1mg/dog)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>0.010</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>0.020</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>13</td>
<td>Effective</td>
<td>Predonine (1.25mg/dog)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.020</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>0.020</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>0.020</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>0.020</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

1) Day of administration: defined such that the initial day of administration is day 0.
2) Severity of clinical symptoms: 0 (none), 1 (weak), 2 (moderate), and 3 (severe).
### Table 3(1) Therapeutic effects of dog IFN-γ on dog intractable dermatitis (dog IFN-γ alone)

<table>
<thead>
<tr>
<th>Test dog No</th>
<th>Disease</th>
<th>Day of administration 1</th>
<th>Dose of dog IFN-γ (MU/kg)</th>
<th>Severity of clinical symptoms 2</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Erythema</td>
<td>Papule</td>
</tr>
<tr>
<td>12</td>
<td>Atopic dermatosis</td>
<td>0</td>
<td>0.030</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>0.030</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>0.030</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>0.030</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23</td>
<td>0.030</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
<td>0.030</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>Atopic dermatosis</td>
<td>0</td>
<td>0.01</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21</td>
<td>0.01</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>Atopic dermatosis</td>
<td>0</td>
<td>0.002</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>0.002</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>Atopic dermatosis</td>
<td>0</td>
<td>0.004</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>0.004</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>0.004</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>0.004</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19</td>
<td>0.004</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>Pemphigus</td>
<td>0</td>
<td>0.01</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>0.01</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

1) Day of administration: defined such that the initial day of administration is day 0.
2) Severity of clinical symptoms: 0 (none), 1 (weak), 2 (moderate), and 3 (severe).
<table>
<thead>
<tr>
<th>Test Dog No.</th>
<th>Disease</th>
<th>Day of administration</th>
<th>Dose of dog IFN-γ (MU/kg)</th>
<th>Severity of clinical symptoms 2)</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Erythema</td>
<td>Papule</td>
</tr>
<tr>
<td>17 Acanthosis</td>
<td>0</td>
<td>0.010</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.010</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.010</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>0.010</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0.010</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>0.010</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>18 Chronic dermatitis/ ulcerative dermatitis</td>
<td>0</td>
<td>0.005</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.005</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.005</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>0.005</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0.005</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>0.005</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>19 Chronic eczema</td>
<td>0</td>
<td>0.002</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>0.002</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20 Chronic eczema</td>
<td>0</td>
<td>0.002</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0.002</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>0.002</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

1) Day of administration: defined such that the initial day of administration is day 0.
2) Severity of clinical symptoms: 0 (none), 1 (weak), 2 (moderate), and 3 (severe).
References Cited

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: TORAY INDUSTRIES, INC.

(ii) TITLE OF INVENTION: THERAPEUTIC AGENT AND TREATMENT FOR CANINE INTRACTABLE DERMATITIS

(iii) NUMBER OF SEQUENCES: 12

(iv) CORRESPONDENCE ADDRESS:
    (A) ADDRESSEE: SMART & BIGGAR
    (B) STREET: P.O. BOX 2999, STATION D
    (C) CITY: OTTAWA
    (D) STATE: ONT
    (E) COUNTRY: CANADA
    (F) ZIP: K1P 5Y6

(v) COMPUTER READABLE FORM:
    (A) MEDIUM TYPE: Floppy disk
    (B) COMPUTER: IBM PC compatible
    (C) OPERATING SYSTEM: PC-DOS/MS-DOS
    (D) SOFTWARE: ASCII (text)

(vi) CURRENT APPLICATION DATA:
    (A) APPLICATION NUMBER: CA 2,219,275
    (B) FILING DATE: 30-DEC-1997
    (C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
    (A) APPLICATION NUMBER: JP 9-51612
    (B) FILING DATE: 06-MAR-1997

(viii) ATTORNEY/AGENT INFORMATION:
    (A) NAME: SMART & BIGGAR
    (B) REGISTRATION NUMBER:
    (C) REFERENCE/DOCKET NUMBER: 76199-76

(ix) TELECOMMUNICATION INFORMATION:
    (A) TELEPHONE: (613)-232-2486
    (B) TELEFAX: (613)-232-8440

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 498 base pairs
    (B) TYPE: nucleic acid
    (C) STRANDEDNESS: not relevant
    (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:
    (A) NAME/KEY: sig_peptide
    (B) LOCATION: 1..72

