

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
16 June 2005 (16.06.2005)

PCT

(10) International Publication Number
WO 2005/053732 A1

(51) International Patent Classification⁷:
A61P 35/00, C12Q 1/68

A61K 38/31,

(74) Agent: GRUBB, Philip; Novartis AG, Corporate Intellectual Property, 4002 Basel (CH).

(21) International Application Number:

PCT/EP2004/013350

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date:

24 November 2004 (24.11.2004)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/525,079 25 November 2003 (25.11.2003) US

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except AT, US*): NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant (*for AT only*): NOVARTIS PHARMA GMBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

Published:

— with international search report

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): SAULNIER, Muriel [FR/US]; 190 Millburn Avenue, 3J, Millburn, NJ 07041 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BIOMARKERS FOR THE EFFICACY OF SOMATOSTATIN ANALOGUE TREATMENT

(57) Abstract: Gene expression assays were performed using tissues of monkeys treated with the somatostatin analogue pasireotide at sub-therapeutic dose for 14 days. The assays were analyzed to identify the modes of actions of pasireotide with relationships to therapeutic applications. The effects on the growth hormone /IGF-1 and glucagon/insulin axes were reflected in transcript level changes in several organs. The expressed genes are useful as surrogate markers of the biological activity of pasireotide, especially the findings for IGF-2 in the pituitary and kidneys.



WO 2005/053732 A1

BIOMARKERS FOR THE EFFICACY OF SOMATOSTATIN ANALOGUE TREATMENT

FIELD OF THE INVENTION

[01] This invention relates generally to the analytical testing of tissue samples *in vitro*, and more particularly to aspects of gene expression profiling concerning growth regulation.

BACKGROUND OF THE INVENTION

[02] Somatostatin (SST-14; SRIF) is a cyclic tetradecapeptide hypothalamic hormone containing a disulfide bridge between position 3 and position 14. See, U.S. Pat. No. 6,225,284, incorporated herein by reference. Somatostatin also occurs as a 28 amino acid peptide (SST-28). Among its mechanisms, somatostatin inhibits the release of growth hormone (GH) and thyroid-stimulating hormone (TSH), thus inhibiting the release of insulin and glucagon, and reducing gastric secretion. Metabolism of somatostatin by aminopeptidases and carboxypeptidases leads to a short duration of action. Somatostatin binds to five distinct high affinity membrane associated receptor (SSTR) subtypes with relatively high affinity for each subtype. Growth hormone and thyroid-stimulating hormone secretion are regulated by somatostatin receptor subtypes SSTR2 and SSTR5, with an additional effect on growth hormone secretion via SSTR1. Activation of somatostatin receptor types SSTR2 and SSTR5 have been associated with growth hormone suppression and more particularly growth hormone secreting adenomas (acromegaly) and thyroid-stimulating hormone secreting adenomas. Prolactin is regulated by SSTR5 alone.

[03] The clinically available somatostatin analogues, octreotide (Sandostatin®) and lanreotide, are used for the treatment of acromegaly patients for whom surgery has failed to adequately control growth and insulin-like growth factor I (IGF-I) levels or where surgery is contra-indicated. Both analogues exhibit selective high affinity for somatostatin receptor subtype 2 (SSTR2). Sandostatin® binds mainly to SSTR2 and to some extent to the SSTR3 and SSTR5.

[04] Pasireotide was developed for the approved Sandostatin® indications, but as a more potent somatostatin analogue with a longer plasma half-life *in vivo*. Lewis I *et al.*, *J Med Chem* 46(12): 2334-44 (June 5, 2003); Weckbecker G *et al.*, *Endocrinology* 143(10): 4123-30 (October 2002). In contrast with other analogues, pasireotide binds to all somatostatin

receptors except SSTR4. The binding affinity for the different somatostatin receptors was a basis for defining the scope of possible new clinical indications for pasireotide. Bruns C *et al.*, *Eur J Endocrinol* 143(Suppl 1): S3-7 (2000); Bruns C *et al.*, *Eur J Endocrinol.* 146(5):707-16 (May 2002). In addition, other possible new indications were suggested due to the improved activity of pasireotide for growth hormone and IGF-1 regulation and its different inhibitory effects on insulin and glucagon secretions.

[05] A somatostatin analogue with universal high affinity somatostatin binding, such as pasireotide, will not only have greater efficacy for growth hormone inhibition, but will also regulate secretion of additional anterior pituitary hormones. Murray RD *et al.*, *Endocrine Abstracts* 5: P186 (2003). A clear signature for pasireotide, even at sub-therapeutic dose, could identify the somatostatin agonist activity consistent with the known pharmacological action of the pasireotide class of compounds. This signature would be potentially usable to compare the activity in different tissues treated with somatostatin or somatostatin analogues.

[06] Accordingly, there is a need in the art for an organism-wide understanding of the activity of somatostatin analogues.

SUMMARY OF THE INVENTION

[07] The invention also provides a method for treating a condition in a subject, wherein the condition is one for which administration of somatostatin or a somatostatin analogue is indicated. The method involves, first administering a compound of interest to the subject (*e.g.*, a primate subject) and then obtaining the gene expression profile of the subject following administration of the compound. The gene expression profile of the subject is compared to a biomarker gene expression profile. The biomarker gene expression profile is indicative of efficacy of treatment by somatostatin or a somatostatin analogue. In one embodiment, the biomarker gene expression profile is the baseline gene expression profile of the subject before administration of the compound. In another embodiment, the biomarker gene expression profile is the gene expression profile or average of gene expression profiles of a vertebrate to whom somatostatin or a somatostatin analogue (*e.g.*, pasireotide) has been administered. A similarity in the gene expression profile of the subject to whom the compound was administered to the biomarker gene expression profile is indicative of efficacy of treatment with the compound.

[08] The invention provides biological markers of somatostatin or somatostatin analogue efficacy. The effects on the growth hormone/IGF-1 and glucagon/insulin axes were reflected in transcript level changes in several organs. The expressed genes are useful as surrogate markers of the biological activity of pasireotide, especially the findings for IGF-2 in the pituitary and kidneys. The biomarker signature can be used to compare treatment efficacy in different tissues in an organism treated with somatostatin or somatostatin analogues.

[09] The invention provides methods for determining a subject for inclusion in a clinical trial, based upon an analysis of biomarkers expressed in the subject to be treated. The compound to be tested is administered to the subject. In one embodiment, the compound to be tested is administered in a sub-therapeutic dose. For example, a clear signature for pasireotide, even at sub-therapeutic dose, could identify the somatostatin agonist activity consistent with the known pharmacological action of the pasireotide class of compounds. This signature would be potentially usable to compare the activity in different tissues treated with somatostatin or somatostatin analogues. Then, the gene expression profile of the subject following administration of the compound is obtained. The subject may be included in the clinical trial when the gene expression profile of the subject to whom the compound was administered is similar to a biomarker gene expression profile indicative of efficacy of treatment by somatostatin or a somatostatin analogue. The subject may be excluded from the clinical trial when the gene expression profile of the subject is dissimilar to the biomarker gene expression profile indicative of efficacy of treatment. Such similarities or dissimilarities are observable to those of skill in the art.

[10] The invention also provides for the use of pasireotide in the manufacture of a medicament for the treatment of disorders of growth regulation in a selected patient population. The patient population is selected on the basis of a gene expression profile indicative of pasireotide efficacy by the patient to whom pasireotide is administered.

[11] The invention also provides a method for determining whether a compound has a therapeutic efficacy similar to that of somatostatin or a somatostatin analogue, such as pasireotide. The compound is administered to the subject, and then a gene expression profile of the subject as a consequence of administration of the compound is obtained. The resulting gene expression profile of the subject is compared to a standard biomarker gene expression profile indicative of efficacy of treatment by somatostatin or a somatostatin analogue. The

compound is determined to have therapeutic efficacy similar to that of somatostatin or a somatostatin analogue when the gene expression profile of the subject is similar to a standard biomarker gene expression profile, but the compound is determined to have therapeutic efficacy different from that of somatostatin or a somatostatin analogue when the gene expression profile of the subject is different from a standard biomarker gene expression profile.

[12] The invention also provides clinical assays, kits and reagents for determining treatment efficacy of a condition for which administration of somatostatin or a somatostatin analogue is indicated. In one embodiment, the kits contain reagents for determining the gene expression of biomarker genes, by hybridization. In another embodiment, the kits contain reagents for determining the gene expression of biomarker genes, by the polymerase chain reaction.

DETAILED DESCRIPTION OF THE INVENTION

[13] The invention provides for the identification of the mode of action and potential therapeutic indication of somatostatin or somatostatin analogues by multiorgan microarray analysis, *e.g.* in cynomolgus monkeys. The invention provides for the assessment as to what extent the transcriptional profiles of the various tissues could be used for a comparison of the pharmacological profile of pasireotide with somatostatin, Sandostatin®, or other somatostatin analogues.

[14] As used herein, a gene expression profile is diagnostic for determining the efficacy of treatment when the increased or decreased gene expression is an increase or decrease (*e.g.*, at least a 1.5-fold difference) over the baseline gene expression following administration of the compound. Alternatively or in addition, the gene expression profile is diagnostic for determining the efficacy of treatment as compared with treatment of somatostatin or somatostatin analogues (*e.g.*, pasireotide) when the gene expression profile of the treated subject is comparable to a standard biomarker gene expression profile. In one embodiment, the standard biomarker gene expression profile is the gene expression profile or average of gene expression profiles of a vertebrate to whom somatostatin or a somatostatin analogue has been administered, this profile or profile being the standard to which the results from the

subject following administration is compared. Such an approach, which contains aspects of therapeutics and diagnostics, is termed "theranostic" by many of those of skill in the art.

[15] In one embodiment, the subject is a vertebrate. In a particular embodiment, the vertebrate is a mammal. In a more particular embodiment, the mammal is a primate, such as a cynomolgus monkey or a human. As used herein, the administration of an agent or drug to a subject or patient includes self-administration and the administration by another.

[16] As used herein, a gene expression pattern is "higher than normal" when the gene expression (*e.g.*, in a sample from a treated subject) shows a 1.5-fold difference (*i.e.*, higher) in the level of expression compared to the baseline samples. A gene expression pattern is "lower than normal" when the gene expression (*e.g.*, in a sample from a treated subject) shows a 1.5-fold difference (*i.e.*, lower) in the level of expression compared to the baseline samples.

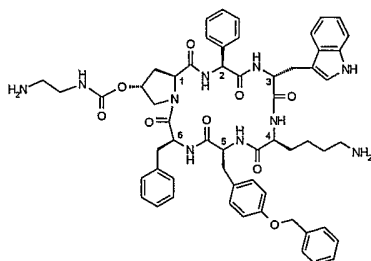
[17] Techniques for the detection of gene expression of the genes described by this invention include, but are not limited to northern blots, RT-PCT, real time PCR, primer extension, RNase protection, RNA expression profiling and related techniques. Techniques for the detection of gene expression by detection of the protein products encoded by the genes described by this invention include, but are not limited to, antibodies recognizing the protein products, western blots, immunofluorescence, immunoprecipitation, ELISAs and related techniques. These techniques are well known to those of skill in the art. Sambrook J *et al.*, *Molecular Cloning: A Laboratory Manual, Third Edition* (Cold Spring Harbor Press, Cold Spring Harbor, 2000). In one embodiment, the technique for detecting gene expression includes the use of a gene chip. The construction and use of gene chips are well known in the art. See, U.S. Pat Nos. 5,202,231; 5,445,934; 5,525,464; 5,695,940; 5,744,305; 5,795,716 and 5,800,992. See also, Johnston, M. *Curr Biol* 8:R171-174 (1998); Iyer VR *et al.*, *Science* 283:83-87 (1999) and Elias P, "New human genome 'chip' is a revolution in the offing" *Los Angeles Daily News* (October 3, 2003).

[18] *Somatostatin and somatostatin analogues*. The peptides and therapeutic uses of somatostatin-14 and somatostatin-28 are well known in the art. See, U.S. Pat. No. 6,225,284; Lewis I *et al.*, *J. Med. Chem.* 46(12): 2334-44 (June 5, 2003); Weckbecker G *et al.*, *Endocrinology* 143(10): 4123-30 (October 2002), each incorporated herein by reference. Somatostatin and somatostatin analogues in free form or in the form of pharmaceutically

acceptable salts and complexes exhibit valuable pharmacological properties as indicated in *in vitro* and *in vivo* tests and are therefore indicated for therapy.

