IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TISSUE TRANSPLANT TECHNOLOGY LTD. &
HUMAN BIOLOGICS OF TEXAS, LTD.
Petitioners
v.
MIMEDX GROUP, INC.
Patent Owner

U.S. Patent No. 8,597,687 to Daniel
Issue Date: December 3, 2013
Title: METHODS FOR DETERMINING THE ORIENTATION OF A TISSUE GRAFT

Inter Partes Review No. _____

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,597,687 UNDER 35 U.S.C. §§ 311–319 and 37 C.F.R. §§ 42.100 *ET SEQ.*

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EXHIBITS

EXHIBIT	NAME	ABBREVIATION
BBA1001	U.S. Pat. No. 8,597,687, issued December 3, 2013	'687 Patent
BBA1002	Declaration of Daniel L. Mooradian, Ph.D.	Mooradian Declaration
BBA1003	Selected Excerpts of the Prosecution History of the '687 Patent	'687 Patent Prosecution History Excerpts
BBA1004	U.S. Pat. Publ. No. 2001/0056303, published Dec. 27, 2001	Caneiro
BBA1005	WEBSTER'S ENCYCLOPEDIC UNABRIDGED DICTIONARY OF THE ENGLISH LANGUAGE 129 (1996).	Definition of Asymmetric.
BBA1006	WEBSTER'S ENCYCLOPEDIC UNABRIDGED DICTIONARY OF THE ENGLISH LANGUAGE 1926 (1996).	Definition of Symmetry.
BBA1007	Thesaurus.com, Label, http://www.thesaurus.com/browse/label (last visited November 21, 2014).	Synonyms of Label.
BBA1008	WEBSTER'S ENCYCLOPEDIC UNABRIDGED DICTIONARY OF THE ENGLISH LANGUAGE 121 (1996).	Definition of Ascertain.
BBA1009	WEBSTER'S ENCYCLOPEDIC UNABRIDGED DICTIONARY OF THE ENGLISH LANGUAGE 636 (1996).	Definition of Emboss.
BBA1010	WEBSTER'S ENCYCLOPEDIC UNABRIDGED DICTIONARY OF THE ENGLISH LANGUAGE 1964 (1996).	Definition of Texture.

BBA1011	WEBSTER'S ENCYCLOPEDIC UNABRIDGED DICTIONARY OF THE ENGLISH LANGUAGE 1238 (1996).	Definition of Mold.
BBA1012	Thesaurus.com, Design, http://www.thesaurus.com/browse/design (last visited November 21, 2014).	Synonyms of Design.
BBA1013	U.S. Pat. No. 6,581,993, issued June 24, 2003	Nigam
BBA1014	H. S. Dua et al., Amniotic Membrane Transplantation, 83 BR. J. OPTHALMOLOGY 748 (1999)	Dua
BBA1015	U.S. Pat. Publ. No. 2004/0048796, published Mar. 11, 2004	Hariri

I. INTRODUCTION

Tissue Transplant Technology Ltd. (d/b/a Bone Bank Allografts) & Human Biologics of Texas, Ltd. (collectively "Petitioners") petition for *Inter Partes* Review ("IPR"), seeking cancellation of claims 1 - 7 of U.S. Patent No 8,597,687 ("'687 Patent") which is owned MiMedx Group, Inc. ("MiMedx").

All elements of claims 1 - 7 are obvious as explained below in the proposed grounds of unpatentability. The institution of an IPR requires a threshold showing of "a reasonable likelihood that the petitioner [will] prevail with respect to at least one of the claims challenged in the petition." 35 U.S.C. § 314(a). This Petition meets that threshold.

II. NOTICES AND DISCLOSURES

A. *Real Party-In-Interest*

Petitioners are the real parties-in-interest for this petition.

B. *Standing Certification*

Petitioners certify that the '687 Patent is available for IPR. Petitioners are not barred or estopped from requesting an IPR challenging the claims of the '687 Patent on the grounds identified in this petition. Furthermore, this petition is filed within one year of Petitioners being served the identified below patent infringement lawsuit.

C. ***Related Matters***

MiMedx, the Patent Owner, filed a lawsuit against the Petitioners asserting infringement of claims 1, 3, 4, 6, and 7 of the '687 Patent and claim 9 of U.S. Pat. No. 8,709,494 ('494 Patent). The lawsuit, Case No. 1:14-CV-719-HLH, was filed May 16, 2014 and is currently pending in the Western District of Texas, San Antonio Division. Petitioner previously filed an IPR against the '494 Patent.

D. ***Petitioners' Counsel***

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E. ***Service Information***

Please address all correspondence and service to the address of both counsel listed above. Petitioner consents to electronic service by email at robert.mcrae@gunn-lee.com and jason.mckinnie@gunn-lee.com.

F. ***Payment of Fees***

The required fee is paid via online credit card payment.

III. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art ("POSITA"), as of the priority date of the '687 Patent, is an M.D. or clinician that uses tissue implants in surgical

procedures or a person with a Ph.D. or Master's degree education with knowledge of surgical procedures, implantation technique and the requirements of a surgeon (user) who would use tissue implants. A POSITA as of the priority date of the '687 Patent would likely have an M.D. degree with surgical training and/or a Ph.D. (or at least Master of Science) degree in chemistry, biochemistry, biology, cell biology, or a medical science degree in pathology or medicine. *Declaration of Daniel L. Mooradian, Ph.D [BBA1002] at ¶ 15.* When used in this report, the term POSITA refers to the ordinary skill as of the priority date of the '687 patent.

IV. STATEMENT OF PRECISE RELIEF

A. *Overview of the '687 Patent*

1. The '687 Patent Discloses Labeling a Placental Tissue Graft to Distinguish a First Side from a Second Side

The claimed subject matter of the '687 Patent concerns the placement of an asymmetric label on a placental tissue graft. *BBA1001.* The asymmetric label permits a clinician to directly and visually distinguish between the stromal side and basement membrane side of the placental tissue graft. According to the claimed subject matter, the asymmetric label exists in multiple forms including an embossment or raised or indented texture. Further, the asymmetric label may be a logo, design, name, or text. In the claimed invention the label itself is asymmetric. *'687 Patent Prosecution History Excerpts [BBA1003] at 14.* It is not required that the label be asymmetrically placed on the placental tissue graft. *Id.*

Importantly, the claimed method does not dictate how the asymmetric label is placed on the tissue graft. While the specification discloses a drying fixture, the drying fixture is not a claimed element. As a result, the actual method of affixing the label is not relevant for the '687 Patent. *BBA1003 at 22.*

2. Priority Date of the '687 Patent

The '687 Patent was filed on August 7, 2012 as a continuation of U.S. Pat. App. Ser. No. 11/840,728, filed on Aug. 17, 2007, now U.S. Pat. No. 8,372,437, which claimed the benefit under 35 U.S.C. §119(e) of U.S. Provisional Pat. App. No. 60/838,467 filed Aug. 17, 2006. *BBA1003 at 50.* The above applications were expressly incorporated by reference in the '687 Patent. *Id.* The '687 Patent issued on December 3, 2013. *BBA1001.* MiMedx claims a priority date of Aug. 17, 2006.