(ix) FEATURE:
    (A) NAME/KEY: mat_peptide
    (B) LOCATION: 73..498
(ix) FEATURE:
   (A) NAME/KEY: CDS
   (B) LOCATION: 1..498

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
ATG AAT TAT ACA AGC TAT ATC TTA GCT TTT CAG CTT TGC GTG ATT TTG
  10  -24  -20  -15  -10

TGT TCT TCT GCC TGT AAC TGT CAG GCC ATG TTT TTT AAA GAA ATA GAA
  15  48  1  5

Cys Ser Ser Gly Cys Asn Cys Gln Ala Met Phe Phe Lys Glu Ile Glu
  -5

AAA CTA AAG GAA TAT TTT AAT GCA AGT AAT CCA GAT GTA TCG GAC GGT
  20  144

Asn Leu Lys Glu Tyr Phe Asn Ala Ser Asn Pro Asp Val Ser Asp Gly
  10  20

GGG TCT CTT TTC GTA GAT ATT TTG AAG AAA TGG AGA GAG GAG AGT GAC
  25  192

Gly Ser Leu Phe Val Asp Ile Leu Lys Lys Trp Arg Glu Glu Ser Asp
  15  30  35  40

AAA ACA ATC ATT CAG AGC CAA ATT GTC TCT TTC TAC TTG AAA CTG TTT
  30  240

Lys Thr Ile Ile Gln Ser Gln Ile Val Ser Phe Tyr Leu Lys Leu Phe
  20  45  50  55

GAC AAC TTT AAA GAT AAG CAC AGC ATT CAA AGA AGC AGT GAT ACC ATC
  35  288

Asp Asn Phe Lys Asp Asn Gln Ile Ile Gln Arg Ser Met Asp Thr Ile
  15  30  60  65  70

AAG GAA GAC ATG CTT GCC AAG TTC TTA AAT AGC AGC ACC AGT AAG AGG
  40  336

Lys Glu Asp Met Leu Gly Lys Phe Leu Asn Ser Ser Thr Ser Lys Arg
  20  75  80  85

GAG GAC TTT CTT AAG CTG ATT CAA ATT CCT GTC AAC GAT CTG CAG GTC
  45  384

Glu Asp Phe Leu Lys Leu Ile Gln Ile Pro Val Asn Asp Leu Gln Val
  15  30  90  95  100

CAG CGC AAG GCG ATA AAT GAA CTC ATC AAA GTG ATG AAT GAT CTC TCA
  50  432

Gln Arg Lys Ala Ile Asn Glu Leu Ile Lys Val Met Asn Asp Leu Ser
  20  105  110  115  120

CCA AGA TCC AAC CTA AGG AAG CGG AAA AGG AGT CAG AAT CTG TTT CGA
  55  480

Pro Arg Ser Asn Leu Arg Lys Arg Lys Arg Ser Gln Asn Leu Phe Arg
  20  125  130  135

GCC CGC AGA GCA TCG AAA
  60

Gly Arg Arg Ala Ser Lys
  20  140
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 166 amino acids
   (B) TYPE: amino acid
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xii) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Met Asn Tyr Thr Ser Tyr Ile Leu Ala Phe Glu Leu Cys Val Ile Leu
  -24  -20  -15  -10

