Filed on behalf of RTI Surgical, Inc.

By: Herbert D. Hart III
David D. Headrick
Alejandro Menchaca
McAndrews, Held & Malloy, Ltd.
500 West Madison Street
Chicago, Illinois 60661
Tel.: (312) 775-8000
Fax: (312) 775-8100
Email: hhart@mcandrews-ip.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

RTI SURGICAL, INC.,
Petitioner

v.

LIFENET HEALTH,
Patent Owner

Case IPR2019-00571
Patent No. 6,569,200

PETITION FOR INTER PARTES REVIEW

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PETITIONER'S EXHIBIT LIST

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1005	WO 9807452 ("Walker")
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1015	R.E. Billingham, et al., "The Freezing, Drying and Storage of Mammalian Skin," J. Exp. Biol. 29:454-468 (1952) ("Billingham")
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1030	Ronald L. Levin and Thomas W. Miller, "An Optimum Method for the Introduction or Removal of Permeable Cryoprotectants: Isolated Cells," 18 Cryobiology 32-48 (1981)
1031	J. van Baare et. al., "Virucidal effect of glycerol as used in donor skin preservation," 20 Burns Suppl. 1, S77-S80 (1994)

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I. Introduction

RTI Surgical, Inc. ("RTI" or "Petitioner") petitions for *inter partes* review of claims 1-10, 12-13, and 15 of U.S. Patent No. 6,569,200 ("the 200 patent"; Ex. 1001), which is owned by LifeNet Health ("LifeNet" or "Patent Owner"). The application for the 200 patent was filed on June 5, 2001 and issued as a patent on May 27, 2003.

The 200 patent describes incorporating chemical compounds, identified as "plasticizers," within a cleaned soft tissue graft to replace water at the molecular level with the object of providing a soft tissue graft that "exhibits the materials properties that approximate those properties present in normal hydrated tissue, is not brittle and does not necessitate rehydration prior to implantation." (Ex.1001, 5:33-40.) The claims are directed to a "plasticized soft tissue graft" wherein the plasticizer(s) is/are "not removed from [the] internal matrix of [the graft] prior to the transplantation [of the graft] into a human." (*See, e.g., id.* at 24:12-15.) Patent Owner added this limitation to overcome a prior art rejection during prosecution. The claims were thereafter allowed. However, neither incorporating chemical compounds, such as glycerol (described as a "plasticizer" in the 200 patent), into a soft tissue graft nor specifying that they are "not removed" before transplantation were new in the art at the time of the alleged invention.

The process of incorporating chemical compounds into a soft tissue graft to produce a graft that "exhibits the materials properties that approximate those properties present in normal hydrated tissue, is not brittle and does not necessitate rehydration prior to implantation" had been widely used in tissue preservation before the filing date of the 200 patent. For example, both U.S. Patent No. 5,336,616 (Ex. 1004; "Livesey"), issued in 1994, and WO 98/07452 (Ex. 1005; "Walker"), published February 26 1998, disclose methods of incorporating chemical compounds, including glycerol, into the internal matrix of a soft tissue graft to produce a pliable graft with properties, such as structure, flexibility, and strength, that approximate those of normal hydrated tissue. (Ex.1004, 25:12-17; Ex.1005, 2:14-34.) Similarly, U.S. Patent No. 4,357,274 (Ex. 1006; "Werner"), issued in 1982, discloses a method of incorporating glycerol into the internal matrix of a tissue and that the resulting tissue does not require rehydration before use. (Ex.1006, 2:12-14, 2:37-41.)

The limitation that the plasticizers are "not removed from [the] internal matrix of [the graft] prior to the transplantation [of the graft] into a human" does not distinguish the claimed subject matter from the known process of incorporating chemical compounds into a soft tissue graft. The benefits of "not removing [the plasticizer] from [the] internal matrix" were already known in the art. For example, it was known that glycerol was non-toxic to humans and that it exhibited powerful

antiseptic action in the body. (Ex. 1021 at 969-971; Ex. 1013 at S6; Ex. 1022 at S44; Ex. 1023 at 394-395.) It was further known that glycerol-treated tissue retained the pliability of natural tissue and that glycerol did not alter the cellular characteristics of the tissue, such as the structure of the internal matrix. (Ex. 1023 at 396-397; Ex. 1022 at S44-45; Ex. 1021 at 971.) Thus, the claims of the 200 patent recite nothing more than the known benefits of a known process disclosed in the prior art. As such, there is at least a reasonable likelihood that the claims of the 200 patent are unpatentable over Livesey, Walker, and Werner.

II. Mandatory Notices

Real Parties-In-Interest: RTI Surgical, Inc. is the real party-in-interest.

Related Matters: The following judicial or administrative matter would affect or be affected by a decision in the proceedings:

1. *LifeNet Health v. RTI Surgical, Inc.*, Case No. 3:18-CV-817 (M.D. Fla.), filed June 25, 2018 ("the LifeNet-RTI Litigation").

Lead and Backup Counsel:

Lead Counsel	Backup Counsel
Herbert D. Hart III Registration No. 30,063 McAndrews, Held & Malloy, Ltd. 500 West Madison Street Chicago, Illinois 60661 Tel.: (312) 775-8000 Email: hhart@mcandrews-ip.com	David D. Headrick Registration No. 40,642 McAndrews, Held & Malloy, Ltd. 500 West Madison Street Chicago, Illinois 60661 Tel.: (312) 775-8000 Email: dheadrick@mcandrews-ip.com
	Alejandro Menchaca Registration No. 34,389 McAndrews, Held & Malloy, Ltd. 500 West Madison Street Chicago, Illinois 60661 Tel.: (312) 775-8000 Email: amenchaca@mcandrews-ip.com
	Gregory C. Schodde Registration No. 36,668 McAndrews, Held & Malloy, Ltd. 500 West Madison Street Chicago, Illinois 60661 Tel.: (312) 775-8000 Email: gschodde@mcandrews-ip.com
	Scott P. McBride Registration No. 42,853 McAndrews, Held & Malloy, Ltd. 500 West Madison Street Chicago, Illinois 60661 Tel.: (312) 775-8000 Email: smcbride@mcandrews-ip.com

Service Information: RTI Surgical, Inc., consents to service by email at:

RTI200IPR@mcandrews-ip.com.

III. Grounds for Standing

The 200 patent is available for *inter partes* review and RTI is not barred or estopped from requesting an *inter partes* review challenging claims 1-10, 12-13, and 15 on the grounds identified in this Petition.

IV. Identification of Challenge

Petitioner identifies five grounds of unpatentability:

Ground 1: Claims 1-3, 5, 7-10, 12, and 15 are anticipated by Walker.

Ground 2: Claims 1-3 and 5-10, 12-13, and 15 are obvious over Walker.

Ground 3: Claims 1-3, 7-8, 10, and 15 are anticipated by Livesey.

Ground 4: Claims 1-3, 7-8, 10, and 15 are obvious over Livesey.

Ground 5: Claim 4 is obvious over Walker or Livesey in view of Werner.

V. The 200 Patent

A. The Subject Matter of the 200 Patent

The 200 patent describes a "plasticized soft tissue graft" suitable for transplantation into a human and methods of producing such a graft. The patent discloses that one or more chemical compounds (called "plasticizers") are incorporated within the internal matrix of the soft tissue graft and act to replace water at the molecular level without increasing the brittleness of the graft. (Ex.1001, 1:14-19.) It further discloses that "[r]eplacement of the chemical plasticizers by water prior to implantation is not required." (*Id.*, 1:19-21.)

Most of the 200 patent specification is devoted to describing the treatment of bone tissue as opposed to soft tissue. (*See, e.g., id.,* 1:29-3:3.) For example, while the claims are directed toward a "cleaned *soft tissue* graft," the specification defines only the term "cleaned *bone* graft" and examples of well-known cleaning processes for *bone* tissue. (*Id*., 6:31-34, 9:38-41). It discloses two examples of a plasticization method using soft tissue (fascia lata and pericardium). (*Id.*, 22:32-24:2.) Definitions of other words relevant to the claims are also specific to bone, rather than soft tissue grafts, including the terms "incubating," "impregnating," and "materials properties." (*Id.,* 6:46-58, 7:4-8.)

The 200 patent explains that "[s]oft tissue products are typically provided as fresh-frozen or freeze-dried." (*Id.,* 3:37-40.) This allegedly "causes [such] grafts to be brittle and typically causes shrinkage where the shrinkage is not uniform, thereby causing graft failure." (*Id.*, 3:49-53.) The patent further states that "solvent preservation using for example, acetone or alcohol, can cause irreversible denaturation of proteins, and solubilization of solvent soluble components, including for example, lipids." (*Id.*, 3:53-55.) The patent states that these methods "necessitate[] a rehydration step in preparation of the bone and soft tissue product for implantation." (*Id*., 3:55-64.)

The 200 patent purports to describe a solution to the alleged problems associated with freeze-drying and solvent preservation by incorporating a

"plasticizer" within the internal matrix of the tissue graft and not removing the plasticizer before implantation of the graft. (*Id.,* 5:33-39.) Examples 9 and 10 (the only examples directed toward soft tissue) use glycerol as the plasticizer; however, the specification provides other examples of suitable plasticizers, including sorbitol, ethylene glycol, sucrose, and mannitol. (*Id.,* 7:35-50, 8:19-21, 8:44-52.) The 200 patent states that "[t]he plasticizer can be introduced into the bone or soft tissue matrix at any number of steps in the processing procedures and at a variety of concentrations" but states that it is preferable to introduce the plasticizer before freeze-drying or dehydrating because "the plasticizer is used to stabilize the matrix and load bearing components of the soft tissue graft such that the graft can be used with rehydration/reconstitution." (*Id.,* 9:4-8, 10:9-12, 11:1-2, 11:45-53.) The patent acknowledges that, "[u]nder freeze-drying, the water present in the bone . . . is removed by sublimation, however, *the glycerol will remain and replace the free and bound water* as the water is removed from the bone tissue." (*Id.* at 10:12-17 (emphasis added).)

