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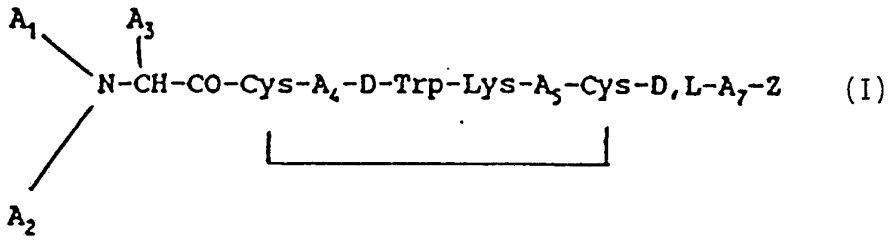
(54) Title: PERFORATED BALLOON CATHETER DELIVERY OF SOMATOSTATIN ANALOGUES FOR REDUCING CELL PROLIFERATION



(I)

(57) Abstract

The present invention is directed to a device for preventing or alleviating smooth muscle cell proliferation in a coronary artery to a patient in need thereof which comprises: (a) a perforated balloon catheter capable of use during an angioplasty procedure to come into contact with said cell proliferation in said coronary artery; (b) contained within said perforated baloon catheter, an effective anti-cell proliferating amount of a compound having formula (I) wherein each A_1 and A_2, independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl, R_1CO wherein R_1 is C_{1-20} alkenyl, C_{3-20} alkenyl, C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl, or R_2OCO wherein R_2 is C_{1-10} alkyl or C_{7-20} phenylalkyl, provided that when one of A_1 or A_2 is R_1CO or R_2OCO, the other must be H; A_3 is CH_2A_6 wherein A_6 is pentafluorophenyl, naphthyl, pyridyl, or phenyl; A_4 is o-, m- or, p-substituted X-Phe wherein X is a halogen, H, NH_2, NO_2, OH, or C_{1-13} alkyl, pentafluoro-Phe, β-Nal or Tyr; A_5 is Thr, Ser, Phe, Val, α-aminobutyric acid, or Ile; A_7 is Thr, Trp, or β-Nal and can be either the D- or L-isomer; and Z is NH_2 or OH; or a pharmaceutically acceptable salt thereof.

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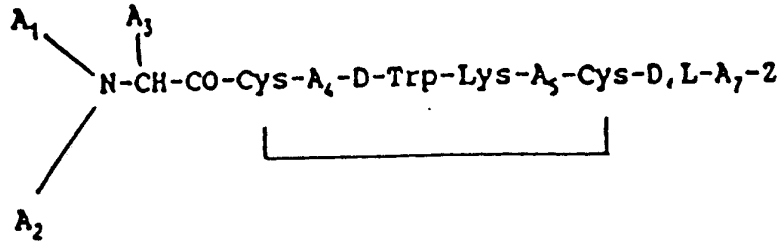
PERFORATED BALLOON CATHETER DELIVERY OF SOMATOSTATIN ANALOGUES FOR REDUCING CELL PROLIFERATION

FIELD OF THE INVENTION

The present invention is directed to a method for preventing or alleviating smooth muscle cell proliferation in a coronary artery to a patient in need thereof which comprises:

(a) inserting a perforated balloon catheter during an angioplasty procedure to come into contact with said cell proliferation in said coronary artery;

(b) and administering, through said perforated balloon catheter, an effective anti-cell proliferating amount of a compound having the formula:



wherein each A_1 and A_2, independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl, R_1CO wherein R_1 is C_{1-20} alkenyl, C_{3-20} alkenyl, C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl, or R_2OCO wherein R_2 is C_{1-10} alkyl or C_{7-20} phenylalkyl, provided that when one of A_1 or A_2 is R_1CO or R_2OCO, the other must be H; A_3 is CH_2A_6 wherein A_6 is pentafluorophenyl, naphthyl, pyridyl, or phenyl; A_4 is o-, m- or, p-substituted X-Phe wherein X is a halogen, H, NH_2, NO_2, OH, or C_{1-13} alkyl, pentafluoro-Phe, β-Nal or Tyr; A_5 is Thr, Ser, Phe, Val, ε-aminobutyric acid, or Ile; A_7 is Thr, Trp, or β-Nal and can be either the D- or L-isomer; and Z is NH_2 or OH; or a pharmaceutically acceptable salt thereof.