[19] By "somatostatin analogue" as used herein is meant a straight-chain or cyclic peptide derived from that of the naturally occurring somatostatin-14, wherein one or more amino acid units have been omitted or replaced by one or more other amino acid radicals or wherein one or more functional groups have been replaced by one or more other functional groups and/or one or more groups have been replaced by one or several other isosteric groups. See, U.S. Pat. No. 6,225,284, incorporated herein by reference. Cyclic, bridge cyclic and straight-chain somatostatin analogues are known compounds. Such compounds and their preparation are described *e.g.* in European Patent Specifications EP-A-1295; 29,579; 215,171; 203,031; 214,872; 298,732; 277,419. In general the term "somatostatin analogue" covers all modified derivatives of the native somatostatin-14 that have binding affinity in the nM range to at least one somatostatin receptor subtype.

[20] One somatostatin analogue of interest is pasireotide, which has a chemical structure cyclo[4-(NH₂-C₂H₄-NH-CO-O)Pro-Phg-DTrp-Lys-Tyr(4-Bzl)-Phe] as follows:



(I)

[21] Here, Phg means -HN-CH(C₆H₅)-CO- and Bzl means benzyl. See, PCT patent application WO 02/10192. Pasireotide is a somatostatin analogue with binding affinities for the five somatostatin receptors except somatostatin receptor 4 (SSTR4). Pasireotide has been developed for several indications, including those disclosed above for other somatostatin analogues. See, Lewis I *et al.*, *J. Med. Chem.* 46(12):2334-44 (June 5, 2003); Weckbecker G *et al.*, *Endocrinology* 143(10): 4123-4130 (2002); Kneissel M *et al.*, *Bone* 28:237-250 (2001); and Thomsen JS *et al.*, *Bone* 25:561-569 (1999), the contents of which are incorporated herein by reference.

[22] Somatostatins and somatostatin analogues bind to somatostatin receptors (SSTR). The cellular effects of somatostatin receptor activation are currently understood to be as

follows: Binding to somatostatin receptors results in the activation of the PI3 kinase signalling pathway, inhibition of adenylyl cyclase, activation of protein tyrosine phosphatases, modulation of mitogen activated protein kinase (MAPK), coupling to inward rectifying K⁺ channels, voltage dependent Ca⁺⁺ channels, a Na⁺/H⁺ exchanger, AMPA/kainate glutamate channels, PLC, and PLA2. Patel YC, *Frontiers in Neuroendocrinology* 20: 157-98 (1999). Somatostatin receptor activation blocks cell secretion by inhibiting intracellular cAMP and Ca⁺⁺ and by a receptor-linked distal effect on exocytosis. Somatostatin receptor 1, 2, 4 and 5 (SSTR1, 2, 4, 5) induce cell cycle arrest by phosphotyrosine phosphatase-dependent modulation of MAPK, associated with induction of the retinoblastoma (Rb) tumour suppressor protein and p21. SSTR3 triggers phosphotyrosine phosphatase-dependent apoptosis accompanied by activation of p53 and Bax.

[23] Additional effects of treatment of primates with somatostatin, in particular with the somatostatin analogue pasireotide, are provided in the EXAMPLE below.

[24] Somatostatin and somatostatin analogues bind to at least one somatostatin receptor subtype. Five somatostatin receptor subtypes, SST-1, SST-2, SST-3, SST-4 and SST-5 have been cloned and characterized. Human somatostatin receptors hSST-1, hSST-2 and hSST-3 and their sequences have been disclosed by Yamada Y *et al.*, *Proc. Nat. Acad. Sci. U.S.A.* 89: 251-255 (1992). Human somatostatin receptor hSST-4 and its sequence have been disclosed by Rohrer L *et al.*, *Proc. Acad. Sci. U.S.A.* 90: 4196-4200 (1993). Human somatostatin receptor hSST-5 and its sequence have been described by Panetta R *et al.*, *Mol. Pharmacol.* 45: 417-427 (1993).

[25] Binding assays may be carried out using membranes prepared from hSST-1, hSST-2, hSST-3, hSST-4 or hSST-5 selective cell lines, e.g. CHO cells stably expressing hSST-1, hSST-2, hSST-3, hSST-4 or hSST-5. See, U.S. Pat. No. 6,225,284. Somatostatin and somatostatin analogues have in the above binding assays towards hSST-1, hSST-2, hSST-3, hSST-4 and/or hSST-5 an IC₅₀ in the nM range.

[26] Furthermore, somatostatin and somatostatin analogues show growth hormone-release inhibiting activity as indicated by the inhibition of GH release in vitro from cultured pituitary cells. See, U.S. Pat. No. 6,225,284. Somatostatin and somatostatin analogues inhibit the release of growth hormone concentration-dependent from 10⁻¹¹ to 10⁻⁶ M.

[27] Somatostatin and somatostatin analogues also inhibit the release of insulin and/or glucagon, as indicated in standard tests using male rats. See, U.S. Pat. No. 6,225,284. The determination of the blood serum insulin and glucagon levels is effected by radioimmunoassay. Somatostatin and somatostatin analogues are active in this test when administered at a dosage in the range of from 0.02 to 1000 µg/kg subcutaneous (s.c.), *e.g.* to 10 µg/kg s.c.

[28] As described above, however, the administration of somatostatin or somatostatin analogues, even in sub-therapeutic doses, can usefully provide biomarker signature information.

[29] Somatostatin and somatostatin analogues are useful for the treatment of disorders with an aetiology comprising or associated with excess growth-secretion, *e.g.* in the treatment of acromegaly as well as in the treatment of diabetes mellitus, especially complications thereof (*e.g.* angiopathy, proliferative retinopathy, dawn phenomenon and nephropathy and other metabolic disorders related to insulin or glucagon release). See, U.S. Pat. No. 6,225,284. Somatostatin and somatostatin analogues also inhibit gastric acid secretion, exocrine and endocrine pancreatic secretion and the secretion of various peptides of the gastrointestinal tract. Somatostatin and somatostatin analogues additionally are useful for the treatment of gastrointestinal disorders, for example in the treatment of peptic ulcers, enterocutaneous and pancreaticocutaneous fistula, irritable bowel syndrome and disease, dumping syndrome, watery diarrhoea syndrome, AIDS-related diarrhoea, chemotherapy-induced diarrhoea, acute or chronic pancreatitis and gastrointestinal hormone secreting tumours (*e.g.* vipomas, glucagonomas, insulinomas, carcinoids and the like) as well as gastrointestinal bleeding. Somatostatin and somatostatin analogues are also effective in the treatment of tumours which are somatostatin receptor positive, particularly tumours bearing human somatostatin receptors hSST-1, hSST-2, hSST-3, hSST-4 and/or hSST-5. Somatostatin and somatostatin analogues are useful for treating an aetiology comprising or associated with excess growth hormone-secretion, for treating gastrointestinal disorders, for inhibiting proliferation or keratinisation of epidermal cells, or for treating degenerative senile dementia in a subject in need of such a treatment. See, U.S. Pat. No. 6,123,916, incorporated herein by reference. Somatostatin and somatostatin analogues are also useful for treating tuberculosis, sarcoidosis, malignant lymphoma, Merkel cell tumour of the skin, osteosarcoma, focal lymphocytic reaction,

localized autoimmune disease, and organ rejection after transplantation. See, U.S. Pat. No. 6,123,916. Somatostatin and somatostatin analogues are particularly indicated for the treatment of somatostatin receptor positive tumours, *e.g.* cancers of the breast, prostate, colon, pancreas, brain, lung and lymph nodes.

[30] To reiterate, somatostatin and somatostatin analogues have been developed and are being used to treat several indications, including acromegaly, diabetes mellitus and complications (*e.g.* angiopathy, diabetic proliferative retinopathy, diabetic macular oedema, nephropathy, neuropathy, hypothalamic or hyperinsulinaemic obesity), morbid obesity, Grave's Disease, polycystic kidney disease gastrointestinal disorders (*e.g.* irritable bowel syndrome and disease or enterocutaneous and pancreaticocutaneous fistula), dumping syndrome, watery diarrhoea syndrome, AIDS-related diarrhoea, chemotherapy-induced diarrhoea, pancreatitis, gastrointestinal hormone secreting tumours (*e.g.* GEP tumours, for example vipomas, glucagonomas, insulinomas, carcinoids and the like), somatostatin receptor positive tumours (*e.g.* pituitary, gastroenteropancreatic, carcinoids, central nervous system, breast, prostatic (including advanced hormone-refractory prostate cancer), ovarian or colonic tumours, small cell lung cancer, malignant bowel obstruction, paragangliomas, kidney cancer, skin cancer, neuroblastomas, pheochromocytomas, medullary thyroid carcinomas, myelomas, lymphomas, Hodgkins and non Hodgkins lymphomas, bone tumours and metastases, chronic allograft rejection and other vascular occlusive disorders (*e.g.* vein graft stenosis, restenosis and/or vascular occlusion following vascular injury, *e.g.* caused by cauterisation procedures or vascular scraping procedures such as percutaneous transluminal angioplasty, laser treatment or other invasive procedures which disrupt the integrity of the vascular intima or endothelium), angiogenesis, hepatocellular carcinoma as well as gastrointestinal bleeding (*e.g.* variceal oesophageal bleeding), macular oedema (*e.g.* cystoid macular oedema, idiopathic cystoid macular oedema, exudative age-related macular degeneration, choroidal neovascularisation related disorders) and proliferative retinopathy. Somatostatin and somatostatin analogues are used for treating Cushing disease, a subtype of pituitary tumours. Somatostatin and somatostatin analogues are also used for treating sleep apnoea.

[31] Somatostatin and somatostatin analogues, either free or in complexed form, may be administered by any conventional route, in particular intraperitoneally or intravenously, *e.g.* in the form of injectable solutions or suspensions. They may also be administered

advantageously by infusion, *e.g.* an infusion of 30 to 60 min. Depending on the site of the tumour, they may be administered as close as possible to the tumour site, *e.g.* by means of a catheter. A pharmaceutical composition comprising somatostatin or somatostatin analogues in free or complexed form together with one or more pharmaceutically acceptable carriers or diluents may be manufactured in conventional manner and may be presented, *e.g.* for imaging, in the form of a kit. See, U.S. Pat. No. 6,225,284.

[32] Somatostatin and somatostatin analogues can be administered in combination with other drugs, such as Starlix® or other anti-diabetic drugs, or a chemotherapeutic agent, *e.g.* paclitaxel, gemcitabine, doxorubicin, 5-fluorouracil, taxol, an anti-androgen, mitoxanthrone, antioestrogen, *e.g.* letrozole, an antimetabolite, a plant alkaloid, a lymphokine, interferons, an inhibitor of protein tyrosine kinase and/or serine/threonine kinase, epothilone, or an anti-angiogenic agent.

[33] The kits of the invention may contain a written product on or in the kit container. The written product describes how to use the reagents contained in the kit to determine whether a patient is being treated with a compound for which treatment by somatostatin or a somatostatin analogue is indicated. In several embodiments, the use of the reagents can be according to the methods of the invention. In one embodiment, the reagent is a gene chip for determining the gene expression of relevant genes.

[34] The following EXAMPLE is presented in order to more fully illustrate the preferred embodiments of the invention. This EXAMPLE should in no way be construed as limiting the scope of the invention, as defined by the appended claims.

EXAMPLE

PASIREOTIDE-INDUCED GENE EXPRESSION PROFILING IN MONKEYS

[35] *Introduction and summary.* Microarray gene expression assays were performed using tissues of monkeys treated with pasireotide at sub-therapeutic dose for 14 days. The assays were analyzed to identify the modes of actions of pasireotide with relationships to therapeutic applications.

[36] All monkey tissues examined (thyroid, brown fat, pituitary, pancreas, liver, kidney, spleen) demonstrated changes in the genes regulated by the binding of the natural somatostatin

14 (SST-14) and somatostatin 28 (SST-28) to somatostatin receptors (SSTRs). The transcript profiles reflected the known somatostatin actions on the growth hormone/insulin-like growth factor 1 (GH/IGF-1), glucagon/insulin axes and on cell proliferation. However, the compound affected significantly the transcript levels of other related genes like insulin-like growth factor 2 (IGF-2) in the pituitary and kidneys. This could be a candidate biological marker (biomarker) of drug efficacy provided that the change in protein biosynthesis would be reflected in an easily accessible tissue like the blood. Other known effects of somatostatin and agonists on growth factors, cells of the immune system and the cardio-vascular and renal functions were also reflected by the changes in the profiles of these classes of genes after pasireotide.

[37] *Origin of tissue and processing.* Male and female cynomolgus monkeys received subcutaneously pasireotide (100 µg/animal/day) or the vehicle for 14 days. On day 15, all animals were sacrificed and tissues for RNA extraction were immediately snap-frozen and kept at -80° C until processing.