The 200 patent further states that "[p]rior to transplantation into a patient, excess glycerol may optionally be removed from the plasticized bone or soft tissue graft." It describes a method of centrifuging the grafts to remove excess glycerol, explaining that "[t]he plasticizer tightly associated with the molecular and chemical structure of the tissue will not exit the graft and the tissue will remain

plasticized without retaining physically discernable quantities of plasticizer." (*Id.*, 11:63-12:2.) But the claims expressly recite that the one or more plasticizers are "not removed from [the] internal matrix of [the graft] prior to the transplantation [of the graft] into a human." (*See, e.g., id.* at 24:13-15.) Patent Owner added this limitation during prosecution to overcome a rejection over U.S. Patent No. 5,718,012 (Ex. 1012; "Cavallaro"). Treatment of soft tissue grafts with chemical compounds to produce soft, pliable, and functional soft tissue grafts for transplantation was known in the art and it would have been obvious to a person of ordinary skill in the art ("POSITA") to "not remove" the chemical compound from the graft before use because of the known benefits of chemical compounds such as glycerol. (Ex.1034, ¶¶28-30.)

B. Prosecution History

The 200 patent issued on May 27, 2003, from U.S. Patent Application No. 09/874,862, filed June 4, 2001, and claims priority as a divisional of application No. 09/107,458, filed on June 30, 1998, which issued as U.S. Patent No. 6,293,970, and therefore may have an effective filing date of June 30, 1998.[1]

On June 4, 2001, before examination, claims 1-15 and 30-31 were cancelled and the title was changed from "Plasticized Bone and Soft Tissue Grafts, and

[1] The reference to divisional application No. 09/107,458 appearing on the face of the 200 patent is a mistake. The correct application is No. 09/107,459.

Methods of Making and Using Same" to "Plasticized Soft Tissue Grafts, and Methods of Making and Using Same." On September 13, 2002, the Examiner issued a non-final office action rejecting claims 16-19, 28, 29, and 32 under 35 U.S.C. 102(e) as anticipated by U.S. Patent No. 5,718,012 (Ex. 1012; "Cavallaro"). The Examiner stated that Cavallaro disclosed plasticizing soft tissue with a plasticizer, such as glycerol:

> Cavallaro teaches a method of strength enhancement of collagen constructs intended for implantation to replace or repair tissue or organs. Cavallaro forms collagen threads from collagen harvested from a bovine common digital extensor tendon. During processing, the formed thread is rinsed with purified water or phosphate buffered saline (col. 5, lines 19-31). To improve tensile strength, a collagen thread or bundle comprising collagen threads is plasticized with water or aqueous solution or buffers and/or glycerol.

(Ex. 1032 at pg. 2.) The examiner also objected to claims 20-27 as depending on a rejected base claim but stated that they would be allowable if rewritten in independent form to include the limitations of the base claim and any intervening claims. Livesey (Ex. 1004) was cited on the "Notice of References Cited" sheet of the non-final office action but was not substantially discussed nor was it the basis of any rejection.

On November 4, 2002, applicants amended the rejected claims, adding the limitation "said one or more plasticizers are not removed from an internal matrix of said plasticized soft tissue graft prior to transplantation into a human" to avoid the rejection based on Cavallaro. (Ex. 1033 at pg. 3-4.) The claims were thereafter allowed. As discussed *infra*, each of Walker, Livesey, and Werner discloses the feature that the Examiner thought to be missing in the prior art—"said one or more plasticizers are not removed from an internal matrix of said plasticized soft tissue graft prior to transplantation into a human."

C. Person of Ordinary Skill in the Art

As Dr. McQuillan explains, a POSITA relating to the subject matter of the 200 patent would have had at least either (a) a Master of Science degree in biology, biochemistry, biomaterials engineering, biomedical engineering, or a related field and approximately three years of research or work experience related to preparing and/or processing tissue for transplantation into a human, or (b) a Bachelor of Science degree in one of those fields and approximately five years of research or work experience related to preparing and/or processing tissue for transplantation into a human recipient.[2] (Ex.1034, ¶18.)

[2] Patent Owner advocated for a slight variation of this level of skill in prior litigation involving the 200 patent in *LifeNet Health v. LifeCell Corp.*, Case No.

Such a person would have been familiar with the need for cleaning of soft tissue grafts before transplantation and also with the use of chemical compounds to protect and preserve soft tissue grafts as explained in more detail below. (Ex.1034, ¶¶16-17.)

1. Cleaning soft tissue grafts to remove cellular elements

At least as early as 1994, it was known that the "extracellular protein matrix [of a soft tissue graft] is made up of collagen and other proteins and provides a structural template which may be repopulated with new viable cells." (Ex.1034, ¶21; Ex.1004, 1:26-30.) By February 1998, a POSITA would have known that soft tissue grafts presented a risk of adverse immunogenic response in transplant patients.[3] (Ex.1034, ¶22.) Therefore, a POSITA by February 1998 would have known that soft tissue grafts used for transplantation must be cleaned to remove potentially adverse cellular materials present in the graft from the donor. (Ex.1034, ¶¶23-24; *see also* Ex. 1023 at 390-391.) A POSITA in February 1998 would have been familiar with the various methods for cleaning soft tissue grafts to remove

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13-CV-00486 in the Eastern District of Virginia ("the LifeNet Litigation"). (*See* Ex. 1017 at 4.)

[3] In the LifeNet-RTI Litigation, LifeNet has asserted that its invention date was in March 1998. The unpatentability analysis in this Petition is made as of February 1998 (the latest publication date of the primary prior art references in this Petition).

cellular elements such as the cleaning methods disclosed in Livesey, Klement, Wang, Brendel, and Werner. (Ex.1034, ¶¶23-24.)

While the 200 patent explains the cleaning procedures conventionally used for bone tissue, it provides little detail regarding the cleaning procedures used for soft tissue. (Ex.1001, 9:18-10:5.) The only examples of the cleaning procedure for soft tissue are found in Examples 9 and 10 of the 200 patent, which describe soaking the soft tissue graft in a 1:100 dilution of Allowash™ Solution for at least 15 minutes. (*Id.*, 22:44-49.) A POSITA would have understood that such a brief soak in Allowash™ Solution would not remove all of the cellular elements from the soft tissue because soft tissues comprise densely organized collagen and therefore would require a more extensive cleaning procedure for complete removal of cellular components. (Ex.1034, ¶¶33-35.) Examples of more extensive methods for cleaning soft tissue can be found in Livesey (Ex.1004, 23:62-65), Klement (Ex.1009, 3:27-66), and Wang (Ex.1011, 3:47-4:35). Such processes include, for example, exposure to detergent solutions for up to one hour while on a rotator at 40 ± 5 RPM. (Ex.1004, 23:62-65.) Therefore, a POSITA would have recognized that the cleaning process described in the 200 patent only partially removes cellular components from a soft tissue graft. (Ex.1034, ¶35.)

2. Use of chemical compositions to preserve soft tissues

By February 1998, preservation and protection of soft tissue grafts using chemical compounds was known in the art. (Ex.1034, ¶¶25-27.) The use of glycerol to preserve and protect tissue was disclosed in patent literature as early as 1981. (Ex.1034, ¶26; Ex.1006, 2:21-32.) Further, non-patent literature discussed the benefits of glycerol preservation including that "[g]lycerol is . . . a useful plasticizer in biomaterials . . . to make these materials soft, pliable and easy to use." (Ex.1034, ¶28; Ex.1022 at S44; Ex.1023 at 396-397; Ex.1021 at 971.) Therefore, a POSITA in February 1998 would have known that to maintain the softness, pliability, and ease of use of the tissue, the glycerol would have to remain within the internal matrix of the graft. (Ex.1034, ¶28.)

By February 1998, it was also known that glycerol was non-toxic to humans and exhibited antiseptic action in the human body. (Ex.1034, ¶25; Ex.1021 at 969-971; Ex.1013 at S6; Ex.1022 at S44; Ex.1023 at 394-395.) These properties of glycerol reduced the risk of adverse immunogenic responses in transplant patients. Therefore, a POSITA would be motivated to avoid removing glycerol from the tissue before transplantation. (Ex.1034, ¶¶25-26.)

By February 1998, it was also well known that glycerol preservation did not affect the fundamental architecture of tissues and that tissues preserved with glycerol kept properties approximating those of their natural counterparts.

(Ex.1034, ¶30; Ex. 1022 at S4; Ex. 1023 at 396-397; Ex. 1021 at 971.) Therefore, a POSITA in February 1998 would have known that leaving glycerol in the internal matrix of a natural soft tissue graft would not result in any fundamental changes to the architecture of the graft. (Ex.1034, ¶30.)

In February 1998, a POSITA would have known that the alternative—i.e., removing the glycerol from the soft tissue—would require extensive washing. (Ex.1034, ¶29; Ex. 1029 at 244.) Non-patent literature as early as 1981 described the extensive dilution steps required to remove plasticizers (such as glycerol) from biomaterials without causing damage to their structure. (Ex. 1030.) Thus, a POSITA in February 1998 would have been motivated to keep the plasticizer in the soft tissue graft rather than subjecting the graft to a removal process that would make the tissue susceptible to degradation.

In short, a POSITA in February 1998 would have known that it was advantageous to not to remove the plasticizer from the internal matrix of a plasticized soft tissue graft in order to produce a soft, pliable graft, that minimized risk of adverse immunogenic response, preserved the natural properties of the tissue, and prevented damage to the structure of the tissue. (Ex.1034, ¶¶28-30.)

D. Claim Construction

The following terms are expressly defined in the 200 patent:

- **"internal matrix" -** "in soft tissue, the intercellular substance of such soft tissue including for example ligaments and tendons, including collagen and elastin fibers and base matrix substances." (Ex.1001, 6:59-65.)
- **"plasticizer"** - "any biocompatible compounds which are soluble in water and can easily displace/replace water at the molecular level and preferably have a low molecular weight such that the plasticizer fits into the spaces available to water within the hydrated molecular structure of the bone or soft tissue." (*Id.*, 7:29-35.) "Such plasticizers are preferably not toxic to the cellular elements of tissue into which the graft is to be placed, or alternately, the plasticizer is easily removed from the graft product prior to implantation" and that "[s]uitable plasticizers are preferably compatible with and preferably readily associates [sic] with the molecular elements of the bone tissue and/or soft tissue." (*Id.*, 7:35-41.) Disclosed examples of suitable plasticizers including glycerol, ethylene glycol, propylene glycol, and mannitol. (*Id.*, 7:41-52.)
- **"soft tissue graft" -** "load-bearing and non-load-bearing soft tissue products." (*Id.*, 8:3-5.) Disclosed examples of non-load bearing tissue grafts

are cadaveric skin and load-bearing tissue grafts such as pericardium, dura mater, and fascia lata. (*Id.*, 8:6-8.)

