Filed on behalf of RTI Surgical, Inc.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

RTI SURGICAL, INC.,
Petitioner

v.

LIFENET HEALTH,
Patent Owner

Case IPR2019-00573
Patent No. 9,585,986

PETITION FOR INTER PARTES REVIEW

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PETITIONER'S EXHIBIT LIST

EX.	DESCRIPTION
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1002	Reserved
1003	USPN 9,585,986 ("The 986 patent")
1004	USPN 5,336,616 ("Livesey")
1005	WO 9807452 ("Walker")
1006	USPN 4,357,274 ("Werner")
1007	USPN 6,326,019 ("Tseng")
1008	USPN 6,630,001 ("Duran")
1009	USPN 4,776,853 ("Klement")
1010	USPN 4,801,299 ("Brendel")
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1013	A.C.J. de Backere, "Euro Skin Bank: large scale skin-banking in Europe based on glycerol-preservation of donor skin," 20 Burns S4-S9 (1994) ("Backere")
1014	D. Michael Strong, "The US Navy Tissue Bank: 50 years on the cutting edge," Cell and Tissue Banking 1:9-16 (2000) ("Strong")
1015	R.E. Billingham, et al., "The Freezing, Drying and Storage of Mammalian Skin," J. Exp. Biol. 29:454-468 (1952) ("Billingham")
1016	LifeNet Health's Opening Claim Construction Brief, D.I. 65; ("LifeNet Opening Claim Construction Brief")
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1028	U.S. Pat. Appl. No. 14/193,040, Amendment, Oct. 5, 2016
1029	Jens O.M. Karlsson and Mehmet Toner, "Long-term storage of tissues by cryopreservation: critical issues," 17 Biomaterials 243-256 (1996)
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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1034	Declaration of David J. McQuillan, Ph.D.

I. Introduction

RTI Surgical, Inc. ("RTI" or "Petitioner") petitions for *inter partes* review of claims 1-27 of U.S. Patent No. 9,585,986 ("the 986 patent"; Ex.1003), which is owned by LifeNet Health ("LifeNet" or "Patent Owner"). The application for the 986 patent was filed on February 28, 2014, and issued as a patent on March 7, 2017.

The 986 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 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.1003, 5:42-49.) The claims are directed to a "plasticized soft tissue graft" suitable for transplantation into a human (including methods of producing such a graft) and recite that the treated graft must have "mechanical properties approximating the mechanical properties of natural soft tissue." Patent Owner added this limitation to overcome a prior art rejection over U.S. Patent No. 5,336,616 ("Livesey"; Ex.1004). Patent Owner argued that "Livesey does not disclose, teach, or suggest a plasticized soft tissue graft having mechanical properties approximating those of natural soft tissue." (Ex. 1028 at 7-8.) The claims were thereafter allowed.

To the contrary, Livesey does disclose a plasticized soft tissue graft having mechanical properties approximating those of natural soft tissue. Livesey expressly states 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 person of ordinary skill in the art ("POSITA") at the time of the alleged invention would have understood that the presence of collagen bundles and the preservation of the lamina densa and anchoring fibrils provides evidence that the structural integrity of treated tissue is the same as untreated tissue. (Ex.1034, ¶¶79-81.) Further, a POSITA would have understood that preservation of the structure of the tissue (one of the goals of Livesey) necessarily meant that the mechanical properties are maintained. (Ex.1034, ¶81.)

The process of incorporating chemical compounds into a soft tissue graft to produce a graft that "has mechanical properties approximating the mechanical properties of natural soft tissue" had been widely used in tissue preservation before the filing date of the 986 patent. For example, both Livesey, issued in 1994, and WO 98/07452 (Ex.1005; "Walker"), published on 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 that

approximate the properties of normal hydrated tissue such as structure, flexibility, and strength. (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 to produce a pliable soft tissue that does not require rehydration before use. (Ex.1006, 2:12-14, 2:37-41.)

Each of these references discloses "a plasticized soft tissue graft having mechanical properties approximating those of natural soft tissue." The limitation that the "mechanical properties [of the treated tissue] approximat[e] mechanical properties of natural soft tissue," does not make the known process of incorporating chemical compounds into a soft tissue graft novel, unexpected, or inventive because maintaining the mechanical properties of natural tissue was an expected and known result of the preservation process. Thus, the claims 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 986 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").

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III. Grounds for Standing

The 986 patent is available for *inter partes* review, and RTI is not barred or estopped from requesting an *inter partes* review challenging claims 1-27 on the grounds identified in this Petition.

