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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
WO 01/26563 A1

(51) International Patent Classification[7]: A61B 17/08

(21) International Application Number: PCT/US00/27902

(22) International Filing Date: 10 October 2000 (10.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/158,233 8 October 1999 (08.10.1999) US

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(81) Designated States *(national)*: JP, US.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

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.

WO 01/26563 A1

(54) Title: METHOD OF ADMINISTRATING MEDICAMENT TO TROCAR ADAPTED PORT SITE

(57) Abstract: The present invention provides materials and methods for adding medicaments to an entry or port site. The present invention also provides method of inhibiting the attachment of tumor cells to an entry or port site.

METHOD OF ADMINISTRATING MEDICAMENT TO TROCAR ADAPTED PORT SITE

FIELD OF THE INVENTION

This invention relates to the administration of medicaments for therapeutic purposes to a specific area of tissue, which is an entry site or a port site isolated from the body cavity in which a device, such as a trocar, has been inserted. In one aspect this invention relates to a method of inhibiting tumor cell adhesion in and around entry sites and particularly to those sites, generally referred to as port sites, which are used to gain entry into the abdominal cavity or other body cavities during minimally-invasive procedures, including thoracic and laparoscopic procedures, including surgeries, both exploratory and extractive, and including gasless procedures in addition to gas-assisted procedures, laparoscopic biopsy, and the administration of therapeutics via laparoscopic access to the abdominal cavity.

The invention also relates to a surgical device uniquely designed to inhibit tumor cell adhesion at the port sites or administer therapeutic agents to the port sites.

The pressure associated with laparoscopic surgery stimulates adhesion of tumor cells that have been shed from a tumor, thus contributing to the observation of what is known in the art as "port site recurrence", which has been the cited reason to recommend against removal of tumors found in colon cancer via laparoscopy or other minimally-invasive procedure

BACKGROUND

Concerns over port site recurrence, tumor implantation at the sites in the abdominal wall through which laparoscopic instruments, gases and other devices, such as cameras, have been introduced into the abdominal cavity during laparoscopic resections for cancer, have impeded the adoption of laparoscopic techniques for cancer surgery. Port site recurrence occurs in humans and animal models. See the discussions in the following articles each of which is incorporated by reference thereto: Champault G. et al., "Port-site metastases. A prospective study of 131 cases". J Chir. 134:423-8,1997; Berends F. J. et al., "Subcutaneous metastases after laparoscopic colectomy", Lancet 344:58,1994; Wexner S. D. et al., "Port site metastases after laparoscopic colorectal surgery for cure of malignancy", Br J Surg. 82:295-8,1995; and, Vukasin P. et al., "Wound recurrence following laparoscopic colon cancer resection. Results of the American Society of Colon and Rectal Surgeons Laparoscopic Registry", Dis Colon Rectum. 39:S20-3, 1996, which discuss port site recurrence in human patients.

Similar reports in animal models are also known in the literature. See, for example, the following articles, each of which is incorporated by reference thereto: Mathew G. et al., "Adverse impact of pneumoperitoneum on intraperitoneal implantation and growth of tumour cell suspension in an experimental model", Aust N Z J Surg. 67:289-92,1997; Koster S. et al., "Effect of CO2 pneumoperitoneum on intraperitoneal tumor growth in the animal model", Geburtshilfe Frauenheilkd, 56:458-61,1996; Jones D. B. et al., "Impact of pneumoperitoneum on trocar site implantation of colon cancer in hamster model", Dis Colon Rectum, 38:1182-8,1995; and, Lee S. W. et al., "Abdominal

wound tumor recurrence after open and laparoscopic-assisted splenectomy in a murine model", Dis Colon Rectum.,41:824-31,1998.