The following terms are not expressly defined in the patent, but were construed by the Court in the LifeNet Litigation:

- **"cleaned" –** "a process during which cellular elements and small molecular weight solutes are removed" (Ex. 1019 at 9.)

Petitioner's view is that to fully understand the term "cleaned" as used in the 200 patent, a POSITA in February 1998 would have taken into account the cleaning process disclosed in Examples 9 and 10. (*See* Section V.C.1., *supra*.) A POSITA would have understood that the cleaning process disclosed in the 200 patent only partially removes cellular elements from the soft tissue. (Ex.1034, ¶¶33-35, 48-49.)

- **"plasticized soft tissue graft" -** "a load-bearing and/or non-load-bearing soft tissue product, including skin, pericardium, dura mater, fascia lata, and a variety of ligaments and tendons composed of an internal matrix where free and loosely bound waters of hydration in the tissue have been replaced with one or more plasticizers without altering the orientation of the collagen fibers, such that the mechanical properties, including the material, physical

and use properties, of the tissue product are similar to those of normal hydrated tissue." (Ex. 1019 at 7-9.)

This definition combines the definitions for "plasticization" and "soft tissue graft." (Ex.1001, 7:24-28, 8:3-6.) The court in the LifeNet Litigation included the language "such that the mechanical properties, including the material, physical and use properties, of the tissue product are similar to those of normal hydrated tissue," as part of the definition of "plasticized soft tissue graft" stating that it was supported by the specification and that it clarified the claim term. (Ex. 1019 at 7-9.) A POSITA would have agreed with this construction of the claim term "plasticized soft tissue graft" because the term as used in the 200 patent requires that the tissue is being preserved in a way that would both preserve the native orientation of the collagen fibers and preserve the mechanical properties of the tissue so the tissue can function as a natural tissue would when used as a transplant. (Ex.1034, ¶¶51-52.) LifeNet and its expert advocated for this additional language in the LifeNet Litigation. (Ex. 1016 at 6-8; Ex. 1018 at 8-9.)

The court in the LifeNet Litigation considered but did not construe the term "one or more plasticizers are not removed from the internal matrix." The court said that this phrase "required no further construction." (Ex. 1019 at 10.) The court further commented that the term "not removed" was "easily understood by a POSITA to have its plain meaning that no plasticizers are removed prior to

transplantation." (Ex. 1019 at 10.) The court also noted that "[LifeNet] argues that some quantity of the plasticizer may escape during formulation or transplantation, but such events may be distinguished from deliberate removal." (Ex. 1019 at 11.) Therefore, this phrase should be given its plain and ordinary meaning that "plasticizers are not removed from the internal matrix," as distinguished from deliberate removal.

VI. Summary of the Asserted Prior Art

A. Livesey

Livesey (USPN 5,336,616, Ex. 1004) is titled "Method for Processing and Preserving Collagen-Based Tissues for Transplantation." As a U.S. patent that issued on August 9, 1994, Livesey is prior art to the 200 patent under 35 U.S.C. 102(b). Livesey is cited on the face of the 200 patent, but it was neither addressed in any substantive manner nor was it the basis of any claim rejection during prosecution of the 200 patent.

Livesey discloses a method for processing and preserving an acellular collagen-based tissue matrix for transplantation into a human. (Ex. 1004, Abstract.) The method includes the steps of cleaning the tissue and incorporating a chemical compound, named a "cryoprotectant," within the internal matrix of the tissue. (Ex.1034, ¶¶59-60.)

Livesey discloses that the tissue graft is cleaned to remove viable antigenic cells to prevent adverse immunogenic reactions. (Ex.1034, ¶61; Ex. 1004, 5:1-3.) It states that "[t]hese methods produce a tissue product that consists of a selectively preserved extracellular protein matrix that is devoid of certain viable cells which normally express major histocompatibility complex antigenic determinants and other antigens which would be recognized as foreign by the recipient." (Ex.1034, ¶61; Ex. 1004, 1:21-26, 1:34-39.) In Example 1, Livesey discloses the use of sodium dodecyl sulfate detergent as a cleaning solution. (Ex. 1004, 23:65-67.) A POSITA would have understood that Livesey discloses a "cleaned soft tissue graft." (Ex.1034, ¶61.)

Like the plasticization method disclosed in the 200 patent, Livesey discloses treating soft tissue grafts by incorporating chemical compounds (called "cryoprotectants") within the internal matrix of the graft. (Ex.1034, ¶¶62-64; Ex.1004, 14:47-54.) Livesey discloses use of a cryopreservation solution containing a buffer and one or more cryoprotectants. (Ex.1004, 5:15-30.) Suitable cryoprotectants include many of the same compounds identified in the 200 patent as plasticizers, such as sucrose, glycerol, and propylene glycol. (*Compare* Ex.1004, 11:49-55 *with* Ex.1001, 7:41-49.) Livesey discloses that the tissue graft is exposed to the cryosolution until complete penetration of the cryoprotectants is achieved. (Ex.1004, 12:34-37, 15:11-13.) A POSITA would have understood that the

cryoprotectants replace free or loosely bound water within the internal matrix of the tissue and preserve the structure of the tissue. (Ex.1034, ¶62.) Further, no steps described by Livesey would remove the cryoprotectant from the internal matrix of the graft before transplantation.

Livesey discloses that "analysis of the end product by light and electron microscopy has demonstrated it to be structurally intact with normal collagen banding and the presence of collagen bundles in the matrix of the dermis and with structural preservation of the lamina densa and anchoring fibrils of basement membrane complex." (Ex. 1004, 25:12-17.) A POSITA would have understood that those structures, particularly the anchoring fibrils, are difficult to preserve and therefore would recognize that Livesey's method maintains the structural integrity of the graft. (Ex.1034, ¶65.)

B. Walker

Walker (WO 98/07452, Ex. 1005) is titled "Method for Sterilizing Material for Implantation." It is a PCT application published on February 26, 1998. (*Id.*) Therefore, Walker is prior art under 35 U.S.C. 102(b). Walker was not cited or addressed during prosecution of the 200 patent.

Walker discloses a method of sterilizing biological materials while preserving the flexibility and structure of the material and preventing it from becoming brittle. (Ex. 1005, cover page.) Walker's process involves cleaning the

material, incorporating a chemical compound into the material, and then sterilizing the material. (Ex.1034, ¶83; Ex. 1005, 2:14-21.)

Walker discloses that the material is stored in ethanol before treatment with glycerol. (Ex. 1005, 7:19-20, 15:3-5.) A POSITA in February 1998 would have understood that storage of the tissue in ethanol as described in Walker would at least partially remove cellular components from the tissue by solubilizing the lipid-containing cell membrane. (Ex.1034, ¶84.) A POSITA would have understood that Walker discloses a "cleaned soft tissue graft." (Ex.1034, ¶84.)

Like the plasticization method disclosed in the 200 patent, Walker discloses the incorporation of glycerol, or another protective chemical compound, into the internal matrix of the material. (Ex.1034, ¶¶85-86; Ex. 1005, 2:14-21, 2:30-34, 3:17-20.) Walker discloses glycerol solutions of various concentrations and states that the material is incubated in the solutions for 16 hours or more. (Ex. 1005, 5:7-8, 5:11-13, 6:27-7:21, 15:13-17, 20:4-8, 25:27-28.) A POSITA would have understood from Walker that the glycerol replaces free and loosely bound water within the internal matrix of the material, thus preserving the physical properties of the material and preventing the material from becoming brittle. (Ex.1034, ¶¶85, 88-89.)

Further, Walker's method does not describe or suggest removing the glycerol from the internal matrix before use. (Ex.1034, ¶87.) Though Walker states

that the material can be "drained and/or washed to remove *excess* glycerol or other substance, prior to implantation," it does not instruct one to remove glycerol from the internal matrix of the material. (Ex.1034, ¶87; Ex.1005, 4:29-31 (emphasis added).)

The 200 patent differentiates between brief and extended washing. (Ex.1001, 11:55-12:26.) For example, the patent states that "excess glycerol may optionally removed from the plasticized bone or soft tissue graft using [a centrifuging method]" and that "excess glycerol or similar plasticizer exits the grafts and collects in the bottom of the centrifuge… [t]he plasticizer tightly associated with the molecular and chemical structure of the tissue will not exit the graft and the tissue with remain plasticized without retaining physically discernable quantities of plasticizer." (*Id.*) In that context, a POSITA would have understood that the step in Walker that allows the material to be "drained and/or washed to remove excess glycerol" is best described as a brief washing that would not remove the glycerol from the internal matrix, but would remove only excess glycerol on the surface or exterior of the graft. (Ex.1034, ¶87; *see also* Ex. 1019 at 10-11.)

Walker discloses that the glycerol maintains the flexibility and the microstructure of collagen in the material. (Ex. 1005, 2:16-27, 4:20-24.) Referring to tests of suture retention and maximum load, (*id.*, Tables 9-14), Walker reports that "[t]he results show that the physical properties of treated bovine arteries are

unaffected by the plasticization and sterilization processes." (*Id.*, 8:25-32.) It further discloses that "[s]ince glycerol keeps the dimensions of the graft stable there would be little dimensional change during processing, therefore limiting concern over shrinkage or swelling on implantation." (*Id.*, 19:9-15.) A POSITA would have understood that the plasticization method disclosed in Walker would maintain the structural and mechanical properties of the biological material. (Ex.1034, ¶¶88-89.)

C. Werner

Werner (USPN 4,357,274, Ex. 1006) is titled "Process for the manufacture of sclera protein transplants with increased biological stability." As a U.S. patent issued on November 2, 1982, Werner is prior art to the 200 patent under 35 U.S.C. 102(b). Werner is cited on the face of the 200 patent, but it was not addressed in any substantive manner and was not the basis of any claim rejection during prosecution of the 200 patent.