TABLE 1
Origin of Tissues Used for Analysis

<u>Tissue</u> <u>Sample</u>	<u>Animal or</u> <u>sample no.</u>	<u>Sex</u>	<u>Tissue/ organ</u>	<u>Compound</u>	<u>Dose</u> <u>(µg/animal/day)</u>
x547e	W62405	Male	Brown fat	Pasireotide	100
x548e	W62406	Male	Brown fat	Pasireotide	100
x549e	W62425	Female	Brown fat	Pasireotide	100
x550e	W62426	Female	Brown fat	Pasireotide	100
x673e	W62401	Male	Brown fat	Control	0
x675e	W62421	Female	Brown fat	Control	0
x676e	W62422	Female	Brown fat	Control	0
x857e	W62501*	Male	Brown fat	Control	0
x858e	W62502*	Male	Brown fat	Control	0
x859e	W62551*	Female	Brown fat	Control	0
x860e	W62552*	Female	Brown fat	Control	0
d32e	W62551	Female	Kidney	Control	0
d35e	W62502	Male	Kidney	Control	0
d37e	W62552	Female	Kidney	Control	0
d45e	W62501	Male	Kidney	Control	0
x407e	W62401	Male	Kidney	Control	0
x408e	W62402	Male	Kidney	Control	0
x409e	W62421	Female	Kidney	Control	0
x410e	W62422	Female	Kidney	Control	0
x521e	W62405	Male	Kidney	Pasireotide	100
x522e	W62406	Male	Kidney	Pasireotide	100
x523e	W62425	Female	Kidney	Pasireotide	100
x524e	W62426	Female	Kidney	Pasireotide	100
x401e	W62401	Male	Liver left lateral lobe	Control	0
x402e	W62402	Male	Liver left lateral lobe	Control	0
x403e	W62421	Female	Liver left lateral lobe	Control	0
x404e	W62422	Female	Liver left lateral lobe	Control	0
x517e	W62405	Male	Liver left lateral lobe	Pasireotide	100
x518e	W62406	Male	Liver left lateral lobe	Pasireotide	100
x519e	W62425	Female	Liver left lateral lobe	Pasireotide	100
x520e	W62426	Female	Liver left lateral lobe	Pasireotide	100
x529e	W62405	Male	Pancreas	Pasireotide	100
x530e	W62406	Male	Pancreas	Pasireotide	100
x531e	W62425	Female	Pancreas	Pasireotide	100
x532-2e	W62426	Female	Pancreas	Pasireotide	100
x641e	W62401	Male	Pancreas	Control	0
x642e	W62402	Male	Pancreas	Control	0
x645e	W62421	Female	Pancreas	Control	0
x646e	W62422	Female	Pancreas	Control	0

TABLE 1
Origin of Tissues

<u>Tissue</u> <u>Sample</u>	<u>Animal or</u> <u>sample no.</u>	<u>Sex</u>	<u>Tissue/ organ</u>	<u>Compound</u>	<u>Dose</u> <u>(μg/animal/day)</u>
x413e	W62401	Male	Pituitary gland	Control	0
x414e	W62402	Male	Pituitary gland	Control	0
x415e	W62421	Female	Pituitary gland	Control	0
x513-2e	W62405	Male	Pituitary gland	Pasireotide	100
x514e	W62406	Male	Pituitary gland	Pasireotide	100
x515e	W62425	Female	Pituitary gland	Pasireotide	100
x516e	W62426	Female	Pituitary gland	Pasireotide	100
x425e	W62401	Male	Spleen	Control	0
x426e	W62402	Male	Spleen	Control	0
x427e	W62421	Female	Spleen	Control	0
x428e	W62422	Female	Spleen	Control	0
x525e	W62405	Male	Spleen	Pasireotide	100
x526e	W62406	Male	Spleen	Pasireotide	100
x527e	W62425	Female	Spleen	Pasireotide	100
x528e	W62426	Female	Spleen	Pasireotide	100
d33e	W62501	Male	Thyroid	Control	0
d40e	W62551	Female	Thyroid	Control	0
d43e	W62502	Male	Thyroid	Control	0
d48e	W62552	Female	Thyroid	Control	0
x443e	W62401	Male	Thyroid	Control	0
x445e	W62421	Female	Thyroid	Control	0
x446e	W62422	Female	Thyroid	Control	0
x505e	W62425	Female	Thyroid	Pasireotide	100
x506e	W62426	Female	Thyroid	Pasireotide	100
x507e	W62405	Male	Thyroid	Pasireotide	100
x508e	W62406	Male	Thyroid	Pasireotide	100

[38] RNA expression profiling was conducted by means of the HG-U95A gene expression probe array (Affymetrix; Santa Clara, Calif., USA), containing more than 12,600 probe sets interrogating primarily full-length human genes and also some control probe sets. The experiment was conducted according to the recommendations of the manufacturer. Briefly, total RNA was obtained by acid guanidinium thiocyanate-phenol-chloroform extraction (Trizol®, Invitrogen Life Technologies, San Diego, Calif., USA) from each frozen tissue section. The total RNA was then purified on an affinity resin (Rneasy®, Qiagen) and quantified. Double stranded cDNA was synthesized with a starting amount of approximately 5 μ g full-length total RNA using the Superscript® Choice System (Invitrogen Life Technologies, Carlsbad, Calif. USA) in the presence of a T7-(dT)24 DNA oligonucleotide primer. Following synthesis, the cDNA was purified by phenol/chloroform/isoamyl alcohol extraction and ethanol precipitation. The purified cDNA was then transcribed in vitro using

the BioArray® High Yield RNA Transcript Labeling Kit (ENZO, Farmingdale, New York USA) in the presence of biotinylated ribonucleotides form biotin labelled cRNA. The labelled cRNA was then purified on an affinity resin (Rneasy®, Qiagen), quantified and fragmented. An amount of approximately 10 µg labelled cRNA was hybridized for 16 hours at 45°C to an expression probe array. The array was then washed and stained twice with streptavidin-phycoerythrin (Molecular Probes,) using the GeneChip® Fluidics Workstation 400 (Affymetrix, Santa Clara, Calif. USA). The array was then scanned twice using a confocal laser scanner (GeneArray® Scanner, Agilent, Palo Alto, Calif. USA) resulting in one scanned image. This resulting ".dat-file" was processed using the MAS4 program (Affymetrix) into a ".cel-file". The ".cel file" was captured and loaded into the Affymetrix GeneChip® Laboratory Information Management System (LIMS). The LIMS database is connected to a UNIX Sun Solaris server through a network filing system that allows for the average intensities for all probes cells (CEL file) to be downloaded into an Oracle database (NPGN). Raw data was converted to expression levels using a "target intensity" of 150. The data were evaluated for quality control and loaded in the GeneSpring® software 4.2.4 (Silicon Genetics, Calif. USA) for analysis.

[39] On the human Affymetrix HGU95Av2 chip, probe sets for individual genes contain 20 oligonucleotide pairs, each composed of a "perfect match" 25-mer and a "mismatch" 25-mer differing from the "perfect" match oligonucleotide at a single base. After probe labelling, hybridization, and laser scanning, the expression level was estimated by averaging the differences in signal intensity measured by oligonucleotide pairs of a given probe (AvgDiff value). The fold changes and directions were calculated for selected genes, from the differences of the AvgDiff values between controls and treated.

[40] To identify genes that were impacted by pasireotide, the dataset was initially filtered to exclude in a first wave of analysis, genes whose values were systematically in the lower expression ranges where the experimental noise is high (at least 80 in a number of experiments corresponding to the smallest number of replicas of any experimental point). In a second round of selection a threshold p-value of 0.05 (based on a t-test) identified differences between treated and control based on a two component error model (Global Error Model) and, whenever possible, with a stepdown correction for multi-hypothesis testing (Benjamini and Hochberg false discovery rate). The decision to keep or reject a specific gene was based on the

conjunction of numerical changes identified by comparative and statistical algorithms and the relationship to other modulated genes that point to a common biological theme. The weight of this relationship was assessed by the analyst through a review of the relevant scientific literature.

[41] For the assay analysis described herein: (1) the increase and decrease in expression referred to the RNA expression level unless specifically stated; (2) if there were multiple probe sets representing the same gene, the probe set designed for sense target was favoured; and (3) the changes in gene expression indicated that a pathway, a cellular activity or component represented by an individual gene might be impacted. Understanding the functional implication is dependent on the information available on the biological context of the transcript level change (gene function, physiological variation, other gene changes, tissue, compound, *etc.*). RT-PCR is used to identify the extent of absolute change in mRNA levels, but this method in general does not add more information on the relevance of the transcript level changes.

[42] Among the 12,600 genes per chip, about 100 genes were found to reflect the compound signature in a particular tissue. For clarity, they were divided in different classes and subdivided, with many overlaps, into functional categories in the following TABLE.

TABLE 2
Pasireotide Gene Expression Profiling

<u>CLASS</u>	<u>PITUITARY</u>	<u>BROWN FAT</u>	<u>PANCREAS</u>
SIGNAL TRANSDUCTION			
1) <i>Phosphatidylinositol and related pathways/PKC, phospholipases</i>	• IP-4-phosphatase, type 1, isoform b ↓ x2 • PI-3-kinase, catalytic, α polypeptide ↓ x3 • PI-3-kinase, catalytic, δ polypeptide ↓ x2 • 1-PI-4-phosphate 5-kinase isoform C ↓ x1.5 • PI transfer protein, β ↓ x2.5 • PLCγ 1 ↓ x1.5 • PKC inhibitor ↑ x2 • IP3 receptor, type 1 ↑ x1.5	• PI-3-kinase, regulatory subunit, polypeptide 2 (p85 β) ↓ x3.5 • PI glycan, class F ↓ x2 • PLC β 4 ↑ x2 • PI glycan, class L ↑ x3.5	• IP-1-phosphatase ↑ x2.5 • PI-4-kinase, catalytic, α polypeptide ↑ x1.5 • PL A2, group IVC (cytosolic, calcium-independent) ↑ x1.5
2) <i>Other calcium/calmodulin/calcineurin/ calmodulin dependent pathways and associated proteins</i>	• Calcium/calmodulin-dependent protein kinase I ↑ x2.5 • Receptor (calcitonin) activity modifying protein 2 precursor ↑ x3.5	• Calcium/calmodulin-dependent protein kinase I ↓ x3.5	

TABLE 2
Pasireotide Gene Expression Profiling

<u>CLASS</u>	<u>PITUITARY</u>	<u>BROWN FAT</u>	<u>PANCREAS</u>
3) <i>Ras/MAPK kinase/ERK kinase related pathways and adaptor proteins</i>	• Rab geranylgeranyl transferase, α subunit $\downarrow$ x1.5 • Rab3 GTPase-activating protein, non catalytic subunit $\downarrow$ x2 • SHB adaptor protein (a Src homology 2 protein) $\downarrow$ x2.5 • MAPKKK5 $\uparrow$ x2 • Rab geranyltransferase, β subunit $\uparrow$ x2 • RAB 5C, member RAS oncogene family $\uparrow$ x3	• Ras homolog gene family, member G (rho G) • MAPKAPK 3 • MAPKK1 • MAPK 8 • RAB6, member RAS oncogene family • Adaptor-related protein complex 3, σ 1 subunit • Ras-related nuclear protein • Rab acceptor 1 (prenylated) • RAB 2, member RAS oncogene family • IQ motif containing GTPase activating protein 2 • JAK 3	• SH3 domain binding glutamic acid-rich protein • MAPKAPK 3 • Ras like GTPase • RaP2 interacting protein 8
4) <i>JAK/STAT pathway and related kinases</i>	• STAT 1, 91kδ $\downarrow$ x2 • JAK 1 $\uparrow$ x2		• STAT 5B • STAT 1, 91kδ • STAT 2 • PTP δ
5) <i>Protein tyrosine phosphatases/other phosphatases</i>	• Dual specificity phosphatase 8 $\downarrow$ x3 • Phosphatase and tensin homolog (mutated in multiple advanced cancers 1) $\downarrow$ x3.5 • PTP, receptor type, T $\uparrow$ x2 • PP 1, regulatory (inhibitor) subunit 5 $\uparrow$ x3.5	• PP 2, regulatory subunit B (B56), γ isoform $\downarrow$ x1.5 • PP 5, catalytic subunit $\uparrow$ x2.5 • Dual specificity PP MKP-5 $\uparrow$ x2.5	• PP 1, regulatory (inhibitor) subunit 8 • PP 2A, catalytic subunit B' • PP 1A (formerly 2C), magnesium-dependent, α isoform • PP 2A, regulatory subunit B' • Dual specificity phosphatase 8
6) <i>Other protein kinases and associated binding proteins</i>	• Arg PTK-binding protein $\downarrow$ x2.5	• PTK 9-like (A6-related protein) • PTK A kinase (PRKA) anchor protein 1 • cAMP-dependent protein kinase R1-β regulatory subunit • Ribosomal protein S6 kinase, 90kD, polypeptide	• Protein kinase (c AMP-dependent, catalytic), inhibitor γ • Serine/ threonine protein kinase • Receptor PTK • Serine/ threonine kinase 11 (Peutz-Jeghers syndrome) • Tyrosine kinase • Ribosomal protein S6 kinase, 90kδ, polypeptide 3