DESCRIPTION OF RELATED ART

Recently an alternative approach to coronary bypass surgery has been developed. In this non-operative procedure for the improvement of blood flow in patients with coronary artery disease, a catheter with an inflatable balloon at the distal end is inserted into the femoral

artery or by brachial cutdown, and is positioned by fluroscopic control at the appropriate coronary ostium. The process is known as percutaneous transluminal coronary angioplasty (PTCA).

Angioplasty is not limited to the cardiac vasculature. It has been employed for treatment of single, large atherosclerotic lesions of the renal, iliac and even vertebral arteries. The effect of the expanded balloon is to literally blow open the stenotic zone. Disruption of the wall is marked, including fracture of the calcium in the lesion, tearing of the plaque itself and extravasation of plaque lipid and gruel into the adjacent vessel wall.

The clinical reslults of angioplasty include endothelial denudation, vascular wall damage, and rupture of the tunica intima vasorum. These injuries have been found to result in many cases in unregulated proliferation of the arterial smooth muscle cells (SMC) with a resulting restenosis. A recent study by Levine et al. (The American Journal of Cardiology, Volume 55, pages 673 to 676, March 1985) has shown that restenosis may be expected to occur in as many as 40% of patients that have undergone angioplasty. Often the only practical treatment for restenosis is to repeat the treatment. This may cause further damage to the cell wall and the need for subsequent repetition of the angioplasty procedure.

The major limiting factor of percutaneous transluminal coronary angioplasty (PTCA) is a 30-50% restenosis rate within the first six months following a successful procedure (Gruentzig AR, King SB III, Schlumpf M, Siegenthaler W., N Engl. J Med. 1987; 316:1127-1132; Klein LW, Rosenblum J. Restenosis, Progress in Cardiovascular Diseases 1990; 32:365-382). No successful inhibition of restenosis has been obtained in spite of extensive studies of the pathology after experimental and human angioplasty (Steele PM, Chesebro JH, Stanson AW, Holmes DR Jr., Dewanjee MK, Badimon L, Fuster V., Circ. Res. 1985; 57:105-112; Block PC, Myler RK, Stertzer S, Fallon JT, N

Engl. J Med. 1981; 305:382-385; Waller BF, J Am. Coll. Cardiol. 1989; 13:969-987; Potkin BN, Roberts WC, Am J Cardiol. 1988; 62:41-50), pathogenesis (Clowes AW, Reidy MA, Clowes MM, Lab Invest 1983; 49:208-215; Gruenwald J, Haudenschild CC, Arteriosclerosis 1984; 4:183-188; Austin GE, Ratliff NB, Hollmann J, Tabei S, Phillips DF, J Am. Coll. Cardiol. 1985; 6:369-375; Liu MW, Roubin GS, King SB III, Circulation 1989; 79:13741387; Forrester JS, Fishbein M, Helfant R, Fagin J., J Am. Coll. Cardiol. 1991: 17:758-769), time course (Joelson JM, Most AS, Williams DO, Am. J Cardiol. 1987; 60:792-795; Serruys PW, Luijten HE, Beatt KJ, Geuskens R, De Feyter PJ, Van den Brand M, Reiber JHC, Ten Katen HJ, Van Es GA, Hugenholtz PG, Circulation 1988; 77:361-371; Nobuyoshi M, Kimura T, Nosaka H, Mioka S, Ueno K, Yokoi H, Hamasaki N, Horiuchi H, Ohishi H., J Am. Coll. Cardiol. 1988; 12:616-623), and clinical predictors (Pompa JJ, Topol EJ, The Am. J. of Med. 1990; 88:1-16N-1-24N; Califf RM, Ohman EM, Frid W, Fortin DF, Mark DB, Hlatky MA, Herndon JE, Bengtson JR, Textbook of Interventional Cardiology, 1990, pp. 363-394) of restenosis.