3. File Wrapper Analysis of the '687 Patent

The originally filed independent claim of the '687 Patent was significantly narrowed before it was in condition for allowance. The originally filed independent claim did not have an element requiring the tissue graft to be of placental origin nor did it require the label itself be asymmetric. *BBA1003 at 51.* Additionally, the originally filed claim did not include the requirement of the user ascertaining the orientation by direct visual determination. *Id.*

The USPTO initially rejected all claims of the '687 Patent. *BBA1003 at 18.* Two claims, including the only independent claim, were rejected under § 102 based on Caneiro. *Id.* Caneiro teaches construction of a prosthetic sheet that is used in abdominal surgery. *Caneiro [BBA1004] at ¶ 1.* One side, or face, of the prosthesis contains a smooth surface and the other face contains a discontinuous textured surface. *Id. at ¶¶ 17-18, Fig. 2.* The discontinuous textured surface is affixed to the smooth surface through adhesive, molding, or heat sealing. *Id. at ¶ 18.* The Examiner construed the attachment of the discontinuous textured surface as reading on the originally filed independent claim. *BBA1003 at 21.* Specifically, the Examiner stated it corresponded to the claim language of "placing a label on a portion of at least one side of said tissue graft." *Id.*

The Examiner additionally rejected all the claims under § 103 in view of Bilbo. *BBA1003 at 22.* According to the Examiner, Bilbo, a patent publication, taught lamination of intestinal collagen layers (ICL) to form a tissue graft. *Id.* The tissues had a "sidedness quality" that was relevant in some applications. *Id.* The Examiner concluded "it would have been *prima facie* obvious to one having ordinary skill in the art to include a visual label, such as a written mark, tag, or colored feature on one side of said prosthesis in order to permit a surgeon at the point of use to directly identify the different faces having the distinct properties." *Id. at 23.*

MiMedx sought to overcome the rejections through the following amendment to the independent claim:

> 21. (Currently amended) A method for permitting direct, visual determination of the orientation of a placental tissue graft [[to]] by a user, wherein the placental tissue graft has a first side and a second side, said method comprising placing an asymmetric label on a portion of at least one side of said tissue graft, which label visibly distinguishes one side from the other side, thereby ~~defining~~ permitting direct, visual determination of the orientation for application of said tissue graft; and ascertaining the orientation of the placental tissue graft by direct visual determination.

BBA1003 at 10. Notably, MiMedx's amendment a) limits the tissue graft to placenta tissue, b) requires the label itself to be asymmetric, and c) requires the user be the one ascertaining the orientation of the graft by directly viewing the label. *Id.* MiMedx argued there was no teaching in Bilbo that the "sidedness" of the graft mattered, thus there is no reason to put a label on the tissue graft. *Id. at 13-14.* Furthermore, MiMedx states the sole reason a user is able to ascertain the proper orientation is "because the label is asymmetric." *Id. at 14.*

Ultimately the Examiner accepted the amendment and allowed the application to issue. In the stated reasons for allowance, the Examiner noted the "active step" of placing an asymmetric label on a placenta tissue graft was novel and non-obvious. *BBA1003 at 7.* The Examiner acknowledged that placenta tissue

inherently possessed a maternal side and a fetal side as disclosed by the prior art, but that the prior art failed to disclose any use of a placenta tissue graft that required a specific orientation. *Id.* The Examiner seemed to conclude that it would not be obvious to include a label on placental tissue graft if the prior art failed to teach a reason to distinguish the sides of the placenta tissue graft. *Id.*

B. ***Claims at Issue***

1. A method for permitting direct, visual determination of the orientation of a placental tissue graft by user, wherein the placental tissue graft has a first side and a second side, said method comprising: placing an asymmetric label on a portion of at least one side of said tissue graft, which label visibly distinguishes one side from the other side, thereby permitting direct, visual determination of the orientation for application of said tissue graft; and ascertaining the orientation of the placental tissue graft by direct visual determination.

2. The method of claim 1, wherein said label is an embossment.

3. The method of claim 1, wherein said label is a raised or indented texture.

4. The method of claim 1, wherein said label is a logo, a design, a name, or text.

5. The method of claim 1, wherein said tissue graft contains multiple tissue layers.

6. The method of claim 1, wherein said label visibly distinguishes a basement side of the placental tissue graft.

7. The method of claim 1, wherein said label visibly distinguishes a stromal side of the placental tissue graft.

C. ***Construction of Relevant Claim Terms***

There are several terms/phrases of the '687 Patent that should be construed. "A claim in an unexpired patent shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R.§ 42.100(b). A claim term must be given its "ordinary and customary meaning [as it] . . . would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005); *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2006); *accord* M.P.E.P. § 2111.01(I). All claim terms not specifically addressed below have been accorded their broadest reasonable interpretation in light of the patent specification and its plain and ordinary meaning to a POSITA.

1. "user"

A POSITA would define "user" as "a surgeon or clinician who uses the tissue grafts in medical applications or surgical procedures." *BBA1001 at 2:10-14, 8:25-29; BBA1003 at 14; BBA1002 at ¶ 22.*

2. "asymmetric"

A POSITA would define "asymmetric" as "lacking any mirror image symmetry." *BBA1001 at 8:25-29; BBA1003 at 14; Definition of Asymmetric [BBA1005]; Definition of Symmetry [BBA1006]; BBA1002 at ¶ 23.*

3. "label"

A POSITA would define "label" as "an identifying mark." *BBA1001 at 2:33-36, Fig. 5; Synonyms of Label [BBA1007]; BBA1002 at ¶ 24.*

4. "placing an asymmetric label on a portion"

A POSITA would define "placing an asymmetric label on a portion" as "placing and identifying mark which lacks any mirror image symmetry on a middle portion." *BBA1001 at 2:62-67, 8:25-29; BBA1002 at ¶ 25.*

5. "for application"

A POSITA would define "for application" as "for use by a surgeon or clinician who uses the tissue graft in medical applications or surgical procedures." *BBA1001 at 2:10-14; BBA1002 at ¶ 26.*

6. "ascertaining the orientation"

A POSITA would define "ascertaining the orientation" as "distinguishing said first side from said second side by a surgeon or clinician who uses the tissue graft in medical applications or surgical procedures." *BBA1001 at 2:27-33; Definition of Ascertain [BBA1008]; BBA1002 at ¶ 27.*

7. "embossment"

A POSITA would define "embossment" as "a label raised in relief from a surface." *BBA1001 at 2:27-30; Definition of Emboss [BBA1009]; BBA1002 at ¶ 28.*

8. "raised or indentured texture"

A POSITA would define "raised or indentured texture" as "molded tissue." *BBA1001 at 8:15-25; Definition of Texture [BBA1010]; Definition of Mold [BBA1011]; BBA1002 at ¶ 29.*

9. "design"

A POSITA would define "design" as "a raised decorative or artistic depiction." *BBA1001 at 2:62-67; Synonyms of Design [BBA1012]; BBA1002 at ¶ 30.*

10. "basement side"

A POSITA would understand the reference to the "basement side" in claim 6 as referring to the epithelial or fetal side of the placental tissue graft. *BBA1001 at 1:39-41, 6:59-60; BBA1002 at ¶ 31.*

11. "stromal side"

A POSITA would understand the reference to the "stromal side" in claim 7 as referring to the mesenchymal or maternal side of the placenta tissue graft. *BBA1001 at 6:57-59; BBA1002 at ¶ 32.*

D. ***State of the Art on or Before August 17th, 2005.***

A POSITA would have understood that tissue grafts from placental tissues are naturally asymmetric having one surface that is interchangeably termed the fetal, epithelial or basement side and another surface that is interchangeably called the mesenchymal or stromal side. *BBA1002 at ¶ 16.*

A POSITA would also have known that the orientation of the sides of the placental tissue grafts with respect to the implantation site (e.g., the cornea) was important for purposes including ensuring proper graft adherence. *BBA1002 at ¶ 17.*

A POSITA would have known that users of these grafts would therefore have reason to distinguish the two sides of the tissue graft during a surgical procedure. *BBA1002 at ¶ 18.*

A POSITA would also have known that users of these grafts had developed a number of methods permitting one to distinguish the sides of placental tissue grafts and that those methods included. *BBA1002 at ¶ 19.*

A POSITA would have understood that in addition to labeling methods utilized by the surgeon at the time of surgery, methods incorporated into the manufacture of these grafts including the application of a nitrocellulose membrane to one side of the graft were possible. *BBA1002 at ¶ 20.*

A POSITA would understand the benefits of eliminating the need for the surgeon to distinguish between the sides of the graft based on an assessment of the grafts intrinsic asymmetry alone. *BBA1002 at ¶ 21.*

E. ***Nomenclature of the Industry***

The ’687 Patent and the references identified below utilize varying nomenclature that a POSITA would understand to mean the same or similar things. The subject matter of the ’687 Patent concerns placental tissue grafts. The specification of the ’687 Patent helps define the term placental tissue by stating “[h]uman placental membrane (e.g. amniotic membrane or tissue).” *BBA1001 at 1:25-26.* For purposes of the ’687 Patent and the references cited, a POSITA would understand that a tissue graft constructed of amniotic membrane is a placental tissue graft as utilized in the ’687 Patent. *BBA1002 at ¶ 33.*

