Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 3058265 C 2023/03/14

(11)(21) 3 058 265

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2018/03/30
(87) Date publication PCT/PCT Publication Date: 2018/10/04
(45) Date de délivrance/Issue Date: 2023/03/14
(85) Entrée phase nationale/National Entry: 2019/09/27
(86) N° demande PCT/PCT Application No.: EP 2018/058346
(87) N° publication PCT/PCT Publication No.: 2018/178364
(30) Priorité/Priority: 2017/03/30 (EP17305382.8)

(51) Cl.Int./Int.Cl. *G01N 33/574* (2006.01), *C07K 16/26* (2006.01), *G01N 33/74* (2006.01)

(72) Inventeur/Inventor:
PRIEUR, ALEXANDRE, FR

(73) Propriétaire/Owner:
PROGASTRINE ET CANCERS S.A R.L., LU

(74) Agent: NORTON ROSE FULBRIGHT CANADA LLP/S.E.N.C.R.L., S.R.L.

(54) Titre : COMPOSITIONS ET METHODES DE TRAITEMENT DU CANCER DU POUMON
(54) Title: COMPOSITIONS AND METHODS FOR TREATING LUNG CANCER

(57) Abrégé/Abstract:
The present invention relates to compositions and methods for the prevention or the treatment of lung cancer, wherein said compositions comprise an antibody binding to progastrin and said methods comprise the use of an antibody binding to progastrin.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
04 October 2018 (04.10.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/178364 A1

(51) International Patent Classification:
G01N 33/574 (2006.01) *C07K 16/26* (2006.01)
G01N 33/74 (2006.01)

(21) International Application Number:
PCT/EP2018/058346

(22) International Filing Date:
30 March 2018 (30.03.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
17305382.8 30 March 2017 (30.03.2017) EP

(71) Applicant: **PROGASTRINE ET CANCERS S.À R.L.** [LU/LU]; 11, Côte d'Eich, L - 1450 LUXEMBOURG (LU).

(72) Inventor: **PRIEUR, Alexandre**; 24 rue de la Cavalerie, 34000 MONTPELLIER (FR).

(74) Agent: **REGIMBEAU**; 20, rue de Chazelles, 75847 PARIS CEDEX 17 (FR).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*

WO 2018/178364 A1

(54) Title: COMPOSITIONS AND METHODS FOR TREATING LUNG CANCER

(57) Abstract: The present invention relates to compositions and methods for the prevention or the treatment of lung cancer, wherein said compositions comprise an antibody binding to progastrin and said methods comprise the use of an antibody binding to progastrin.

COMPOSITIONS AND METHODS FOR TREATING LUNG CANCER

INTRODUCTION

The present invention relates to the prevention and the treatment of cancer, more particularly it relates to methods and compositions for the prevention or the treatment of lung cancer. Compositions according to the invention comprise a progastrin-binding molecule, in particularly an anti-hPG antibody, whereas methods according to the invention comprise the use of a progastrin-binding molecule, and particularly to an anti-hPG antibody.

Lung cancer remains the most lethal malignancy in the world. Despite improvements in surgical treatment, systemic therapy, and radiotherapy, the 5-year survival rate for all patients diagnosed with lung cancer remains between 15 and 20%.

Lung cancer comprises two main types of tumors, namely small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC represents 15-18% of all lung cancers, while NSCLC make up about 80% to 85% of lung cancers. Other types of lung cancer such as adenoid cystic carcinomas, lymphomas, and sarcomas, as well as benign lung tumors such as hamartomas are rare.

Small cell and non-small cell lung cancers are treated differently. In particular, SCLC is more responsive to chemotherapy and radiation therapy than other cell types of lung cancer. However, a cure is difficult to achieve because SCLC has a greater tendency to be widely disseminated by the time of diagnosis. To date, there are no molecular biomarkers that have been translated to widespread clinical practice of lung cancer. Treatments depend on the development of the cancer, and usually include surgery, for small-localized tumors, or chemotherapy, possibly in combination with radiation therapy.

Therefore, there is still a need for new compositions and methods for the prevention or the treatment of lung cancer.

This is the object of the present invention.

DESCRIPTION

The present invention now provides an antibody binding specifically to progastrin for use in the prevention or the treatment of lung cancer. The present invention also provides a composition for use in the prevention or the treatment of lung cancer, wherein said composition comprises an antibody binding to progastrin, and methods for the prevention or the treatment of lung cancer comprising the use of a composition comprising an antibody binding to progastrin, alone or in combination with any other known prevention or therapeutic methods against lung cancer.

The anti-hPG antibodies described herein, particularly the neutralizing anti-hPG antibodies, inhibit PG-dependent proliferation of lung tumor cells, making them useful therapeutic agents for the treatment of lung cancer. Accordingly, also provided are pharmaceutical compositions comprising an anti-hPG antibody and methods of using the anti-hPG antibodies and/or pharmaceutical compositions to treat lung cancer. The pharmaceutical compositions can be formulated for any convenient route of administration, including, e.g., parenteral, subcutaneous or intravenous injection, and will typically include an anti-hPG antibody, and one or more acceptable carriers, excipients, and/or diluent suitable for the desired mode of administration, and can include other optional components as will be described further below. For therapeutic uses, the compositions can be packaged in unit dosage form for ease of use.

The treatment methods generally comprise administering to a subject in need of treatment, for example a subject diagnosed with lung cancer, an amount of an anti-PG antibody and/or pharmaceutical composition thereof effective to provide a therapeutic benefit. Therapeutic benefit, described below in more detail, includes any amelioration of lung cancer, for example, slowing or halting the progression of lung cancer, reducing the severity of lung cancer, inhibiting the growth of lung tumors or the proliferation of lung cancer cells, reducing the size of lung tumors, and/or reducing PG serum levels in lung cancer patients. The subject can be a human or non-human, including a domesticated animal (e.g., cat, dog, cow, pig, horse) or a non-domesticated animal. Preferably, the subject to be treated is a human. Subjects in whom anti-hPG antibody therapy is useful can be: patients in any stage of disease progression (*e.g.*, lung cancer Stage 0, I, II, III, or IV), patients who have received

therapy for lung cancer (e.g., chemotherapy, radiation therapy, surgical resection) or patients who are receiving other therapy for lung cancer.

Methods are also provided for inhibiting the growth of a lung cancer stem cell in a patient by administering to a patient in need of inhibition of growth of a lung cancer stem cell an anti-PG antibody and/or pharmaceutical composition thereof in an amount effective to inhibit said lung cancer stem cell.

In a number of embodiments, the anti-PG antibodies are effective to reduce the proliferation or increase the differentiation or rate of cell death of lung cancer stem cells, or reduce the blood concentration of progastrin in treated patients. In other embodiments, the anti-PG antibodies and/or pharmaceutical composition thereof can be administered concurrently with or after a second therapeutic agent effective to inhibit the growth of colorectal cancer stem cells, for example, an antibody having specificity other than for progastrin.

Treatment with anti-hPG antibodies as described herein can be combined with, or adjunctive to, other therapy. Non-limiting examples of other therapy for lung cancer include chemotherapeutic treatment, radiation therapy, surgical resection, and antibody therapy, as described herein. In a specific example, anti-hPG antibodies are administered in combination with chemotherapeutic agents. In another specific example, anti-hPG antibodies are administered adjunctive to surgical resection.

The present invention also relates to pharmaceutical compositions comprising the anti-PG antibodies, preferably with a pharmaceutically acceptable carrier and/or an excipient. In some embodiments, the pharmaceutical composition further comprises a second therapeutic agent. In some embodiment, the second therapeutic agent is a biological agent or a chemotherapeutic agent. Examples of biological agents include anti-EGFR monoclonal antibodies and anti-VEGF monoclonal antibodies, whereas chemotherapeutic agents comprise such compounds as e.g. alkylating agents, anti-metabolites, anti-tumor antibiotics, mitotic inhibitors, chromatin function inhibitors, anti-angiogenesis agents, anti-estrogens, anti-androgens and immunomodulators.

Human pre-progastrin, a 101 amino acids peptide (Amino acid sequence reference: AAB19304.1), is the primary translation product of the gastrin gene.

Progastrin is formed by cleavage of the first 21 amino acids (the signal peptide) from preprogastrin. The 80 amino-acid chain of progastrin is further processed by cleavage and modifying enzymes to several biologically active gastrin hormone forms: gastrin 34 (G34) and glycine-extended gastrin 34 (G34-Gly), comprising amino acids 38-71 of progastrin, gastrin 17 (G17) and glycine-extended gastrin 17 (G17-Gly), comprising amino acids 55 to 71 of progastrin.

Anti-human progastrin (anti-hPG) monoclonal antibodies and their use for diagnosis or therapy have been described in the following documents: WO 2011/083 088 for colorectal cancer, WO 2011/083 090 for breast cancer, WO 2011/083 091 for pancreatic cancer, WO 2011/116 954 for colorectal and gastrointestinal cancer, and WO 2012/013 609 and WO 2011/083089 for liver pathologies.

The present invention will become more fully understood from the detailed description given herein and from the accompanying drawings, which are given by way of illustration only and do not limit the intended scope of the invention.

In a first aspect, the present invention relates to a progastrin-binding molecule for use in the prevention or the treatment of lung cancer. The present disclosure also provides a composition for use in the prevention or the treatment of prostate cancer, wherein said composition comprises a progastrin-binding antibody, or an antigen-binding fragment thereof.

By “progastrin-binding molecule”, it is herein referred to any molecule that binds progastrin, but does not bind gastrin-17 (G17), gastrin-34 (G34), glycine-extended gastrin-17 (G17-Gly), or glycine-extended gastrin-34 (G34-Gly). The progastrin-binding molecule of the present invention may be any progastrin-binding molecule, such as, for instance, an antibody molecule or a receptor molecule. Preferably, the progastrin-binding molecule is an anti-progastrin antibody (an anti-PG antibody) or an antigen-binding fragment thereof.

The term “progastrin” designates the mammalian progastrin peptide, and particularly human progastrin. For the avoidance of doubt, without any specification, the expression “human progastrin” or “hPG” refers to the human PG of sequence SEQ ID No. 1. Human progastrin comprises notably a N-terminus and a C-terminus domains which are not present in the biologically active gastrin hormone forms mentioned above. Preferably, the sequence of said N-terminus domain is represented by SEQ ID

NO. 2. In another preferred embodiment, the sequence of said C-terminus domain is represented by SEQ ID NO. 3.

Thus, in a first embodiment, the invention relates to an antibody which binds progastrin but not any of the other gastrin-gene derived products, for use in the treatment of lung cancer.

By "binding", "binds", or the like, it is intended that the antibody, or antigen binding fragment thereof, forms a complex with an antigen which, under physiologic conditions, is relatively stable. Methods for determining whether two molecules bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. In a particular embodiment, said antibody, or antigen-binding fragment thereof, binds to progastrin with an affinity that is at least two-fold greater than its affinity for binding to a non-specific molecule such as BSA or casein. In a more particular embodiment, said antibody, or antigen-binding fragment thereof, binds only to progastrin.

The expression "lung cancer" designates a cancer that originates in tissues of the lung, usually in the cells lining air passages. A "lung cancer" as used herein encompasses in particular small cell lung cancer (SCLC), including small cell carcinoma and combined small cell carcinoma, and non-small cell lung cancers (NSCLC), including squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. Other types of lung cancer such as adenoid cystic carcinomas, lymphomas, and sarcomas, as well as benign lung tumours such as hamartomas are also included in the lung cancers as used herein.

