

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
2 September 2010 (02.09.2010)

(10) International Publication Number
WO 2010/096927 A1

(51) International Patent Classification:

A61L 27/50 (2006.01) A61L 27/04 (2006.01)
A61F 2/02 (2006.01) A61L 27/06 (2006.01)
A61F 2/28 (2006.01)

(21) International Application Number:

PCT/CA2010/000273

(22) International Filing Date:

26 February 2010 (26.02.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/202,433 27 February 2009 (27.02.2009) US

(71) Applicant (for all designated States except US): **HALIFAX BIOMEDICAL INC.** [CA/CA]; 11493 Route 19, Mabou, Nova Scotia B0E 1X0 (CA).

(72) Inventor: **MUNRO, Chad**; 1721 Lower Water Street, Halifax, Nova Scotia B3J 1S5 (CA).

(74) Agent: **TANDAN, Susan**; Gowling Lafleur Henderson LLP, One Main Street West, Hamilton, Ontario L8P 4Z5 (CA).

(81) Designated States (unless otherwise indicated, for every kind of national protection available):

AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available):

ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

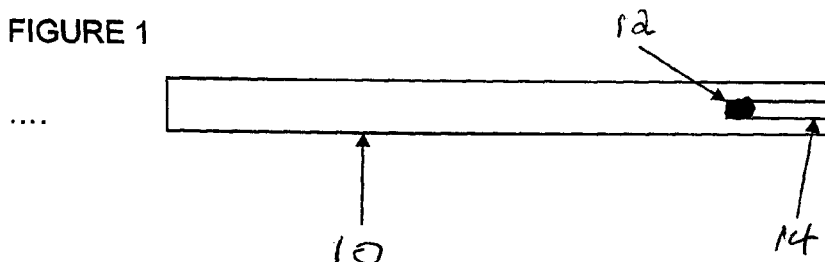
Published:

— with international search report (Art. 21(3))

WO 2010/096927 A1

(54) Title: DEVICE AND METHOD FOR BONE IMAGING

FIGURE 1



(57) Abstract: The invention comprises a modified implant useful to assess bone by imaging. The modified implant comprises a medical implant and at least one detectable marker element associated with the implant that serves as a reference point in medical imaging. Preferably, the implant and the detector marker elements have different radiolucencies such that one element can be seen through the other in medical imaging.

Device and Method for Bone Imaging

FIELD OF INVENTION

[0001] The present invention relates to medical devices, and in particular, a medical implant that is useful in bone imaging to track bone growth, healing and motion.

BACKGROUND OF THE INVENTION

[0002] Medical implants are frequently used to support bones during healing. However, assessment of healing is difficult. Diagnostic techniques such as MRI or CT do not have sufficient resolution to determine if healing has occurred.

[0003] The current standard for the assessment of fracture healing is a planar radiograph and the current standard for assessment of spinal fusion for example is direct palpation of the spine in a second exploratory operation. Flexion extension comparisons using MRI have reported accuracy of 5 degrees which is not sufficient for the determination of fusion.

[0004] Thus, there exists a need to establish a method and device that provides assessment of fusion and bone healing. Having the ability to assess bone healing would assist surgeons in clinical decision-making regarding the treatment of patients, such as whether to apply or avoid surgical intervention.

SUMMARY OF THE INVENTION

[0005] The present invention addresses the need for an improved method of assessing bone.

[0006] In one aspect of the invention, there is provided a modified implant comprising:

- i) a medical implant; and
- ii) at least one detectable marker element associated with the implant that can serve as a reference point in medical imaging.

[0007] In a preferred embodiment, the implant and the detectable marker element have different radiolucencies such that the detectable marker element can be seen through the implant in medical imaging.

[0008] In a further preferred embodiment, the implant comprises titanium and the detectable marker comprises tantalum.

[0009] In another embodiment of the invention, the detectable marker comprises a void in the implant.

[0010] The modified implant preferably comprises a detectable marker that is spherical in shape.

[0011] In yet another embodiment of the invention, the modified implant has a unique outer geometry that acts as a detectable marker such that the position of the implant can be precisely established by medical imaging.

[0012] In a further preferred embodiment, the modified implant comprises a radio-opaque substance applied to one or both ends of the implant as the detectable marker.

