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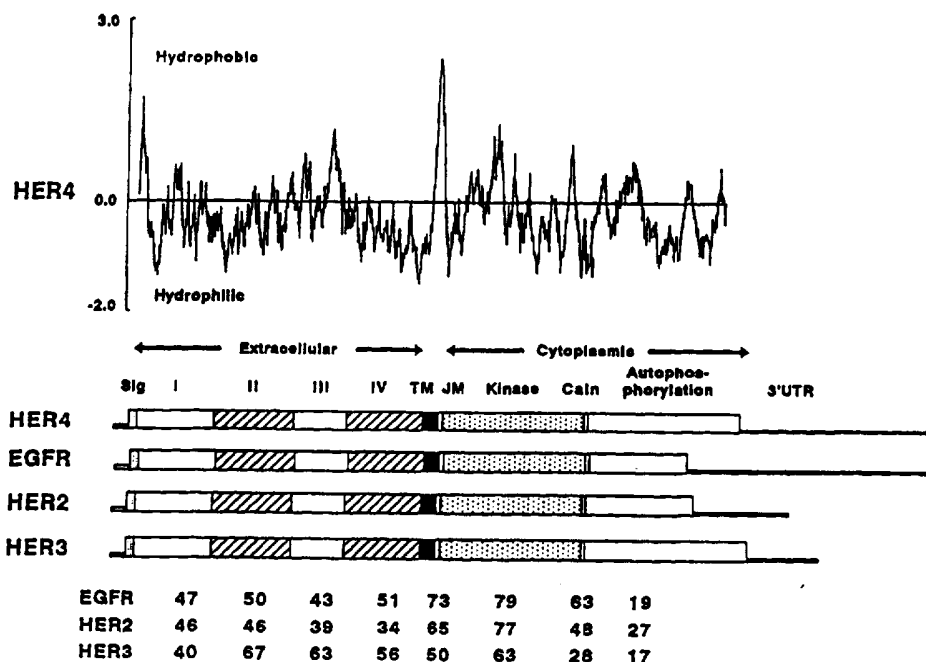
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amendments.*

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15 August 1996 (15.08.96)

(54) Title: HER4, HUMAN RECEPTOR TYROSINE KINASE OF THE EPIDERMAL GROWTH FACTOR RECEPTOR FAMILY

**(57) Abstract**

The molecular cloning, expression, and biological characteristics of a novel receptor tyrosine kinase related to the epidermal growth factor receptor, termed HER4/p180^{erbB4}, are described. An HER4 ligand capable of inducing cellular differentiation of breast cancer cells is also disclosed. In view of the expression of HER4 in several human cancers and in certain tissues of neuronal and muscular origin, various diagnostic and therapeutic uses of HER4-derived and HER4-related biological compositions are provided.

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INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 95/13524

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C12N15/62 C12N5/28 C12N5/10 C07K14/71
C12P21/08 G01N33/68 G01N33/577 A61K39/395 C07K16/30
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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 C07K C12N A61K G01N

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	EP,A,0 599 274 (BRISTOL-MYERS SQUIBB COMPANY) 1 June 1994 cited in the application see the whole document, especially sequences 1A, 1B; pages 6, 12-14 and 20-24 (examples 8-10)	1-47, 49, 61-64, 71, 72
A	---	69
X	PROC. NATL ACAD. SCI., vol. 90, March 1993, pages 1746-1750, XP002004419 PLOWMAN ET AL.: "Ligand-specific activation of HER4/p180erbB4, a fourth member of the epidermal growth factor receptor family" see the whole document ---	1-45
	-/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

31 May 1996

Date of mailing of the international search report

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Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 95/13524

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/485

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Minimum documentation searched (classification system followed by classification symbols)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PROC. AM. ASSOC. CANCER RES. ANN. MEET., vol. 35, March 1994, page 382 XP002004420 SIEGALL ET AL.: "Activity of HER4 targeted ligand-toxin fusion proteins against human tumors" see abstract nr2276	49-51, 56,58, 65-67,72
Y	---	54,57, 71,73
	-/--	

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/13524

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. BIOL. CHEM., vol. 269, no. 40, 7 October 1994, pages 25226-25233, XP002004421 TZA HAR ET AL.: "ErbB-3 and ErbB-4 function as the respective low and high affinity receptors of all Neu differentiation factor/herregulin isoforms" see the whole document	40,41, 45-47
Y	---	50-55, 57,59, 60, 65-70,73
X	EMBO J., vol. 13, no. 15, 1 August 1994, pages 3517-3523, XP002004422 NAGATA ET AL.: "Solution structure of the epidermal growth factor-like domain of heregulin-alpha, a ligand for p180erbB-4" see the whole document	40,45,46
Y	---	50-55
X	J. BIOL. CHEM., vol. 268, no. 25, 5 September 1993, pages 18407-18410, XP002004423 CULOUSCOU ET AL.: "Characterization of a breast cancer cell differentiation factor that specifically activates the HER4/p180erbB4 receptor" see the whole document	45,47,48
P,X	J. BIOL. CHEM., vol. 270, no. 13, 31 March 1995, pages 7623-7630, XP002004424 SIEGAL, ET AL.: "HER4 expression correlates with cytotoxicity directed by a hergulin-toxin fusion protein" see the whole document	18-27, 40-42, 49-60, 65-70
P,X	CANCER RES., vol. 55, 1 January 1995, pages 71-77, XP002004425 KIHARA ET AL.: "Cytotoxic activity of chimeric toxins containg the epidermal growth factor-like domain of heregulins fused to PE38KDEL, a truncated recombinant form of Pseudomonas exotoxin" see the whole document	49-53, 55,58,72
Y	---	57,59, 60,65-73
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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 95/13524

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	INT. J. CANCER, vol. 60, no. 5, 3 March 1995, pages 730-739, XP000571537 JESCHKE ET AL.: "Targeted inhibition of tumor-cell growth by recombinant heregulin-toxin fusion proteins" see the whole document	45,46, 49-52, 56,58, 65-67
Y	-----	57,60, 71-73

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/13524

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.: 44, 65-73
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 44 and 65-73 (as far as they concern an in vivo method) of treatment of the human/animal body (Art.17.2.a)1) and Rule 39-2.iv), the search has been carried out and based on the alleged effects of the compound/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.

Information on patent family members

PCT/US 95/13524

Form PCT/ISA/210 (patent family annex) (July 1992)