Furthermore, the placental tissue, including the amniotic membrane, has a side that faces the fetus and a side that faces the mother. *BBA1002 at ¶ 34.* These sides, especially for amniotic membrane, have a variety of names that refer to the same side. *Id.* In the ’687 Patent, claims 6 and 7 disclose a basement side and a stromal side. The basement side is also referred to as the epithelial side and/or fetal side. *Id.* The stromal side is also referred to as the mesenchymal side and/or maternal side. *Id.* The following chart identifies the term used in the ’687 Patent

and the corresponding term, as it would be understood by a POSITA, for the cited references:

'687 Patent Claim Term	Dua	Hariri
Claim 6 - Basement side	Epithelial side	Fetal side
Claim 7 - Stromal side	Mesenchymal side	Maternal side

F. ***Petitioner Seeks Cancellation of all Claims of the '687 Patent***

Petitioners requests an *Inter Partes* Review and cancellation of claims 1-7 of the '687 Patent. The chart below identifies the basis for cancellation of claims 1-7. Petitioners' full statement of the reasons for the relief requested is set forth in detail in § V.

Ground	Statutory Basis	Reference(s)	'687 Patent Claims
1	103(a)	Nigam	1-4, 6, 7
2	103(a)	Dua	1, 3, 4, 6, 7
3	103(a)	Nigam in view of Dua	1-4, 6, 7
4	103(a)	Nigam in view of Hariri	1-7
5	103(a)	Dua in view of Hariri	1-7

V. GROUNDS FOR UNPATENTABILITY

A. ***Standard for Obviousness***

A patent is invalid as obvious when "the differences between the claimed invention and the prior art are such that the claimed invention as a whole would

have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a); *see KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

An invention is obvious under *KSR* if the improvement claims no more than "the predictable use of prior art elements according to their established functions." *Id.* at 417; MPEP § 2141. "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious[,]" unless such use would require skill beyond that of a person of ordinary skill in the art. *KSR* at 417. Simply put, if a person of ordinary skill in the art implements a predictable variation of the prior art, that variation is obvious. *Id.*

Rejecting the need for an explicitly stated motivation to combine prior art elements, the Supreme Court in *KSR* held that in determining whether there was an apparent reason to combine, the court should look to a variety of factors, including but not limited to (1) the teachings of the prior art patents, (2) the effects of marketplace demand, and (3) the background knowledge of a person of ordinary skill in the art. *Id.* at 418. The court's analysis should not rely solely upon explicit teachings of the claimed subject matter, but also the inferences that a person of ordinary skill in the art might exercise. *Id.*

B. *Ground 1. Claims 1-4, 6, and 7 are Obvious Under 35 U.S.C. § 103(a) over Nigam*

Nigam is a U.S. Patent concerning an implant packaging and handling system. *Nigam [BBA1013].* The patent, issued on June 24, 2003, is more than one year prior to the August 17, 2006 effective filing date of the '687 Patent. Accordingly, Nigam is prior art under § 103(a). Nigam was not identified in the Information Disclosure Statement for the '687 Patent. *BBA1003 at 17, 27-32.*

Nigam teaches a system for placing a lens implant on the surface of a person's cornea. The lens implant may be made of "various types of hydrogels, but can include other polymers, **tissue implants**, or the like." *BBA1013 at 1:37-39 (emphasis added).* Nigam teaches the placement of "special asymmetric markings" "[t]o ensure that the implant is properly oriented." *Id. at 12:6-8.* The user, or the clinician, utilizes the asymmetrical markings to determine which side should face the cornea for proper implantation. *Id. at 12:8-10.* Nigam further describes the type of asymmetry necessary to achieve the desired goal through the examples of placing letters such as the lowercase "a," "R," "P," and "C" on the posterior surface of the implant. *Id. at 12:15-23.* Nigam teaches that if the implant is not placed with the correct side up, the letter will read backwards indicating the orientation is not correct. *Id.* Nigam teaches that other asymmetric markings or designs may be utilized to achieve this goal. *Id. at 12:23-26.* Nigam teaches the

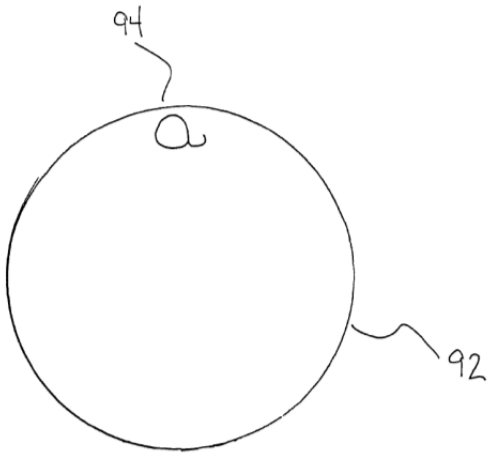
asymmetric markings may be made onto the implant through laser engraving or through printing with ink. *Id. at 12:27-28.*

It would be obvious to a POSITA to apply asymmetrical markings as taught by Nigam to a placental tissue graft. *BBA1002 at ¶ 41.* Nigam expressly teaches a lens implant may be constructed of "tissue." *BBA1013 at 1:37-39.* It is well known in the art that an ocular tissue implant may be, and commonly is, constructed or manufactured of placenta tissue. *BBA1002 at ¶ 41*; *see also Dua [BBA1014]; Hariri [BBA1015] at Abstract.* As such, it would be obvious to a POSITA to utilize the label to visibly distinguish the basement side of the placental tissue graft as well as the stromal side of the placental tissue graft. *BBA1002 at ¶ 17.*

Nigam expressly teaches the label may be engraved into the tissue or printed onto the tissue through use of ink. *BBA1013 at 12:27-28.* A POSITA would understand the teaching of laser engraving to mean manipulation of the tissue itself to create a contour or topography within the tissue. *BBA1002 at ¶ 42.* In contrast, printing a label with ink does not necessarily physically manipulate the tissue. A POSITA, in light of the laser engraving teachings of Nigam, would find it obvious to use a variety of equivalent tissue manipulation methods to impart a label onto the graft such as embossment and raised or indented texture. *Id.* Engraving, embossing, and raised or indented texture are known to achieve similar purposes

and result in a manipulated tissue having a label. M.P.E.P § 2144.06(II) (citing *Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980)).

The following chart identifies the specific disclosure of Nigam relating to the limitations of claims 1-4, 6, and 7 that render the claims obvious. *BBA1002 at ¶¶ 45-46.*

CLAIMS	NIGAM (BBA1013)
[Claim 1] A method for permitting direct, visual determination of the orientation of a placental tissue graft by user, wherein the placental tissue graft has a first side and a second side, said method comprising:	"To ensure that the implant is properly oriented, however, the implant is provided with special asymmetric markings, which the user views to make a determination that the implant is resting against the corneal surface in a proper orientation." *BBA1013 at 12:6-10.*
placing an asymmetric label on a portion of at least one side of said tissue graft,	 *BBA1013 at Fig. 20.*

	"Referring to FIGS. 18-20, there are shown three examplary embodiments of asymmetric markings 94 that can be utilized to properly orient the lens implant. As shown by FIGS. 18 and 19, the markings are preferably positioned in a clockwise orientation. In another embodiment, shown in FIG. 20, a letter can be placed on the posterior surface of the implant." *BBA1013 at 12:10-16.*
which label visibly distinguishes one side from the other side, thereby permitting direct, visual determination of the orientation for application of said tissue graft; and ascertaining the orientation of the placental tissue graft by direct visual determination.	"In this way, if the implant's posterior surface is placed onto the cornea surface, then the letter will not read properly. For instance, FIG. 20 shows the letter 'a' on the posterior surface of the implant 92. If the implant 92 is not positioned right side up on the cornea surface, then the letter will read backwards. In this embodiment, any letter can be used so long as it has an asymmetric design. For instance, 'R', 'P', 'C', etc." *BBA1013 at 12:16-23.* "the implant is provided with special asymmetric markings, which the user views to make a determination that the implant is resting against the corneal surface in a proper orientation." *BBA1013 at 12:6-10.*
[Claim 2] The method of claim 1, wherein said label is an embossment.	"the markings 94 can be positioned onto the lens using laser engraving" *BBA1013 at 12:27-28.*
[Claim 3] The method of claim 1, wherein said label is a raised or indented texture.	"the markings 94 can be positioned onto the lens using laser engraving" *BBA1013 at 12:27-28.*