[0013] In another aspect of the invention, a method of assessing bone is provided. The method comprises the steps of:

- i. implanting a modified implant into a portion of bone adjacent to a target site;
- ii. determining the position of the modified implant through medical imaging;

- iii. applying load to the bone;
- iv. determining the position of the implant under load bearing conditions;
- v. comparing the position of the modified implant in an unloaded state with the position of the modified implant under load bearing conditions; and
- vi. determining the distance the modified implant moved;

wherein the less the difference in position of the implant in the unloaded state as compared to the load-bearing state, the better the assessment.

In a preferred embodiment of this method, a modified implant is implanted into the bone on each side of a target site and the distance between the modified implants under unloaded and loaded conditions is determined.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] These and other features of the invention will become more apparent from the following description in which reference is made to the appended drawings wherein:

[0015] Figure 1 is an illustration of one embodiment of a modified implant device in accordance with the invention;

[0016] Figure 2 is an illustration of another embodiment of a modified implant device in accordance with the invention; and

[0017] Figure 3 is an illustration of a further embodiment of a modified implant device in accordance with the invention.

DETAILED DESCRIPTION

[0018] The invention relates to modified medical implants that can be used in bone assessment. The modified implant includes an implant modified with a detectable marker that can readily be detected to determine the position of the modified implant.

[0019] The term "bone assessment" is used herein to encompass the assessment of bone healing following injury by fracture or surgical intervention that create the same biological conditions as an injury, assessment of surgical fusions such as spine and ankle fusion operations, the assessment of bone growth and bone motion for any other reason.

[0020] In one aspect of the invention, medical implants comprising small radio-opaque elements as the detectable marker are provided in which these elements are embedded or attached to the medical implant. These elements are more radio-opaque than the medical implant itself. The result is that in an x-ray of the implant/ bone construct, the embedded elements can be clearly seen. The embedded elements are preferably in the shape of a sphere since this shape is readily detected as a point in an X-ray. Comparisons between a loaded state of an implant/bone construct may be compared to an unloaded state of the same region. The embedded elements may be used as precise reference points on medical images. The relative motion of the embedded elements across a target bone zone when a load is applied is a representative measure of the stiffness of that zone and, thus, is useful to assess the bone. For example, with respect to bone healing, as a bone heals, the bone healing zone stiffness will approach the stiffness of healthy bone.

[0021] Figure 1 illustrates a medical implant 10 that can be associated with a bone to be assessed, e.g. a bone that is undergoing healing. In this embodiment, the implant device includes an embedded element 12 that has a different radiolucency than that medical implant.

The embedded element is shown as press-fitted into a channel 14 that is machined into the implant.

[0022] In one preferred embodiment, the medical implant is made of titanium and the embedded element is a tantalum sphere.

[0023] In another embodiment, the shape of the medical implant is modified such that partial spheres 16 are clearly visible in the implant contour as shown in Figure 2. At least one end of the implant may have a curved (half sphere) contour 16 that is embedded with a radio-opaque element as a detectable marker. The position of the implant end can be measured as described above by imaging of the embedded element. In this case, even without having a more radio-opaque element associated with the implant, the modified shape alone can act as a reference point for the purposes of assessing bone.

[0024] In another embodiment of the device, the detectable marker is in the shape of machined voids or cavities 18 in the medical implant 10 as shown by the empty sphere in Figure 3. Such empty spheres, which may include air or bodily fluids, provide sufficient differences in radiolucency that the position of the void can be precisely determined by imaging.

[0025] In use, a modified implant according to the invention is implanted in the bone adjacent to a target site, such as damaged bone. A baseline measurement is taken, load is applied to the bone and the distance of travel of the modified implant is measured. Preferably a modified implant is implanted on each side of the target site. A baseline measurement indicating the distance between the detectable markers on each implant in an unloaded state is recorded and compared to the distance between the two markers under a loaded state. The relative distance between the markers is recorded and this distance is an

indicator of rigidity in the bone and thus enables assessment of bone, for example, assessment of bone healing.

[0026] As will be appreciated by one of skill in the art, the present modified implant is useful to track any motion of a bone in the body under loaded conditions or under dynamic x-ray acquisition. For example, the implant may be in the form of a pedical screw for a device that is designed to preserve the motion of the spine. In this case, detectable marker embedded within the screw implant may be used to track the motion of bone segments under dynamic imaging modalities such as fluoroscopic, stereo fluoroscopic, dynamic DR imaging or stereo DR imaging.