The invention described herein is based on the discovery that tumor cell adhesion is pressure-responsive. In addition, cation-dependent integrin-mediated adhesion, such as via FAK-related tyrosine phosphorylation , is suspected and the presence of serum potentiates this effect. These critical observations and their impact on port site recurrence are not recognized in the literature. Thus the targeting of these mechanisms is also not evident from the literature. The claimed invention is directed to methods and devices designed to inhibit tumor cell adhesion and consequently inhibit or prevent port site recurrence, by reducing pressure during laparoscopic surgery, washing serum from the port sites, or using chelators to block cation-dependent adhesion or compounds which directly inhibit cell adhesion.

In addition to treating an isolated port site with a material capable of inhibiting tumor cell adhesion, one could administer any medicament to such an isolated site.

SUMMARY OF THE INVENTION

This invention comprises minimally-invasive methods and apparatus useful for adding medicaments including those which will inhibit cell adhesion to an entry or port site. Other medicaments include anesthetics, antibiotics, cytotoxic agents, including osmotic agents, growth factors and other cell-function-stimulants.

The present invention also provides a method of inhibiting attachment of tumor cells to an entry or port site comprising administering a composition capable of inhibiting

or eliminating cell adhesion to a entry or port site, such as saline solution; antibodies to cell surface proteins; cell adhesion inhibitors; and, salts or chelators effective to inhibit integrin-mediated cell adhesion.

The present invention also provides a method of evacuating fluids, both endogenous and previously administered fluids, including cell-containing fluids such as blood, from patient through an entry or port site.

In addition, the present invention is directed to the administration of medicaments through multiple port sites.

The present invention provides a method of inhibiting attachment of tumor cells to a port site or the peritoneal wall adjacent to a port site via employment of a trocar assembly which provides the following features, an expandable member, such as a balloon, of a sufficient size when inflated and disposed on the trocar assembly in such a way that when inflated or expanded the expandable member forms a protective barrier between the port site and the peritoneum; means of engaging the external skin above the port site in a manner which stabilizes the trocar and provides sufficient compression of the tissue at the port site so as to, in conjunction with the expandable member, isolate the port site from the abdominal cavity; and, at least one side port positioned in the wall of the trocar; and administering fluid materials capable of minimizing or eliminating cell adhesion through the at least one side port during the surgical procedure.

This invention further provides a trocar assembly which provides isolation of insertion sites from a body cavity when inserted into the body cavity which contains a sleeve having a distal end and a proximal end, wherein the distal end of the sleeve is

adapted for insertion into the abdominal cavity, and the proximal end is open and is adapted for insertion of surgical instruments through the sleeve; and an expandable member positioned near the insertable end of the sleeve and of a size upon inflation such that a barrier is formed between the body cavity and the insertion site; and at least one side port coupled to the sleeve in communication with an opening near the distal end of the tubular member but proximal to the expandable member, the side port being adapted for administering fluids to the port site.

The disclosed trocar assemblies of this invention include those which further comprising engaging means which abut the external skin above the port site in a manner which stabilizes the trocar and provides sufficient compression of the tissue at the port site so as to, in conjunction with the expandable member, isolate the port site from the abdominal cavity. For example, the engaging means comprises a clip slidably mounted on the sleeve for securing the sleeve to the insertion site.

The invention disclosed herein further provides a trocar assembly which contains a side port coupled to the sleeve that is a valved gas inlet and an additional side port coupled to the sleeve that is adapted for aspirating materials from the body.

The invention further provides a trocar device in which the sleeve of the trocar has an outer tubular member and an inner tubular member, wherein the inner tubular member is located inside of, and is concentrically aligned with, the outer tubular member, and wherein the space between the outer and inner tubular members forms a passage for the transfer of gases or liquids.

One skilled in the art can easily make any necessary adjustments in accordance with the necessities of a particular situation when practicing this invention.

Further objects and advantages of the present invention will be clear from the description that follows.

DETAILED DESCRIPTION OF THE INVENTION

Laparoscopic colectomy procedures provide multiple advantages for patients compared to open wound surgery. Patients experience less pain, less post-operative pulmonary compromise, less immune depression, less ileus and typically a shorter period when hospitalization is necessary. To summarize, patients experience less pain and a faster return to their pre-operative life style.