In a specific embodiment, the invention provides an anti-PG antibody for use in the prevention or the treatment of lung cancer, said antibody recognizing an epitope including an amino acid sequence corresponding to an amino acid sequence of progastrin.

In a more specific embodiment, said anti-PG antibody for use in the prevention or the treatment of lung cancer recognizes an epitope of progastrin wherein said epitope includes an amino acid sequence corresponding to an amino acid sequence of the N-terminal part of progastrin, wherein said amino acid sequence may include residues 10 to 14 of hPG, residues 9 to 14 of hPG, residues 4 to

10 of hPG, residues 2 to 10 of hPG or residues 2 to 14 of hPG, wherein the amino acid sequence of hPG is SEQ ID N°1.

In a more specific embodiment, the anti-PG antibody for use in the prevention or the treatment of lung cancer recognizes an epitope of progastrin wherein said epitope includes an amino acid sequence corresponding to an amino acid sequence of the C-terminal part of progastrin, wherein said amino acid sequence may include residues 71 to 74 of hPG, residues 69 to 73 of hPG, residues 71 to 80 of hPG (SEQ ID N°40), residues 76 to 80 of hPG, or residues 67 to 74 of hPG, wherein the amino acid sequence of hPG is SEQ ID N°1.

In a more particular embodiment, the anti-PG antibody for use in the prevention or the treatment of lung cancer has an affinity for progastrin of at least 5000 nM, at least 500 nM, 100 nM, 80 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 7 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM, 0.1nM, 50 pM, 10 pM, 5 pM, 1 pM, or at least 0.1 pM, as determined by a method such as above-described.

Preferably, the anti-PG antibody for use in preventing or treating lung cancer is a neutralizing anti-PG antibody.

The expression “neutralizing anti-PG antibody” designates an antibody that binds PG and blocks PG-dependent signalling, resulting in the inhibition of PG-induced responses in tumour cells, and particularly in lung tumour cells. Inhibiting PG-induced responses of lung cancer cells may be mediated by repression of cell differentiation, repression of cell death, and/or stimulation of cell proliferation.

The term “antibody” as used herein is intended to include polyclonal and monoclonal antibodies. An antibody (or “immunoglobulin”) consists of a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain comprises a heavy chain variable region (or domain) (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region comprises three domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region comprises one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed “complementarity determining regions” (CDR) or “hypervariable regions”, which are primarily responsible for binding an epitope of an antigen, and which are

interspersed with regions that are more conserved, termed framework regions (FR). Method for identifying the CDRs within light and heavy chains of an antibody and determining their sequence are well known to the skilled person. For the avoidance of doubt, in the absence of any indication in the text to the contrary, the expression CDRs means the hypervariable regions of the heavy and light chains of an antibody as defined by IMGT, wherein the IMGT unique numbering provides a standardized delimitation of the framework regions and of the complementary determining regions, CDR1-IMGT: 27 to 38, CDR2.

The IMGT unique numbering has been defined to compare the variable domains whatever the antigen receptor, the chain type, or the species [Lefranc M.-P., Immunology Today 18, 509 (1997) / Lefranc M.-P., The Immunologist, 7, 132-136 (1999) / Lefranc, M.-P., Pommié, C., Ruiz, M., Giudicelli, V., Foulquier, E., Truong, L., Thouvenin-Contet, V. and Lefranc, Dev. Comp. Immunol., 27, 55-77 (2003)]. In the IMGT unique numbering, the conserved amino acids always have the same position, for instance cystein 23 (1st-CYS), tryptophan 41 (CONSERVED-TRP), hydrophobic amino acid 89, cystein 104 (2nd-CYS), phenylalanine or tryptophan 118 (J-PHE or J-TRP). The IMGT unique numbering provides a standardized delimitation of the framework regions (FR1-IMGT: positions 1 to 26, FR2-IMGT: 39 to 55, FR3-IMGT: 66 to 104 and FR4-IMGT: 118 to 128) and of the complementarity determining regions: CDR1-IMGT: 27 to 38, CDR2-IMGT: 56 to 65 and CDR3-IMGT: 105 to 117. As gaps represent unoccupied positions, the CDR-IMGT lengths (shown between brackets and separated by dots, e.g. [8.8.13]) become crucial information. The IMGT unique numbering is used in 2D graphical representations, designated as IMGT Colliers de Perles [Ruiz, M. and Lefranc, M.-P., Immunogenetics, 53, 857-883 (2002) / Kaas, Q. and Lefranc, M.-P., Current Bioinformatics, 2, 21-30 (2007)], and in 3D structures in IMGT/3Dstructure-DB [Kaas, Q., Ruiz, M. and Lefranc, M.-P., T cell receptor and MHC structural data. Nucl. Acids. Res., 32, D208-D210 (2004)].

Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g. effector cells) and the first component (Clq)

of the classical complement system. Antibodies can be of different isotypes (namely IgA, IgD, IgE, IgG or IgM).

In a particular embodiment, said progastrin-binding antibody, or an antigen-binding fragment thereof, is selected from the group consisting of: polyclonal antibodies, monoclonal antibodies, chimeric antibodies, single chain antibodies, camelized antibodies, IgA1 antibodies, IgA2 antibodies, IgD antibodies, IgE antibodies, IgG1 antibodies, IgG2 antibodies, IgG3 antibodies, IgG4 antibodies and IgM antibodies.

A "polyclonal antibody" is an antibody which was produced among or in the presence of one or more other, non-identical antibodies. In general, polyclonal antibodies are produced from a B-lymphocyte in the presence of several other B-lymphocytes producing non-identical antibodies. Usually, polyclonal antibodies are obtained directly from an immunized animal.

The term "monoclonal antibody" designates an antibody arising from a nearly homogeneous antibody population, wherein population comprises identical antibodies except for a few possible naturally-occurring mutations which can be found in minimal proportions. A monoclonal antibody arises from the growth of a single cell clone, such as a hybridoma, and is characterized by heavy chains of one class and subclass, and light chains of one type.

By the expression "antigen-binding fragment" of an antibody, it is intended to indicate any peptide, polypeptide, or protein retaining the ability to bind to the target (also generally referred to as antigen) of the said antibody, generally the same epitope, and comprising an amino acid sequence of at least 5 contiguous amino acid residues, at least 10 contiguous amino acid residues, at least 15 contiguous amino acid residues, at least 20 contiguous amino acid residues, at least 25 contiguous amino acid residues, at least 40 contiguous amino acid residues, at least 50 contiguous amino acid residues, at least 60 contiguous amino residues, at least 70 contiguous amino acid residues, at least 80 contiguous amino acid residues, at least 90 contiguous amino acid residues, at least 100 contiguous amino acid residues, at least 125 contiguous amino acid residues, at least 150 contiguous amino acid residues, at least 175 contiguous amino acid residues, or at least 200 contiguous amino acid residues, of the amino acid sequence of the antibody.

In a particular embodiment, the said antigen-binding fragment comprises at least one CDR of the antibody from which it is derived. Still in a preferred embodiment, the said antigen binding fragment comprises 2, 3, 4 or 5 CDRs, more preferably the 6 CDRs of the antibody from which it is derived.

The "antigen-binding fragments" can be selected, without limitation, in the group consisting of Fv, scFv (sc for single chain), Fab, $F(ab')_2$, Fab', scFv-Fc fragments or diabodies, or fusion proteins with disordered peptides such as XTEN (extended recombinant polypeptide) or PAS motifs, or any fragment of which the half-life time would be increased by chemical modification, such as the addition of poly(alkylene) glycol such as poly(ethylene) glycol ("PEGylation") (pegylated fragments called Fv-PEG, scFv-PEG, Fab-PEG, $F(ab')_2$-PEG or Fab'-PEG) ("PEG" for Poly(Ethylene) Glycol), or by incorporation in a liposome, said fragments having at least one of the characteristic CDRs of the antibody according to the invention. Preferably, said "antigen-binding fragments" will be constituted or will comprise a partial sequence of the heavy or light variable chain of the antibody from which they are derived, said partial sequence being sufficient to retain the same specificity of binding as the antibody from which it is descended and a sufficient affinity, preferably at least equal to 1/100, in a more preferred manner to at least 1/10, of the affinity of the antibody from which it is descended, with respect to the target.

In another particular embodiment, in a method for the diagnosis of lung cancer according to the invention, a biological sample from a subject is contacted with an antibody binding to progastrin, wherein said antibody has been obtained by an immunization method known by a person skilled in the art, wherein using as an immunogen a peptide which amino acid sequence comprises the totality or a part of the amino-acid sequence of progastrin. More particularly, said immunogen comprises a peptide chosen among:

- a peptide which amino acid sequence comprises, or consists of, the amino acid sequence of full length progastrin, and particularly full length human progastrin of SEQ ID N°1,
- a peptide which amino acid sequence corresponds to a part of the amino acid sequence of progastrin, and particularly full length human progastrin of SEQ ID N°1,

- a peptide which amino acid sequence corresponds to a part or to the whole amino acid sequence of the N-terminal part of progastrin, and in particular peptides comprising, or consisting of, the amino acid sequence: SWKPRSQQPDAPLG (SEQ ID N°2), and
- a peptide which amino acid sequence corresponds to a part or to the whole amino acid sequence of the C-terminal part of progastrin, and in particular peptides comprising, or consisting of, the amino acid sequence: QGPWLEEEEEAYGWMDFGRRSAEDEN (SEQ ID N°3),
- a peptide which amino acid sequence corresponds to a part of the amino acid sequence of the C-terminal part of progastrin, and in particular peptides comprising the amino acid sequence FGRRSAEDEN (SEQ ID N°40) corresponding to amino acids 71-80 of progastrin

The skilled person will realize that such immunization may be used to generate either polyclonal or monoclonal antibodies, as desired. Methods for obtaining each of these types of antibodies are well known in the art. The skilled person will thus easily select and implement a method for generating polyclonal and/or monoclonal antibodies against any given antigen.

Examples of monoclonal antibodies which were generated by using an immunogen comprising the amino-acid sequence “SWKPRSQQPDAPLG”, corresponding to the amino acid sequence 1-14 of human progastrin (N-terminal extremity) include, but are not restricted to, monoclonal antibodies designated as: mAb3, mAb4, mAb16, and mAb19 and mAb20, as described in the following Table 1 to Table 4. Other monoclonal antibodies have been described, although it is not clear whether these antibodies actually bind progastrin (WO 2006/032980). Experimental results of epitope mapping show that mAb3, mAb4, mAb16, and mAb19 and mAb20 do specifically bind an epitope within said hPG N-terminal amino acid sequence. Polyclonal antibodies recognizing specifically an epitope within the N-terminus of progastrin represented by SEQ ID NO. 2, have been described in the art (see e.g, WO 2011/083088).