[0027] Specific detectable markers, such as an embedded sphere of radio-opaque material, the insertion of a radio-opaque element at a specific site on the implant, the shape of the implant itself, and a cavity with or without air have been described above. It is clearly apparent however that any type of detectable marker that indicates the position of the modified implant may be used in the devices and methods of the invention.

CLAIMS

I claim:

1. A modified implant comprising:
 - i) a medical implant; and
 - ii) at least one detectable marker element associated with the implant that serves as a reference point in medical imaging.
2. The modified implant of claim 1 wherein the implant and the detector marker elements have different radiolucencies such that one element can be seen through the other in medical imaging.
3. The modified implant of claim 2 wherein the implant comprises titanium and the detectable marker comprises tantalum.
4. The modified implant of claim 1 wherein the detectable marker comprises a void in the implant.
5. The modified implant of claim 1 wherein the implant has a unique outer geometry as a detectable marker such that the position of the implant can be precisely established by medical imaging.
6. The modified implant of claim 3 or 4 wherein the detectable marker is spherical in shape.
7. The modified implant of claim 1 wherein the detectable marker comprises a radio-opaque substance applied to one or both ends of the implant.
8. A method of assessing a bone, said method comprising the steps of: i) implanting a modified implant as defined in claim 1 into a portion of bone adjacent to a target site; ii) determining the position of the modified implant through medical imaging; iii) applying load to the

target bone; iv) determining the position of the implant under load bearing conditions; v) comparing the position of the modified implant in an unloaded state with the position of the modified implant under load bearing conditions; and vi) determining the distance the modified implant moved; wherein the less the difference in position of the implant in the unloaded state as compared to the load-bearing state, the better the assessment.

9. The method according to claim 8 wherein a modified implant is inserted into the bone on either side of a target site and the distance between the two detectable markers under unload and loaded conditions is determined.

1/1

FIGURE 1

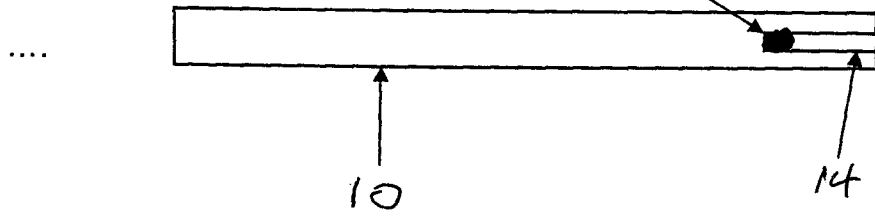


FIGURE 2

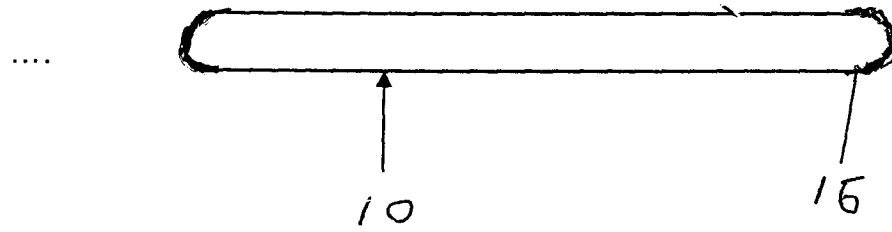
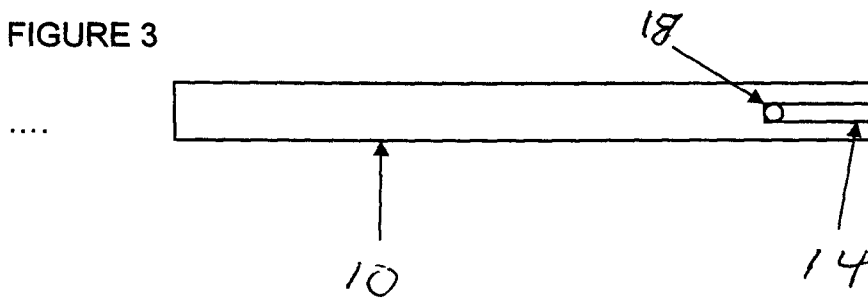