IV. Identification of Challenge

Petitioner identifies the following six grounds of unpatentability:

Ground 1: Claims 11 and 12 are anticipated by Walker.

Ground 2: Claims 1-3, 9, 11-15, and 23-25 are obvious over Walker.

Ground 3: Claims 1-6, 9-20, and 23-24 are anticipated by Livesey.

Ground 4: Claims 1-6, 9-20, and 23-24 are obvious over Livesey.

Ground 5: Claims 1-10, 13-25, and 27 are obvious over Walker in view of Livesey.

Ground 6: Claim 26 is obvious over Walker in view of Livesey and Werner.

V. The 986 Patent

A. The Subject Matter of the 986 Patent

The 986 patent describes a "plasticized soft tissue graft" suitable for transplantation into a human and methods of producing such a graft. It 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.1003, 1:24-29.)

The patent states that "[s]oft tissue products are typically provided as fresh-frozen or freeze-dried." (*Id.*, 3:47-51.) This allegedly "causes [such] grafts to be brittle and typically causes shrinkage where the shrinkage is not uniform, thereby causing graft failure." (*Id.*, 3:57-61.) 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.*, 3:61-63.) The patent states that these methods "necessitate[] a rehydration step in preparation of the bone and soft tissue product for implantation." (*Id.*, 3:63-66.)

The 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. (*Id.*, 5:42-49.) Examples 9 and 10 (the only soft tissue examples) use glycerol as the plasticizer; however, the specification provides other examples of suitable plasticizers, including sorbitol, ethylene glycol, sucrose, and mannitol. (*Id.*, 7:54-63, 8:46-9:5.) 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.*, 10:31-36 (emphasis added).)

The claims recite that the "plasticized soft tissue graft [has] mechanical properties approximating those of natural soft tissue." (*Id.*, 24:46-48, 25:30-32, 25:41-43, 25:49-51, 26:50-52.)

B. Prosecution History

The 986 patent issued on March 7, 2017, from U.S. Patent Application No. 14/193,040, filed February 28, 2014, and claims priority as a divisional of application No. 09/107,459, filed on June 30, 1998, which issued as U.S. Patent No. 6,293,970. Therefore, the 986 patent may be entitled to the effective filing date of June 30, 1998.

On December 2, 2015, the Examiner issued a non-final office action rejecting many claims under 35 U.S.C. 102(b) as being anticipated by Livesey. (Ex. 1027 at 2-3.) The Examiner further objected to several claims under 35 U.S.C. 103(a) as being unpatentable over Livesey in view of Werner. (*Id.*) On October 5, 2016, applicants responded arguing that "Livesey does not disclose, teach, or suggest a plasticized soft tissue graft having mechanical properties approximating those of natural soft tissue." (Ex. 1028 at 7-8.) The claims were thereafter allowed.

As discussed *infra*,[1] both Walker and Livesey disclose the feature that applicants argued was missing from the prior art – "the plasticized soft tissue graft has mechanical properties approximating mechanical properties of natural soft tissue."

C. Person of Ordinary Skill in the Art

As Dr. McQuillan explains, a POSITA relating to the subject matter of the 986 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.)

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

[1] Petitioner has provided a summary of 325(d) considerations in §VIII.

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

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

The only examples of the cleaning procedure for soft tissue are found in Examples 9 and 10 of the 986 patent, which describe soaking the soft tissue graft

[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).

in a 1:100 dilution of Allowash™ Solution for at least 15 minutes. (Ex.1003 at 23:2-5.) 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). Therefore, a POSITA would have recognized that the cleaning process described in the 986 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.)

By February 1998, it was known that glycerol was non-toxic to humans and exhibited powerful antiseptic action in the body. (Ex.1034, ¶25; Ex.1021 at 969-

971; Ex.1013 at S6; Ex.1022 at S44; Ex.1023 at 394-395.) Further, by February 1998, it was known that glycerol preservation did not affect the fundamental architecture of tissues and that tissues preserved with glycerol have properties approximating those of their natural counterparts. (Ex.1034, ¶30; Ex.1022 at S4; Ex.1023 at 396-397; Ex.1021 at 971.)

D. Claim Construction

The following terms are expressly defined in the 986 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.1003, 7:5-11.)
- **"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.*, 7:42-48.) "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.*, 7:48-54.) Disclosed examples of suitable

plasticizers including glycerol, ethylene glycol, propylene glycol, and mannitol. (*Id.*, 7:54-63.)