Hybridoma deposit	mAb	Amino acid sequences		SEQ ID N°
6B5B11C10	mAb3	VH CDR 1	GYIFTSYW	SEQ ID N°4
		VH CDR 2	FYPGNSDS	SEQ ID N°5
		VH CDR 3	TRRDSPQY	SEQ ID N°6
		VL CDR 1	QSIVHSNGNTY	SEQ ID N°7
		VL CDR 2	KVS	SEQ ID N°8
		VL CDR 3	FQGSHVPFT	SEQ ID N°9
		mVH 3	EVQLQQSGTVLARPGASVKMSCK ASGYIFTSYWVHWVKQRPGQGLE WIGGFYPGNSDSRYNQKFKGKAT LTAVTSASTAYMDLSSLTNEDSAV YFCTRRDSPQYWGQGTTLTVSS	SEQ ID N° 41
		mVL 3	DVLMTQTPLSLPVSLGDQASISCR SSQSIVHSNGNTYLEWYLQKPGQS PKLLIYKVSNRFSGVPDRFSGSGS GTDFTLKISRLEAEDLGVYYCFQG SHVPFTFGGGTKLEIK	SEQ ID N° 42
		huVH 3	QVQLVQSGAEVKKPGASVKVSCK ASGYIFTSYWVHWVRQAPGQRLE WMGGFYPGNSDSRYSQKFQGRV TITRDTSASTAYMELSSLRSEDTAV YYCTRRDSPQYWGQGTLVTVSS	SEQ ID N° 53
		huVL 3	DVVMTQSPLSLPVTLGQPASISCR SSQSIVHSNGNTYLEWFQQRPGQ SPRRLIYKVSNRFSGVPDRFSGSGS GTDFTLKISRVEAEDVGVYYCFQG SHVPFTFGGGTKVEIK	SEQ ID N° 54

Table 1

Hybridoma deposit	mAb	Amino acid sequences		SEQ ID N°
20D2C3G2	mAb4	VH CDR 1	GYTFSSW	SEQ ID N°10
		VH CDR 2	FLPGSGST	SEQ ID N°11
		VH CDR 3	ATDGNYDWFAY	SEQ ID N°12
		VL CDR 1	QSLVHSSGVTY	SEQ ID N°13
		VL CDR 2	KVS	SEQ ID N°14
		VL CDR 3	SQSTHVPPT	SEQ ID N°15
		mVH 4	QVQLQQSGAELMKPGASVKISCK ATGYTFSSSWIEWLKQRPGHGLE WIGEFLPGSGSTDYNEKFKGKATF TADTSSDTAYMLLSSLTSEDSAVY YCATDGNYDWFAYWGQGTLVTV SA	SEQ ID N° 43
		mVL 4	DLVMTQTPLSLPVSLGDQASISCR SSQSLVHSSGVTYLHWYLQKPGQ SPKLLIYKVSNRFSGVPDRFSGSGS GTDFTLKISRVEAEDLGVYFCSQS THVPPTFGSGTKLEIK	SEQ ID N° 44
		huVH 4	QVQLVQSGAEVKKPGASVKVSCK ASGYTFSSSWMHWVRQAPGQGL EWMGIFLPGSGSTDYAQKFQGRV TMTRDTSTSTVYMELSSLRSEDTA VYYCATDGNYDWFAYWGQGTLV TVSS	SEQ ID N° 55
		huVL 4	DIVMTQTPLSLSVTPGQPASISCKS SQSLVHSSGVTYLYWYLQKPGQS PQLLIYKVSNRFSGVPDRFSGSGS GTDFTLKISRVEAEDVGVYYCSQS THVPPTFGQGTKLEIK	SEQ ID N° 56

Table 2

Hybridoma deposit	mAb	Amino acid sequences		SEQ ID N°
1E9D9B6	mAb16	VH CDR 1	GYTFTSYY	SEQ ID N°16
		VH CDR 2	INPSNGGT	SEQ ID N°17
		VH CDR 3	TRGGYYPFDY	SEQ ID N°18
		VL CDR 1	QSLLDSDGKTY	SEQ ID N°19
		VL CDR 2	LVS	SEQ ID N°20
		VL CDR 3	WQGTHSPYT	SEQ ID N°21
		mVH 16	QVQLQQSGAELVKPGASVKLSCK ASGYTFTSYYMYWVKQRPGQGLE WIGEINPSNGGTNFNEKFKSKATL TVDKSSSTAYMQLSSLTSEDSAVY YCTRGGYYPFDYWGQGTTLTVSS	SEQ ID N° 45
		mVL 16	DVVMTQTPLTLSVTIGRPASISCKS SQSLLDSDGKTYLYWLLQRPGQS PKRLIYLVSELDSGVPDRITGSGSG TDFTLKISRVEAEDLGVYYCWQG THSPYTFGGGTKLEIK	SEQ ID N° 46
		huVH 16a	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYYMYWVRQAPGQGLE WMGIINPSNGGTSYAQKFQGRVT MTRDTSTSTVYMELSSLRSEDTAV YYCTRGGYYPFDYWGQGTTVTV SS	SEQ ID N° 57
		huVH 16b	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYYMHWVRQAPGQGL EWMGIINPSNGGTSYAQKFQGRV TMTRDTSTSTVYMELSSLRSEDTA VYYCTRGGYYPFDYWGQGTTVT VSS	SEQ ID N° 58
		huVH 16c	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYYMYWVRQAPGQGLE WMGEINPSNGGTNYAQKFQGRV TMTRDTSTSTVYMELSSLRSEDTA	SEQ ID N° 59

			VYYCTRGGYYPFDYWGQGTTVT VSS	
		huVL 16a	DVVMTQSPLSLPVTLGQPASISCR SSQSLLDSDGKTYLYWFQQRPGQ SPRRLIYLVSNRDSGVPDRFSGSGS GTDFTLKISRVEAEDVGVYYCWQ GTHSPYTFGQGTKLEIK	SEQ ID N° 60
		huVL 16b	DVVMTQSPLSLPVTLGQPASISCR SSQSLLDSDGKTYLNWFQQRPGQ SPRRLIYLVSNRDSGVPDRFSGSGS GTDFTLKISRVEAEDVGVYYCWQ GTHSPYTFGQGTKLEIK	SEQ ID N° 61
		huVL 16c	DVVMTQSPLSLPVTLGQPASISCR SSQSLLDSDGKTYLYWFQQRPGQ SPRRLIYLVSERDSGVPDRFSGSGS GTDFTLKISRVEAEDVGVYYCWQ GTHSPYTFGQGTKLEIK	SEQ ID N° 62

Table 3

Hybridoma deposit	mAb	Amino acid sequences		SEQ ID N°
1B3B4F11	mAb19	VH CDR 1	GYSITSDYA	SEQ ID N°22
		VH CDR 2	ISFSGYT	SEQ ID N°23
		VH CDR 3	AREVNYGDSYHFDY	SEQ ID N°24
		VL CDR 1	SQHRTYT	SEQ ID N°25
		VL CDR 2	VKKDGSH	SEQ ID N°26
		VL CDR 3	GVGDAIKGQSVFV	SEQ ID N°27
		mVH 19	DVQLQESGPGLVKPSQSLSLTCTV TGYSITSDYAWNWIRQFPGNKLE WMGYISFSGYTSYNPSLKSRISVTR DTSRNQFFLQLTSVTTEDTATYYC AREVNYGDSYHFDYWGQGTIVTV SS	SEQ ID N° 47

		mVL 19	QLALTQSSSASFSLGASAKLTCTLS SQHRTYTIEWYQQQSLKPPKYVM EVKKDGSHSTGHGIPDRFSGSSSG ADRYLSISNIQPEDEAIYICGVGDAI KGQSVFVFGGGTKVTVL	SEQ ID N° 48
		huVH 19a	QVQLQESGPGLVKPSQTLSLTCT VSGYSITSDYAWNWIRQHPGKGL EWIGYISFSGYTYYNPSLKSRVTIS VDTSKNQFSLKLSSVTAADTAVYY CAREVNYGDSYHFDYWGQGTLV TVSS	SEQ ID N° 63
		huVH 19b	QVQLQESGPGLVKPSQTLSLTCT VSGYSITSDYAWSWIRQHPGKGLE WIGYISFSGYTYYNPSLKSRVTISV DTSKNQFSLKLSSVTAADTAVYYC AREVNYGDSYHFDYWGQGTLVT VSS	SEQ ID N° 64
		huVH 19c	QVQLQESGPGLVKPSQTLSLTCT VSGYSITSDYAWNWIRQHPGKGL EWIGYISFSGYTSYNPSLKSRVTIS VDTSKNQFSLKLSSVTAADTAVYY CAREVNYGDSYHFDYWGQGTLV TVSS	SEQ ID N° 65
		huVL 19a	QLVLTQSPSASASLGASVKLTCTL SSQHRTYTIEWHQQQPEKGPRYL MKVKKDGSHSKGDGIPDRFSGSSS GAERYLTISSLQSEDEADYYCGVG DAIKGQSVFVFGGGTKVEIK	SEQ ID N° 66
		huVL 19b	QLVLTQSPSASASLGASVKLTCTL SSQHRTYTIAWHQQQPEKGPRYL MKVKKDGSHSKGDGIPDRFSGSSS GAERYLTISSLQSEDEADYYCGVG DAIKGQSVFVFGGGTKVEIK	SEQ ID N° 67
		huVL 19c	QLVLTQSPSASASLGASVKLTCTL	SEQ ID N° 68

			SSQHRTYTIEWHQQQPEKGPRYL MEVKKDGSHSKGDGIPDRFSGSSS GAERYLTISSLQSEDEADYYCGVG DAIKGQSVFVFGGGTKVEIK	

Table 4

Examples of monoclonal antibodies that can be generated by using an immunogen comprising the amino-acid sequence "QGPWLEEEEEAYGWMDFGRRSAEDEN", (C-terminal part of progastrin) corresponding to the amino acid sequence 55-80 of human progastrin include, but are not restricted to antibodies designated as: mAb8 and mAb13 in the following Table 5 and 6. Experimental results of epitope mapping show that mAb13 do specifically bind an epitope within said hPG C-terminal amino acid sequence.

Hybridoma deposit	mAb	Amino acid sequences		SEQ ID N°
1C10D3B9	mAb8	VH CDR 1	GFTFTTYA	SEQ ID N°28
		VH CDR 2	ISSGGTYT	SEQ ID N°29
		VH CDR 3	ATQGNYSLDF	SEQ ID N°30
		VL CDR 1	KSLRHTKGITF	SEQ ID N°31
		VL CDR 2	QMS	SEQ ID N°32
		VL CDR 3	AQNLELPLT	SEQ ID N°33
		mVH 8	EVQLVESGGGLVKPGGSLRLSC AASGFTFTTYAMSWVRQAPGK GLEWVATISSGGTYTYYADSVK GRFTISRDNAKNSLYLQMNSLRA EDTAVYYCATQGNYSLDFWGQ GTTVTVSS	SEQ ID N° 49
		mVL 8	DIVMTQSPLSLPVTPGEPASISCR SSKSLRHTKGITFLYWYLQKPGQ	SEQ ID N° 50

			SPQLLIYQMSNLASGVPDRFSSS GSGTDFTLKISRVEAEDVGVYYC AQNLELPLTFGGGTKVEIK	
		VH hZ8CV1	EVQLVESGGGLVKPGGSLRLSC AASGFTFTTYAMSWVRQAPGK GLEWVSSISSGGTYTYYADSVKG RFTISRDNAKNSLYLQMNSLRAE DTAVYYCATQGNYSLDFWGQG TTVTVSS	SEQ ID N° 69
		VL hZ8CV1	DIVMTQSPLSLPVTPGEPASISCR SSKSLRHTKGITFLYWYLQKPGQ SPQLLIYQMSNRASGVPDRFSGS GSGTDFTLKISRVEAEDVGVYYC AQNLELPLTFGGGTKVEIK	SEQ ID N° 70
		VH hZ8CV2	EVQLVESGGGLVKPGGSLRLSC AASGFTFTTYAMSWVRQAPGK GLEWVATISSGGTYTYYADSVK GRFTISRDNAKNSLYLQMNSLRA EDTAVYYCATQGNYSLDFWGQ GTTVTVSS	SEQ ID N° 71
		VL hZ8CV2	DIVMTQSPLSLPVTPGEPASISCR SSKSLRHTKGITFLYWYLQKPGQ SPQLLIYQMSNLASGVPDRFSSS GSGTDFTLKISRVEAEDVGVYYC AQNLELPLTFGGGTKVEIK	SEQ ID N° 72
		CH hZ8CV2	EVQLVESGGGLVKPGGSLRLSC AASGFTFTTYAMSWVRQAPGK GLEWVATISSGGTYTYYADSVK GRFTISRDNAKNSLYLQMNSLRA EDTAVYYCATQGNYSLDFWGQ GTTVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYIC	SEQ ID N° 73

