UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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HYPERBRANCH MEDICAL TECHNOLOGY, INC.
Petitioner

v.

INCEPT LLC
Patent Owner

_____

Case No. IPR2016-_____

Patent No. 7,009,034

Filing Date: November 9, 2001
Issue Date: March 7, 2006

Title: BIOCOMPATIBLE CROSSLINKED POLYMERS

_____

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,009,034

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EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent No. 7,009,034 ("the '034 patent")
1002	File history of the '034 patent (excerpts)
1003	Expert Declaration of Dr. Anthony Lowman
1004	U.S. Patent No. 5,874,500 ("Rhee '500")
1005	U.S. Patent No. 5,614,587 ("Rhee '587")
1006	U.S. Patent No. 5,292,362 ("Bass")
1007	Tse *et al.*, *Cyanoacrylate Adhesive Used to Stop CSF Leaks During Orbital Surgery*, Arch Opthalmol, 102:1337-1339 (1984) ("Tse")
1008	U.S. Patent No. 6,566,406 ("the '406 patent")
1009	Quinn, J. and Kissick, J., *Tissue Adhesives for Laceration Repair During Sporting Events*, Clinical Journal of Sport Medicine, 4:245-248 (1994) ("Quinn")
1010	"Histoacryl Topical Skin Adhesive" (located at http://www.tissueseal.com)
1011	Brothers *et al.*, *n-Butyl 2-Cyanoacrylate—Substitute for IBCA in Interventional Neuroradiology: Histopathologic and Polymerization Time Studies*
1012	U.S. Patent No. 4,162,162 ("Dueber '162")
1013	U.S. Patent No. 5,475,052 ("Rhee '052")
1014	Histoacryl® and Histoacryl® Blue Topical Skin Adhesive Foil Pouch Packaging Package Insert
1015	File history of U.S. Patent No. 7,332,566 (excerpts)
1016	U.S. Patent No. 7,332,566 ("the '566 patent")
1017	Hermanson, G.T., *Bioconjugate Techniques*, Chapter 2, The Chemistry of Reactive Groups (1996)
1018	West J. and Hubbell, J., *Comparison of Covalently and physically Cross-linked Polyethylene Glycol-based Hydrogels for the Prevention of Postoperative Adhesions in a Rat Model*, Biomaterials, Vol. 16, No. 15 (1995)

I. INTRODUCTION

HyperBranch Medical Technology, Inc. ("HyperBranch" or "Petitioner") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311–319 and 37 C.F.R. § 42 of claims 1-12 of U.S. Patent No. 7,009,034 ("the '034 patent," Ex. 1001), owned by Incept LLC (individually, or with predecessors in interest, "Patent Owner"). Review should be instituted because there is a reasonable likelihood that Petitioner will prevail in demonstrating that claims 1-12 of the '034 patent are anticipated and obvious, as set forth below.

The '034 patent is directed to the use of hydrogels in medical applications, formed by the chemical reaction between electrophilic and nucleophilic reaction groups. This electrophilic-nucleophilic chemistry for creating the claimed hydrogels is not novel. In fact, as the background sections of the '034 patent and its parent application—the '406 patent—make clear, there are numerous prior art patents that disclose the identical chemistry for making the claimed hydrogels. (*See* Ex. 1001, 1:61-2:3; Ex. 1008, 3:6-27.) In particular, the patentees acknowledged in the parent of the '034 patent two prior art Rhee patents, including U.S. Patent No. 5,874,500 (Ex. 1004 ("Rhee '500")), as "describe[ing] biocompatible crosslinked polymers, formed from electrophilic-nucleophilic

polymerization of polymers having multiple electrophilic or nucleophilic functionalities." (Ex. 1008, 3:23-27.)

The patentees also expressly noted that the hydrogels made using Rhee's prior art methods are "especially useful for use in the body" and noted the various different "medical purposes" for which they could be employed, including for "surgical sealing." (Ex. 1001, 1:52-60.) Other prior art patents disclosed the same chemistry used by Rhee, and patentees recognized that disclosed process as a method for making biocompatible hydrogels for use in medical applications, including tissue coatings. The Rhee prior art relied on in this petition uses the same disclosures that the patentees have already admitted to be within the prior art.

The alleged invention of the '034 patent is the mere addition of a "visualization agent" to hydrogels in order to enhance the visibility of what the inventors characterized as the "essentially colorless" hydrogels of the prior art. (Ex. 1001, 2:4-10.) Noting that a "colorless solution or film is . . . difficult to visualize" in comparison to a colored film, the patentees claimed to have been the first to "have realized that use of color in biocompatible crosslinked polymers and precursors greatly improves their performance in a surgical environment . . . ." (Ex. 1001, 2:4-10, 18-20 (Summary of the Invention).)

Claims 1-12 are invalid because the inventors' purported "realization" that colored hydrogels are easier to see than those that are colorless is nothing more

than an anticipated, obvious, and routine application of known elements. Within this field the common sense idea of adding color in order to enhance the visibility of *in situ* polymerizing tissue sealants or adhesives, of which there are various chemistries and members, has been known for decades. For example, the tissue adhesive Histoacryl® Blue, which has been in use for over 40 years, "***contains a blue dye in order to make it easier to see the adhesive being applied***." (Ex. 1010.) It was also widely known that "***Histoacryl Blue . . . is colored to increase its visibility in surgical use***" (Ex. 1011 at 2 (emphasis added)) and that the "***color additive in the tissue adhesive . . . facilitates visualization***" during application (Ex. 1007 at 7 (emphasis added)).

Furthermore, Rhee prior art patents that disclose hydrogels made using the identical chemistry to the '034 patent also disclose the use of a "visualization agent" to impart color and opacity that increases the visibility of hydrogels. Accordingly, the Rhee prior art anticipates the majority of the challenged claims. For example, Rhee '500 discloses the synthesis of hydrogels using a material—fibrillar collagen—that results in opaque hydrogels that would be easily visible (as distinguished from other "optically clear" and colorless hydrogels). (*See* Ex. 1003, ¶ 100.) Rhee '500 also discloses the addition of barium sulfate to the hydrogels, which would form hydrogels with a "milky" appearance. (*See id.*, ¶ 72; Ex. 1002 at 120 ("barium sulfate is a 'milky solution'").) These express disclosures in Rhee

'500 therefore satisfy the allegedly missing "visualization agent" of the prior art to invalidate the challenged claims. (*See* Ex. 1003, ¶¶ 68-72.)

The invalidity of the presently challenged claims is further supported by the file history. The prosecution histories for the '034 patent and the child '566 patent—both of which were in front of the same examiner—suggest that allowance of the challenged claims was an error. During prosecution of the '034 patent, the examiner repeatedly rejected the pending claims that recited the use of a visualization agent to make colored hydrogels. (Ex. 1002 at 170, 124, 106-107, 40-41.) Indeed, it wasn't until the introduction of a limitation that requires a correlation between the color imparted by the "visualization agent" and an "indicat[ion] that a hydrogel having a predetermined thickness has been formed on the tissue of the patient" that the examiner issued a notice of allowance. (Ex. 1002 at 23-24.) However, this functional requirement of the use of a visualization agent to "indicate[] … a predetermined thickness," as introduced during examination into claims 13-22 of the '034 patent to overcome the prior art, remained absent from the claims that ultimately issued as claims 1-12.

In contrast to the prosecution of the '034 patent, the examiner only allowed similar claims of the '566 patent after the functional requirement that the visualization agent "indicate a predetermined thickness" was incorporated as a limitation into ***every claim*** before allowance. (Ex. 1015 at 36-37.) Additionally,

the examiner rejected the claims over prior art combinations that were not considered during the earlier prosecution of the '034 patent. (Ex. 1015 at 60-66.) One such prior art patent, U.S. Patent No. 5,292,362 ("Bass"), teaches the use of dyes "in sufficient quantity to allow visualization" of polymeric compositions used to bond or coat tissues. (Ex. 1006, claim 30.) Bass teaches that the dyes "facilitate visualization of the material during placement into warm blooded animals. (Ex. 1006, 11:18-21.) Had the examiner considered Bass in the prosecution of the '034 patent, as set forth below, claims 1-12 should not have issued as they did.

In light of the fact that the prior art discloses all of the claim elements, including hydrogels made by the same chemistry that include a visualization agent that results in opaque hydrogels that are white or off-white, as set forth below, there is a reasonable likelihood that challenged claims 1-5 and 7-12 are invalid for anticipation. Additionally, the disclosures of the prior art hydrogels and the clear motivation and expectation of success in the use of dyes as "visualization agents" to increase the visibility of such polymeric coatings render claims 1-6 and 8-12 invalid for obviousness. Petitioner therefore respectfully requests institution of *inter partes* review of claims 1-12.

II. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

HyperBranch is the real party-in-interest.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Petitioner and Patent Owner are parties to a patent infringement action in which Patent Owner asserts infringement of the '034 patent by Petitioner: *Integra LifeSciences Corp., et al., v. HyperBranch Med. Tech., Inc.*, C.A. No. 15-819-LPS-CJB (D. Del.).

Patent Owner is the owner of the following U.S. applications and patents that claim the benefit of priority of the '034 patent or from which the '034 patent claims priority: U.S. Patent Nos. 6,566,406, 7,332,566, 7,592,418, 7,592,418, 8,003,705, 7,347,850; U.S. Appl. Nos. 60/039,904, 60/040,417, 60/026,526, 09/147,897, 60/110,849, 12/496,060, 12/008,8-2; and PCT/US97/16897.

C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

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D. Service Information

Petitioner may be served at the above addresses provided in Section II.C for lead and back-up counsel and consents to electronic service at the e-mail addresses provided above, which include both individual e-mail addresses and a general docketing e-mail address.

E. Power of Attorney (37 C.F.R. § 42.10(b))

Power of attorney is being filed concurrently with this petition.

III. PAYMENT OF FEES (37 C.F.R. § 42.103)

This Petition requests review of claims 1-12 of the '034 patent and is accompanied by a payment of $23,000, which comprises a $9,000 request fee and $14,000 post-institution fee. 37 C.F.R. § 42.15(a). This Petition meets the fee requirements of 35 U.S.C. § 312(a)(1).

IV. REQUIREMENTS FOR *INTER PARTES* REVIEW (37 C.F.R. §§ 42.104, 42.108)

A. Grounds for Standing (37 C.F.R. § 42.104(a))

Petitioner certifies that the '034 patent is eligible for *inter partes* review, and that the Petitioner is not barred or estopped from requesting *inter partes* review on

the grounds identified in the present Petition.