[Claim 4] The method of claim 1, wherein said label is a logo, a design, a name, or text.	"In this embodiment, any letter can be used so long as it has an asymmetric design. For instance, 'R', 'P', 'C', etc." *BBA1013 at 12:21-23*
[Claim 6] The method of claim 1, wherein said label visibly distinguishes a basement side of the placental tissue graft.	"In this way, if the implant's posterior surface is placed onto the cornea surface, then the letter will not read properly. For instance, FIG. 20 shows the letter "a" on the posterior surface of the implant 92. If the implant 92 is not positioned right side up on the cornea surface, then the letter will read backwards." *BBA1013 at 12:16-21.*
[Claim 7] The method of claim 1, wherein said label visibly distinguishes a stromal side of the placental tissue graft.	"In this way, if the implant's posterior surface is placed onto the cornea surface, then the letter will not read properly. For instance, FIG. 20 shows the letter 'a' on the posterior surface of the implant 92. If the implant 92 is not positioned right side up on the cornea surface, then the letter will read backwards." *BBA1013 at 12:16-21.*

C. ***Ground 2. Claims 1, 3, 4, 6, and 7 are Obvious Under 35 U.S.C. § 103(a) over Dua***

Dua is a printed publication concerning the utilization of amnion tissue grafts in ophthalmology. *Dua [BBA1014].* The article, published in 1999 in the British Journal of Ophthalmology, is more than one year prior to the August 17, 2006 effective filing date of the '687 Patent. Accordingly, Dua is prior art under § 103(a). Dua was not identified in any of the Information Disclosure Statements submitted by the Applicant in the '687 Patent. *BBA1003 at 17, 27-32.*

Dua describes how amniotic membrane, acquired from placenta, is utilized in ophthalmology. Dua notes that amniotic membrane acts as a "transplanted basement membrane" which promotes epithelialisation of the cornea and states that in "some instances the amniotic membrane . . . acts as a 'bandage contact lens' allowing epithelialisation to occur under its cover." *BBA1014 at 748.* Dua expressly teaches that the amniotic membrane should be sutured to the surface of the eye with the "epithelial side up and the mesenchymal surface in contact with the eye, to facilitate adherence of the membrane to the ocular surface." *Id.* at 750.

Dua further describes several surgical methods that permit the user or clinician to distinguish between the two sides of the amniotic membrane prior to implantation onto the surface of the eye. *BBA1014 at 750-51.* One technique includes the use of applying a suture with a knot marking one side of the membrane. *Id.* A second technique uses a pen to mark one side of the membrane. *Id.* A third technique involves using blunt forceps to pinch each side of the amniotic membrane and lift. *Id.* at 751. The pinching results in "[a] fine strand of 'vitreous-like' substance . . . from the mesenchymal [side] but not the epithelial (basement membrane) side of the amniotic membrane." *Id.* A fourth technique occurs at the creation of the amniotic membrane as the membrane is mounted on nitrocellulose with a predetermined side facing up. *Id.* at 750.

As an initial matter, a POSITA would know that a placental tissue graft as claimed in the '687 Patent would encompass the amniotic tissue graft disclosed in Dua. *BBA1002 at ¶ 54.* Amnion is a component of the fetal membranes of placenta as disclosed by Dua and the '687 Patent. *BBA1013 at 748; BBA1001 at 1:25-26.* To the extent Applicant attempts to distinguish placenta from amnion, it would be obvious to a POSITA that the methods of Dua would naturally apply to a "placental" tissue graft. *Id.*

The claimed element of an asymmetric label would have been obvious to a POSITA based on Dua's four different techniques for labeling and distinguishing the sides of the tissue graft. All four techniques constitute labels that permit a user to distinguish one side from the other side as disclosed by the '687 Patent. *BBA1002 at ¶¶ 54-64.*

Although Dua does not expressly teach what type of mark would be made with the indelible pen, it would have been obvious to a POSITA to utilize an asymmetric mark. *BBA1002 at ¶ 56.* Considering the point of the mark is to distinguish one side from the other, utilizing the capital letter "A" or "O" would not make sense. *Id.* However, using an asymmetric letter such as "P" or "R" would make sense and permit the user to distinguish one side from the other. *Id.* Furthermore, it would be obvious to utilize a mark such as those identified in Figure 5 of the '687 Patent or to utilize a phrase, word, logo, design, or letter that is

readable when one side is facing up but backwards when the opposing side is facing up. *Id.*

Dua's teaching of a knot directly anticipates the claimed element of an asymmetric mark or, at a minimum, accomplishes the same result. Some forms of knots are asymmetric while others possess varying degrees of symmetry. *BBA1002 at ¶ 57.* Dua does not disclose what type of knot is utilized but given the teachings and the purpose behind the knot as taught by Dua, a POSITA would understand that an asymmetric knot may be utilized to accomplish the purpose disclosed by Dua. *Id.*

Furthermore, the use of a knot, the "fine strand of vitreous-like substance," and the mounting of nitrocellulose paper in a predetermined manner achieve the same desired result of an asymmetric label. *BBA1002 at ¶ 58.* A POSITA would understand that a knot and the "fine strand of vitreous-like substance" would extend from one side of the placenta tissue graft. *Id.* The three dimensional nature of that extension, or raised texture, would be readily seen by a user and would be sufficient to distinguish one side from the other side. *Id.* The absence of a knot or the "fine strand of vitreous-like substance" would similarly identify the opposing side. *Id.* Similarly, the placement of the nitrocellulose paper specifically identifies a designated side. The '687 Patent expressly contemplates the three dimensional nature of labels through disclosure of an embossment in claim 2 and raised or

indented texture in claim 3. It would be obvious to a POSITA to substitute the asymmetric label of the '687 Patent for a label having a three dimensional component, such as a knot, a "fine strand of vitreous-like substance," or affixing nitrocellulose paper. The methods of Dua are equivalents to the asymmetric label considering they are all capable of distinguishing the two sides of a placental tissue graft. *Id.;* M.P.E.P § 2144.06(II) (citing *Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980)).

Dua's teaching of a knot and/or mark is sufficient to satisfy the elements of claim 4. Claim 4 utilizes alternative limitations in stating the "label is a logo, a design, a name, or text." The use of alternative limitations in claims is permitted, but "[w]hen a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art." *Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001). A POSITA would have understood Dua's teaching of a knot and/or mark to be a design, logo, name, and/or text. *BBA1002 at ¶ 59.*

Finally, Dua's labeling of a side of the placental membrane tissue graft obviously teaches the identification of the epithelial (basement) side and the mesenchymal (stromal) side. *BBA1002 at ¶ 60.* A POSITA would understand Dua's reference to the epithelial side to correspond to the '687 Patent's reference

to the basement side in claim 6. *Id.* Similarly, a POSITA would understand Dua's reference to the mesenchymal side to correspond to the '687 Patent's reference to the stromal side in claim 7. *Id.*

It is important to note that the Examiner allowed the '687 Patent to issue, at least in part, on the basis that no prior art disclosed a necessity for orienting a placental tissue graft. *BBA1003 at 7.* Not only does Dua indicate a specific orientation is necessary, but Dua teaches a method to distinguish between the two sides.

