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(54) Title: INHIBITION OF TRAUMA-INDUCED TUMOR GROWTH (57) Abstract A method for inhibiting in a mammal the accelerated growth of a solid primary or metastatic tumor resulting from tissue trauma caused surgically, non-surgically, or by tissue ulceration, which method comprises the step of administering to the mammal a therapeutically effective amount of somatostatin or a somatostatin agonist.		

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- 1 -

INHIBITION OF TRAUMA-INDUCED TUMOR GROWTH**FIELD OF THE INVENTION**

This invention relates to a therapeutic method for
5 inhibiting tumor growth.

BACKGROUND OF THE INVENTION

Cytoreductive surgery has been used as adjuvant
treatment for cancer patients whose tumor is believed to
be too extensive for cure by either drugs or surgery
10 alone. Accelerated growth of metastases following
surgical excision or debulking of a primary tumor is a
recognized clinical problem, and has been noted, in
particular, in osteogenic sarcoma and testicular cancer.

The phenomenon of accelerated growth of metastases
15 has been attributed to release of viable cells resulting
from the manipulation of the tumor during surgery, or to
acceleration of growth of metastases which originates
before surgery on the tumor occurred. Accelerated growth
of pre-surgical metastases has been attributed to changes
20 in the immune status of the host secondary to removal of
a major portion of the tumor or to other direct or
indirect effects of the surgical procedure. It has been
postulated that microscopic tumor remaining after surgery
is able to grow more rapidly than is the primary tumor
25 because the former is not subjected to factors
restricting its growth, e.g., anatomical boundaries,
anoxia, and nutritional deficiencies.

Enhanced growth of metastases following partial
excision of implanted tumors in mice was first reported
30 by Marie and Clunet in 1910, and by Tyzzer in 1913.

These workers stated that partial removal of implanted
tumors made available larger supplies of some "nutritive
substances" to enhance the growth of metastases. This
theory was a modification of Ehrlich's hypothesis that an

- 2 -

actively growing tumor removed certain specific growth substances from a host animal.

More recently, Simpson-Herren et al. [Cancer Treat. Rep. 60:1749 (1976)] described a study in which a
5 surgical procedure which was designed to simulate tumor excision but which left both the primary tumor and its spontaneous metastases undisturbed (a sham procedure) resulted in a slight increase in the thymidine index of Lewis lung tumor pulmonary metastases, and a decrease in
10 the animals' life-spans.

Other investigators have reported similar enhanced growth of metastases as a result of surgical or non-surgical trauma or stress. Of particular note, Fisher et al. [Cancer Res. 49:1996 (1989)] evaluated the effect of
15 removal of a primary tumor on the kinetics of cells in the metastasis of six different tumors. They found an increase in the labelling index of distant tumor focus (metastasis) associated with the removal of each of the tumor types. Serum, obtained from mice following removal
20 of a tumor, when transferred to a mouse-recipients with the same type of tumor, resulted in an increase in the labelling index of the recipients' tumors. However, if the serum was obtained less than 18 hours after surgery, or if the mice with tumors were not subjected to surgery,
25 then the serum failed to augment substantially the labelling index of tumors in mouse-recipients. These investigators concluded that their results refute the premise that removal of a primary tumor is a local phenomenon with no biological consequences.

30 Alexander et al. [Adv. Exp. Med. Biol. 233:345 (1988)] studied the phenomenon of preferential growth of blood-borne cancer cells at sites of trauma, and concluded that while several factors contribute to making a wound a more favorable growth environment for
35 metastases, a major mechanism is the release of growth

- 3 -

factors from macrophages which have infiltrated the wound.

Adenocarcinoma of the prostate gland is a common malignancy with an incidence that rapidly rises with age after 50. It is the single most common site of cancer in males over 70. Despite advances in surgical and medical therapy for carcinoma of the prostate, this malignancy continues to be a leading cause of cancer-related death in American men. During the last 30 years, the mortality rate from prostate cancer has remained essentially unchanged.

There are a number of similarities between benign prostatic hyperplasia (BPH) and cancer. Although no casual relationship has been found between BPH and prostate cancer, there are a number of compelling similarities, including increasing incidence and prevalence with age, concordant natural history, and hormonal requirements for growth and development.

Although patients with localized disease are often asymptomatic, localized advanced disease can be accompanied by symptoms of bladder outlet obstruction requiring therapeutic surgical intervention. Benign outlet obstruction from central prostatic hypertrophy is also common, requiring transurethral resection of the prostate (TURP).

Prostatectomy for benign disease is a misnomer. Regardless of the type of prostatectomy performed for benign obstructive disease (suprapubic, retropubic, perineal or transurethral), the prostate is not removed. A variable but substantial thickness of glandular prostatic tissue remains after removal of an adenomatous enlargement of the periurethral glands. Cancer can and does develop in the remaining prostatic tissues.

Early diagnosis of carcinoma of the prostate is hindered by the lack of symptoms in men with localized

- 4 -

tumors. Whereas most studies of prostate cancer screening have been conducted in asymptomatic men, others have dealt with screening of men before prostatectomy for presumed benign glandular involvement. Of particular
5 importance, therefore, is that pathologic evidence of clinically occult cancer is found in 10% to 20% of men undergoing surgery for BPH. See Denton, S. E. et al. J. Urol. 93:296 (1965); Sheldon, C. A. et al. J. Urol 124:626 (1980).

10 Stage A carcinoma of the prostate has been defined as cancer found at autopsy incidentally and in pathologic sections of resected glands believed preoperatively to have been benign. Whitmore, W. F., Jr., Amer. J. Med. 21:697 (1956). Autopsy studies indicate that the
15 incidence of such cases is 25% to 30% in men who were >50 years old. Hudson, P. B. et al., J.A.M.A. 155:426 (1954).