Recently Angiopeptin, a synthetic cyclic octapeptide analogue of somatostatin, has been shown to inhibit cellular proliferation following balloon injury both in vivo and in vitro in animal studies when given subcutaneously (Vargas B, Bormes GW, Wroblewska B, Rego A, Foegh ML, Kot PA, Ramwell PW, Transpl Proc 1989; 21:3702-3704; Asotra S, Foegh ML, Conte JV, Cai BR, Ramwell PW, Transpl Proc 1989; 21:3695-3696; Conte JV, Foegh ML, Calcagno D, Wallace RB, Ramwell PW, Transpl. Proc. 1989; 21:3686-3688; Lundergan C, Foegh ML, Vargas R, Eufemio M, Bormes GW, Kot PA, Ramwell PW, Atherosclerosis 1989; 80:49-55). Angiopeptin has also been shown to be effective in reducing neointimal hyperplasia in vein grafts (Calcagno D, Conte JV, Howell MH, Foegh ML, J. Vasc. Surg. 13(4): 475-479, 1991) and in inhibiting accelerated transplant atherosclerosis (Foegh ML, Khirabadi BS, Chambers E, Amamoo

S, Ramwell PW, Atherosclerosis 78:229, 1989; Foegh ML, Khirabadi BS, Chambers E, Ramwell PW, Transpl. Proc. 21:3674, 1989; Fellstrom B, Foegh ML, Larsson E, Wanders A, Tufveson G, Transpl. Proc. 23(1):525, 1991) which are proliferative processes resembling restenosis following balloon injury.

Angiopeptin has a prolonged plasma half life when compared with somatostatin-14 (Coy DH, Heiman ML, Rossowski J, Murphy WA, Taylor JE, Moreau S, Moreau JP, Peptides Chemistry and Biology, Garland R. Marshall (Ed.). ESCOM, Leiden 1988). An attractive and possibly more effective method of administering drugs is local delivery at the time and the site of PTCA (Goldman B, Blanke H, Wolinsky H, Atherosclerosis 1987; 65:215-225.). The Wolinsky perforated infusion catheter (USCI, Billerica, Mass.) offers this possibility and has been used successfully to deliver various drugs intramurally at the time of angioplasty (Wolinsky H, Thung SN, J. Am. Coll. Cardiol. 1990; 15:475481; Gellman J, Enger CD, Sigal SL, True LD, Helie M, Esquivel E, Chen Q, Azrin MA, Ezekowitz MD, J. Am. Coll. Cardiol. 1990; 15(Suppl A):164A; Gimple LW, Owen RM, Lodge VP, Powers E, Sarembock IJ, Circulation 1990; 82(Suppl III): III-338; Leung W, Kaplan AV, Grant GW, Leung LLK, Fischell TA, Circulation 1990; 82(Suppl III): III-428; Muller DWM, Topol EJ, Abrams G, Gallagher K, Ellis SG, Circulation 1990; 82(Suppl III): III-429; Wilensky RL, March KL, Hathaway DR, J. Am. Coll. Cardiol. 1991; 17(Suppl A):268A).

Local delivery of somatostatin analogues to the arterial wall enables one-time local delivery at the time of angioplasty at a higher dose than that tolerated by systemic application as a result of the side effects, i.e., gastrointestinal side effects, associated therewith. Local delivery will also result in a more efficacious inhibition of intimal hyperplasia. Further, patients may not have to continue to receive subcutaneous administration. The

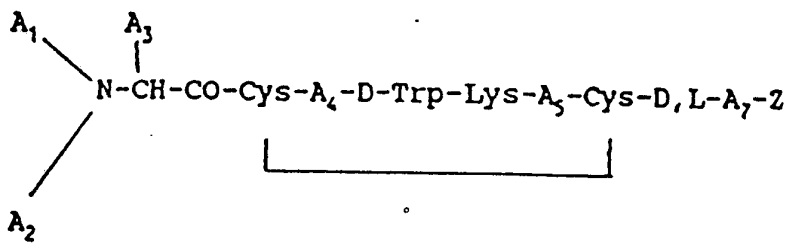
present invention has been accomplished with the above in mind.