1. Tumor cell adhesion

Tumors may spread by direct invasion, by vascular or lymphatic channels, or by intra-abdominal dissemination to mesentery, peritoneum, or the abdominal wall during surgery. Each process except for invasion requires viable non-adherent tumor cells to re-adhere to a new extracellular matrix. Not all tumor cells adhere, particularly within the peritoneum, and both local tissue factors and the adhesiveness of the tumor may influence initial adhesion. After adhesion, proliferation, angiogenesis, and invasion must outstrip immune surveillance for a clinically evident tumor to develop, but adhesion is a critical first step. Malignant colonocytes experience fluctuations in pressure, strain, and shear stress *in situ* in the colonic lumen, intravascularly, during surgical manipulation, and

during peritoneal insufflation during laparoscopic surgery, which typically involves a pressure of 15 mm Hg. Whether port site recurrence is more common than wound implantation after open surgery in humans is controversial and may be clarified by multicenter studies. The incidence of recurrence have been reported as 0-4% for laparoscopic port sites and 0-1.6% for open surgery wound implants. See Stocchi L and Nelson H., "Laparoscopic colectomy for colon cancer: trial update", J Surg Oncol. 68:255-67,1998 which is incorporated herein by reference thereto.

Immune function and surveillance against malignant cells appear superior after laparoscopic compared with open surgery. This phenomenon may well act to offset the pressure-stimulated adhesion of shed tumor cells. See Cristaldi M. et al., "Lymphocytic subpopulation changes after open and laparoscopic cholecystectomy: a prospective and comparative study on 38 patients", Surg Laparosc Endosc. 7:255-61,1997; Kehlet H. and Nielsen H. J., " Impact of laparoscopic surgery on stress responses, immunofunction, and risk of infectious complications", New Horiz. 6:S80-8,1998; and, Vittimberga, F.J., Jr. et al., "Laparoscopic surgery and the systemic immune response", Ann Surg. 227:326-34,1998.

Furthermore, some tumor handling during open surgery may be rougher than some minimally-invasive procedures, such as laparoscopic manipulation. Thus, the hypothesis that physical forces activate tumor cell adhesion neither implies that port site recurrence is more common than wound implantation after open surgery nor would be invalidated if port site recurrence were not more common. However, if tumor cell adhesion is activated by force during tumor manipulation or peritoneal insufflation, then

open wound implantation, port site recurrence, and tumor dissemination in either laparoscopic or open surgery might be further reduced by minimizing forces applied to the tumor or by targeting the mechanisms of pressure-stimulated adhesion, regardless of the relative frequency of wound implantation in laparoscopic and open surgery. Increased intraperitoneal pressure during laparoscopic procedures stimulates adhesion of shed intraperitoneal tumor cells and thus potentiates port site recurrence.

The effects of increased ambient pressure on the adhesion to various matrix proteins of 4 colon cancer cell lines (SW620, HT-29, SW1116 and Caco-2) and cells from 3 human colon cancers isolated by mechanical disruption and collagenase digestion were studied. Plastic dishes were precoated with matrix proteins for these studies as described in Basson M. D. et al., "Human enterocyte (Caco-2) migration is modulated in vitro by extracellular matrix composition and epidermal growth factor", J Clin Invest 90: 15-23, 1992, which is incorporated herein by reference thereto. Cell adhesion was measured as described in the same article by Basson et al. (J Clin Invest 90: 15-23, 1992) except that adhesion studies under pressure were performed within a prewarmed (37°C) pressure-tight lucite box pressurized with warmed and filtered air or nitrogen.

Simultaneous control experiments were performed in each experiment with cells passed from the same flask at the same time and allowed to adhere in the same incubator outside the pressurized box. Preliminary studies demonstrated our ability to maintain constant temperature and pressure conditions using this apparatus within +/- 2°C for temperature and +/- 1.5 mm Hg for pressure. Each experiment was performed in triplicate and these triplicate results averaged to yield a single data point. All experiments were performed at least four times with similar results.

