Filed on behalf of Visionsense Corp.

By: Joseph M. Casino, Reg. No. 57,224
Wiggin and Dana LLP
450 Lexington Avenue
Suite 3800
New York, New York 10017
Tel: (212) 551-2842
Email: JCasino@wiggin.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

---

BEFORE THE PATENT TRIAL AND APPEAL BOARD

---

VISIONSENSE CORP.

Petitioner,

v.

Patent Owner of

U.S. Patent No. 8,892,190 to

IPR Trial No. TBD

**PETITION FOR *INTER PARTES* REVIEW OF**

**U.S. Patent No. 8,892,190**

**UNDER 35 U.S.C. § 312 AND 37 C.F.R. § 42.104**

## Exhibits

| Exhibit | Description | Abbreviation |
|---|---|---|
| 1001 | U.S. Patent No. 8,892,190. "Method and apparatus for performing intra-operative angiography," filed March 13, 2012. | '190 Patent |
| 1002 | Little, John R., et al. "Superficial temporal artery to middle cerebral artery anastomosis: intraoperative evaluation by fluorescein angiography and xenon-133 clearance." Journal of neurosurgery 50.5 (1979): 560-569. | Little |
| 1003 | U.S. Patent 6,351,663. "Methods for diagnosing and treating conditions associated with abnormal vasculature using fluorescent dye angiography and dye-enhanced photocoagulation," filed September 10, 1999. | Flower I |
| 1004 | Japanese Laid Open Patent Publication No. H9-309845 (Translation). "NEAR-INFRED FLUORESCENT TRACER AND FLUORESCENE IMAGING METHOD," filed May 21, 1996. | Jibu |
| 1005 | U.S. Patent No. 5,394,199. "Methods and apparatus for improved visualization of choroidal blood flow and aberrant vascular structures in the eye using fluorescent dye angiography," filed May 17, 1993. | Flower II |
| 1006 | Specification of Argus 20 with C2400-75i, dated May 1997 | Argus 20 Specification |
| 1007 | Goldstein et al., "Intraoperative Angiography to Assess Graft Patency After Minimally Invasive Coronary Bypass," Ann Thorax Surg, 66: 1978-1982, (1998). | Goldstein |
| 1008 | Eren, Serdar, et al. "Assessment of microcirculation of an axial skin flap using indocyanine green fluorescence angiography." Plastic and reconstructive surgery 96.7 (1995): 1636-1649 | Eren |
| 1009 | Decision of European Patent Office Technical Board of Appeal revoking Counterpart Patent No. 1143852 | EPO Decision |

| | | |
|---|---|---|
| 1010 | Translation of Decision of Japanese Patent Office Trial Board revoking Counterpart Patent No. Patent No. 3,881,550 | JPO Decision |
| 1011 | Summary of Invention Submitted to EPO | Invention Summary |
| 1012 | Novadaq 510K showing X-Ray Fluoroscopy as Predicate Device | 510K |
| 1013 | Takayama et al., Intraoperative Coronary Angiography Using Fluorescein, Ann Thorac Surg. 51:140-143 (1991) | Takayama |
| 1014 | Hyvarinen, Lea and Robert W. Flower. "Indocyanine green fluorescence angiography." Acta ophthalmological 58.4 (1980): 528-538 | Hyvarinen |
| 1015 | The Sony U-Matic Videocassette Recorder | Sony U-Matic |
| 1016 | Joseph, et al. "Evaluation of the circulation of reconstructive flaps using laser-induced fluorescence of indocyanine green." Annals of plastic surgery 42.3 (March 1999): 266-274. | Joseph |

## Table of Challenged Claims

| Claim Limitations | Abbreviation |
|---|---|
| 1. A method for assessing blood flow moving through a vessel graft anastomosed in fluid communication with an interconnected group of blood vessels in an animal, the vessel graft and at least a portion of the blood vessels being exposed during a surgical procedure on the animal, the method comprising the steps of: | Vessel Graft Preamble |
| (a) administering a fluorescent dye to the animal such that the dye enters the vessel graft and the interconnected group of blood vessels; | Administering Step |
| (b) exciting the fluorescent dye within the vessel graft and said exposed portion of the interconnected group of blood vessels with a source of illumination, thus causing the dye to emit radiation; | Illuminating Step |
| (c) capturing the radiation emitted by the fluorescent dye with a camera capable of imaging a series of angiographic images within the vessel graft and said exposed portion of the interconnected group of blood vessels, the images including at least an image of a fluorescent wavefront corresponding to an interface between the flowing blood that first contains the fluorescent dye introduced, such image being captured by the camera as the fluorescent wavefront transitions | Wavefront Capturing Step |

| | |
|---|---|
| through the exposed vessel graft and interconnected croup of blood vessels; and | |
| (d) evaluating the angiographic images to assess blood flow through the vessel graft relative to blood flow through the interconnected group of blood vessels. | Evaluation Step |
| 2. The method of claim 1, further comprising:<br>modifying said anastomosed vessel graft based on results of said evaluating step, thereby improving resultant blood flow through said vessel graft. | Modifying Step |
| 3. A method for assessing blood flow moving through an vessel graft in an animal, the vessel graft being exposed during a surgical procedure on the animal, comprising the steps of: | Vessel Graft Preamble |
| (a) administering a fluorescent dye to the animal such that the dye enters the vessel graft; | Administering Step |
| (b) exciting the fluorescent dye within the vessel graft with a source of illumination, thus causing the dye to emit radiation, the fluorescent dye having a peak absorption and emission in the range of 800 to 850 nm; | Illuminating Step<br><br>800-850 Wavelength Requirement |
| (c) capturing the radiation emitted by the fluorescent dye with a camera capable of imaging a series of angiographic images of the vessel graft at a rate of at least 15 images per second while the subject's heart is beating, the images including at least an image of a fluorescent wavefront corresponding to an | 15 Images/Second Requirement<br><br>Wavefront Capture Step |

| | |
|---|---|
| interface between the flowing blood that first contains the fluorescent dye introduced, such image being captured by the camera as the fluorescent wavefront transitions through the exposed vessel graft; and | |
| (d) evaluating the angiographic images to assess blood flow through the vessel graft relative to blood flow through a group of blood vessels interconnected to the vessel graft. | Evaluation Step |

Visionsense Corp. ("Petitioner" or "Visionsense") petitions for *Inter Partes* Review ("IPR") under 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42 of claims 1-3 ("the Challenged Claims") of U.S. Patent No. 8,892,190 ("the '190 patent"). As explained in this petition, and in the accompanying declaration of David J. Langer, M.D., Chief of Neurosurgery at Lenox Hill Hospital, New York, there exists a reasonable likelihood that Visionsense will prevail with respect to at least one of the Challenged Claims.

The Challenged Claims are invalid based on teachings set forth in at least the references presented in this petition. Visionsense respectfully submits that an IPR should be instituted, and that the Challenged Claims should be canceled as being invalid.

## I. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(A)(1)

### A. REAL PARTY-IN-INTEREST UNDER 37 C.F.R. § 42.8(B)(1)

Petitioner, Visionsense Corp., is the real party-in-interest.

### B. RELATED MATTERS UNDER 37 C.F.R. § 42.8(B)(2)

No litigation matters exist related to this proceeding.

### C. COUNSELUNDER 37 C.F.R. § 42.8(B)(3)

| LEAD COUNSEL | BACKUP COUNSEL |
|---|---|
| Joseph M. Casino, Reg. No. 57,224<br>Wiggin and Dana LLP<br>450 Lexington Avenue<br>New York, NY 10017 | Abraham Kasdan, Reg. No. 32,997<br>Wiggin and Dana LLP<br>450 Lexington Avenue<br>New York, NY 10017 |

| | |
|---|---|
| T: 212-551-2841<br>Email: jcasino@wiggin.com | T: 212-551-2841<br>Email: akasdan@wiggin.com |

### D. SERVICE INFORMATIONUNDER 37 C.F.R. § 42.8(B)(4)

Please address all correspondence and service to counsel at the address provided in Section I(C). Petitioner also consents to electronic service by email at jcasino@wiggin.com and akasdan@wiggin.com.