That surgical trauma may trigger these latent cancer cells into increased proliferation and/or
20 metastasis is indicated by the following clinical examples. Armenian, et al. [Armenian, H. K. et al., Lancet 2:115-117, 1974] obtained follow-up on 611 patients up to 18 years after TURP and open prostatectomy, and found a significantly greater
25 frequency of cancer in those with BPH (11.4%) compared with controls without BPH (3.2%). The death rate for prostate cancer was 3.7 times higher among patients with BPH than among controls. The authors also retrospectively compared 290 cancer patients with age-
30 matched controls, and noticed a relative risk of 5.1 for prostate cancer in patients treated for BPH.

A study done by Hanks, et al. [J. Urol. U 129:309 (1983)] on 443 patients treated with radiation therapy for cancer of the prostate, compared survival of patients
35 whose cancer was diagnosed by TURP to those diagnosed by

- 5 -

needle biopsy, a significantly less traumatic procedure. This analysis indicated a doubling of recurrence and of deaths of patients diagnosed by TURP.

McGowan [Int. J. Radiat. Oncol. Biol. Phys. 6:1121
5 (1980)] reported a retrospective study of 291 patients treated with definitive radiotherapy at the Cross Cancer Institute of Edmonton. Actuarial disease-free survival and survival corrected for intercurrent death were determined for each stage and by method of diagnosis. A
10 significant difference in 5-year disease-free survival for Stages B and C was demonstrated: 72% and 51% for needle versus TURP, respectively ($p=0.005$ by Gehan's Wilcoxon two-sided test).

The literature is replete with clinical examples
15 illustrating the poorer prognosis and shorter survival of prostate cancer patients subjected to the more surgical trauma of TURP as compared to needle biopsy.

A surgical procedure which is gaining in popularity for the treatment of early breast cancer is
20 "lumpectomy". Although lumpectomy is not as traumatic as mastectomy, it is a surgical procedure which does not explore, or remove, the draining lymph nodes which may contain residual cancer cells. Lumpectomy is relatively new on the surgical scene, and does not have the
25 repertoire of clinical studies illustrating the effects of surgical trauma on tumor recurrence and survival. However, a parallelism with the prostate is likely.

Wide margin surgical excision is the first therapeutic modality applied to the treatment of primary
30 cutaneous malignant melanoma. Depending upon the degree of local infiltration or involvement of the draining lymph nodes, surgery may be followed with radiation and/or chemotherapy. However, recurrence of tiny melanotic lesions at the surgical site or along the
35 draining lymph channels are clinically readily recognized

- 6 -

and a common indication of progressive disease. Because of the difficulty in treating advanced malignant melanoma, ethical considerations have not permitted clinical studies comparing survival or metastatic spread
5 of cutaneous malignant melanoma in patients subjected or not subjected to surgical excision of the primary cutaneous lesion.

It has recently been reported that a somatostatin analog inhibits growth but not wound healing. See
10 Abribat T. et al. Endocrine Society, 74th Annual Meeting, Abstract #1384 (1992).

SUMMARY OF THE INVENTION

The present invention relates to a therapeutic method for inhibiting in a mammal the accelerated growth
15 of a solid primary or metastatic tumor resulting from tissue trauma caused surgically, non-surgically, or by tissue ulceration. The method includes the step of administering to said mammal a therapeutically effective amount of somatostatin or a somatostatin agonist.

20 Also within the scope of this invention is a method for making a medicament for inhibiting in a mammal the accelerated growth of a solid primary or metastatic tumor resulting from tissue trauma caused surgically, non-surgically, or by tissue ulceration, said method
25 comprising admixing somatostatin or a somatostatin agonist with a pharmaceutically acceptable carrier substance.

Definition of "somatostatin agonist" will be defined below. A therapeutically effective amount
30 depends upon the condition being treated, the route of administration chosen, and the specific activity of the compound used, and ultimately will be decided by the attending physician or veterinarian.

- 7 -

The tumors which can be treated by the therapeutic method of this invention include, but are not limited to, epithelial tumors (tumors of epithelial tissues) such as prostate tumor, breast tumor, colon tumor, lung tumor, and melanoma. Preferably, the administering step is performed by topical or subcutaneous application to the site of the trauma.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Abbreviations

- β -Nal = β -naphthylalanine
 β -Pal = β -pyridylalanine
hArg(Bu) = N-guanidino-(butyl)-homoarginine
15 hArg(Et)₂ = N, N'-guanidino-(dimethyl)-homoarginine
hArg(CH₂CF₃)₂ = N, N'-guanidino-bis-(2,2,2,-trifluoroethyl)-homoarginine
hArg(CH₃, hexyl) = N, N'-guanidino-(methyl, hexyl)-homoarginine
20 Lys(Me) = N^ε-methyllysine
Lys(iPr) = N^ε-isopropyllysine
AmPhe = aminomethylphenylalanine
ACHxAla = aminocyclohexylalanine
Abu = α -aminobutyric acid
25 Tpo = 4-thiaproline
MeLeu = N-methyllleucine
Orn = ornithine
Nle = norleucine
Nva = norvaline
30 Trp(Br) = 5-bromo-tryptophan
Trp(F) = 5-fluoro-tryptophan
Trp(NO₂) = 5-nitro-tryptophan
Gaba = γ -aminobutyric acid
Bmp = β -mercaptopropionyl

- 8 -

Ac = acetyl

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Somatostatin and its agonists

Somatostatin (somatotropin release inhibiting
5 factor, or SRIF) is an inhibitor of secretion of the
growth hormone and was originally isolated from the
hypothalamus. Brazeau et al. Science 179:77 (1973).
Somatostatin has a broad spectrum of biological effects,
participates in a high number of biological processes and
10 in the majority of cases, plays a role of an inhibitory
factor. E.g., it inhibits the release of prolactin,
insulin, glucagon, gastrin, secretin, and
cholecystokinin. Reichlin, S. Somatostatin, N. Eng. J.
Med. 309:1495 and 1556 (1983).

15 One of the most important effects of somatostatin
as growth-inhibiting factor consists in its capability to
influence various forms of pathological cell growth. It
is well known from the literature that it exerts an
inhibitory action on the growth of cancerous cells. See
20 Schally, A.V. Cancer Res. 48:6988 (1988); and Taylor et
al. Biochem. Biophys. Res. Commun. 153:81 (1988).