The following chart identifies the specific disclosure of Dua relating to the limitations of claims 1, 3, 4, 6, and 7 that renders the claims obvious. *BBA1002 at ¶¶ 65-66.*

CLAIMS	DUA [BBA1014]
[Claim 1] A method for permitting direct, visual determination of the orientation of a placental tissue graft by user, wherein the placental tissue graft has a first side and a second side, said method comprising:	"The [**amniotic**] membrane is always sutured to the ocular surface with its **epithelial side up** and the **mesenchymal surface in contact with the eye** . . . [f]or this reason it is important **to be able to distinguish** its two surfaces . . . [m]ost surgeons have developed a technique that suit them best . . ." *BBA1014 at 750.*

placing an asymmetric label	"use a suture, with the **knot as the marker or indelible marker pen**" *BBA1014 at 750-51.*
on a portion of at least one side of said tissue graft,	"to mark one side of the membrane." *BBA1014 at 751.*
which label visibly distinguishes one side from the other side, thereby permitting direct, visual determination of the orientation for application of said tissue graft; and ascertaining the orientation of the placental tissue graft by direct visual determination.	"The membrane is always sutured to the ocular surface with its epithelial side up and the mesenchymal surface in contact with the eye . . . For this reason it is important to be able to distinguish its two surfaces . . . Most surgeons have developed a technique that suits them best . . . Others will use a suture, with the knot as the marker or indelible marker pen, to mark one side of the membrane." *BBA1014 at 750-51.*
[Claim 3] The method of claim 1, wherein said label is a raised or indented texture.	"it is important to be able to distinguish its two surfaces . . . Most surgeons have developed a technique that suits them best . . . After spreading the membrane on the ocular surface we apply the tips of a blunt fine forceps to one surface of membrane and pinch lightly with the forceps and lift. A fine strand of 'vitreous-like' substance can usually be drawn up from the mesenchymal but not

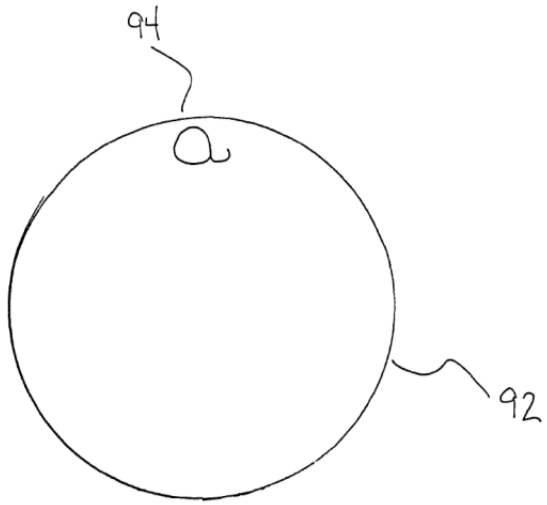
	the epithelial (basement membrane) side of the amniotic membrane." *BBA1014 at 750-51.*
[Claim 4] The method of claim 1, wherein said label is a logo, a design, a name, or text.	"use a suture, with the **knot** as the marker or indelible marker pen to mark one side of the membrane." *BBA1014 at 750-51.*
[Claim 6] The method of claim 1, wherein said label visibly distinguishes a basement side of the placental tissue graft.	"The membrane is always sutured to the ocular surface with its epithelial side up and the mesenchymal surface in contact with the eye . . . For this reason it is important to be able to distinguish its two surfaces . . . Most surgeons have developed a technique that suits them best—for example, mounting the membrane on nitrocellulose paper, the right way up, so that the correct side can be determined when the membrane is thawed. Others will use a suture, with the knot as the marker or indelible marker pen, to mark one side of the membrane." *BBA1014 at 750-51.*
[Claim 7] The method of claim 1, wherein said label visibly distinguishes a stromal side of the placental tissue graft.	"The membrane is always sutured to the ocular surface with its epithelial side up and the mesenchymal surface in contact with the eye . . . For this reason it is important to be able to distinguish its two surfaces . . . Most surgeons have developed a technique that suits them best—for example, mounting the membrane on nitrocellulose paper, the right way up, so that the correct side can be determined when the membrane is thawed. Others will use a suture, with the knot as the marker or indelible marker pen, to mark one side of the membrane." *BBA1014 at 750-51.*

D. *Ground 3. Claims 1-4, 6 & 7 are Obvious Under 35 U.S.C. § 103(a) over Nigam in view of Dua*

Grounds 1 and 2 are incorporated by reference. A POSITA would have combined the teachings of Nigam in view of Dua to render claims 1-4, 6 and 7 of the '687 Patent obvious. A POSITA would look to combining elements of Nigam and Dua because both concern the surface orientation of tissue grafts in ophthalmic uses and teach methods of distinguishing the two sides. *BBA1002 at ¶ 72.* Specifically, Dua teaches a placental-based graft constructed of amnion while Nigam is broader in application and covers "tissue implants."

It would be obvious to a POSITA to combine the asymmetric label as disclosed in Nigam to a placental tissue graft disclosed in Dua. *BBA1002 at ¶ 74.* Dua teaches the use of a mark to distinguish the epithelial side from the mesenchymal side and it would be obvious to combine the asymmetrical mark taught by Nigam. *Id.* Furthermore, in light of the laser engraving teachings of Nigam, and the three dimensional labels of Dua, a POSITA would find it obvious to use a variety of tissue manipulation methods to impart a label onto the graft including embossment and raised or indented texture. *Id.*

The following chart identifies the specific disclosure of Nigam and Dua relating to the limitations of claims 1-4, 6, and 7 that renders the claims obvious. *BBA1002 at ¶¶ 75-76.*

CLAIMS 1-4, 6, 7	DISCLOSURE
A method for permitting direct, visual determination of the orientation of a placental tissue graft by user, wherein the placental tissue graft has a first side and a second side, said method comprising:	**DUA**
	"The [**amniotic**] membrane is always sutured to the ocular surface with its **epithelial side up** and the **mesenchymal surface in contact with the eye** . . . [f]or this reason it is important **to be able to distinguish** its two surfaces . . . [m]ost surgeons have developed a technique that suit them best . . ." *BBA1014 at 750.*
	NIGAM
	"To ensure that the implant is properly oriented, however, the implant is provided with special asymmetric markings, which the user views to make a determination that the implant is resting against the corneal surface in a proper orientation." *BBA1013 at 12:6-10.*
placing an asymmetric label on a portion of at least one side of said tissue graft,	**DUA**
	"use a suture, with the **knot as the marker or indelible marker pen** to mark **one side** of the membrane." Dua at 751." *BBA1014 at 750-51.*
	NIGAM
	

	BBA1013 at Fig. 20. "Referring to FIGS. 18-20, there are shown three examplary embodiments of asymmetric markings 94 that can be utilized to properly orient the lens implant. As shown by FIGS. 18 and 19, the markings are preferably positioned in a clockwise orientation. In another embodiment, shown in FIG. 20, a letter can be placed on the posterior surface of the implant." *BBA1013 at 12:10-16.*
which label visibly distinguishes one side from the other side, thereby permitting direct, visual determination of the orientation for application of said tissue graft; and ascertaining the orientation of the placental tissue graft by direct visual determination.	**DUA**
	"The membrane is always sutured to the ocular surface with its epithelial side up and the mesenchymal surface in contact with the eye . . . For this reason it is important to be able to distinguish its two surfaces . . . Most surgeons have developed a technique that suits them best . . . Others will use a suture, with the knot as the marker or indelible marker pen, to mark one side of the membrane." *BBA1014 at 750-51.*
	NIGAM
	"In this way, if the implant's posterior surface is placed onto the cornea surface, then the letter will not read properly. For instance, FIG. 20 shows the letter 'a' on the posterior surface of the implant 92. If the implant 92 is not positioned right side up on the cornea surface, then the letter will read backwards. In this embodiment, any letter can be used so long as it has an asymmetric design. For instance, 'R', 'P', 'C', etc." *BBA1013 at 12:16-23.* "the implant is provided with special asymmetric markings, which the user views to make a determination that the implant is resting against the corneal surface in a proper orientation." *BBA1013 at 12:6-10.*
[Claim 2] The	**NIGAM**