- **"soft tissue graft" -** "load-bearing and non-load-bearing soft tissue products." (*Id.*, 8:16-18.) 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.*, 8:18-21.)

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 986 patent, a POSITA in February 1998 would have taken into account the cleaning process disclosed in Examples 9 and 10. (*See* §V.C.1., *supra.*) A POSITA would have understood that the cleaning process disclosed in the 986 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.1003, 7:37-41, 8:16-18.) 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 986 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 constitute 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 following claim term were not expressly defined in the 986 patent and should be given the plain and ordinary meaning to a POSITA:

- **"mechanical properties approximating mechanical properties of natural soft tissue" -** "mechanical properties, including material properties,

physical, and use properties, of tissue are similar to those of normal hydrated tissue."

Petitioner's view is that the "mechanical properties" of natural soft tissue include the material, physical and use properties of the tissue. (Ex.1034, ¶¶54-55.) Similar language was included by the court in the LifeNet Litigation for defining the claim term "plasticized soft tissue graft." (Ex.1019 at 7-9.) A POSITA would have understood that the plasticization process results in the preservation of the mechanical and structural properties of the tissue. (Ex.1034, ¶¶54-55.)

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 986 patent under 35 U.S.C. 102(b). Livesey was the basis of a rejection of the 986 patent.[4]

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.)

[4] Petitioner has provided a summary of 325(d) considerations in §VIII.

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.1004, 1:21-26; *see also* 1:34-39.) In Example 1, Livesey discloses the use of sodium dodecyl sulfate detergent 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 986 patent, Livesey discloses treating soft tissues grafts by incorporating chemical compounds (called "cryoprotectants") within the internal matrix of the graft. (Ex.1034, ¶¶62-64; Ex.1004, 5:15-30, 14:47-54.) Suitable cryoprotectants include many of the same compounds identified in the 986 patent as plasticizers such as sucrose, glycerol, and propylene glycol. (*Compare* Ex.1004, 11:49-55 *with* Ex.1003, 7:52-61.) Livesey discloses that the soft tissue graft is incubated in the cryosolution long enough to allow complete penetration of the cryoprotectants. (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 to preserve the structural integrity of the tissue. (Ex.1034, ¶62.)

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 anchoring fibrils, are difficult to preserve and therefore would have recognized that the process described in Livesey maintains the structural and mechanical properties of the soft tissue. (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. Therefore, Walker is prior art under 35 U.S.C. 102(b). Walker is among the references cited on the face of the 986 patent, but it was neither addressed in any substantive manner nor was it the basis of any rejection.

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 986 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.)

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 sclero protein transplants with increased biological stability." As a U.S. patent that issued on November 2, 1982, Werner is prior art to the 986 patent under 35 U.S.C. 102(b). Werner was the basis of a rejection of the 986 patent during prosecution.[5]

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 exposing it to 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

[5] Petitioner has provided a summary of 325(d) considerations in §VIII.

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 986 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 transplantation. (Ex.1034, ¶94; Ex.1006, 2:37-41.)

VII. Grounds for Unpatentability

Petitioner seeks review of claims 1-27. Claims 1, 10-13, and 27 are independent claims; the rest are dependent.

A. Ground 1: Walker anticipates claims 11 and 12

Claim 11 can be divided into a preamble and five elements, 1 through 5 (*see* Ex.1003, 25:24-32), and Walker discloses every element.

Claim 11, preamble: *A soft tissue graft, comprising:*

To the extent the preamble is limiting, Walker discloses a soft tissue graft. (Ex.1034, ¶300.) 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.) A

POSITA would have understood that, therefore, Walker discloses a soft tissue graft. (Ex.1034, ¶300.)

Claim 11, element 1: *soft tissue obtained from a human or animal donor;*

Walker discloses that "[b]iologic tissue grafts of human and animal origin such as heart and venous valves and blood vessels are well known." (Ex.1005, 1:6-8.) Walker discloses a method of sterilizing and treating a biological material for implantation in the human body (*id.*, 2:14-21) and provides examples of its method using soft tissue obtained from an animal donor. (*Id.*, 7:19-20, 15:3-8; *see also* Ex.1034, ¶301.)

Claim 11, element 2: *and a plasticizer,*

Walker discloses treating a biological material with a water-soluble non-volatile substance by incubating the material in the substance solution for at least 12 hours. (Ex.1005, 2:30-34, 3:23-24.) Walker provides several examples in which the substance used is glycerol and the biological material is incubated for 16 hours or more. (Ex.1005, 5:11-13, 15:16-17, 20:7-8.) A POSITA would have understood that glycerol acts as the plasticizer in the method of Walker. (Ex.1034, ¶¶85-86, 302.)