SUMMARY OF THE INVENTION

The present invention is directed to a method for preventing or alleviating smooth muscle cell proliferation in a coronary artery to a patient in need thereof which comprises:

(a) inserting a perforated balloon catheter during an angioplasty procedure to come into contact with said cell proliferation in said coronary artery;

(b) and administering, through said perforated balloon catheter, an effective anti-cell proliferating amount of a compound having the formula:



wherein each A_1 and A_2, independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl, R_1CO wherein R_1 is C_{1-20} alkenyl, C_{3-20} alkenyl, C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl, or R_2OCO wherein R_2 is C_{1-10} alkyl or C_{7-20} phenylalkyl, provided that when one of A_1 or A_2 is R_1CO or R_2OCO, the other must be H; A_3 is CH_2A_6 wherein A_6 is pentafluorophenyl, naphthyl, pyridyl, or phenyl; A_4 is o-, m- or, p-substituted X-Phe wherein X is a halogen, H, NH_2, NO_2, OH, or C_{1-13} alkyl, pentafluoro-Phe, β-Nal or Tyr; A_5 is Thr, Ser, Phe, Val, α-aminobutyric acid, or Ile; A_7 is Thr, Trp, or β-Nal and can be either the D- or L-isomer; and Z is NH_2 or OH; or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1A is an electron microphotograph of a coronary artery wall of a control. Fig. 1B is an electron

microphotograph of Angiopeptin treated coronary artery wall. L = lumen, Smc = smooth muscle cells.

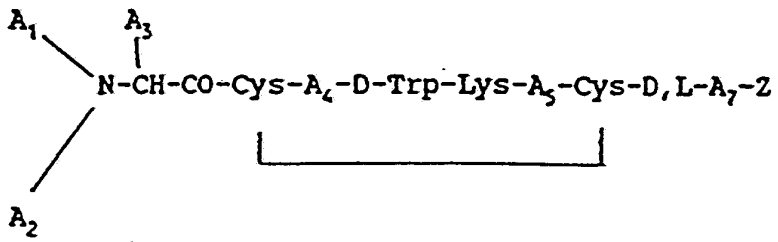
Fig. 2 is an electron microphotograph of a coronary artery wall exhibiting intimal hyperplasia as a control. L = lumen, IEL = internal elastic lamina; and E = endothelial cells.

Fig. 3 is an electron microphotograph of Angiopeptin treated coronary artery wall. L = lumen, IEL = internal elastic lamina, and Smc = smooth muscle cell.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Catheters useful in carrying out the method of the present invention are not particularly limiting so long as the catheter is capable of delivering the somatostatin analogue to the artery to relieve smooth muscle cell proliferation. Examples of perforated catheters which are useful are described in U.S. Patent No. 4,636,195 and Wolinsky and Thung, JACC (1990), Volume 15, No. 2, pp. 475-481, hereinafter the "Wolinsky Perforated Balloon Catheter" (from USCI, Billerica, MA). Perforated autoinfusion catheters are also contemplated within the scope of the method of the present invention. A preferred perforated catheter is the Wolinsky Perforated Balloon Catheter, USCI, Billerica, MA.