Likely, somatostatin antagonizes the effect of
some growth factors on tumor proliferation. It has been
shown recently that somatostatin and some somatostatin
25 analogs are capable of activating the tyrosine
phosphatase enzyme which antagonizes the effect of
tyrosine kinases, a mediator on the mitotic effect of
growth factors (e.g., epidermal growth factor, insulin-
like growth factor, etc.). Schally, A.V. Cancer Res.
30 48:6977 (1988); Yarden, et al. Ann. Rev. Biochem. 57:443
(1989).

Native somatostatin has a very short duration of
effect *in vivo* since it is rapidly inactivated by endo-
and exopeptidase. Many novel analogs have been prepared

- 9 -

in order to enhance the duration of effect, biological activity and selectivity of this hormone. Such analogs will be called somatostatin agonists herein.

Somatostatin agonists which can be used to
5 practice the therapeutic method of the present invention include, but are not limited to, those covered by formulas or those specifically recited in the publications set forth below.

EP Application No. P5 164 EU (Inventor: G. Keri);
10 Van Binst, G. et al. Peptide Research 5:8 (1992);
Horvath, A. et al. Abstract, "Conformations of Somatostatin Analogs Having Antitumor Activity", 22nd European peptide Symposium, September 13-19, 1992, Interlaken, Switzerland;

15 EP Application 0 363 589 A2 (1990);
U.S. Patent No. 4,904,642 (1990);
U.S. Patent No. 4,871,717 (1989);
U.S. Patent No. 4,853,371 (1989);
U.S. Patent No. 4,725,577 (1988);
20 U.S. Patent No. 4,650,787 (1987);
U.S. Patent No. 4,603,120 (1986);
U.S. Patent No. 4,585,755 (1986);
EP Application 0 203 031 A2 (1986);
U.S. Patent No. 4,522,813 (1985);
25 U.S. Patent No. 4,486,415 (1984);
U.S. Patent No. 4,485,101 (1984);
U.S. Patent No. 4,435,385 (1984);
U.S. Patent No. 4,395,403 (1983);
U.S. Patent No. 4,369,179 (1983);
30 U.S. Patent No. 4,360,516 (1982);
U.S. Patent No. 4,358,439 (1982);
U.S. Patent No. 4,328,214 (1982);
U.S. Patent No. 4,316,890 (1982);
U.S. Patent No. 4,310,518 (1982);
35 U.S. Patent No. 4,291,022 (1981);

- 10 -

U.S. Patent No. 4,238,481 (1980);

U.S. Patent No. 4,235,886 (1980);

U.S. Patent No. 4,211,693 (1980);

U.S. Patent No. 4,190,648 (1980);

5 U.S. Patent No. 4,146,612 (1979); and

U.S. Patent No. 4,133,782 (1979).

Preferred somatostatin agonists include, but are not limited to, the following somatostatin analogs which are disclosed in the above-cited references:

- 10 H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-OH;
 H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;
 H-D-Trp-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂;
 H-D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;
 H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂;
 15 H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH₂;
 H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂;
 Ac-D-Phe-Lys^{*}-Tyr-D-Trp-Lys-Val-Asp-Thr-NH₂ (an
 amide bond formed between Lys^{*} and Asp);
 Ac-hArg(Et)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-
 20 NH₂;
 Ac-D-hArg(Et)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-
 NH₂;
 Ac-D-hArg(Bu)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-
 NH₂;
 25 Ac-D-hArg(Et)₂-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;
 Ac-L-hArg(Et)₂-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;
 Ac-D-hArg(CH₂CF₃)₂-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-
 NH₂;
 Ac-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-
 30 Thr-NH₂;
 Ac-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-
 Phe-NH₂;
 Ac-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-
 Thr-NH₂

- 11 -

- Ac-L-hArg(CH₂-CF₃)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂
- Ac-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-NH₂
- 5 Ac-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys(Me)-Thr-Cys-Thr-NHEt
- Ac-hArg(CH₃, hexyl)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂
- 10 H-hArg(hexyl)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;
- Ac-D-hArg(Et)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NHEt;
- Ac-D-hArg(Et)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH₂;
- 15 Propionyl-D-hArg(Et)₂-Gly-Cys-Phe-D-Trp-Lys(iPr)-Thr-Cys-Thr-NH₂;
- Ac-D-β-Nal-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Gly-hArg(Et)₂-NH₂;
- Ac-D-Lys(iPr)-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;
- 20 Ac-D-hArg(CH₂CF₃)₂-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys-thr-Cys-Thr-NH₂;
- Ac-D-hArg(CH₂CF₃)₂-D-hArg(CH₂CF₃)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Phe-NH₂;
- 25 Ac-D-hArg(Et)₂-D-hArg(Et)₂-Gly-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂;
- Ac-Cys-Lys-Asn-4-Cl-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-Ser-D-Cys-NH₂;
- Bmp-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂;
- 30 Bmp-Tyr-D-Trp-Lys-Val-Cys-Phe-NH₂;
- Bmp-Tyr-D-Trp-Lys-Val-Cys-p-Cl-Phe-NH₂;
- Bmp-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH₂
- H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂;
- H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH₂;
- 35 H-D-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-β-Nal-NH₂;