TABLE 2
Pasireotide Gene Expression Profiling

<u>CLASS</u>	<u>PITUITARY</u>	<u>BROWN FAT</u>	<u>PANCREAS</u>
7) Adenylate/guanylate cyclases and related pathways	• Soluble adenylyl cyclase ↓ x2		
CELL SURFACE RECEPTORS			
1) G-protein coupled receptors and related binding proteins/ G proteins	• GTP-binding protein (G protein), q polypeptide ↓ x2.5 • GTP-binding protein like-1 ↓ x3 • G-protein coupled receptor 49 ↓ x2 • G protein-coupled receptor, family C, group 5, member B ↑ x2 • GTP-binding protein 11 ↑ x2.5 • Receptor tyrosine kinase-like orphan receptor 2 ↑ x2 • ATP(GTP)-binding protein ↑ x1.5 • G-protein coupled receptor 9 ↑ x2.5 • Regulator of G-protein signalling 9 ↑ x2 • SSTR3 ↑ x3	• G α inhibiting activity polypeptide 3 interacting protein ↓ x5 • G protein-coupled receptor 1 ↓ x2.5 • Guanine nucleotide binding protein (G protein), β polypeptide 3 ↑ x2.5 • SSTR3 ↑ x6.5 • Endothelial differentiation, sphingolipid G-protein-coupled receptor, 5 ↑ x2.5	• G protein-coupled receptor 39 • G protein-coupled receptor 49 • G protein-coupled receptor 3 • Regulator of G-protein signalling 10 • GTP-binding protein • SSTR2 ↓ x1.5

TABLE 2
Pasireotide Gene Expression Profiling

<u>CLASS</u>	<u>PITUITARY</u>	<u>BROWN FAT</u>	<u>PANCREAS</u>
2) <i>Growth factors, their receptors and related binding proteins</i>	• FGFR 2 ↓ x2 • EGFRBP 2 ↓ x1.5 • Fms-related tyrosine kinase 1 (VEGF/vascular permeability factor receptor) ↓ x1.5 • Catenin (cadherin-associated protein), α 1 (102kD) ↓ x1.5 • PDGFβ ↓ x2 • GFR bound protein 10 ↑ x1.5 • Butyrate response factor 2 (EGF-response factor 2) ↑ x3 • VEGF B ↑ x1.5	• Fms-related tyrosine kinase 1 (VEGF/vascular permeability factor receptor) ↓ x4.5 • EGF receptor pathway substrate 15 ↓ x2 • CSF 1 (macrophage) ↓ x2 • Cadherin 13, H-cadherin (heart) ↓ x2 • Cadherin F1B1 ↓ x4 • Endothelial cell GF 1 (platelet derived) ↓ x2 • TGF β -activated kinase-binding protein 1 ↑ x2.5 • CSF 3 receptor (granulocyte) ↑ x3 • TGF β 3 ↑ x2.5 • Cadherin 5, VE-cadherin (vascular epithelium) ↑ x3 • VGF nerve growth factor inducible ↑ x2 • IL 3 (CSF, multiple) ↑ x2 • IL 7R precursor ↑ x2 • GLUR, metabotropic 1 ↑ x2	• Smad 3 ↓ x1.5 • G-CSF protein ↓ x2 • PDGFR α ↑ x2.5 • PDGFR, α polypeptide ↑ x1.5
3) <i>Glutamate receptor and related binding proteins</i>	• GLUR 2, precursor ↑ x1.5		• GLUR precursor, flip isoform ↑ x3

TABLE 2
Pasireotide Gene Expression Profiling

<u>CLASS</u>	<u>PITUITARY</u>	<u>BROWN FAT</u>	<u>PANCREAS</u>
ATP-DEPENDENT TRANSPORT PROTEINS <i>Ion channels and related pathways</i>	• K⁺ channel, subfamily K, member 3 (TASK) ↓ x4 • K⁺ voltage-gated channel, Shab-related subfamily, member 1 ↓ x2 • ATPase, H⁺/K⁺ exchanging, α polypeptide ↓ x5 • ATPase, Na⁺/K⁺ transporting, α 2 (+) polypeptide ↑ x2.5 • ATPase, Na⁺/K⁺ transporting, β 3 polypeptide ↑ x2.5 • ATPase, Ca⁺⁺ transporting cardiac muscle, slow twitch 2 ↑ x1.5 • Putative Ca⁺⁺ transporting ATPase ↑ x2	• Ca⁺⁺ channel, voltage dependent, α 1H subunit ↑ x3 • G protein-activated inwardly rectifying K⁺ channel ↑ x3.5	• K⁺ voltage-gated channel, KQT-like subfamily, member3 ↓ x2.5 • Ca⁺⁺ channel, voltage dependent, α 1F subunit ↓ x4.5 • Na⁺ channel, voltage-gated, type I, β polypeptide ↑ x2
CELL BIOLOGY/ SPECIALIZED FUNCTIONS <i>1) Neuromediators/ neuromodulators and related pathways</i>	• Cholinergic receptor, nicotinic, β polypeptide 4 ↓ x2 • Cholinergic receptor, muscarinic 3 ↓ x3 • Brain cannabinoid receptor 1 ↑ x2 • GABA-B R 1, isoform a precursor ↑ x1.5	• Dopamine receptor D3 ↑ x2.5 • Adrenergic, β-3-, receptor ↑ x2.5	
<i>2) Pancreatic/ gastro- intestinal secretions and related pathways</i>	• Cholecystokinin receptor ↓ x4.5 • Gastrin receptor ↓ x2		• Chymotrypsin-like ↑ x3.5 • Gastrin-releasing peptide receptor ↓ x5

TABLE 2
Pasireotide Gene Expression Profiling

<u>CLASS</u>	<u>PITUITARY</u>	<u>BROWN FAT</u>	<u>PANCREAS</u>
3) <i>Hormones and related pathways</i>	• IGF-2 ↓ x1.5 • Thyroid transcription factor 1 ↑ x2.5 • Glucagon receptor ↑ x7 • IGFBP, acid labile subunit ↑ x3.5 • Adrenomedullin ↑ x2.5 • ANP (atrial natriuretic peptide precursor B) ↑ x2 • SSTR3 ↑ x3	• THR interactor 10 ↓ x3 • THR interactor 12 ↓ x1.5 • IGF-1 ↓ x1.5 • IGF-binding protein 4 ↓ x2 • IRS (insulin receptor substrate) 2 ↑ x2.5 • T3 receptor ↑ x2 • SSTR3 ↑ x6.5 • Oxytocin, prepro- (neurophysin I) ↑ x2.5 • FSHR ↑ x2.5 • Capping protein (actin filament), gelsolin-like ↓ x2.5 • Actin related protein 2/3 complex, subunit 1A (41kD) ↓ x2.5 • Coagulation factor XIIIaI subunit precursor ↓ x5	• CRHR 1 ↓ x2 • THR binding protein ↓ x2 • THR interactor 10 ↑ x2.5 • IGF-1 ↑ x4.5 • Prostacyclin synthase ↑ x2 • SSTR2 ↓ x1.5
4) <i>Cytoskeleton and associated proteins</i>	• Thrombospondin-p50 ↓ x2 • CD36 antigen ↓ x2		• Integrin α 2b precursor ↑ x1.5
5) <i>Enzymes</i>			• Thrombospondin 2 ↑ x3.5
IMMUNITY	• TNFR-associated factor 2 ↓ x4 • TNFR subfamily, member 14; herpesvirus entry mediator ↓ x2.5 • IFNR2 (α, β and ω) ↓ x2.5 • CC chemokines STCP-1 ↑ x1.5 • IFN stimulated gene ↑ x3.5 • IFNγ-inducible protein 30 (IP30) ↑ x1.5	• IFN γ-inducible protein 30 (IP30) ↓ x3.5 • Pentaxin-related gene, rapidly induced by IL-1 ↓ x7.5 • IFN induced transmembrane protein 1 ↑ x2.5 • TNF type 1 receptor associated protein ↓ x2 • IL 5R, α ↑ x2.5 • CD2 antigen (cytoplasmic tail)-binding protein 2 ↑ x2.5	• IL 1 receptor antagonist ↓ x2 • LT b4 receptor (chemokine receptor like- 1) ↓ x1.5 • Phosphotyrosine independent ligand p62B for the Lck SH2 domain B-cell isoform ↓ x2 • IFN regulatory factor 3 ↑ x5

TABLE 2
Pasireotide Gene Expression Profiling

<u>CLASS</u>	<u>PITUITARY</u>	<u>BROWN FAT</u>	<u>PANCREAS</u>
CELL CYCLE	• Forkhead box O3A ↓ x1.5 • Cyclin F ↓ x2 • Core-binding factor, runt domain, α subunit 2; translocated to, 1; cyclin D-related ↑ x3 • S-phase response (cyclin-related) ↑ x2 • Cell division cycle 25B ↑ x5 • Cyclin D3 ↑ x2.5 • Cdk12C (p18, inhibits CDK4) ↑ x2 • Cdk12D (p19, inhibits CDK4) ↑ x1.5 • Forkhead box H1 ↑ x2	• G1 to S phase transition ↓ x1.5 • Extra spindle poles, <i>S. cerevisiae</i>, homologue of ↓ x2.5 • PCNA ↓ x2.5 • Follistatin-like 3 glycoprotein ↑ x3 • Cyclin T2 ↑ x2.5	• Cyclin T2 ↓ x2 • Cyclin D1 ↑ x2 • Cdk1 1C ↑ x2
APOPTOSIS	• BCL2-associated athanogene ↑ x2 • BCL2-antagonist of cell death ↑ x2 • Bax γ ↑ x1.5 • BCL2/adenovirus E1B 19kD-interacting protein 3 ↑ x1.5 • Programmed cell death 6 ↑ x1.5 • Neuroblastoma-amplified protein ↑ x1.5	• Neuroblastoma ↓ x2.5 • Neuroblastoma apoptosis-related RNA binding protein ↓ x3 • Apoptosis-associated tyrosine kinase ↑ x3.5	• BCL2/adenovirus E1B 19kD-interacting protein 1, isoform BNIP1-a ↓ x1.5 • Neuro-blastoma apoptosis-related RNA binding protein ↓ x3

TABLE 3
Pasireotide Gene Expression Profiling (Continued)

<u>CLASS</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>SPLEEN</u>	<u>THYROID</u>
SIGNAL TRANSDUCTION 1) <i>Phosphatidylinositol and related pathways/PKC, phospholipases</i>	• PI-3- kinase, catalytic, α polypeptide $\downarrow$ x3	• PI transfer protein, β $\downarrow$ x1.5 • 1- PI-4- phosphate 5- kinase isoform C $\downarrow$ x2 • Glycosylphosphatidylinositol specific phospholipase D1 $\downarrow$ x1.5 • PKC, ι $\downarrow$ x1.5 • PLC, γ 1 (formerly subtype 148) $\uparrow$ x2 • PKC substrate 80K-H $\uparrow$ x1.5 • PLA2, group IIA (platelets, synovial fluid) $\uparrow$ x5.5 • PI transfer protein $\uparrow$ x3.5 • Nck, Ash and PLC γ binding protein NAP4 $\uparrow$ x3.5 • DAG kinase, α (80kD) $\uparrow$ x3 • DAG kinase, δ (130kD) $\uparrow$ x1.5 • IP 5- phosphatase $\uparrow$ x2	• PI-3-kinase, catalytic, α polypeptide $\downarrow$ x2.5 • PI-3- kinase, class 3 $\uparrow$ x2 • PLA2 $\uparrow$ x2 • PKC, α binding protein $\uparrow$ x2 • IP-4- phosphatase, type 1, isoform b $\uparrow$ x2 • PI-3-kinase, class 2, β polypeptide $\uparrow$ x1.5 • Phosphatidylinositol glycan, class B $\uparrow$ x1.5	• IP3 receptor type 3 $\downarrow$ x1.5 • PLC, γ 1 (formerly subtype 148) $\downarrow$ x2 • PIP 5- phosphatase type IV $\downarrow$ x3 • DAG 1 kinase, α (80kD) $\downarrow$ x4

TABLE 3
Pasireotide Gene Expression Profiling (Continued)