Somatostatin analogues useful in carrying out the method of the present invention are described in WO 89/12068, the entire contents of which are incorporated herein by reference. These somatostatin analogues are octapeptides having the formula:



wherein each A_1 and A_2, independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl, R_1CO wherein R_1 is C_{1-20} alkenyl, C_{3-20} alkenyl,

C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl, or R_2OCO wherein R_2 is C_{1-10} alkyl or C_{7-20} phenylalkyl, provided that when one of A_1 or A_2 is R_1CO or R_2OCO, the other must be H; A_3 is CH_2A_6 wherein A_6 is pentafluorophenyl, naphthyl, pyridyl, or phenyl; A_4 is o-, m- or, p-substituted X-Phe wherein X is a halogen, H, NH_2, NO_2, OH, or C_{1-13} alkyl, pentafluoro-Phe, β-Nal or Tyr; A_5 is Thr, Ser, Phe, Val, α-aminobutyric acid, or Ile; A_7 is Thr, Trp, or β-Nal and can be either the D- or L-isomer; and Z is NH_2 or OH; or a pharmaceutically acceptable salt thereof. A preferred somatostatin analogue has the formula D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2 and is known as angiopeptin.

According to the method of the present invention, the somatostatin analogues are administered in an amount of from about 5 to 500 μg, preferably from about 10 to 70 μg; and more preferably, from about 30 to 50 μg in a one-time bolus.

The duration of administration of the somatostatin analogues via the perforated balloon catheter can range anywhere from about 10 seconds to about 5 minutes, and preferably, from about 10 seconds to about less than one minute.

The effective anti-cell proliferating amount of the somatostatin analogue is first dissolved in a pharmaceutically acceptable carrier prior to administration via the perforated balloon catheter. Once the perforated balloon catheter is insertd in place, the somatostatin analogue is forced under pressure through the perforations into the surrounding areas according to conventional angioplasty procedures. Pressures of 200 to 1000 mm HG are acceptable for this purpose. A preferred pressure range is from 300 to 1000 mm Hg.

The local delivery of the somatostatin analogues via a perforated balloon catheter can, preferably, accompany systemic administration in order to provide the greatest benefit in the reduction of intimal hyperplasia and

restenosis. Methods for systemic administration are described in WO 89/12068.

EXPERIMENTAL SECTION

Animals:

Adult male New Zealand White rabbits weighing 2.5 to 2.8 kg (Hazleton Farms, Vienna, VA) were housed at constant temperature and a 12-hour cycle of light and darkness in the Research Resources Facility of Georgetown University Medical Center for a period of one week for adaptation prior to studies. The rabbits had access to Purina regular rabbit chow and water ad libitum during the entire period.

Autoradiographic Localization of Angiopeptin:

Iodinated Angiopeptin was prepared by iodinating the tyrosine ring of the authentic Angiopeptin (10 µg/5µl) (Henri Beaufour Institute USA, Inc., Washington D.C.) according to the method described by Greenwood and Hunter (Nature 1962; 194:495-496 "Preparation of Iodine-131 Labelled Human Growth Hormone of High Specific Activity" and then purified by column chromatography. The I^{125}-Angiopeptin was loaded onto a 20 x 1 cm column, packed with carboxy methyl cellulose (CMC-52) and eluted with 0.2 m ammonium acetate at pH 4.6. Elution was performed at 0.5 ml/min. Sixty fractions (1 ml) were collected and each was co-chromatographed with authentic Angiopeptin on silica gel TLC plates Analtech, Inc., Newark, Delaware, then lyophilized and kept at -20 C until use. The purity of the resulting compound was checked by high pressure liquid chromatography prior to use.

Three rabbits underwent balloon injury of the abdominal aorta under ketamine-xylazine anesthesia (i.m.) with a 3.25 mm USCI (Billerica, Mass.) angioplasty balloon repeated three times. I^{125}-Angiopeptin (activity/ml), was administered to the mid-abdominal aorta under direct observation for 1 minute at 5 atmospheres with the 3.25 mm perforated infusion balloon (USCI, Billerica, MA). The

animals were sacrificed 30 minutes later and the mid-abdominal aorta was removed and fixed in formalin overnight. Following progressive dehydration in increasing concentrations of ethanol, the fixed tissues were embedded in paraffin. Cross sections of 7 microns were cut and stained with Mayer's hematoxylin and prepared for autoradiography (Baserga P, Malamud D., "Modern Methods in Experimental Pathology" in Autoradiography: techniques and application. New York, Hoeber Medical Division, Harper & Row (c1969). The stained sections were rehydrated overnight and covered with NTB3 emulsion (Eastman Kodak Co., Rochester, NY). After overnight exposure, the sections were developed for 45 seconds with Dektol (Eastman Kodak) and fixed 5 minutes with GBX (Eastman Kodak). Blood was drawn on several occasions for determination of serum Angiopeptin levels.

