

632528

AUSTRALIA

The Patents Act 1952

CONVENTION APPLICATION FOR A PATENT

WE, ROUSSEL-UCLAF, of 35, Boulevard des Invalides, 75007, Paris, France, hereby apply for the grant of a Patent for an invention entitled: **USE OF CERTAIN GAMMA INTERFERONS IN THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS INTENDED FOR THE TREATMENT OF CANCER OF THE OVARY BY INTRA-PERITONEAL ROUTE**

which is described in the accompanying complete specification.

This application is a Convention application and is based on the Application Numbered 89-01346 for a patent or similar protection made in France on 2nd February, 1989.

Our address for service is: **CALLINAN LAWRIE**, Patent and Trade Mark Attorneys, of 278 High Street, Kew, Victoria 3101, Australia.

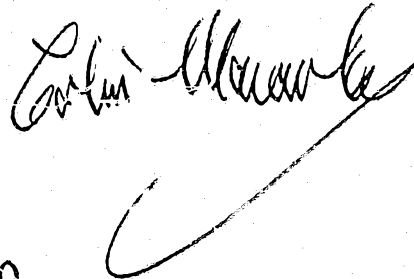
D A T E D this 1st day of February, 1990.

ROUSSEL-UCLAF

By its Patent Attorneys:

CALLINAN LAWRIE

To: The Commissioner of Patents



M 515535 -10290

COMMONWEALTH OF AUSTRALIA

The Patents Act 1952

DECLARATION IN SUPPORT

of the (Convention) Application made by: ROUSSEL-UCLAF

(hereinafter termed "the applicant ") for a patent (of addition) for an invention entitled USE OF CERTAIN GAMMA INTERFERONS IN THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS INTENDED FOR THE TREATMENT OF CANCER OF THE OVARY BY INTRA-PERITONEAL ROUTE

I/We..... HUBERT FRIEDEL..... of ..... 35, BOULEVARD DES INVALIDES, 75007, PARIS, FRANCE

do solemnly and sincerely declare as follows:

~~I am/We are the applicant~~ , ~~or~~

I am/~~We are~~ authorised by the applicant to make this declaration on its/~~their~~ behalf.

The basic application as defined by sections 141 and 142 of the Act was/were made

In FRANCE on 2ND FEBRUARY, 1989

in on

In on

by THE APPLICANT

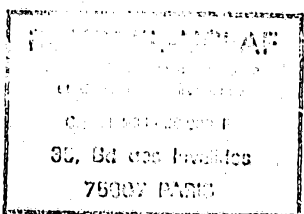
The basic application referred to in this paragraph is/~~are~~ the first application made in a Convention country in respect of the invention the subject of the application.

~~I/We~~ ~~am/are~~

MAUD BRANDELY, of 135, Boulevard Malesherbes, 75017 Paris, France; and DANIELLE LANDO, of 17-19 rue de la Plaine, 75020, Paris, France

~~or~~

~~I/are~~ the actual inventor of the invention and the facts upon which the applicant is/~~are~~ entitled to make the application are as follows:



The applicant would, if the patent were to be granted upon an application made by the said actual inventors, be entitled to have the patent assigned to it.

Declared at PARIS, FRANCE this 4th day of JANUARY 19 90

Signed: Par procuration : Hubert FRIEDEL, Chef du Département



AU9048953

(12) PATENT ABRIDGMENT (11) Document No. AU-B-48953/90  
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 632528

- (54) Title  
USE OF CERTAIN GAMMA INTERFERONS IN THE PREPARATION OF PHARMACEUTICAL  
COMPOSITIONS INTENDED FOR THE TREATMENT OF CANCER OF THE OVARY BY  
INTRA-PERITONEAL ROUTE
- International Patent Classification(s)  
(51)<sup>5</sup> A61K 037/66
- (21) Application No. : 48953/90 (22) Application Date : 01.02.90
- (30) Priority Data.
- (31) Number (32) Date (33) Country  
89 01346 02.02.89 FR FRANCE
- (43) Publication Date : 09.03.90
- (44) Publication Date of Accepted Application : 07.01.93
- (71) Applicant(s)  
ROUSSEL-UCLAF
- (72) Inventor(s)  
MAUD GRANDELY; DANIELLE LANDO
- (74) Attorney or Agent  
CALLINAN LAWRIE , Private Bag 7, KEW VIC 3101
- (57) Claim

1. A method for treating cancer of the ovary in a patient requiring such treatment which method comprises intraperitoneally administering to said patient by perfusion a recombinant polypeptide of human gamma interferon type with a specific activity at least equal to  $1 \times 10^7$  U/mg.
2. The method of claim 1, wherein said polypeptide is gamma interferon.
3. The method of claim 1 or claim 2, wherein said polypeptide is administered at a dose of 10 to  $50 \times 10^6$  U/M<sup>2</sup> per injection.