## II. CERTIFICATE OF GROUNDS FOR STANDING

Petitioner certifies pursuant to Rule 42.104(a) that the patent for which review is sought is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

## III. OVERFIEW OF CHALLENGE AND RELIEF REQUESTED

Pursuant to Rules 42.22(a)(1) and 42.104(b)(1)-(2), Petitioner requests that each Challenged Claim be cancelled.

### A. PRIOR ART PATENTS AND PRINTED PUBLICATIONS

Petitioner relies on the Exhibits 1001 – 1008 and 1013 -1016 in the Table of Exhibits as prior art.

### B. GROUNDS OF CHALLENGE

Petitioner requests cancellation of the Challenged Claims as unpatentable under (pre-AIA) 35 U.S.C. §§ 102 and 103 on the following grounds:

**Ground 1: Claims 1 and 2 are anticipated by Little**

**Ground 2: Claims 1-3 are obvious in view of Little, Flower I and Flower II.**

**Ground 3: Claims 1-3 are obvious in view of Flower I, Flower II and Little or Goldstein**

**Ground 4: Claims 1-3 are obvious in view of Jibu, Flower II and Little or Goldstein**

## IV. TECHNOLOGY BACKGROUND

### A. BRIEF DESCRIPTION AND SUMMARY OF CLAIMS 1-3

The technology in this case relates to imaging blood flow by adding a fluorescent dye to the blood, exciting it with excitation light to emit fluorescence, and taking a video image using a CCD camera to visualize how the dye transitions through vessels. Claims 1-3 at issue (which constitute all claims of the '190 Patent) are method claims that claim use of this well-known fluorescence imaging technique to analyze the patency (i.e., degree of openness; the relative absence of blockage) of a vascular graft. All claims require a camera capable of capturing images of the "wavefront," i.e. the boundary between fluorescent and non-fluorescent regions of the blood, where the fluorescent dye is first introduced. Claim 3 requires that the fluorescent dye have its peak absorption and emission spectrum in the range of 800-850 nm, which corresponds to that of the well-known dye, indocyanine green (ICG) (Ex. 1001, 14:29), and that the image capture rate

of the CCD camera be at least 15 images per second, which is what a conventional off the shelf CCD camera could obtain. (*See* Ex. 1011.)

The prior art relied on herein shows that the equipment needed to perform the claimed methods was known in the prior art. The use of such methods to assess blood flow in grafts during surgery was also known and was an obvious way to use such equipment.

Claim 1's preamble ("Vessel Graft Preamble") broadly sets the environment to view vessel grafts in an animal during surgery:

"A method for assessing blood flow moving through a vessel graft anastomosed in fluid communication with an interconnected group of blood vessels in an animal, the vessel graft and at least a portion of the blood vessels being exposed during a surgical procedure on the animal, the method comprising the steps of:"

Limitation (a) requires administering of a fluorescent dye so that it enters the vessel graft and related blood vessels ("the Administering Step"):

"(a) administering a fluorescent dye to the animal such that the dye enters the vessel graft and the interconnected group of blood vessels;"

Limitation (b) requires exciting the dye with a source of illumination, such as a laser, so that it emits fluorescence radiation ("the Illuminating Step"):

"(b) exciting the fluorescent dye within the vessel graft and said exposed portion of the interconnected group of blood vessels with a source of illumination, thus causing the dye to emit radiation;"

Limitation (c) requires the capturing of a series of images of the fluorescent wavefront as it "transitions", i.e., moves, through the graft and related blood vessels due to the blood flow. ("the Wavefront Capture Step"):

"(c) capturing the radiation emitted by the fluorescent dye with a camera capable of imaging a series of angiographic images within the vessel graft and said exposed portion of the interconnected group of blood vessels, the images including at least an image of a fluorescent wavefront corresponding to an interface between the flowing blood that first contains the fluorescent dye introduced, such image being captured by the camera as the fluorescent wavefront transitions through the exposed vessel graft and interconnected group of blood vessels;"

Finally, limitation (d) requires evaluation of those images to assess blood flow through the vessel graft ("the Evaluation Step"):

(d) evaluating the angiographic images to assess blood flow through the vessel graft relative to blood flow through the interconnected group of blood vessels

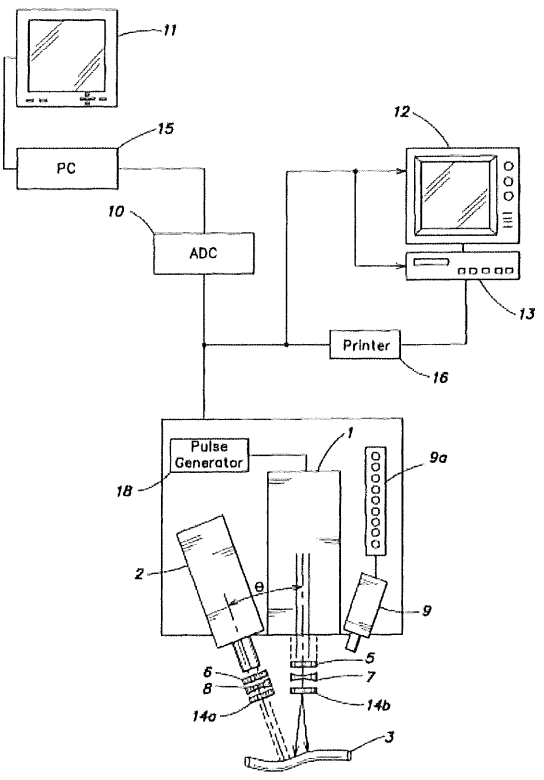
Dependent Claim 2 adds the step of modifying the vessel graft based on the Evaluation Step ("the Modifying Step"):

"modifying said anastomosed vessel graft based on results of said evaluating step, thereby improving resultant blood flow through said vessel graft."

Claim 3 is largely the same as Claim 1 but adds two additional details. First, it adds a requirement to the Administering Step that the fluorescent dye has "a peak absorption and emission in the range of 800 to 850 nm" ("the 800-850 Wavelength Requirement"). Second, it adds a requirement to the Wavefront Capture Step that the camera be capable of imaging "at least 15 images per second while the subject's heart is beating," ("the 15 Image/Second Requirement").

## B. OVERVIEW OF THE '190 PATENT

U.S. Patent No. 8,892,190 was filed on March 13, 2012 almost thirteen years after a provisional application was filed on September 24, 1999. The sole figure shows the exemplary device proposed for looking at vessel grafts during an operation using fluorescence:




In the figure, a laser 1 is emits radiation through bandpass filter 5 and optics 7 using a wavelength that will illuminate a fluorescent dye injected into the tissues of interest 3 in a patient. The preferred dye injected into the tissue of interest 3 is ICG. CCD camera 2 captures the emissions from the dye and can be fitted with a bandpass filter 6, polarizing filter 14a and lens system 8. A distance detection system 9, 9a may be used. The camera 2 may relay the captured images to an analog-to-digital converter 10, PC 15 and monitor 11. A printer 13, VCR 13 and monitor 12 may also be used for recording, printing or playback.

During the course of the prosecution, the applicants were faced with several rejections due to Flower I in the parent and grandparent applications to the application issuing as the '190 Patent.