FIGURE 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/000273

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC: A61L 27/50 (2006.01) , A61F 2/02 (2006.01) , A61F 2/28 (2006.01) , A61L 27/04 (2006.01) , A61L 27/06 (2006.01) According to International Patent Classification (IPC) or to both national classification and IPC</p>																							
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) IPC: A61L 27 (2006.01)</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used) Canadian Patent Database, WEST, English Full Text (Epoque) Keywords: implant, prosthesis, medical device, stent, graft, catheter; bone, osteo*; assess*, growth, heal*; detect*, imag*, visualiz*, analy*, diagnos*; marker, radio*, x*ray, mri, ct; load, compress*, strain, stress</p>																							
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1" style="width:100%; border-collapse: collapse;"> <thead> <tr> <th style="width:10%;">Category*</th> <th style="width:60%;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="width:30%;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td align="center">X</td> <td>US 2008/0269898 (Carls, T. et al.) 30 October 2008 (30.10.2008) Entire Document</td> <td align="center">1 and 2</td> </tr> <tr> <td align="center">X</td> <td>CA 2,238,784 (Stinson, J. S.) 01 February 1999 (01.02.1999) Claims, pages 2-5, 8-11, 17-20, Examples and Figures 10-12</td> <td align="center">1, 2, 4, 6 and 7</td> </tr> <tr> <td align="center">X</td> <td>CA 2,427,767 (Weaver, T. J. et al.) 23 May 2003 (23.05.2003) Entire Document</td> <td align="center">1-3</td> </tr> <tr> <td align="center">X</td> <td>CA 2,485,013 (Knapp, D. et al.) 20 November 2003 (20.11.2003) Claims, pages 2-4, 6-9 and Figure 2</td> <td align="center">1, 2 and 7</td> </tr> <tr> <td align="center">X</td> <td>CA 2,446,573 (Scarborough, N. L.) 19 March 1998 (19.03.1998) Entire Document</td> <td align="center">1, 2 and 5</td> </tr> <tr> <td align="center">X</td> <td>CA 2,536,947 (Violante, M. R. et al.) 10 March 2005 (10.03.2005) Claims, pages 2-7, Examples and Figures</td> <td align="center">1 and 4</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	US 2008/0269898 (Carls, T. et al.) 30 October 2008 (30.10.2008) Entire Document	1 and 2	X	CA 2,238,784 (Stinson, J. S.) 01 February 1999 (01.02.1999) Claims, pages 2-5, 8-11, 17-20, Examples and Figures 10-12	1, 2, 4, 6 and 7	X	CA 2,427,767 (Weaver, T. J. et al.) 23 May 2003 (23.05.2003) Entire Document	1-3	X	CA 2,485,013 (Knapp, D. et al.) 20 November 2003 (20.11.2003) Claims, pages 2-4, 6-9 and Figure 2	1, 2 and 7	X	CA 2,446,573 (Scarborough, N. L.) 19 March 1998 (19.03.1998) Entire Document	1, 2 and 5	X	CA 2,536,947 (Violante, M. R. et al.) 10 March 2005 (10.03.2005) Claims, pages 2-7, Examples and Figures	1 and 4
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																					
X	US 2008/0269898 (Carls, T. et al.) 30 October 2008 (30.10.2008) Entire Document	1 and 2																					
X	CA 2,238,784 (Stinson, J. S.) 01 February 1999 (01.02.1999) Claims, pages 2-5, 8-11, 17-20, Examples and Figures 10-12	1, 2, 4, 6 and 7																					
X	CA 2,427,767 (Weaver, T. J. et al.) 23 May 2003 (23.05.2003) Entire Document	1-3																					
X	CA 2,485,013 (Knapp, D. et al.) 20 November 2003 (20.11.2003) Claims, pages 2-4, 6-9 and Figure 2	1, 2 and 7																					
X	CA 2,446,573 (Scarborough, N. L.) 19 March 1998 (19.03.1998) Entire Document	1, 2 and 5																					
X	CA 2,536,947 (Violante, M. R. et al.) 10 March 2005 (10.03.2005) Claims, pages 2-7, Examples and Figures	1 and 4																					
<p><input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.</p>																							
<table border="0" style="width:100%;"> <tr> <td style="width:50%; vertical-align: top;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="width:50%; vertical-align: top;"> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p> </td> </tr> </table>			<p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>																			
<p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>																						
<p>Date of the actual completion of the international search 25 May 2010 (25-05-2010)</p>		<p>Date of mailing of the international search report 14 June 2010 (14-06-2010)</p>																					
<p>Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476</p>		<p>Authorized officer Stephen Decker (819) 934-2333</p>																					

