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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

SUPERINDUSTRIA Y COMERCIO

Radicacion : 00034695 00000004

Folios: 2

Fecha (AMD): 2002-09-04 10:12:56

Tramite : 002 PATENTES D 1 REGISTRO/ 338 PETICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REF: Expediente No.: **00-034.695**

Patente de Invención: "METODO PARA EL TRATAMIENTO
DE LA FAMILIA DE TUMORES DE
EWING"

Titulares: INSTITUT NATIONAL DE LA SANTÉ
ET DE LA RECHERCHE MEDICALE
(INSERM)
INSTITUT CURIE

Publicada en la Gaceta de la Propiedad Industrial No. 517 del 27 de Junio del 2.002

SOLICITUD DE EXAMEN DE PATENTABILIDAD

HUMBERTO RUBIO CAMACHO, mayor de edad, domiciliado en Bogotá, D.C., identificado con la cédula de ciudadanía número 17.192.062 de Bogotá, abogado Titulado con Tarjeta Profesional No. 50.007 del Consejo Superior de la Judicatura, actuando en carácter de **APODERADO** de la Sociedades **INSTITUT NATIONAL DE LA SANTÉ ET DE LA RECHERCHE MEDICALE (INSERM), INSTITUT CURIE** domiciliadas en Paris, Francia; en forma respetuosa solicito se sirvan proceder a efectuar el examen de patentabilidad de la Invención de la referencia; de conformidad con lo establecido en el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, precisando que me encuentro dentro del término legal de seis meses contados desde la publicación de la Solicitud en la Gaceta No. 517 de 27 de Junio del 2.002.

Para que la presente petición sea viable estoy anexando Recibo No. 02 - 18,409 del 15 de Marzo de 2.002 por la suma de \$318.000.00, de acuerdo con la Resolución No. 44691 de 31 de Diciembre de 2.001

Del Señor Superintendente,


HUMBERTO RUBIO CAMACHO
C.C. 17.192.062 de Bogotá
T.P. 50.007 Consejo Superior
de la Judicatura.
COD.4134

1442-01//PI



Industria y Comercio

SUPERINTENDENCIA

PARA USO EXCLUSIVO DE
HUMBERTO RUBIO & CIA. LTDA

EXAMEN DE PATENTABILIDAD
Expediente No.: 00-034.695
Patente de Invención: "METODO
PARA EL TRATAMIENTO DE LA
FAMILIA DE TUMORES DE EWING"

NIT : 800175099-2

SUPERINDUSTRIA Y COMERCIO

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
FINIKE STOL	CONSIGNACION	BANCO POPULAR	050-00110-6	2407526	15/03/2002	5,617,000.00

***** CONCEPTO *****

CANT.	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN
		TOTAL : \$ 318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

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375
2005.04.21

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Humberto Rubio Camacho
Apoderado

Oficio N° 17076

REFERENCIA	Radicación	00 34695
	Trámite	002
	Evento	001
	Actuación	430
	Folios	007

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 34694, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 4-15
- . Ejemplos: folios 15-23
- . Capítulo reivindicatorio estudiado: folios 24-25
- . No se reivindica prioridad

Objeto de la invención

Según las reivindicaciones 1 a 25 de la presente solicitud, se refiere a un método para el tratamiento de la familia de los tumores de Ewing caracterizado porque comprende en tratar células tumorales con interferón beta

Clasificación internacional de patentes A 61 K 38/19

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Excepciones a la patentabilidad

El art. 20d de la decisión 486 establece que *“No serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*

Teniendo en cuenta lo anterior, el contenido de las reivindicaciones 1-24, que trata de “Un método para el tratamiento de...”, no es patentable

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de presentación de la presente solicitud - 15.05.00-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	EP 0783891	“Remedio para enfermedades de los huesos”	16.07.97

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la NOVEDAD

El artículo 16 de la decisión 486 establece que *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica”*

La publicación EP 0783891 se relaciona métodos y composiciones para el tratamiento de enfermedades de los huesos tales como cáncer que comprenden el interferón beta.

Comparando elemento por elemento, los métodos y las composiciones de las reivindicaciones 1-25 son iguales a los de los documentos citados y pueden afectar la novedad de la presente solicitud.