- 24 -
```

76199-76
<table>
<thead>
<tr>
<th>Cys</th>
<th>Ser</th>
<th>Ser</th>
<th>Gly</th>
<th>Cys</th>
<th>Asn</th>
<th>Cys</th>
<th>Gln</th>
<th>Ala</th>
<th>Met</th>
<th>Phe</th>
<th>Phe</th>
<th>Lys</th>
<th>Glu</th>
<th>Ile</th>
<th>Glu</th>
<th>1</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asn</td>
<td>Leu</td>
<td>Lys</td>
<td>Glu</td>
<td>Tyr</td>
<td>Phe</td>
<td>Asn</td>
<td>Ala</td>
<td>Ser</td>
<td>Asn</td>
<td>Pro</td>
<td>Asp</td>
<td>Val</td>
<td>Ser</td>
<td>Asp</td>
<td>Gly</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Gly</td>
<td>Ser</td>
<td>Leu</td>
<td>Phe</td>
<td>Val</td>
<td>Asp</td>
<td>Ile</td>
<td>Leu</td>
<td>Lys</td>
<td>Lys</td>
<td>Trp</td>
<td>Arg</td>
<td>Glu</td>
<td>Glu</td>
<td>Ser</td>
<td>Asp</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Lys</td>
<td>Thr</td>
<td>Ile</td>
<td>Ile</td>
<td>Gln</td>
<td>Ser</td>
<td>Gln</td>
<td>Ile</td>
<td>Val</td>
<td>Ser</td>
<td>Phe</td>
<td>Tyr</td>
<td>Leu</td>
<td>Lys</td>
<td>Leu</td>
<td>Phe</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Asp</td>
<td>Asn</td>
<td>Phe</td>
<td>Lys</td>
<td>Asp</td>
<td>Asn</td>
<td>Gln</td>
<td>Ile</td>
<td>Ile</td>
<td>Gln</td>
<td>Arg</td>
<td>Ser</td>
<td>Met</td>
<td>Asp</td>
<td>Thr</td>
<td>Ile</td>
<td>60</td>
</tr>
<tr>
<td>Lys</td>
<td>Glu</td>
<td>Asp</td>
<td>Met</td>
<td>Leu</td>
<td>Gly</td>
<td>Lys</td>
<td>Phe</td>
<td>Leu</td>
<td>Asn</td>
<td>Ser</td>
<td>Ser</td>
<td>Thr</td>
<td>Ser</td>
<td>Lys</td>
<td>Arg</td>
<td>75</td>
<td>80</td>
</tr>
<tr>
<td>Glu</td>
<td>Asp</td>
<td>Phe</td>
<td>Leu</td>
<td>Lys</td>
<td>Leu</td>
<td>Ile</td>
<td>Gln</td>
<td>Ile</td>
<td>Pro</td>
<td>Val</td>
<td>Asn</td>
<td>Asp</td>
<td>Leu</td>
<td>Gln</td>
<td>Val</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>Gln</td>
<td>Arg</td>
<td>Lys</td>
<td>Ala</td>
<td>Ile</td>
<td>Asn</td>
<td>Glu</td>
<td>Leu</td>
<td>Ile</td>
<td>Lys</td>
<td>Val</td>
<td>Met</td>
<td>Asn</td>
<td>Asp</td>
<td>Leu</td>
<td>Ser</td>
<td>105</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>Pro</td>
<td>Arg</td>
<td>Ser</td>
<td>Leu</td>
<td>Arg</td>
<td>Lys</td>
<td>Arg</td>
<td>Lys</td>
<td>Arg</td>
<td>Ser</td>
<td>Gln</td>
<td>Asn</td>
<td>Leu</td>
<td>Phe</td>
<td>Arg</td>
<td>125</td>
<td>130</td>
</tr>
<tr>
<td>Gly</td>
<td>Arg</td>
<td>Arg</td>
<td>Ala</td>
<td>Ser</td>
<td>Lys</td>
<td>140</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 498 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(ix) FEATURE:
(A) NAME/KEY: sig_peptide
(B) LOCATION: 1..72

(ix) FEATURE:
(A) NAME/KEY: mat_peptide
(B) LOCATION: 73..498

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..498

(x) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

ATG AAT TAT ACA AGC TAT ATC TTA GCT TTT CAG CTT TGC GTG ATT TTG
Met Asn Tyr Thr Ser Tyr Ile Leu Ala Phe Glu Leu Cys Val Ile Leu
-24
-20
-15
-10
TGT TCT TCT GGC TGT AAC TGT CAG GCC ATG TTT TTT AAA GAA ATA GAA
Cys Ser Ser Gly Cys Asn Cys Gln Ala Met Phe Phe Lys Glu Ile Glu
-5
1
5

- 25 -

76199-76
<table>
<thead>
<tr>
<th></th>
<th>Sequence</th>
<th>Length</th>
<th>Type</th>
<th>Topology</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2) INFORMATION FOR SEQ ID NO:4:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) SEQUENCE CHARACTERISTICS:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(A) LENGTH: 166 amino acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(B) TYPE: amino acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(D) TOPOLOGY: linear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ii) MOLECULE TYPE: protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met Asn Tyr Thr Ser Tyr Ile Leu Ala Phe Gln Leu Cys Val Ile Leu</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cys Ser Ser Gly Cys Asn Cys Gln Ala Met Phe Phe Lys Glu Ile Glu</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asn Leu Lys Glu Tyr Phe Asn Ala Ser Asn Pro Asp Val Ser Asp Gly</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gly Ser Leu Phe Val Asp Ile Leu Lys Trp Arg Glu Glu Ser Asp</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lys Thr Ile Ile Gln Ser Gln Ile Val Ser Phe Tyr Leu Lys Leu Phe</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asp Asn Phe Lys Asp Asn Gln Ile Ile Gln Arg Ser Met Asp Thr Ile</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 26 -