- 12 -

- H-pentafluoro-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂;
 Ac-D-β-Nal-Cys-pentafluoro-Phe-D-Trp-Lys-Val-Cys-Thr-NH₂;
 5 H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH₂;
 H-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH₂;
 H-D-β-Nal-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH₂;
 H-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH₂;
 Ac-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Abu-Cys-Thr-NH₂;
 10 H-D-Phe-Cys-β-Nal-D-Trp-Lys-Val-Cys-Thr-NH₂;
 H-D-Phe-Cys-Tyr-D-Trp-Lys-Cys-Thr-NH₂;
 cyclo (Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe);
 cyclo (Pro-Phe-D-Trp-N-Me-Lys-Thr-Phe);
 cyclo (Pro-Phe-D-Trp-Lys-Thr-N-Me-Phe);
 15 cyclo (N-Me-Ala-Tyr-D-Trp-Lys-Thr-Phe);
 cyclo (Pro-Tyr-D-Trp-Lys-Thr-Phe);
 cyclo (Pro-Phe-D-Trp-Lys-Thr-Phe);
 cyclo (Pro-Phe-L-Trp-Lys-Thr-Phe) (SEQ ID NO:1);
 cyclo (Pro-Phe-D-Trp(F)-Lys-Thr-Phe);
 20 cyclo (Pro-Phe-Trp(F)-Lys-Thr-Phe) (SEQ ID NO:2);
 cyclo (Pro-Phe-D-Trp-Lys-Ser-Phe);
 cyclo (Pro-Phe-D-Trp-Lys-Thr-p-Cl-Phe);
 cyclo (D-Ala-N-Me-D-Phe-D-Thr-D-Lys-Trp-D-Phe);
 cyclo (D-Ala-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Phe);
 25 cyclo (D-Ala-N-Me-D-Phe-D-Thr-Lys-D-Trp-D-Phe);
 cyclo (D-Abu-N-Me-D-Phe-D-Val-Lys-D-Trp-D-Tyr);
 cyclo (Pro-Tyr-D-Trp-t-4-AchxAla-Thr-Phe);
 cyclo (Pro-Phe-D-Trp-t-4-AchxAla-Thr-Phe);
 cyclo (N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe);
 30 cyclo (N-Me-Ala-Tyr-D-Trp-t-4-AchxAla-Thr-Phe);
 cyclo (Pro-Tyr-D-Trp-4-Amphe-Thr-Phe);
 cyclo (Pro-Phe-D-Trp-4-Amphe-Thr-Phe);
 cyclo (N-Me-Ala-Tyr-D-Trp-4-Amphe-Thr-Phe);
 cyclo (Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba);
 35 cyclo (Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba-Gaba);

- 13 -

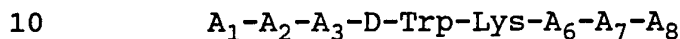
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 cyclo (Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-β-Ala) ;
 cyclo (Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-D-Glu)-OH;
 5 cyclo (Phe-Phe-D-Trp-Lys-Thr-Phe) ;
 cyclo (Phe-Phe-D-Trp-Lys-Thr-Phe-Gly) ;
 cyclo (Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba) ;
 cyclo (Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gly) ;
 cyclo (Asn-Phe-Phe-D-Trp(F)-Lys-Thr-Phe-Gaba) ;
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 Pro-Cys)-OH;
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 Pro-Cys)-OH;
 cyclo (Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-
 20 Tpo-Cys)-OH;
 cyclo (Bmp-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-
 MeLeu-Cys)-OH;
 cyclo (Phe-Phe-D-Trp-Lys-Thr-Phe-Phe-Gaba) ;
 cyclo (Phe-Phe-D-Trp-Lys-Thr-Phe-D-Phe-Gaba) ;
 25 cyclo (Phe-Phe-D-Trp(5F)-Lys-Thr-Phe-Phe-Gaba) ;
 cyclo (Asn-Phe-Phe-D-Trp-Lys(Ac)-Thr-Phe-NH-
 (CH₂)₃-CO) ;
 cyclo (Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba) ;
 cyclo (Lys-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba) ; and
 30 cyclo (Orn-Phe-Phe-D-Trp-Lys-Thr-Phe-Gaba) .

Note that for all somatostatin agonists described
 herein, each amino acid residue represents the structure
 of NH-C(R)H-CO-, in which R is the side chain. However,
 in the two generic formulas set forth immediately below,
 35 the N-terminal A₁ and A¹ stand for NH₂-C(R)H-CO- and =N-

- 14 -

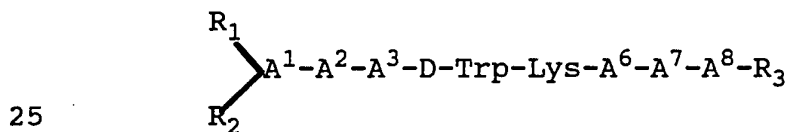
C(R)H-CO-, respectively. Lines between amino acid residues represent peptide bonds which join the amino acids. Also, where the amino acid residue is optically active, it is the L-form configuration that is intended
 5 unless D-form is expressly designated. A disulfide bridge is formed between two Cys residues; however, it is not shown.

Also preferred somatostatin agonists of the invention is of the following formula:



wherein A_1 is a D- or L-isomer of β -Nal, Trp, β -Pal, Phe, substituted Phe, or deleted; A_2 and A_7 , independently, is Cys, Asp, or Lys, and are covalently linked either via a disulfide bridge or an amide bridge;
 15 A_3 is Phe or o-, m- or p-substituted X-Phe where X is a halogen, OH, NH_2 , NO_2 or C_{1-3} alkyl; A_6 is Val, Thr, Ser, Ala, Phe, β -Nal, Abu, Ile, Nle, or Nva; and A_8 is Phe, Tyr, Trp, Ser, β -Nal, or deleted; providing that when one of A_2 and A_7 is Cys, the other is also Cys, and that when
 20 neither of A_2 and A_7 is Cys, A_2 is different from A_7 .

Use of linear somatostatin agonists of the following formula is also within the invention:



wherein

A^1 is a D- or L- isomer of Ala, Leu, Ile, Val, Nle, Thr, Ser, β -Nal, β -Pal, Trp, Phe, 2,4-dichloro-Phe, pentafluoro-Phe, p-X-Phe, or o-X-Phe, wherein X is CH_3 ,
 30 Cl, Br, F, OH, OCH_3 or NO_2 ;

A^2 is Ala, Leu, Ile, Val, Nle, Phe, β -Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-

- 15 -

Phe, or p-X-Phe, wherein X is CH₃, Cl, Br, F, OH, OCH₃ or NO₂;

A³ is pyridyl-Ala, Trp, Phe, β-Nal, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is
 5 CH₃, Cl, Br, F, OH, OCH₃ or NO₂;

A⁶ is Val, Ala, Leu, Ile, Nle, Thr, Abu, or Ser;

A⁷ is Ala, Leu, Ile, Val, Nle, Phe, β-Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, o-X-Phe, or p-X-Phe, wherein X is CH₃, Cl, Br, F, OH, OCH₃ or
 10 NO₂;

A⁸ is a D- or L-isomer of Ala, Leu, Ile, Val, Nle, Thr, Ser, Phe, β-Nal, pyridyl-Ala, Trp, 2,4-dichloro-Phe, pentafluoro-Phe, p-X-Phe, or o-X-Phe, wherein X is CH₃, Cl, Br, F, OH, OCH₃ or NO₂;

15 each R₁ and R₂, independently, is H, lower acyl or lower alkyl; and R₃ is OH or NH₂; provided that at least one of A¹ and A⁸ and one of A² and A⁷ must be an aromatic amino acid; and further provided that A¹, A², A⁷ and A⁸ cannot all be aromatic amino acids.