First, in the grandparent application, the applicant received anticipation and obviousness rejections of the pending claims on the basis of Flower I and Flower I in view of certain other references. In its obviousness rejection, the examiner wrote:

"Flower I discloses a method and diagnosis and treating conditions associated with abnormal vasculature using a fluorescent dye angiography . . . but fails to show explicitly a . . . bypass graft." (Application No. 09/744,034, Non-final Rejection dated Mar. 10, 2004.) However, a secondary reference, the examiner observed, showed a "coronary artery bypass grafting on a beating heart whereby an angiographic image is obtained before and after the invasive procedure." (*Id.*) The examiner also observed that while Flower I did not show the use of a video monitor, a secondary reference disclosed a method of performing heart surgery using thermographic imaging that uses a plurality of images. (*Id.*) Among other things, the examiner also pointed to other secondary references that disclosed the use of CCD camera, in a relevant clinical setting. (*Id.*)

In response to the obviousness rejections, the applicants argued that there was insufficient motivation to apply Flower I to the intraoperative assessment of the patency of a coronary artery. (Application No. 09/744,034, Applicant Remarks, Feb. 14, 2005.) In addition, the applicants argued, while the prior art showed the capturing of before-and-after angiographic images, there was insufficient motivation to "record a dynamic event concurrent with surgery." (*Id.*) The applicants also argued that there was insufficient motivation to combine Flower I with other prior art, including those that disclosed the use of a CCD camera. (*Id.*)

In the only prior art rejection in the application leading to the '190 Patent the applicants received an anticipation rejection on the basis of Takayama et al., Intraoperative Coronary Angiography Using Fluorescein, Ann Thorac Surg. 51:140-143 (1991) ("Takayama," Ex. 1013). The examiner reasoned wrote that Takayama "discloses a method of assessing patency of a portion of a blood vessel included the steps of administering a fluorescent dye to an animal . . . obtaining at least one angiographic image of the vessel portion . . . , and evaluating the image to assess patency of the vessel portion." (Application No. 13/419,368, Final Rejection, Conf. No. 5106, Feb. 4, 2013.)

In response, the applicants argued that Takayama was not anticipatory because it did not disclose the use of a camera. For example, the applicants noted, Takayama is "directed to naked eye visualization . . . and, as such, does not disclose or suggest fluorescent dye imaging of moving blood through the vessel graft . . . . Therefore, there would be no need for a camera to obtain angiographic images of blood flow." (Application No. 13/419,368, Applicant Remarks, Oct. 2, 2013.) The applicants' arguments and certain amendments overcame the examiner's rejections, and the patent ultimately issued.

The Little reference, showing the use of fluorescent imaging to assess graft patency, was not reviewed by the patent examiner. The Jibu reference, which resulted in cancellation of parallel device claims in the Europe and Japan, was not used by the examiner. Further, and very significantly, the arguments made by applicant during prosecution about the relevance of Flower I were incomplete and misleading as the work by Flower I was crucial to the purported invention of applicant. As a result, while the Flower I reference was examined by the patent examiner, it was not reviewed in combination with Little or Jibu.

## C. BACKGROUND TO THE INVENTION

Despite having argued during prosecution of the '190 Patent that the Flower I reference was not relevant to the then-pending claims, the patent owner later revealed that the work by Flower was actually the linchpin of the purported invention. During proceedings in the Japanese Patent Office, the patent owner submitted a statement from one of the inventors describing the invention process. (Ex. 1011.) This summary describes that several of the inventors spent "a considerable amount of time trying to obtain fluorescence images of ICG." (*Id.*) But they "were unable to observe any fluorescence." (*Id.*) They studied "mainly Bob Flower's publications" in the literature and wanted to bring Bob Flower to Winnipeg to help. (*Id.*) After getting funding for Flower to come to Winnipeg for "a weekend" he helped the inventors determine they should introduce "ICG as a bolus of higher concentration" and replace their $40K lab camera with "an $800 camera that acquired images at video rate i.e. 30 frames per second." (*Id.*)

After Flower's visit, they acquired "very promising images of coronary arteries in the rat heart." (*Id.*) The team then reached out to cardiac surgeon who tried and helped refine the equipment. (*Id.*)

Curiously, and fatally, Flower (one of the named inventors on the '190 Patent) had already filed patents that disclosed the use of fluorescence

imaging to evaluate blood flow using a CCD camera that could image 30 frames a second before the provisional filing date of the '190 Patent. (Flower I and Flower II). Further, it was already well known that imaging, including fluorescence imaging, was useful to examine a graft during surgery so that revisions could be made to fix any blood flow issues in the graft. (Little and Goldstein). As the identified prior art demonstrates, Claims 1-3 cover nothing more than what was already known in the prior art.

## V. LEVEL OF ORDINARY SKILL IN THE ART

The claims of the '190 Patent relate to the method of using fluorescent imaging to look at a vessel graft during surgery. A medical doctor with 2-3 years' experience using or designing imaging equipment for use during medical procedures would be one of ordinary skill in the art. (Declaration of David J. Langer, M.D., dated March 21, 2017 ("Langer Decl.") ¶ 10.)

## VI. CLAIM CONSTRUCTION

### A. LEGAL PRINCIPLES

During an *inter partes* review, claims are given the broadest reasonable construction. 37 C.F.R. § 42.100. "[C]onstruing a patent claim according to its broadest reasonable construction helps to protect the public . . . [b]ecause an examiner's (or reexaminer's) use of the broadest reasonable

construction standard increases the possibility that the examiner will find the claim too broad (and deny it) . . . ." *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–45 (2016).

## B. CLAIM CONSTRUCTION

Under the broadest reasonable construction, there would appear to be no limiting construction of the claims that avoids the prior art. Petitioner reserves the right to respond to any claim construction arguments made by the patent owner. While the plain language of the claims appears understandable under the broadest reasonable construction, petitioner makes the following comments:

- "Vessel graft" can be the graft of any vessels. It can be vessels in the leg, heart or brain. ('190 Patent, 1:36-41.)
- "Animal" can be a human or non-human animal. ('190 Patent, 4:15-17).
- The amount of "fluorescent dye" is not limited as to minimum or maximum quantities in the Administering Step, nor is there any requirement that the dye be injected in a single administration (bolus) or in multiple successive administrations.

- The method of exciting the fluorescent dye is not limited in the Illuminating Step and may be done in any manner (e.g., laser, filtered broad-band light source, etc.).
- The Modifying Step is not limited to a particular modification of the vessel graft.
- Evaluation of blood flow through the vessel graft relative to interconnected vessels is not limited to numerical comparisons of fluorescence intensities in the vessel graft and connected vessels. Any type of comparison (e.g., fluorescence signal in the graft and no signal in the downstream vessels) would qualify as relative evaluation.

## VII. THE PRIMARY REFERENCES

### A. LITTLE (EX. 1002)

Little is prior art under (pre-AIA) 35 U.S.C. § 102(b) based on its 1979 publication date. Little describes a method for using fluorescent-dye angiography to assess blood flow intraoperatively, during an anastomosis (graft) of two cerebral arteries. (Little, Ex. 1002, 561-62.) In particular, Little describes administering the dye (sodium fluorescein) to the patient; exciting the dye ( with a strobe light to induce fluorescence); capturing multiple images of the resultant fluorescence in a manner that permits

observation of the changing interface between the fluorescing and non-fluorescing portions of the vasculature (i.e., the dye wavefront; *id.* Figs. 1-3) as the dye flows through the vasculature; and evaluating the efficacy (in particular the patency) of the graft on the basis of the angiograms. (*Id.* at 562.)

Little further discloses that where the angiogram shows an occlusion in the graft, further surgical intervention may be carried out to improve blood flow, and offers clinical examples of such modifications to the graft. (*Id.* at 562.)

Little is relied on for Ground 1 (anticipation of Claims 1 and 2) and for Grounds 2, 3, and 4 (obviousness of Claims 1, 2 and 3).

### B. FLOWER I (EX. 1003)

Flower I describes a variety of methods for using fluorescent dyes in the treatment and observation of animal (including human) vasculature, and in particular vascular abnormalities. (Flower, I, Ex. 1003, 2:27-30; 10:8-19) The methods include techniques for enhancing the clarity of the fluorescent angiograms and observing the direction of the blood flow through the vasculature. (*Id.* at 2:31-67.) Flower I discloses that the angiograms may be captured during surgery. (*Id.* at 9:23-26.)

Flower I recommends the use of the "readily available" dye ICG, which Flower I discloses as having its peak absorption and emission spectra in the range of 800-850 nm. (*Id.* at 5:41-55.) Flower I also describes the use of a CCD video camera to aid the visualization. (*Id.* at 1:42-47, 10:3-7.) Flower I observes that the disclosed methods permit observation of the wavefront of the dye as it transits through the blood vessels. (*Id.* at 4:36-46.)