All cells exhibited 20-80% increased adhesion in response to a 15 mm Hg increase in pressure for 30 min. Studies in SW620, HT-29, and primary cells showed that pressure stimulated adhesion to collagen I, Matrigel, fibronectin, laminin, and tissue culture plastic. SW620 adhesion to Matrigel was pressure-responsive, exhibiting a 16.3±2.1% increase at 10 mmHg above ambient, and a 50.5 ± 3.3% increase at 15 mm Hg. (*$p<0.002$). Pressure also stimulated adhesion during gassing with filtered nitrogen.

We have previously demonstrated that another physical force, repetitive deformation, has the ability to initiate intracellular signals in human Caco-2 colonocytes and alter other aspects of colonocyte biology. See the discussions in Basson M. D. et al., "Amplitude-dependent modulation of brush border enzymes and proliferation by cyclic strain in human intestinal Caco-2 monolayers", J Cell Physiol 168: 476-88, 1996; and, Han O. et al., "Strain induces Caco-2 intestinal epithelial proliferation and differentiation via PKC and tyrosine kinase signals", Am J Physiol 275: G534-498, 1998 each of which is incorporated herein by reference. Although different physical forces are likely to have different effects, we hypothesized that increased pressure might alter some aspect of human malignant colonocyte biology in a manner which might contribute to port site recurrence. Indeed, the data presented here would be consistent with the further hypothesis that increased abdominal pressure due to peritoneal insufflation may stimulate cation-dependent integrin-mediated adhesion by tumor cells shed during laparoscopy, perhaps via FAK-related tyrosine phosphorylation. Serum potentiates both basal and pressure-stimulated adhesion, suggesting the possibility that serum in port sites potentiates tumor recurrence as well.

2. Serum Potentiation and Integrin-mediated Adhesion

SW620 adhesiveness was substantially decreased in the absence of serum. Nevertheless, increased pressure stimulated adhesion even in studies performed in a balanced electrolyte solution (phosphate buffered saline supplemented with 1 mM $MgCl_2$ and 1 mM $CaCl_2$) without serum ($p<0.005$). This increased adhesion was blocked by chelation (1 mM EDTA, 1 mM EGTA) and did not occur in phosphate buffered saline without calcium or magnesium, suggesting integrin and cation-dependence. Pressure-stimulated adhesion was accompanied by tyrosine phosphorylation of intracellular proteins and phosphorylation (activation) of the integrin-associated Focal Adhesion [tyrosine] Kinase even when studies were performed in dishes to which the cells cannot adhere. Pressure-stimulated adhesion was blocked by a functional antibody to the β1 integrin subunit (1 ug/ml), by the p38 inhibitor SB203580 (50 ug) and by the tyrosine kinase inhibitors genistein (75 ug/ml) tyrphostin (50 mM) and erbstatin (10 uM). No effect on pressure-stimulated adhesion was observed upon the addition of the tyrosine kinase inhibitor DMSO vehicle without tyrosine kinase inhibitor addition.

The invention provides a means to inhibit cell adhesion, whether pressure-induced or integrin-mediated, by the administration of any fluid material. The fluid material may be a saline solution used to wash cells away from the isolated port site or the material may act upon the cells to directly inhibit cell adhesion, and could be selected from materials such as antibodies to cell surface proteins, cell adhesion inhibitors, and salts or chelators effective to inhibit integrin-mediated cell adhesion.

3. Modified Surgical Device

One type of medical device that can be used for these procedures is a trocar assembly. A disclosed in U.S. Patent Nos. 5,147,316 to Castillenti, 5,445,615 to Yoon, and 4,810,244 to Allen, all three of which are hereby specifically incorporated by reference herein, one of the main components of a trocar assembly is an elongated sleeve. The sleeve can be formed from an outer tubular member having a handle at its proximal end and an expandable member at or near its distal end. The expandable member may be a balloon.