AUSTRALIA

Form 10

PATENTS ACT 1952

COMPLETE SPECIFICATION

632528

(ORIGINAL)

FOR OFFICE USE

Short Title:

Int. Cl:

Application Number:  
Lodged:

Complete Specification - Lodged:  
Accepted:  
Lapsed:  
Published:

Priority:

Related Art:

---

TO BE COMPLETED BY APPLICANT

Name of Applicant:

ROUSSEL-UCLAF

Address of Applicant:

35, Boulevard des Invalides, 75007, Paris, France

Actual inventors:

MAUD BRANDELY and DANIELLE LANDO

Address for Service:

CALLINAN LAWRIE, Patent Attorneys, 278 High Street, Kew,  
Victoria 3101, Australia.

Complete Specification for the invention entitled: **USE OF CERTAIN GAMMA INTERFERONS IN THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS INTENDED FOR THE TREATMENT OF CANCER OF THE OVARY BY INTRA-PERITONEAL ROUTE**

The following statement is a full description of this invention, including the best method of performing it known to me:-

USE OF CERTAIN GAMMA INTERFERONS IN THE PREPARATION OF  
PHARMACEUTICAL COMPOSITIONS INTENDED TO THE TREATMENT OF  
CANCER OF THE OVARY BY INTRA-PERITONEAL ROUTE

5           Use of certain gamma interferons in the preparation of pharmaceutical  
compositions intended for the treatment of cancer of the ovary by intra-peritoneal  
route.

          Gamma interferon, in addition to its anti-viral and anti-proliferative  
properties, possesses a powerful immunomodulatory activity which distinguishes  
10   it from the alpha and beta interferons. It stimulates the phagocytic cells, enabling  
in particular the lysis of certain tumour cells. The study of the tolerance of  
gamma interferon in patients at the terminal stage of cancer has not led to  
observations of remissions from these cancers (Vadhan-Raj, S et al. (1986) J. Clin.  
Oncol. 4 (2) 137-146 or Van Der Burg, M et al. (1985) J. Biol. Resp. Mod. 4 (264-  
15   272)).

          The effectiveness of gamma interferon on various fresh, human cancer cells,  
according to the so-called "human tumor cloning system" test described by  
Hamburger et al., was shown in Patent Application WO 87/05518, notably on  
ovarian cancer colonies. Following these observations, clinical studies were carried  
20   out, in particular with patients having cancer of the ovary. However, the  
effectiveness of the gamma interferon in vivo was not observed either for  
administration by intravenous route (Welandar, C.E. et al. Am. J. Clin. Oncol.  
(1988) 11 (4) 465-469), or according to a protocol using administration by intra-  
peritoneal route [(D'Acquisto, R et al. J. Clin. Oncol. (1988) 6 (689-695)]. In a



general way, it is recognized that the anti-cancerous action of gamma interferon necessitates its use in combination with other therapeutic agents [(Saito, T et al., Cancer Chemother. Pharmacol. (1989) 19 (233-239)]. Now the Applicant has just obtained results showing that, in certain conditions of use, certain gamma  
5 interferons show an activity on cancer of the ovary.

Therefore the invention relates to a method for treating cancer of the ovary in a patient requiring such treatment which method comprises intraperitoneally administering to said patient by perfusion a recombinant polypeptide of human gamma interferon type with a specific activity at least equal to  $1 \times 10^7$  U/mg.



~~effective treatment of ovarian cancer, characterized in that the~~  
~~polypeptide used is a product having a specific activity at least~~  
~~equal to  $1 \cdot 10^7$  U/mg.~~ These results are contrary to the absence of  
effectiveness reported by D'Acquisto, R, for a recombinant gamma  
5 interferon administered through perfusion by intra-peritoneal route in  
the treatment of refractory ovarian cancers. The invention describes  
the use of human gamma interferon in a treatment, the effectiveness of  
which is shown by a response rate of 58%, for an administration by  
intra-peritoneal route through perfusion, in patients with ovarian  
10 cancer having residual tumour lesions after exeresis surgery and  
chemotherapy. The specific activity of the recombinant products used  
in the invention is at least equal to  $1 \cdot 10^7$  U/mg, determined according  
to the standard test by measurement of the anti-viral activity  
relative to an NIH scale on Wish human cells infected by the vesicular  
15 stomatitis virus, and enables the administration of effective doses  
which are lower than the tolerated maximum dose expressed in mg of  
product. The use according to the invention therefore makes use of  
recombinant polypeptides having an activity of gamma interferon type  
and possessing a high degree of purity. The pharmaceutical  
20 compositions prepared according to the invention preferably contain a  
recombinant human gamma interferon, that is, obtained by the  
technology of recombinant DNA, for example as described by Gray et al.  
in Nature (1982) 295 503-508 or in Patent Application EP 77670,  
alleles or derivatives of these products as described for example in  
25 Patent Application EP 161504. Purification techniques known to an  
expert are then used, which enable the preparation of high-purity  
products. The gamma interferon is notably that obtained starting with  
a strain of E. coli and containing 143 amino acids corresponding to  
the sequence of natural gamma interferon with a supplementary N-  
30 terminal methionine.