B. Identification of Challenge (37 C.F.R. § 42.104(b)) and Statement of Precise Relief Requested

Petitioner requests *inter partes* review of claims 1-12 of the '034 patent on the grounds set forth in the following table, and requests that they be found unpatentable. The '034 patent is to be reviewed under pre-AIA §§ 102 and 103. This Petition, supported by the accompanying declaration of Dr. Anthony Lowman, demonstrates that there is a reasonable likelihood that Petitioner will prevail with respect to challenged claims 1-12.

Ground	Claims	Basis for Unpatentability
Ground I	1-5, 7-12	Anticipated under 35 U.S.C. § 102(b) by Rhee '500
Ground II	1-6, 8-12	Obvious under 35 U.S.C. § 103 over Rhee '500 in view of Bass
Ground III	1-6, 8-12	Obvious under 35 U.S.C. § 103 over Rhee '500 in view of Tse
Ground IV	1-5, 7-12	Anticipated under 35 U.S.C. § 102(b) by Rhee '587
Ground V	1-6, 8-12	Obvious under 35 U.S.C. § 103 over Rhee '587 in view of Bass
Ground VI	1-6, 8-12	Obvious under 35 U.S.C. § 103 over Rhee '587 in view of Tse

The grounds asserted by Petitioner rely on art that is at least either 102(b) and/or 102(e) prior art to the challenged claims. Rhee '500 and Rhee '587 are presumptive § 102(b) prior art to the '034 patent because each was published more than one year before the filing date of the '034 patent and would remain prior art under § 102(e), unless Patent Owner can establish an invention date prior to their

respective filing dates. Bass and Tse are absolute § 102(b) prior art to the '034 patent because each was published more than one year before the earliest theoretical effective filing date of the '034 patent. Petitioner reserves the right to respond to any assertion by Patent Owner that any of the challenged claims are entitled to a priority date earlier than the presumptive priority date, which is the November 9, 2001 filing date of the continuation-in-part '034 patent.

V. TECHNICAL BACKGROUND

A. Polymers, Hydrogels, and Cross-Linking Chemistry

Polymers are comprised or built up of smaller units, and generally include various materials that can be synthesized by linking molecules together to build up chain-like molecules with different linear or branched structures. (Ex. 1003, ¶ 29.) When polymer chains are "cross-linked" together, they are capable of forming gel-like materials. When such polymeric gels are capable of including water within their cross-linked framework of polymer chains, such as when the polymers are hydrophilic (i.e., "water loving"), the gels are commonly referred to as "hydrogels." (*Id.*) Due to their biocompatibility and favorable properties, polyethylene glycol ("PEG") polymers have long been popular synthetic hydrophilic polymers for use in the biomedical application of hydrogels. (*Id.*)

The cross-linking of polymeric chains to form a hydrogel typically occurs through formation of chemical bonds that link the individual polymer chains

together into an interconnected matrix. (*Id.*, ¶ 30-31.) There are many ways to crosslink polymers together to form a hydrogel. (*Id.*) Of particular relevance to the present issues are chemical reactions that occur between complementary "electrophilic" and "nucleophilic" groups that are present on the polymer chains themselves and/or cross-linking molecules that react with each other to form chemical bonds to connect the polymer chains together. (*Id.*)

There are many types of electrophilic and nucleophilic reactive groups that can be used to form cross-linking bonds. Amine groups are by far the most common nucleophilic functional groups used in cross-linking reactions. (*Id.* at 32; Ex. 1017 at 3.) Succinimidyl-based electrophilic groups, such as n-hydroxysuccinimide (NHS) ester or sulfo-NHS ester, represent a commonly used type of electrophilic group for reactive cross-linking with nucleophiles. (*Id.*; *see* Ex. 1017 at 5-6.)

B. The Use of Visualization Agents in Polymeric Materials for Medical Applications

The idea of adding color to polymeric materials used in medical applications has long been known. For example, the polymeric tissue adhesives Histoacryl® and Histoacryl® Blue have been used extensively since the early 1970s. (*See* Ex. 1009 at 1.) "Histoacryl® is translucent, and Histoacryl® Blue ***contains a blue dye in order to make it easier to see the adhesive being applied***." (*See* Ex. 1003, ¶ 33;

Ex. 1010 (emphasis added).) Over the past 40 years of clinical experience, there have been more than 1,000 articles published on Histoacryl® and Histoacryl® Blue (*see* Ex. 1010), including articles that expressly note that "***Histoacryl Blue . . . is colored to increase its visibility in surgical use***" (Ex. 1011 at 2 (emphasis added)) and that the "***color additive in the tissue adhesive . . . facilitates visualization***" during application (Ex. 1007 at 7 (emphasis added)). The current package insert also acknowledges what was expressly described in the prior art for the Histoacryl tissue adhesives: "The two products are different in only one respect: Histoacryl® is provided as a colorless liquid, and Histoacryl® Blue is colored with the dye D&C Violet #2 in order to make it easier to see the thickness of the layer of Histoacryl® Blue being applied." (Ex. 1014.)

Visualization agents have also been used to increase the visibility of various polymeric materials used in biomedical applications that are similar or even identical to those discussed in the '034 patent and long before the patentees' purported "realization" that color makes an otherwise colorless film easier to see. (Ex. 1003, ¶ 34.) For example, a prior art patent claims compositions, such as gels, "for bonding separated tissues together or for coating tissues," including the use of dyes "in sufficient quantity to allow visualization of the composition." (Ex. 1003, ¶ 35; Ex. 1006, claim 30). The patent describes how the use of such dyes "facilitate[s] visualization of the material during placement into warm blooded

animals." (Ex. 1006, 11:18-21.) Another prior art patent directed to polymer compositions expressly teaches the addition of "inert components such as . . . dyes and pigments to increase visibility" and that such "inert additives such as dyes [and] pigments . . . are known to those skilled in the art." (Ex. 1003, ¶ 36; Ex. 1012, 3:41-43, 8:56-58.) As a further example, a prior art paper describes adding fluorescent polystyrene beads to the polymer precursors "to aid in the visualization of hydrogel coatings." (Ex. 1003, ¶ 37; Ex. 1018 at 1154.) There is simply nothing novel or non-obvious about adding an agent to polymers used as biomedical materials in order to give them an observable color or opacity. (*See* Ex. 1003, ¶ 38.)

VI. THE '034 PATENT AND ITS PROSECUTION HISTORY

A. The '034 Patent

The '034 patent is entitled "Biocompatible Crosslinked Polymers." It describes biocompatible crosslinked polymers, formed from the reaction of water soluble precursors having electrophilic and nucleophilic groups, and methods for their preparation and use. The disclosed polymers include visualization agents, as, according to the specification, "[t]he present inventors have realized that the use of color in biocompatible crosslinked polymers and precursors greatly improves their performance in a surgical environment…." (Ex. 1001, 2:18-20.)

The '034 patent contains 22 claims, of which claims 1-12 are the subject of

this Petition.

1. A method of preparing a composition suitable to coat a tissue of a patient, the method comprising:

mixing reactive precursor species comprising nucleophilic functional groups, reactive precursor species comprising electrophilic functional groups, and a visualization agent such that the nucleophilic functional groups and electrophilic functional groups crosslink after contact with the tissue to form a hydrogel having an interior and an exterior, with the exterior having at least one substrate coating surface and the visualization agent being at least partially disposed within the interior and reflecting or emitting light at a wavelength detectable to a human eye to thereby provide a means for visualization of the coating by a human eye.

2. The method of claim 1, wherein the hydrogel comprises crosslinked polymers that are selected from the group consisting of collagen, fibrinogen, albumin, and fibrin.

3. The method of claim 1, wherein the hydrogel is made of synthetic materials.

4. The method of claim 1, wherein the hydrogel is hydrolytically biodegradable.

5. The method of claim 1, wherein the hydrogel comprises covalently crosslinked hydrophilic polymers.

6. The polymeric coating method of claim 1, wherein the visualization agent is chosen from the group consisting of FD&C Blue #1, FD&C Blue #2, methylene blue, indocyanine green, visualization agents that provide a blue color, and visualization agents that provide a green color.

7. The method of claim 1, wherein the visualization agent is covalently linked to the hydrogel.
8. The method of claim 1, wherein the hydrogel comprises a biologically active agent.
9. The method of claim 1, wherein the hydrogel forms within 60 seconds after contact with the substrate.
10. The method of claim 1, wherein the hydrogel forms within 5 seconds after contact with the substrate.
11. The method of claim 1, wherein the biodegradable hydrogel is adherent to the tissue.
12. A hydrogel composition adapted for use with a tissue of a patient, the composition being made by the process of claim 11.

B. The U.S. Prosecution History of the '034 Patent

The '034 patent issued on March 7, 2006 from U.S. Application No. 10/010,715 (the "'715 application"), filed on November 9, 2001. The '715 application was a continuation-in-part that combined the disclosures of U.S. Application Nos. 09/147,897 (the "'897 application"), filed on December 3, 1999, and 09/454,900 (the "'900 application"), filed on August 30, 1999. The '897 and '900 applications were based on earlier provisional applications.

During prosecution, all claims of the '715 application were rejected repeatedly as obvious over the combination of U.S. Pat. No. 5,410,016

("Hubbell"[1]) and one of the patents in the Rhee family (Rhee '500). (Ex. 1002 at 170, 124, 106-107, 40-41.) Hubbell was cited, *inter alia*, for the use of a visualization agent. (*See, e.g., id*. at 170-182.) It described the use of precursors containing colored material, which served as a photoinitiator for the light-induced reaction that polymerized the precursors. (*Id.*) Rhee '500 was cited for the use of the chemistry claimed in the '715 application. (*Id.*) Rhee '500 was never used as an anticipation reference and was never combined with any other art that disclosed the use of visualizations agents besides Hubbell. The claims that were ultimately allowed over Hubbell-Rhee '500 included the presently challenged claims that included any "visualization agent" and those that narrowly confine the claims by requiring the "visualization agent" to impart discernable visual features onto the hydrogel so that it could be used by the person applying the hydrogel as a means to apply the hydrogel until a "predetermined thickness" was achieved. (Ex. 1001, claims 13-22.)

The issuance of claims that do not have the "predetermined thickness" requirement, as those challenged here, is in contrast to the prosecution of U.S. Pat. No. 7,332,566 ("the '566 patent"), which is the child to the '034 patent. Originally, the application for the '566 patent had three claims that covered hydrogels with visualization agents for use in coating tissues, and methods for

[1] Two of the three named inventors on the '034 patent were inventors on Hubbell.

making them. (Ex. 1015 at 82-83.) One claim required that the visualization agent be used to apply the hydrogel to a predetermined thickness, and two required the mere presence of a visualization agent. (*Id.*) The claims of the '566 patent were allowed only after they were amended such that all claims contained the "predetermined thickness" limitation (*id.* at 36-37), and Patent Owner made that amendment only after the examiner rejected the claims as obvious over a combination that included the prior art Bass patent. (*Id.* at 60-66.)