			NVNHKPSNTKVDKRVEPKSCDK THTCPPCPAPELLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPG K	
		CL hZ8CV2	DIVMTQSPLSLPVTPGEPASISCR SSKSLRHTKGITFLYWYLQKPGQ SPQLLIYQMSNLASGVPDRFSSS GSGTDFTLKISRVEAEDVGVYYC AQNLELPLTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLS SPVTKSFNRGEC	SEQ ID N° 74

Table 5

Hybridoma deposit	mAb	Amino acid sequences		SEQ ID N°
2C6C3C7	mAb13	VH CDR 1	GFIFSSYG	SEQ ID N°34
		VH CDR 2	INTFGDRT	SEQ ID N°35
		VH CDR 3	ARGTGTY	SEQ ID N°36
		VL CDR 1	QSLLDSDGKTY	SEQ ID N°37

		VL CDR 2	LVS	SEQ ID N°38
		VL CDR 3	WQGTHFPQT	SEQ ID N°39
		mVH 13	EVQLVESGGGLVQPGGSLKLSC AASGFIFSSYGMSWVRQSPDRRL ELVASINTFGDRTYYPDSVKGRF TISRDNAKNTLYLQMTSLKSEDT AIYYCARGTGTYWGQGTTLTVS S	SEQ ID N° 51
		mVL 13	DVVLTQTPLTLSVTIGQPASISCK SSQSLLDSDGKTYLNWLLQRPG QSPKRLIYLVSKLDSGVPDRFTG SGSGTDFTLKISRVEAEDLGVYY CWQGTHFPQTFGGGTKLEIK	SEQ ID N° 52
		huVH 13a	EVQLVESGGGLVQPGGSLRLSC AASGFIFSSYGMSWVRQAPGKG LEWVANINTFGDRTYYVDSVKG RFTISRDNAKNSLYLQMNSLRAE DTAVYYCARGTGTYWGQGTLV TVSS	SEQ ID N° 75
		huVH 13b	EVQLVESGGGLVQPGGSLRLSC AASGFIFSSYGMSWVRQAPGKG LEWVASINTFGDRTYYVDSVKG RFTISRDNAKNSLYLQMNSLRAE DTAVYYCARGTGTYWGQGTLV TVSS	SEQ ID N° 76
		huVL 13a	DVVMTQSPLSLPVTLGQPASISC RSSQSLLDSDGKTYLNWFQQRP GQSPRRLIYLVSNRDSGVPDRFS GSGSGTDFTLKISRVEAEDVGVY YCWQGTHFPQTFGGGTKVEIK	SEQ ID N° 77
		huVL 13b	DVVMTQSPLSLPVTLGQPASISC RSSQSLLDSDGKTYLNWFQQRP GQSPRRLIYLVSKRDSGVPDRFS	SEQ ID N° 78

			GSGSGTDFTLKISRVEAEDVGVY YCWQGTHFPQTFGGGTKVEIK	

Table 6

Other examples include anti-hPG monoclonal and/or polyclonal antibodies generated by using an immunogen comprising an amino acid sequence of SEQ ID N°40.

The terms "N-terminal anti-hPG antibodies" and "C-terminal anti-hPG antibodies" designate antibodies binding to an epitope comprising amino acids located in the N-terminal part of hPG or to an epitope comprising amino acids located in the C-terminal part of hPG, respectively. Preferably, the term "N-terminal anti-hPG antibodies" refers to antibodies binding to an epitope located in a domain of progastrin whose sequence is represented by SEQ ID NO. 2. In another preferred embodiment, the term "C-terminal anti-hPG antibodies" refers to antibodies binding to an epitope located in a domain of progastrin whose sequence is represented by SEQ ID NO. 3.

The term "epitope" refers to a region of an antigen that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those amino acids that directly contribute to the affinity of the interaction. Epitopes may also be conformational. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics. The determination of the epitope bound by an antibody may be performed by any epitope mapping technique, known by a man skilled in the art. An epitope may comprise different amino acids which located sequentially within the amino acid sequence of a protein. An epitope may also comprise amino acids which are not located sequentially within the amino acid sequence of a protein.

In a particular embodiment, said antibody is a monoclonal antibody selected in the group consisting of:

- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and

CDR-H3 of amino acid sequences SEQ ID N°4, 5 and 6, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°4, 5 and 6, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°7, 8 and 9, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°7, 8 and 9, respectively,

- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°10, 11 and 12, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°10, 11 and 12, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°13, 14 and 15, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°13, 14 and 15, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°16, 17 and 18, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°16, 17 and 18, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°19, 20 and 21, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°19, 20 and 21, respectively,
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°22, 23 and 24, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°22, 23 and 24, respectively, and a light chain comprising at least one, preferentially at

least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°25, 26 and 27, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°25, 26 and 27, respectively,

- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially at least three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°28, 29 and 30, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°28, 29 and 30, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°31, 32 and 33, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°31, 32 and 33, respectively, and
- A monoclonal antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°34, 35 and 36, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°34, 35 and 36, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°37, 38 and 39, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°37, 38 and 39, respectively.

In the sense of the present invention, the “percentage identity” or “% identity” between two sequences of nucleic acids or amino acids means the percentage of identical nucleotides or amino acid residues between the two sequences to be compared, obtained after optimal alignment, this percentage being purely statistical and the differences between the two sequences being distributed randomly along their length. The comparison of two nucleic acid or amino acid sequences is traditionally carried out by comparing the sequences after having optimally aligned them, said comparison being able to be conducted by segment or by using an “alignment window”. Optimal alignment of the sequences for comparison

can be carried out, in addition to comparison by hand, by means of methods known by a man skilled in the art.

For the amino acid sequence exhibiting at least 80%, preferably 85%, 90%, 95% and 98% identity with a reference amino acid sequence, preferred examples include those containing the reference sequence, certain modifications, notably a deletion, addition or substitution of at least one amino acid, truncation or extension. In the case of substitution of one or more consecutive or non-consecutive amino acids, substitutions are preferred in which the substituted amino acids are replaced by "equivalent" amino acids. Here, the expression "equivalent amino acids" is meant to indicate any amino acids likely to be substituted for one of the structural amino acids without however modifying the biological activities of the corresponding antibodies and of those specific examples defined below.

Equivalent amino acids can be determined either on their structural homology with the amino acids for which they are substituted or on the results of comparative tests of biological activity between the various antibodies likely to be generated.

In a more particular embodiment, said antibody is a monoclonal antibody selected in the group consisting of:

- A monoclonal antibody comprising a heavy chain of amino acid sequence SEQ ID N°41 and a light chain of amino acid sequence SEQ ID N°42;
- A monoclonal antibody comprising a heavy chain of amino acid sequence SEQ ID N°43 and a light chain of amino acid sequence SEQ ID N°44;
- A monoclonal antibody comprising a heavy chain of amino acid sequence SEQ ID N°45 and a light chain of amino acid sequence SEQ ID N°46;
- A monoclonal antibody comprising a heavy chain of amino acid sequence SEQ ID N°47 and a light chain of amino acid sequence SEQ ID N°48;
- A monoclonal antibody comprising a heavy chain of amino acid sequence SEQ ID N°49 and a light chain of amino acid sequence SEQ ID N°50; and
- A monoclonal antibody comprising a heavy chain of amino acid sequence SEQ ID N°51 and a light chain of amino acid sequence SEQ ID N°52.

In another particular embodiment, the antibody used in the method of the invention is a humanised antibody.

As used herein, the expression "humanized antibody" means an antibody that contains CDR regions derived from an antibody of nonhuman origin, the other parts of the antibody molecule being derived from one or several human antibodies. In addition, some of the skeleton segment residues (called FR for framework) can be modified to preserve binding affinity, according to techniques known by a man skilled in the art (Jones *et al.*, Nature, 321:522-525, 1986). The goal of humanisation is a reduction in the immunogenicity of a xenogenic antibody, such as a murine antibody, for introduction into a human, while maintaining the full antigen binding affinity and specificity of the antibody.

The humanized antibodies of the invention or fragments of same can be prepared by techniques known to a person skilled in the art (such as, for example, those described in the documents Singer *et al.*, J. Immun., 150:2844-2857, 1992). Such humanized antibodies are preferred for their use in methods involving *in vitro* diagnoses or preventive and/or therapeutic treatment *in vivo*. Other humanization techniques are also known to the person skilled in the art. Indeed, Antibodies can be humanized using a variety of techniques including CDR- grafting (EP 0 451 261; EP 0 682 040; EP 0 939 127; EP 0 566 647; US 5,530,101; US 6,180,370; US 5,585,089; US 5,693,761; US 5,639,641; US 6,054,297; US 5,886,152; and US 5,877,293), veneering or resurfacing (EP 0 592 106; EP 0 519 596; Padlan E. A., 1991 , Molecular Immunology 28(4/5): 489-498; Studnicka G. M. et al., 1994, Protein Engineering 7(6): 805-814; Roguska M.A. et al., 1994, Proc. Natl. Acad. ScL U.S.A., 91:969-973), and chain shuffling (U.S. Pat. No. 5,565,332). Human antibodies can be made by a variety of methods known in the art including phage display methods. See also U.S. Pat. Nos. 4,444,887, 4,716,111, 5,545,806, and 5,814,318; and international patent application publication numbers WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741.

In a more particular embodiment, said antibody is a humanized antibody selected in the group consisting of:

- A humanized antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and

CDR-H3 of amino acid sequences SEQ ID N°4, 5 and 6, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°4, 5 and 6, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°7, 8 and 9, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°7, 8 and 9, respectively,

- A humanized antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°10, 11 and 12, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°10, 11 and 12, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°13, 14 and 15, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°13, 14 and 15, respectively,
- A humanized antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°16, 17 and 18, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°16, 17 and 18, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°19, 20 and 21, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°19, 20 and 21, respectively,
- A humanized antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°22, 23 and 24, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°22, 23 and 24, respectively, and a light chain comprising at least one, preferentially at

least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°25, 26 and 27, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°25, 26 and 27, respectively,

- A humanized antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°28, 29 and 30, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°28, 29 and 30, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°31, 32 and 33, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°31, 32 and 33, respectively, and
- A humanized antibody comprising a heavy chain comprising at least one, preferentially at least two, preferentially three, of CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°34, 35 and 36, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°34, 35 and 36, respectively, and a light chain comprising at least one, preferentially at least two, preferentially three, of CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°37, 38 and 39, respectively, or sequences with at least 80%, preferably 85%, 90%, 95% and 98% identity after optimal alignment with sequences SEQ ID N°37, 38 and 39, respectively,

wherein said antibody also comprises constant regions of the light-chain and the heavy-chain derived from a human antibody.