20 Particularly preferred linear agonists to be used in the method of this invention include:

H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH₂.

H-D-Phe-p-NO₂-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH₂;

25 H-D-Nal-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH₂.

H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH₂.

H-D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH₂.

30 H-D-Phe-p-chloro-Phe-Tyr-D-Trp-Lys-Val-Phe-Thr-NH₂.

H-D-Phe-Ala-Tyr-D-Trp-Lys-Val-Ala-β-D-Nal-NH₂

If desired, a hydrophobic moiety (e.g., an acyl group) can be attached to the nitrogen of the amino group at the N terminus of a somatostatin agonist.

- 16 -

Proliferation of tumor following trauma

Before disclosing preferred methods of using somatostatin or its agonist to inhibit in a mammal the accelerated growth of a solid primary or metastatic tumor resulting from tissue trauma caused surgically, non-surgically, or by tissue ulceration, experimental evidence of the trauma-induced tumor growth is first provided.

The proliferative surge of residual tumor in surgically treated animals would indicate the release of growth factors from the trauma area. To determine duration of the release of such factors post trauma, surgical trauma was induced in five groups (10 animals per group), and five groups (10 animals per group) were retained as non-surgically treated controls. Treatment of the various groups is summarized in Table 1.

TABLE I

Trauma Induced Proliferation of Subcutaneous Melanoma

Group No.	Treatment	Day Post Implantation	Tumor Weight	Growth Rate
25	1 Surgery left flank, day 0. Tumor implanted s.c., right flank, day 0.	14	1031±112	73.6
	2 Surgery left flank, day 0. Tumor implanted s.c., right flank, day 1.	15	1391±166	92.7
30	3 Surgery left flank, day 0. Tumor implanted s.c., right flank, day 2.	14	1333±244	95.2
	4 Surgery left flank, day 0. Tumor implanted s.c., right flank, day 3	15	764±166	50.9
	5 Surgery left flank, day 0. Tumor implanted s.c., right flank, day 4.	14	558±200	39.8
35	6 No surgery control. Tumor implanted s.c., right flank, day 0.	14	454±76	32.5
	7 No surgery control. Tumor implanted s.c., right flank, day 1.	15	972±232	64.8
40	8 No surgery control. Tumor implanted s.c., right flank, day 2.	14	813±268	58.1

- 17 -

9	No surgery control. Tumor implanted s.c., right flank, day 3.	15	950±185	63.3
10	No surgery control. Tumor implanted s.c., right flank, day 4.	14	448±111	31.9

5

Surgical Procedure: Sterile excision of a full thickness skin graft from the left flank. Wound edges immediately approximated and closed with Michel clamps. Surgically treated animals were carefully randomized.

B16 Melanoma: Implant 10^5 B16-F10 cells, s.c., right flank in p.m.

The units of tumor weight and growth rate are mg and mg/day, respectively.

10

Tumor sizes were determined three times weekly with Vernier calipers, and the growth rate per day was calculated at the end of the test period. In Table 1, comparisons are made between Group 1 and Group 6; Group 2 and Group 7; Group 3 and Group 8; Group 4 and Group 9; and Group 5 and Group 10. The percent increase in the growth rate per day in the surgically treated groups over that of the corresponding non-traumatized control indicates that the stimulus to tumor growth begins to occur on the day of traumatization. The resultant effect on tumor growth is easily measurable thereafter, and declines to normal growth levels by day 4.

These results correlate very closely with the observations by Aamdal, et al. [Br. J. Cancer 51:347 (1985)], who measured the mitotic activity of human tumor xenografts implanted subrenal capsule in mice. In his studies, human melanomas, colon carcinomas and sarcomas exhibited a proliferative surge following the surgical trauma of subrenal capsule implantation,

30 Inhibition of trauma-induced growth of prostate tumor

The following study was designed to demonstrate the therapeutic effect of applying BIM-23014 (a somatostatin agonist with the structure of H-D- β -Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂), topically, either to the tumor site or to the surgically traumatized site, for

- 18 -

inhibiting the proliferative surge of prostate tumor following surgical trauma. The results, as well as a brief description of the experiment, are presented in Table 2 below. Data are reported as means $\pm$ s.e.m. on 10 animals/group.

TABLE 2

Treatment of Surgical Trauma-Induced Proliferation
(Prostate Tumor)

Group No.	Treatment	Change in Tumor Weight Day 6-17 (mgs)	Percent Test/Control
15	1 Tumor implanted s.c., right flank, day 0. No surgery. Shelf control.	1921 $\pm$ 260	123
20	2 Tumor implanted s.c., right flank, day 0. Surgery left flank, day 3. Shelf control.	2366 $\pm$ 434	
25	3 Tumor implanted s.c., right flank, day 0. Surgery left flank, day 3. 10% DMSO/saline vehicle, topical to tumor, b.i.d., q.d. 3(p.m.).	2100 $\pm$ 321	98
30	4 Tumor implanted s.c., right flank, day 0. Surgery left flank, day 3. BIM-23014 topical to tumor, b.i.d., q.d. 3(p.m.).	2052 $\pm$ 196	
35	5 Tumor implanted s.c., right flank, day 0. Surgery left flank, day 3. 10% DMSO/saline vehicle, topical to surgery area, b.i.d., q.d. 3(p.m.).	2410 $\pm$ 289	77
40	6 Tumor implanted s.c., right flank, day 0. Surgery left flank, day 3. BIM-23014, topical to surgery area, b.i.d., q.d. 3(p.m.).	1854 $\pm$ 328	

More specifically, tumor implantation was performed on all test animals, i.e., Groups 1-6, by implanting subcutaneously a 2 mm³ mince of 2PR121D(1), a

- 19 -

prostate tumor cell line, in the right flank on day 0. Surgical trauma was induced in the left flank of five groups of Noble male rats, i.e., Groups 2-6. The surgical procedure was carried out by first excising
5 under sterile precautions a full thickness skin graft from the left flank. A 15 mmD test tube marker was used to outline the skin to be excised for standardizing the surgical area. The wound edges were immediately approximated and closed with Michel clamps. The surgery
10 was performed on day 3 following implantation of prostate tumor cells.