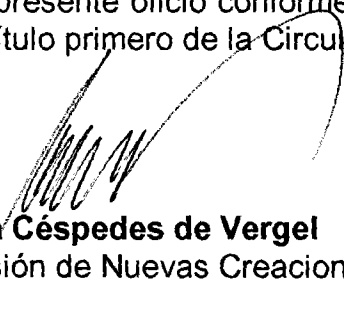
En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

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Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	EP 0783891	1-25	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001


Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 21 ABR. 2005

CONCEPTO TÉCNICO Número 0458	EXAMINADOR TÉCNICO Código 202024
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published in accordance with Art. 158(3) EPC

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(54) **REMEDY FOR BONE DISEASES**

(57) By the present invention, the relative action to promote bone formation by IFN β was proved. The action to inhibit mineralization as shown by interferon γ is not observed with interferon β . Especially, usefulness of interferon β as a drug for treating bone disorders was shown, whose effect for prevention and therapy of bone disorders was confirmed in the bone disorder model animals in terms of increase in the bone volume.

Further, the possibility of using interferon inducers as drugs for treating bone disorders was discovered.

process of completing the present invention, use of IFN α , β and γ inducers as a drug for preventing and treating bone disorders is provided by the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows inhibition actions of murine IFN β and γ against the formation of osteoclast like cells. The bone marrow cells are originated from mice of ddy strain.

Fig. 2 shows inhibition actions of murine IFN β and γ against the formation of osteoclast like cells. The bone marrow cells are originated from mice of C 57 BL/6 strain.

Fig. 3 shows actions of murine IFN β and γ on the proliferation of murine osteoblastic cells MC3T3-E1.

Fig. 4 shows the difference between the actions by murine IFN β and γ on the mineralization of murine osteoblastic cells MC3T3-E1.

Fig. 5 shows the amount of calcium extracted from the calcified foci of murine osteoblastic cells MC3T3-E1 treated with murine IFN.

Fig. 6 shows the amount of inorganic phosphorus extracted from the calcified foci of murine osteoblastic cells MC3T3-E1 treated with murine IFN.

Fig. 7 shows effect for promoting mineralization in murine osteoblastic cells MC3T3-E1 by frequent administration of murine IFN β .

Fig. 8 shows the effect for restoring bone volume of mice by administration of IFN β , which bone volume was decreased by ovariectomy.

Fig. 9 shows inhibition effect by administration of murine IFN β on the bone resorption which was increased by ovariectomy.

Fig. 10 shows change in body weights of mice during the experiment of administration of murine IFN β .

BEST MODE FOR CARRYING OUT THE INVENTION

To eliminate the ambiguity of the substance, the present inventors used highly purified murine IFN. For this purpose, large scale production by genetic engineering technique followed by purification of the product is one of good ways. Details of this method have been reported (Murine IFN α : Shaw, G.D. et al., Nucleic Acids Research, 11, 556-573, 1982; Murine IFN β : Higashi, Y. et al., J. Biol. Chem., 258, 9522, 1983; Senda, T. et al., Proc. Japan Acad., 66, Ser.B, 77, 1990; Murine IFN γ : Gray, P.W. and Goeddel, D.V., Proc. Natl. Acad. Sci., 80, 5842, 1983). Needless to say, naturally occurring murine IFN may be used without any problem if it is sufficiently purified. In the examples of the present invention, as the murine IFN α , a commercially available product (Lot. B13010, 10^6 units/ml/vial, Calbiochem-Novabiochem International, San Diego, CA) was used. As the murine IFN γ , a standard product Lot 254F3, 2.06×10^6 units/ml, provided by Genentech, San Francisco, CA was used. As the murine IFN β , a product Lot M-0034, 10^7 units/ml/vial, prepared by Toray Industries,

Inc. was used. The process for producing the murine IFN β by genetic engineering technique as well as the method for purifying the obtained product have been reported in detail (Tanaka, T. et al., J. Interferon Res., 6, 429, 1986; Matsuda, S. et al., J. Interferon Res., 6, 519, 1986). Alternatively, since highly purified murine IFNs are also commercially available from other manufacturers (e.g., Hycult biotechnology, Paesel GmbH, Cosmo Bio and Genzyme), these may also be employed.