In another more particular embodiment, said antibody is a humanized antibody selected in the group consisting of:

- A humanized antibody comprising a heavy chain variable region of amino acid sequence SEQ ID N°53, and a light chain variable region of amino acid sequence SEQ ID N°54;

- A humanized antibody comprising a heavy chain variable region of amino acid sequence SEQ ID N°55, and a light chain variable region of amino acid sequence SEQ ID N°56;
- A humanized antibody comprising a heavy chain variable region of amino acid sequence selected between SEQ ID N°57, 58, and 59, and a light chain variable region of amino acid sequence selected between SEQ ID N°60, 61, and 62;
- A humanized antibody comprising a heavy chain variable region of amino acid sequence selected between SEQ ID N°63, 64, and 65, and a light chain variable region of amino acid sequence selected between SEQ ID N°66, 67, and 68;
- A humanized antibody comprising a heavy chain variable region of amino acid sequence selected between SEQ ID N°69 and 71, and a light chain variable region of amino acid sequence selected between SEQ ID N°70 and 72; and
- A humanized antibody comprising a heavy chain variable region of amino acid sequence selected between SEQ ID N°75 and 76, and a light chain variable region of amino acid sequence selected between SEQ ID N°77 and 78;

wherein said antibody also comprises constant regions of the light-chain and the heavy-chain derived from a human antibody.

More preferably, said antibody comprises a heavy chain variable region of amino acid sequence SEQ ID N°71 and a light chain variable region of amino acid sequence SEQ ID N°72, said antibody also comprising constant regions of the light-chain and the heavy-chain derived from a human antibody.

Even more preferably, said antibody comprises a heavy chain of amino acid sequence SEQ ID N°73 and a light chain of amino acid sequence SEQ ID N°74.

In another aspect, the invention also provides immunoconjugates (interchangeably referred to as "antibody-drug conjugates," or "ADCs") comprising an progastrin-binding antibody as described herein, said antibody being conjugated to one or more cytotoxic agents, such as a chemotherapeutic agent, a drug, a growth inhibitory agent, a toxin (e.g., a protein toxin, an enzymatically active toxin of

bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Immunoconjugates have been used for the local delivery of cytotoxic agents, i.e., drugs that kill or inhibit the growth or proliferation of cells, in the treatment of cancer (Lambert, J. (2005) Curr. Opinion in Pharmacology 5:543-549; Wu et al (2005) Nature Biotechnology 23(9): 1137-1146; Payne, G. (2003) i 3:207-212; Syrigos and Epenetos (1999) Anticancer Research 19:605-614; Niculescu-Duvaz and Springer (1997) Adv. Drug Deliv. Rev. 26:151-172; U.S. Pat. No. 4,975,278). Immunoconjugates allow for the targeted delivery of a drug moiety to a tumor, and intracellular accumulation therein, where systemic administration of unconjugated drugs may result in unacceptable levels of toxicity to normal cells as well as the tumor cells sought to be eliminated (Baldwin et al, Lancet (Mar. 15, 1986) pp. 603-05; Thorpe (1985) "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review," in Monoclonal Antibodies '84: Biological And Clinical Applications (A. Pinchera et al., eds) pp. 475-506. Both polyclonal antibodies and monoclonal antibodies have been reported as useful in these strategies (Rowland et al., (1986) Cancer Immunol. Immunother. 21 :183-87). Drugs used in these methods include daunomycin, doxorubicin, methotrexate, and vindesine (Rowland et al., (1986) supra). Toxins used in antibody-toxin conjugates include bacterial toxins such as diphtheria toxin, plant toxins such as ricin, small molecule toxins such as geldanamycin (Mandler et al (2000) J. Nat. Cancer Inst. 92(19): 1573-1581; Mandler et al (2000) Bioorganic & Med. Chem. Letters 10:1025-1028; Mandler et al (2002) Bioconjugate Chem. 13:786-791), maytansinoids (EP 1391213; Liu et al., (1996) Proc. Natl. Acad. Sci. USA 93:8618-8623), and calicheamicin (Lode et al (1998) Cancer Res. 58:2928; Hinman et al (1993) Cancer Res. 53:3336-3342). The toxins may exert their cytotoxic effects by mechanisms including tubulin binding, DNA binding, or topoisomerase inhibition. Some cytotoxic drugs tend to be inactive or less active when conjugated to large antibodies or protein receptor ligands.

In certain embodiments, an immunoconjugate comprises an antibody and a chemotherapeutic agent or other toxin. Chemotherapeutic agents useful in the generation of immunoconjugates are described herein (e.g., above). Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from

Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. See, e.g., WO 93/21232 published October 28, 1993. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi, ^{131}I, ^{131}In, ^{90}Y, and ^{186}Re. Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N- succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p- diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as l,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et ah, Science, 238: 1098 (1987). Carbon- 14-labeled l-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

Conjugates of an antibody and one or more small molecule toxins, such as a calicheamicin, maytansinoids, dolastatins, aurostatins, a trichothecene, and CC 1065, and the derivatives of these toxins that have toxin activity, are also contemplated herein.

The immunoconjugate of the invention may further comprise a linker.

“Linker”, “Linker Unit”, or “link” means a chemical moiety comprising a covalent bond or a chain of atoms that covalently attaches a binding protein to at least one cytotoxic agent.

Linkers may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds

(such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of cyctotoxic agents to the addressing system. Other cross-linker reagents may be BMPS, EMCS, GMBS, HBVS, LC-SMCC, MBS, MPBH, SBAP, SIA, SIAB, SMCC, SMPB, SMPH, sulfo-EMCS, sulfo-GMBS, sulfo-KMUS, sulfo-MBS, sulfo-SIAB, sulfo-SMCC, and sulfo-SMPB, and SVSB (succinimidyl-(4-vinylsulfone)benzoate) which are commercially available (e.g., from Pierce Biotechnology, Inc., Rockford, Ill., U.S.A).

The linker may be a “non-cleavable” or “cleavable”.

In another aspect, the invention provides a composition for use in the prevention or the treatment of lung cancer, said composition comprising an antibody recognizing an epitope including an amino acid sequence corresponding to an amino acid sequence of progastrin.

In a more specific embodiment, said composition for use in the prevention or the treatment of lung cancer comprises an antibody recognizing an epitope of progastrin wherein said epitope includes an amino acid sequence corresponding to an amino acid sequence of the N-terminal part of progastrin, wherein said amino acid sequence may include residues 10 to 14 of hPG, residues 9 to 14 of hPG, residues 4 to 10 of hPG, residues 2 to 10 of hPG or residues 2 to 14 of hPG, wherein the amino acid sequence of hPG is SEQ ID N°1.

In a more specific embodiment, the composition for use in the prevention or the treatment of lung cancer comprises an antibody recognizing an epitope of progastrin wherein said epitope includes an amino acid sequence corresponding to an amino acid sequence of the C-terminal part of progastrin, wherein said amino acid sequence may include residues 71 to 74 of hPG, residues 69 to 73 of hPG, residues 71 to 80 of hPG (SEQ ID N°40), residues 76 to 80 of hPG, or residues 67 to 74 of hPG, wherein the amino acid sequence of hPG is SEQ ID N°1.

In a more particular embodiment, the composition for use in the prevention or the treatment of lung cancer comprises a progastrin-binding antibody, or an antigen-binding fragment thereof which has an affinity for progastrin of at least 5000

nM, at least 500 nM, 100 nM, 80 nM, 60 nM, 50 nM, 40 nM, 30 nM, 20 nM, 10 nM, 7 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM, 0.1nM, 50 pM, 10 pM, 5 pM, 1 pM, or at least 0.1 pM, as determined by a method such as above-described.

In an even more particular embodiment, the composition for use in the prevention or the treatment of lung cancer comprises a progastrin-binding antibody, wherein said progastrin-binding molecule, or an antigen-binding fragment thereof, is a neutralizing antibody.

In another particular embodiment, a composition for use in the prevention or the treatment of lung cancer comprises a progastrin-binding antibody, wherein said progastrin-binding molecule, or an antigen-binding fragment thereof, is a humanized antibody.

In a particular embodiment, a composition for use in the prevention or the treatment of lung cancer comprises a progastrin-binding antibody, wherein said progastrin-binding molecule, or an antigen-binding fragment thereof, is conjugated to one or more cytotoxic agents, such as a chemotherapeutic agent, a drug, a growth inhibitory agent, a toxin (e.g., a protein toxin, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate), as described above.

In another particular embodiment, a composition for use in the prevention or the treatment of lung cancer for a patient comprises a progastrin-binding antibody, wherein said patient has been diagnosed with lung cancer, wherein a concentration of progastrin is higher in a biological sample from said patient than in a reference sample. Preferably, said patient has been diagnosed with lung cancer by contacting an anti-PG antibody with a biological sample of said patient.

A “biological sample” as used herein is a sample of biological tissue or fluid that contains nucleic acids or polypeptides, e.g., of a lung cancer protein, polynucleotide or transcript. Such a sample must allow for the determination of the expression levels of progastrin. Progastrin is known to be a secreted protein. Preferred biological samples for the determination of the level of the progastrin protein thus include biological fluids. A “biological fluid” as used herein means any fluid that includes material of biological origin. Preferred biological fluids for use in the present invention include bodily fluids of an animal, e.g. a mammal, preferably a

human subject. The bodily fluid may be any bodily fluid, including but not limited to blood, plasma, serum, lymph, cerebrospinal fluid (CSF), saliva, sweat and urine. Preferably, said preferred liquid biological samples include samples such as a blood sample, a plasma sample, or a serum sample. More preferably, the biological sample is a blood sample. Indeed, such a blood sample may be obtained by a completely harmless blood collection from the patient and thus allows for a non-invasive assessment of the risks that the subject will develop a tumor.

A "biological sample" as used herein also includes a solid cancer sample of the patient to be tested, when the cancer is a solid cancer. Such solid cancer sample allows the skilled person to perform any type of measurement of the level of the biomarker of the invention. In some cases, the methods according to the invention may further comprise a preliminary step of taking a solid cancer sample from the patient. By a "solid cancer sample", it is referred to a tumor tissue sample. Even in a cancerous patient, the tissue which is the site of the tumor still comprises non tumor healthy tissue. The "cancer sample" should thus be limited to tumor tissue taken from the patient. Said "cancer sample" may be a biopsy sample or a sample taken from a surgical resection therapy.

A biological sample is typically obtained from a eukaryotic organism, most preferably a mammal, or a bird, reptile, or fish. Indeed, a "subject" which may be subjected to the method described herein may be any of mammalian animals including human, dog, cat, cattle, goat, pig, swine, sheep and monkey; or a bird; reptile; or fish. Preferably, a subject is a human being; a human subject may be known as a "patient".

By "obtaining a biological sample," it is herein meant to obtain a biological sample for use in methods described in this invention. Most often, this will be done by removing a sample of cells from an animal, but can also be accomplished by using previously isolated cells (e.g., isolated by another person, at another time, and/or for another purpose), or by performing the methods of the invention in vivo. Archival tissues, having treatment or outcome history, will be particularly useful.

This sample may be obtained and if necessary prepared according to methods known to a person skilled in the art. In particular, it is well known in the art that the sample should be taken from a fasting subject.