Both placebo (10% dimethyl sulfoxide ["DMSO"] in saline) and BIM-23014 (10 mg/ml in 10% DMSO/saline vehicle) were applied topically with gentle rubbing for a
15 duration of exactly one minute, volume applied being 0.1 ml.

As shown in Table 2, prostate tumor cells implanted s.c. in non-surgically traumatized animals on day 0 produced tumors with a mean weight of 1921 mgs
20 between day 6-17 (Group 1). The same size inoculum of prostate tumor cells, implanted opposite to the traumatized area, produced tumors weighing 2366 mgs in the same time period (Group 2). Thus, surgical trauma did induce accelerated proliferation of prostate tumor as
25 indicated by the Test/Control value of 123%. BIM-23014 applied directly to the tumor site resulted in tumors weighing 2052 mgs (Group 4); whereas the 10% DMSO/saline placebo applied directly to the tumor site resulted in tumors weighing 2100 mgs (Group 3), producing a
30 Test/Control value of only 98%.

When the 10% DMSO/saline vehicle was applied to the surgically traumatized area on the left flank (Group 5), there was no apparent effect with the tumors on the right flank growing to an average of 2410 mgs (cf. 2366
35 mgs for Group 2). Importantly, when BIM-23014 was

- 20 -

applied topically to the surgically traumatized area (left flank) rather than to the non-traumatized area (right flank) (Group 6), tumor growth was markedly inhibited resulting in tumors weighing 1854 mgs, a
 5 Test/Control value of 77%.

In another study, a fine mince of 11095 rat prostate tumor tissue, 1-2 mm³, was implanted s.c., right flank, in Fischer 344 strain rats on day 0. On day 2, 48 hours later, all animals were surgically traumatized by
 10 excising a 1 cm² full dermal thickness graft from the opposite (left) flank. Topical application of the 40% DMSO/saline vehicle, or BIM-23014, to the surgical site was initiated in the p.m. of day 2 and continued b.i.d. to day 9. Tumor sizes were determined with Vernier
 15 calipers and weight calculated from the formula for an ellipsoid length x width²/2 (mg). As shown in Table 3 application of BIM-23014 resulted in a test/control value of 48% (Group 3/Group 1).

20

TABLE 3

Suppression of the Proliferative Surge Following Surgical Trauma
 (11095 Prostate Tumor)

25	Group No.	Treatment	Tumor Weight* (mg) Day 9	Percent Test/Control
	1	Surgery Day 2, untreated shelf control.	1973±312	--
30	2	Surgery Day 2, 40% DMSO/saline to surgical area, b.i.d., q.d. 2-9.	1132±62	57
	3	Surgery Day 2, BIM-23014 in 40% DMSO/saline to surgical area, b.i.d., q.d. 2-9.	957±13	48

35 * Data presented as means ± s.e.m. on 6 to 10 animals/group. Significance of difference:
 Group 1 and Group 2 = p<0.001; Group 1 and Group 3 = p<0.001.

- 21 -

Inhibition of trauma-induced growth of breast tumor

The response of human breast tumor xenografts to surgical trauma resulting from a tumor debulking procedure (cytoreduction) is demonstrated by an
5 experiment in which athymic nude female mice were used as xenograft recipients of the undifferentiated human breast tumor cells, MX-1. One group of mice were implanted bilaterally with MX-1 cells; whereas another group of animals were implanted only on the right flank on day 0.
10 On day 13, the left flank tumors on the first group mice were surgically excised. The results show that tumors in animals subjected to a cytoreductive (lumpectomy) procedure experienced an increase in the growth rate over that of the non-surgically traumatized animals, i.e., the
15 change in tumor size (weight) during the 10 day period post surgery being 747 mgs vs 618 mgs.

The following study was designed to demonstrate the therapeutic effect of applying BIM-23014 topically, either to the tumor site or to the surgically traumatized
20 site, for inhibiting the proliferative surge of breast tumor following surgical trauma. The results, as well as a brief description of the experiment, are presented in Table 4 below. Data are reported as means $\pm$ s.e.m. on 8 animals/group.

- 22 -

TABLE 4
Treatment of Surgical Trauma-Induced Proliferation
(Human Breast Tumor)

5			
Group No.	Treatment	Tumor Weight (mg) Day 14	Percent Test/Control
10	1 Tumor implanted s.c., right flank, day 0. No surgery. Shelf control.	245±40	135
	2 Tumor implanted s.c., right flank, day 0. Surgery left flank, day 3. Shelf control.	332±46	
15	3 Tumor implanted s.c., right flank, day 0. Surgery left flank, day 3. 10% DMSO/saline vehicle, topical to tumor, b.i.d., q.d. 3 (p.m.).	339±63	147
20	4 Tumor implanted s.c., right flank, day 0. Surgery left flank, day 3. BIM-23014, topical to tumor, b.i.d., q.d. 3 (p.m.).	500±116	
25	5 Tumor implanted s.c., right flank, day 0. Surgery left flank, day 3. 10% DMSO/saline vehicle, topical to surgery area, b.i.d., q.d. 3 (p.m.).	408±159	72
30	6 Tumor implanted s.c., right flank, day 0. Surgery left flank, day 3. BIM-23014, topical to surgery area, b.i.d., q.d. 3 (p.m.).	296±52	
35			

More specifically, tumor implantation was performed on all test animals, i.e., Groups 1-6, by implanting subcutaneously a 2 mm³ mince of MX-1 cells in the right flank on day 0. Surgical trauma was induced in the left flank of five groups of athymic nude female mice, i.e., Groups 2-6. A 15 mmD test tube marker was used to outline the skin to be excised for standardizing the surgical area. The surgical procedure was carried

- 23 -

out by first excising under sterile precautions a full thickness skin graft from the left flank. The wound edges were immediately approximated and closed with Michel clamps. The surgery was performed on day 3
5 following implantation of MX-1 cells.