This petition cites Flower I for Grounds 2, 3, and 4 (obviousness as to Claims 1, 2 and 3). Flower I is prior art under (pre-AIA) 35 U.S.C. § 102(e).[1]

### C. FLOWER II (EX. 1005)

Flower II describes a method for generating ICG angiograms to show blood flow through aberrant blood vessels such as choroidal neovascularization in the eye. (Flower II, Ex. 1005 at 3:56-62.)

Flower II recognizes the "obvious[ ]" utility of tracking a sharply-defined wavefront through the vascular network. (*Id.* at 2:40-42.) Flower II

[1] To the extent that the patent owner argues Flower I can be removed as prior art through this will be disputed. Further, Flower II, prior art under 35 U.S.C. § 102(b) has the same pertinent disclosure, i.e., the use of ICG dye, illumination with a laser with 805 nm range (*see* light source 44 at Flower II, Ex. 1005, 9:12), use a CCD camera 36 that captures at up to 29 frames a second (claim 5) and visualization of aberrant vascular structures (Abstract).

also discloses taking a sequence of angiograms "at high speeds (15-30 images/second)." (*Id.* at 4:64-65.)

This petition cites Flower II for Grounds 2, 3, and 4 (obviousness as to Claims 1, 2 and 3). Flower II is prior art under (pre-AIA) 35 U.S.C. § 102(b).

**D. JIBU (EX. 1004)**

Jibu describes a method of administering fluorescent dye into a living body that is illuminated to cause it to fluoresce. (Jibu, Ex. 1004, 3). Jibu discloses the use of the dye during surgery. (*Id.* at 15.)

Jibu describes detection of the fluorescence with a CCD camera (C24000-75i, manufactured by Hamamatsu Photonics K.K.) outfitted with an image processing device (Argus 20, manufactured by Hamamatsu Photonics K.K.) (Jibu, Ex. 1004, 13-14), a combination whose frame rate exceeds 15 images per second. (Ex. 1006; *see also* Ex. 1010, 5-6.)

Jibu discloses ICG, a dye that fluoresces at a wavelength of at least 700nm, but that is preferably 800 nm or higher, and describes one such dye (ICG) that fluoresces at 835 nm. (Jibu, Ex. 1004, 7-8, 13.)

This petition cites Jibu for Ground 4 (obviousness as to Claims 1, 2 and 3). Jibu, published December 2, 1997, is prior art under (pre-AIA) 35 U.S.C. § 102(b).

Jibu was the main reference used in the successful oppositions to parallel device claims in Japan and Europe. (Exs. 1009 and 1010).

The Japanese patent office observed that Jibu "illustrates a flow of blood as the flow of an in vivo liquid medium in which the tracer moves, as well as describes angiography using the ICG single entity as the prior art . . . ." (Ex. 1010, 4.) Therefore, the office concluded, "the person skilled in the art can easily conceive . . . the well-known ICG . . . as the tracer so that the movement of the fluorescent dye being carried in the blood flow in the coronary artery bypass graft may be observed. (*Id.* at 5.)

The Japanese patent office also concluded that camera, together with the image-processing device, disclosed in Jibu obtains the requisite brightness "at the image acquisition rate of 15 images per second." (*Id.* at 6.) In short, the Japanese patent office stated, "the person skilled in the art could have easily conceived [the device patent] based on [Jibu] and [other] well-known technologies." (*Id.*)

The European Appeal Board likewise upheld the invalidation of the device patent on the basis of Jibu. Among other things, the European patent office stated that Jibu discloses that imaging "was performed in real time with an exposure time of one second . . . The imaging capabilities of [Jibu] is however not restricted to the particular use described in [Jibu]. Consequently, when the device of [Jibu] is used for a different purpose, such the presently claimed imaging of the fluorescent dye carried in the bloodstream of a cardiovascular graft, the skilled person . . . will be able to obtain an image revealing the passage, i.e., the 'movement', of the fluorescent dye through the cardiovascular graft 'during surgical procedure' and 'while the heart is beating.'" (Ex. 1009, 21-22.)

### E. GOLDSTEIN (EX. 1007)

Goldstein describes a method the use of intraoperative fluoroscopic angiography to assess a coronary artery bypass graft. (Goldstein, Ex. 1007, 1979.) Goldstein touts the benefits of the intraoperative angiogram, which provides real-time imaging and thus permits "surgical revision" and optimal surgical result. (*Id.* at 1979; *see also, e.g., id.* at 1980 ("[I]ntrapoerative coronary angiography using a portable fluoroscopic system documents the immediate results of MINCAB [minimally invasive coronary artery bypass grafting] . . . and provides timely data that could influence intraoperative

treatment and patient outcome").) Goldstein discloses the use of 30/frame per second fluoroscope. (*Id.* at 1979.)

Goldstein is directly pertinent prior art as one using a more complex (x-ray based) fluoroscope during open heart surgery would consider simpler equipment shown in Flower I, Flower II or Jibu. (Langer Decl. ¶ 33.) This is evidenced by Novadaq Technologies, Inc. the exclusive licensee of the patent owner's own submissions to the Food and Drug Administration, which cites fluoroscopy equipment as a predicate device. (Ex. 1012).

This petition cites Goldstein for Ground 3 (obviousness as to Claims 1, 2 and 3). Goldstein is prior art under (pre-AIA) 35 U.S.C. § 102(b).

## VIII. SPECIFIC GROUNDS FOR PETITION

### A. Ground 1: Claims 1 and 2 are anticipated by Little

The **Vessel Graft Preamble** of Claim 1 recites "[a] method for assessing blood flow moving through a vessel graft anastomosed in fluid communication with an interconnected group of blood vessels in an animal, the vessel graft and at least a portion of the blood vessels being exposed during a surgical procedure on the animal." Assuming the preamble provides a claim limitation, it is disclosed by Little. Little describes "[f]luorescein angiography [that] provided an immediate assessment of anastomotic patency and clearly displayed the distribution of blood entering the

epicerebral circulation through" an artery. (Little, Ex. 1002, 560). In other words, Little discloses using a dye-fluorescence angiography procedure to intraoperatively evaluate blood flow through a graft. (Langer Decl. ¶ 35.)

**Limitation (a), the Administering Step**, describes "administering a fluorescent dye to the animal such that the dye enters the vessel graft and the interconnected group of blood vessels." Little discloses this element. Recognizing that "[t]he technique of fluorescein angiography has been described in detail elsewhere," Little discloses the use of fluorescein angiography "performed before and after anastomosis" by way of sodium fluorescein dye being "injected rapidly into the ipsilateral [common carotid artery] through the indwelling catheter." (Little, Ex. 1002, 562.) Little thus discloses the administration of a fluorescent dye in a vessel graft. (Langer Decl. ¶ 37.)

**Element (b), the Illuminating Step**, describes "exciting the fluorescent dye within the vessel graft and said exposed portion of the interconnected group of blood vessels with a source of illumination, thus causing the dye to emit radiation." Little discloses this element as well, describing that "[i]illumination for photography was provided by a strobe light . . . [and] [b]arrier filters . . . were used to keep unwanted exciting radiation from reaching the film." (Little, Ex. 1002, 562.) In other words,

the strobe light excites the fluorescein dye, which fluoresces in response. (Langer Decl. ¶ 39.)

**Element (c), the Wavefront Capture Step**, describes "capturing the radiation emitted by the fluorescent dye with a camera capable of imaging a series of angiographic images within the vessel graft and said exposed portion of the interconnected group of blood vessels, the images including at least an image of a fluorescent wavefront corresponding to an interface between the flowing blood that first contains the fluorescent dye introduced, such image being captured by the camera as the fluorescent wavefront transitions through the exposed vessel graft and interconnected group of blood vessels."