Werner describes a process for the treatment of sclero protein transplants. (Ex. 1006, Abstract.) The method disclosed in Werner includes cleaning the material and then treating it with glycerin or polyethylene glycol. (Ex.1034, ¶91; Ex. 1006, 2:21-29.) In an example, Werner discloses the cleaning of raw dura mater with a solution of 2-20% H_2O_2 for 48 hours, then degreasing it in a Soxhlet apparatus in an acetone-diethylether 1:1 mixture for 4 hours, and then rinsing it

with water for 12-24 hours. (Ex. 1006, 2:50-57.) A POSITA would have understood that Werner discloses a "cleaned soft tissue graft." (Ex.1034, ¶92.)

As does the 200 patent, Werner discloses treatment of a material with a glycerin solution to increase biological stability. (Ex.1034, ¶93; Ex. 1006, 2:1-4, 2:8-11.) Specifically, it discloses that the glycerin solution impregnates the tissue via diffusion and remains in the tissue throughout the drying process prior to transplantation. (Ex.1034, ¶93; Ex. 1006, 2:5-8.) Werner discloses several advantages over the prior art, including that the resulting product is soft and that no rehydration is necessary prior to implantation. (Ex.1034, ¶94; Ex. 1006, 2:37-41.)

VII. Grounds for Unpatentability

Petitioner seeks review of claims 1-10, 12-13, and 15. Claims 1-3, 7 and 15 are independent claims. Claims 4-6 and 8-14 are dependent.

A. Ground 1: Walker anticipates claims 1-3, 5, 7-10, 12, and 15

Walker (Ex. 1005) describes a method for treating biological materials for implantation into humans or animals. In that method, the biological material is cleaned (Ex.1034, ¶84; Ex.1005, 7:19-20) and impregnated with a plasticizer, such as glycerol, by soaking the biological material in a glycerol solution. (Ex.1034, ¶85; Ex.1005, 7:20-22). Though Walker discloses that the material can be drained or washed to remove excess glycerol, a POSITA would have known that the Walker method includes no steps that would remove the plasticizer from the

internal matrix of the material before use. (Ex.1034, ¶87; Ex.1005, 4:29-31.) A POSITA would recognize that the Walker method maintains the physical characteristics of the biological material, such as its flexibility and structure. (Ex.1034, ¶¶88-89; Ex.1005, 2:23-27, Tables on pgs. 9-14.) Therefore, Walker anticipates claims 1-3, 5, 7-10, 12 and 15.

Claim 1 can be divided into a preamble and three elements, 1 through 3 (*see* Ex.1001, 24:9-16), and Walker discloses every element.

Claim 1, preamble: ***A plasticized soft tissue graft suitable for transplantation into a human, comprising***

To the extent the preamble is limiting, Walker discloses a plasticized soft tissue graft suitable for transplantation into a human. (Ex.1034, ¶97.) Walker discloses a method for plasticization of a biological material such as vascular tissues. (Ex.1034, ¶83; Ex. 1005, 2:14-21, 4:17-18.) The disclosed method involves incubating the biological material in a solution containing a plasticizer, such as glycerol, resulting in the incorporation of the plasticizer within the tissue. (Ex.1034, ¶85; Ex. 1005, 3:23-24, 15:16-18.) Walker discloses that the plasticized biological material substantially retains certain physical characteristics of the untreated material, such as flexibility. (Ex. 1005, 4:20-22.) As evidence that the plasticized material maintains its structural and mechanical properties, Walker reports the results of suture pull-out experiments (Ex. 1005, 7:31-9:31; Tables 9-

10) and maximum loading tests. (Ex. 1005, 8:13-23; Tables 11-14.) Those results show that the plasticization method disclosed in Walker does not degrade the physical properties of the tissue as compared to untreated tissue. (Ex.1034, ¶¶88-89; Ex. 1005, 8:25-32.) Walker therefore discloses a plasticized soft tissue graft suitable for transplantation into a human. (Ex.1034, ¶97.)

Claim 1, element 1: ***a cleaned soft tissue graft having an internal matrix;***

In the Walker method, the biological material is stored in ethanol before treatment with glycerol. (Ex.1005, 7:19-20, 15:3-5.) A POSITA would have recognized that storing the biological tissue in ethanol would at least partially remove potentially harmful immunogenic cellular components. (Ex.1034, ¶¶84, 98.) Walker therefore discloses a cleaned soft tissue graft.

Claim 1, element 2: ***one or more plasticizers contained in said internal matrix;***

Walker discloses treatment of the material with a water-soluble, non-volatile substance for at least 12 hours, reporting examples in which the material is treated with glycerol for 16 hours or more. (Ex. 1005, 2:30-34, 3:23-24, 5:11-13, 15:16-17, 20:7-8.) Incubation for 16 hours or more gives the glycerol sufficient time to impregnate the internal matrix of the material. (Ex.1034, ¶99.) Walker discloses that the glycerol keeps the dimensions of the material stable during processing, evidencing that the glycerol is incorporated within the internal matrix. (Ex.1034,

¶¶88-89, 99; Ex. 1005, 19:9-12.) Walker therefore discloses that one or more plasticizers are contained in the internal matrix of the material.

Claim 1, element 3: ***said one or more plasticizers are not removed from said internal matrix of said plasticized soft tissue graft prior to transplantation into a human.***

As discussed in relation to Claim 1, element 2, Walker discloses that the plasticizer (glycerol) is incorporated into the internal matrix of the material. And, though Walker discloses that the material can be drained or washed to remove excess glycerol, a POSITA would have recognized that such brief washing would not remove the glycerol from the internal matrix. (Ex.1034, ¶¶87, 100; Ex.1005, 4:29-31.) Therefore, Walker discloses that glycerol is not removed from the internal matrix of the biological material before transplantation.

Element	Claim 1	Walker (Ex. 1005)
Preamble	A plasticized soft tissue graft suitable for transplantation into a human, comprising:	"This invention relates to a method of treating a graft for implantation into a body." (Ex.1005, 1:3-4.) "The pre-sterilizing treatment enables the material substantially to retain certain physical characteristics, such as flexibility, and can suitably replace at least some of the water contained in the material." (Ex.1005, 4:20-24.) "The results from suture pull out, maximum load and maximum stress are shown below. Each sample is compared to an untreated natural sample, which is the partner of the treated sample. The results show that the physical properties of treated bovine arteries are unaffected by the plasticization and sterilization processes." (Ex.1005, 8:25-32.) "Since glycerol keeps the dimensions of the grafts stable there would be little dimensional change during processing, therefore limiting concern over shrinkage or swelling on implantation." (Ex.1005, 19:9-12.) See Suture Retention Results (Ex.1005, 9-10) showing that the tissues described in Examples 3 and 4 retained certain physical characteristics. See Maximum Load and Stress Results (Ex.1005, 11-14) showing that the tissues described in Examples 3 and 4 retained certain physical characteristics.

Element	Claim 1	Walker (Ex. 1005)
1	a cleaned soft tissue graft having an internal matrix	See Examples 3-4 showing tissue stored in ethanol. (Ex.1005, 7:19-20, 15:3-5.)
2	one or more plasticizers contained in said internal matrix	"Preferably the sterilizing agent and the substance are different. The substance preferably comprises a water-soluble non-volatile substance, and the sterilizing agent can comprise, for example, ethylene oxide. A suitable substance might be glycerol. Other possible substances include sugars such as sorbitol." (Ex.1005, 2:29-34.) "The pre-sterilizing treatment enables the material substantially to retain certain physical characteristics, such as flexibility, and can suitably replace at least some of the water contained in the material." (Ex.1005, 4:20-24.) "Since glycerol keeps the dimensions of the grafts stable there would be little dimensional change during processing, therefore limiting concern over shrinkage or swelling on implantation." (Ex.1005, 19:9-12.)

Element	Claim 1	Walker (Ex. 1005)
3	said one or more plasticizers are not removed from said internal matrix of said plasticized soft tissue graft prior to transplantation into a human	"The material can, after being treated, be drained and/or washed to remove excess glycerol or other substance, prior to implantation." (Ex.1005, 4:29-31.) "All samples were plasticized in a solution of 50% glycerol in 50% ethanol. Once plasticized, samples were drained and allowed to dry for 1 hour, to remove excess glycerol." (Ex.1005, 7:20-23.) "Since glycerol keeps the dimensions of the grafts stable there would be little dimensional change during processing, therefore limiting concern over shrinkage or swelling on implantation." (Ex.1005, 19:9-12.)

Claim 2 can be divided into a preamble and four elements, 1 through 4 (*see* Ex.1001, 24:17-23), and Walker discloses every element. (*See* Ex.1034, ¶¶100-106.)

Element	Claim 2	Walker (Ex. 1005)
Preamble	A plasticized soft tissue graft, comprising: a cleaned, soft tissue graft;	See Claim 1 table, Preamble.
1	A plasticized soft tissue graft, comprising: a cleaned, soft tissue graft;	See Claim 1 table, Element 1.
2	and one or more plasticizers,	See Claim 1 table, Element 2.

Element	Claim 2	Walker (Ex. 1005)
3	wherein said cleaned soft tissue graft is impregnated with one or more plasticizers,	See Claim 1 table, Element 2.
4	and said one or more plasticizers are not removed from an internal matrix of said plasticized soft tissue graft prior to transplantation into a human	See Claim 1 table, Element 3.

Claim 3 can be divided into a preamble and three elements, 1 through 3 (*see* Ex.1001, 24:24-28), and Walker discloses every element. (*See* Ex.1034, ¶¶107-111.)

Element	Claim 3	Walker (Ex. 1005)
Preamble	A plasticized soft tissue graft, comprising: a cleaned, soft tissue graft	See Claim 1 table, Preamble.
1	A plasticized soft tissue graft, comprising: a cleaned, soft tissue graft	See Claim 1 table, Element 1.
2	comprising one or more plasticizers,	See Claim 1 table, Element 2.
3	and said one or more plasticizers are not removed from an internal matrix of said plasticized soft tissue graft prior to transplantation into a human.	See Claim 1 table, Element 3.