Both placebo (10% DMSO in saline) and BIM-23014 (10 mg/ml in 10% DMSO/saline vehicle) were applied topically with gentle rubbing for a duration of exactly one minute, volume applied being 0.05 ml (1 drop).

10 As shown in Table 4, breast tumor cells implanted s.c. in non-surgically traumatized animals on day 0 produced tumors with a mean weight of 245 mgs on day 14 (Group 1). The same size inoculum of breast tumor cells, implanted opposite to the traumatized area, produced
15 tumors weighing 332 mgs in the same time period (Group 2). Thus, surgical trauma did induce accelerated proliferation of breast tumor as indicated by the Test/Control value of 135%. BIM-23014 applied directly to the tumor site resulted in tumors weighing 500 mgs
20 (Group 4); whereas the 10% DMSO/saline placebo applied directly to the tumor site resulted in tumors weighing 339 mgs (Group 3), producing a Test/Control value of 147%.

When the 10% DMSO/saline vehicle was applied to
25 the surgically traumatized area on the left flank of animals bearing a tumor in the non-traumatized right flank (Group 5), there was no inhibitory effect with the tumors growing to an average of 408 mgs (cf. 332 mgs for Group 2). Importantly, when BIM-23014 was applied
30 topically to the surgically traumatized area (left flank) rather than to the non-traumatized area (right flank) (Group 6), tumor growth was markedly inhibited resulting in tumors weighing 296 mgs, a Test/Control value of 72%.

- 24 -

Inhibition of trauma-induced growth of malignant melanoma

In one experiment, the effect of local surgical trauma on growth and responsiveness of cutaneous malignant melanoma (B16-F10) to BIM-23014 was studied.

5 Under sterile precautions, a piece of full thickness skin, approximately 1 cm diameter, was excised from the right flank of syngeneic C57BL/6 conventional mice and wound immediately closed with Michel clamps on day 0. On day 1 all animals were implanted s.c. in the surgical
10 area with B16-F10 cells. Treatment with BIM-23014 either on the side opposite from the tumor or intralesionally, was initiated on day 2.

Results of this experiment are summarized in Table 5 with data reported as means $\pm$ sem on 10 animal
15 groups. Mean tumor weight in the non-surgically traumatized animals (Group 1) on day 15 was 765 mgs, whereas mean tumor weight in the surgically traumatized animals (Group 2) was 2280 mgs. Tumors implanted in the surgically traumatized area were almost three times
20 larger (Test/Control value of 298%, $p < 0.001$) than tumors in non-traumatized animals. Administration of BIM-23014 to non-surgically traumatized animals (Group 4) subcutaneously, distant from the tumor, had little tumor inhibitory effect inducing only a 90% Test/Control value
25 (Group 4/Group 3). The same concentration of BIM-23014 administered intralesionally (surgical site) had a greater tumor inhibitory effect, inducing a 78% Test/Control value (Group 6/Group 5). The response to intralesional administration of BIM-23014 suggested the
30 feasibility of applying BIM-23014 to the tumor or surgical site.

- 25 -

TABLE 5

Treatment of Surgical Trauma-Induced Proliferation
(Malignant Melanoma)

Group No.	Treatment	Tumor Weight Day 15* (mg)	Percent Test/Control
10	1 No surgical trauma. Saline vehicle treated control, 0.2 ml/inj., s.c., b.i.d., q.d. 2-14.	765±191	298
15	2 Surgical trauma day 0. Saline vehicle treated control, 0.2 ml/inj., s.c., b.i.d., q.d. 2-14.	2280±330	
	3 No surgical trauma. 25% DMSO/saline vehicle treated control, 0.4 ml/inj., s.c., b.i.d., q.d. 2-14.	1034±195	90
20	4 No surgical trauma. BIM-23014, 500 µg/inj. in 25% DMSO/saline s.c., b.i.d., q.d. 2-14.	928±167	
25	5 Surgical trauma. Saline vehicle treated control, 0.2 ml/inj., s.c., intralesional, b.i.d., q.d. 2-14.	2039±373	78
30	6 Surgical trauma. BIM-23014, 500 µg/inj., s.c., intralesional, b.i.d., q.d. 2-14.	1581±311	

* Data presented as means ± s.e.m. on 10 animals/group. Significance of difference: Group 1 and Group 2 = $p < 0.001$;
Group 2 and Group 4 = $p < 0.05$.

The following study was designed to demonstrate the therapeutic effect of applying BIM-23014 topically, either to the tumor site or to the surgically traumatized site, for inhibiting the proliferative surge of malignant melanoma following surgical trauma. The results, as well as a brief description of the experiment, are presented

- 26 -

in Table 6 below. Data are reported as means $\pm$ s.e.m. on 8 animals/group. Syngeneic C57BL/6 conventional mice were used.