As an added feature the device also comprises a means of engaging the external skin above the port site in a manner which stabilizes the trocar and provides sufficient compression of the tissue at the port site so as to, in conjunction with the expandable member, isolate the port site from the abdominal cavity. This external engaging means can be situated on the anterior aspect of the abdominal wall. This external engaging means can be in the form of a clip that is slidably coupled circumferentially along the outside of the outer tubular member. Such a clip is capable of being selectively slid and fixed along various points on the outer tubular member. An alternative design would be a hinged circular clip with can either be a fixed part of the device or detachable from the device that would be fastened around the trocar at a position externally juxtaposed to the insertion site. Alternatively, continuous upward traction or other similar technique can be applied to the engaging means.

A penetrating member can be inserted through the handle of the sleeve so that it lies fairly concentrically along the length of the outer tubular member. The penetrating

member may be an elongated cylindrical structure having either a hollow or solid length. At the proximal end of the penetrating member, like the sleeve, is a handle, and when the penetrating member is fully inserted into the sleeve, the handle of the penetrating member lies proximal to the sleeve's handle. The distal end of the penetrating member is sharp, and could be a blade, needle, or other similar structure. When the penetrating member is fully inserted into the sleeve, the sharp distal end of the penetrating member lies distally to the distal end of the sleeve. In this configuration, the penetrating member is able to pierce tissue, enabling the trocar assembly to be inserted into body cavities. In the alternative a blunt port device can be surgically inserted.

The sleeve also has a series of ports to facilitate the entry and removal of instruments, gases, and liquids. The proximal end of the handle of the sleeve has a port for receiving the penetrating member and other surgical instruments. In order to provide a means for administering medicaments and other fluid materials for the purposes discussed above, various ports are located on the side or sides of the outer sleeve, either at the outer tubular member or handle of the sleeve. One side port can be in communication with the expandable member, such that air, saline solution, or other suitable substances can enter and exit the port to expand and deflate the expandable member.

As an alternative one can use a mechanical means for expanding and deflating the expandable member, such as one with an umbrella style mechanism.

Another side port can be adapted to receive fluids. A passage leads from this side port towards the distal end of the sleeve such that fluids can enter and exit the sleeve from openings at or near the sleeve's distal end, but proximal to the expandable member,

whereby the fluids are released into the port site rather than into the body cavity.

Two additional side ports having passages leading towards the distal end of the sleeve can also be present. One can be adapted to allow for the aspiration of liquids, including endogenous and administered fluids, such as serum, blood, other cell-containing fluids and, if desired fluids which have been administered. These side ports can have either single or multiple exits from the fluid input and fluid aspiration ports and they are located distal to the expandable member. In the alternative, the side port adapted for passing fluids can also be adapted to allow for aspiration.

Another useful port has a valved gas inlet to allow for the entry and exit of various gases at a position distal to the expandable member so as to allow delivery of the gas directly into the body cavity.

Various combinations of passageways can be utilized to link the respective side ports with the expandable member and/or the distal end of the sleeve. For instance, passages can be made within, or coupled to, the wall of the sleeve and the sleeve's outer tubular member. In the alternative, the sleeve could be formed of various tubular members oriented concentrically within the sleeve's outer tubular member, providing separate or shared passages for each of the ports. With respect to the ports in communication with the distal end of the sleeve, it would also be possible to have these ports share a single passage formed by a single tubular member.

A typical use for the above described trocar assembly is described as follows. After inserting the penetrating member fully inside of the sleeve, the sharp end of the penetrating member is used to create an incision in the tissue surrounding the abdominal

cavity. Alternatively, a surgical incision may be made in the fascia and peritoneum within a purse string suture or other tightening technique, and a blunt tipped trocar may then be inserted through the hole which is then tightened around it. The sleeve is then pushed to the desired depth within the cavity such that the expandable member on the sleeve is through the insertion site and in the cavity.