76199-76
Lys Glu Asp Met Leu Gly Lys Phe Leu Gln Ser Ser Thr Ser Lys Arg 75 80
Glu Asp Phe Leu Lys Leu Ile Gln Ile Pro Val Asn Asp Leu Gln Val 90
Gln Arg Lys Ala Ile Asn Glu Leu Ile Lys Val Met Asn Asp Leu Ser 105
Pro Arg Ser Asn Leu Arg Lys Arg Ser Gln Asn Leu Phe Arg 125 130 135
Gly Arg Arg Ala Ser Lys
140

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 498 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(ix) FEATURE:
(A) NAME/KEY: sig_peptide
(B) LOCATION: 1..72

(ix) FEATURE:
(A) NAME/KEY: mat_peptide
(B) LOCATION: 73..498

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..498

(x) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

ATG AAT TAT ACA AGC TAT ATC TTA GCT TTT CAG CTT TGC GTG ATT TTG
Met Asn Tyr Thr Ser Tyr Ile Leu Ala Phe Gln Leu Cys Val Ile Leu
-24 -15

TGT TCT TCT GGC TGT AAC TGT CAG GCC ATG TTT TTT AAA GAA ATA GAA
Cys Ser Ser Gly Cys Asn Cys Gln Ala Met Phe Phe Lys Glu Ile Glu
50

AAC CTA AAG GAA TAT TTT CAG GCA AGT AAT CCA GAT GTA TCG GAC GGT
Asn Leu Lys Glu Tyr Phe Gln Ala Ser Asn Pro Asp Val Ser Asp Gly
10

GGG TCT CTT TTC GTA GAT ATT TTG AAG AAA TGG AGA GAG GAG AGT GAC
Gly Ser Leu Phe Val Asp Ile Leu Lys Lys Trp Arg Glu Glu Ser Asp
25 30 35

AAA ACA ATC ATT CAG AGC CAA ATT GTC TCT TTC TAC TTG AAA CTG TTT
Lys Thr Ile Ile Gln Ser Gln Ile Val Ser Phe Tyr Leu Lys Leu Phe
45 50 55

GAC AAC TTT AAA GAT AAC CAG ATC ATT CAA AGG AGC ATG GAT ACC ATC
Asp Asn Phe Lys Asp Asn Gln Ile Ile Gln Arg Ser Met Asp Thr Ile
60 65 70

76199-76
AAG GAA GAC ATG CTT GGC AAG TCC TTA AGC AGC ACC AGT AAG AGG
Lys Glu Asp Met Leu Gly Lys Phe Leu Asn Ser Ser Thr Ser Lys Arg
75 80 85

GAG GAC TTC CTT AAG CTG ATT CAA ATT CCT GTC AAC GAT CTG CAG GTC
Glu Asp Phe Leu Lys Leu Ile Gln Ile Pro Val Asn Asp Leu Gln Val
90 95 100

CAG CGC AAG GCG AAT GAC CTC ATC AAA GTG ATG AAT GAT CTC TCA
Gln Arg Lys Ala Ile Asn Glu Leu Ile Lys Val Met Asn Asp Leu Ser
105 110 115 120

CCA AGA TCC AAC CTA AGG AAG CGG AAA AGG AGT CAG AAT CTG TTT CGA
Pro Arg Ser Asn Leu Arg Lys Arg Ser Gln Asn Leu Phe Arg
125 130 135

GGC CGC AGA GCA TCG AAA
Gly Arg Arg Ala Ser Lys
140

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 166 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Asn Tyr Thr Ser Tyr Ile Leu Ala Phe Glu Leu Cys Val Ile Leu
-24 -20 -15 -10

Cys Ser Ser Gly Cys Asn Cys Gln Ala Met Phe Phe Lys Glu Ile Glu
-5 1 5

Asn Leu Lys Glu Tyr Phe Glu Ala Ser Asn Pro Asp Val Ser Asp Gly
10 15 20

Gly Ser Leu Phe Val Asp Ile Leu Lys Lys Trp Arg Glu Glu Ser Asp
25 30 35 40

Lys Thr Ile Ile Glu Ser Gln Ile Val Ser Phe Tyr Leu Lys Leu Phe
45 50 55

Asp Asn Phe Lys Asp Asn Glu Ile Ile Gln Arg Ser Met Asp Thr Ile
60 65 70

Lys Glu Asp Met Leu Gly Lys Phe Leu Asn Ser Ser Thr Ser Lys Arg
75 80 85

Glu Asp Phe Leu Lys Leu Ile Gln Ile Pro Val Asn Asp Leu Gln Val
90 95 100

Gln Arg Lys Ala Ile Asn Glu Leu Ile Lys Val Met Asn Asp Leu Ser
105 110 115 120

Pro Arg Ser Asn Leu Arg Lys Arg Lys Arg Ser Gln Asn Leu Phe Arg
125 130 135

Gly Arg Arg Ala Ser Lys
140
(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 498 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(ix) FEATURE:
(A) NAME/KEY: sig_peptide
(B) LOCATION: 1..72

(ix) FEATURE:
(A) NAME/KEY: mat_peptide
(B) LOCATION: 73..498

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..498

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

