European Patent Office

SUPPLEMENTARY PARTIAL EUROPEAN SEARCH REPORT

under Rule 46, paragraph 1 of the European Patent Convention

Application Number EP 97 92 9783

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X,D	HARFST E ET AL: "Interaction of thyrotropin and thyroid-stimulating antibodies with recombinant extracellular region of human TSH receptor." LANCET. 18 JAN 1992, vol. 339, no. 8786, 18 January 1992 (1992-01-18), pages 193-194, XP001202882 ISSN: 0140-6736	1,2, 8-13, 18-23,27	A61K38/16 C07K14/435 C07K14/705 C07K14/72
Y	* the whole document *	3-7, 14-17	
X	CHAZENBALK GREGORIO D ET AL: "Expression of the Extracellular Domain of the Thyrotropin Receptor in the Baculovirus System Using a Promoter Active Earlier than the Polyhedrin Promoter: Implications for the expression of functional highly glycosylated proteins" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 4, 1995, pages 1543-1549, XP002296093 ISSN: 0021-9258 * the whole document *	1,2,8, 12,13, 18-22,27	
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TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07K

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

The present partial European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.

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Place of search	Date of completion of the search	Examiner
The Hague	13 September 2004	Madruga, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C23)

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	COSTAGLIOLA S ET AL: "BINDING ASSAY FOR THYROTROPIN RECEPTOR AUTOANTIBODIES USING THE RECOMBINANT RECEPTOR PROTEIN" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, NEW YORK, NY, US, vol. 75, no. 6, 1992, pages 1540-1544, XP001000292 ISSN: 0021-972X * the whole document *	21,22	
D,X	DATABASE EMBL 1 November 1996 (1996-11-01), XP002296098 retrieved from EBI Database accession no. Q16503 * abstract *	1,2,8,9, 12,13	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X,D	& TAKESHITA AKIRA ET AL: "Molecular cloning and sequencing of an alternatively spliced form of the human thyrotropin receptor transcript" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 188, no. 3, 1992, pages 1214-1219, XP001194873 ISSN: 0006-291X * the whole document *	1,2,8,9, 12,13	
Y	CHAZENBALK GREGORIO D ET AL: "Cleavage of the thyrotropin receptor does not occur at a classical subtilisin-related proprotein convertase endoproteolytic site" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 269, no. 51, 1994, pages 32209-32213, XP002296094 ISSN: 0021-9258 * the whole document *	3-7, 14-17	

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EPO FORM 1503 03.82 (P04C10)

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
P,X, D	RAPOPORT BASIL ET AL: "Critical relationship between autoantibody recognition and thyrotropin receptor maturation as reflected in the acquisition of complex carbohydrate" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, vol. 81, no. 7, July 1996 (1996-07), pages 2525-2533, XP002296095 ISSN: 0021-972X	1,2, 8-13, 18-23,27	
Y	* the whole document *	3-7, 14-17	
T	CHAZENBALK GREGORIO D ET AL: "Engineering the human thyrotropin receptor ectodomain from a non-secreted form to a secreted, highly immunoreactive glycoprotein that neutralizes autoantibodies in Graves' patients' sera" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 30, 25 July 1997 (1997-07-25), pages 18959-18965, XP002296096 ISSN: 0021-9258 * the whole document *		TECHNICAL FIELDS SEARCHED (Int.Cl.6)
T	CHEN CHUN-RONG ET AL: "Evidence that the C terminus of the A subunit suppresses thyrotropin receptor constitutive activity." ENDOCRINOLOGY, vol. 144, no. 9, September 2003 (2003-09), pages 3821-3827, XP002296097 ISSN: 0013-7227 * the whole document *		

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European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 97 92 9783

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	WO 92/08726 A (AKAMIZU TAKASHI ; IKUYAMA SHOICHIRO (US); KOSUGI SHINJI (US); SAJI MOT) 29 May 1992 (1992-05-29) * page 11, line 16 - line 27; claims 14-16 * -----		
A	HUNT N; WILLEY K P; ABEND N; BALVERS M; JAHNER D; NORTHEMANN W; IVELL R: "Novel splicing variants of the human thyrotropin receptor encode truncated polypeptides without a membrane-spanning domain" ENDOCRINE, vol. 3, no. 3, 1995, pages 233-240, XP008035227 UNITED KINGDOM * the whole document * -----		TECHNICAL FIELDS SEARCHED (Int.Cl.6)

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EPO FORM 1503 03.82 (P04C10)

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-23, 27

A C-terminally truncated, soluble, complex carbohydrate containing form of the tyrotropin receptor (TSHR) ectodomain, the nucleic acid encoding for said protein, a vector comprising said nucleic acid, a host cell comprising said vector, TSH (tyrotropin) binding inhibition assay using said cells or said polypeptide

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2. claims: 24-26, 28-31

A TSH binding inhibition assay using as intact cells a Chinese Hamster Ovary cell line over-expressing the TSHR holoreceptor, a method of detecting by flow cytometry, binding of autoantibodies in a patient's serum to native TSHR comprising use of a Chinese Hamster Ovary cell line over-expressing the TSHR holoreceptor.

The use of truncated forms of the tyrotropin receptor (TSHR) and of cells lines expressing the TSHR in TSH binding inhibition assays and in assays to detect autoantibodies against TSHR in patient's serum, have been well documented in the prior art (e.g. Chazenbalk et al, (1994) J. Biol. Chem, 269: 32209-32213, Chazenbalk et al, (1995) J. Biol. Chem, 270: 1543-1549, Costagliola et al (1992), J. Clinical Endocrinol andd Metabol. 75: 1540-1544)

In view of the prior art, the problem undelying the application can be defined as the provision of further antigenically active TSHR in order to improveTSH binding inhibition assays and in assays to detect autoantibodies against TSHR in patient's serum .

The solutions proposed in underlying application can be summarized as follows:

1. Secreted, complex carbohydrate-containing forms of the TSHR ectodomain (truncated forms of the TSHR)

2.Use of a chinese hamster ovary cell line which over-expresses the TSHR holoreceptor.

Due to the fact that the use of both, truncated forms of the tyrotropin receptor (TSHR) and cells lines expressing the TSHR in TSH binding inhibition assays and their use in assays to detect autoantibodies against TSHR in patient's serum is known in the art, due to the essential difference in structure of the different groups of solutions, and due to the fact that no other technical features can be distinguished which in the light of the prior art could be regarded as special technical features,the Search Authority is of the opinion that there is no single inventive concept underlying the plurality of the claimed inventions in

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LACK OF UNITY OF INVENTION
SHEET B

Application Number
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The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

the present application, in the sense of Article 82 EPC.Consequently there is lack of unity and the different inventions, not belonging to a common inventive concept, are formulated as different subjects.