The expandable member is inflated or expanded so as to create a barrier between the cavity and insertion site by abutting against the inner or posterior aspect of the abdominal wall, thus engaging the abdominal wall. The penetrating member is then removed from the sleeve and the external engaging means is positioned. For example, a clip can be slid distally along the tubular member until it is in engagement with the external or anterior aspect of the abdominal wall, at which point the clip is fixed into place. The sleeve is now held firmly in place at the insertion site and the site is isolated from the peritoneal cavity.

Once secure, the gas can be introduced in the side port having the gas valve inlet in order to pressurize the abdominal cavity. An appropriate instrument can be inserted in the port at the proximal end of the sleeve. While manipulating the instrument in the abdominal cavity, a liquid capable of minimizing or eliminating cell adhesion can be introduced via a fluid line in the side port adapted for passing fluids in order to irrigate the cavity. The fluid can then be aspirated out of the cavity via a side port, and the irrigation and aspiration steps repeated as desired.

Alternatively, the side ports may be used simply for aspiration of accumulating serum, blood and/or any tumor cells which have gotten into the port.

Also, the side ports can be used for the administration of other medicaments, such as local anesthetics, antibiotics, growth factors or cytotoxic agents, including osmotic agents, such as distilled and de-ionized water.

Although the use of only a single trocar assembly was described, multiple trocar assemblies could be utilized. For example, if multiple trocar assemblies are required for the surgical procedure, then any or all of them can administer the liquid or medicament to each port site. In such circumstances, the use of a central supply (container) of fluid branching out into different supply lines, such as flexible tubes, may prove easier to use than separate fluid supplies. The multiple lines can either branch directly out of the central container, or can branch out from a single line originating from the central container. The branched out fluid lines would each attach to a side port of a different trocar assembly, and each line could have its own valve to independently control the flow of the liquid. The multiple lines could be prevented from tangling with one another by securing each of them with a securing mechanism (such as a clip) to a stabilizing apparatus that would maintain the spacing of the lines at or near the point where they begin to diverge from one another.

All publications cited herein are incorporated by reference in their entirety .

The foregoing detailed description has been given for clearness of understanding only and no unnecessary limitations should be understood therefrom as modifications will be obvious to those skilled in the art.

Claims

1. A method of inhibiting attachment of tumor cells to an entry or port site comprising administering a composition capable of inhibiting or eliminating cell adhesion to a entry or port site.

2. A method according to claim 1 further comprising the step of evacuating fluids from patient through an entry or port site.

3. A method according to claim 2 wherein the evacuated fluids are endogenous.

4. A method according to claim 2 wherein the evacuated fluids have been administered to the patient.

5. A method according to claim 3 wherein the evacuated fluid contains cells

6. A method according to claim 4 wherein the evacuated fluid contains cells.

7. A method according to claim 1 wherein multiple entry or port sites are used and the composition is administered to any or all of the sites.

8. A method of inhibiting attachment of tumor cells to a surgical entry site or port site comprising administering a fluid material capable of minimizing or eliminating cell adhesion to a surgical entry site or port site during a surgical procedure.

9. A method according to claim 8 wherein the fluid material is selected from the group consisting of saline solution; antibodies to cell surface proteins; cell adhesion inhibitors; salts or chelators effective to inhibit integrin-mediated cell adhesion; agents which inhibit basal or pressure-stimulated adhesion; and, agents that are toxic to tumor cells.

10. A method of inhibiting attachment of tumor cells to a port site or the peritoneal wall adjacent to a port site, comprising employment of a trocar assembly which provides the following features, an expandable member of a sufficient size when inflated and disposed on the trocar assembly in such a way that when inflated or expanded the expandable member forms a protective barrier between the port site and the peritoneum; means of engaging the external skin above the port site in a manner which stabilizes the trocar and provides sufficient compression of the tissue at the port site so as to, in conjunction with the expandable member, isolate the port site from the abdominal cavity; and, at least one side port positioned in the wall of the trocar; and administering fluid materials capable of minimizing or eliminating cell adhesion through the at least one side port during the surgical procedure.