method of claim 1, wherein said label is an embossment.	"the markings 94 can be positioned onto the lens using laser engraving" *BBA1013 at 12:27-28.*
[Claim 3] The method of claim 1, wherein said label is a raised or indented texture.	**DUA**
	"it is important to be able to distinguish its two surfaces . . . Most surgeons have developed a technique that suits them best . . . After spreading the membrane on the ocular surface we apply the tips of a blunt fine forceps to one surface of membrane and pinch lightly with the forceps and lift. A fine strand of 'vitreous-like' substance can usually be drawn up from the mesenchymal but not the epithelial (basement membrane) side of the amniotic membrane." *BBA1014 at 750-51.*
	NIGAM
	"the markings 94 can be positioned onto the lens using laser engraving" *BBA1013 at 12:27-28.*
[Claim 4] The method of claim 1, wherein said label is a logo, a design, a name, or text.	**DUA**
	"use a suture, with the **knot** as the marker or indelible marker pen to mark one side of the membrane." *BBA1014 at 750-51.*
	NIGAM
	"In this embodiment, any letter can be used so long as it has an asymmetric design. For instance, 'R', 'P', 'C', etc." *BBA1013 at 12:21-23.*
[Claim 6] The method of claim 1, wherein said label visibly distinguishes a basement side of the placental tissue	**DUA**
	"The membrane is always sutured to the ocular surface with its epithelial side up and the mesenchymal surface in contact with the eye . . . For this reason it is important to be able to distinguish its two surfaces . . . Most surgeons have developed a technique that suits them best . . . Others will use a suture, with the knot as the marker or indelible marker

graft.	pen, to mark one side of the membrane . . . A fine strand of "vitreous-like" substance can usually be drawn up from the mesenchymal but not the epithelial (basement membrane) side of the amniotic membrane." *BBA1014 at 750-51.*
	NIGAM
	"In this way, if the implant's posterior surface is placed onto the cornea surface, then the letter will not read properly. For instance, FIG. 20 shows the letter "a" on the posterior surface of the implant 92. If the implant 92 is not positioned right side up on the cornea surface, then the letter will read backwards." *BBA1013 at 12:16-21.*
[Claim 7] The method of claim 1, wherein said label visibly distinguishes a stromal side of the placental tissue graft.	**DUA**
	"The membrane is always sutured to the ocular surface with its epithelial side up and the mesenchymal surface in contact with the eye . . . For this reason it is important to be able to distinguish its two surfaces . . . Most surgeons have developed a technique that suits them best . . . Others will use a suture, with the knot as the marker or indelible marker pen, to mark one side of the membrane . . . A fine strand of "vitreous-like" substance can usually be drawn up from the mesenchymal but not the epithelial (basement membrane) side of the amniotic membrane." *BBA1014 at 750-51.*
	NIGAM
	"In this way, if the implant's posterior surface is placed onto the cornea surface, then the letter will not read properly. For instance, FIG. 20 shows the letter "a" on the posterior surface of the implant 92. If the implant 92 is not positioned right side up on the cornea surface, then the letter will read backwards." *BBA1013 at 12:16-21.*

E. *Ground 4. Claims 1-7 are Obvious Under 35 U.S.C. § 103(a) over Nigam in view of Hariri*

Nigam is identified and discussed in Ground 1 and incorporated by reference. Hariri is a U.S. Patent Publication directed to methods for preparation and use of collagen biofrabrics made of placenta tissue. *Hariri [BBA1015] at ¶¶ 7, 14.* Hariri published on March 11, 2004 which is more than one year prior to the August 17, 2006 effective filing date of the '687 Patent. Accordingly, Hariri is prior art under § 103(a). Hariri was disclosed in the Information Disclosure Statement submitted by the Applicant in the '687 Patent. *BBA1003 at 27.*

Hariri teaches the preparation of laminated collagen biofabrics or grafts consisting of placental membranes. *BBA1015 at ¶¶ 7, 14.* Hariri specifically teaches the use of amnion and/or chorion. *Id.* These collagen biofabrics may be utilized for blood vessel repair, wound dressing, surgical grafts, and ophthalmic uses among others. *Id. at Abstract.* Hariri's specification teaches processing of single layer biofabrics as well as "a laminate comprising at least two layers of the biofabric." *Id. at ¶ 20.* The preparation of the biofabric according to Hariri includes drying the membrane with its fetal (basement) side up on a drying frame. *Id. at ¶ 20.* Hariri's preferred drying frame is a plastic mesh drying frame. *Id. at ¶ 20.* Hariri teaches identification of the surface orientation of the membrane, distinguishing the maternal side from the fetal side, by examining the grid pattern created from the drying frame. *Id. at ¶ 121.* The fetal side will show as having a

concave or recessed grid pattern whereas the maternal side will show as having a convex or elevated grid pattern. *Id. at ¶ 121.* Hariri teaches magnification may be necessary to determine the surface orientation. *Id. at ¶ 121.*

It would have been obvious to a POSITA to combine the teachings of Nigam with the teachings of Hariri. *BBA1002 at ¶ 81.* As stated supra, Nigam teaches the need to distinguish sides of a tissue lens implant and includes asymmetric labels to accomplish that task. Hariri expressly discloses use of its placental tissue biofabrics for use in ophthalmology and a method to distinguish the sides of the biofabric based on an embossed grid design.

Hariri teaches the concept of imparting or molding a design into placental tissue that is capable of being viewed. Hariri's disclosure of concave (indented) and convex (raised) surfaces in the shape of a grid (design) falls within the scope of claims 2, 3, and 4. While Hariri discloses these features as visible with a microscope, it would be obvious to a POSITA to make the design visible without the need for a microscope. *BBA1002 at ¶ 80*; *Application of Rose*, 220 F.2d 459, 463 (C.C.P.A. 1955) (finding that changing size of an object "is not ordinarily a matter of invention"). In *Application of Rose*, the applicant sought to claim a reduced size of an item as patentable because the prior art article needed a forklift to move whereas Applicant's claimed article may be lifted by hand. *Application of Rose*, 220 F.2d 459, 463 (C.C.P.A. 1955). The Court of Customs and Patent

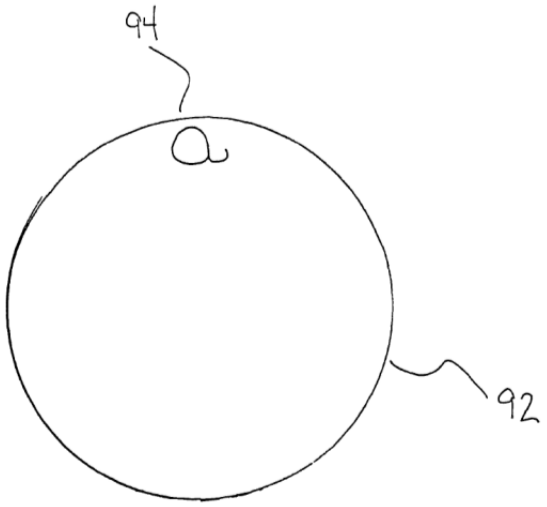
Appeals noted that "relative dimensions" among other items "are all deemed matters of choice involving differences in degree and/or size and (are) not patentable distinctions." *Id.*

Considering Nigam teaches a form of tissue manipulation through laser engraving of an asymmetric label, it would be obvious to a POSITA to utilize the methods of Hariri to impart an asymmetric label of Nigam into tissue through embossment or raised/indented texture. *BBA1002 at ¶ 81.* Engraving, embossing, and raised or indented texture are known to achieve similar purposes and result in a manipulated tissue having a label. M.P.E.P § 2144.06(II) (citing *Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980)). Furthermore, it would be obvious to substitute the grid design, or add to the grid design, of Hariri, an asymmetrical marking taught by Nigam as they would result in the same intended purpose – to distinguish between the sides of the placental tissue graft. *Id.*

Furthermore, it would be obvious to impart an asymmetric label onto a tissue graft having multiple layers. Hariri teaches creation of a multi-layered biofabric laminate and teaches the ability to distinguish between sides. It would be obvious to a POSITA to utilize the teachings of Nigam to label a placenta tissue graft having more than one layer in view of Hariri. *BBA1002 at ¶ 82.*