Bass describes gels for bonding separated tissues and for coating tissues, and describes adding visualization agents to the material "to facilitate visualization of the material during placement into warm blooded animals." (Ex. 1006, 11:18-21.)[2] The visualization agents in Bass are chromophores, including some of the same agents listed in claim 6 of the '034 patent (indocyanine green and methylene blue). Patent Owner avoided Bass by amending the claims and arguing, *inter alia*, that Bass did not teach that the visualization agent can be correlated with any particular thickness of the composition. (Ex. 1015 at 50.)

Notably, Bass issued in 1994, and was prior art to the entire family of related patents, including the presently challenged '034 patent. But Bass was never cited during the '034 patent prosecution. Nor were any other of the many patents and

[2] *See also*, Bass claim 30, directed to a composition "wherein the chromophore is present in sufficient quantity to allow visualization of the composition." (Ex. 1006, claim 30.)

publications describing the use of a visualization agent to better see hydrogels and other materials as they are applied to a patient. Instead, the examiner relied only on Hubbell for the element of a visualization agent. Even so, it does not appear in the prosecution history record that Patent Owner ever managed to sufficiently distinguish its non-"predetermined thickness" claims over Hubbell, and there is no apparent rationale for allowing those claims (claims 1-12) after the remaining claims (13-22) were amended to include that limitation.

The examiner's citation to Bass during prosecution of the '566 patent—and the allowance only of claims that included the "predetermined thickness" limitation—occurred nearly two years after the claims of the '034 patent were allowed. Both patents were in front of the same examiner. These circumstances and their timing suggest that allowance of the challenged claims 1-12 in the '034 patent was the result of an oversight and/or a lack of diligence (by failing to reject the claims in view of highly relevant and invalidating art, such as Bass).

VII. CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(b)(3)

A claim subject to *inter partes* review must 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); *see also In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1275-76 (Fed. Cir. 2015), *affirmed* 136 S. Ct. 2131 (2016). Accordingly, the construction proposed in this Petition represents the broadest reasonable

interpretation that one of ordinary skill in the art would assign to the terms below. For the claim terms not addressed below, Petitioner has applied the plain and ordinary meaning of the term.

A. Terms for construction

1. "visualization agent"

As used in the '034 patent, the broadest reasonable construction of a "visualization agent" is "a substance or material that imparts a visibly discernable color or obscures the optical clarity of the hydrogel."[3] The '034 patent repeatedly uses the term "visualization agent" broadly, as any substance or material that "reflects or emits light at a wavelength detectable to a human eye." (Ex. 1001, 2:31-32, 62-63, 3:10-11.) This same broad scope of "visualization agent" is expressly recited in the text of claim 1. The patent further teaches that the "visualization agent reflects or emits light at a wavelength detectable to a human eye so that a user applying the hydrogel can observe the gel" (*id.* at 6:26-29), and

[3] In the co-pending litigation, Patent Owner adopted the position that bubbles transiently formed by the application process of a hydrogel satisfy the "visualization agent" claimed in the '034 patent. Even under the broadest reasonable construction standard applied by the Board, air entrained into a hydrogel during the application process to form bubbles does not constitute a "visualization agent" as that term is used in the '034 patent. There is nothing in the intrinsic or extrinsic record that would support a reading that air could be a "visualization agent," and Patent Owner can provide none. Thus, for clarity, Petitioner's construction of "visualization agent" does not include entrapped air in the form of bubbles.

also teaches that particles entrapped within the hydrogel can serve as a "visualization agent." (*id.*, 34:28-32) Such particles would reflect light, and therefore serve as a "visualization agent" consistent with the teaching of the patent.

While the patent teaches that the "visualization agent is *preferably* an agent that provides a color that is visible to the human eye," (*id.*, 5:11-12 (emphasis added)), it further explains that a user "may observe the hydrogel by looking through the free surface into the hydrogel and at the coated tissue" and that the "visualization agent in the hydrogel makes the hydrogel change in its appearance" (*id.*, 5:48-51.) The patent teaches that the visual effect caused by the "visualization agent," such as the disclosed particles included within the gel, need only be able to obscure the user's ability to view the underlying tissue. (*id.*, 7:32-33.) The different visual features imparted by a visualization agent are also demonstrated by claim 25 of the '566 patent, which is the child to the '034 patent. In that claim, the "visualization" agent can cause the gel to be completely opaque—i.e., "not being able to see the substrate tissue through the polymer composition"—or it can cause "the features of the substrate to be obscured," such as when the gel has any minimally observable opacity. (Ex. 1016, claim 25.)

Accordingly, any definition of "visualization agent" must meet all of the functional requirements disclosed in the patent. It therefore must include at least any substance or material that obscures the user's ability to view the underlying

tissue by reducing the optical clarity of the hydrogel, including materials that impart *any* visually observable opacity to the hydrogel.

2. "light at a wavelength detectable to a human eye"

As used in the '034 patent, "light at a wavelength detectable to a human eye" means "light that is within the range of wavelengths that are visible to a human eye." Many colors, including some of those provided by the visualization agents claimed in claim 6, are made up of more than one wavelength of light. The color white is likewise made up of multiple wavelengths. Therefore, "light at a wavelength detectable to a human eye" must include visualization agents that impart a white color to the hydrogel or that reflect white light to reduce the optical clarity of the hydrogel.

3. "wherein the hydrogel is hydrolytically biodegradable"

As used in the '034 patent, "wherein the hydrogel is hydrolytically biodegradable" means "wherein the hydrogel includes hydrolytically biodegradable portions or chemical linkages." The '034 patent discusses making the hydrogel more susceptible to degradation by using precursors that polymerize using chemical linkages that can be degraded by water, without requiring the presence of an enzyme. However, the '034 patent does not require that ***all*** portions or chemical linkages be hydrolytically biodegradable. Rather, the '034 patent states that "[t]he polymers preferably also have a hydrolytically biodegradable

portion or linkage, for example an ester, carbonate, or an amide linkage. (Ex. 1001, 6:44-47.) The '034 patent further contemplates hydrogels consisting of both hydrolytically biodegradable portions and enzymatically biodegradable portions. (*See, e.g.*, *id*, 24:49-54 ("The resultant crosslinked hydrogel is a semisynthetic hydrogel whose degradation depends on the degradable segment in the crosslinker as well as degradation of albumin by enzymes. In the absence of any degradable enzymes, the crosslinked polymer will degrade solely by the hydrolysis of the biodegradable segment.".)

VIII. PERSON OF ORDINARY SKILL IN THE ART

As of the presumptive November 9, 2001 priority date of the '034 patent (and for several years prior), a person of ordinary skill in the art ("POSA") would be a person with either: (1) a Ph.D. in the field of chemistry, polymer chemistry, chemical engineering, materials science and/or a related field and having at least one year of educational or work experience in the synthesis and development of biocompatible polymer materials; (2) a bachelor's degree in in the field of chemistry, polymer chemistry, chemical engineering, materials science and/or a related field and at least two years of work experience in the synthesis and development of biocompatible polymer materials; or (3) any education and experience equivalent to (1) or (2). (Ex. 1003, ¶ 49.)

IX. THE SCOPE AND CONTENT OF THE PRIOR ART

As described above, various prior art references teach the same or similar polymer chemistry as the ’034 patent, and various prior art references teach the use of a visualization agent in a biomedical material. Petitioner relies on a subset of these prior art references, described below:

A. Rhee ’500 (Ex. 1004)

Rhee ’500 is a patent that issued on February 23, 1999, from an application filed on December 18, 1996. Rhee ’500 qualifies as presumptive prior art under 35 U.S.C. §102(b) because it was published and publicly available more than one year before the filing date of the ’034 patent. Furthermore, Rhee ’500 qualifies as prior art under 35 U.S.C. §102(e), unless Patent Owner can establish an invention date prior to its filing date.

As it expressly discloses, Rhee ’500 “relates generally to crosslinked polymer compositions comprising a first synthetic polymer containing multiple nucleophilic groups crosslinked using a second synthetic polymer containing multiple electrophilic groups, and to methods of using such compositions as bioadhesives, for tissue augmentation, in the prevention of surgical adhesions, and for coating surfaces of synthetic implants, as drug delivery matrices and for ophthalmic applications.” (Ex. 1004, 1:13-20.)

Rhee ’500 discloses various compositions that can be used for coating

tissues of a patient. Rhee '500 also discloses gelation times as fast as 5 seconds. (*Id*., Table 6.) Rhee '500 further discloses that "opaque" fibrillar collagen "may be preferred for use in adhesive compositions intended for long-term persistence in vivo, if optical clarity is not a requirement." (*Id*., 13:6-13.) Rhee '500 additionally discloses hydrogels that include "barium sulfate," which likewise would result in opaque hydrogels. Rhee '500 therefore discloses that its compositions may include a visualization agent.

B. Rhee '587 (Ex. 1005)

Rhee '587 is a patent that issued on March 25, 1997, from an application filed on June 7, 1995. Rhee '587 qualifies as prior art under 35 U.S.C. §102(b) because it was published and publicly available more than one year before the presumptive priority date of the '034 patent. Furthermore, Rhee '587 qualifies as prior art under 35 U.S.C. §102(e), unless Patent Owner can establish an invention date prior to its filing date.

Rhee '587 relates generally to compositions useful as biological or surgical adhesives, and discloses a variety of collagen-based bioadhesive compositions and their uses. Example 4 of Rhee '587 is representative of disclosures of particular relevance to this Petition. Example 4 describes several formulations of gels applied to a wound site. These gels would be understood by one skilled in the art to be hydrogels. The gels were formed by mixing a precursor having nucleophilic

groups (methylated collagen) with a precursor having electrophilic groups (SG-PEG), and the material was allowed to gel (crosslink) on the wound site. Both precursors in this example were synthetic, and the resulting hydrogel was hydrolytically biodegradable and adherent to the tissue.

Rhee '587 also describes hydrogels made from the same precursors (methylated collagen and SG-PEG) that gelled/crosslinked in times ranging from several minutes down to immediately. (Ex. 1005, Table 2.)

Rhee '587 also discloses that its compositions may be made using fibrillar collagen, which is opaque. Rhee '587 is generally concerned with creating gels that are optically clear, for use in ophthalmic applications. But "if optical clarity is not a requirement," the opaque fibrillar collagen may be used. Rhee '587 therefore discloses that its compositions may include a visualization agent.

C. Bass (Ex. 1006)

Bass is a patent that issued on March 8, 1994, from an application filed on July 9, 1991. Bass qualifies as prior art under 35 U.S.C. §102(b) because it was published and publicly available as of 1994—years before the earliest filing to which the '034 patent claims priority.