Intimal Hyperplasia at 21 Days Post Balloon Injury:

Forty rabbits were randomized into four different groups (n=10 per group); a control group received local delivery of saline (0.9%), the vehicle for Angiopeptin, and three experimental groups were treated by local delivery of three different concentrations of Angiopeptin (1, 10, or 100 µg/ml). Animals were anesthetized with ketamine (5 mg/kg) and xylazine (50 mg/kg). The right carotid artery was isolated, and a 3.25 mm regular angioplasty balloon (USCI, Billerica, MA) was inserted and advanced to the abdominal aorta, where the injury was performed with the balloon inflated to 5 atmospheres and withdrawn from the iliac bifurcation to the diaphragm three times under fluoroscopic guidance. This was followed by local delivery of Angiopeptin with a 3.25 mm Wolinsky infusion balloon (USCI) at mid-abdominal aorta defined as the fourth vertebral body above the iliac crests. This procedure was done under fluoroscopy. The Angiopeptin or saline was delivered intramurally for one minute at 5 atmospheres, with a volume ranging from 5 to 8 ml/min. The infusion

balloon was then removed and the carotid artery proximal to the arteriotomy site was ligated and the skin closed with sutures. The animals were sacrificed after three weeks by intracardiac potassium injection, and thoracic and abdominal aortas were fixed in situ via left thoracotomy by flushing with heparinized lactated Ringer's solution for 20 minutes, followed by Karnovsky's fixative (Karnovsky MJ, J. Cell. Biol. 1956; 27:137-138) for 20 minutes at 80 mmHg perfusion pressure.

Transmission Electron Microscopy:

Tissue blocks for electron microscopy were fixed in Karnovsky's fixative containing 2% glutaraldehyde in 0.1 M sodium cacodylate buffer pH 7.3 for an additional 3-5 hours. Post fixation was carried out in 1% osmium tetroxide for 1 1/2 hour, dehydrated through graded ethanol and embedded in epon. Sections were cut at 1 g thickness with glass knives and stained with toluidine blue for light microscopic examination. Silver-gray sections from selected blocks were picked up on 200-300 mesh naked copper grids and stained with uranyl acetate and lead citrate. Tissues were examined with a Jeol 1200 EX Electron Microscope (Jeol, Tokyo, Japan).

Light Microscopy:

Sections stained with hematoxylin and eosin were evaluated. The histological evaluation was performed in a blinded fashion.

Statistics:

The data for the morphometric study are presented as mean +/- standard error of the mean. Statistical analysis was done by the Student's unpaired T-test and statistical significance is represented by p values ≤ 0.05.

RESULTS

Autoradiography:

Radioactivity was found throughout the media but in a patchy, non-uniform distribution. Radioactivity was localized both in the cytoplasm and in the nuclei of the medial smooth muscle cells. There were thus areas of intense radioactive particles interspersed by adjacent areas devoid of any radioactivity. This suggests a linear or jet intramural penetration of I^{125}-Angiopeptin which may correspond to the holes in the infusion balloon.

Histology:

In the control group, the intimal hyperplasia was concentric and consisted of multiple layers of smooth muscle cells (Fig. 1A) whereas in the Angiopeptin-treated groups (Fig. 1B) there was a substantial decrease in the population of smooth muscle cells. In the Angiopeptin-treated groups, the intimal thickening varied within regions of a given section. This variation in intimal hyperplasia probably reflects the small number of holes for drug delivery in the balloon.