Claim 5 recites "[t]he soft tissue graft of any one of claims 1, 2, or 3, wherein said soft tissue graft is a load-bearing soft tissue graft." (Ex.1001, 24:32-34.) Walker discloses the use of its plasticization method on biological materials such as vascular tissues. (Ex.1005, 4:17-18.) Included are examples of the use of its method to treat bovine carotid and thoracic arteries. (*Id.*, 7:19-20.) The 200 patent provides a non-exhaustive listing of load-bearing soft tissues, including pericardium, dura mater, fascia lata, ligaments, and tendons. (Ex.1001, 8:6-8.) As a POSITA would have known, carotid and thoracic arteries are also examples of load-bearing soft tissues. (Ex.1034, ¶112.)

Claim 7 can be divided into a preamble and two elements, 1 through 2. Walker discloses every element of Claim 7. (*See* Ex.1001, 24:39-45.)

Claim 7, preamble: ***A method for producing a plasticized soft tissue graft suitable for transplantation into a human, comprising:***

To the extent the preamble is limiting, Walker discloses a method for producing a plasticized soft tissue graft. (Ex.1034, ¶114.) Walker discloses a method for plasticization of a biological material such as vascular tissues. (Ex.1034, ¶83; Ex. 1005, 2:14-21, 4:17-18.) The disclosed method involves incubating the biological material in a solution containing a plasticizer, such as glycerol, resulting in the incorporation of the plasticizer within the tissue. (Ex.1034, ¶85; Ex. 1005, 3:23-24, 15:16-18.) Walker discloses that the plasticized

biological material substantially retains certain physical characteristics of the untreated material, such as flexibility. (Ex. 1005, 4:20-22.) As evidence that the plasticized material maintains its structural and mechanical properties, Walker reports the results of suture pull-out experiments (Ex. 1005, 7:31-9:31; Tables 9-10) and maximum loading tests. (Ex. 1005, 8:13-23; Tables 11-14.) Those results show that the plasticization method disclosed in Walker does not degrade the physical properties of the tissue as compared to untreated tissue. (Ex.1034, ¶¶88-89; Ex. 1005, 8:25-32.) Walker therefore discloses a method for producing a plasticized soft tissue graft. (Ex.1034, ¶114.)

Claim 7, element 1: ***impregnating a cleaned, soft tissue graft with one or more plasticizers to produce a plasticized soft tissue graft;***

In the Walker method, the biological material is stored in ethanol before treatment with glycerol. (Ex.1005, 7:19-20, 15:3-5.) A POSITA would have recognized that storing the biological tissue in ethanol would at least partially remove potentially harmful immunogenic cellular components. (Ex.1034, ¶¶84, 115.) Walker therefore discloses a cleaned soft tissue graft. Further, Walker discloses treatment of the material with a water-soluble, non-volatile substance for at least 12 hours, providing examples in which the material is treated with glycerol for 16 hours or more. (Ex. 1005, 2:30-34, 3:23-24, 5:11-13, 15:16-17, 20:7-8.) Incubation for 16 hours or more gives the glycerol sufficient time to impregnate

the internal matrix of the material. (Ex.1034, ¶116.) Walker discloses that the glycerol keeps the dimensions of the material stable during processing, evidencing that the glycerol is incorporated within the internal matrix. (Ex.1034, ¶¶88-89, 116; Ex. 1005, 19:9-12.) A POSITA would have recognized, therefore, that Walker discloses a clean soft tissue graft impregnated with one or more plasticizers.

Claim 7, element 2: ***and said one or more plasticizers are not removed from an internal matrix of said plasticized soft tissue graft prior to transplantation into a human.***

As discussed in relation to Claim 7, element 1, Walker discloses that the plasticizer (glycerol) is incorporated into the internal matrix of the material. And, though Walker discloses that the material can be drained or washed to remove excess glycerol, a POSITA would have recognized that such brief washing would not remove the glycerol from the internal matrix. (Ex.1034, ¶¶87, 117; Ex.1005, 4:29-31.) Therefore, Walker discloses that glycerol is not removed from the internal matrix of the biological material before transplantation.

Element	Claim 7	Walker (Ex. 1005)
Preamble	A method for producing a plasticized soft tissue graft suitable for transplantation into a human, comprising:	"This invention relates to a method of treating a graft for implantation into a body." (Ex.1005, 1:3-4.) "According to the present invention there is provided a method of sterilizing material for implantation into a human or animal body" (Ex.1005, 2:14-16.)

Element	Claim 7	Walker (Ex. 1005)
		"The pre-sterilizing treatment enables the material substantially to retain certain physical characteristics, such as flexibility, and can suitably replace at least some of the water contained in the material." (Ex.1005, 4:20-24.) "The results from suture pull out, maximum load and maximum stress are shown below. Each sample is compared to an untreated natural sample, which is the partner of the treated sample. The results show that the physical properties of treated bovine arteries are unaffected by the plasticization and sterilization processes." (Ex.1005, 8:25-32.) "Since glycerol keeps the dimensions of the grafts stable there would be little dimensional change during processing, therefore limiting concern over shrinkage or swelling on implantation." (Ex.1005, 19:9-12.) See Suture Retention Results (Ex.1005, 9-10) showing that the tissues described in Examples 3 and 4 retained certain physical characteristics. See Maximum Load and Stress Results (Ex.1005, 11-14) showing that the tissues described in Examples 3 and 4 retained certain physical characteristics.

Element	Claim 7	Walker (Ex. 1005)
1	impregnating a cleaned, soft tissue graft with one or more plasticizers to produce a plasticized soft tissue graft,	See Examples 3-4 showing tissue stored in ethanol. (Ex.1005, 7:19-20, 15:3-5.) "Preferably the sterilizing agent and the substance are different. The substance preferably comprises a water-soluble non-volatile substance, and the sterilizing agent can comprise, for example, ethylene oxide. A suitable substance might be glycerol. Other possible substances include sugars such as sorbitol." (Ex.1005, 2:29-34.) "The pre-sterilizing treatment enables the material substantially to retain certain physical characteristics, such as flexibility, and can suitably replace at least some of the water contained in the material." (Ex.1005, 4:20-24.)
2	and said one or more plasticizers are not removed from an internal matrix of said plasticized soft tissue graft prior to transplantation into a human	"The material can, after being treated, be drained and/or washed to remove excess glycerol or other substance, prior to implantation." (Ex.1005, 4:29-31.) "All samples were plasticized in a solution of 50% glycerol in 50% ethanol. Once plasticized, samples were drained and allowed to dry for 1 hour, to remove excess glycerol." (Ex.1005, 7:20-23.) "Since glycerol keeps the dimensions of the grafts stable there would be little dimensional change during processing, therefore limiting concern over shrinkage or swelling on implantation." (Ex.1005, 19:9-12.)

Claim 8 recites: "The method of claim 7, said step of impregnating, comprising: incubating said cleaned, soft tissue graft with a plasticizer composition comprising one or more plasticizers and one or more biocompatible solvents." (Ex.1001, 24:46-50.) In Example 3, Walker discloses that the samples were plasticized in a solution of 50% glycerol in 50% ethanol. (Ex.1005, 7:20-22.) Walker therefore discloses a plasticizer composition comprising one or more plasticizers (i.e., glycerol) and one or more biocompatible solvents (i.e., ethanol). (Ex.1034, ¶118.)

Claim 9 recites: "The method of claim 8, wherein said one or more biocompatible solvents comprise one or more alcohols." (Ex.1001, 24:51-52.) As explained above in relation to Claim 8, Walker discloses in Example 3 that the samples were plasticized in a solution of 50% glycerol in 50% ethanol. (Ex.1005, 7:20-22.) Ethanol is an alcohol and, therefore, Walker discloses the added limitation of Claim 9. (Ex.1034, ¶119.)

Claim 10 recites: "The method of claim 8, wherein incubating comprises soaking said cleaned, soft tissue graft in said plasticizer composition." (Ex.1001, 24:53-55.) As discussed above in relation to Claim 1, element 2, Walker discloses that the material is incubated in the substance solution for at least 12 hours, describing several examples of the material being incubated in glycerol for 16

hours. (Ex.1034, ¶¶85-86, 120; Ex.1005, 3:23-25, 15:16-17.) Therefore, Walker discloses a method in which "incubating comprises soaking." (Ex.1034, ¶120.)

Claim 12 recites: "The method of claim 3, wherein said one or more plasticizers are present in said plasticizer composition in a weight ratio of from 30 to 90 wt %, and said one or more alcohols are present in said plasticizer composition in weight ratio of from 10% to 70 wt %."[4] (Ex.1001, 24:58-62.) As discussed above in relation to Claim 8, Walker provides an example in which the samples were plasticized in a solution of 50% glycerol ("plasticizer composition in a weight ratio of from 30 to 90 wt %") in 50% ethanol ("alcohols are present . . . in weight ratio of from 10% to 70 wt %"). Walker therefore discloses the concentration limitation of Claim 12. (Ex.1034, ¶121.)

Claim 15 can be divided into a preamble and three elements, 1 through 3. (*See* Ex.1001, 25:1-26:2.) Walker discloses every element of claim 15. (*See* Ex.1034, ¶¶122-126.)

[4] Claim 12 is a method claim that depends from claim 3, which recites an article of manufacture, and is thus improper and invalid under 35 U.S.C. §§ 101 and/or 112(b). To the extent that claim 12 can be understood to depend from any of the preceding method claims, claims 7-11, it is unpatentable for the reasons stated.

Element	Claim 15	Walker (Ex. 1005)
Preamble	A plasticized load-bearing soft tissue graft, comprising:	See Claim 1 table, Preamble, and Claim 5
1	a cleaned, load-bearing soft tissue graft	See Claim 1 table, Element 1, and Claim 5.
2	comprising one or more plasticizers,	See Claim 1 table, Element 2.
3	and said one or more plasticizers are not removed from an internal matrix of said plasticized soft tissue graft prior to transplantation into a human.	See Claim 1 table, Element 3.

B. Ground 2: Claims 1-3 and 5-10, 12-13, and 15 are obvious over Walker

Claims 1-3, 5-10, 12-13, and 15 are obvious over Walker. The explanation of Ground 1 (§VII.A.) details how Walker anticipates claims 1-3, 5, 7-10, 12, and 15. To the extent any limitation of those claims is not explicitly disclosed in Walker, the subject matter as a whole of those claims would have been obvious to a POSITA at the time of the alleged invention in view of Walker's disclosure. (*See* Ex.1034, ¶¶127-136.)