<u>CLASS</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>SPLEEN</u>	<u>THYROID</u>
2) <i>Other calcium/calcineurin/calmodulin dependent pathways and associated proteins</i>	• PP 3 (formerly 2B), catalytic subunit, β isoform (calcineurin A β) $\downarrow$ x2 • Calmodulin 3 (phosphorylase kinase, δ) $\downarrow$ x1.5 • Calcium/calmodulin-dependent protein kinase kinase 2 β $\uparrow$ x1.5	• Calcium/calmodulin-dependent protein kinase kinase 2, β $\uparrow$ x3 • Calmodulin 2 (phosphorylase kinase, δ) $\uparrow$ x2 • Receptor (calcitonin) activity modifying protein 1 precursor $\uparrow$ x1.5	• Nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1 $\downarrow$ x5 • Calmodulin 1 (phosphorylase kinase, δ) $\uparrow$ x2 • Calmodulin 2 (phosphorylase kinase, δ) $\uparrow$ x1.5 • Calcium/calmodulin-dependent protein kinase (CaM kinase) II β $\uparrow$ x2	• FKBP-associated protein $\downarrow$ x2.5 • Calmodulin-dependent PK IV (CaM-kinase IV) $\downarrow$ x7.5 • Calcium/calmodulin-dependent PK IV $\downarrow$ x7.5 • c-AMP responsive element binding protein 1 $\downarrow$ x2 • Calcium/calmodulin dependent protein kinase 1 $\downarrow$ x2

TABLE 3
Pasireotide Gene Expression Profiling (Continued)

<u>CLASS</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>SPLEEN</u>	<u>THYROID</u>
3) <i>Ras/MAPK kinase/ERK kinase related pathways and adaptor proteins</i>	• Ras suppressor protein 1 • Rho GTPase activating protein 4 • MAPKK 5 • Rho GTPase activating protein 5 • RAB4, member RAS oncogene family • RAB interacting factor • Related RAS viral (r-ras) oncogene homolog • RAP2A, member of RAS oncogene family • Human rho GDP-dissociation inhibitor • MAPKK 1	• Ras association (RalGDS/AF-6) domain family 1 • Rho GDP dissociation inhibitor (GDI) γ • Rab geranylgeranyl-transferase, α subunit • MAPK 10 • RAB13, member RAS oncogene family • Ras homolog gene family, member G (rho G) • RAB2, member RAS oncogene family • MAPK 1 • C-src tyrosine kinase • MAPK 14 • Rho GTPase-activating protein 1 • MAPKK 1 • ATP(GTP)-binding protein • RAB interacting factor • MAPK 6 • KAPKK 5 • RAB 30, member RAS oncogene family • RAB 4, member RAS oncogene family • MAPKK 13 • MAP/ERK kinase kinase 4, isoform a	• Rho/rac guanine nucleotide exchange factor (GEF) 2 • Rab geranylgeranyl-transferase • Human rho GDP-dissociation inhibitor 2 (IEF 8120) • SHP2 interacting transmembrane adaptor • RAS p21 protein activator (GTPase activating protein) 1 • SH3 domain binding glutamic acid-rich protein like • Neuronal shc • MAPKK 1 • MAKKK 5 • RAB11B, member of RAS oncogene family • GTPase • RAB5B, member RAS oncogene family • MAPKAPK 2 • MAPK 6 • Ras-related C3 botulinum toxin substrate 1 isoform Rac 1b • RAB1, member ras oncogene family • RAP1A, member of ras oncogene family • MAPKKKK • RAS guanyl releasing protein 2 (calcium and DAG-regulated) • Grb2-associated binder 2	• Ras homolog gene family, member B • Ras-GTPase activating protein • SH3 domain-binding protein 2 • Rho-associated, coiled-coil containing protein kinase 1 • RAD54 (<i>S. cerevisiae</i>)-like • RAB6, member RAS oncogene family • RAB5A, member RAS oncogene family • MAPKK 4 • SH3 domain binding glutamic acid-rich protein • MAPK 8 • Adaptor protein with pleckstrin homology and src homology 2 domains • SHP2 interacting transmembrane adaptor • Ras homolog gene family, member H • RaP2 interacting protein 8 • RAB5C, member RAS oncogene family • Grb2-associated binder 2

TABLE 3
Pasireotide Gene Expression Profiling (Continued)

<u>CLASS</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>SPLEEN</u>	<u>THYROID</u>
4) JAK/STAT pathway and related kinases	• STAT 2, 113kD • STAT 5B	• STAT 1, 91kδ	• JAK 3	• JAK 1 • STAT 6, IL-4 induced • Protein inhibitor of STATX • STAT 1, 91kδ • STAT 3 (acute-phase response factor)
5) Protein tyrosine phosphatases/other phosphatases	• PP 1, regulatory subunit 7 • PP 1A (formerly 2C), Mg-dependent, α isoform • PTP • PP 2A, regulatory subunit B' (PR 53) • PP 2A, regulatory subunit -β • PTP, non-receptor type 1 • PTP type IVA, member 3 • PP5, catalytic subunit	• PTP • PP 2 (formerly 2A), regulatory subunit A (PR 65), α Isoform • PP2A subunit- α • PTP, non receptor type 1 • PTP, non receptor type substrate 1 • PP 6, catalytic subunit • PTP, receptor type, C • PP 1, regulatory (inhibitor) subunit 5 • PTP, receptor type, f polypeptide (PTPRF), interacting protein (liprin), α 1	• Dual specificity phosphatase 8 • Myosin phosphatase target subunit 1 • Dual specificity phosphatase 9 • PTP, non-receptor type 1 • PP 1, regulatory (inhibitor) subunit 8 • PTP, receptor type, N • PTP type IVA, member 3 • PP 5, catalytic subunit • PTP σ	• PTP σ • Phosphatase and tensin homolog 2 • PP 5, catalytic subunit • PTP, non-receptor type 6 • PP 1A (formerly 2C), Mg-dependent, α isoform • PTP, receptor type, C • PTP, receptor type, N • Phosphatidic acid phosphatase type 2A • PTP, receptor type, A

TABLE 3
Pasireotide Gene Expression Profiling (Continued)

<u>CLASS</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>SPLEEN</u>	<u>THYROID</u>
6) <i>Other protein kinases and associated binding proteins</i>	• Receptor tyrosine kinase • Protein kinase • Serine/threonine kinase 3 • SNF1-like protein kinase • Serine/threonine kinase 9 • Membrane-associated kinase • Ser-Thr protein kinase related to the myotonic dystrophy protein kinase • cAMP-dependent protein kinase • RI-β regulatory subunit • Ribosomal protein S6 kinase, 90kδ, polypeptide 4 • Serine/threonine kinase 25 • Fms-related tyrosine kinase 3	• Protein kinase, cAMP-dependent, catalytic, inhibitor α • Tyrosine kinase 2 • Protein kinase • PTK2 protein tyrosine kinase 2 • Ribosomal protein S6 kinase, 90kδ, polypeptide 3 • Protein kinase, cAMP-dependent, catalytic, γ • Serine threonine protein kinase	• Serine/threonine kinase 14 α • Serine/threonine kinase • Protein kinase, AMP-activated, γ 1 non-catalytic subunit • Protein kinase, cAMP-dependent, catalytic inhibitor α • Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A • Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 2 isoform 1 • Serine/threonine kinase 19	• Serine kinase • Serine/threonine kinase 25 • Serine/threonine protein kinase • Ste-20 related kinase • Ribosomal protein S6 kinase, 90kδ, polypeptide 3 • Serine/threonine kinase 13 (aurora/IPL1-like) • Protein-tyrosine kinase • Membrane-associated kinase • Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 2 isoform 1 • Adenylate cyclase activating polypeptide precursor
7) <i>Adenylate/guanylate cyclases and related pathways</i>	• Natriuretic peptide receptor A/guanylate cyclase A (atrionatriuretic peptide receptor A) $\uparrow$ x2	• Natriuretic peptide receptor A/guanylate cyclase A (atrionatriuretic peptide receptor A) $\uparrow$ x6 • Adenyl cyclase-associated protein $\uparrow$ x1.5		• Adenylate cyclase activating polypeptide precursor $\downarrow$ x1.5

TABLE 3
Pasireotide Gene Expression Profiling (Continued)

<u>CLASS</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>SPLEEN</u>	<u>THYROID</u>
CELL SURFACE RECEPTORS				
1) <i>G-protein coupled receptors and related binding proteins/G proteins</i>	• Guanine nucleotide binding protein (G protein), β polypeptide 1 • G protein-coupled receptor 20 • G protein-coupled receptor 9 • G protein-coupled receptor 39 • G protein-coupled receptor kinase • G protein-coupled receptor 15 • Guanine nucleotide binding protein (G protein), β polypeptide 2 • G protein-coupled receptor 35 • SSTR 3$\uparrow$ x3 • SSTR 2$\uparrow$ x2	• G protein-coupled receptor 12 • G protein-coupled receptor kinase • G protein-receptor coupled 35 • G protein-coupled receptor 3 • G protein-receptor coupled 39 • Regulator of G-protein signalling 6 • Coagulation factor II (thrombin) receptor-like 1 precursor	• Guanine nucleotide binding protein 11 • Guanine nucleotide binding protein (G protein); β polypeptide 3 • G protein-coupled receptor 56 • Regulator of G-protein signalling 9 • Guanine nucleotide binding protein (G protein), α 11 (Gq class) • G protein-coupled receptor 35 • Angiotensin receptor-like 1 $\uparrow$ x1.5 • SSTR2 $\uparrow$ x2 • GDP dissociation inhibitor	• Guanine nucleotide binding protein (G protein), α 15 (Gq class) • G α inhibiting activity polypeptide 3 interacting protein • Regulator of G protein signalling • Guanine nucleotide binding protein 11 • G protein – coupled receptor 3 • G protein – coupled receptor kinase 1 • Ca^{++}-sensing receptor (hypocalcemic hypocalcaemia 1, severe neonatal hyperparathyroidism) • G protein-coupled receptor, family C, group 5, member B • Guanine nucleotide binding protein 11 • 5-hydroxy-tryptamine 7 receptor isoform b • Developmentally regulated • GTP-binding protein 2 • Endothelial differentiation-related factor 1 $\uparrow$

TABLE 3
Pasireotide Gene Expression Profiling (Continued)

<u>CLASS</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>SPLEEN</u>	<u>THYROID</u>
2) <i>Growth factors, their receptors and related binding proteins</i>	• GFR- bound protein 7 ↑ x2 • GFR- bound protein 14 ↑ x2 • CSF-1 receptor, formerly McDonough feline sarcoma viral (v-fms) oncogene homolog ↑ x2.5 • IL-7 R precursor ↑ x2 • PDGFR, α polypeptide ↑ x1.5 • TGF, β 1 ↑ x1.5	• Fms-related tyrosine kinase 1(VEGF /vascular permeability factor receptor) ↓ x1.5 • GFR- bound protein 2 ↓ x2.5 • Bone-derived GF ↑ x3 • Growth differentiation factor 1 ↑ x3 • TGF, β 1 ↓ x1.5 • TGFβR III (betaglycan, 300kδ) ↓ x2 • EGF (β- urogastrone) ↓ x2.5 • EGFR (avian erythroblastic leukaemia viral (v-erb-b) oncogene homolog) ↑ x2 • Butyrate response factor 2 (EGF-response factor 2) ↑ x2 • FGFR 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysplasia) ↑ x2 • TGFβ activated kinase-binding protein 1 ↑ x2.5 • GCSF ↑ x3.5 • EGF-like repeats and discoidin I-like domains 3 ↓ x1.5 • PDGFR, α polypeptide ↑ x2 • PDGF, α polypeptide ↑ x1.5	• EGF (β- urogastrone) ↓ x2 • TGF induced protein ↑ x1.5 • VEGF ↑ x1.5 • PDGF α polypeptide ↑ x2.5 • PDGFR, α polypeptide ↑ x1.5 • TGFβ receptor III (betaglycan, 300kD) ↓ x1.5 • HGF activator inhibitor precursor ↑ x1.5	• COL1A1 and PDGFB fusion transcript ↓ x6 • EGF-like module containing, mucin-like, hormone receptor-like sequence 1 ↓ x5 • PDGFR α ↓ x3 • Fms-related tyrosine kinase 1 (VEGF/ vascular permeability factor receptor) ↓ x2 • PDGF-associated Protein ↑ x2 • PDGFR β ↑ x2 • Cadherin 13, H-cadherin (heart) ↑ x2

TABLE 3
Pasireotide Gene Expression Profiling (Continued)