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/CA2010/000273

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2,679,691 (Headley, F. A. Jr. et al.) 18 September 2008 (18.09.2008) Entire Document	1, 2 and 5
A	US 2008/0161729 (Bush, S. T.) 03 July 2008 (03.07.2008) Entire Document	1-7
A	US 2003/0040806 (MacDonald, S. G.) 27 February 2003 (27.02.2003) Entire Document	1-7
A	US 2008/0294258 (Revie, I. et al.) 27 November 2008 (27.11.2008) Entire Document	1-7

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/CA2010/000273**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)**

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

1. Claim Nos. : 8 and 9
because they relate to subject matter not required to be searched by this Authority, namely :

Claims 8 and 9 are directed to a diagnostic method performed on the human or animal body which the International Search Authority is not required to search. In particular, the diagnostic methods of claims 8 and 9 include a surgical step of implanting the detectable marker-modified medical implant.
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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

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 additional fees, this Authority did not invite payment of additional fees.
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 claim 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 claim Nos. :

Remark on Protest The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2010/000273

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US2008269898A1	30-10-2008	US2008269898A1	30-10-2008
CA2238784A1	01-02-1999	AT348638T CA2238784C DE69836656D1 DE69836656T2 EP0894503A2 EP0894503A3 EP0894503B1 ES2274556T3 JP11057020A JP4284427B2 US6174330B1 US2001021873A1 US6626936B2 US2004111149A1 US7553325B2 US2006004440A1 US2009259125A1	15-01-2007 05-08-2003 01-02-2007 27-09-2007 03-02-1999 27-09-2000 20-12-2006 16-05-2007 02-03-1999 24-06-2009 16-01-2001 13-09-2001 30-09-2003 10-06-2004 30-06-2009 05-01-2006 15-10-2009
CA2427767A1	23-05-2003	AU3251902A AU2002232519B2 DE60108524D1 DE60108524T2 EP1341566A2 EP1341566B1 JP2004513709T US6641776B1 US2004092818A1 WO0240077A2 WO0240077A3	27-05-2002 01-03-2007 24-02-2005 23-06-2005 10-09-2003 19-01-2005 13-05-2004 04-11-2003 13-05-2004 23-05-2002 03-01-2003
CA2485013A1	20-11-2003	AU2003231202A1 EP1505907A1 JP2005524467T US2003212324A1 US6904310B2 US2005169842A1 US7398118B2 WO03094735A1	11-11-2003 16-02-2005 18-08-2005 13-11-2003 07-06-2005 04-08-2005 08-07-2008 20-11-2003
CA2446573A1	19-03-1998	AT394078T AU4270397A AU739912B2 BR9711829A CA2266047A1 CA2446573C DE69738669D1 EP0932373A1 EP0932373B1 EP1839622A2 ES2307302T3 JP2001500409T KR20000036113A US5676146A US5676146B1 WO9810712A1	15-05-2008 02-04-1998 25-10-2001 18-01-2000 19-03-1998 31-03-2009 19-06-2008 04-08-1999 07-05-2008 03-10-2007 16-11-2008 16-01-2001 26-06-2000 14-10-1997 18-04-2000 19-03-1998

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/000273

CA2536947A1	10-03-2005	CA2536947A1	10-03-2005
		EP1663108A2	07-06-2006
		EP1663108A4	10-06-2009
		JP2007503263T	22-02-2007
		US6106473A	22-08-2000
		US6610016B1	26-08-2003
		US2004077948A1	22-04-2004
		US7229413B2	12-06-2007
		US2007255140A1	01-11-2007
		WO2005020905A2	10-03-2005
		WO2005020905A3	22-06-2006
CA2679691A1	18-09-2008	CA2679691A1	18-09-2008
		EP2117463A1	18-11-2009
		US2008221670A1	11-09-2008
		WO2008112076A1	18-09-2008
US2008161729A1	03-07-2008	US2008161729A1	03-07-2008
US2003040806A1	27-02-2003	AU2002326669A1	10-03-2003
		US6610096B2	26-08-2003
		WO03017821A2	06-03-2003
		WO03017821A3	11-03-2004
US2008294258A1	27-11-2008	EP1720452A1	15-11-2006
		GB0405010D0	07-04-2004
		JP2007528243T	11-10-2007
		WO2005084544A1	15-09-2005