To the extent it is determined that Walker does not explicitly disclose the claim element "the plasticizers are not removed from the internal matrix," claims 1-3, 5-10, 12-13, and 15 would have been obvious to a POSITA at the time of the alleged invention for at least the following reasons:

As detailed above in Ground 1, nothing in Walker would have led a POSITA to understand that the plasticizer had been removed from the internal matrix before implantation. Though Walker discloses that excess plasticizer (glycerol) can be washed from the soft tissue graft, a POSITA in February 1998 would have understood that Walker's washing step would remove only excess plasticizer from the exterior of the graft and that it would not actually remove the plasticizer from the internal matrix. (Ex.1034, ¶¶87, 127-128.)

But if it is determined that Walker does not explicitly disclose that the plasticizer is not removed, a POSITA in February 1998 would have understood from Walker that it would be advantageous to permit the plasticizer to remain in the internal matrix rather than remove it. A POSITA in February 1998 would have known that incorporating chemical compounds into the internal matrix of a tissue would preserve the tissue as "soft, pliable and easy to use." (*See* §V.C.2.; Ex.1034, ¶¶129-130.) Further, a POSITA in February 1998 would have known that incorporating chemical compounds, such as glycerol, within the internal matrix of a soft tissue graft would not degrade the fundamental architecture of the graft. (Ex.1034, ¶131.) A POSITA in February 1998 would also have known that removing a chemical compound, such as glycerol, from the internal matrix of a soft tissue graft would require extensive washing and would leave the tissue susceptible to degradation. (Ex.1034, ¶132.) Therefore, a POSITA in February 1998, being

aware of the teachings in Walker, would have known that it was advantageous not to remove the plasticizer from the internal matrix. (Ex.1034, ¶¶133-134.)

Even if Claims 1-3, 5-10, 12-13, and 15 are not anticipated by Walker, their subject matter would have been obvious to a POSITA because (1) Walker disclosed a method of incorporating chemical compounds into the internal matrix of a soft tissue graft, (2) if Walker does not explicitly teach that the "plasticizers are not removed from the internal matrix," a POSITA in February 1998 would have understood from Walker that avoiding removal of plasticizers from the internal matrix was advantageous, and (3) a POSITA in February 1998 would have recognized that allowing the plasticizer to remain in the soft tissue graft would have yielded the predictable result of a soft tissue graft where the plasticizer is not removed from the internal matrix. Such a resulting soft tissue graft would have been soft and pliable, and would have had the desirable structural characteristics and mechanical properties of a natural soft tissue graft. (Ex.1034, ¶¶127-134.)

The additional subject matter of claims 6 and 13 would also have been obvious to a POSITA in view of Walker.

Claim 6 recites "The soft tissue graft of any one of claims 1, 2, or 3, wherein said soft tissue graft is selected from the group consisting of: dura, pericardium, fascia lata, tendons and ligaments." (Ex.1001, 24:35-38.) A POSITA would have been motivated to apply the teachings of Walker to the recited types of load-

bearing soft tissues because of the common use of such types of soft tissue grafts. (Ex.1034, ¶135.) As explained above for Claim 5, Walker discloses examples of its method using bovine carotid and thoracic arteries, which are other types of load-bearing soft tissue. A POSITA would therefore have been motivated to apply the method disclosed in Examples 3 and 4 specifically to the recited "pericardium" because Walker itself discloses that it is possible to plasticize and sterilize bovine pericardium in the same way as bovine arteries and that doing so would not compromise the physical strength of the tissue. (Ex.1034, ¶135; Ex.1005, 25:1-2.) Therefore, Claim 6 would have been obvious to a POSITA in view of Walker. (Ex.1034, ¶135.)

Claim 13 recites "The method of claim 12, wherein said plasticizer is glycerol and said alcohol is isopropyl alcohol." (Ex.1001, 24:63-64.) The disclosure of Walker would have motivated a POSITA to carry out the Walker's plasticization process using glycerol as the plasticizer and isopropyl alcohol as the alcohol. (Ex.1034, ¶136.) Walker specifically teaches that using glycerol is advantageous (Ex.1005, 4:26-27) and that glycerol is a suitable pre-sterilizing substance. (*Id.* at 7:20-23, 15:13-14.) The examples disclosed in Walker also teach the use of ethanol as a solvent. (*Id.*) A POSITA would have known that ethanol is readily interchangeable with other short-chain alcohols such as isopropyl alcohol. (Ex.1034, ¶136.) Further, a POSITA would have known that isopropyl alcohol is

less expensive than ethanol and would therefore have been motivated to use isopropyl alcohol to decrease cost. (Ex.1034, ¶136.) Therefore, Claim 13 would have been obvious to a POSITA in view of Walker.

C. Ground 3: Livesey anticipates claims 1-3, 7-8, 10, and 15

Livesey (Ex. 1004) describes a method for processing and preserving acellular collagen-based tissue for transplantation. (Ex.1004, cover page.) In the Livesey method, soft tissue is cleaned to remove antigenic cellular components (Ex.1034, ¶61; Ex.1004, 9:38-40, 23:62-68) and incubated in a cryosolution for a time long enough to obtain complete penetration of the cryoprotectants into the tissue (Ex.1034, ¶62; Ex.1004, 12:31-39). The Livesey method does not require removal of the cryoprotectants from the internal matrix of the tissue before use. Further, the Livesey method maintains the structure of the collagen in the internal matrix. (Ex.1034, ¶65; Ex.1004, 25:12-17.) Therefore, Livesey anticipates claims 1-3, 7-8, 10, and 15.

Claim 1 can be divided into a preamble and three elements, 1 through 3 (*see* Ex.1001, 24:9-16), and Livesey discloses every element.

Claim 1, preamble: ***A plasticized soft tissue graft suitable for transplantation into a human, comprising:***

To the extent the preamble is limiting, Livesey discloses a plasticized soft tissue graft. (Ex.1034, ¶138.) Livesey describes a method for processing and

preserving collagen-based biological tissues for transplantation. (Ex.1004, 4:39-42.) Livesey discloses a method wherein the soft tissue is incubated in a cryosolution for a time long enough to obtain complete penetration of the cryoprotectants into the tissue. (Ex.1034, ¶61; Ex.1004, 12:31-39.) Livesey teaches that treatment of the tissue with the processing solution must be done at a concentration and for a duration that avoids degradation of the basement membrane complex and maintains the structural integrity of the matrix, including collagen fibers and elastin. (Ex.1004, 5:1-14.) It discloses that the end product was analyzed using light and electron microscopy, demonstrating that the tissue remained structurally intact with normal collagen banding and that the collagen bundles in the matrix of the dermis were preserved. (Ex.1034, ¶65; Ex.1004, 25:12-17.) Therefore, a POSITA would have recognized that Livesey discloses a plasticized soft tissue graft suitable for transplantation into a human. (Ex.1034, ¶138.)

Claim 1, element 1: ***a cleaned soft tissue graft having an internal matrix;***

Livesey discloses that the soft tissue grafts are decellularized by treatment with a 0.5% sodium dodecyl sulfate solution for 1 hour on a rotator at 40±5 RPM. (Ex.1004, 23:65-67.) A POSITA would have recognized that treatment under those conditions would cause cellular elements to be at least partially, if not

substantially, removed, resulting in a cleaned graft with an internal matrix. (Ex.1034, ¶¶61, 139.)

Claim 1, element 2: ***one or more plasticizers contained in said internal matrix;***

As noted, Livesey discloses a soft tissue graft incubated in a cryosolution containing one or more cryoprotectants (Ex.1004, 11:17-23) and discloses a non-exhaustive list of cryoprotectants that can be used in the invention. (Ex.1004, 11:49-55.) Also disclosed is that the soft tissue graft is exposed to the cryosolution containing the cryoprotectants for a time long enough to obtain complete penetration of the cryoprotectants. (Ex.1034, ¶61; Ex.1004, 12:33-37.) The "cryoprotectants" described in Livesey constitute the "plasticizer" described in the 200 patent. (Ex.1034, ¶¶62-64, 140.) Several examples of plasticizer components identified in the 200 patent match the non-exclusive examples of cryoprotectant disclosed in Livesey. (*Compare* Ex.1004, 11:49-55 *with* Ex.1001, 7:42-52.) Therefore, Livesey discloses the recited one or more plasticizers contained in the internal matrix. (Ex.1034, ¶140.)

Claim 1, element 3: ***said one or more plasticizers are not removed from said internal matrix of said plasticized soft tissue graft prior to transplantation into a human.***

As discussed in relation to Claim 1, element 2, Livesey discloses that the cryoprotectants (called plasticizers in the 200 patent) are contained in the internal matrix of the tissue. A POSITA would have understood that to completely remove the cryoprotectants from the internal matrix, the tissue would need to be extensively washed. (Ex.1034, ¶87.) Livesey's method contains no steps of extensive washing and therefore would not have completely removed the cryoprotectants from the internal matrix of the tissue prior to transplantation into a human. Ex.1034, ¶¶87, 141.)

Element	Claim 1	Livesey (Ex. 1004)
Preamble	A plasticized soft tissue graft suitable for transplantation into a human, comprising:	"This invention relates to methods for procuring [,] decellularizing and further processing and dry preserving collagen-based tissues derived from humans and animals for transplantation into humans or other animals." (Ex.1004, 1:17-21.) "In the preferred embodiment, the tissue is then incubated in a processing solution to remove viable antigenic cells (including epithelial cells, endothelial cells, smooth muscle cells and fibroblasts) from the structural matrix without damaging the basement membrane complex or the structural integrity of the collagen matrix." (Ex.1004, 5:1-6.) "Analysis of the end product by light and electron microscopy has demonstrated it to be structurally intact with normal collagen banding and the presence of collagen bundles in the matrix of the dermis and with structural preservation of the lamina densa and anchoring fibrils of basement membrane complex." (Ex.1004, 25:12-17.)