In particular a subject of the invention is the use, character-  
ized in that the polypeptide employed, preferably gamma interferon, is  
administered at a dose of 10 to  $50 \cdot 10^6$  U/M<sup>2</sup> per injection and more  
particularly the use characterized in that the polypeptide employed,  
preferably gamma interferon, is administered at a dose of  $20 \cdot 10^6$  U/M<sup>2</sup>  
per injection.



Notably a subject of the invention is the use, characterized in that the polypeptide employed, preferably gamma interferon, is administered repeatedly for at least two non-consecutive days per week and quite especially the use characterized in that the polypeptide  
5 employed, preferably gamma interferon, is administered repeatedly for at least two months, for example for three months.

The dose administered, the frequency of the injection and the duration of the treatment vary as a function of the condition of the patient.

10 The polypeptide employed, preferably gamma interferon, is contained in a pharmaceutical composition, preferably lyophilized in dropping bottles containing from 0.2 to 1 mg of active principle and which is re-constituted with distilled water for injection. The solution obtained is immediately diluted with a solute which  
15 contributes to the stability of the active principle during perfusion, for example sodium chloride at 0.9%.

By way of example, a preparation was made for intra-peritoneal perfusion of formula:

20	gamma interferon	1 mg
	excipient	50 mg
	sterilized water	4.1 ml
	sodium chloride at 0.9%	250 ml

According to the preferred use of the invention, the polypeptide used, preferably gamma interferon, has a specific activity of  
25  $2.10^7$  U/mg, the dose is  $20.10^6$  U/M<sup>2</sup>, the frequency of the injection is twice weekly and the duration of the administration is 4 months, representing in total about  $720.10^6$  U/M<sup>2</sup> and  $36$  mg/M<sup>2</sup> of gamma interferon administered to the patient by intra-peritoneal route.

30 The following results illustrate the invention without however limiting it:

The study includes patients having residual tumour lesions the size of which varies from microscopic to more than 20 mm after treatment by chemotherapy and exeresis surgery, the effectiveness of which was evaluated at 20% of complete response after a histological  
35 examination carried out during a second operation.

The gamma interferon compositions prepared according to the

invention allow the injection of doses of  $20 \cdot 10^6$  U/M<sup>2</sup>, that is 1 mg/M<sup>2</sup> per injection, at a rate of 2 injections per week for 2 to 4 months, by intra-peritoneal route according to an ambulatory method. The compositions described above are used, containing 1 mg of active principle which is perfused in the patient for a time not exceeding 2 hours, after previous perfusion of dialysis fluid varying, according to the condition of the patient, from 1 to 2 litres and constituted by Dianeal<sup>R</sup> 137 with 1.35% of glucose from TRAVENOL.

The evaluation of the patients' responses is effected during a laparotomy by macroscopic and histological examinations with biopsies of the previously affected sites and biopsies at random.

For 12 re-evaluated patients, the following responses were obtained:

15	Patient	Size of lesions	Duration of treatment (months)	Response (*)
	201	≥ 20	4 months	S
	301	micro	3 months	P
	503	micro	4 months	CR
20	801	< 5	4 months	P
	803	< 20	3 months	PR
	1001	> 20	4 months	S
	1002	< 20	3 months	CR
	1004	< 5	2.5 months	CR
25	1101	micro	4 months	CR
	1102	micro	4 months	P
	1901	micro	4 months	PR
	1902	micro	4 months	PR

30 (\*) S = stabilization  
P = progression  
CR = complete response  
PR = partial response

35 The results show 4 complete responses and 3 partial responses, that is a response rate of 58%.

The claims defining the invention are as follows:

1. A method for treating cancer of the ovary in a patient requiring such treatment which method comprises intraperitoneally administering to said patient by perfusion a recombinant polypeptide of human gamma interferon type with a specific activity at least equal to  $1 \times 10^7$  U/mg.
2. The method of claim 1, wherein said polypeptide is gamma interferon.
3. The method of claim 1 or claim 2, wherein said polypeptide is administered at a dose of  $10$  to  $50 \times 10^6$  U/M<sup>2</sup> per injection.
4. The method of claim 1 or claim 2, wherein said polypeptide is administered at a dose of  $20 \times 10^6$  U/M<sup>2</sup> per injection.
5. The method of any one of claims 1 to 4, wherein said polypeptide is administered twice a week on non-consecutive days per week.
6. The method of any one of claims 1 to 5, wherein said polypeptide is administered repeatedly for at least two months.

DATED this 14th day of October 1992.

ROUSSEL-UCLAF

By their Patent Attorneys:

CALLINAN LAWRIE

*Michael J. Houlihan.*