Bass discloses "a composition for bonding separated tissues together or for coating tissues or prosthetic materials including at least one natural or synthetic peptide and at least one support material which may be activated by energy and to

methods of making and using the same." (Ex. 1006, Abstract.) The components form "a matrix or gel or sol" when mixed. (*Id*., 5:9-12.)

Bass discloses that "[t]he composition of the present invention may also include indogenous [sic] or exogenous chromophores to facilitate visualization of the material during placement into warm blooded animals." (*Id*., 11:18-21.) Bass then cites to two articles from the mid-1980's as disclosing use of endogenous and exogenous chromophores, including "for aid in the placement of biological glues." (*Id*., 11:25-34.)

Bass's claims are directed to "matrix, sol or gel" compositions and methods for "bonding separated tissue together," and several claims further include the use of chromophores. For example, claim 30 requires that "the chromophore is present in sufficient quantity to allow visualization of the composition." (*Id*., claim 30.) Claims 31 and 40 further list "indocyanine green" and "methylene blue" as possible chromophores. (*Id*., claims 31, 40.) These are both among the visualization agents listed in claim 6 of the '034 patent.

D. Tse (Ex. 1007)

Tse is an article entitled, "Cyanoacrylate Adhesive Used to Stop CSF Leaks During Orbital Surgery," and published in *Arch Opthalmol,* 102:1337-1339 (1984). Tse qualifies as prior art under 35 U.S.C. §102(b) because it was published and publicly available as of 1984—many years before the earliest filing to which the

'034 patent claims priority. A copy of the journal containing Tse from the National Library of Medicine bears a stamp on the back indicating "National Library of Medicine" and the date of "September 11, 1984," indicating the date the journal was received by the library. (Ex. 1007 at 10, 12-13). The hardcover binding the journal bears a stamp that says "JRSI 1985." (*Id*., at 11.) The stamps on the face of the journal obtained from the National Library of Medicine are proof of publication, and are subject to the FRE 803(8) public records exception to hearsay. In addition, the inside cover of the journal indicates "Monthly Circulation in Excess of 18,000." (*Id*., at 3.) This circulation figure, the stated September 1984 date on the article, and the proof of indexing by the National Library of Medicine are all more than 20 years old, and are subject to the FRE 803(16) ancient document exception to hearsay.

Tse describes a polymeric tissue adhesive that includes a visualization agent and is used during surgeries to stop cerebrospinal fluid leaks. Tse specifically describes an adhesive that is applied to the tissue and has a color additive which "facilitates visualization and assessment of…thickness" of the applied adhesive. (Ex 1007 at 7, third column.) Tse therefore goes beyond the mere inclusion of a visualization agent, further teaching the use of the visualization agent to gauge thickness. Tse demonstrates the application of the adhesive, and states that the "faint gray-blue tint indicates adequate thickness of adhesive film" on the tissue of

the site of the CSF leak, thereby informing the surgeon that the desired and adequate thickness of the adhesive film was applied to the patient. (*Id.* at 8, Fig. 1.)

E. Additional Prior Art Confirming the General Knowledge of the POSA

In addition to the specific references discussed in detail above, Dr. Lowman addresses additional prior art confirming the general knowledge of the POSA as of the presumptive November 9, 2001 priority date of the '034 patent (and several years prior). These disclosures are described in his declaration as also briefly discussed above in Section V.

X. THERE IS A REASONABLE LIKELIHOOD THAT CLAIMS 1-12 OF THE '034 PATENT ARE ANTICIPATED AND/OR OBVIOUS

A. Legal Standards

1. Anticipation

Under 35 U.S.C. § 102(b), a patent is invalid if the purported invention "was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for a patent in the United States." It is black letter law that a patent claim is anticipated when every limitation is found either expressly or inherently in a single prior art reference. *King Pharmaceuticals, Inc. v. Elan Pharmaceuticals, Inc.* 616 F.3d 1267, 1274 (Fed. Cir. 2010) (citing *Celeritas Techs., Ltd. V. Rockwell Int'l Corp*., 150 F.3d 1354,

1361 (Fed. Cir. 1998)). Further, "[a]s long as the reference discloses all of the claim limitations and enables the 'subject matter that falls within the scope of the claims at issue,' the reference anticipates—no actual creation or reduction to practice is required." *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (citations omitted).

2. Obviousness

The question of obviousness requires analyzing (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co*., 383 U.S. 1, 17-18 (1966). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 416 (2007).

B. Invalidity Grounds Based on Rhee '500

1. Ground I: Claims 1-5 and 7-12 Are Anticipated Under § 102(b) or (e) by Rhee '500

As discussed below and in Dr. Lowman's declaration, Rhee '500 discloses every limitation of every challenged claim, with the exception of the particular visualization agents listed in claim 6. (*See* Ex. 1003, ¶¶ 65-82.) Claims 1-5 and 7-

12 are therefore anticipated by Rhee '500.[4]

a. Rhee '500 expressly discloses electrophilic-nucleophilic hydrogels for coating tissues

Rhee '500 expressly discloses a class of hydrogel materials made from the same electrophilic-nucleophilic chemistry and useful for "surgical sealing" as the Rhee patents that were expressly identified in the background section of the '034 patent as prior art. (*See* Ex. 1001, 1:52-2:3 (Rhee patents: 5,527,856, 5,550,188).) "A statement in the patent that something is in the prior art is binding on the applicant and patentee for determinations of anticipation and obviousness." *See Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1570 (Fed. Cir. 1988).

b. Rhee '500 expressly discloses the "visualization agents" barium sulfate or fibrillar collagen

Rhee '500 also expressly discloses at least two substances that can be

[4] Although Rhee '500 was before the examiner and used in combination with another prior art reference to Hubbell as the basis for obviousness rejections during prosecution of the '034 patent, the examiner never considered Rhee '500 as an anticipatory reference to the challenged claims of the '034 patent. Patentees' arguments regarding the combination of Hubbell and Rhee '500 were primarily focused on the examiner's reliance on Hubbell to provide the "visualization agent" to the combination. The patentees submitted a declaration from named inventor Dr. Sawhney that stated the dyes in Hubbell were "bleached" during the photopolymerization process used to create the Hubbell hydrogels and thereby rendered the resulting hydrogels colorless. (Ex. 1002 at 56-57.) Here, Petitioner relies on the express disclosures of the "visualization agents" in Rhee '500, Bass, and Tse, to demonstrate the invalidity of the claims. These references involve "visualization agents" that would not be bleached when added to the hydrogels taught by Rhee. (Ex. 1003, ¶ 71.)

included within the hydrogels that would impart color and opacity, thereby satisfying the "visualization requirement" in such hydrogels. First, Rhee '500 discloses that "[t]he crosslinked polymer compositions can also be prepared to contain various imaging agents such as . . . barium sulfate. . . ." (Ex. 1004, 10:63-65.) During prosecution, the patentees admitted that "barium sulfate is a 'milky' solution." (Ex. 1002 at 120.)

Thus, Rhee '500 expressly teaches hydrogels that include barium sulfate as a "visualization agent", resulting in "milky" hydrogels that have an off-white, milk-like color, thereby reducing the transparency of the gel. (Ex. 1003, ¶¶ 54, 72.) Rhee '500's further teaching that in addition to imparting a milky appearance to the hydrogels, the barium sulfate can also be used "to aid visualization of the compositions after administration via X-ray or ^{19}F-MRI" does not negate the fact that the barium sulfate also causes the hydrogels to have a visible color and a reduction in transparency. (Ex. 1003, ¶ 72.) The barium sulfate can serve both visual purposes when included in the hydrogels. (*Id*.)

Second, Rhee '500 discloses the incorporation of the opaque material known as "fibrillar collagen," which also acts as a visualization agent when, as is expressly taught, it is incorporated into the disclosed hydrogels, thereby making them appear white or milky and therefore less transparent. (Ex. 1003, ¶¶ 68-70.) In the section entitled "Incorporation of Other Components into the Crosslinked

Synthetic Polymer," Rhee '500 expressly teaches that:

> Naturally occurring proteins, such as collagen . . . can additionally be incorporated into the compositions of the invention. When these other components also contain functional groups which will react with the functional groups on the synthetic polymers, their presence during mixing and/or crosslinking of the first and second synthetic polymer will result in formation of a crosslinked synthetic polymer-naturally occurring polymer matrix. In particular, when the naturally occurring polymer (protein or polysaccharide) also contains nucleophilic groups such as primary amino groups, the electrophilic groups on the second synthetic polymer will react with the primary amino groups on these components, as well as the nucleophilic groups on the first synthetic polymer, to cause these other components to become part of the polymer matrix.

(Ex. 1004, 11:3-19.)

Rhee '500 further explains that in the context of the inventions, "[t]he term 'collagen' or 'collagen material' as used herein refers to all forms of collagen." (Ex. 1004, 11:62-65.) Rhee '500 teaches that fibrillar collagen is "opaque" and explains that "fibrillar collagen, or mixtures of nonfibrillar and fibrillar collagen, may be preferred for use in adhesive compositions intended for long-term persistence in vivo, ***if optical clarity is not a requirement***." (*Id.*, 13:6-13.) In sum, Rhee '500 expressly teaches that the opaque fibrillar collagen is a visualization agent when it is incorporated into the hydrogels formed between a first synthetic

polymer and a second synthetic polymer through electrophilic-nucleophilic chemistry and becomes part of the polymer matrix. (Ex. 1003, ¶¶ 68-70.)

While Rhee '500 expressly discloses that fibrillar collagen is opaque, the opacity imparted into hydrogels made according to the teachings is further confirmed by other Rhee patents:

> The term "fibrillar collagen" refers to collagens in which the triple helical molecules aggregate to form thick fibers due to intermolecular charge interactions, such that ***a composition containing fibrillar collagen will be more or less opaque***.

(Ex. 1013, 4:58-62.) Thus, when fibrillar collagen is incorporated into the hydrogels taught in Rhee '500, the inherent opacity imparted to those hydrogels demonstrates that the fibrillar collagen is acting as a "visualization agent."

c. Rhee '500 element-by-element anticipation chart

As set forth in the chart below, the broad teaching of electrophilic-nucleophilic hydrogels as well as the specifically disclosed hydrogel embodiments of Rhee '500 that incorporate either barium sulfate or fibrillar collagen satisfy all elements of the claims challenged in Ground I. (*See* Ex. 1003, ¶¶ 65-82.)