Element	Claim 1	Livesey (Ex. 1004)
1	a cleaned soft tissue graft having an internal matrix	"These methods produce a tissue product that consists of a selectively preserved extracellular protein matrix that is devoid of certain viable cells which normally express major histocompatibility complex antigenic determinants and other antigens which would be recognized as foreign by the recipient." (Ex.1004, 1:21-26.) "the tissue is then incubated in a processing solution to remove viable antigenic cells (including epithelial cells, endothelial cells, smooth muscle cells and fibroblasts) from the structural matrix without damaging the basement membrane complex or the structural integrity of the collagen matrix." (Ex.1004, 5:1-6.) "The dermis is then treated with 50 ml. of De-Cellularizing solution and the petri dish is placed on a rotator at 40+/-5 RPM for 1 hour at room temperature (20-26 C.). The decellularizing solution for human skin consists of 0.5% sodium dodecyl sulfate in Hanks balanced salt solution and for porcine skin contains 1mM disodium ethylenediamine tetraacetic acid (EDTA)." (Ex.1004, 23:62-67.)

Element	Claim 1	Livesey (Ex. 1004)
2	one or more plasticizers contained in said internal matrix	"After the tissue is decellularized, it is preferably incubated in a cryopreservation solution. In the preferred embodiment, this solution generally contains one or more cryoprotectants to minimize ice crystal damage to the structural matrix that could occur during freezing, and one or more dry-protective components, to minimize structural damage alteration during drying and may include a combination of an organic solvent and water which undergoes neither expansion or contraction during freezing." (Ex.1004, 5:15-24.) "The initial steps of cryopreserving the decellularized tissue includes incubating the tissue in a cryosolution prior to the freezing step. The cryosolution comprises an appropriate buffer, one or more cryoprotectants and/or dry protectants with or without an organic solvent which in combination with water undergoes neither expansion or contraction." (Ex.1004, 11:17-23.) "Various cryoprotectants can be used in the present invention. These include: dimethylsulfoxide (DMSO), dextran, sucrose, 1,2 propanediol, glycerol, sorbitol, fructose, trehalose, raffinose, propylene glycol, 2-3 butane diol, hydroxyethyl starch, polyvinylpyrrolidone (PVP), proline, (or other protein stabilizers),

Element	Claim 1	Livesey (Ex. 1004)
		human serum albumin and combinations thereof." (Ex.1004, 11:49-55.) See Example 1 where the plasticizers are dextran and sucrose. (Ex.1004, 24:10-19.)
3	said one or more plasticizers are not removed from said internal matrix of said plasticized soft tissue graft prior to transplantation into a human	"In general, cryopreservation is performed as a continuous sequence of events. The tissue is first incubated in the cryosolution for a defined period (0.5 to 2 hours) until complete penetration of the components of the cryosolution is achieved . . ." (Ex.1004, 12:33-37.)

Claim 2 can be divided into a preamble and four elements, 1 through 4 (*see* Ex.1001, 24:17-23), and Livesey discloses every element. (*See* Ex.1034, ¶¶142-147.)

Element	Claim 2	Livesey (Ex. 1004)
Preamble	A plasticized soft tissue graft, comprising:	See Claim 1 table, Preamble.
1	a cleaned, soft tissue graft;	See Claim 1 table, Element 1.
2	and one or more plasticizers,	See Claim 1 table, Element 2.
3	wherein said cleaned soft tissue graft is impregnated with one or more plasticizers,	See Claim 1 table, Element 2.

Element	Claim 2	Livesey (Ex. 1004)
4	and said one or more plasticizers are not removed from an internal matrix of said plasticized soft tissue graft prior to transplantation into a human	See Claim 1 table, Element 3.

Claim 3 can be divided into a preamble and three elements, 1 through 3 (*see* Ex.1001, 24:24-28), and Livesey discloses every element. (*See* Ex.1034, ¶¶148-152.)

Element	Claim 3	Livesey (Ex. 1004)
Preamble	A plasticized soft tissue graft, comprising:	See Claim 1 table, Preamble.
1	a cleaned, soft tissue graft	See Claim 1 table, Element 1.
2	comprising one or more plasticizers,	See Claim 1 table, Element 2.
3	and said one or more plasticizers are not removed from an internal matrix of said plasticized soft tissue graft prior to transplantation into a human.	See Claim 1 table, Element 3.

Claim 7 can be divided into a preamble and two elements, 1 through 2 (*see* Ex.1001, 24:39-45), and Livesey discloses every element.

Claim 7, preamble: ***A method for producing a plasticized soft tissue graft suitable for transplantation into a human, comprising:***

To the extent the preamble is limiting, Livesey discloses a method for producing a plasticized soft tissue graft, specifically a method for processing and preserving collagen-based biological tissues for transplantation. (Ex.1034, ¶154; Ex.1004, 4:39-42.) In the Livesey method, the soft tissue is incubated in a cryosolution for a time long enough to obtain complete penetration of the cryoprotectants into the tissue. (Ex.1034, ¶61; Ex.1004, 12:31-39.) Livesey teaches that treatment of the tissue with the processing solution must be done at a concentration and for a duration that avoids degradation of the basement membrane complex and maintains the structural integrity of the matrix, including collagen fibers and elastin. (Ex.1004, 5:1-14.) Livesey reports that the end product was analyzed using light and electron microscopy, demonstrating that the tissue is structurally intact with normal collagen banding and collagen bundles in the matrix of the dermis is preserved. (Ex.1034, ¶65; Ex.1005, 25:12-17.) Therefore, Livesey discloses a method for producing a plasticized soft tissue graft. (Ex.1034, ¶154.)

Claim 7, element 1: ***impregnating a cleaned, soft tissue graft with one or more plasticizers to produce a plasticized soft tissue graft;***

Livesey discloses that the soft tissue grafts are decellularized by treatment with a 0.5% sodium dodecyl sulfate solution for 1 hour on a rotator at 40±5 RPM. (Ex.1004, 23:65-67.) A POSITA would have recognized that treatment of a soft tissue graft as described in Livesey would cause cellular elements to be at least partially, if not substantially, removed leaving a cleaned soft tissue with an internal matrix. (Ex.1034, ¶¶61, 155.) Therefore, Livesey discloses a cleaned soft tissue graft.

Livesey further discloses a soft tissue graft incubated in a cryosolution that contains one or more cryoprotectants (Ex.1004, 11:17-23), providing a non-exhaustive list of cryoprotectants that can be used in the invention. (Ex.1004, 11:49-55.) It additionally discloses that the soft tissue graft is exposed to the cryosolution containing the cryoprotectants for a time long enough to obtain complete penetration of the cryoprotectants. (Ex.1034, ¶61; Ex.1004, 12:33-37.) A POSITA would have recognized that the "cryoprotectants" described in Livesey function as the "plasticizer" described in the 200 patent. (Ex.1034, ¶¶62-64, 156.) Several examples of plasticizer components identified in the 200 patent match the non-exclusive examples of cryoprotectant disclosed in Livesey. (*Compare*

Ex.1004, 11:49-55 *with* Ex.1001, 7:42-52.) Therefore, Livesey discloses the recited cleaned soft tissue graft impregnated with one or more plasticizers.

Claim 7, element 2: ***and said one or more plasticizers are not removed from an internal matrix of said plasticized soft tissue graft prior to transplantation into a human.***

As discussed in relation to Claim 7, element 1, Livesey discloses that the cryoprotectant (called a plasticizer in the 200 patent) is incorporated into the internal matrix of the soft tissue graft. A POSITA would have understood that in order to completely remove the cryoprotectants from the internal matrix, the tissue would need to be extensively washed. (Ex.1034, ¶87.) Livesey's method contains no steps involving extensive washing and therefore would not have completely removed the cryoprotectants from the internal matrix of the tissue prior to transplantation into a human. (Ex.1034, ¶¶87, 157.)

Element	Claim 7	Livesey (Ex. 1004)
Preamble	A method for producing a plasticized soft tissue graft suitable for transplantation into a human, comprising:	"This invention relates to methods for procuring [,] decellularizing and further processing and dry preserving collagen-based tissues derived from humans and animals for transplantation into humans or other animals." (Ex.1004, 1:17-21.) "In the preferred embodiment, the tissue is then incubated in a processing solution to remove viable antigenic cells (including epithelial cells, endothelial cells, smooth muscle cells and fibroblasts) from the structural matrix without damaging the basement membrane complex or the structural integrity of the collagen matrix." (Ex.1004, 5:1-6.) "Analysis of the end product by light and electron microscopy has demonstrated it to be structurally intact with normal collagen banding and the presence of collagen bundles in the matrix of the dermis and with structural preservation of the lamina densa and anchoring fibrils of basement membrane complex." (Ex.1004, 25:12-17.)
1	impregnating a cleaned, soft tissue graft with one or more plasticizers to produce a plasticized soft tissue graft,.	"These methods produce a tissue product that consists of a selectively preserved extracellular protein matrix that is devoid of certain viable cells which normally express major histocompatibility complex antigenic determinants and other antigens which would be recognized as foreign by

Element	Claim 7	Livesey (Ex. 1004)
		the recipient." (Ex.1004, 1:21-26.) "the tissue is then incubated in a processing solution to remove viable antigenic cells (including epithelial cells, endothelial cells, smooth muscle cells and fibroblasts) from the structural matrix without damaging the basement membrane complex or the structural integrity of the collagen matrix." (Ex.1004, 5:1-6.) "The dermis is then treated with 50 ml. of De-Cellularizing solution and the petri dish is placed on a rotator at 40+/-5 RPM for 1 hour at room temperature (20-26 C.). The decellularizing solution for human skin consists of 0.5% sodium dodecyl sulfate in Hanks balanced salt solution and for porcine skin contains 1mM disodium ethylenediamine tetraacetic acid (EDTA)." (Ex.1004, 23:62-67.) "After the tissue is decellularized, it is preferably incubated in a cryopreservation solution. In the preferred embodiment, this solution generally contains one or more cryoprotectants to minimize ice crystal damage to the structural matrix that could occur during freezing, and one or more dry-protective components, to minimize structural damage alteration during drying and may include a combination of an organic solvent and water which undergoes neither expansion or contraction during

Element	Claim 7	Livesey (Ex. 1004)
		freezing." (Ex.1004, 5:15-24.) "The initial steps of cryopreserving the decellularized tissue includes incubating the tissue in a cryosolution prior to the freezing step. The cryosolution comprises an appropriate buffer, one or more cryoprotectants and/or dry protectants with or without an organic solvent which in combination with water undergoes neither expansion or contraction." (Ex.1004, 11:17-23.) "Various cryoprotectants can be used in the present invention. These include: dimethylsulfoxide (DMSO), dextran, sucrose, 1,2 propanediol, glycerol, sorbitol, fructose, trehalose, raffinose, propylene glycol, 2-3 butane diol, hydroxyethyl starch, polyvinylpyrrolidone (PVP), proline, (or other protein stabilizers), human serum albumin and combinations thereof." (Ex.1004, 11:49-55.) See Example 1 where the plasticizers are dextran and sucrose. (Ex.1004, 24:10-19.)