<u>CLASS</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>SPLEEN</u>	<u>THYROID</u>
3) <i>Glutamate receptor and related binding proteins</i> ATP-DEPENDENT TRANSPORT PROTEINS <i>Ion channels and related pathways</i>	• Glutamate receptor metabotropic 2 precursor ↓ x3 • Solute carrier family 6 (neurotransmitter transporter, creatin), member 8 ↓ x3 • Na⁺ channel, nonvoltage-gated 1, β (Liddle syndrome) ↓ x2 • Ca⁺⁺ channel, voltage-dependent, α 1H subunit ↑ x2 • K⁺ voltage-gated channel, Shaw-related subfamily, member 3 ↑ x2.5 • Solute carrier family 9 (Na⁺/H⁺ exchanger) isoform 3 regulatory factor 1 ↑ x2	• Glutamate receptor, metabotropic 4 ↑ x1.5 • Ca⁺⁺ channel, voltage-dependent, P/Q type, alpha 1A subunit ↓ x2.5 • ATPase, H⁺/K⁺ exchanging, beta polypeptide ↓ x2 • Solute carrier family 9 (sodium/hydrogen exchanger), isoform 3 regulatory factor 1 ↑ x11.5 • Solute carrier family 11 (Na⁺/phosphate symporters), member 1 ↑ x2.5	• K⁺ voltage-gated channel, shaker-related subfamily, member 3 ↓ x3 • Solute carrier family 9 (Na⁺/H⁺ exchanger) isoform 3 regulatory factor 1 ↑ x10.5 • ATPase, Na⁺/K⁺ transporting, β 1 polypeptide ↑ x2.5 • K⁺ large conductance Ca⁺⁺-activated channel, subfamily M, β member 1 ↑ x2.5 • Ca⁺⁺ channel, voltage-dependent, α 2/δ subunit 2 ↑ x1.5 • Ca⁺⁺ channel, voltage-dependent, α 2/δ subunit 1 ↑ x2	• Glutamate receptor, metabotropic 2 precursor ↓ 3.5 • K⁺ voltage-gated channel, shaker-related subfamily, member 3 ↓ x4.5 • ATPase, Ca⁺⁺ transporting, cardiac muscle, fast twitch 1 ↓ x4.5

TABLE 3
Pasireotide Gene Expression Profiling (Continued)

<u>CLASS</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>SPLEEN</u>	<u>THYROID</u>
CELL BIOLOGY/ SPECIALIZED FUNCTIONS				
1) <i>Neuro- mediators/ neuromodulators and related pathways</i>	• δ sleep inducing peptide, immunoreactor $\uparrow$ x2.5 • Opioid receptor, $\delta 1 \uparrow$ x2.5 • GABA (A) receptor, $\gamma 2$ precursor $\uparrow$ x2 • Acetylserotonin O-methyl transferase-like $\downarrow$ x3 • LIF (cholinergic differentiation factor) $\uparrow$ x2 • Dopamine receptor D2 $\uparrow$ x4.5	• GABA (A) receptor, $\gamma 2$ precursor $\uparrow$ x4 • Dopamine receptor D2 $\uparrow$ x3.5 • GABA(A) receptor-associated protein $\uparrow$ x1.5 • Dopamine receptor D3 $\uparrow$ x2 • δ sleep inducing peptide, immunoreactor $\uparrow$ x2.5 • 5-hydroxytryptamine (serotonin) receptor 6 $\uparrow$ x2.5	• Dopamine receptor D4 $\downarrow$ x2 • Adrenergic α-2C- receptor $\downarrow$ x2 • β adrenergic receptor kinase 1 $\uparrow$ x3	• GABA (A) receptor, $\gamma 2$ precursor $\downarrow$ x1.5 • Brain cannabinoid receptor 1 $\downarrow$ x2 • GABA (B) receptor 1, isoform a precursor $\uparrow$ x2.5 • Cannabinoid receptor 2 (macrophage) $\uparrow$ x3 • Phosphatidyl ethanolamine N-methyl-transferase $\uparrow$ x2 • Adrenergic, α-2C-, receptor $\downarrow$ x2.5
2) <i>Pancreatic/ gastro-intestinal secretions and related pathways</i>			• Gastric inhibitory polypeptide receptor $\uparrow$ x2	• Cholecystokinin B receptor $\downarrow$ x3 • Gastric inhibitory polypeptide 1 receptor $\downarrow$ x2

TABLE 3
Pasireotide Gene Expression Profiling (Continued)

<u>CLASS</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>SPLEEN</u>	<u>THYROID</u>
3) <i>Hormones and related pathways</i>	• Angiotensin receptor 1B ↓ x1.5 • Glucocorticoid receptor DNA binding factor 1 ↓ x4.5 • Insulin receptor ↓ x3 • THR, α (avian erythroblastic leukaemia viral (v-erb-a) oncogene homolog) ↑ x1.5 • Arginine vasopressin (neurophysin II, antidiuretic hormone, diabetes insipidus, neurohypophyseal) ↑ x2 • Vasopressin-activated calcium-mobilizing receptor-1 ↓ x2 • Corticotropin releasing hormone receptor type 2 beta isoform ↑ x1.5 • IGF-2 ↓ x2 • IGF-1 ↓ x2.5 • IGFBP2 ↑ x1.5 • THR-associated protein, 240kδ subunit ↓ x1.5 • THR binding protein ↑ x1.5 • PG-endo-peroxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase) ↓ x3.5 • Adrenomedullin ↑ x1.5 • SSTR 3 ↑ x3 • SSTR 2 ↑ x2	• Insulin promoter factor 1, homeodomain transcription factor ↓ x1.5 • IGF-2 ↓ x2.5 • Corticosteroid binding globulin precursor ↑ x2 • THR interacting protein 15 ↑ x1.5 • IGFBP2 ↑ x2 • Arginine vasopressin receptor 2 ↑ x2.5 • THR sulfo transferase ↑ x2.5 • Glucagon receptor ↑ x5	• PTHR 1 ↓ x2.5 • Arginine vasopressin receptor 1B ↑ x2 • IGFBP6 ↑ x2.5 • IGF-1 ↑ x1.5	• TSHR ↓ x2 • IGF-1 ↓ x1.5 • Solute carrier family 21 (PG transporter), member 2 ↑ x2

TABLE 3
Pasireotide Gene Expression Profiling (Continued)

<u>CLASS</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>SPLEEN</u>	<u>THYROID</u>
4) Cytoskeleton and associated proteins	• VWF precursor ↑ x2		• Vasodilator-stimulated phosphoprotein ↑ x2	• VWF precursor ↑ x2
5) Enzymes				• Thrombospondin 2 ↑ x2 • Pro-platelet basic protein (includes platelet basic protein, β-thromboglobulin, connective tissue-activating peptide III, neu) 2 ↑ x3.5
IMMUNITY	• TNF, α-induced protein 3 ↓ x1.5 • IRF5 ↑ x2 • Putative chemokine receptor; GTP-binding protein ↑ x2 • TNFR superfamily, member 12 ↑ x2	• TNF-α converting enzyme ↓ x2 • IFN-stimulated protein, 15kDa ↓ x2 • IFN-related developmental regulator 2 ↓ x1.5 • IFN-inducible RNA-dependent protein kinase ↑ x4 • IL2 R, γ chain, precursor ↑ x2.5 • IFN regulatory factor 5 ↑ x2.5 • Bruton agammaglobulinaemia tyrosine kinase ↑ x1.5 • B lymphoid tyrosine kinase ↑ x3.5 • IFN γ responsive transcript ↑ x1.5 • TNF (ligand) superfamily, member 10 ↑ x1.5 • IFN-induced leucine zipper protein ↑ x1.5	• IFN-inducible RNA-dependent protein kinase ↑ x2.5 • TNF (cachectin) ↑ x2 • TNF (ligand) superfamily, member 13 ↑ x2.5 • IL 1 receptor-like 1 ↑ x2 • IFNγ responsive transcript ↑ x2 • LTb4 (chemokine receptor-like 1) ↑ x3 • Putative chemokine receptor; GTP-binding protein ↑ x2.5 • IFNγ receptor 2 (IFNγ transducer 1) ↑ x1.5 • TNFR superfamily, member 12 ↑ x1.5 • IL-8 receptor type B ↑ x1.5 • IFN regulatory factor 2 ↑ x3.5	• LTB4 receptor (chemokine receptor-like 1) ↓ x1.5 • IL2-inducible T-cell kinase ↓ x12 • P56lck ↓ x18 • RAG1 ↓ x18 • IFNγ responsive transcript ↓ x1.5 • SH2 domain protein 1A, Duncan's disease (lymphoproliferative syndrome) ↓ x7.5 • CD2 antigen (p50), sheep red blood cell receptor ↓ x7.5 • TCR ζ chain precursor ↓ x5.5 • RAG2 ↓ x5 • Signalling lymphocytic activation molecule ↓ x4.5 • Flt3 ligand ↓ x4.5 • Lymphocyte specific protein tyrosine kinase ↓ x4

TABLE 3
Pasireotide Gene Expression Profiling (Continued)

<u>CLASS</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>SPLEEN</u>	<u>THYROID</u>
IMMUNITY (Continued)				• Chemokine (C-X-C motif), receptor 4 (fusin) ↓ x3 • Transcription factor 7 (T-cell specific, HMG-box) ↓ x16.5 • IL9 receptor ↓ x2 • RANTES ↑ x10.5 • CD2 antigen (cytoplasmic tail)-binding protein 2 ↑ x3.5 • IFNγ - inducible protein 30 ↑ x3.5 • IFNα-inducible protein 27 ↑ x3 • TNF (ligand) superfamily member 10 ↑ x2
CELL CYCLE	• Cdk (CDC2-like) ↓ x2 • Growth arrest-specific 6 ↑ x1.5 • Cdk 5, regulatory subunit 2 (p39) ↑ x1.5 • CDC37 (cell division cycle 37, <i>S. cerevisiae</i>, homolog) ↑ x1.5 • Cdk1 1A (p21, Cip 1) ↑ x5	• Cdk1 2D (p19, inhibits CDK4) ↓ x2.5 • Cdk like-2 ↓ x2 • Cdk 5, regulatory subunit 1 ↑ x2.5 • Cdk1A (p21/Cip1) ↑ x6 • Cdk like-2 ↓ x2	• Cyclin I ↓ x1.5 • S-phase kinase-associated protein 1A (p19A) ↑ x2 • Cdk 6 ↑ x3 • Cdk 5, regulatory subunit 1 (p35) ↑ x2 • Cyclin D2 ↑ x1.5 • S-phase kinase-associated protein 1A ↑ x2 • Cdk 2 ↑ x1.5 • Follistatin-like 1 ↑ x1.5	• Cdc-like 5 (cholinesterase-related cell division controller) ↓ x2 • Cdk (CDC2-like) ↓ x9 • Cdk 5, regulatory subunit 1 (p35) ↓ x5 • Growth arrest-specific 1 ↓ x2.5 • Cyclin B2 ↓ x2.5

TABLE 3
Pasireotide Gene Expression Profiling (Continued)

<u>CLASS</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>SPLEEN</u>	<u>THYROID</u>
APOPTOSIS	• Death effector domain-containing ↓ x3.5 • Fas/Apo-1/CD95 ↑ x1.5	• BCL2-like 1 ↓ x3.5 • Rb 1 (including osteosarcoma) ↓ x2 • Death-associated protein 6 ↓ x2.5 • Rb binding protein ↑ x2.5 • Rb-like 2 (p130) ↑ x3 • Fas-activated serine/threonine kinase ↑ x1.5	• Rb binding protein ↑ x2 • Caspase 8, apoptosis-related cysteine protease ↑ x2.5 • TNF (cachectin) ↑ x2 • TNF (ligand) superfamily, member 13 ↑ x2.5 • Bcl-2 binding component 3 ↑ x2.5 • Death-associated protein ↑ x1.5 • Tumour protein p53-binding protein ↑ x1.5 • Rb-binding protein 8 ↑ x1.5 • Programmed cell death 10 ↑ x1.5	• Bcl-2 binding component 3 ↓ x2

[43] These results show that several signal transduction pathways were affected. They included the phosphatidylinositol/PKC/phospholipases/calcium-calcineurin-calmodulin pathway, the Ras/MAPK kinase/ERK kinase dependent pathway, the JAK/STAT pathway, and adenylate/guanylate cyclases with their dependent pathways. The changes for the cell surfaces receptors included numerous G-protein coupled receptors, receptors for growth factors and glutamate receptors. The changes in ATP-dependent transport proteins involved ion channels and associated proteins. The compound also affected neuromediators/neuromodulators, pancreatic and gastrointestinal secretions, hormones, cytoskeletal proteins and enzymes/catalysts.

[44] Examples of genes reflecting several SSTR signalling pathways in the pituitary are shown in TABLE 4. Selected genes from the primary gene lists were produced by a succession of filtering and statistical algorithms (t-test: p value: 0.05). The numerical values correspond to the AvgDiff (see above) of the relevant probe set for each experiment with the range of observed values between brackets. Of particular interest in this analysis were the transcript level changes for molecules known to be closely associated with the binding of the natural peptides, SST-14 and SST-28, to the SSTRs.