U.S. Patent No. 7,009,034	**US 5,874,500 (Rhee '500) (Ex. 1004)**
1. A method of preparing a composition suitable to coat a tissue of a patient,	"Another use of the crosslinked polymer compositions of the invention is to ***coat tissue***s in order to prevent the formation of adhesions following surgery or injury to internal tissues or organs." (19:6-10 (emphasis added).)

<table>
<tr><th>U.S. Patent No. 7,009,034</th><th colspan="2">US 5,874,500 (Rhee ’500) (Ex. 1004)</th></tr>
<tr><td>the method comprising:</td><td colspan="2">“The compositions can also be used as biosealants to seal fissures or crevices within a tissue or structure (such as a vessel), or junctures between tissues or structures, to prevent leakage of blood or other biological fluids.” (20:15-18.)</td></tr>
<tr><td>mixing reactive precursor species comprising nucleophilic functional groups, reactive precursor species comprising electrophilic functional groups, and</td><td colspan="2">“In a general method for preventing the formation of adhesions following surgery, ***a first synthetic polymer containing two or more nucleophilic groups is mixed with a second synthetic polymer containing two or more electrophilic groups to provide a reaction mixture***. . .” (3:9-19 (emphasis added).)</td></tr>
<tr><td rowspan="2">a visualization agent</td><td>Barium sulfate as the visualization agent</td><td>Fibrillar collagen as the visualization agent</td></tr>
<tr><td>“[t]he crosslinked polymer compositions can also be prepared to contain various imaging agents such as . . . barium sulfate. . . .” (10:63-65.)

“barium sulfate is a ‘milky’ solution.” (Ex. 1002 at 120.)</td><td>“Because it is ***opaque*** . . . fibrillar collagen, or mixtures of nonfibrillar and fibrillar collagen, may be preferred for use in adhesive compositions intended for long-term persistence in vivo, ***if optical clarity is not a requirement***.” (13:6-13.)</td></tr>
<tr><td>such that the nucleophilic functional groups and electrophilic functional groups crosslink after contact with the tissue to form a hydrogel having an interior and an</td><td colspan="2">“In a general method for preventing the formation of adhesions following surgery, a first synthetic polymer containing two or more nucleophilic groups is mixed with a second synthetic polymer containing two or more electrophilic groups to provide a reaction mixture; ***the reaction mixture is applied to tissue comprising, surrounding, or adjacent to a surgical site before substantial cross linking has occurred between the nucleophilic groups and the electrophilic groups; the reaction mixture is allowed to continue crosslinking in situ***</td></tr>
</table>

<table>
<tr><th>U.S. Patent No. 7,009,034</th><th colspan="2">US 5,874,500 (Rhee ’500) (Ex. 1004)</th></tr>
<tr><td>exterior, with the exterior having at least one substrate coating surface and</td><td colspan="2">until equilibrium crosslinking has been achieved; and the surgical site is closed by conventional methodologies.” (3:9-19.)</td></tr>
<tr><td rowspan="2">the visualization agent being at least partially disposed within the interior and reflecting or emitting light at a wavelength detectable to a human eye to thereby provide a means for visualization of the coating by a human eye.</td><td>Barium sulfate as the visualization agent</td><td>Fibrillar collagen as the visualization agent</td></tr>
<tr><td>“[t]he crosslinked polymer compositions can also be prepared to contain various imaging agents such as . . . barium sulfate. . . .” (10:63-65.)

“barium sulfate is a ‘milky’ solution.” (Ex. 1002 at 120.)</td><td>Naturally occurring proteins, such as collagen…can additionally be incorporated into the compositions of the invention.” (11:3-6.)

“Because it is ***opaque*** . . . fibrillar collagen, or mixtures of nonfibrillar and fibrillar collagen, may be preferred for use in adhesive compositions intended for long-term persistence in vivo, ***if optical clarity is not a requirement***.” (13:6-13.)</td></tr>
<tr><td>2. The method of claim 1, wherein the hydrogel comprises crosslinked polymers that are selected from the group consisting of collagen, fibrinogen, albumin, and fibrin.</td><td colspan="2">Naturally occurring proteins, such as ***collagen***…can additionally be incorporated into the compositions of the invention. When these other components also contain functional groups which will react with the functional groups on the synthetic polymers, ***their presence during mixing and/or crosslinking of the first and second synthetic polymer will result in formation of a crosslinked synthetic polymer-naturally occurring polymer matrix***.” (11:3-12.)

“For use in tissue adhesion as discussed below, it may also be desirable to incorporate proteins such as ***albumin, fibrin or fibrinogen*** into the crosslinked polymer composition to promote cellular adhesion.” (13:30-33.)</td></tr>
<tr><td>3. The method of claim 1, wherein</td><td colspan="2">“The present invention discloses a crosslinked polymer composition comprising ***a first synthetic polymer*** containing</td></tr>
</table>

U.S. Patent No. 7,009,034	US 5,874,500 (Rhee '500) (Ex. 1004)
the hydrogel is made of synthetic materials.	two or more nucleophilic groups, and ***a second synthetic polymer*** containing two or more electrophilic groups which are capable of covalently bonding to one another to form a three dimensional matrix." (2:25-32 Summary of the Invention.)
4. The method of claim 1, wherein the hydrogel is hydrolytically biodegradable.	"Preferred multifunctionally activated polyethylene glycols for use in the compositions of the present invention are polyethylene glycols containing succinimidyl groups, such as SG-PEG and SE-PEG (shown in FIGS. 4-7), preferably in trifunctionally or tetrafunctionally activated form." (8:64-9:2) "Figs 4 to 13 show the formation of various crosslinked synthetic polymer compositions from hydrophilic polymers." (4:17-18.) "The structure in FIG. 5 results in a conjugate which includes an 'ether' linkage which is less ***subject to hydrolysis***. This is distinct from the conjugate shown in FIG. 4, wherein an ester linkage is provided. ***The ester linkage is subject to hydrolysis*** under physiological conditions." (8:8-12.)
5. The method of claim 1, wherein the hydrogel comprises covalently crosslinked hydrophilic polymers.	"FIGS. 4 to 13 show the formation of various ***crosslinked synthetic polymer compositions from hydrophilic polymers***." (4:17-18.) "***Hydrophilic polymers*** and, in particular, various polyethylene glycols, ***are preferred*** for use in the compositions of the present invention." (7:52-55.)
7. The method of claim 1, wherein the visualization agent is covalently linked to the hydrogel.	Fibrillar collagen as the visualization agent Naturally occurring proteins, such as collagen…can additionally be incorporated into the compositions of the invention. When these other components also contain functional groups which will react with the functional groups on the synthetic polymers, their presence during mixing and/or crosslinking of the first and second synthetic polymer will result in formation of a crosslinked synthetic polymer-

U.S. Patent No. 7,009,034	US 5,874,500 (Rhee '500) (Ex. 1004)
	naturally occurring polymer matrix." (11:3-11.) "Because ***it is opaque*** and less tacky than nonfibillar collagen, fibrillar collagen is less preferred for use in bioadhesive compositions. However, as disclosed in commonly owned, U.S. application Ser. No. 08/476,825, fibrillar collagen, or mixtures of nonfibrillar and fibrillar collagen, may be preferred for use in adhesive compositions intended for long-term persistence in vivo, ***if optical clarity is not a requirement***." (13:6-13.)
8. The method of claim 1, wherein the hydrogel comprises a biologically active agent.	"The crosslinked polymer compositions of the present invention may also be used for localized delivery of various drugs and other ***biologically active agents***." (14:60-65.) "***Biologically active agents may be incorporated into the crosslinked synthetic polymer composition*** by admixture. Alternatively, the agents may be incorporated into the crosslinked polymer matrix, as described above, by binding these agents with the functional groups on the synthetic polymers." (15:38-43.)
9. The method of claim 1, wherein the hydrogel forms within 60 seconds after contact with the substrate.	"[T]he time required for complete crosslinking to occur is dependent on a number of factors, including the types and molecular weights of the two synthetic polymers and, most particularly, the concentrations of the two synthetic polymers (i.e., higher concentrations result in faster crosslinking times)." (17:33-38.)

U.S. Patent No. 7,009,034	US 5,874,500 (Rhee '500) (Ex. 1004)
	TABLE 6 Effect of pH on Gel Formation of Tetra-amino PEG/Tetra SE-PEG Formulations Tetra-amino PEG Conc. (mg/ml) / Tetra SE-PEG Conc. (mg/ml) / pH / Gelation Time 20 / 20 / 6 / >90.0 min 20 / 20 / 7 / 20.0 min 20 / 20 / 8 / 1.4 min 50 / 50 / 6 / 24.0 min 50 / 50 / 7 / 3.5 min 50 / 50 / 8 / 10.0 sec 100 / 100 / 6 / 9.0 min 100 / 100 / 7 / 47.0 sec 100 / 100 / 8 / 10.0 sec 200 / 200 / 6 / 2.0 min 200 / 200 / 7 / 9.0 sec 200 / 200 / 8 / 5.0 sec (24:8-24.)
10. The method of claim 1, wherein the hydrogel forms within 5 seconds after contact with the substrate.	"[T]he time required for complete crosslinking to occur is dependent on a number of factors, including the types and molecular weights of the two synthetic polymers and, most particularly, the concentrations of the two synthetic polymers (i.e., higher concentrations result in faster crosslinking times)." (17:31-38.) TABLE 6 Effect of pH on Gel Formation of Tetra-amino PEG/Tetra SE-PEG Formulations Tetra-amino PEG Conc. (mg/ml) / Tetra SE-PEG Conc. (mg/ml) / pH / Gelation Time 20 / 20 / 6 / >90.0 min 20 / 20 / 7 / 20.0 min 20 / 20 / 8 / 1.4 min 50 / 50 / 6 / 24.0 min 50 / 50 / 7 / 3.5 min 50 / 50 / 8 / 10.0 sec 100 / 100 / 6 / 9.0 min 100 / 100 / 7 / 47.0 sec 100 / 100 / 8 / 10.0 sec 200 / 200 / 6 / 2.0 min 200 / 200 / 7 / 9.0 sec 200 / 200 / 8 / 5.0 sec (24:8-24.)
11. The method of claim 1, wherein the biodegradable hydrogel is adherent to the	"In a general method for effecting the nonsurgical attachment of a first surface to a second surface, a first synthetic polymer containing two or more nucleophilic groups is mixed with a second synthetic polymer containing two or more electrophilic groups to provide a reaction mixture; the

U.S. Patent No. 7,009,034	US 5,874,500 (Rhee '500) (Ex. 1004)
tissue.	reaction mixture is applied to a first surface before substantial crosslinking has occurred; and the first surface is contacted with a second surface ***to effect adhesion between the two surfaces***." (2:56-64.)
12. A hydrogel composition adapted for use with a tissue of a patient, the composition being made by the process of claim 11.	This composition is just the product of the claim 11 process.