In a more particular aspect, the present invention relates to a composition for use in the prevention or the treatment of lung cancer according to the invention, wherein said progastrin-binding antibody, or an antigen-binding fragment thereof, is selected among N-terminal anti-progastrin antibodies and C-terminal anti-progastrin antibodies.

Antibody compositions for use in the methods of the invention can be prepared as different formulations, including, but not limited to, an aqueous suspension, for administration by a variety of routes, including, but not limited to, parenteral, intrathecal, subcutaneous, intravenous, intramuscular, intraperitoneal, infusion or bolus administration. In some embodiments, the composition is formulated for parenteral administration, and in some specific embodiments, intravenous injection by infusion.

In a particular embodiment, a composition for use in the prevention or the treatment of lung cancer, according to the invention, comprises an effective dose the anti-progastrin antibodies of the invention ranges from 0.001 mg/kg to about 250 mg/kg, which may be given in one administration, or over multiple, spaced administrations.

In a particular embodiment, a composition for use in the prevention or the treatment of lung cancer, according to the invention, comprises a progastrin-binding antibody, or an antigen-binding fragment thereof selected among polyclonal antibodies, monoclonal antibodies, chimeric antibodies, single chain antibodies, camelized antibodies, IgA1 antibodies, IgA2 antibodies, IgD antibodies, IgE antibodies, IgG1 antibodies, IgG2 antibodies, IgG3 antibodies, IgG4 antibodies and IgM antibodies. Preferably, said antibodies are those described above. More preferably, said antibodies are humanized antibodies.

Preferably, the present invention relates to a pharmaceutical composition comprising a composition for use in the prevention or the treatment of lung cancer according to the invention, and a pharmaceutically acceptable carrier. More specifically, the pharmaceutical composition for use in the prevention or the treatment of lung cancer according to the invention, comprises an antibody as described above and a pharmaceutically acceptable carrier.

In a more particular aspect, the present invention relates to a pharmaceutical composition comprising a composition for use in the prevention or the treatment of lung cancer according to the invention, and a pharmaceutically acceptable carrier, wherein said anti-progastrin antibody is administered at a dose from 0.001 mg/kg to 250 mg/kg, and preferably at a dose of at least 0.005 mg/kg, at least 0.01 mg/kg, at least 0.05 mg/kg, at least 0.1 mg/kg, at least 0.5 mg/kg, at least 1 mg/kg, at least 5 mg/kg, at least 10 mg/kg, at least 50 mg/kg or at least 100 mg/kg. In another aspect, the present invention relates to a kit of parts comprising a composition for use in the prevention or the treatment of lung cancer, according to the invention, and an anti-cancer therapeutic molecule.

Indeed, treatment with anti-PG monoclonal antibodies as described herein can be combined with, or adjunctive to, other therapy. Non-limiting examples of other therapy include chemotherapeutic treatment, radiation therapy, surgical resection, and antibody therapy.

In another aspect, the present invention relates to a kit of part comprising a composition for use in the prevention or the treatment of lung cancer, according to the invention, and an anti-cancer therapeutic molecule chosen among: a chemotherapeutic molecule, a targeted therapy molecule.

In a particular embodiment, the present invention relates to kits of part comprising, for the simultaneous, sequential or separate administration, a composition for the treatment of lung cancer according to the invention and a chemotherapeutic molecule. Useful chemotherapeutic molecules for this purpose, include, but are not limited to folate antagonists, purine antagonists, pyrimidine antagonists, DNA alkylating molecules, DNA cross- linking drugs, antibiotics, platinum complexes, proteasome inhibitors, mitotic spindle poisons, topoisomerase inhibitors, tyrosine kinase inhibitors, and others.

In another particular embodiment, the present invention relates to kits of part comprising, for the simultaneous, sequential or separate administration, a composition according to the invention and a composition comprising another targeted therapy molecule. Such targeted therapy molecule include, but are not limited to antibodies that target EGFR, such as cetuximab or panitumumab, antibodies that target VEGF, such as bevacizumab, antibodies that target HER2, such

as trastuzumab or pertuzumab, antibodies that target PD-1 and PDL-1, such as pembrolizumab, antibodies that target CTLA-4, such as ipilimumab, small molecule drugs that target EGFR, such as erlotinib, small molecule drugs that target BRAF, such as vemurafenib or dabrafenib, a recombinant fusion protein that target VEGF, such as Aflibercept.

In another particular aspect, the present invention relates to the use of a progastrin-binding antibody, or an antigen-binding fragment thereof, for the diagnosis of lung cancer.

In another particular aspect, the present invention relates to the use of a progastrin-binding antibody, or an antigen-binding fragment thereof, for the prevention or the treatment of lung cancer.

In a more particular aspect, the present invention relates to the use of a progastrin-binding antibody, or an antigen-binding fragment thereof, for the prevention or the treatment of lung cancer for a patient, wherein the concentration of progastrin in a biological sample of said patient has been determined and is higher than the concentration of progastrin of a reference biological sample.

In another particular aspect, the invention relates to the use of a pharmaceutical composition of the invention to prevent recurrence of lung cancer. Accordingly, the present disclosure provides methods and compositions useful for treating lung cancer and preventing recurrence of lung cancer in animals, including humans. The methods of treatment involve administering to a subject diagnosed with lung cancer an amount of an antibody that specifically binds progastrin effective to provide a therapeutic benefit. The anti-PG antibody may be administered alone, as monotherapy, or in conjunction with, or adjunctive to, other treatment modalities, such as tumour resection, radiation therapy, chemotherapy, therapy with another antibody, etc.

Solid tumours are not necessarily homogenous tissues. Rather, some tumours comprise a plurality of aberrant cell types having distinct phenotypic and functional properties. In this respect, such tumours are analogous to abnormal organs. Cells comprising solid tumours differ with respect to the extent to which they are capable of initiating formation of a new tumour when transplanted to a new site in the same host, or to a new host of the same or different species. Cells having this property are

known as tumour or cancer initiating cells, or alternatively, tumour or cancer stem cells. See, e.g., Hardavella et al., 2016, "Lung cancer stem cells—characteristics, phenotype," Transl Lung Cancer Res. 2016, 5(3): 272-279. Such cells are highly tumorigenic.

Generally, cancer stem cells are defined by two properties: the ability to self-renew and the ability to give rise to daughter cells that differentiate into non-stem cells. Self-renewal is the ability to undergo cell division whereby one or both daughter cells remain undifferentiated, retaining the ability to give rise to yet another cancer stem cell with similar capacity to proliferate as the parental cell. This property allows cancer stem cells to ultimately give rise to the great number cells that comprise the growing tumour. Cancer stem cells also have the ability to produce daughter cells that differentiate, giving rise to a spectrum of more differentiated non-stem, or bulk, tumour cells found in many solid tumours. Thus, when transplanted, cancer stem cells can reconstitute the type of tumour from which they originated, even after multiple, serial transplantations. Furthermore, it is thought that cancer stem cells harbour genetic mutations and/or epigenetic changes that result in altered proliferation patterns and/or low rates of apoptosis.

Cancer stem cells can be identified according to a number of phenotypic characteristics that distinguish them from bulk tumour cells. Methods useful for assessing whether a tumour or cell line contains cancer stem cells are familiar to those of skill in the art. Such methods are described for example in Hardavella et al., 2016, "Lung cancer stem cells—characteristics, phenotype," Transl Lung Cancer Res. 2016, 5(3): 272-279, as well as in WO 2012/013609. Particular instances of these methods are also described in the examples of the present application.

In a more particular aspect, the present invention relates to the use of a progastrin-binding antibody, or an antigen-binding fragment thereof, for the prevention or the treatment of lung cancer for a patient, wherein said patient presents metastasis.

In an even more particular aspect, the present invention relates to the use of a progastrin-binding antibody, or an antigen-binding fragment thereof, for the prevention or the treatment of lung cancer for a patient, wherein said patient presents metastasis and wherein the concentration of progastrin in a biological

sample of said patient has been determined and is higher than the concentration of progastrin of a reference biological sample.

The constituents of which the combination is composed may be administered simultaneously, separately, or sequentially so as to obtain the maximum efficacy of the combination; it being possible for each administration to vary in its duration from a rapid administration to a continuous perfusion.

As used herein, “simultaneous administration” refers to the administration of the two compounds of the composition according in a single and unique pharmaceutical form. As used herein, “separate administration” refers to the administration, at the same time, of the two compounds of the composition according to the invention in distinct pharmaceutical forms. As used herein, “sequential administration” refers to the successive administration of the two compounds of the composition according to the invention, each in a distinct pharmaceutical form.

A "therapeutically effective amount", as used herein, refers to the minimum concentration or amount of a compound (or of compounds) which is effective to prevent, alleviate, reduce or ameliorate symptoms of disease or prolong the survival of the patient being treated.

In another aspect, the present disclosure provides a method for preventing prostate cancer recurrence, comprising administering an effective amount of an anti-PG antibody to a subject in need of prevention. Methods of preventing liver cancer recurrence according to the present disclosure are accomplished by administering one or more anti-PG antibody capable of neutralizing PG, described above, to individuals at risk for lung cancer recurrence.

Subjects in need of prevention of prostate cancer recurrence are individuals previously treated for lung cancer, who are at risk of, but have not, been diagnosed with lung cancer again. Suitable subjects include individuals previously treated for lung cancer by any means, including surgical resection, chemotherapy, or any other therapy.

Effective prevention of lung cancer recurrence includes, but is not limited to, a complete and ongoing absence of lung cancer recurrence. In some embodiments,

effective prevention is measured by an absence of lung cancer tumours or lung cancer stem cells obtained from a subject at risk for lung cancer recurrence. In some embodiments, effective prevention is determined by a lack of increase in blood concentration of PG in a subject at risk for lung cancer recurrence.

Anti-PG treatment can be administered alone, as monotherapy, or in combination with, or adjunctive to, one or more other treatments. Other treatments include, without limitation, surgical resection, and treatment with a second therapeutic agent, such as a chemotherapeutic agent or an antibody, as described above. Combination treatment as provided herein involves the administration of at least two treatments to a patient, one of which is anti-PG treatment with at least one anti-PG antibody, and the other of which is treatment with a therapeutic agent or procedure.

The anti-PG antibody and a second agent can be administered simultaneously, successively, or separately. As used herein, the anti-PG antibody and the second agent are said to be administered successively if they are administered to the patient on the same day, for example during the same patient visit. Successive administration can occur 1, 2, 3, 4, 5, 6, 7 or 8 hours apart. In contrast, the anti-PG antibody and the second agent are said to be administered separately if they are administered to the patient on different days, for example, the anti-PG antibody and the second therapeutic agent can be administered at a 1-day, 2-day or 3-day, one-week, 2-week or monthly intervals. In the methods of the present disclosure, administration of the anti-PG antibody of the disclosure can precede or follow administration of the second agent. As a non-limiting example, the anti-PG antibody and second agent can be administered concurrently for a period of time, followed by a second period of time in which the administration of anti-PG antibody and the second agent are alternated.

The characteristics of the embodiments of the invention will become further apparent from the following detailed description of examples below.

FIGURE LEGENDS

Figure 1:

Cell proliferation assay: NCI-H358 cells were treated with either a control antibody or the anti-hPG Hz 8CV2 (PG Hz), a C-terminal anti-hPG humanized antibody.

EXAMPLES

Example 1: Neutralizing activity of anti-hPG antibodies on cancer cell lines

1.1. Neutralizing activity of anti-hPG monoclonal antibodies

Monoclonal antibodies to PG are tested for their ability to inhibit proliferation of several cell lines commonly used to study lung cancer, which produce and secrete progastrin. Survival of cells from each of these cell lines is tested using different anti-hPG monoclonal antibodies.