Claim 11, element 3: *wherein cellular elements are substantially removed from said soft tissue,*

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, if not substantially, remove cellular components from the soft tissue. (Ex.1034, ¶¶84, 303.)

Claim 11, element 4: ***said plasticizer is contained in said soft tissue;***

Walker discloses treatment of the material with a water-soluble, non-volatile substance for at least 12 hours, providing examples of treatment with glycerol for 16 hours or more. (Ex.1005, 2:30-34, 3:23-24, 5:11-13, 15:16-17, 20:7-8.) That incubation gives the glycerol sufficient time to impregnate the internal matrix. (Ex.1034, ¶304.) 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, 304; Ex.1005, 19:9-12.) Walker therefore discloses that one or more plasticizers are contained in the internal matrix of the material.

Claim 11, element 5: ***and the plasticized soft tissue has mechanical properties approximating mechanical properties of natural soft tissue.***

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.) Therefore, a POSITA would have understood that Walker's method results in a plasticized soft tissue graft that "has mechanical properties approximating mechanical properties of natural soft tissue." (Ex.1034, ¶¶88-89, 305.)

Element	**Claim 11**	**Walker (Ex.1005)**
Preamble	A soft tissue graft, comprising:	"This invention relates to a method of treating a graft for implantation into a body." (Ex.1005, 1:3-4.) "Preferably the material is biological material, such as vascular tissue . . ." (Ex.1005, 4:17-18.)
1	soft tissue obtained from a human or animal donor;	"Bovine Carotid and Thoracic arteries . . . were plasticized in glycerol solution..." (Ex.1005, 15:3-8.)

Element	Claim 11	Walker (Ex.1005)
2	and a plasticizer,	"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, 4:29-34.) "All samples were plasticized in a solution of 50% glycerol in 50% ethanol." (Ex.1005, 7:20-22.)
3	wherein cellular elements are substantially removed from said soft tissue,	See Examples 3-4 showing tissue stored in ethanol. (Ex.1005, 7:19-20, 15:3-5.)
4	said plasticizer is contained in said soft tissue,	"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, 4:29-34.) "Plasticization was carried out overnight (≥16h) at 37°C, with gentle agitation . . ." (Ex.1005, 15:16-18.) "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, 91:9-12.)

Element	Claim 11	Walker (Ex.1005)
5	and the plasticized soft tissue has mechanical properties approximating mechanical properties of natural soft tissue	"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, 6:20-24.) "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.) See Suture Retention Results (Ex.1005, 9-10) and Maximum Load and Stress Results (Ex.1005, 11-14) showing that the tissues described in Examples 3 and 4 retained certain physical characteristics. "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 12 can be divided into a preamble and four elements, 1 through 4 (*see* Ex.1003, 25:33-43), and Walker discloses every element.

Claim 12, preamble: ***A method for producing a soft tissue graft, comprising:***

To the extent the preamble is limiting, Walker discloses a method for producing a soft tissue graft. (Ex.1034, ¶307.) 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.) Walker therefore discloses a method for producing a soft tissue graft. (Ex.1034, ¶307.)

Claim 12, element 1: ***substantially removing cellular elements from soft tissue obtained from a human or animal donor;***

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, if not substantially, remove cellular components from the soft tissue. (Ex.1034, ¶¶84, 308.)

Walker discloses that "[b]iologic tissue grafts of human and animal origin such as heart and venous valves and blood vessels are well known." (Ex.1005, 1:6-8.) Walker discloses a method of sterilizing and treating a biological material for implantation in the human body (*id.*, 2:14-21) and provides examples of its method

using soft tissue obtained from an animal donor. (*Id.*, 7:19-20, 15:3-8; *see also* Ex.1034, ¶308.)

Claim 12, element 2: ***impregnating the soft tissue with a biocompatible, water-soluble plasticizer,***

Walker discloses treatment of the material with a water-soluble, non-volatile substance for at least 12 hours, providing examples of treatment with glycerol for 16 hours or more. (Ex.1005, 2:30-34, 3:23-24, 5:11-13, 15:16-17, 20:7-8.) That incubation gives the glycerol sufficient time to impregnate the internal matrix. (Ex.1034, ¶309.) 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, 309; Ex.1005, 19:9-12.) A POSITA would have understood from Walker that the soft tissue graft is impregnated with the plasticizer. (Ex.1034, ¶309.)