TABLE 4
Examples of Genes Reflecting Several SSTR Signalling Pathways in the Pituitary

<u>GENES</u>	<u>CONTROL</u>	<u>Pasireotide</u> <u>(0.1 mg/animal/14 day)</u>
<u>SIGNAL TRANSDUCTION</u>		
<u>1) Phosphatidylinositol and related pathways/PKC, phospholipases</u>		
• IP-4-phosphatase, type 1, isoform b	296 (241 to 342)	177 (107 to 232)
• PI-3-kinase, catalytic, δ polypeptide	91 (45 to 146)	34 (20 to 67)
• PI-3-kinase, catalytic, α polypeptide	72 (26 to 135)	21 (20 to 24)
• PI transfer protein, β	125 (93 to 187)	42 (34 to 50)
• PKC inhibitor	2,351 (2,135 to 2,755)	3,333 (2,339 to 3,878)
• PLC, γ 1 (formerly subtype 148)	111 (100 to 131)	40 (20 to 63)
• PKC inhibitor	2,351 (2,135 to 2,755)	3,332 (2,339 to 3,878)
<u>2) Ras/MAPK kinase/ERK kinase related pathways and adaptor proteins</u>		
• MAPKKK5	171 (148 to 207)	278 (221 to 351)
• Rab geranylgeranyltransferase, α subunit	164 (152 to 173)	104 (70 to 172)
• Rab geranylgeranyltransferase, β subunit	230 (187 to 250)	284 (246 to 374)
• SHB adaptor protein (a Src homology 2 protein)	112 (43 to 190)	38 (20 to 55)
• RAB 5C, member RAS oncogene family	72 (20 to 138)	162 (109 to 212)
<u>3) Protein tyrosine phosphatases/other phosphatases</u>		
• Dual specificity phosphatase 8	493 (344 to 625)	170 (67 to 238)
• Phosphatase and tensin homolog (mutated in multiple advanced cancers 1)	129 (58 to 228)	36 (20 to 63)
• PTP, receptor type, T	58 (41 to 78)	101 (48 to 129)
• PP 1, regulatory (inhibitor) subunit 5	20	75 (60 to 90)
<u>4) Adenylate/guanylate cyclases and related pathways</u>		
• Soluble adenylyl cyclase	54 (51 to 57)	22 (20 to 27)
<u>CELL SURFACE RECEPTORS</u>		
<u>1) G-protein coupled receptors</u>		
• SSTR3	22 (20 to 24)	57 (20 to 90)
<u>2) Glutamate receptor and related binding proteins</u>		
• GLUR 2, precursor	42 (20 to 86)	59 (20 to 177)

TABLE 4
Examples of Genes Reflecting Several SSTR Signalling Pathways in the Pituitary

<u>GENES</u>	<u>CONTROL</u>	<u>Pasireotide</u> (0.1 mg/animal/14 day)
<u>ATP-DEPENDENT TRANSPORT PROTEINS</u>		
<u>Ion channels and related pathways</u>		
ATPase, Na ⁺ /K ⁺ transporting, β 3 polypeptide	292 (246 to 353)	610 (335 to 949)
ATPase, Na ⁺ /K ⁺ transporting, α 2 (+) polypeptide	86 (52 to 130)	184 (69 to 325)
ATPase, H ⁺ /K ⁺ exchanging, α polypeptide	128 (50 to 245)	20
K ⁺ channel, subfamily K, member 3 (TASK)	132 (69 to 188)	26 (20 to 43)
K ⁺ voltage-gated channel, Shab-related subfamily, member 1	66 (20 to 112)	22 (20 to 31)
Putative Ca ⁺⁺ transporting ATPase	61 (38 to 98)	101 (84 to 112)
<u>CELL CYCLE</u>		
Core-binding factor, runt domain, α subunit 2; translocated to, 1; cyclin D-related	225 (113 to 343)	491 (251 to 677)
Forkhead box O3A	497 (447 to 553)	257 (186 to 324)
Forkhead box H1	225 (113 to 343)	117 (251 to 677)
Cyclin F	198 (171 to 229)	74 (48 to 132)
Cyclin D3	187 (173 to 201)	338 (202 to 446)
S-phase response (cyclin-related)	91 (88 to 97)	129 (111 to 148)
Cell division cycle 25B	40 (20 to 67)	162 (134 to 187)
Cdk inhibitor 2C (p18, inhibits CDK4)	81 (58 to 99)	184 (140 to 229)
Cdk inhibitor 2D (p19, inhibits CDK4)	198 (171 to 229)	99 (83 to 118)
<u>APOPTOSIS</u>		
BCL2-associated athanogene	216 (207 to 231)	318 (235 to 409)
BCL2-antagonist of cell death	44 (33 to 47)	69 (42 to 89)
Bax gamma	258 (207 to 297)	326 (221 to 448)
BCL2/adenovirus E1B 19kD-interacting protein 3	342 (288 to 401)	458 (388 to 526)
Programmed cell death 6	504 (443 to 547)	635 (513 to 747)
Neuroblastoma-amplified protein	178 (149 to 210)	237 (201 to 258)

[45] The effects on the GH/IGF-1 and glucagon/insulin axes (Macaulay VM, *Br. J. Cancer* 65: 311-20 (1992); Pollak MN & Schally AV, *Proc. Soc. Exp. Biol. Med.* 217: 143-52 (1998)) were reflected in transcript level changes in several organs. The results are shown in TABLE 5. Beside the expected change in IGF-1 transcript level, there was an effect on IGF-2 as well (in the pituitary and kidneys) that might be useful as a biological marker of pasireotide activity if reflected in the blood. The genes were selected as above in TABLE 4.

TABLE 5
Example of genes reflecting the effects of pasireotide
on the GH/IGF and glucagon/insulin axes in different tissues

<u>ORGANS/GENES</u>	<u>CONTROL</u>	<u>PASIREOTIDE</u> (0.1mg/animal/14day)
<u>PITUITARY</u>		
IGF-2	126 (40 to 179)	70 (20 to 150)
GR	20	109 (51 to 215)
IGFBP, acid labile subunit	30 (20 to 49)	83 (20 to 110)
SSTR3	22 (20 to 24)	57 (20 to 90)
<u>BROWN FAT</u>		
IGF-1	548 (279 to 810)	389 (315 to 449)
IGFBP 4	1410 (916 to 2173)	763 (429 to 1058)
IRS 2	48 (20 to 84)	146 (80 to 222)
SSTR3	25 (20 to 52)	194 (87 to 248)
<u>PANCREAS</u>		
IGF-1	20	89 (20 to 298)
SSTR2	258 (205 to 366)	156 (120 to 210)
<u>KIDNEY</u>		
IR	654 (187 to 1,187)	196 (163 to 265)
IGF-2	117 (47 to 176)	49 (20 to 39)
IGF-1	65 (24 to 103)	25 (20 to 39)
IGFBP2	375 (211 to 625)	563 (457 to 655)
SSTR 3	31 (20 to 69)	82 (33 to 120)
SSTR 2	74 (20 to 153)	126 (93 to 158)
<u>LIVER</u>		
Insulin promoter factor 1, homeodomain transcription factor	89 (58 to 160)	42 (23 to 52)
IGF-2	701 (403 to 961)	269 (224 to 291)
IGFBP2	2,722 (1,321 to 3,363)	4,476 (3,191 to 5,422)
GR	44 (20 to 82)	80 (70 to 360)
<u>SPLEEN</u>		
IGFBP6	495 (130 to 982)	1,043 (853 to 1,155)
IGF-1	72 (42 to 103)	85 (52 to 125)
SSTR2	56 (20 to 83)	93 (87 to 95)
<u>THYROID</u>		
IGF-1	91 (20 to 179)	58 (20 to 114)

[46] Other genes of interest affected by pasireotide were the transcript levels of growth factors (PDGF, FGF, EGF, TGF β), their receptors and factors of angiogenesis (PDGF, VEGF, thrombospondin) involved in tumour growth and spreading (Woltering EA *et al.*, *New Drugs* 15: 77-86 (1997)). Also reported for somatostatin and analogues, genes involved in immunity were changed, *i.e.* cytokines (IL-1, TNF, IFN), regulators of T and B cell genesis and function (CD2 antigen, IL-2 receptor, B-lymphoid tyrosine kinase, IL-2 inducible T cell kinase, p56lck, RAG1, TCR ζ chain precursor, RAG2, FLT 3 ligand) (van Hagen PM *et al.* *Eur. J. Clin. Invest.* 24: 91-9 (1994)), as well as genes involved in blood pressure control and diuresis, *i.e.* atrial natriuretic peptide and its receptor guanylyl cyclase A, arginine vasopressin and its

receptor (Aguilera G *et al.*, *Nature* 292: 262-3 (1981); Aguilera G *et al.*, *Endocrinology* 111: 1376-84 (1982); Ray C *et al.*, *Clin. Sci. (Lond)* 84: 455-60 (1993); Cheng H *et al.*, *Biochem. J.* 364: 33-9 (2002)). A specific gene involved in the control of fat storage is the adrenergic β 3 receptor in brown fat (Bachman E *et al.*, *Science* 297: 843- 45 (2002)).

[47] Protein products of the above genes are useful as surrogate markers of the biological activity of pasireotide, especially the findings for IGF-2 in the pituitary and kidneys.

[48] To conclude, the gene profiling of monkey tissues treated with pasireotide at sub-therapeutic is a sensitive approach to identify signalling and effector pathways known for somatostatin.

[49] All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. In addition, all GenBank accession numbers, Unigene Cluster numbers and protein accession numbers cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each such number was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

[50] The present invention is not to be limited in terms of the particular embodiments described in this application, which are intended as single illustrations of individual aspects of the invention. Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and apparatus within the scope of the invention, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications and variations are intended to fall within the scope of the appended claims. The present invention is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled.

CLAIMS

We claim:

1. Use of pasireotide in the manufacture of a medicament for the treatment of disorders of growth regulation in a selected patient population, wherein the patient population is selected on the basis of the gene expression profile indicative of pasireotide efficacy by the patient to whom pasireotide is administered.
2. The use of claim 1, where the disorder of growth regulation is a tumour.
3. The use of claim 1 or 2, where the pasireotide is administered in a therapeutic dose prior to determining the gene expression profile by the patient.
4. The use of claim 1 or 2, where the pasireotide is administered in a sub-therapeutic dose prior to determining the gene expression profile by the patient.
5. A method for treating a condition in a subject, wherein the condition is a condition for which somatostatin or a somatostatin analogue is indicated, comprising the steps of:
 - (a) administering a compound to the subject;
 - (b) obtaining the gene expression profile of the subject, wherein the gene expression profile comprises the gene expression pattern of one or more genes, where the expression patterns of the one or more genes are a consequence of administration of the compound; and
 - (c) comparing the gene expression profile of the subject to whom the compound was administered to a biomarker gene expression profile indicative of efficacy of treatment by somatostatin or a somatostatin analogue, wherein a similarity in the gene expression profile of the subject to whom the compound was administered to the biomarker gene expression profile is indicative of efficacy of treatment with the compound.

6. The method of claim 5, wherein the compound is somatostatin or a somatostatin analogue.
7. The method of claim 5, wherein the compound is pasireotide.
8. The method of any one of claims 5 to 7, wherein the subject is a mammal.
9. The method of claim 8, wherein the mammal is a primate.
10. The method of claim 9, wherein the primate is a cynomolgus monkey or a human.
11. The method of any one of claims 5 to 10, wherein the biomarker gene expression profile is the baseline gene expression profile of the subject before administration of the compound.
12. The method of any one of claims 5, 6 or 7 to 11, wherein the biomarker gene expression profile is the gene expression profile or average of gene expression profiles of a vertebrate to whom somatostatin or a somatostatin analogue has been administered.
13. The method of any one of claims 5 to 12, wherein the gene expression profile comprises a decrease in the gene expression in the pituitary of a gene selected from the group consisting of PKC inhibitor; MAPKKK5; rab geranylgeranyltransferase, α subunit; SHB adaptor protein (a Src homology 2 protein); dual specificity phosphatase 8; phosphatase and tensin homolog; soluble adenylyl cyclase; ATPase, H⁺/K⁺ exchanging, α polypeptide; K⁺ channel, subfamily K, member 3 (TASK); K⁺ voltage-gated channel, Shab-related subfamily, member 1; forkhead box O3A; forkhead box H1; cyclin F; cdk inhibitor 2D (p19, inhibits CDK4) and combinations thereof.

14. The method of any one of claims 5 to 12, wherein the gene expression profile comprises an increase in the gene expression in the pituitary of a gene selected from the group consisting of IP-4-phosphatase, type 1, isoform b; PI-3-kinase, catalytic, δ polypeptide; PI-3-kinase, catalytic, α polypeptide; PI transfer protein, β ; PLC, γ 1 (formerly subtype 148); Rab geranylgeranyltransferase β subunit; RAB 5C, member RAS oncogene family; PTP, receptor type, T; PP 1, regulatory (inhibitor) subunit 5; SSTR3; GLUR 2, precursor; ATPase, Na^+/K^+ transporting, $\beta 3$ polypeptide; ATPase, Na^+/K^+ transporting, $\alpha 2$ (+) polypeptide; putative Ca^{++} transporting ATPase; core-binding factor, runt domain, α subunit 2; translocated to, 1; cyclin D-related; cyclin D3; S-phase response (cyclin-related); cell division cycle 25B; cdk inhibitor 2C (p18, inhibits CDK4); BCL2-associated athanogene; BCL2-antagonist of cell death; Bax gamma; BCL2/adenovirus E1B 19kD-interacting protein 3; programmed cell death 6; neuroblastoma-amplified protein and combinations thereof.
15. The method of any one of claims 5 to 12, wherein the gene expression profile comprises a decrease in the gene expression in the pituitary of a gene selected from the group consisting of IGF-2.
16. The method of any one of claims 5 to 12, wherein the gene expression profile comprises an increase in the gene expression in the pituitary of a gene selected from the group consisting of glucagon receptor (GR), IGFBP (acid labile subunit) and SSTR3.
17. The method of any one of claims 5 to 12, wherein the gene expression profile comprises a decrease in the gene expression in brown fat of a gene selected from the group consisting of IGF-1 and IGFBP 4.