For each experiment, 50,000 cells are seeded into 6-well plates in medium containing fetal calf serum and incubated for 8 hours. Cells are serum-starved overnight, and starting at 24 hours after seeding (time "T0"), cells are treated in sextuplicates every 12h for 48 hours, in the absence of fetal calf serum, with 1 to 20 µg/ml of monoclonal control antibodies (monoclonal antibody anti-puromycin)(CT mAb), or with 1 to 20 µg/ml anti-hPG mAb, wherein said mAb is a C-terminal anti-hPG monoclonal antibody or a N-terminal anti-hPG monoclonal antibody.

Said mAb is a C-terminal anti-hPG antibody, selected among:

- An antibody comprising a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°28, 29 and 30, and a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°31, 32 and 33,
- An antibody comprising a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°34, 35 and 36, and a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°37, 38 and 39.

or a N-terminal anti-hPG antibody selected among:

- An monoclonal antibody comprising a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°4, 5 and 6, respectively, and a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°7, 8 and 9,
- An antibody comprising a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°10, 11 and 12, respectively, and a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°13, 14 and 15, respectively,
- An antibody comprising a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°16, 17 and 18, respectively, and a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°19, 20 and 21, respectively,
- An antibody comprising a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°22, 23 and 24, respectively, and a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°25, 26 and 27, respectively,

The number of cells at T0 is counted in a control well, for each experiment.

Specifically, the number of live cells in both control and anti-hPG mAb treated wells is counted at 48 hours, then the difference between each cell count and the cell count determined at T0, is calculated. The resulting number of anti-hPG mAb-treated cells is then expressed as a percentage of the number of control mAb-treated cells.

Treatment with anti-hPG monoclonal antibodies reduces cell number as compared to treatment with control antibody. Statistical significance is determined using a one-way ANOVA with a Tukey post-hoc test: * = $p<0.05$, ** = $p<0.01$, and *** = $p<0.001$. In each cell line, anti-hPG antibodies reduce cell survival.

1.2. Neutralizing activity of anti-hPG humanized antibodies on cell survival

Humanized antibodies to PG are tested for their ability to inhibit proliferation of several cell lines commonly used to study lung cancer, which produce and secrete progastrin. Survival of cells from each of these cell lines is tested using different anti-hPG monoclonal antibodies.

For each experiment, 50,000 cells are seeded into 6-well plates in medium containing fetal calf serum and incubated for 8 hours. Cells are serum-starved overnight, and starting at 24 hours after seeding (time "T0"), cells are treated in sextuplicates every 12h for 48 hours, in the absence of fetal calf serum, with 1 to 20 µg/ml of humanized control antibodies (anti-human FcG1, from BioXCell)(CT Hz), or with 1 to 20 µg/ml anti-hPG Hz, wherein said Hz is a C-terminal anti-hPG humanized antibody or a N-terminal anti-hPG humanized antibody. The number of cells at T0 is counted in a control well, for each experiment.

Specifically, the number of live cells in both control and anti-hPG Hz treated wells is counted at 48 hours, then the difference between each cell count and the cell count determined at T0, is calculated. The resulting number of anti-hPG Hz-treated cells is then expressed as a percentage of the number of control mAb-treated cells.

Treatment with anti-hPG Hz antibodies reduces cell number as compared to treatment with control antibody. Statistical significance is determined using a one-way ANOVA with a Tukey post-hoc test: * = $p<0.05$, ** = $p<0.01$, and *** = $p<0.001$. In each cell line, anti-hPG antibodies reduce cell survival.

1.3. Neutralizing activity of anti-hPG monoclonal antibodies on cancer stem cell frequency

Monoclonal antibodies to PG are tested for their ability to reduce cancer stem cell (CSC) frequency using Extreme Limiting Dilution Assay (ELDA), in several cell lines commonly used to study lung cancer, which produce and secrete progastrin. CSC frequency from each of these cell lines is tested using different anti-hPG monoclonal antibodies.

For each experiment, cells are seeded in ultra-low attachment (ULA) P96 (96-well plates) at fixed cellular concentrations per well using a FACS Aria flow cytometer, and a range of concentrations is used from one to 500 cells per well. The cells are cultivated for up to 11 days in ULA plates with M11 medium (Macari et al, Oncogene, 2015) and treated every 3 or 4 days with 1 to 20 µg/ml of monoclonal control antibodies (monoclonal antiboby anti-puromycin)(CT mAb), or with 1 to 20 µg/ml anti-hPG mAb, wherein said mAb is a C-terminal anti-hPG monoclonal antibody or a N-terminal anti-hPG monoclonal antibody.

Specifically, at the end of the incubation phase, the plates are observed with a phase-contrast microscope and the number of positive wells per cellular concentration is assessed. Finally, the ELDA webtool (http://www.bioinf.wehi.edu.au/software/elda/) is used to calculate the CSC frequencies of each treatment group and test for any statistical difference between groups (modified Chi-square test).

Treatment with anti-hPG monoclonal antibodies reduces CSC frequency as compared to treatment with control antibody.

1.4. Neutralizing activity of anti-hPG humanized antibodies on cancer stem cell frequency

- Sphere formation assay

Humanized antibodies to PG are tested for their ability to reduce cancer stem cell (CSC) frequency using sphere formation assay in several cell lines commonly used to study lung cancer, which produce and secrete progastrin.

For each experiment, 700 cells are seeded in 24-well ultra-low attachment (ULA). The cells are cultivated for up to 7 days in ULA plates with M11 medium (Macari et al, Oncogene, 2015) and treated every 3 or 4 days with 20 µg/ml of humanized control antibodies (anti-human FcG1, from BioXCell)(CT Hz), or with 20 µg/ml anti-hPG Hz (PG Hz), wherein said Hz is a C-terminal anti-hPG humanized antibody or a N-terminal anti-hPG humanized antibody.

Specifically, at the end of the incubation phase, the wells are photographed via brightfield microscopy, the pictures are analyzed and the spheres with a mean diameter above 25 µm are counted.

Treatment with anti-hPG humanized antibodies reduces CSC frequency as compared to treatment with control antibody.

- Extreme Limiting Dilution Assay

Humanized antibodies to PG are tested for their ability to reduce cancer stem cell (CSC) frequency using Extreme Limiting Dilution Assay (ELDA) in several cell lines commonly used to study lung cancer, which produce and secrete progastrin. CSC frequency from each of these cell lines is tested using different anti-hPG humanized antibodies.

For each experiment, cells are seeded in ultra-low attachment (ULA) P96 (96-well plates) at fixed cellular concentrations per well using a FACS Aria flow cytometer, and a range of concentrations is used from one to 500 cells per well. The cells are cultivated for up to 11 days in ULA plates with M11 medium (Macari et al, Oncogene, 2015) and treated every 3 or 4 days with 1 to 20 µg/ml of humanized control antibodies (anti-human FcG1, from BioXCell)(CT Hz), or with 1 to 20 µg/ml anti-hPG Hz, wherein said Hz is a C-terminal anti-hPG humanized antibody or a N-terminal anti-hPG humanized antibody.

Specifically, at the end of the incubation phase, the plates are observed with a phase-contrast microscope and the number of positive wells per cellular concentration is assessed. Finally, the ELDA webtool (http://www.bioinf.wehi.edu.au/software/elda/) is used to calculate the CSC frequencies of each treatment group and test for any statistical difference between groups (modified Chi-square test).

Treatment with anti-hPG humanized antibodies reduces CSC frequency as compared to treatment with control antibody.

1.5. Neutralizing activity of anti-hPG monoclonal antibodies on the WNT/ß-catenin pathway

Monoclonal antibodies to PG are tested for their ability to inhibit the WNT/ß-catenin pathway in several cell lines commonly used to study lung cancer, which produce and secrete progastrin, using the expression of the protein survivin, a well-known WNT/ß-catenin pathway targeted gene, as read-out. Survivin expression from each of these cell lines is tested using different anti-hPG monoclonal antibodies.

For each experiment, 50,000 cells are seeded into 6-well plates in medium containing fetal calf serum and incubated for 8 hours. Cells are serum-starved overnight, and starting 24 hours after seeding cells are treated in quadruplicate every 12h for 72 hours, in the absence of fetal calf serum, with 1 to 20 µg/ml of monoclonal control antibodies (monoclonal antiboby anti-puromycin)(CT mAb), or with 1 to 20 µg/ml anti-hPG mAb, wherein said mAb is a C-terminal anti-hPG monoclonal antibody or a N-terminal anti-hPG monoclonal antibody.

Specifically, after 72 hours of treatment, cells are harvested and total proteins are extracted using RIPA buffer. An equal amount of protein from CT mAb or anti-hPG mAb treated cells are then subjected to a western blot using anti-survivin antibody (monoclonal antibody, #2802 from Cell Signaling) and anti-actin antibody as loading control (monoclonal antibody, #A4700 from SIGMA). Quantification is performed using the GBOX chemi system from Syngene.

Treatment with anti-hPG monoclonal antibodies reduces survivin expression as compared to treatment with control antibody. Statistical significance is determined using a unpaired Student's T-test: * = $p<0.05$, ** = $p<0.01$, and *** = $p<0.001$.

1.6. Neutralizing activity of anti-hPG humanized antibodies on the WNT/ß-catenin pathway

Humanized antibodies to PG are tested for their ability to inhibit the WNT/ß-catenin pathway in several cell lines commonly used to study lung cancer, which produce and secrete progastrin, using the expression of the protein survivin, a well-known WNT/ß-catenin pathway targeted gene, as read-out. Survivin expression from each of these cell lines is tested using different anti-hPG humanized antibodies.

For each experiment, 50,000 cells are seeded into 6-well plates in medium containing fetal calf serum and incubated for 8 hours. Cells are serum-starved overnight, and starting 24 hours after seeding cells are treated in quadruplicate every 12h for 72 hours, in the absence of fetal calf serum, with 1 to 20 µg/ml of humanized control antibodies (anti-human FcG1, from BioXCell)(CT Hz), or with 1 to 20 µg/ml anti-hPG Hz, wherein said Hz is a C-terminal anti-hPG humanized antibody or a N-terminal anti-hPG humanized antibody.

Specifically, after 72 hours of treatment, cells are harvested and total proteins are extracted using RIPA buffer. An equal amount of protein from CT Hz or anti-hPG Hz treated cells are then subjected to a western blot using anti-survivin antibody (monoclonal antibody, #2802 from Cell Signaling) and anti-actin antibody as loading control (monoclonal antibody, #A4700 from SIGMA). Quantification is performed using the GBOX chemi system from Syngene.

Treatment with anti-hPG humanized antibodies reduces survivin expression as compared to treatment with control antibody. Statistical significance is determined using a unpaired Student's T-test: * = $p<0.05$, ** = $p<0.01$, and *** = $p<0.001$.

Example 2: Neutralizing activity of anti-hPG antibodies on cancer cell lines

Neutralizing activity of anti-hPG humanized antibodies on cell survival

Humanized antibodies to PG were tested for their ability to inhibit proliferation of several cell lines commonly used to study lung cancer (i.e., NCI-H358, A549 or NCI-H460), which produce and secrete progastrin. Survival of cells from each of these cell lines was assayed using different anti-hPG monoclonal antibodies.