11. A method according to claim 10 wherein the expandable member is an inflatable balloon.

12. A method according to claim 10 wherein the expandable member comprises a mechanical means of expansion.

13. A trocar assembly which provides isolation of insertion sites from a body cavity when inserted into the body cavity comprising:

a sleeve having a distal end and a proximal end, wherein the distal end of the sleeve is adapted for insertion into the abdominal cavity, and the proximal end is open and is adapted for insertion of surgical instruments through the sleeve; and

an expandable member positioned near the insertable end of the sleeve and of a size and configuration that upon inflation or expansion such that a barrier is formed between the body cavity and the insertion site; and

at least one side port coupled to the sleeve in communication with an opening near the distal end of the tubular member but proximal to the expandable member, the side port being adapted for administering fluids to the port site and/or evacuation of fluids or cells from the port site.

14. The trocar assembly of claim 13 further comprising engaging means which abut the external skin above the port site in a manner which stabilizes the trocar and provides sufficient compression of the tissue at the port site so as to, in conjunction with the expandable member, isolate the port site from the abdominal cavity.

15. The trocar assembly of claim 14 wherein the engaging means comprises a clip slidably mounted on the sleeve for securing the sleeve to the insertion site.

16. The trocar assembly of claim 13 further comprising a second side port coupled to the sleeve that is a valved gas inlet.

17. The trocar assembly of claim 13 further comprising a second port coupled to the sleeve that is adapted for aspirating materials from the body and is positioned proximal to the expandable member.

18. The trocar assembly of claim 16 wherein the sleeve has an outer tubular member and an inner tubular member, wherein the inner tubular member is located inside of, and is concentrically aligned with, the outer tubular member, and wherein the space between the outer and inner tubular members forms a passage for the transfer of gases or liquids.

INTERNATIONAL SEARCH REPORT

Interna al application No.

PCT/US00/27902

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61B 17/08

US CL : 606/198, 104, 213, 214; 604/96, 97, 98, 104

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. : 606/198, 104, 213, 214; 604/96, 97, 98, 104

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
TROCAR ASSEMBLY AND TUMOR OR CANCER OR TROCAR METASTASIS

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN/CAS, MEDLINE, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,725,553 A (MOENNING) 10 March 1998 (10.03.1998), see entire document.	1-18
X	US 5,951,588 A (MOENNING) 14 September 1999 (14.09.1999), see claims 1-19.	10-18
A	KAWAMURA et al. Gasless laparoscopically assisted colonic surgery. Am. J. Surg., June 1999, Vol. 177, No. 6, pages 515-7, abstract only.	1-18

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent 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

"&" document member of the same patent family

Date of the actual completion of the international search

30 January 2001 (30.01.2001)

Date of mailing of the international search report

21 MAR 2001

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Inter onal application No.
PCT/US00/27902

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter pnal application No.
PCT/US00/27902

Continuation of Item 4 of the first sheet:
The title is deficient under PCT Rule 4.3 because the title was found by the Examiner to be too long (18 words).
The suggested NEW TITLE should be:

METHOD OF ADMINISTRATING MEDICAMENT TO TROCAR ADAPTED PORT SITE

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-7, drawn to a method of inhibiting attachment of cells by removing fluid and administering composition.

Group II, claim(s) 8-9, drawn to a method of inhibiting attachment of cells by administering fluids.

Group III, claim(s) 10-12, drawn to a method of inhibiting attachment of cells using trocar assembly.

Group IV, claim(s) 13-18, drawn to a trocar assembly.

The inventions listed as Groups I, II, III and IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature of Group III and IV are drawn a trocar assembly and its method of use to inhibit tumor cell attachment. It was found by the Examiner that this special technical feature is not novel over the prior art as it has been disclosed by Moenning et al (US 572553).