```
ATG AAT TAT ACA AGC TAT ATC TTA GCT TTT CAG CTT TGC GTG ATT TTG
Met Asn Tyr Thr Ser Tyr Ile Leu Ala Phe Gln Leu Cys Val Ile Leu
-24 -20 15 -15 -10

TGT TCT TCT GGC TGT AAC TGT CAG GCC ATG TTT TTT AAA GAA ATA GAA
Cys Ser Ser Gly Cys Asn Cys Gln Ala Met Phe Phe Lys Glu Ile Glu
-5 1 5

AAC CTA AAG GAA TAT TTT CAG GCA AGT AAT CCA GAT GTA TCG GAC GGT
Asn Leu Lys Glu Tyr Phe Gln Ala Ser Asn Pro Asp Val Ser Asp Gly
40 10 15 20

GGG TCT CTT TTC GGA GAT ATT TTT AAG AAA TGG AGA GAG GAG AGT GAC
Gly Ser Leu Phe Val Asp Ile Leu Lys Lys Trp Arg Glu Glu Ser Asp
25 30 35 40

AAA ACA ATC ATT CAG AGC CAA ATT GTC TCT TTC TAC TTG AAA CTG TTT
Lys Thr Ile Ile Glu Ser Gln Ile Val Ser Tyr Leu Leu Phe
45 50 55

GAC AAC TTT AAA GAT AAC CAG ATC ATT CAA AGG AGC ATG GAT ACC ATC
Asp Asn Phe Lys Asp Asn Glu Ile Ile Gln Arg Ser Met Asp Thr Ile
50 60 65 70

AAG GAA GAC ATG CTT GGC AAG TTC TTA CAG AGC AGC ACC AGT AAG AGG
Lys Glu Asp Met Leu Gly Lys Phe Leu Gln Ser Ser Thr Ser Lys Arg
75 80 85

GAG GAC TTC CTT AAG CTG ATT CAA ATT CCT GTC AAC GAT CTG CAG GTC
Glu Asp Phe Leu Lys Leu Ile Gln Ile Pro Val Asp Leu Gln Val
90 95 100

CAG CGC AAG GCG ATA AAT GAA CTC ATC AAA GTG ATG AAT GAT CTC TCA
Gln Arg Lys Ala Ile Asn Glu Leu Ile Lys Val Met Asn Asp Leu Ser
105 110 115 120