2. Ground II: Claims 1-6 and 8-12 Are Obvious Under § 103 Over The Combination of Rhee '500 and Bass

Challenged claims 1-6 and 8-12 of the '034 patent would have been obvious over Rhee '500 in combination with Bass, as set forth in the declaration of Dr. Lowman. (*See* Ex. 1003, ¶¶ 83-94.) As discussed above, Rhee '500 discloses every element of every challenged claim, with the exception of the specific visualization agents listed in claim 6. (*Id.*, ¶¶ 65-82.) Combining Rhee '500's teaching of methods for making nucleophilic-electrophilic hydrogels to coat a tissue with the visualization agents taught by Bass, as opposed to the visualization agents expressly disclosed in Rhee '500, also meets all of the elements of claims 1-6 and 8-12. (*Id.*, ¶¶ 83-94.)

As discussed above, like Rhee '500, Bass also discloses "compositions[s] for

bonding separated tissues together or for coating tissues," where the components are chosen so as "to form a matrix, sol or gel." (Ex. 1006, claim 1.) Bass further expressly discloses the use of "chromophores ***to facilitate visualization of the material during placement into warm blooded animals***." (*Id*., 11:18-21 (emphasis added).) The chromophores "enhance the visualization of the material." (*Id*., 13:26-27.) Among the chromophores claimed by Bass "to allow the visualization of the composition" are indocyanine green and methylene blue. (*Id*., claims 30-31.) These are two of the specific "visualization agents" in the group recited in claim 6 of the '034 patent.

a. Motivation to Combine

A POSA would be motivated to combine the teachings of Bass and Rhee '500 to arrive at each of claims 1-6 and 8-12 of the '034 patent. (*See* Ex. 1003, ¶¶ 87-88.) Bass teaches the use of common colorants for the express purpose of "allow[ing] visualization of the composition." (Ex. 1006, *e.g.*, claims 30-31.) Rhee '500 teaches methods of synthesizing the hydrogels claimed in the '034 patent. Furthermore, while generally teaching the synthesis of optically clear compositions—well-suited for ophthalmic applications, where optical clarity is a requirement (Ex. 1004, 3:28-32)—Rhee '500 also teaches the synthesis of "opaque" compositions, which "may be preferred for use in adhesive compositions intended for long-term persistence in vivo, if optical clarity is not a requirement."

(*Id*., 13:6-13.)

A POSA who wanted to visualize the hydrogels of Rhee '500 through means other than (or in addition to) by making them opaque would not need to consult any other reference, and would take advantage of the general knowledge in the art that dyes and other colorants can be mixed with the hydrogel precursors. (*See* Ex. 1003, ¶ 88.) Regardless, a POSA would also look to Bass, which is in the same field as the '034 patent, namely "biocompatible crosslinked polymers" (Ex. 1001, 1:24-25, Field of the Invention), and also concerns bonding or coating tissues, e.g., during surgery. (*Id.*) For example, Bass notes:

> All surgical disciplines are concerned with the repair of damaged tissues and vessels. Damage can be the result of direct trauma to the body or as part of a surgical procedure in which there is a separation of normally continuous tissue such as in vein or artery anastomoses. Regardless of the cause, proper repair of the tissue or blood vessel is an essential step in the positive outcome of surgery.

(Ex.1006, 1:17-25, Background of the Invention.) A POSA would therefore be motivated to combine the visualization teachings of Bass with the hydrogel synthesis chemistry of Rhee '500. (*See* Ex. 1003, ¶¶87-88.)

b. Reasonable Expectation of Success

A POSA combining Rhee '500 with Bass would have a reasonable expectation of success. In particular, given the disclosures in Bass (and the general

knowledge of color additives in polymers), a POSA would have every reason to expect success in combining the hydrogels of Rhee '500 with the visualization agents of Bass to produce colored hydrogels. (*See* Ex. 1003, ¶ 89.) The challenged claims of the '034 patent do not require any particular concentration of visualization agent—all that is required is a minimal amount to make the color of the hydrogel visible to the human eye. Nonetheless, to the extent different concentrations of visualization agent must be tried before arriving at a suitable concentration, such work is the realm of routine experimentation. (*See* Ex. 1003, ¶ 90.)

c. Rhee '500 and Bass element charts for obviousness

As set forth in the declaration of Dr. Lowman, the combination of Rhee '500 and Bass discloses all of the elements of claims 1-6, 8-12. (*See* Ex. 1003, ¶¶ 91-94.) The "visualization agent" is provided by the disclosure of Bass, and the other elements are satisfied by Rhee '500 in the same way as Ground I. (*Id*.)

(1) Bass discloses the "visualization agent" elements of claim 1 and claim 6 to render claims 1-6 and 8-12 obvious in combination with Rhee '500

The disclosures in Bass that satisfy the "visualization agent" limitations in independent claim 1 and dependent claim 6 are as follows. (*Id.* at ¶ 92.)

U.S. Patent No. 7,009,034	US 5,292,362 (Bass) (Ex. 1006)
a visualization agent (claim 1)	"The composition of the present invention may also include indogenous [sic] or exogenous chromophores to facilitate visualization of the material during placement into warm blooded animals." (11:18-21.) "The composition of claim 29 wherein the chromophore is present in sufficient quantity to allow visualization of the composition." (Claim 30.) "The composition of claim 29 wherein the chromophore is selected from indocyanine green, fluorescein, rose bengal, gentian violet, and methylene blue." (Claim 31.)
the visualization agent being at least partially disposed within the interior and reflecting or emitting light at a wavelength detectable to a human eye to thereby provide a means for visualization of the coating by a human eye. (claim 1)	"The composition of the present invention may also include indogenous or exogenous chromophores to facilitate visualization of the material during placement into warm blooded animals." (11:18-21.) "The composition of claim 29 wherein the chromophore is present in sufficient quantity to allow visualization of the composition." (Claim 30.) "The composition of claim 29 wherein the chromophore is selected from indocyanine green, fluorescein, rose bengal, gentian violet, and methylene blue." (Claim 31.)
6. The polymeric coating method of claim 1, wherein the visualization agent is chosen from the group consisting of FD&C Blue #1, FD&C Blue #2, methylene blue, indocyanine green, visualization agents that provide a blue color,	"The composition of claim 29 wherein the chromophore is selected from ***indocyanine green***, fluorescein, rose bengal, gentian violet, and ***methylene blue***." (Claim 31 (emphasis added).)

U.S. Patent No. 7,009,034	US 5,292,362 (Bass) (Ex. 1006)
and visualization agents that provide a green color.	

Introducing these claim elements into the charts provided in Ground I demonstrates that all elements of claims 1-6 and 8-12 are disclosed by the combination of Rhee '500 and Bass, and therefore all of those claims are obvious.

(2) Dependent claims 9 and 10 are obvious

Dependent claims 9 and 10 add the limitations on claim 1 that the hydrogel forms within 60 or 5 seconds after contact with the substrate, respectively. (Ex. 1001, 40:21-24.) These limitations are expressly disclosed in Rhee '500 and, when combined with Bass, the claims are invalid for obviousness. To the extent it is argued that there is a distinguishable difference between the disclosure of Rhee '500 and the formation of hydrogels within 60 or 5 seconds, any such difference is insufficient to render the claims non-obvious. (Ex. 1003, ¶ 93.) "[T]he mere existence of differences between the prior art and an invention does not establish the invention's nonobviousness." *Dann v. Johnston*, 425 U.S. 219, 230 (1976). Rather, a POSA would deem any such difference obvious because "the relatively small logical gap between the prior art and the claim in this case is closed by a person of ordinary skill in the art pursuing known options within his or her technical grasp." *Scanner Techs. Corp. v. ICOS Vision Sys. Corp. N.V.*, 528 F.3d

1365, 1382 (Fed. Cir. 2008) (quotations omitted).

In Table 6, Rhee '500 reports experimental "Gelation Time" for hydrogels made with nucleophilic "Tetra-amino PEG" and electrophilic "Tetra SE-PEG." (Ex. 1004, 24:8-25.) The experiments demonstrate that hydrogels made from these two components at concentrations of 200 mg/ml had gelation times of 9.0 seconds at a pH of 7 and 5.0 seconds at a pH of 8. (*Id.*) Rhee '500 expressly teaches that "the time required for complete crosslinking to occur is dependent on a number of factors, including the types and molecular weights of the two synthetic polymers and, most particularly, the concentrations of the two synthetic polymers (i.e., ***higher concentrations result in faster crosslinking times***)." (*Id.*, 17:33-38 (emphasis added); *see also id.*, 24:25-30.) Thus, one of skill in the art would be able to easily achieve faster gelation times than those disclosed following the express teaching of Rhee '500 to create hydrogels that form within 5 seconds, thereby rendering claims 9 and 10 obvious. (*See* Ex. 1003, ¶¶ 93-94.)

3. Ground III: Claims 1-6, 8-12 Are Obvious Under § 103 Over Rhee '500 In View Of Tse

Claims 1-6 and 8-12 of the '034 patent would have been obvious over Rhee '500 in combination with Tse. (*See* Ex. 1003, ¶¶ 95-102.) As discussed above, Rhee '500 discloses every element of every challenged claim, with the exception of the specific visualization agents listed in claim 6.

Tse describes a cyanoacrylate adhesive polymer that includes a visualization agent and that can be used during surgeries to stop cerebrospinal fluid leaks. Tse specifically describes an adhesive that is applied to the tissue and has a color additive which "facilitates visualization and assessment of…thickness" of the applied adhesive. (Ex. 1007 at 7, third column.) The particular adhesive used in Tse, Histoacryl® Blue, had been in use for decades, and was known to differ from the clear Histoacryl® only by the addition of a blue dye. (Ex. 1003, ¶ 97.) Additionally, the dye used in Tse was used in the context of a polymeric reaction to form a polymer film. (*Id.*, ¶ 98.) Thus, the blue color additive from Tse satisfies the "visualization agent" limitations of claim 1 and dependent claim 6. (*Id*.) When the "visualization agent" of Tse is combined with materials taught by Rhee '500, all limitations of claims 1-6 and 8-12 are met by the combination and render the claims obvious for the same reasons as set forth in Ground II (with Tse replacing Bass). (*Id.*)

a. Motivation to Combine

A POSA would be motivated to combine the teachings of Tse and Rhee '500 to arrive at each of claims 1-6 and 8-12 of the '034 patent. (*See* Ex. 1003, ¶¶ 99-101.) Tse describes a well-known tissue adhesive being used for sealing dural tears and stopping cerebrospinal fluid leaks. (Ex. 1007 at 7.) Tse notes that

"[t]here is a color additive in the tissue adhesive, which facilitates visualization and assessment of plaque thickness." (*Id*.)