To eliminate the ambiguity in biological evaluations, the relative activities to the cells in the bone formation system and the bone resorption system from the same species, especially from the same strain, were quantitatively dealt with, thereby overcoming the drawback in the prior art. That is, even if experimental animals of the same species are used, the response to various hormones largely differ from strain to strain, so that it is necessary to examine the relative effectiveness on the bone resorption system-bone formation system using the same strain. For example, it is known that the rates of decrease in bone volume by ovariectomy in mice which are the model of type I osteoporosis are clearly different depending on the strain (T. Hosaka, ANITEX, Vol. 5, 243, 1992). Thus, the present inventors strictly and quantitatively compared the actions on the osteoblasts responsible for the bone formation system and on the osteoclasts responsible for the bone resorption system using highly purified murine IFN, the osteoblasts and the osteoclasts being originated from the same murine strain.

As a result, IFN β very strongly inhibits formation of osteoclasts. On the other hand, IFN β does not substantially inhibit any of the proliferation, differentiation and mineralization of osteoblasts, and IFN β even promotes the mineralization depending on the conditions. The present inventors revealed these facts for the first time, thereby completing the present invention. The present inventors confirmed the strong inhibition of formation of osteoclasts by IFN γ . However, in addition, the present inventors revealed for the first time that IFN γ strongly inhibits mineralization in the bone formation system in the simple *in vitro* system including osteoblasts alone. This result well explains the above-mentioned result of osteoid formation in mineralization disorder *in vitro* by IFN γ (Mann, G.N. et al., Endocrinology, 135, 1077, 1994). Mineralization is an indispensable process to the completion of bone tissues which are hard tissues. Thus, the present inventors proved that the property of IFN β is much more preferred to that of IFN γ for the improvement of bone volume, thereby completing the present invention.

Needless to say, the present inventors know that the strong inhibition by IFN β against the formation of osteoclasts can be effectively utilized for prevention and treatment of bone disorders related to cancer, such as bone metastasis of, for example, mammary carcinoma, lung cancer, prostate cancer, thyroid gland carcinoma, renal cancer, colon cancer, cancer of digestive tract, cancer of esophagus and the like (Stoll, B.A., Bone

Metastasis: Monitoring and Treatment, Raven Press, N.Y., 1983). This is because that the formation and development of bone metastatic foci of tumors are intimately related to increase and activation of osteoclasts (Galasco, C.B.S., Skeletal Metastases, Butterworths, pp.22-51, 1986). Therefore, needless to say, IFN β may be effectively used for therapy of hypercalcemia (a mode of tumor-related bone disorders) accompanied by tumors. The fact that IFN strongly inhibits formation of osteoclasts *in vitro* and, on the other hand, it does not hinder the proliferation, differentiation and mineralization of the cells of the bone formation system or even promotes the mineralization depending on the conditions, and the fact that IFN inhibits *in vivo* the bone resorption and increase the bone volume which is once decreased in osteoporosis model animals clearly show that the relative evaluations in both the bone resorption system and the bone formation system are indispensable. No matter how strong the inhibition by a substance against the bone resorption system may be, this alone does not promise that the substance increases the bone volume. This is apparent from the experiments using IFN γ described here and from the reported results (Mann, G.N. et al., Endocrinology, 135, 1077, 1994). That is, even if the bone resorption-inhibition action by IFN is discovered, unless the action on the bone formation system is not clarified, the invention directed to the use of IFN as a drug for preventing or treating bone disorders is incomplete.

The ambiguity was first overcome by the *in vitro* test in the present invention, and the invention was completed by the proof in the *in vivo* test. Further, IFN β puts the body forward to relative bone formation, and this action is more prominently exhibited in the body in which the bone volume is abnormal (e.g., ovariectomized mice which are post menopausal osteoporosis models employed in the examples of the present invention) than in the body having the normal bone volume. That is, as described in the examples of the present invention, administration of IFN β at a dose of 10^3 units/head/time to mice which became osteoporosis by ovariectomy exhibited prevention effect against further loss in the bone volume. On the other hand, although the action (bone resorption-inhibition action) inhibiting excretion of urinary deoxypyridinoline (hereinafter referred to as "D-Pyr" for short) is exhibited also in the sham operation groups, this did not immediately bring about sharp increase in the bone volume of the mice. This may be because of the homeostasis which prevents abnormal increase in the bone volume, thereby adjusting the bone volume not to reach the state such as marble bone disease. In fact, the dry bone weight was about the same as that of the control group to which physiological saline was administered. Thus, it was proved that the effect by IFN β to increase the bone volume is more effectively exhibited in the individuals having abnormally low bone volume (due to disorders or disturbed homeostasis) than in the individuals having the normal bone volume.