Element	Claim 7	Livesey (Ex. 1004)
2	and said one or more plasticizers are not removed from an internal matrix of said plasticized soft tissue graft prior to transplantation into a human	"In general, cryopreservation is performed as a continuous sequence of events. The tissue is first incubated in the cryosolution for a defined period (0.5 to 2 hours) until complete penetration of the components of the cryosolution is achieved . . ." (Ex.1004, 12:33-37.)

Claim 8 recites: "The method of claim 7, said step of impregnating, comprising: incubating said cleaned, soft tissue graft with a plasticizer composition comprising one or more plasticizers and one or more biocompatible solvents." (Ex.1001, 24:46-50.) In Example 1, Livesey discloses a cryosolution which contains dextran and sucrose in Hanks balanced salt solution. (Ex.1004, 24:10-19.) A POSITA would have recognized, therefore, that Livesey discloses a plasticizer composition comprising one or more plasticizers (i.e. dextran and sucrose) and one or more biocompatible solvents (i.e. Hanks balanced salt solution). (Ex.1034, ¶158.)

Claim 10 recites: "The method of claim 8, wherein incubating comprises soaking said cleaned, soft tissue graft in said plasticizer composition." (Ex.1001, 24:53-55.) As discussed above relating to Claim 1, element 2, Livesey discloses that the soft tissue is incubated in the cryosolution until complete penetration of the

components of the cryosolution is achieved, therefore, Livesey discloses the added "soaking" limitation of Claim 10. (Ex.1034, ¶159; Ex.1004, 12:33-37.)

Claim 15 can be divided into a preamble and three elements, 1 through 3 (*see* Ex.1001, 25:1-26:2), and Livesey discloses every element. (*See* Ex.1034, ¶¶160-164.)

Element	Claim 15	Livesey (Ex. 1004)
Preamble	A plasticized load-bearing soft tissue graft, comprising:	See Claim1 table, Preamble, and Claim 5
1	a cleaned, load-bearing soft tissue graft	See Claim 1 table, Element 1, and Claim 5.
2	comprising one or more plasticizers,	See Claim 1 table, Element 2.
3	and said one or more plasticizers are not removed from an internal matrix of said plasticized soft tissue graft prior to transplantation into a human.	See Claim 1 table, Element 3.

D. Ground 4: Claims 1-3, 7-8, 10, and 15 are obvious over Livesey

Claims 1-3, 7-8, 10, and 15 are obvious over Livesey. The discussion of Ground 3 (§VII.C.) shows how Livesey anticipates claims 1-3, 7-8, 10, and 15 of the 200 patent. To the extent any limitation of those claims is not explicitly disclosed in Livesey, the subject matter as a whole of those claims would have

been obvious to a POSITA at the time of the alleged invention from the disclosure of Livesey. (*See* Ex.1034, ¶¶165-172.)

To the extent it is determined that Livesey does not explicitly disclose the claim element "the plasticizers are not removed from the internal matrix," claims 1-3, 7-8, 10, and 15 would have been obvious to a POSITA at the time of the alleged invention for at least the following reasons:

As detailed above in Ground 3, nothing in Livesey would have led a POSITA to understand that the cryoprotectants had been completely removed from the internal matrix before transplantation. (Ex.1034, ¶166.) But if it is determined that Livesey does not explicitly disclose that the plasticizer is not removed, a POSITA in February 1998 would have understood from Livesey that it was advantageous to allow the plasticizer to remain in the internal matrix rather than remove it. A POSITA in February 1998 would have known that incorporating chemical compounds into the internal matrix of a tissue caused the tissue to be "soft, pliable and easy to use." (*See* §V.C.2., *supra*; Ex.1034, ¶¶167-168.) Further, a POSITA in February 1998 would have known that incorporation of chemical compounds, such as glycerol, within the internal matrix of a soft tissue graft did not compromise the fundamental architecture of the graft. (Ex.1034, ¶169.) A POSITA in February 1998 would have known that removal of a chemical compound, such as glycerol, from the internal matrix of a soft tissue graft would

require extensive washing and would leave the tissue susceptible to degradation. (Ex.1034, ¶170.) Therefore, a POSITA in February 1998, being aware of the teachings in Livesey, would have known that it was advantageous to avoid removing the plasticizer from the internal matrix. (Ex.1034, ¶¶171-172.)

Even if Claims 1-3, 7-8, 10, and 15 are not anticipated by Livesey, their subject matter would have been obvious to a POSITA because (1) Livesey disclosed a method of incorporating chemical compounds into the internal matrix of a soft tissue graft, (2) if Livesey does not explicitly teach that the "plasticizers are not removed from the internal matrix," a POSITA in February 1998 would have understood from Livesey that avoiding removal of plasticizers from the internal matrix was advantageous, and (3) a POSITA in February 1998 would have recognized that allowing the plasticizer to remain in the soft tissue graft would have yielded the predictable result of a soft tissue graft where the plasticizer is not removed from the internal matrix. Such a resulting soft tissue graft would have been soft and pliable, and would have had the desirable structural characteristics and mechanical properties of a natural soft tissue graft. (Ex.1034, ¶¶165-172.)

E. Ground 5: Claim 4 is obvious over Walker or Livesey in view of Werner

Both Walker and Livesey anticipate many claims of the 200 patent. (*See* Grounds 1 and 3 *supra*.) Claim 4 of the 200 patent recites "[t]he soft tissue graft of

any one of claim 1, 2, or 3, wherein said soft tissue graft is suitable for direct transplant into a human without rehydration." (Ex.1001, 24:29-31.)

If neither Walker nor Livesey discloses that the plasticized soft tissue graft does not require rehydration, that limitation is taught by Werner. Werner discloses a process of glycerol treatment of a tissue to increase biological stability. (Ex.1006, cover page.) Werner discloses that the resulting tissue product is soft and that no rehydration of the product is necessary before transplantation. (Ex.1006, 2:37-41.) A POSITA would have recognized an advantage to be achieved by adapting Werner's teaching of the use of glycerol for use in the method of either Walker or Livesey; namely, that no rehydration of the tissue product is necessary before implantation, and would have had a reasonable expectation of success in that adaptation. (Ex.1034, ¶¶173-175, 183-185.)

A POSITA in February 1998 would have been motivated to simplify the steps for the processing of a soft tissue graft both during preparation and at the time of implantation and would have explored avenues for simplifying that process. (Ex.1034, ¶176.) A POSITA by February 1998 would have sought to modify the method of Walker or Livesey by following Werner's teaching in order to simplify the processing of the soft tissue graft during implantation. (Ex.1034, ¶177.) Doing so would achieve the known advantage of allowing for direct implantation of the plasticized soft tissue graft instead of requiring rehydration

before implantation. (Ex.1034, ¶177.) Indeed, Werner teaches the same processing steps as Walker and Livesey, and its further teaching to implant the graft without first rehydrating the graft would have been recognized as desirable by a POSITA. (Ex.1034, ¶177.) It would therefore have been evident to a POSITA that Werner's teaching could be advantageously incorporated into the method of Walker or Livesey. (Ex.1034, ¶¶178-182, 184-185.) Further, a POSITA would expect a result similar to that achieved in Werner for the soft tissue grafts referenced in Walker or Livesey by utilizing the processing steps of Werner. (Ex.1034, ¶178.)

As explained in Grounds 1 and 3, both Walker and Livesey both disclose every element of, and anticipate, claims 1-3, from which claim 4 depends. Therefore, Claim 4 would have been obvious to a POSITA at the time of the invention over Walker or over Livesey in view of Werner.

VIII. Secondary Considerations

Petitioner is not aware of any secondary considerations that would tend to show non-obviousness that have a provable nexus with claims 1-10, 12-13, and 15 of the 200 patent. There is nothing in those claims that is not already taught in the prior art.

IX. Conclusion

Petitioner has established a reasonable likelihood of prevailing as to each of claims 1-10, 12-13, and 15 of the 200 patent, and therefore respectfully requests that the Board institute *inter partes* review of those claims.

Respectfully submitted,

McANDREWS, HELD & MALLOY, LTD.

Dated: January 29, 2019

By: /Herbert D. Hart III/
Herbert D. Hart III
Reg. No. 30,063
Lead Counsel for Petitioner
RTI Surgical, Inc.

CERTIFICATE OF WORD COUNT

I hereby certify, pursuant to 37 CFR § 42.24, that this **PETITION FOR INTER PARTES REVIEW** contains fewer than 14,000 words, as determined by Microsoft Word.

Dated: January 29, 2019

By: /Herbert D. Hart III/
Herbert D. Hart III *for Petitioner*
RTI Surgical, Inc.

CERTIFICATE OF SERVICE

Under 37 C.F.R. §§ 42.6(e)(4) and 42.105, the undersigned certifies on this date, a copy of this Petition for *Inter Partes* Review and all supporting exhibits were served by Federal Express to the Patent Owner at the following correspondence address of record for U.S. Patent No. 6,569,200:

Morgan, Lewis & Bockius LLP
1111 Pennsylvania Avenue, N.W.
Washington DC 20004

With a courtesy copy by email to:

Crowell & Moring, LLP
11th Floor
1001 Pennsylvania Ave NW
Washington, DC 20004−2595
LifeNet-RTI@crowell.com

RatnerPrestia
Suite 1200
1090 Vermont Avenue, N.W.
Washington, DC 20005
LNHvRTI@ratnerprestia.com

Dated: January 29, 2019

By: /Herbert D. Hart III/
Herbert D. Hart III *for Petitioner*
RTI Surgical, Inc.