CCA AGA TCC AAC CTA AGG AAG CGG AAA AGG AGT CAG AAT CTG TTT CGA
Pro Arg Ser Asn Leu Arg Lys Arg Lys Arg Ser Gln Asn Leu Phe Arg
125 130 135
```

- 29 -

76199-76
(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 166 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Asn Tyr Thr Ser Tyr Ile Leu Ala Phe Gln Leu Cys Val Ile Leu
-24 -20 -15 -10

20  Cys Ser Ser Gly Cys Asn Cys Gln Ala Met Phe Phe Lys Glu Ile Glu
     -5

Asn Leu Lys Glu Tyr Phe Glu Ala Ser Asn Pro Asp Val Ser Asp Gly
   10   15   20

25  Gly Ser Leu Phe Val Asp Ile Leu Lys Trp Arg Glu Glu Ser Asp
       30   35   40

30  Lys Thr Ile Ile Gln Ser Gln Ile Val Ser Phe Tyr Leu Lys Leu Phe
       45   50   55

Asp Asn Phe Lys Asp Asn Gln Ile Ile Gln Arg Ser Met Asp Thr Ile
   60   65   70

35  Lys Glu Asp Met Leu Gly Lys Phe Leu Gln Ser Ser Thr Ser Lys Arg
       75   80   85

40  Glu Asp Phe Leu Lys Leu Ile Gln Ile Pro Val Asn Asp Leu Gln Val
       90   95  100

45  Gln Arg Lys Ala Ile Asn Glu Leu Ile Lys Val Met Asn Asp Leu Ser
      105  110  115  120

50  Pro Arg Ser Asn Leu Arg Lys Arg Ser Gln Asn Leu Phe Arg
      125  130  135

Gly Arg Arg Ala Ser Lys
140

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 435 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(ix) FEATURE:
(A) NAME/KEY: mat_peptide
(B) LOCATION: 1..435
(ix) FEATURE:
   (A) NAME/KEY: CDS
   (B) LOCATION: 1..435

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

| ATG GCT CAG GCC ATG TTT TTT AAA GAA ATA GAA AAC CTA AAG GAA TAT |
| Met Ala Gln Ala Met Phe Phe Lys Glu Ile Glu Asn Leu Lys Glu Tyr |
| 1  5  10 15 |

| TTT AAT GCA AGT AAT CCA GAT GTA TCG GAC GGT GTC TCT TTC GTA |
| Phe Asn Ala Ser Asn Pro Asp Val Ser Asp Gly Gly Ser Leu Phe Val |
| 20 25 30 |

| GAT ATT TTG AAG AAA TGG AGA GAG GAG AGT GAC AAA ACA ATC ATT CAG |
| Asp Ile Leu Lys Lys Trp Arg Glu Glu Ser Asp Lys Thr Ile Ile Gln |
| 35 40 45 |

| AGC CAA ATT GTC TCT TAC TTG AAA CTG TTT GAC AAC TTT AAA GAT |
| Ser Gln Ile Val Ser Phe Tyr Leu Lys Leu Phe Asp Asn Phe Lys Asp |
| 50 55 60 |

| AAC CAG ATC ATT CTA AGG AGC ATG GAT ACC ATC AAG GAA GAC GAT CTT |
| Asn Gln Ile Ile Gln Arg Ser Met Thr Ile Lys Glu Asp Met Leu |
| 65 70 75 80 |

| GCC AAG TCT TTA AAT AGC ACC AGT AAG AGG GAG GAC TCC CTT AAG |
| Ala Lys Phe Leu Asn Ser Ser Thr Ser Lys Arg Glu Asp Phe Leu Lys |
| 85 90 95 |

| CTG ATT CAA ATT CCT GTC AAC GAT CTG CAG GTC CAG CGC AAG GCG ATA |
| Leu Ile Gln Ile Pro Val Asp Leu Gln Val Gln Arg Lys Ala Ile |
| 100 105 110 |

| AAT GAA CTC ATC AAA GTG AGT AAT GAT CTC TCA CCA AGA TCC AAC CTA |
| Asn Glu Leu Ile Lys Val Met Asn Asp Leu Ser Pro Arg Ser Asn Leu |
| 115 120 125 |

| AGG AAG CGG AAA AGG AGT CAG AAT CTG TTT CGA GSC CGC AGA GCA TCG |
| Arg Lys Arg Lys Arg Ser Gln Asn Leu Phe Arg Gly Arg Ala Ser |
| 130 135 140 |

| AAA |
| Lys |
| 145 |

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
   (A) LENGTH: 145 amino acids
   (B) TYPE: amino acid
   (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

| ATG GCT CAG GCC ATG TTT TTT AAA GAA ATA GAA AAC CTA AAG GAA TAT |
| Met Ala Gln Ala Met Phe Phe Lys Glu Ile Glu Asn Leu Lys Glu Tyr |