5

TABLE 6

Treatment of Surgical Trauma-Induced Proliferation
(Malignant Melanoma)

10	Group No.	Treatment	Tumor Weight Day 12* (mgs)	Percent Test/Control
	1	Melanoma Implanted, right flank, day 0. No surgery, untreated shelf control.	339 $\pm$ 60	212
15	2	Surgically treated, melanoma implanted, right flank, day 0. Untreated shelf control.	719 $\pm$ 134	
	3	Surgically treated, melanoma implanted, right flank, day 0.	593 $\pm$ 214	
20		Placebo treated control, 0.05 ml 50% DMSO/saline vehicle, topical, b.i.d., q.d. 1-11.		89
	4	Surgically treated, melanoma implanted, right flank, day 0.	527 $\pm$ 117	
25		BIM-23014 treated, 0.05 ml 50% DMSO/saline containing 10 mg/ml BIM-23014, topical, b.i.d., q.d. 1-11.		
	5	Surgically treated left flank, melanoma implanted right flank, day 0. Surgical area treated placebo control, 0.05 ml 50% DMSO/saline vehicle, topical, b.i.d., q.d. 1-11.	856 $\pm$ 248	57
30				
35	6	Surgically treated left flank, melanoma implanted right flank, day 0. Surgical area treated with BIM-23014, 0.05 ml 50% DMSO/saline vehicle containing 10 mg/ml BIM-23014, topical, b.i.d., q.d. 1-11.	488 $\pm$ 187	
40				

* Data presented as means $\pm$ s.e.m. on 8 animals/group. Significance of difference: Group 1 and Group 2 = $p < 0.05$.

45

- 27 -

More specifically, under sterile precautions, a piece of skin (full thickness) approximately 1 cm diameter was excised from the right flank of Groups 2, 3 and 4, and from the left flank of Groups 5 and 6. The wound was immediately closed with Michel clamps. The surgical procedure was carried out early in the a.m. of day 0. In the p.m. of the same day, 10^5 B16-F10 melanoma cells were implanted, via syringe and needle, directly into the surgically treated (wound) area of Group 2, 3, and 4 and on the opposite, non-surgically treated right flank of Groups 1, 5 and 6.

Topical treatment with BIM-23014 (10 mg/ml in 50% DMSO/saline vehicle) and placebo (50% DMSO/saline) was initiated on day 1. Topical application was applied gently over and around surgical area. For Groups 5 and 6 animals, only surgical areas on the left flank were treated.

As shown in Table 6, malignant melanoma cells implanted s.c. in non-surgically traumatized animals on day 0 produced tumors with a mean weight of 339 mgs on day 12 (Group 1). The same size inoculum of melanoma cells, implanted directly into the traumatized area, produced tumors weighing 719 mgs in the same time period (Group 2), a trauma induced proliferative increase of over two times (Test/Control value of 212%, $p < 0.05$). BIM-23014 applied directly to the tumor site resulted in tumors weighing 527 mgs (Group 4); whereas the 50% DMSO/saline placebo applied directly to the tumor site resulted in tumors weighing 593 mgs (Group 3), producing a Test/Control value of only 89%.

When the 50% DMSO/saline vehicle was applied to the surgically traumatized area on the left flank of animals bearing a tumor in the non-traumatized right flank (Group 5), there was no inhibitory effect with the tumors growing to an average of 856 mgs (cf. 719 mgs for

- 28 -

Group 2). Importantly, when BIM-23014 was applied topically to the surgically traumatized area (left flank) rather than to the non-traumatized area (right flank) (Group 6), tumor growth was markedly inhibited resulting
5 in tumors weighing 488 mgs, a Test/Control value of 57%.

OTHER EMBODIMENTS

The foregoing description has been limited to specific embodiments of this invention. It will be apparent, however, that variations and modifications may
10 be made to the invention, with the attainment of some or all of the advantages of the invention. Such embodiments are also within the scope of the following claims.

- 29 -

CLAIMS

1. A method for inhibiting in a mammal the accelerated growth of a solid primary or metastatic tumor resulting from tissue trauma caused surgically, non-surgically, or by tissue ulceration, said method comprising the step of administering to said mammal a therapeutically effective amount of somatostatin or a somatostatin agonist.

2. The method of claim 1, wherein said tumor growth is caused surgically.

3. The method of claim 2, wherein said administering step is performed by application to the site of said trauma.

4. The method of claim 3, wherein said administering step is performed topically.

5. The method of claim 3, wherein said administering step is performed subcutaneously.

6. The method of claim 2, wherein said method comprises the step of administering to said mammal a therapeutically effective amount of a somatostatin agonist.

7. The method of claim 7, wherein said administering step is performed topically.

8. The method of claim 7, wherein said administering step is performed subcutaneously.

9. The method of claim 7, wherein said method comprises the step of administering to said mammal a

- 30 -

therapeutically effective amount of a somatostatin agonist.

10. The method of claim 1, wherein said method comprises the step of administering to said mammal a
5 therapeutically effective amount of a somatostatin agonist.

11. The method of claim 1, 2, 6, 7 or 11 wherein said tumor is epithelial tumor.

12. The method of claim 12, wherein said tumor
10 is prostate tumor, breast tumor, lung tumor, colon tumor, or melanoma.

13. The method of claim 13, wherein said tumor is prostate tumor, breast tumor, or melanoma.

14. A method for making a medicament for
15 inhibiting in a mammal the accelerated growth of a solid primary or metastatic tumor resulting from tissue trauma caused surgically, non-surgically, or by tissue ulceration, said method comprising admixing somatostatin or a somatostatin agonist with a pharmaceutically
20 acceptable carrier substance.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/01412

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : Please See Extra Sheet.

US CL : 514/11, 14, 15, 16; 530/329, 328, 327

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)

U.S. : 514/11, 14, 15, 16; 530/329, 328, 327

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 practicable, search terms used)

APS, STN CAS ONLINE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Biochemical and Biophysical Research Communications, Volume 153, Number 1, issued 31 May 1988, Taylor et al., "In Vitro and In Vivo Inhibition of Human Small Cell Lung Carcinoma (NCI-H69) Growth by a Somatostatin Analogue", pages 81-86, see entire document.	1-14
X	Cancer Research, Volume 48, issued 15 December 1988, Schally, "Oncological Applications of Somatostatin Analogues", pages 6977-6985, see entire document.	1-14
X	EP, A1, 0, 505, 680 (KERI ET AL) 30 September 1992, see entire document.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*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
A document defining the general state of the art which is not considered to be part of particular relevance	*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
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Date of the actual completion of the international search 09 MAY 1994	Date of mailing of the international search report 19 MAY 1994
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INTERNATIONAL SEARCH REPORT

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