



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 48/00, 9/22	A3	(11) International Publication Number: WO 95/05452 (43) International Publication Date: 23 February 1995 (23.02.95)
(21) International Application Number: PCT/US94/09299 (22) International Filing Date: 12 August 1994 (12.08.94) (30) Priority Data: 08/105,278 12 August 1993 (12.08.93) US (60) Parent Application or Grant (63) Related by Continuation US 08/105,278 (CIP) Filed on 12 August 1993 (12.08.93) (71) Applicant (for all designated States except US): CYTOTHER- APEUTICS, INC. [US/US]; 2 Richmond Square, Provi- dence, RI 02906-5118 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BAETGE, E., Edward [US/US]; 73 Sowams Road, Barrington, RI 02806 (US). HAMMANG, Joseph, P. [US/US]; 3 Prospect Street, Bar- rington, RI 02806 (US). GENTILE, Frank, T. [US/US]; 57 Lawn Avenue, Warwick, RI 02888 (US). LINDNER, Mark, D. [US/US]; 62 Beachmont, Bristol, RI 02809 (US). WINN, Shelley, R. [US/US]; 13 Haven Street, Smithfield, RI 02917		(US). EMERICH, Dwaine, F. [US/US]; 13 Eleventh Street, Providence, RI 02906 (US). (74) Agents: HALEY, James, F., Jr. et al.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020-1104 (US). (81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD). Published With international search report. (88) Date of publication of the international search report: 30 March 1995 (30.03.95)
(54) Title: BIOCOMPATIBLE IMMUNOISOLATORY CAPSULES CONTAINING GENETICALLY ALTERED CELLS (57) Abstract This invention provides improved devices and methods for long-term, stable expression of a biologically active molecule using a biocompatible capsule containing genetically engineered cells for the effective delivery of biologically active molecules to effect or enhance a biological function within a mammalian host. The novel capsules of this invention are biocompatible and are easily retrievable. This invention specifically provides improved methods and compositions which utilize cells transfected with recombinant DNA molecules comprising DNA sequences coding for biologically active molecules operatively linked to promoters that are not subject to down regulation <i>in vivo</i> upon implantation into a mammalian host. Furthermore, the methods of this invention allow for the long-term, stable and efficacious delivery of biologically active molecules from living cells to specific sites within a given mammal. In addition, this invention provides a general means for maintaining, for extended periods of time, the <i>in vivo</i> expression of transgenes.		

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INTERNATIONAL SEARCH REPORT

In tional Application No

PCT/US 94/09299

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K48/00 A61K9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 19195 (BROWN UNIVERSITY RESEARCH FOUNDATION) 12 November 1992 cited in the application see page 5, line 3 - line 26 see page 6, line 8 - page 7, line 17 see page 26, line 17 - page 27, line 13 see page 31, line 26 - line 33 see page 32, line 32 - page 33, line 21 see page 51, line 5 - page 52, line 4 see page 72 - page 73; example 4 ---	1-5,9, 12-15, 17-21,23
X	EXP. NEUROL., vol.122, no.1, July 1993 pages 100 - 106 HOFFMAN D. ET AL 'TRANSPLANTATION OF A POLYMER-ENCAPSULATED CELL LINE GENETICALLY ENGINEERED TO RELEASE NGF' see the whole document --- -/--	1-5, 12-15, 18-21, 23,31-42

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

16 January 1995

Date of mailing of the international search report

21.01.95

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INTERNATIONAL SEARCH REPORT

In tional Application No

PCT/US 94/09299

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	PROC. NATL. ACAD. SCI. U.S.A., vol.91, no.6, March 1994 pages 2324 - 2328 WINN, SHELLEY R. ET AL 'POLYMER-ENCAPSULATED CELLS GENETICALLY MODIFIED TO SECRETE HUMAN NERVE GROWTH FACTOR PROMOTE THE SURVIVAL OF AXOTOMIZED SEPTAL CHOLINERGIC NEURONS' see the whole document ---	1-9, 12-23, 31-42
X	WO,A,89 04655 (BROWN UNIVERSITY RESEARCH FOUNDATION) 1 June 1989 cited in the application & US-A-5284761 see page 10, paragraph 2 - page 11, paragraph 1 see page 13 - page 15; example 1 ---	1-4, 12-14, 18-20
X	EP,A,0 161 640 (MERCK AND CO) 21 November 1985 see page 10 - page 12 ---	1-3, 12-14, 18-20
X	WO,A,93 00439 (BROWN UNIVERSITY RESEARCH FOUNDATION) 7 January 1993 see page 20, paragraph 2 - page 21, paragraph 1 see page 22, paragraph 3 - page 23, paragraph 2 see page 24 - page 26; example 1 ---	1-5, 11-15, 17-21,23
A	WO,A,91 10425 (BROWN UNIVERSITY RESEARCH FOUNDATION) 25 July 1991 cited in the application see page 7, paragraph 2 ---	24
A	WO,A,93 02635 (BAXTER INTERNATIONAL) 18 February 1993 see page 13 - page 14; example 2 -----	24

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/09299

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-17, 30-35
because they relate to subject matter not required to be searched by this Authority, namely:
Although these claims are directed to a method of treatment of the human body (rule 39.1(iv) PCT) the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 94/09299

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9219195	12-11-92	AU-A- 2004192	21-12-92
		EP-A- 0585368	09-03-94
		JP-T- 6507412	25-08-94
		NO-A- 933842	25-10-93
WO-A-8904655	01-06-89	US-A- 4892538	09-01-90
		AU-A- 2718488	14-06-89
		DE-A- 3878918	08-04-93
		EP-A, B 0388428	26-09-90
		JP-T- 3502534	13-06-91
		US-A- 5158881	27-10-92
		US-A- 5106627	21-04-92
		US-A- 5283187	01-02-94
		US-A- 5182111	26-01-93
		US-A- 5284761	08-02-94
		US-A- 5156844	20-10-92
EP-A-0161640	21-11-85	US-A- 4686098	11-08-87
		AU-B- 584088	18-05-89
		AU-A- 4240885	21-11-85
		JP-A- 60246317	06-12-85
WO-A-9300439	07-01-93	US-A- 5182111	26-01-93
		AU-B- 652071	11-08-94
		AU-A- 2296192	25-01-93
		CA-A- 2090719	29-12-92
		EP-A- 0547203	23-06-93
		JP-T- 6502080	10-03-94
WO-A-9110425	25-07-91	US-A- 5158881	27-10-92
		EP-A- 0462269	27-12-91
		JP-T- 4507423	24-12-92
		US-A- 5283187	01-02-94
		US-A- 5284761	08-02-94
WO-A-9302635	18-02-93	EP-A- 0555428	18-08-93
		JP-T- 6502577	24-03-94
		US-A- 5344454	06-09-94