| 1  5  10 15 |

| TTT AAT GCA AGT AAT CCA GAT GTA TCG GAC GGT GTC TCT TTC GTA |
| Phe Asn Ala Ser Asn Pro Asp Val Ser Asp Gly Gly Ser Leu Phe Val |
| 20 25 30 |

| GAT ATT TTG AAG AAA TGG AGA GAG GAG AGT GAC AAA ACA ATC ATT CAG |
| Asp Ile Leu Lys Lys Trp Arg Glu Glu Ser Asp Lys Thr Ile Ile Gln |
| 35 40 45 |

| AGC CAA ATT GTC TCT TAC TTG AAA CTG TTT GAC AAC TTT AAA GAT |
| Ser Gln Ile Val Ser Phe Tyr Leu Lys Leu Phe Asp Asn Phe Lys Asp |
| 50 55 60 |

| AAC CAG ATC ATT CTA AGG AGC ATG GAT ACC ATC AAG GAA GAC GAT CTT |
| Asn Gln Ile Ile Gln Arg Ser Met Thr Ile Lys Glu Asp Met Leu |
| 65 70 75 80 |

| GCC AAG TCT TTA AAT AGC ACC AGT AAG AGG GAG GAC TCC CTT AAG |
| Ala Lys Phe Leu Asn Ser Ser Thr Ser Lys Arg Glu Asp Phe Leu Lys |
| 85 90 95 |

| CTG ATT CAA ATT CCT GTC AAC GAT CTG CAG GTC CAG CGC AAG GCG ATA |
| Leu Ile Gln Ile Pro Val Asp Leu Gln Val Gln Arg Lys Ala Ile |
| 100 105 110 |

| AAT GAA CTC ATC AAA GTG AGT AAT GAT CTC TCA CCA AGA TCC AAC CTA |
| Asn Glu Leu Ile Lys Val Met Asn Asp Leu Ser Pro Arg Ser Asn Leu |
| 115 120 125 |

| AGG AAG CGG AAA AGG AGT CAG AAT CTG TTT CGA GSC CGC AGA GCA TCG |
| Arg Lys Arg Lys Arg Ser Gln Asn Leu Phe Arg Gly Arg Ala Ser |
| 130 135 140 |

| AAA |
| Lys |
| 145 |

- 31 -
Asp Ile Leu Lys Lys Trp Arg Glu Glu Ser Asp Lys Thr Ile Ile Gln  
35  
Ser Glu Ile Val Ser Phe Tyr Leu Lys Leu Phe Asp Asn Phe Lys Asp  
50  
Asn Gln Ile Ile Gln Arg Ser Met Asp Thr Ile Lys Glu Asp Met Leu  
65  
10  
Ala Lys Phe Leu Asn Ser Ser Thr Ser Lys Arg Glu Asp Phe Leu Lys  
85  
90  
Leu Ile Gln Ile Pro Val Asn Leu Gln Val Gln Arg Lys Ala Ile  
105  
110  
Asn Glu Leu Ile Lys Val Met Asn Asp Leu Ser Pro Arg Ser Asn Leu  
115  
120  
125  
Arg Lys Arg Lys Arg Ser Glu Asn Leu Phe Arg Gly Arg Arg Ala Ser  
130  
135  
140  
Lys  
145  

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 432 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(ix) FEATURE:
(A) NAME/KEY: mat_peptide
(B) LOCATION: 1..432

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..432

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

ATG CAG GCC ATG TTT TTT AAA GAA ATA GAA AAG CTA AAG GAA TAT TTT  
Met Gln Ala Met Phe Phe Lys Glu Ile Glu Asn Leu Lys Glu Tyr Phe  
1  
5  
10  
15  
AAT GCA AGT AAT CCA GAT GTA TCG GAC GGT GGG TCT CTT TTC GTA GAT  
Asn Ala Ser Asn Pro Asp Val Ser Asp Gly Ser Leu Phe Val Asp  
20  
25  
30  
ATT TTG AAG AAA TGG AGA GAG GAG AGT GAC AAA ACA ATC ATT CAG AGC  
Ile Leu Lys Lys Trp Arg Glu Glu Ser Asp Lys Thr Ile Ile Gln Ser  
35  
40  
45  
CAA ATT GTC TCT TTC TAC TGG AAA CTG TTT AAC TTT AAA GAT AAC  
Gln Ile Val Ser Phe Tyr Leu Lys Leu Phe Asp Asn Phe Lys Asp Asn  
50  
55  
60  

- 32 -

76199-76
(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 144 amino acids
(B) TYPE: amino acid
(C) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xii) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Gln Ala Met Phe Phe Lys Glu Ile Glu Asn Leu Lys Glu Tyr Phe
  1      5
Asn Ala Ser Asn Pro Asp Val Ser Asp Gly Gly Ser Leu Phe Val Asp
  20    25    30
Ile Leu Lys Lys Trp Arg Glu Glu Ser Asp Lys Thr Ile Ile Gln Ser
  40    45