These facts clearly indicate that IFN β is very effective for prevention and therapy of bone disorders which show abnormal bone volume in the whole or a part of the bone tissues, such as metabolic bone disorders, hormonal bone disorders, osteoporosis, bone fracture, alveolar bone disorders. In view of the effect discovered by the present invention, it is apparent that IFN can be used for bone disorders of animals other than human. However, in view of the species specificity of IFN, it is preferred to use the IFN originated from the same species as the animal to be treated. In recent years, the environments for raising companion animals such as dogs and cats have been very much improved. That is, highly advanced medical technologies are applied to the animals and feeds containing well-balanced nutrients are prevailing. As a result, the ages of the companion animals are now rapidly getting higher and higher. The various bone disorders including those in the dental field of the aged animals are surprisingly similar to those of human. Thus, the IFNs from various animals may be used for prevention and treatment of metabolic bone disorders, hormonal bone disorders, osteoporosis, bone fracture, alveolar bone disorders of the corresponding animals.

The IFN used in the present invention may be IFN β , or consensus type or hybrid type containing the amino acid sequence of IFN β , and may be one naturally occurring, produced by genetic engineering or by chemical synthesis.

For the production of naturally occurring IFN β , fibroblasts as well as established cell lines thereof are preferably employed. In cases of producing IFN by genetic engineering technique, as the host cells, mammalian cells such as CHO (Chinese hamster ovary) cells and mouse C127 cells; cells of insects such as silkworm and *Barathra*; cells of microorganisms such as *E. coli*, *B. subtilis* and yeasts may be employed. Further, mouse, rat, hamster, rabbit, goat, ovine, swine, bovine and the like may be employed.

The thus prepared IFN β may be purified by applying the culture supernatant of the cells, insect extract, bacterium extract or body extract to various chromatography. Any chromatography may be employed as long as it has an affinity to IFN β . For example, columns containing silica or calcium phosphate as an adsorbent; columns having heparin, dye or a hydrophobe as a ligand; metal chelating columns; ion-exchange columns; and gel permeation columns may be employed.

The present invention provides a novel method for search and evaluation of drugs for treating bone disorders. That is, in the conventional method, a test substance is added *in vitro* to osteoblastic cells or osteoclasts (osteoclast-forming cells) and the bone formation ability or bone resorption ability is evaluated. Similarly, in the conventional *in vivo* test, a test substance is administered to animals and bone volumes are measured. Although these methods are direct methods, the methods are time-consuming and costly when a number of test substances are tested. On the other

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bone volumes provides a high advantage to the industrial use of IFN β as a drug for treating bone disorders.

Further, the possibility to use interferon inducers as drugs for treating bone disorders was discovered, which provides a high advantage to the industrial use of IFN β as a drug for treating bone disorders.

Claims

1. A drug for treating bone disorders comprising as an effective component interferon β or an interferon inducer. 10
2. The drug according to claim 1, wherein said interferon β is a naturally occurring or a recombinant interferon β . 15
3. The drug according to claim 1, wherein the interferon produced by said interferon inducer is interferon α , β or γ . 20
4. The drug according to any one of claims 1 - 3, wherein said bone disorder is osteoporosis, a tumor-related disorder, metabolic disorder, periodontal disease-related disorder or bone fracture. 25
5. A pharmaceutical composition for treating bone disorders comprising interferon β or an interferon inducer and a pharmaceutically acceptable carrier or diluent. 30
6. Use of interferon β or an interferon inducer as a drug for treating bone disorders.
7. A method for treating bone disorders comprising using interferon β or an interferon inducer. 35
8. A method for searching and evaluating a substance effective for prevention or therapy of bone disorders comprising employing ability to induce interferon production as an index. 40

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