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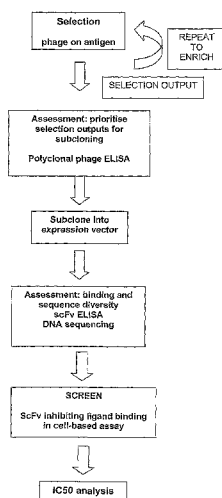
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- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

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15 October 2009

(54) **Title:** SCREENING

Figure 29
Schematic representation of typical lead isolation process for the identification of inhibitory scFv binders



(57) **Abstract:** A method of producing a conformational specific binding partner of a GPCR, the method comprising: a) providing a mutant GPCR of a parent GPCR, wherein the mutant GPCR has increased stability in a particular conformation relative to the parent GPCR; b) providing a test compound; c) determining whether the test compound binds to the mutant GPCR when residing in a particular conformation; and d) isolating a test compound that binds to the mutant GPCR when residing in the particular conformation. Methods of producing GPCRs with increased stability relative to a parent GPCR are also disclosed.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/004223

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/566 C07K14/72 C12N15/10

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)
G01N C07K C12N

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)

EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D'ANTONA A M ET AL: "A cannabinoid receptor 1 mutation proximal to the DRY motif results in constitutive activity and reveals intramolecular interactions involved in receptor activation" BRAIN RESEARCH, ELSEVIER, AMSTERDAM, NL, vol. 1108, no. 1, 7 September 2006 (2006-09-07), pages 1-11, XP025101414 ISSN: 0006-8993 [retrieved on 2006-09-07] the whole document ----- -/--	1-23, 32-44

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

☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *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.
- *G* document member of the same patent family

Date of the actual completion of the international search

12 March 2009

Date of mailing of the international search report

19/08/2009

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/004223

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STANDFUSS ET AL: "Crystal Structure of a Thermally Stable Rhodopsin Mutant" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 372, no. 5, 11 September 2007 (2007-09-11), pages 1179-1188, XP022242879 ISSN: 0022-2836 the whole document	1-23, 32-44
A	LEE N H ET AL: "ALANINE SCANNING MUTAGENESIS OF CONSERVELD ARGININE/LYSINE-ARGININE/L YSINE-X-X-ARGININE/LYSINE G PROTEIN/ACTIVATING MOTIFS ON M1 MUSCARINIC ACETYLCHOLINE RECEPTORS" MOLECULAR PHARMACOLOGY, BALTIMORE, MD, US, vol. 50, no. 1, 1 July 1996 (1996-07-01), pages 140-148, XP000901009 ISSN: 0026-895X the whole document	1-23, 32-44
A	SAMAMA P ET AL: "A mutation-induced activated state of the beta2-adrenergic receptor" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOCHEMICAL BIOLOGISTS, BIRMINGHAM,; US, vol. 268, no. 7, 5 March 1993 (1993-03-05), pages 4625-4636, XP002135769 ISSN: 0021-9258 the whole document	1-23, 32-44
A	LATTION A-L ET AL: "Constitutively active mutants of the beta1-adrenergic receptor" FEBS LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 457, no. 3, 3 September 1999 (1999-09-03), pages 302-306, XP004260170 ISSN: 0014-5793 the whole document	1-23, 32-44
P,X	WO 2008/114020 A (MEDICAL RES COUNCIL [GB]; HENDERSON RICHARD [GB]; TATE CHRISTOPHER GOR) 25 September 2008 (2008-09-25) cited in the application the whole document	1-23, 32-44
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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/004223

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	SERRANO-VEGA MARIA J ET AL: "Conformational thermostabilization of the betal-adrenergic receptor in a detergent-resistant form" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC.; US, vol. 105, no. 3, 22 January 2008 (2008-01-22), pages 877-882, XP002487473 ISSN: 0027-8424 the whole document -----	1-23, 32-44

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2008/004223

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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.:
because they relate to subject matter not required to be searched by this Authority, namely:
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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
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.:

1-23, 32-44

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-23, 32-44

The claims concern methods of producing a binding partner to a mutant GPCR that has increased stability in a particular conformation relative to the cognate wildtype (parent) GPCR.

2. claims: 24-31

The claims concern methods of producing an antibody for a mutant GPCR that has increased stability in a particular conformation relative to the parent GPCR.

3. claims: 45-66, 78

The claims concern methods for providing a mutant GPCR wherein the binding of a selected ligand has increased stability compared to a parent GPCR.

4. claims: 67-77, 79-92, 94-96

The claims concern methods for providing a mutant GPCRs wherein said mutant has increased stability compared to parent GPCRs.

5. claims: 93, 103-108

The claims concern mutant GPCR and products comprising said GPCR with increased stability compared to parent GPCR.

6. claims: 97-102

The claims concern binding partners to mutant GPCRs with increased stability compared to parent GPCRs and synthesis of said binding partners.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2008/004223

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008114020 A	25-09-2008	GB 2447786 A	24-09-2008
		GB 2456235 A	15-07-2009
		GB 2456236 A	15-07-2009
		GB 2456237 A	15-07-2009