Gln Ile Val Ser Phe Tyr Leu Lys Leu Phe Asp Asn Phe Lys Asp Asn
  50    55    60
Gln Ile Ile Gln Arg Ser Met Asp Thr Ile Lys Glu Asp Met Leu Gly
  65    70    75    80
Lys Phe Leu Asn Ser Ser Thr Ser Lys Arg Glu Asp Phe Leu Lys Leu
  85    90    95
Ile Gln Ile Pro Val Asn Asp Leu Gln Val Gln Arg Lys Ala Ile Asn
 100  105  110
Glu Leu Ile Lys Val Met Asp Leu Ser Pro Arg Ser Asn Leu Arg
 115  120  125
Lys Arg Lys Arg Ser Gln Asn Leu Phe Arg Gly Arg Arg Ala Ser Lys
 130  135  140
CLAIMS:

1. A therapeutic agent for treating or preventing canine dermatitis selected from the group consisting of allergic dermatitis, pemphigus, hypertrophic dermatitis, mycodermatitis, intractable drug eruption, acanthosis, chronic dermatosis and ulcerative dermatosis, comprising an effective amount of canine interferon-γ in admixture with a carrier, excipient or diluent.

2. The therapeutic agent as set forth in claim 1, wherein the canine interferon-γ is produced by a gene recombinant technique.

3. The therapeutic agent as set forth in claim 2, wherein the canine interferon-γ is produced by using Escherichia coli, Bombyx mori cells, or silk worms, into each of which a gene coding for an amino acid sequence of canine interferon-γ has been transduced.

4. The therapeutic agent as set forth in any one of claims 1 to 3, which is in a form adapted for injection.

5. The therapeutic agent as set forth in any one of claims 1 to 4, which further contains predonine or lincomycin.

6. The therapeutic agent as set forth in any one of claims 1 to 5, wherein the canine interferon-γ has an amino acid sequence shown by SEQ ID NO. 4.

7. The therapeutic agent as set forth in any one of claims 1 to 5, wherein the canine interferon-γ has an amino acid sequence shown by SEQ ID NO. 6.
8. The therapeutic agent as set forth in any one of claims 1 to 7, wherein the canine dermatitis is selected from the group consisting of allergic dermatitis, pemphigus, hypertrophic dermatitis, mycodermatitis and intractable drug eruption.

9. The therapeutic agent as set forth in any one of claims 1 to 7, wherein the canine dermatitis is mycodermatitis.

10. The therapeutic agent as set forth in any one of claims 1 to 9, for treating the canine dermatitis which has been treated with a steroid hormone for at least half a year but has not been cured or which has recurred soon after discontinuing a steroid hormone therapy.

11. A kit comprising the therapeutic agent as set forth in any one of claims 1 to 7 and instructions which states that the therapeutic agent is used for treating or preventing canine dermatitis selected from the group consisting of allergic dermatitis, pemphigus, hypertrophic dermatitis, mycodermatitis, intractable drug eruption, acanthosis, chronic dermatosis and ulcerative dermatosis.

12. The kit as set forth in claim 11, wherein the instructions states that the therapeutic agent is used for treating canine dermatitis selected from the group consisting of allergic dermatitis, pemphigus, hypertrophic dermatitis, mycodermatitis and intractable drug eruption.

SMART & BIGGAR
OTTAWA, CANADA
PATENT AGENTS