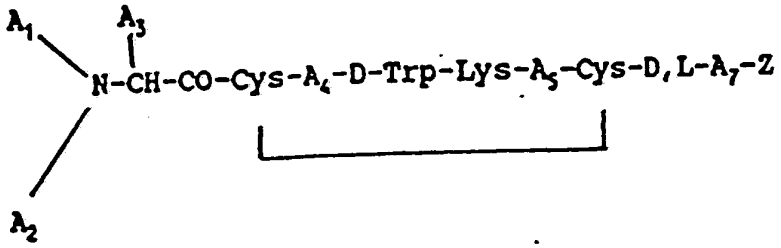
Electron Microscopic Studies:

The electron microscopic observation of tissue from control animals 21 days after endothelial injury showed a uniform circumferential intimal thickening of 5-10 layers of smooth muscle cells (Fig. 2). Among the Angiopeptin-treated groups, the group treated with 10 µg/ml showed no intimal hyperplasia (Fig. 3,) with a few exceptions. Among the 1 µg/ml and 100 µg/ml treated groups, 1-2 layers of intimal thickening with some region showing no internal thickening was frequently observed. In the Angiopeptin-treated groups the lesion was covered by a morphologically intact endothelial cell layer. This was not the case with the control groups which showed loss of endothelial integrity.

1. A device for preventing or alleviating smooth muscle cell proliferation in a coronary artery of a patient in need thereof which comprises:

(a) a perforated balloon catheter capable of use during an angioplasty procedure to come into contact with said cell proliferation in said coronary artery; and

(b) contained within said perforated balloon catheter, an effective anti-cell proliferating amount of a compound having the formula:



wherein each A_1 and A_2, independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl, R_1CO wherein R_1 is C_{1-20} alkenyl, C_{3-20} alkenyl, C_{3-20} alkinyl, phenyl, naphthyl, or C_{7-10} phenylalkyl, or R_2OCO wherein R_2 is C_{1-10} alkyl or C_{7-20} phenylalkyl, provided that when one of A_1 or A_2 is R_1CO or R_2OCO, the other must be H; A_3 is CH_2A_6 wherein A_6 is pentafluorophenyl, naphthyl, pyridyl, or phenyl; A_4 is o-, m- or, p-substituted X-Phe wherein X is a halogen, H, NH_2, NO_2, OH, or C_{1-13} alkyl, pentafluoro-Phe, β-Nal or Tyr; A_5 is Thr, Ser, Phe, Val, α-aminobutyric acid, or Ile; A_7 is Thr, Trp, or β-Nal and can be either the D- or L-isomer; and Z is NH_2 or OH; or a pharmaceutically acceptable salt thereof.