The following chart identifies the specific disclosure of Nigam in combination with Hariri relating to the limitations of claims 1 – 7 that renders the claims obvious. *BBA1002 at ¶¶ 83-84.*

CLAIMS 1-7	DISCLOSURE
A method for permitting direct, visual determination of the orientation of a placental tissue graft by user, wherein the placental tissue graft has a first side and a second side, said method comprising:	**NIGAM**
	"To ensure that the implant is properly oriented, however, the implant is provided with special asymmetric markings, which the user views to make a determination that the implant is resting against the corneal surface in a proper orientation." *BBA1013 at 12:6-10.*
	HARIRI
	"[A] method of preparing a collagen biofabric from a placenta having an amniotic membrane and a chorionic membrane comprising: separating the amniotic membrane from the chorionic membrane" *BBA1015 at ¶ 41.* "In a specific embodiment, the surface orientation of the collagen biofabric is identified under magnification. It will be appreciated by one skilled in the art that the fetal side of the collagen biofabric can be identified by its concave, i.e., recessed, grid pattern. Conversely, the maternal side can be identified by its convex, i.e., elevated grid pattern." *BBA1015 at ¶ 121.*
placing an	**NIGAM**

asymmetric label on a portion of at least one side of said tissue graft,	 *BBA1013 at Fig. 20.* "Referring to FIGS. 18-20, there are shown three examplary embodiments of asymmetric markings 94 that can be utilized to properly orient the lens implant. As shown by FIGS. 18 and 19, the markings are preferably positioned in a clockwise orientation. In another embodiment, shown in FIG. 20, a letter can be placed on the posterior surface of the implant." *BBA1013 at 12:10-16.*
which label visibly distinguishes one side from the other side, thereby permitting direct, visual determination of the orientation for application of said tissue graft; and ascertaining the orientation of the placental tissue graft by direct visual	**NIGAM** "In this way, if the implant's posterior surface is placed onto the cornea surface, then the letter will not read properly. For instance, FIG. 20 shows the letter 'a' on the posterior surface of the implant 92. If the implant 92 is not positioned right side up on the cornea surface, then the letter will read backwards. In this embodiment, any letter can be used so long as it has an asymmetric design. For instance, 'R', 'P', 'C', etc." *BBA1013 at 12:16-23.* "the implant is provided with special asymmetric markings, which the user views to make a determination that the implant is resting against the corneal surface in a proper orientation." *BBA1013 at 12:6-10.*

determination.	
[Claim 2] The method of claim 1, wherein said label is an embossment.	**NIGAM**
	"the markings 94 can be positioned onto the lens using laser engraving" *BBA1013 at 12:27-28.*
	HARIRI
	"Conversely, the maternal side can be identified by its convex, i.e., elevated grid pattern." *BBA1015 at ¶ 121.*
[Claim 3] The method of claim 1, wherein said label is a raised or indented texture.	**NIGAM**
	"the markings 94 can be positioned onto the lens using laser engraving" *BBA1013 at 12:27-28.*
	HARIRI
	"It will be appreciated by one skilled in the art that the fetal side of the collagen biofabric can be identified by its concave, i.e., recessed, grid pattern. Conversely, the maternal side can be identified by its convex, i.e., elevated grid pattern." *BBA1015 at ¶ 121.*
[Claim 4] The method of claim 1, wherein said label is a logo, a design, a name, or text.	**NIGAM**
	"In this embodiment, any letter can be used so long as it has an asymmetric design. For instance, 'R', 'P', 'C', etc." *BBA1013 at 12:21-23.*
	HARIRI
	The collagen biofabric of the invention has a "grid" pattern, which allows for the visual identification of the maternal and detal surfaces by one skilled in the art. *BBA1015 at ¶ 121.*
[Claim 5] The method of claim 1, wherein said tissue graft contains multiple tissue	**HARIRI**
	"[T]he invention provides a method of preparing an amniotic membrane laminate from a placenta having an amniotic membrane and a chorionic membrane comprising: separating

layers.	the amniotic membrane from the chorionic membrane; decellularizing the amniotic membrane; and layering at least two of the decellularized amniotic membranes in contact with each other so that an amniotic membrane laminate is formed." *BBA1015 at ¶ 41.*
[Claim 6] The method of claim 1, wherein said label visibly distinguishes a basement side of the placental tissue graft.	**NIGAM**
	"In this way, if the implant's posterior surface is placed onto the cornea surface, then the letter will not read properly. For instance, FIG. 20 shows the letter "a" on the posterior surface of the implant 92. If the implant 92 is not positioned right side up on the cornea surface, then the letter will read backwards." *BBA1013 at 12:16-21.*
	HARIRI
	"It will be appreciated by one skilled in the art that the fetal side of the collagen biofabric can be identified by its concave, i.e., recessed, grid pattern." *BBA1015 at ¶ 121.*
[Claim 7] The method of claim 1, wherein said label visibly distinguishes a stromal side of the placental tissue graft.	**NIGAM**
	"In this way, if the implant's posterior surface is placed onto the cornea surface, then the letter will not read properly. For instance, FIG. 20 shows the letter "a" on the posterior surface of the implant 92. If the implant 92 is not positioned right side up on the cornea surface, then the letter will read backwards." *BBA1013 at 12:16-21.*
	HARIRI
	"Conversely, the maternal side can be identified by its convex, i.e., elevated grid pattern." *BBA1015 at ¶ 121.*

F. ***Ground 5. Claims 1-7 are Obvious Under 35 U.S.C. § 103(a) over Dua in view of Hariri***

Dua is identified and discussed in Ground 2 and incorporated by reference. Hariri is a U.S. Patent Publication directed to methods for preparation and use of collagen biofrabrics made of placenta tissue. *Hariri [BBA1015] at ¶¶ 7, 14.* Hariri published on March 11, 2004 which is more than one year prior to the August 17, 2006 effective filing date of the '687 Patent. Accordingly, Hariri is prior art under § 103(a). Hariri was disclosed in the Information Disclosure Statement submitted by the Applicant in the '687 Patent. *BBA1003 at 27.*

Hariri teaches the preparation of laminated collagen biofabrics or grafts consisting of placental membranes. *BBA1015 at ¶¶ 7, 14.* Hariri specifically teaches the use of amnion and/or chorion. *Id.* These collagen biofabrics may be utilized for blood vessel repair, wound dressing, surgical grafts, and ophthalmic uses among others. *Id. at Abstract.* Hariri's specification teaches processing of single layer biofabrics as well as "a laminate comprising at least two layers of the biofabric." *Id. at ¶ 20.* The preparation of the biofabric according to Hariri includes drying the membrane with its fetal (basement) side up on a drying frame. *Id. at ¶ 20.* Hariri's preferred drying frame is a plastic mesh drying frame. *Id. at ¶ 20.* Hariri teaches identification of the surface orientation of the membrane, distinguishing the maternal side from the fetal side, by examining the grid pattern created from the drying frame. *Id. at ¶ 121.* The fetal side will show as having a

concave or recessed grid pattern whereas the maternal side will show as having a convex or elevated grid pattern. *Id. at ¶ 121.* Hariri teaches magnification may be necessary to determine the surface orientation. *Id. at ¶ 121.*

Hariri teaches the concept of imparting or molding a design into placental tissue that is capable of being viewed. Hariri's disclosure of concave (indented) and convex (raised) surfaces in the shape of a grid (design) falls within the scope of claims 2, 3, and 4. While Hariri discloses these features as visible with a microscope, it would be obvious to a POSITA to make the design visible without the need for a microscope. *BBA1002 at ¶ 90*; Application of Rose, 220 F.2d 459, 463 (C.C.P.A. 1955) (finding that changing size of an object "is not ordinarily a matter of invention").