Little discloses this element, describing the taking of "[r]apid, serial photographs of the cortex . . . with a motorized camera" that is fitted with a "data-back digital timer [that] automatically printed the time in one-hundredths of a second in the corner of each frame." (Little, Ex. 1002, 562). Little discloses an exemplary sequence of these images that shows the camera capturing the wavefront as the dye as it is introduced and transitions through the graft and the connected vasculature. (Little, Ex. 1002, 562, Fig. 1.) The first image in the sequence was taken before the fluorescence wavefront; the second image is taken as blood with fluorescent dye entered

the vascular system under observation, thus demonstrating that the camera and system described can and did capture the fluorescent wavefront. (Langer Decl. ¶ 41.)

**Element (d), the Evaluation Step**, describes "evaluating the angiographic images to assess blood flow through the vessel graft relative to blood flow through the interconnected group of blood vessels." Little discloses this element as well. For example, in Figure 1, the image bearing the time stamp 01:13 shows the filling of the cortical receptor artery, the site of the vessel graft upstream of the anastomosis (Little, Ex. 1002, 563), while the image bearing the time stamp 03:01 shows the evaluation of the cortical branches. (*Id.*) The accompanying caption notes transition of blood with fluorescent dye to the artery downstream of the graft, thus demonstrating the evaluation of the graft. (*Id.* ("The cortical branches of the middle cerebral artery filled in an anterograde direction. The microcirculation supplied by the receptor artery also has filled.").[2]

[2] Similarly, Little's use of time recordation accurate to 1/100 of second demonstrates that the camera images were used to analyze blood flow; this level of accuracy permitted a comparison of vessel transit times before and after anastomosis. (*See id.* at 562 ("Studies performed before anastomosis showed delayed filling of the cortical branches of the MCA. The mean duration between injection of fluorescein into the ipsilateral CCA and its initial appearance in the epicerebral circulation was 2.4 + 0.4 seconds, compared with 0.7 + 0.3 seconds following anastomosis").

Little discloses the evaluation of the interconnected vessels in particular. The upper left image and the image time stamped 03:01 in Little Figure 1 (Little, Ex. 1002, 563), illustrate a comparison between the blood flow through the vessel graft area and the flow in the interconnected vessels. Little describes this comparison in the body text of the article as well. (Little, Ex. 1002, 564 ("Fluorescein angiography showed the distribution of blood supplied by the STA through the anastomosis. Of the 14 patients who underwent surgery for occlusive disease of the ICA, nine had filling of multiple MCA cortical branches (Fig. 1) and five had filling predominantly in the receptor artery territory (Fig. 2)".) (Langer Decl. ¶¶ 43-44.)

Little thus anticipates Claim 1. (Langer Decl. ¶ 45.)

Little also anticipates Dependent Claim 2, which adds the **Modifying Step**: "modifying said anastomosed vessel graft based on results of said evaluating step, thereby improving resultant blood flow through said vessel graft."

Little discloses the Modifying Step. In several of the surgical cases Little describes, the fluorescence angiogram revealed an occlusion of the graft, on the basis of which the clinicians made corrective surgical modifications. (Little, Ex. 1002, 562 ("Patency of the anastomosis was demonstrated in 13 patients. In one of these patients . . . , partial obstruction

of the STA was seen . . . . This was corrected by gentle manipulation . . . The anastomosis was found to be occluded in two patients. A thrombus was successfully removed and patency restored in one of these patients . . . . In the other [patient] . . ., patency was re-established . . .").) (Langer Decl. ¶ 47.)

Little thus anticipates Dependent Claim 2. (Langer Decl. ¶ 48.)

### B. Ground 2: Claims 1, 2 and 3 are obvious in view of Little, Flower I and Flower II

As discussed, in Part VII.A *supra*, Little anticipates Claims 1 and 2. Flower I and Flower II provide additional support for invalidating these claims. Flower's imaging technology using ICG dye was well known to persons skilled in the art. (Ex. 1011)

As discussed, Little anticipates the **Vessel Graft Preamble**. Little describes "[f]luorescein angiography [that] provided an immediate assessment of anastomotic patency and clearly displayed the distribution of blood entering the epicerebral circulation through" an artery. (Little, Ex. 1002, 560).

Little also anticipates the **Administering Step**, noting that "[t]he technique of fluorescein angiography has been described in detail

elsewhere," and going on to disclose the use of fluorescein angiography "performed before and after anastomosis" by way of sodium fluorescein being "injected rapidly into the ipsilateral [common carotid artery] through the indwelling catheter." (Little, Ex. 1002, 562.)

Also, as noted, Little anticipates the **Illuminating Step**, describing that "[i]llumination for photography was provided by a strobe light . . . [and] [b]arrier filters . . . were used to keep unwanted exciting radiation from reaching the film." (Little, Ex. 1002, 562.)

Little likewise anticipates the **Wavefront Capture Step** describing the taking of "[r]apid, serial photographs of the cortex . . . with a motorized camera" that is fitted with a "data-back digital timer [that] automatically printed the time in one-hundredths of a second in the corner of each frame." (Little, Ex. 1002, 562). Little discloses an exemplary sequence of these images demonstrating that the camera and system described can and did capture the fluorescent wavefront. (Little, Ex. 1002, 562 (Fig. 1.).)

To the extent Little does not fully anticipate the Wavefront Capture Step, it is obvious in light of the Flower references. Specifically, Flower I discloses the angiographic observation of the wavefront of the fluorescent dye as it transits through the blood vessels. (Flower I, Ex. 1003, 4:36-46.) Flower II similarly recognizes the "obvious[ ]" utility of angiographically

tracking a sharply-defined fluorescent-dye wavefront through a vascular network. (Flower II, Ex. 1005 at 2:40-42.) Flower II states that observation of the relevant vasculature "with fluorescent dye angiography is best accomplished when a very small volume dye bolus having a sharply defined wavefront passes through." (*Id.* at 2:28-29.) Thus, in view Flower I and Flower II a person having ordinary skill in the art would be motivated to angiographically capture the wavefront in tracking the flow of dye through a vascular graft.[3] (Langer Decl. ¶ 53.)

As to the **Evaluation Step**, this, too, is disclosed by Little. As noted, in Figure 1, the image bearing the time stamp 01:13 shows the filling of the cortical receptor artery, the site of the vessel graft upstream of the anastomosis (Little, Ex. 1002, 563), while the image bearing the time stamp 03:01 shows the evaluation of the cortical branches. (*Id.*) The accompanying caption notes transition of blood with fluorescent dye to the artery downstream of the graft, thus demonstrating the evaluation of the

[3] This is further confirmed by Eren, Ex. 1008, which describes the influx of fluorescent die through tissue and provides images (Eren, Ex. 1008, 1631 Fig. 3) showing a portion of the vasculature as die transitions through it, thus differentiating the blood containing the dye from that not containing the dye. (*See generally* Eren, Ex. 1008, 1640 (describing the influx of fluorescent die through tissue).) (Langer Decl. ¶ 54.)

graft. (*Id.* ("The cortical branches of the middle cerebral artery filled in an anterograde direction. The microcirculation supplied by the receptor artery also has filled.").[4] Little also discloses the evaluation of interconnected vessels. The upper left image and the image time stamped 03:01 in Little Figure 1 (Ex. 1002 at 563), illustrate a comparison between the blood flow through the vessel graft area and the flow in the interconnected vessels. Little describes this comparison in the body text of the article as well. (Little, Ex. 1002 at 564 ("Fluorescein angiography showed the distribution of blood supplied by the STA through the anastomosis. Of the 14 patients who underwent surgery for occlusive disease of the ICA, nine had filling of multiple MCA cortical branches (Fig. 1) and five had filling predominantly in the receptor artery territory (Fig. 2)".)

To the extent Little does not fully anticipate the Evaluation Step, it is obvious in light of the Flower references. Flower I describes methods for using fluorescent dyes to evaluate vascular abnormalities (Flower I, Ex.

---

[4] Similarly, Little's use of time recordation accurate to 1/100 of second demonstrates that the camera images were used to analyze blood flow; this level of accuracy permitted a comparison of vessel transit times before and after anastomosis. (*See* Ex. 1002 at 562 ("Studies performed before anastomosis showed delayed filling of the cortical branches of the MCA. The mean duration between injection of fluorescein into the ipsilateral CCA and its initial appearance in the epicerebral circulation was 2.4 + 0.4 seconds, compared with 0.7 + 0.3 seconds following anastomosis").