18. The method of any one of claims 5 to 12, wherein the gene expression profile comprises an increase in the gene expression in brown fat of a gene selected from the group consisting of IRS 2 and SSTR 3.
19. The method of any one of claims 5 to 12, wherein the gene expression profile comprises a decrease in the gene expression in the pancreas of IGF-1.
20. The method of any one of claims 5 to 12, wherein the gene expression profile comprises an increase in the gene expression in the pancreas of SSTR 2.
21. The method of any one of claims 5 to 12, wherein the gene expression profile comprises a decrease in the gene expression in the kidney of a gene selected from the group consisting of IGF-1 and IGF-2.
22. The method of any one of claims 5 to 12, wherein the gene expression profile comprises an increase in the gene expression in the pancreas of a gene selected from the group consisting of IGFBP2, SSTR 3 and SSTR 2.
23. The method of any one of claims 5 to 12, wherein the gene expression profile comprises a decrease in the gene expression in the liver of a gene selected from the group consisting of insulin promoter factor 1, homeodomain transcription factor and IGF-2.
24. The method of any one of claims 5 to 12, wherein the gene expression profile comprises an increase in the gene expression in the liver of a gene selected from the group consisting of IGFBP2 and glucagon receptor (GR).
25. The method of any one of claims 5 to 12, wherein the gene expression profile comprises a decrease in the gene expression in the spleen of a gene selected from the group consisting of IGFBP6, IGF-1 and SSTR 2.

26. The method of any one of claims 5 to 12, wherein the gene expression profile comprises an increase in the gene expression in the spleen of a gene selected from the group consisting of IGFBP2, and glucagon receptor (GR).
27. The method of any one of claims 5 to 12, wherein the gene expression profile comprises an increase in the gene expression in the spleen of IGF-1.
28. The method of any one of claims 5 to 12, wherein the gene expression profile comprises a decrease in the gene expression of IGF-2.
29. A method for choosing a subject for inclusion in a clinical trial for determining the efficacy of a compound for a condition for which somatostatin or a somatostatin analogue is indicated, comprising the steps of:
- (a) administering the compound to the subject;
 - (b) obtaining the gene expression profile of the subject, wherein the gene expression profile comprises the gene expression pattern of one or more genes, where the expression patterns of the one or more genes are a consequence of administration of the compound;
 - (c) comparing the gene expression profile of the subject to whom the compound was administered to a biomarker gene expression profile indicative of efficacy of treatment by somatostatin or a somatostatin analogue; and
 - (d) then:
 - (i) including the subject in the clinical trial when the gene expression profile of the subject to whom the compound was administered is similar to the biomarker gene expression profile indicative of efficacy of treatment by somatostatin or a somatostatin analogue; or
 - (ii) excluding the subject from the clinical trial when the gene expression profile of the subject to whom the compound was administered is dissimilar to the biomarker gene expression profile indicative of efficacy of treatment by somatostatin or a somatostatin analogue.

30. The method of claim 29, wherein the compound is administered to the subject at a sub-therapeutic dose.
31. A method for determining whether a compound has a therapeutic efficacy similar to that of somatostatin or a somatostatin analogue, comprising the steps of:
- (a) administering the compound to the subject;
 - (b) obtaining the gene expression profile of the subject, wherein the gene expression profile comprises the gene expression pattern of one or more genes, where the expression patterns of the one or more genes are a consequence of administration of the compound;
 - (c) comparing the gene expression profile of the subject to whom the compound was administered to a biomarker gene expression profile indicative of efficacy of treatment by somatostatin or a somatostatin analogue; and
 - (d) then:
 - (i) determining that the compound has a therapeutic efficacy similar to that of somatostatin or a somatostatin analogue when the gene expression profile of the subject to whom the compound was administered is similar to the biomarker gene expression profile of a subject to whom somatostatin or a somatostatin analogue is administered; or
 - (ii) determining that the compound has a therapeutic efficacy different from that of somatostatin or a somatostatin analogue when the gene expression profile of the subject to whom the compound was administered is different from the biomarker gene expression profile of a subject to whom somatostatin or a somatostatin analogue is administered.
32. The method of claim 31, wherein the somatostatin analogue is pasireotide.
33. The method of claim 31 or 32, wherein the subject is a mammal.

34. The method of claim 33, wherein the mammal is a primate.
35. The method of claim 34, wherein the primate is a cynomolgus monkey or a human.
36. The method of any one of claims 31 to 35, wherein the compound is administered to the subject at a sub-therapeutic dose.
37. A kit for use in determining a treatment strategy for a condition, wherein the condition is a condition for which somatostatin or a somatostatin analogue is indicated, comprising:
 - (a) a reagent for detecting a biomarker of efficacy of somatostatin or a somatostatin analogue treatment;
 - (b) a container for the reagent; and
 - (c) a written product on or in the container describing the use of the biomarker in determining a treatment strategy for the condition.
38. The kit of claim 37, wherein the reagent is a gene chip.
39. The kit of claim 37, wherein the reagent is a hybridization probe.
40. The kit of claim 37, wherein the reagent is a gene amplification reagent.

41. The kit of any one of claims 37 to 40, wherein the biomarker comprises one or more genes selected from the group consisting of:
- (a) PKC inhibitor; MAPKKK5; rab geranylgeranyltransferase, α subunit; SHB adaptor protein (a Src homology 2 protein); dual specificity phosphatase 8; phosphatase and tensin homolog; soluble adenylyl cyclase; ATPase, H⁺/K⁺ exchanging, α polypeptide; K⁺ channel, subfamily K, member 3 (TASK); K⁺ voltage-gated channel, Shab-related subfamily, member 1; forkhead box O3A; forkhead box H1; cyclin F; and cdk inhibitor 2D (p19, inhibits CDK4);
 - (b) IP-4-phosphatase, type 1, isoform b; PI-3-kinase, catalytic, δ polypeptide; PI-3-kinase, catalytic, α polypeptide; PI transfer protein, β ; PLC, γ 1 (formerly subtype 148); Rab geranylgeranyltransferase β subunit; RAB 5C, member RAS oncogene family; PTP, receptor type, T; PP 1, regulatory (inhibitor) subunit 5; SSTR3; GLUR 2, precursor; ATPase, Na⁺/K⁺ transporting, β 3 polypeptide; ATPase, Na⁺/K⁺ transporting, α 2 (+) polypeptide; putative Ca⁺⁺ transporting ATPase; core-binding factor, runt domain, α subunit 2; translocated to, 1; cyclin D-related; cyclin D3; S-phase response (cyclin-related); cell division cycle 25B; cdk inhibitor 2C (p18, inhibits CDK4); BCL2-associated athanogene; BCL2-antagonist of cell death; Bax gamma; BCL2/adenovirus E1B 19kD-interacting protein 3; programmed cell death 6; and neuroblastoma-amplified protein;
 - (c) IGF-2;
 - (d) glucagon receptor (GR), IGFBP (acid labile subunit) and SSTR3;
 - (e) IGF-1 and IGFBP 4;
 - (f) IRS 2;
 - (g) SSTR 2;
 - (h) IGFBP2 and SSTR 2;
 - (i) insulin promoter factor 1 and homeodomain transcription factor;
 - (j) glucagon receptor (GR);
 - (k) IGFBP6; and
 - (l) combinations thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/013350

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/31 A61P35/00 C12Q1/68

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C12Q

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

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

EPO-Internal, CANCERLIT, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEWIS I, BAUER W, ALBERT R, CHANDRAMOULI N, PLESS J, WECKBECKER G, BRUNS C: "A Novel Somatostatin Mimetic with Broad Somatotropin Release Inhibitory Factor Receptor Binding and Superior Therapeutic Potential" JOURNAL OF MEDICINAL CHEMISTRY, vol. 46, no. 12, 13 May 2003 (2003-05-13), pages 2334-2344, XP002320769 cited in the application page 2340, paragraph 4 ----- -/--	1-41

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

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

15 March 2005

Date of mailing of the international search report

31/03/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Ganschow, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/013350

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WECKBECKER G, BRINER U, LEWIS I, BRUNS C: "SOM230: A New Somatostatin Peptidomimetic with Potent Inhibitory Effects on the Growth Hormone/Insulin-Like Growth Factor-I Axis in Rats, Primates and Dogs" ENDOCRINOLOGY, vol. 143, no. 10, 2002, pages 4123-4130, XP002320770 cited in the application page 4129, right-hand column, paragraph 4 -----	1-41
X	AMBLER GR, BUTLER AA, PADMANABHAN J, BREIER BH, GLUCKMAN PD: "The effects of octreotide on GH receptor and IGF-1 expression in the GH-deficient rat" JOURNAL OF ENDOCRINOLOGY, vol. 149, no. 2, 1996, pages 223-231, XP009044946 page 228, paragraph DISCUSSION - page 229 -----	1-41
X	WECKBECKER G ET AL: "SOMATOSTATIN ANALOGS FOR DIAGNOSIS AND TREATMENT OF CANCER" PHARMACOLOGY AND THERAPEUTICS, ELSEVIER, GB, vol. 60, no. 2, 1993, pages 245-264, XP002072560 ISSN: 0163-7258 the whole document -----	1-41
Y	DAVIS MI, WILSON SH, GRANT MB: "The therapeutic problem of proliferative diabetic retinopathy: targeting somatostatin receptors" HORM METAB RES, vol. 33, 2001, pages 295-299, XP009044806 STUTTGART-NEW YORK abstract -----	1-41
Y	HOCKETT RICHARD D ET AL: "Perspective: Pharmacogenomics in endocrinology" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, vol. 87, no. 6, June 2002 (2002-06), pages 2495-2499, XP002321145 ISSN: 0021-972X the whole document -----	1-41
X	US 5 968 903 A (KANEKO ET AL) 19 October 1999 (1999-10-19) abstract -----	1-4
X	WO 98/51332 A (SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES S.A.) 19 November 1998 (1998-11-19) claim 1 -----	1-4
	-/--	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/013350

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	IMAM H ET AL: "INDUCTION OF APOPTOSIS IN NEUROENDOCRINE TUMORS OF THE DIGESTIVE SYSTEM DURING TREATMENT WITH SOMATOSTATIN ANALOGS" ACTA ONCOLOGICA, XX, XX, vol. 36, no. 6, 1997, pages 607-614, XP000866070 the whole document	1-41
A	KRAUS J, WÖLTJE M, HÖLLT V: "Regulation of somatostatin receptor type 2 gene expression by glucocorticoids" FEBS LETTERS, vol. 459, 1999, pages 200-204, XP002320771 page 200, paragraph INTRODUCTION page 203, paragraph DISCUSSION - page 204	1-41
A	WO 03/087404 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; DRESSMAN, MARLENE, MICHELLE; MCLEAN) 23 October 2003 (2003-10-23) the whole document	1-41
A	US 2003/064385 A1 (DRESSMAN MARLENE MICHELLE ET AL) 3 April 2003 (2003-04-03) paragraph '0305! - paragraph '0313! claims 1,4,41,62	1-41

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/013350

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5968903	A	19-10-1999	AU 3975499 A	23-11-1999
			EP 1075273 A2	14-02-2001
			JP 2002513769 T	14-05-2002
			NO 20005588 A	05-01-2001
			WO 9956769 A2	11-11-1999
WO 9851332	A	19-11-1998	AT 262921 T	15-04-2004
			AU 8019898 A	08-12-1998
			CA 2289499 A1	19-11-1998
			DE 69822810 D1	06-05-2004
			DE 69822810 T2	03-02-2005
			DK 980253 T3	05-07-2004
			WO 9851332 A1	19-11-1998
			EP 0980253 A1	23-02-2000
			ES 2216290 T3	16-10-2004
			HK 1026843 A1	31-12-2004
			PT 980253 T	31-08-2004
			US 2004072734 A1	15-04-2004
WO 03087404	A	23-10-2003	AU 2003227639 A1	27-10-2003
			WO 03087404 A1	23-10-2003
			EP 1497463 A1	19-01-2005
US 2003064385	A1	03-04-2003	CA 2443627 A1	21-11-2002
			EP 1399593 A2	24-03-2004
			WO 02092854 A2	21-11-2002