A POSITA would look to combine the elements of Dua and Hariri because both teach utilization of labels to distinguish the basement and stromal sides of a placental tissue graft; both utilize three-dimensional components for the labels, and both labels achieve the same purpose of the asymmetric label of the '687 Patent. *BBA1002 at ¶ 92.* The three-dimensional nature of Dua's labels, embossing of Hariri, and raised or indented texture of Hariri are known to achieve similar purposes as the '687 Patent's asymmetric label in that they all distinguish the sides of a placental tissue graft. Thus the asymmetrical label of the '687 Patent is obvious. M.P.E.P § 2144.06(II) (citing *Smith v. Hayashi*, 209 USPQ 754 (Bd. of

Pat. Inter. 1980)). Furthermore, it would be obvious to substitute the grid design, or add to the grid design, of Hariri, an asymmetrical marking taught by Nigam as they would result in the same intended purpose – to distinguish between the sides of the placental tissue graft. *Id.*

Dua's teaching of a knot and/or mark as well as Hariri's teaching of a grid is sufficient to satisfy the elements of claim 4. Claim 4 utilizes alternative limitations in stating the "label is a logo, a design, a name, or text." The use of alternative limitations in claims is permitted, but "[w]hen a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art." *Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001). A POSITA would have understood Dua's teaching of a knot and/or mark to be a design, logo, name, and/or text. *BBA1002 at ¶ 59.*

Furthermore, it would be obvious to a POSITA to impart a label onto a tissue graft having multiple layers. *BBA1002 at ¶ 94.* Hariri teaches creation of a multi-layered biofabric laminate and teaches the ability to distinguish between sides. It would be obvious to a POSITA to utilize the teachings of Hariri and Dua to label a placenta tissue graft having more than one layer. *Id.*

Finally, Hariri expressly teaches the labeling of the biofabric by stating the fetal side will show a concave or recessed grid pattern whereas the maternal side

will show a convex or elevated grid pattern. *BBA1015 at ¶ 121.* Similarly, Dua disclosing labeling of a side of the placental membrane tissue graft which obviously teaches the identification of the basement (or epithelial side) and the mesenchymal (or stromal side.) *BBA1002 at ¶ 60.* A POSITA would understand Dua's reference to the epithelial side and Hariri's references to the fetal side as corresponding to the '687 Patent's reference to the basement side in claim 6. *BBA1002 at ¶ 34.* Similarly, a POSITA would understand Dua's reference to the mesenchymal side and Hariri's reference to a maternal side as corresponding to the '687 Patent's reference to the stromal side in claim 7. *BBA1002 at ¶ 34.*

The following chart identifies the specific disclosure of Dua in combination with Hariri relating to the limitations of claims 1 – 7 that renders the claims obvious. *BBA1002 at ¶¶ 95-96.*

CLAIMS 1-7	DISCLOSURE
A method for permitting direct, visual determination of the orientation of a placental tissue graft by user, wherein the placental tissue graft has a first side and a second side, said method comprising:	**DUA**
	"The [**amniotic**] membrane is always sutured to the ocular surface with its **epithelial side up** and the **mesenchymal surface in contact with the eye** . . . [f]or this reason it is important **to be able to distinguish** its two surfaces . . . [m]ost surgeons have developed a technique that suit them best . . ." *BBA1014 at 750.*
	HARIRI
	"In a specific embodiment, the surface orientation of the collagen biofabric is identified under magnification. It will be appreciated by one skilled in the art that the fetal side of

	the collagen biofabric can be identified by its concave, i.e., recessed, grid pattern. Conversely, the maternal side can be identified by its convex, i.e., elevated grid pattern." BBA1015 at ¶ 121.
placing an asymmetric label	**DUA**
	"use a suture, with the **knot as the marker or indelible marker pen**" *BBA1014 at 750-51.*
on a portion of at least one side of said tissue graft,	**DUA**
	"to mark one side of the membrane." BBA1014 at 751.
which label visibly distinguishes one side from the other side, thereby permitting direct, visual determination of the orientation for application of said tissue graft; and ascertaining the orientation of the placental tissue graft by direct visual determination.	**DUA**
	"The membrane is always sutured to the ocular surface with its epithelial side up and the mesenchymal surface in contact with the eye . . . For this reason it is important to be able to distinguish its two surfaces . . . Most surgeons have developed a technique that suits them best . . . Others will use a suture, with the knot as the marker or indelible marker pen, to mark one side of the membrane." *BBA1014 at 750-51.*
[Claim 2] The method of claim 1, wherein said label is an embossment.	**HARIRI**
	"Conversely, the maternal side can be identified by its convex, i.e., elevated grid pattern." *BBA1015 at ¶ 121.*
[Claim 3] The method of claim 1, wherein said label	**DUA**
	"it is important to be able to distinguish its two surfaces . . . Most surgeons have developed a technique that suits them

is a raised or indented texture.	best . . . After spreading the membrane on the ocular surface we apply the tips of a blunt fine forceps to one surface of membrane and pinch lightly with the forceps and lift. A fine strand of 'vitreous-like' substance can usually be drawn up from the mesenchymal but not the epithelial (basement membrane) side of the amniotic membrane." *BBA1014 at 750-51.*
	HARIRI
	"It will be appreciated by one skilled in the art that the fetal side of the collagen biofabric can be identified by its concave, i.e., recessed, grid pattern. Conversely, the maternal side can be identified by its convex, i.e., elevated grid pattern." *BBA1015 at ¶ 121.*
[Claim 4] The method of claim 1, wherein said label is a logo, a design, a name, or text.	**DUA**
	"use a suture, with the **knot** as the marker or indelible marker pen to mark one side of the membrane." *BBA1014 at 750-51.*
	HARIRI
	The collagen biofabric of the invention has a "grid" pattern, which allows for the visual identification of the maternal and detal surfaces by one skilled in the art. *BBA1015 at ¶ 121.*
[Claim 5] The method of claim 1, wherein said tissue graft contains multiple tissue layers.	**HARIRI**
	"[T]he invention provides a method of preparing an amniotic membrane laminate from a placenta having an amniotic membrane and a chorionic membrane comprising: separating the amniotic membrane from the chorionic membrane; decellularizing the amniotic membrane; and layering at least two of the decellularized amniotic membranes in contact with each other so that an amniotic membrane laminate is formed." *BBA1015 at ¶ 41.*
[Claim 6] The	**DUA**

method of claim 1, wherein said label visibly distinguishes a basement side of the placental tissue graft.	"The membrane is always sutured to the ocular surface with its epithelial side up and the mesenchymal surface in contact with the eye . . . For this reason it is important to be able to distinguish its two surfaces . . . Most surgeons have developed a technique that suits them best . . . Others will use a suture, with the knot as the marker or indelible marker pen, to mark one side of the membrane . . . A fine strand of "vitreous-like" substance can usually be drawn up from the mesenchymal but not the epithelial (basement membrane) side of the amniotic membrane." *BBA1014 at 750-51.*
	HARIRI
	"It will be appreciated by one skilled in the art that the fetal side of the collagen biofabric can be identified by its concave, i.e., recessed, grid pattern." *BBA1015 at ¶ 121.*
[Claim 7] The method of claim 1, wherein said label visibly distinguishes a stromal side of the placental tissue graft.	**DUA**
	"The membrane is always sutured to the ocular surface with its epithelial side up and the mesenchymal surface in contact with the eye . . . For this reason it is important to be able to distinguish its two surfaces . . . Most surgeons have developed a technique that suits them best . . . Others will use a suture, with the knot as the marker or indelible marker pen, to mark one side of the membrane . . . A fine strand of "vitreous-like" substance can usually be drawn up from the mesenchymal but not the epithelial (basement membrane) side of the amniotic membrane." *BBA1014 at 750-51.*
	HARIRI
	"Conversely, the maternal side can be identified by its convex, i.e., elevated grid pattern." *BBA1015 at ¶ 121.*

VI. CONCLUSION

Petitioners respectfully requests that *inter partes* review of the '687 Patent be instituted and that claims 1 – 7 are found unpatentable for the reasons stated above.

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Respectfully submitted,

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ATTORNEYS FOR PETITIONERS

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.8(b)(4) and 42.105(b), the undersigned certifies that on December 11, 2014, a complete and entire copy of this Petition for *Inter Partes* Review and all supporting exhibits were provided via FEDEX STANDARD OVERNIGHT and email, costs prepaid, to the Patent Owner by serving the correspondence address of record as follows:

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