1003, 10:8-19) during surgery (*id.* at 9:23-26), including specifically in the heart (*id.* at 8:46-49). Flower II, too, describes a method for generating angiograms to show blood flow through certain blood vessels, including aberrant vessels (Flower II, Ex. 1005 at Abstract and 3:56-62), and through a vascular network. (*Id.* at 2:40-42.) Thus, in view Flower I and Flower II a person having ordinary skill in the art would understand that widely-known fluorescent dye evaluative techniques, could be used to track the flow of dye in a clinical situation such as that described in Little, namely during an arterial anastomosis.[5] (Langer Decl. ¶¶ 58-59.)

As to Dependent Claim 2, which adds the **Modifying Step**, this is anticipated by Little, as noted *supra*. In several of the cases Little describes, the fluorescence angiogram revealed an occlusion of the graft, which prompted the authors to make surgical modification. (Little, Ex. 1002, 562 ("[P]artial obstruction of the STA was seen . . . . This was corrected by gentle manipulation . . . The anastomosis was found to be occluded in two patients. A thrombus was successfully removed and patency restored in one of these patients . . . . In the other [patient] . . ., patency was re-established . . .").)

[5] Eren, Ex. 1008, 1640 similarly describes the use of fluorescent dye through vasculature.

Claim 3 adds two requirements to Claim 1: the 800-850 Wavelength Requirement and the 15 Image/Second Requirement. Each of these requirements is obvious in light of the Flower references.

The **800-850 Wavelength Requirement** is obvious. Flower I discloses the use of ICG for angiographic imaging, describing ICG as "[t]he preferred fluorescent dye . . . because it is readily available, has long been approved for administration to humans . . . and is suitable for both diagnosis and treatment procedures." (Flower I, Ex. 1003, 5:47-51.) Flower I discloses that ICG has peak absorption and emission in the range of 800-850 nm. (*Id.* at 5:41-55.)[6] Thus a person having ordinary skill in the art performing an intraoperative angiogram would be motivated to use ICG, the "preferred" and "readily available" dye, which meets the 800-850 Wavelength Requirement. (Langer Decl. ¶¶ 62-63.)

The **15 Image/Second Requirement** is also obvious. Flower I shows the use of a conventional CCD video camera to aid the visualization was a known design choice. (Flower I, Ex. 1003, 1:42-47, 10:3-7.) A video camera captures moving images, which conventionally is done at more than

[6] Flower II also discloses the use of ICG in angiography (Flower II, Ex. 1005 at 3:56-62), as does Eren, Ex. 1008, 1640, which discloses an emission range of ICG in serum of 805 to 835 nm.

15 images per second. Flower II discloses taking a sequence of angiograms "at high speeds (15-30 images/second)." (Flower II, Ex. 1005, 4:64-65.) These references thus make obvious the use of frame rates in excess of 15 frames per second.[7] (Langer Decl. ¶ 64.)

A person skilled in the art would be motivated to combine Little and Flower I or Flower II. The main motivation for combining Little with Flower I or Flower II would be to take advantage for the ICG fluorescence dye for imaging vessel grafts instead of Fluorescein as described in Little. The ICG dye is rapidly cleared from the blood stream by the liver allowing repeat imaging sequences[8]. (Langer Decl. ¶ 66.) Fluorescein, on the other hand is cleared much more slowly (12 to 18 hours). This is clinically

---

[7] Similarly Eren, Ex. 1008, 1638, describes the use of a Sanyo CCD camera and a Sony U-Matic video recorder in to perform ICG angiography. While the images in Eren were stored on the computer at a rate of 2fps, the CCD camera and the U-Matic capture device are capable of frame rates above 15fps. (See Sony U-Matic, Ex. 1015 (analog recording system available in PAL (25 frames per second) and NTSC (30 frames per second) versions). *See also* Hyvarinen, Ex. 1014, 528 (describing a camera used in fluorescence imaging operate at 20 frames per second and stating that this frame rate is "adequate to document the very rapid movement of blood through the vasculature"). (Langer Decl. ¶ 65.)

[8] *See also* Joseph, Ex. 1016, 272 ("ICG has several other advantages over fluorescein; namely, it binds strongly to blood proteins to provide a good marker of blood and is cleared more quickly from the bloodstream to allow for more rapid repeat measurements. Fluorescein is not cleared for 12 to 18 hours.").

important in cases where a graft problem was observed and quickly corrected by the surgeon. After correction, a repeat imaging sequence would be useful to verify that the corrected graft was functioning properly. ICG would allow this relatively quick repeat imaging sequence where Fluorescein would require much more time. ICG is strongly bound to blood proteins and is therefore confined to the blood stream. Fluorescein does not bind to blood proteins and therefore leaks out of the vasculature much more easily than ICG. Thus, to deny a motivation to combine would be incongruent with the facts. (Langer Decl. ¶ 67.)

Starting with Little, a person of skill in the art could easily utilize the electronic video camera of Flower I and II instead of the film camera. (Langer Decl. ¶ 68.) Little's work on imaging grafts was conducted in 1979. By 1999, nearly twenty years later, use of video equipment instead of film proliferated. (Flower I, Flower II, Jibu, Eren). Fluorescence imaging would be carried out by observing (and recording) images on a monitor using a CCD camera. (Langer Decl. ¶ 68.) The motivation for such a change would ease of use, recording and playback. (*Id.*) A video camera and recorder would avoid delays caused by waiting for film to develop and may also eliminate the need for mechanical timer as timing could be derived from frame position. (*Id.*) Additionally, multiple surgeons (e.g., residents,

colleagues, etc. would be able to observe the imaging and participate in clinical decision making). (*Id.*) Video cameras were commonly available prior to the priority date of the '190 patent as shown in Flower I, Flower II and Jibu. (*Id.*) The utility of having a video camera observing the surgical field and a design for such a system are well-described in Flower I and II. (*Id.*)

### C. Ground 3: Claims 1-3 are obvious in view of Flower I, Flower II and Little or Goldstein

All claims are obvious in view of the Flower references and Little or Goldstein.

As for the **Vessel Graft Preamble**, Flower I discloses a method for:

> administering a liquid composition comprising a fluorescent die and a carrier into the animal to at least partially fill the blood vessels of the body cavity with the composition; applying energy of a type and in an amount sufficient to cause the die to fluoresce as the die flows through the blood vessels of the body; obtaining at least one angiographic image of the fluorescing die as the die flows through the blood vessels of the body cavity; and analyzing the angiographic image obtained in the prior step to determine whether a tumor is present in or adjacent to the wall of the body cavity. Related methods for diagnosing other types of lesions, e.g., ruptured blood vessels, abnormal vasculature, are also provided.

Flower I, Ex. 1003, 3:4-17.

While Flower I is not specifically addressed to vessel grafts, it discusses visualizing blood flow through vessels and diagnosing ruptured

blood vessels and abnormal vasculature. (*See also* Flower II, Abstract). A person having ordinary skill in the art could reasonably conclude that this method would be applicable to evaluating blood flow through a vessel graft, in light of Little, which describes the use of intraoperative fluorescent-dye angiography to assess a graft (Little, Ex. 1002, 560 ("Fluorescein angiography provided an immediate assessment of anastomotic patency and clearly displayed the distribution of blood entering the epicerebral circulation through the STA")) and Goldstein, which describes the use of intraoperative angiography to assess a coronary artery bypass graft (Goldstein, Ex. 1007, 1979).) (Langer Decl. ¶ 70.)

The **Administering Step** is also disclosed in Flower I. (Flower I, Ex. 1003, 10:38-41 ("administering a plurality of boluses of about 0.1 ml to about 1.0 ml of a liquid composition at spaced time intervals into the animal, wherein the liquid composition comprises a fluorescent die and a carrier").) While the Administering Step does not describe administering by way of a plurality of boluses, it does not foreclose administration in this manner. (*See also* Flower II, Ex. 1005, 9:39-43.) (Langer Decl. ¶ 71.)