Rhee '500 teaches methods of synthesizing the hydrogels claimed in the '034 patent. Furthermore, while generally teaching the synthesis of optically clear compositions—well-suited for ophthalmic applications, where optical clarity is a requirement (Ex. 1004, 3:28-32)—Rhee '500 also teaches the synthesis of "opaque" compositions, which "may be preferred for use in adhesive compositions intended for long-term persistence in vivo, if optical clarity is not a requirement." (*Id*., 13:6-13.)

A POSA who wanted to visualize the hydrogels of Rhee '500 through means other than (or in addition to) by making them opaque would not need to consult any other reference, and would take advantage of the general knowledge in the art that dyes and other colorants can be mixed with the hydrogel precursors. (Ex. 1003, ¶ 101.) Regardless, a POSA would also look to Tse, which, like the '034 patent, concerns coating the tissue of a patient with an adherent material. Like Tse, the '034 patent also specifically concerns "sealing of the dura mater…to prevent leakage of cerebrospinal fluid." (Ex. 1001, 8:46-48.) A POSA would therefore be motivated to combine the visualization teachings of Tse with the hydrogel synthesis chemistry of Rhee '500. (*See* Ex. 1003, ¶ 99-101.)

b. Reasonable Expectation of Success

A POSA combining Rhee '500 with Tse would have a reasonable expectation of success. In particular, given the disclosures in Tse (and the general knowledge of color additives in polymers), a POSA would have every reason to expect success in combining the hydrogels of Rhee '500 with the visualization agent of Tse to produce colored hydrogels. (*See* Ex. 1003, ¶ 102.) The challenged claims of the '034 patent do not concern any particular concentration of visualization agent. Nonetheless, to the extent different concentrations of visualization agent must be tried before arriving at a suitable concentration, such work is the realm of routine experimentation.

C. Invalidity Grounds Based on Rhee '587

1. Ground IV: Claims 1-5 and 7-12 Are Anticipated Under § 102(b) by Rhee '587

As discussed in Dr. Lowman's declaration and summarized in the claim chart below, Rhee '587 discloses every limitation of every challenged claim, with the exception of the particular visualization agents listed in claim 6. (*See* Ex. 1003, ¶¶ 103-116.) Claims 1-5 and 7-12 are therefore anticipated by Rhee '587. (*Id*.)

Specifically, the '587 patent expressly discloses that:

- "methylated collagen" and "SG-PEG" are both synthetic materials
- "methylated collagen" has nucleophilic functional groups

- "SG-PEG" has electrophilic functional groups
- "methylated collagen" and "SG-PEG" crosslink via covalent bonds to form a hydrogel
- "opaque" fibrillar collagen acts as a visualization agent by reflecting wavelengths of light that make the hydrogel visible to the human eye
- "opaque" fibrillar collagen crosslinks within the hydrogel via covalent bonds
- "SG-PEG" has ester linkages, which are hydrolytically biodegradable
- Table 2 shows results from crosslinking SG-PEG and methylated collagen, including two instances in which the time to gel was "immediate"

(Ex. 1003, ¶¶ 103-116.)

A claim chart identifying how these disclosures of Rhee '587 anticipate the claims 1-5 and 7-12 of the '034 patent is set forth below. (*Id.*)

U.S. Patent No. 7,009,034	US 5,614,587 (Rhee '587) (Ex. 1005)
1. A method of preparing a composition suitable to coat a tissue of a patient, the method comprising:	"This invention relates generally to compositions useful as biological or surgical adhesives; more specifically, it relates to bioadhesive compositions comprising collagen crosslinked using a multifunctionally activated synthetic hydrophilic polymer, as well as methods of using such compositions to effect adhesion between a first surface and a second surface, wherein at least one of the first and second surfaces is preferably a native tissue surface." (1:20-27, Field of the Invention)
mixing reactive precursor species comprising nucleophilic functional groups, reactive precursor species comprising electrophilic functional groups,	"Nine hundred (900) microliters (μl) of methylated collagen…was mixed with approximately 13.5 mg of difunctionally activated SG-PEG…. This material was extruded onto a bloody wound site on the liver of a previously sacrificed rabbit and allowed to gel for 1 minute." (19:12-19)
and a visualization agent such that	"Fibrillar collagen may also be used in the methods of the invention, although it is generally less preferred because it is ***opaque*** and less tacky than nonfibrillar collagen. However, fibrillar collagen, or mixtures of nonfibrillar and fibrillar collagen, may be preferred for use in adhesive compositions intended for long-term persistence in vivo, ***if optical clarity is not a requirement***." (6:50-57)
the nucleophilic functional groups and electrophilic functional groups crosslink after contact with the tissue to form a hydrogel having an interior and an exterior, with the	"Nine hundred (900) microliters (μl) of methylated collagen…was mixed with approximately 13.5 mg of difunctionally activated SG-PEG…. This material was extruded onto a bloody wound site on the liver of a previously sacrificed rabbit and allowed to gel for 1 minute. The skin was then placed on top of the gel and held in place for 1 minute. The skin was removed and the condition of the gel examined. The methylated collagen--SG-PEG gel adhered very well to the liver, not as well to the skin." (19:12-23)

U.S. Patent No. 7,009,034	US 5,614,587 (Rhee '587) (Ex. 1005)
exterior having at least one substrate coating surface and	
the visualization agent being at least partially disposed within the interior and reflecting or emitting light at a wavelength detectable to a human eye to thereby provide a means for visualization of the coating by a human eye.	"Fibrillar collagen may also be used in the methods of the invention, although it is generally less preferred because it is ***opaque*** and less tacky than nonfibrillar collagen. However, fibrillar collagen, or mixtures of nonfibrillar and fibrillar collagen, may be preferred for use in adhesive compositions intended for long-term persistence in vivo, ***if optical clarity is not a requirement***." (6:50-57)
2. The method of claim 1, wherein the hydrogel comprises crosslinked polymers that are selected from the group consisting of collagen, fibrinogen, albumin, and fibrin.	"In accordance with the present invention, compositions suitable for use as biological or surgical adhesives are prepared by crosslinking collagen with a multifunctionally activated synthetic hydrophilic polymer." (4:50-54)
3. The method of claim 1, wherein the hydrogel is made of synthetic materials.	"Nine hundred (900) microliters (μl) of methylated collagen…was mixed with approximately 13.5 mg of difunctionally activated SG-PEG…. This material was extruded onto a bloody wound site on the liver of a previously sacrificed rabbit and allowed to gel for 1 minute." (19:12-19)

U.S. Patent No. 7,009,034	US 5,614,587 (Rhee '587) (Ex. 1005)
4. The method of claim 1, wherein the hydrogel is hydrolytically biodegradable.	"The structure in Formula 2 results in a conjugate which includes an "ether" linkage which is less ***subject to hydrolysis***. This is distinct from the conjugate shown in Formula 1, wherein an ester linkage is provided. The ester linkage ***is subject to hydrolysis*** under physiological conditions." (9:31-36)
5. The method of claim 1, wherein the hydrogel comprises covalently crosslinked hydrophilic polymers.	To prepare the collagen-based bioadhesive compositions of the present invention, collagen is crosslinked using a multifunctionally activated synthetic hydrophilic polymer. The term "multifunctionally activated" refers to synthetic hydrophilic polymers which have, or have been chemically modified to have, two or more functional groups located at various sites along the polymer chain and are capable of reacting with primary amino groups on collagen molecules. Each functional group on a multifunctionally activated synthetic hydrophilic polymer molecule is capable of ***covalently binding*** with a collagen molecule, thereby ***effecting crosslinking*** between the collagen molecules. (8:15-28)
7. The method of claim 1, wherein the visualization agent is covalently linked to the hydrogel.	"Fibrillar collagen may also be used in the methods of the invention, although it is generally less preferred because it is ***opaque*** and less tacky than nonfibrillar collagen. However, fibrillar collagen, or mixtures of nonfibrillar and fibrillar collagen, may be preferred for use in adhesive compositions intended for long-term persistence in vivo, ***if optical clarity is not a requirement***." (6:50-57)
8. The method of claim 1, wherein the hydrogel comprises a biologically active agent.	"The collagen-based bioadhesive compositions of the present invention may also be formulated to ***contain biologically active agents*** in order to facilitate adhesion of tissues or healing of adhered tissues." (7:12-15)

<table>
<tr><th>U.S. Patent No. 7,009,034</th><th>US 5,614,587 (Rhee '587) (Ex. 1005)</th></tr>
<tr><td>9. The method of claim 1, wherein the hydrogel forms within 60 seconds after contact with the substrate.</td><td>TABLE 2
PEG Crosslinking of 20 mg/ml Methylated Collagen
<table><tr><th>Final SG-PEG Conc. (mg/ml)</th><th>Time to Form Gel</th><th>Elasticity</th><th>Gel Strength</th><th>DSC Tm (°C.) Range</th></tr><tr><td>0</td><td>—</td><td>—</td><td>—</td><td>38–43</td></tr><tr><td>2</td><td>5–10 min.</td><td>elastic</td><td>good</td><td>45–60</td></tr><tr><td>6</td><td>5–10 min.</td><td>elastic</td><td>good</td><td>—</td></tr><tr><td>10</td><td>5–10 min.</td><td>very elastic</td><td>very good</td><td>45–68</td></tr><tr><td>20</td><td>5 min.</td><td>slightly elastic</td><td>good</td><td>—</td></tr><tr><td>30</td><td>immediate</td><td>not elastic</td><td>good</td><td>47–62</td></tr><tr><td>50</td><td>immediate</td><td>slightly elastic</td><td>not good</td><td>—</td></tr><tr><td>72</td><td>>10 min.</td><td>not elastic</td><td>not good</td><td>40–70</td></tr><tr><td>106</td><td>>10 min.</td><td>not elastic</td><td>not good</td><td>—</td></tr></table>(17:43-60)</td></tr>
<tr><td>10. The method of claim 1, wherein the hydrogel forms within 5 seconds after contact with the substrate.</td><td>TABLE 2
PEG Crosslinking of 20 mg/ml Methylated Collagen
<table><tr><th>Final SG-PEG Conc. (mg/ml)</th><th>Time to Form Gel</th><th>Elasticity</th><th>Gel Strength</th><th>DSC Tm (°C.) Range</th></tr><tr><td>0</td><td>—</td><td>—</td><td>—</td><td>38–43</td></tr><tr><td>2</td><td>5–10 min.</td><td>elastic</td><td>good</td><td>45–60</td></tr><tr><td>6</td><td>5–10 min.</td><td>elastic</td><td>good</td><td>—</td></tr><tr><td>10</td><td>5–10 min.</td><td>very elastic</td><td>very good</td><td>45–68</td></tr><tr><td>20</td><td>5 min.</td><td>slightly elastic</td><td>good</td><td>—</td></tr><tr><td>30</td><td>immediate</td><td>not elastic</td><td>good</td><td>47–62</td></tr><tr><td>50</td><td>immediate</td><td>slightly elastic</td><td>not good</td><td>—</td></tr><tr><td>72</td><td>>10 min.</td><td>not elastic</td><td>not good</td><td>40–70</td></tr><tr><td>106</td><td>>10 min.</td><td>not elastic</td><td>not good</td><td>—</td></tr></table>(17:43-60)</td></tr>
<tr><td>11. The method of claim 1, wherein the biodegradable hydrogel is adherent to the tissue.</td><td>"Nine hundred (900) microliters (µl) of methylated collagen…was mixed with approximately 13.5 mg of difunctionally activated SG-PEG…. This material was extruded onto a bloody wound site on the liver of a previously sacrificed rabbit and allowed to gel for 1 minute. The skin was then placed on top of the gel and held in place for 1 minute. The skin was removed and the condition of the gel examined. The methylated collagen--SG-PEG gel ***adhered very well to the liver***, not as well to the skin." (19:12-23)</td></tr>
<tr><td>12. A hydrogel composition adapted for use with a tissue of a</td><td>This composition is just the product of the claim 11 process.</td></tr>
</table>

U.S. Patent No. 7,009,034	US 5,614,587 (Rhee '587) (Ex. 1005)
patient, the composition being made by the process of claim 11.	