200,000 NCI-H358 cells were seeded into 6-well plates in medium containing foetal calf serum and incubated for 8 hours. Cells were serum-starved overnight. From 24 hours after seeding (time "T0"), cells were treated in every 12h for 48 hours, in the absence of foetal calf serum, with 20 µg/ml of humanized control antibodies (anti-human FcG1, from BioXCell) (CT Hz), or with 20 µg/ml anti-hPG Hz 8CV2 (PG Hz), wherein said Hz is a C-terminal anti-hPG humanized antibody. The number of cells at T0 was counted in a control well, for each experiment.

Specifically, the number of live cells in both control and anti-hPG Hz treated wells was counted at 48 hours. The difference between each cell count and the cell count determined at T0, was then calculated.

Treatment with anti-hPG Hz antibodies reduced cell number as compared to treatment with control antibody. Statistical significance was determined using a t-test: ** = $p<0.01$, In each cell line, anti-hPG antibodies reduced cell survival (see Fig. 1).

BIBLIOGRAPHIC REFERENCES

- Yanaoka *et al*, Cancer Epidemiol Biomarkers Prev, 2008, 17(4)
- Pepe *et al*, J Natl Cancer Inst, 2008, Oct., 100(20)
- Leja *et al*, Best Practice & Research Clinical Gastroenterology, 2014, Dec., 28(6)

CLAIMS

1. A progastrin-binding antibody, or an antigen-binding fragment thereof, for use in the prevention or the treatment of lung cancer, wherein said antibody is selected in the group consisting of:

   - an antibody comprising a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°4, 5 and 6, respectively, and a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°7, 8 and 9, respectively,

   - an antibody comprising a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°10, 11 and 12, respectively, and a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°13, 14 and 15, respectively,

   - an antibody comprising a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°16, 17 and 18, respectively, and a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°19, 20 and 21, respectively,

   - an antibody comprising a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°22, 23 and 24, respectively, and a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°25, 26 and 27, respectively,

   - an antibody comprising a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°28, 29 and 30, respectively, and a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°31, 32 and 33, respectively, and

   - an antibody comprising a heavy chain comprising CDR-H1, CDR-H2 and CDR-H3 of amino acid sequences SEQ ID N°34, 35 and 36, respectively, and a light chain comprising CDR-L1, CDR-L2 and CDR-L3 of amino acid sequences SEQ ID N°37, 38 and 39, respectively.

2. A progastrin-binding antibody, or an antigen-binding fragment thereof, for the use of claim 1, wherein said progastrin-binding antibody, or antigen-binding fragment thereof, is selected among single chain antibodies, camelized

Date Reçue/Date Received 2022-09-21

antibodies, IgA1 antibodies, IgA2 antibodies, IgD antibodies, IgE antibodies, IgG1 antibodies, IgG2 antibodies, IgG3 antibodies, IgG4 antibodies and IgM antibodies.

3. A progastrin-binding antibody, or an antigen-binding fragment thereof, for the use of claim 1 or 2, wherein said progastrin-binding antibody, or an antigen-binding fragment thereof, is selected among N-terminal anti-progastrin antibodies and C-terminal anti-progastrin antibodies.

4. A progastrin-binding antibody, or an antigen-binding fragment thereof, for the use of any one of claims 1 to 3, wherein said progastrin-binding antibody, or an antigen-binding fragment thereof, is a neutralizing antibody.

5. A progastrin-binding antibody, or an antigen-binding fragment thereof, for the use of any one of claims 1 to 4, wherein said antibody is selected in the group consisting of:

   - A monoclonal antibody comprising a heavy chain of amino acid sequence SEQ ID N°41 and a light chain of amino acid sequence SEQ ID N°42;
   - A monoclonal antibody comprising a heavy chain of amino acid sequence SEQ ID N°43 and a light chain of amino acid sequence SEQ ID N°44;
   - A monoclonal antibody comprising a heavy chain of amino acid sequence SEQ ID N°45 and a light chain of amino acid sequence SEQ ID N°46;
   - A monoclonal antibody comprising a heavy chain of amino acid sequence SEQ ID N°47 and a light chain of amino acid sequence SEQ ID N°48;
   - A monoclonal antibody comprising a heavy chain of amino acid sequence SEQ ID N°49 and a light chain of amino acid sequence SEQ ID N°50; and
   - A monoclonal antibody comprising a heavy chain of amino acid sequence SEQ ID N°51 and a light chain of amino acid sequence SEQ ID N°52.

6. A progastrin-binding antibody, or an antigen-binding fragment thereof, for the use of any one of claims 1 to 4, wherein said antibody is a humanized antibody.

7. A progastrin-binding antibody, or an antigen-binding fragment thereof, for the use of claim 6, wherein said antibody is selected in the group consisting of:

Date Reçue/Date Received 2022-09-21

- A humanized antibody comprising a heavy chain variable region of amino acid sequence SEQ ID N°53, and a light chain variable region of amino acid sequence SEQ ID N°54;
- A humanized antibody comprising a heavy chain variable region of amino acid sequence SEQ ID N°55, and a light chain variable region of amino acid sequence SEQ ID N°56;
- A humanized antibody comprising a heavy chain variable region of amino acid sequence selected between SEQ ID N°57, 58, and 59, and a light chain variable region of amino acid sequence selected between SEQ ID N°60, 61, and 62;
- A humanized antibody comprising a heavy chain variable region of amino acid sequence selected between SEQ ID N°63, 64, and 65, and a light chain variable region of amino acid sequence selected between SEQ ID N°66, 67, and 68;
- A humanized antibody comprising a heavy chain variable region of amino acid sequence selected between SEQ ID N°69 and 71, and a light chain variable region of amino acid sequence selected between SEQ ID N°70 and 72; and
- A humanized antibody comprising a heavy chain variable region of amino acid sequence selected between SEQ ID N°75 and 76, and a light chain variable region of amino acid sequence selected between SEQ ID N°77 and 78;

wherein said antibody also comprises constant regions of the light-chain and the heavy-chain derived from a human antibody.

8. A progastrin-binding antibody, or an antigen-binding fragment thereof, for the use of claim 6 or 7, wherein said antibody comprises a heavy chain variable region of amino acid sequence SEQ ID N°71 and a light chain variable region of amino acid sequence SEQ ID N°72, said antibody also comprising constant regions of the light-chain and the heavy-chain derived from a human antibody.

9. A progastrin-binding antibody, or an antigen-binding fragment thereof, for the use of any one of claims 6 to 8, wherein said antibody comprises a heavy chain of amino acid sequence SEQ ID N°73 and a light chain of amino acid sequence SEQ ID N°74.

Date Reçue/Date Received 2022-09-21

10. A pharmaceutical composition comprising the progastrin-binding antibody, or an antigen-binding fragment thereof, of any one of claims 1 to 9, and a pharmaceutically acceptable carrier and/or an excipient, for use in the prevention or the treatment of lung cancer.

11. The pharmaceutical composition for the use of claim 10, further comprising a second therapeutic agent.

12. The pharmaceutical composition for the use of claim 11, wherein said agent is a biological agent or a chemotherapeutic agent.

13. The pharmaceutical composition for the use of claim 13, wherein said biological agent is an anti-EGFR monoclonal antibody or an anti-VEGF monoclonal antibody.

14. The pharmaceutical composition for the use of claim 12, wherein said chemotherapeutic agent is selected in the group of alkylating agents, anti-metabolites, anti-tumor antibiotics, mitotic inhibitors, chromatin function inhibitors, anti-angiogenesis agents, anti-estrogens, anti-androgens and immunomodulators.

Date Reçue/Date Received 2022-09-21

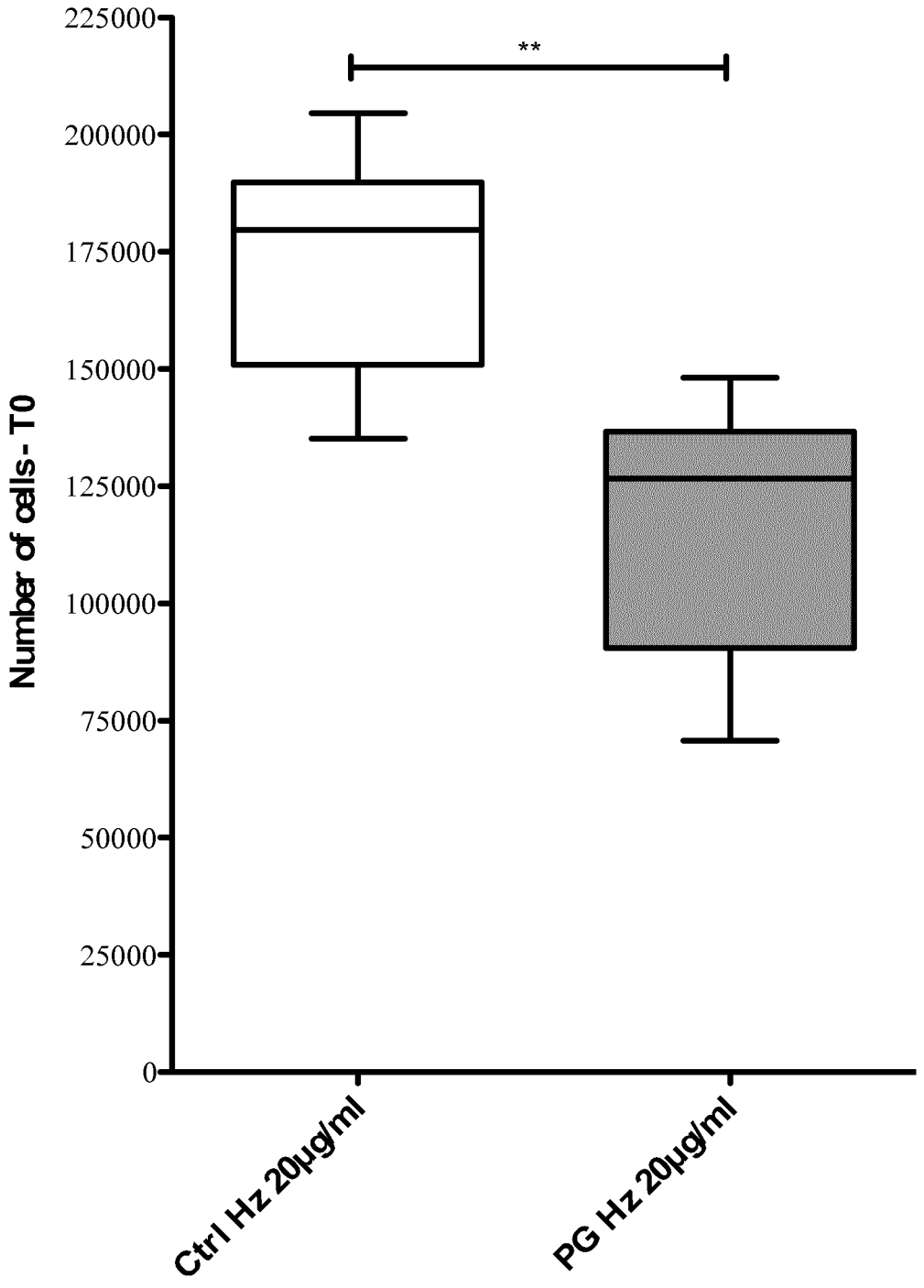
225000
200000
175000
150000
125000
100000
75000
50000
25000
0
Number of cells - T0
**
Ctrl Hz 20µg/ml
PG Hz 20µg/ml

Fig. 1