The **Illuminating Step** is also disclosed in Flower I. (Flower I, Ex. 1003, 10:42-45 ("endoscopically applying energy of a type and in an amount sufficient to cause the die in each bolus to fluoresce as the die flows through

the blood vessels located within the preselected area"). (See also Flower II, Ex. 1005, 10:13-16). The Illuminating Step is not limited to a non-endoscopic illumination and thus does not foreclose an endoscopic illumination. Moreover, Little discloses an extracorporeal illumination (Little, Ex. 1002 (describing illumination by strobe light).) (Langer Decl. ¶ 72.)

The **Wavefront Capture Step** is also disclosed in Flower I. (Flower I, Ex. 1003, 10:46-50 ("obtaining a plurality of angiographic images of the fluorescing die in each bolus using a video camera as the die enters the blood vessels located within the preselected area and continues to flow through the blood vessels"). Flower I moreover discusses observing the wavefront of the dye. (Flower I, Ex. 1003, 4:36-46.) Flower II similarly recognizes the "obvious[ ]" utility of angiographically tracking a sharply-defined fluorescent-dye wavefront through a vascular network. (Flower II, Ex. 1005 at 2:40-42.) (Langer Decl. ¶ 73.)

As to the **Evaluation Step**, Flower I describes methods for using fluorescent dyes to evaluate "abnormalit[ies] associated with blood vessels" (Flower I, Ex. 1003, 10:8-19) during surgery (*id.*, 9:23-26), including specifically in the heart (*id.*, 8:46-49). Flower II similarly describes a method for generating angiograms to show blood flow through certain blood

vessels (Flower II, Ex. 1005 at 3:56-62) and through a vascular network. (*Id.*, at 2:40-42.) The Flower references thus provide a general teaching for using fluorescence imaging to evaluate blood flow through vessels and diagnosing abnormal vasculature. (Langer Decl. ¶ 74.)

Little and Goldstein in turn each explain evaluation of the blood flow through the vessel graft relative to interconnected vessels. (*See* Little, Ex. 1002, 563 Fig. 1 illustrating the filling of the cortical receptor artery, the vessel graft upstream of the anastomosis, and evaluation of the cortical branches; "The cortical branches of the middle cerebral artery filled in an anterograde direction. The microcirculation supplied by the receptor artery also has filled."; Goldstein, Ex. 1007, 1980 Figs. 1-3 (illustrating evaluation of blood flow through graft).) Application of the evaluative techniques described in the Flower references to the clinical settings in Little and Goldstein is obvious. (Langer Decl. ¶ 75.)

As to Dependent Claim 2, which adds the **Modifying Step**, this is anticipated by Little and Goldstein each teach making intraoperative modifications.

As noted, in several of the cases Little describes, the fluorescence angiogram revealed an occlusion of the graft, which prompted the authors to make surgical modification. (Little, Ex. 1002, 562 ("[P]artial obstruction of

the STA was seen . . . . This was corrected by gentle manipulation . . . The anastomosis was found to be occluded in two patients. A thrombus was successfully removed and patency restored in one of these patients . . . . In the other [patient] . . ., patency was re-established . . .").) Goldstein is the same. (Goldstein, Ex. 1007, 1979 (describing "surgical revision"). *Id.*, 1980 ("[I]ntrapoerative coronary angiography using a portable fluoroscopic system documents the immediate results of MINCAB [minimally invasive coronary artery bypass grafting] . . . and provides timely data that could influence intraoperative treatment and patient outcome").) (Langer Decl. ¶ 77.)

As to Claim 3, there are only two additional requirements: the 800-850 Wavelength Requirement and the 15 Image/Second Requirement. As already noted, each of these requirements is obvious in light of the Flower references.

The **800-850 Wavelength Requirement** is obvious. Flower I discloses the use of ICG for angiographic imaging, describing ICG as "[t]he preferred fluorescent dye . . . because it is readily available, has long been approved for administration to humans . . . and is suitable for both diagnosis and treatment procedures." (Flower I, Ex. 1003, 5:47-51.) Flower I discloses that ICG has peak absorption and emission in the range of 800-850

nm. (*Id.* at 5:41-55.)[9] Thus a person having ordinary skill in the art performing an intraoperative angiogram would be motivated to use ICG, the "preferred" and "readily available" dye, which meets the 800-850 Wavelength Requirement. (*See also* Flower II, Ex. 1005, 1:63-2:9.) (Langer Decl. ¶ 79.)

The **15 Image/Second Requirement** is also obvious. Flower I describes the use of a CCD video camera to aid the visualization. (Flower I, Ex. 1003, 1:42-47, 10:3-7.) Flower II discloses taking a sequence of angiograms "at high speeds (15-30 images/second)." These references thus make obvious the use of frame rates in excess of 15 frames per second.[10] (Langer Decl. ¶ 80.)

---

[9] Flower II also discloses the use of ICG in angiography (Flower II, Ex. 1005 at 3:56-62), as does Eren, Ex. 1008, 1640, which discloses an emission range of ICG in serum of 805 to 835 nm.

[10] Similarly Eren, Ex. 1008, 1638, describes the use of a Sanyo CCD camera and a Sony U-Matic video recorder in to perform ICG angiography. While the images in Eren were stored on the computer at a rate of 2fps, the CCD camera and the U-Matic capture device are capable of frame rates above 15fps. (*See* Sony U-Matic, Ex. 1015 (analog recording system available in PAL (25 frames per second) and NTSC (30 frames per second) versions). *See also* Hyvarinen, Ex. 1014, 528 (describing a camera used in fluorescence imaging operate at 20 frames per second and stating that this frame rate is "adequate to document the very rapid movement of blood through the vasculature"). (Langer Decl. ¶ 81.)

There are explicit and implicit reasons to combine Flower I and Flower II with Little. (Langer Decl. ¶ 82.) As explained, Flower I and II are highly relevant to the inventors own developments relating to imaging vessel grafts. Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). Little is using similar process to assess patency of vessel grafts twenty years before Flower I. (Langer Decl. ¶ 82.) One knowing about the process and equipment of Flower I and II would be motivated to use in the experiments described in Little to simplify the imaging and enhance the recording and playback options. (*Id.*) Flower I and II both teach a process that can be used to look at abnormal vasculature (*e.g.*, Flower I at 3:14-17; Flower II at Abstract) which would motivate one to try such a process to look at grafts. Flower I and II both disclose they can be used for any type of medical procedure where one wants to look at blood flow. (*Id.*) (Langer Decl. ¶ 83.)

There is a clinical advantage in using the teachings in Flower I and II in evaluating blood flow through vessel grafts. (Langer Decl. ¶ 84.) Flower I and II use ICG instead of fluorescein. As described in Joseph (Ex. 1016) on page 272, "ICG has several other advantages over fluorescein; namely, it

binds strongly to blood proteins to provide a good marker of blood and is cleared more quickly from the bloodstream to allow for more rapid repeat measurements. Fluorescein is not cleared for 12 to 18 hours." The application of ICG-based methods from Flower I or II to evaluation of blood flow through vessel grafts described in Little would be evaluated by a person of skill in the art to yield predictable results. (Langer Decl. ¶ 84.)

As such, blood flow evaluation is described in Flower I and II as applied to non-modified vessels and extension to grafted vessels would be natural and predictable. (Langer Decl. ¶ 85.)