2. Ground V: Claims 1-6 and 8-12 Are Obvious Under § 103 Over Rhee '587 In View Of Bass

Claims 1-6 and 8-12 of the '034 patent would have been obvious over Rhee '587 in combination with the visualization agents of Bass. (Ex. 1003, ¶¶ 117-122.) As discussed above, Rhee '587 discloses every element of every challenged claim, with the exception of the specific visualization agents listed in claim 6. (*Id*., ¶¶ 103-116.)

As discussed in section X.B.2 above, Bass discloses the use of "chromophores to facilitate visualization of the material during placement into warm blooded animals." (Ex. 1006, 11:18-21.) The chromophores "enhance the visualization of the material." (*Id*., 13:26-27.) Among the chromophores claimed by Bass "to allow the visualization of the composition" are indocyanine green and methylene blue. (*Id*., claims 30-31.) These are two of the visualization agents in the group recited in dependent claim 6 of the '034 patent. The addition of the visualization agents disclosed in Bass to the hydrogel materials taught by Rhee '587 meet every limitation of claims 1-6 and 8-12. (*See* Ex. 1003, ¶¶ 117-118.)

a. Motivation to Combine

A POSA would be motivated to combine the teachings of Bass and Rhee '587 to arrive at claims 1-6 and 8-12 of the '034 patent. (*See* Ex. 1003, ¶¶ 119-120.) Bass teaches the use of common colorants for the express purpose of "allow[ing] visualization of the composition." (Ex. 1006, *e.g.*, claims 30-31.) Rhee '587 teaches methods of synthesizing the hydrogels claimed in the '034 patent. Furthermore, while generally teaching the synthesis of optically clear compositions—well-suited for ophthalmic applications, where optical clarity is a requirement (Ex. 1005, 4:23-27)—Rhee '587 also teaches the synthesis of "opaque" compositions, which "may be preferred for use in adhesive compositions intended for long-term persistence in vivo, if optical clarity is not a requirement." (*Id*., 6:52-57.)

A POSA who wanted to visualize the hydrogels of Rhee '587 through means other than (or in addition to) by making them opaque would not need to consult any other reference, and would take advantage of the general knowledge in the art that dyes and other colorants can be mixed with the hydrogel precursors. (*See* Ex. 1003, ¶ 120.) Regardless, a POSA would also look to Bass, which is in the same field as the '034 patent, namely "biocompatible crosslinked polymers" (Ex. 1001, 1:24-25, Field of the Invention), and also concerns bonding or coating tissues, e.g., during surgery. (*Id*.) For example, Bass notes:

> All surgical disciplines are concerned with the repair of damaged tissues and vessels. Damage can be the result of direct trauma to the body or as part of a surgical procedure in which there is a separation of normally continuous tissue such as in vein or artery anastomoses. Regardless of the cause, proper repair of the tissue or blood vessel is an essential step in the positive outcome of surgery. (Ex. 1006, 1:17-25, Background of the Invention.)

A POSA would therefore be motivated to combine the visualization teachings of Bass with the hydrogel synthesis chemistry of Rhee '587. (*See* Ex. 1003, ¶¶ 119-120.)

b. Reasonable Expectation of Success

A POSA combining Rhee '587 with Bass would have a reasonable expectation of success. (*See* Ex. 1003, ¶ 121.) In particular, given the disclosures in Bass (and the general knowledge of color additives in polymers), a POSA would have every reason to expect success in combining the hydrogels of Rhee '587 with the dyes of Bass to produce colored hydrogels. (*Id*.) The challenged claims of the '034 patent do not concern any particular concentration of visualization agent. (*Id*., ¶ 122.) Nonetheless, to the extent different concentrations of visualization agent must be tried before arriving at a suitable concentration, such work is the realm of routine experimentation. (*Id*.)

3. Ground VI: Claims 1-6 and 8-12 Are Obvious Under § 103 Over Rhee '587 In View Of Tse

Challenged claims 1-6 and 8-12 of the '034 patent would have been obvious over Rhee '587, in view of Tse. (*See* Ex. 1003, ¶¶ 123-130.)As discussed above, Rhee '587 discloses every element of every challenged claim, with the exception of the specific visualization agents listed in claim 6. (*Id*., ¶¶ 103-116.)

Tse describes a cyanoacrylate adhesive polymer that includes a visualization agent and that can be used during surgeries to stop cerebrospinal fluid leaks. Tse specifically describes an adhesive that is applied to the tissue and has a color additive which "facilitates visualization and assessment of…thickness" of the applied adhesive. (Ex. 1007 at 7.) The particular adhesive used in Tse, Histoacryl® Blue had been in use for decades, and was known to differ from the clear Histoacryl® only by the addition of a blue dye. (*See* Ex. 1003, ¶ 124.)

Creating materials based on the disclosure of Rhee '587 that include a blue dye to facilitate visualization, as taught by Tse, satisfy all limitations of claims 1-6 and 8-12. The limitations disclosed by Rhee '587 are provided in the anticipation chart in ground IV and the disclosure of Tse satisfies the visualization agent elements. (*See* Ex. 1003, ¶¶ 124-125.)

a. Motivation to Combine

A POSA would be motivated to combine the teachings of Tse and Rhee '587 to arrive at each of claims 1-12 of the '034 patent. (*See* Ex. 1003, ¶¶ 126-128.) Tse describes a well-known tissue adhesive being used for sealing dural tears and stopping cerebrospinal fluid leaks. (Ex. 1007 at 7.) Tse notes that "[t]here is a color additive in the tissue adhesive, which facilitates visualization and assessment of plaque thickness." (*Id*.)

Rhee '587 teaches methods of synthesizing the hydrogels claimed in the '034 patent. Furthermore, while generally teaching the synthesis of optically clear compositions—well-suited for ophthalmic applications, where optical clarity is a requirement (Ex. 1005, 4:23-27)—Rhee '587 also teaches the synthesis of "opaque" compositions, which "may be preferred for use in adhesive compositions intended for long-term persistence in vivo, if optical clarity is not a requirement." (*Id*., 6:52-57.)

A POSA who wanted to visualize the hydrogels of Rhee '587 through means other than (or in addition to) by making them opaque would not need to consult any other reference, and would take advantage of the general knowledge in the art that dyes and other colorants can be mixed with the hydrogel precursors. (*See* Ex. 1003, ¶ 128.) Regardless, a POSA would also look to Tse, which, like the '034 patent, concerns coating the tissue of a patient with an adherent material. Like Tse,

the ’034 patent also specifically concerns “sealing of the dura mater…to prevent leakage of cerebrospinal fluid.” (Ex. 1001, 8:46-48.) A POSA would therefore be motivated to combine the visualization teachings of Tse with the hydrogel synthesis chemistry of Rhee ’587. (*See* Ex. 1003, ¶¶ 126-128.)

b. Reasonable Expectation of Success

A POSA combining Rhee ’587 with Tse would have a reasonable expectation of success. (*See* Ex. 1003, ¶ 129.) In particular, given the disclosures in Tse (and the general knowledge of color additives in polymers), a POSA would have every reason to expect success in combining the hydrogels of Rhee ’587 with the visualization agent of Tse to produce colored hydrogels. (*Id*.) The challenged claims of the ’034 patent do not concern any particular concentration of visualization agent. (*Id*., ¶ 130.) Nonetheless, to the extent different concentrations of visualization agent must be tried before arriving at a suitable concentration, such work is the realm of routine experimentation. (*See id*.)

D. No Secondary Indicia of Non-Obviousness Exist

As explained above, the prior art and knowledge of a person of ordinary skill in the art render the challenged claims of the ’034 patent anticipated or obvious. Petitioner is not aware of any evidence of any secondary indicia of non-obviousness having a nexus to the alleged claimed invention that challenge that conclusion. Petitioner reserves the right to respond to any additional assertions of

secondary indicia of non-obviousness advanced by Patent Owner.

XI. CONCLUSION

Petitioner respectfully requests institution of *inter partes* review of claims 1-12 of the ’034 patent, and a finding that the claims are unpatentable, based on the grounds presented in this Petition.

Dated: September 16, 2016

Respectfully submitted,

By: /Orion Armon/
Orion Armon
Reg. No. 65,421
Counsel for Petitioner
HYPERBRANCH MEDICAL TECHNOLOGY, INC.

CERTIFICATE OF COMPLIANCE WITH WORD COUNT LIMITS

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). According to the word processing system used to prepare it, this Petition contains 13,274 words, excluding parts that are exempted by 37 C.F.R. § 42.24(a).

Dated: September 16, 2016

By: /Orion Armon/
Orion Armon
Reg. No. 65,421
Counsel for Petitioner
HYPERBRANCH MEDICAL TECHNOLOGY, INC.

CERTIFICATE OF SERVICE

I hereby certify pursuant to 37 C.F.R. §§ 42.6(e) that a complete copy of:

- Petition;
- Exhibits 1001 – 1018; and
- this Certificate of Compliance with Word Count
- this Certificate of Service

are being served via Federal Express on the 16th day of September, 2016, the same day as the filing of the above-identified document in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon the Patent Owner by serving the correspondence address of record with the USPTO as follows:

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Dated: September 16, 2016

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