2. The device according to claim 1, wherein said compound is angiopeptin.

3. The device according to claim 1, wherein said effective anti-cell proliferating amount is from 5 to 500 μg.

4. The device according to claim 3, wherein said effective anti-cell proliferating amount is from 10 μg to 70 μg.

5. The device according to claim 4, wherein said anti-cell proliferating amount is from 30 to 50 μg.

6. The device according to claim 1, wherein said perforated balloon catheter has autoinfusion capabilities.

Fig. 1 A

Fig. 1 B

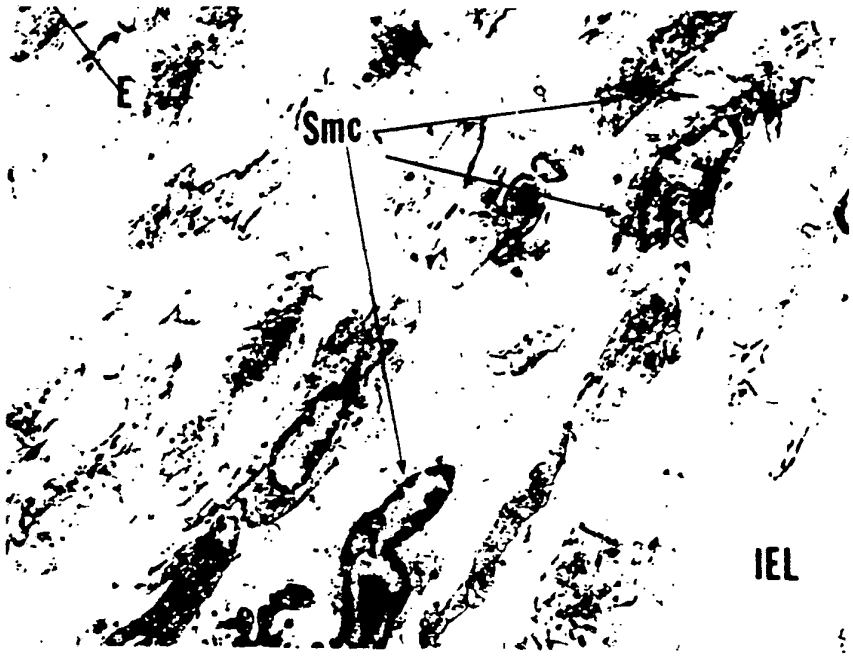


Fig. 2

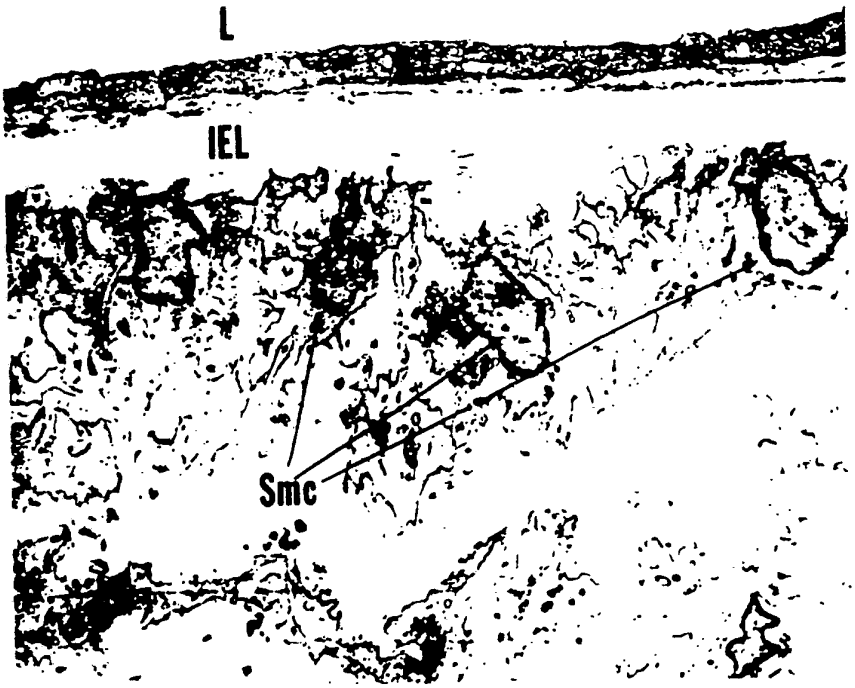


Fig. 3

INTERNATIONAL SEARCH REPORT

PCT/US92/09294

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61M 29/00
US CL :604/96
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. : 604/46-49,51-53,96,99,101,265,266

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 and Literature Search
Angiopeptin; Somatootatin; catheter; balloon catheter; cell, proliferation, or growth; dilation, oligopeptides

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO, 89/12068 (RAMWELL ET AL) 14 DECEMBER 1989 See abstract.	1-6
Y,P	US,A, 5,087,244 (WOLINSKY ET AL) 11 FEBRUARY 1992 See abstract lines 1-11.	1-6
A,P	US,A, 5,120,322 (DAVIS ET AL) 09 JUNE 1992	
Y	US,A, 4,261,885 (SAKAKIBARA ET AL) 14 APRIL 1981 See column 11, lines 32-44.	1-6

☐ 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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"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 12 JANUARY 1993	Date of mailing of the international search report 25 FEB 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer Nguyen Nguyen for MARK O. POLUTTA NGUYEN NGOC-HO INTERNATIONAL DIVISION Telephone No. (703) 308-0058

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