### D. Ground 4: Claims 1-3 are obvious in view of Jibu, Flower I and Little or Goldstein

Parallel device claims, including the 800-850 Wavelength Requirement and the 15 Images/Second Requirement, have been previously revoked in foreign patent offices based on Jibu. For example, the chart below shows a comparison of one claim canceled in the EPO Proceeding to the Challenged Claims of the '190 Patent:[11]

| | |
|---|---|
| A device for visualizing movement of a fluorescent dye carried in the bloodstream of a cardiovascular | Vessel Graft Preamble and Administering Step<br>[Note '190 Patent claims not limited to cardiovascular] |

[11] Missing from the claims in Europe are the Evaluation Step and the Modifying Step. However, the EPO Appeal Board found the Jibu device was perfectly suitable to image a cardiovascular graft of a beating heart during a surgical procedure (Ex. 1009 at 9-11).

| | |
|---|---|
| bypass graft during a surgical procedure, the device comprising | |
| a means capable of providing radiation suitable to excite the fluorescent dye; | Illuminating Step |
| a camera capable of capturing the radiation emitted from the fluorescent dye within the blood vessel as an angiographic image; and | Wavefront Capturing Step<br>Note: more details in limitation below. |
| wherein the camera captures images at the rate of at least 15 images per second; | 15 Images/Second Requirement |
| wherein the fluorescent dye is ICG and/or has a peak absorption and emission in the range 800 to 850 nm; | 800-850 Wavelength Requirement |
| wherein the camera is capable of obtaining multiple images of the cardiovascular bypass graft while the heart is beating;<br>and wherein the device is suitable to convert the images into a viewable image. | The Wavefront Capture Step |

In Japan, the Patent Office found that Jibu disclosed the 15 Images/Second Requirement. (Ex. 1010, 5-6.) In Europe, the challenged patent included the 800-850 Wavelength Requirement, in addition to the 15

Images/Second Requirement. Both requirements were rejected in light of Jibu. (Ex. 1009, 17, 19-20.)

More specifically, all claims are obvious as follows. As for the **Vessel Graft Preamble**,

The use of the Jibu device for imaging of a graft while a subject's heart is beating is obvious in view of Little and/or Goldstein. Jibu itself contemplates using the disclosed device to image living bodies. (Ex. 1004, 10.) Jibu discusses "real time imaging (e.g., during surgery)" and use for angiography of a variety of sites throughout the body. (Ex. 1004 at 15-16). (Langer Decl. ¶ 86.)

Little shows a Jibu-type imaging technique for reviewing grafts in the brain. (Little, Ex. 1002, 560.) Goldstein shows the use of different fluoroscopic x-ray equipment to image the heart before and after vessel grafts during surgery. (Goldstein, Ex. 1007, 1978.) Goldstein could would be motivated to use the simpler Jibu device. (Langer Decl. ¶ 87.)

In light of Jibu's explanation of the benefits of intraoperative fluorescence, a person having ordinary skill would be motivated to apply these technique in the graft surgery setting, such as described in Little or Goldstein, or in the observation of vascular abnormalities, such as described in Flower I. (Langer Decl. ¶ 88.)

As for the **Administering Step**, Jibu discloses "introducing the near-infrared fluorescent tracer . . . into a living body" (Jibu, Ex. 1004, 3), and superficially "in an in vivo medium (e.g., blood or spinal fluid). (*Id.* at 8.)

As for the **Illuminating Step**, Jibu discloses "illuminating the living body with excitation light." (*Id.* at 3.)

As for the **Wavefront Capture Step**, Jibu discloses "a fluorescence detector" and "a device that produces images by processing the obtained fluorescent light data." (*Id.* at 11.) Jibu also discloses the use of a "CCD camera . . . fitted with a TV lens" and states that the method allows for "real time imaging (e.g., during surgery)." (*Id.* at 15.) Jibu's disclosure of the capture technique, in view of Flower I's recommendation to observe the wavefront (Flower I, Ex. 1003, 4:36-46) or Little's disclosure of wavefront imagining during graft surgery (Little, Ex. 1002, 562), demonstrate that the Wavefront Capture Step is obvious. (Langer Decl. ¶ 91.)

As for the **Evaluation Step**, Jibu discloses that the use of fluorescent dye for evaluation during surgery. (Jibu, Ex. 1004, 10 ("Since such measurements can be made in real-time using small-scale imaging devices, the imaging method can be used during surgical resection of tumors."); *id.* at 15 ("because of convenience and inexpensiveness, the application in the real

time imaging (e.g., during surgery) will also be possible.).) In light of Little (Ex. 1002 at 563-64) which discloses the utility of making such evaluative techniques during graft surgery, Jibu's techniques, applied in the graft-surgery setting are obvious. (Langer Decl. ¶ 92.)

As for Dependent Claim 2's **Modifying Step**, as noted, Jibu discloses the use of its method during surgery. (Jibu, Ex. 1004, 10, 15.) In view of Little's description of using real-time fluorescent imaging to modify a surgical result (Little, Ex. 1002, 562), the modifying step is obvious. (Langer Decl. ¶ 93.)

As for Claim 3's **800-850 Wavelength Requirement**, Jibu discloses that "the near-infrared band should be at least 700 but it preferably 800 nm or higher with no upper limit." (Jibu, Ex. 1004, 7-8.)

As for Claim 3's **15 Image/Second Requirement**, Jibu describes detection of the fluorescence with a CCD camera (C24000-75i, manufactured by Hamamatsu Photonics K.K.) outfitted with an image processing device (Argus 20, manufactured by Hamamatsu Photonics K.K.) (Jibu, Ex. 1004, 13-14), a combination whose frame rate exceeds 15 images per second. (Ex. 1006), as both the Japanese and European patent offices concluded. (Ex. 1010, 5-6; Ex. 1009, 19-20.) (Langer Decl. ¶ 95.)

As with the Flower I and II, a person of skill in the art would be

motivated to use the equipment of Jibu to assess graft patency during surgery as shown in Little and/or Goldstein. (Langer Decl. ¶ 96.) Jibu itself suggest use of the equipment "because of convenience and inexpensiveness … during surgery…." (Ex. 1004 at 16). Further, the advantages of video image capture over film capture would motivate one to use Jibu, showing 1997 technology, to conduct the experiments shown in Little or Goldstein, which were published in 1979. (Langer Decl. ¶ 96.)

## IX. CONCLUSION

The cited prior art references cited identified in this petition contain pertinent technological teachings, either explicitly or inherently disclosed, which were not previously considered in the manner presented herein, or relied upon during original examination of the '190 patent.

In sum, these references provide new, non-cumulative technological teachings which indicate a reasonable likelihood of success as to Petitioner's assertion that Claims 1-3 of the '190 patent are not patentable pursuant to the grounds presented in this Petition. Accordingly Petitioner respectfully

requests institution of an IPR for those claims of the '190 patent for each of grounds presented herein.

Dated: May 11, 2017
New York, New York

Respectfully submitted,

Visionsense Corp.

By: /Joseph M. Casino/
Joseph M. Casino
Registration No. 57224
Wiggin and Dana LLP
Customer Number: 27267
Tel: (212) 551-2842
Fax: (212) 498-0536

## CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), I certify that this petition complies with the type-volume limits of 37 C.F.R. § 42.24(a)(1)(i) because it contains 10,637 words, according to the word-processing system used to prepare this petition.

Dated: May 11, 2017
New York, New York

By: /Joseph M. Casino/
Joseph M. Casino
Registration No. 57224
Wiggin and Dana LLP
Customer Number: 27267
Tel: (212) 551-2842
Fax: (212) 498-0536

## CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. Sections 42.6 and 42.105, that a complete copy of the attached **PETITION FOR INTER PARTES REVIEW OF U.S. Patent No. 8,892,190**, including all exhibits (Nos. 1001-1016), the Declaration of David J. Langer, M.D., dated March 21, 2017, and all related documents, are being served on the 11th day of May, 2017, the same day as the filing of the above-identified document in the United States Patent and Trademark Office/Patent Trial and Appeal Board, via Federal Express upon the Patent Owner by serving the correspondence address of record with the USPTO as follows:

Novadaq Technologies Inc.
c/o Morrison & Foerster LLP
755 Page Mill Road
Palo Alto CA 94304-1018

Dated: May 11, 2017
New York, New York

By: /Joseph M. Casino/
Joseph M. Casino
Registration No. 57224
Wiggin and Dana LLP
Customer Number: 27267
Tel: (212) 551-2842
Fax: (212) 498-0536

26236\2\3681718.v1