Claim 12, element 3: ***said plasticizer not requiring substantial removal prior to packaging of the soft tissue graft,***

As discussed in relation to Claim 12, element 2, Walker discloses impregnating the material with glycerol. Walker discloses that the treated samples are packaged after plasticization prior to be sterilized. (Ex.1005, 15:35-36.) Walker discloses that prior to packaging, the samples can optionally be drained to remove excess glycerol but such draining is not required and further, a POSITA would

have recognized that such draining would only remove excess glycerol from the material. (Ex.1034, ¶310; 1005, 15:25-32.) Therefore, Walker discloses that glycerol does not require substantial removal prior to packaging.

Claim 12, element 4: *wherein the plasticized soft tissue has mechanical properties approximating mechanical properties of natural soft tissue.*

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.) Therefore, a POSITA would have understood that Walker's method results in a plasticized soft tissue graft that "has mechanical properties approximating mechanical properties of natural soft tissue." (Ex.1034, ¶¶88-89, 311.)

Element	Claim 12	Walker (Ex.1005)
Preamble	A method for producing a soft tissue graft, comprising:	"This invention relates to a method of treating a graft for implantation into a body." (Ex.1005, 1:3-4.) "Preferably the material is biological material, such as vascular tissue . . ." (Ex.1005, 4:17-18.)
1	substantially removing cellular elements from soft tissue obtained from a human or animal donor	See Examples 3-4 showing tissue stored in ethanol. (Ex.1005, 7:19-20, 15:3-5.) "Bovine Carotid and Thoracic arteries . . . were plasticized in glycerol solution . . . ." (Ex.1005, 15:3-8.)
2	impregnating the soft tissue with a biocompatible, water-soluble plasticizer	"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, 4:29-34.) "Plasticization was carried out overnight (≥16h) at 37°C, with gentle agitation . . ." (Ex.1005, 15:16-18.) "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 12	Walker (Ex.1005)
3	said plasticizer not requiring substantial removal prior to packaging of the soft tissue graft,	"Initially the samples were dried overnight . . . in order to reduce excess glycerol before packaging . . . . The same effect can be obtained by draining the sample against the vessel wall to remove excess glycerol . . . . At higher concentrations of glycerol . . . samples remained slightly tacky to touch." (Ex.1005, 15:25-32.) "Once plasticized, samples were packaged in graft blisters." (Ex.1005, 15:35-36.)

Element	Claim 12	Walker (Ex.1005)
4	wherein the plasticized soft tissue has mechanical properties approximating mechanical properties of natural soft tissue.	"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, 6:20-24.) "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.) See Suture Retention Results (Ex.1005, 9-10) and Maximum Load and Stress Results (Ex.1005, 11-14) showing that the tissues described in Examples 3 and 4 retained certain physical characteristics. "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.)

B. Ground 2: claims 1-3, 9, 11-15, and 23-25 are obvious over Walker

Claims 1-3, 9, 11-15, and 23-25 are obvious over Walker. The explanation of Ground 1 (§VII.A.) details how Walker anticipates claims 11 and 12. To the extent any limitation of those claims is not explicitly disclosed in Walker, the

subject matter 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, ¶¶312-326.)

To the extent it is determined that Walker does not explicitly disclose the following claim elements, the subject matter of the claims reciting those elements would have been obvious to a POSITA at the time of the alleged invention for at least the following reasons:

1. It would have been obvious to a POSITA that the soft tissue graft of Walker contained plasticizers in the internal matrix

As detailed above in Ground 1, Walker discloses that the plasticizer is contained in the internal matrix. Walker explicitly discloses that the glycerol keeps the dimensions of the material stable during processing, indicating that the glycerol is contained within the internal matrix. (Ex.1034, ¶¶312-313; Ex.1005, 19:9-12.) But if it is determined that Walker does not explicitly disclose that the plasticizer is contained in the internal matrix or that the plasticizer impregnates the soft tissue graft, a POSITA in February 1998 would have understood from Walker that small chemical compounds, such as glycerol, act by replacing free and loosely bound water within the tissue thereby incorporating themselves within the internal matrix. (Ex.1034, ¶313.)

Thus, even if claims 1-3, 9, 11-15, and 23-25 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 "one or more plasticizers [are] contained in said internal matrix," or that the soft tissue graft is "impregnate[ed] . . . with . . . a plasticizer," a POSITA in February 1998 would have understood from Walker that small chemical compounds such as the ones disclosed in Walker act by penetrating the soft tissue graft and replacing free and loosely bound water within the internal matrix, and (3) a POSITA in February 1998 would have recognized that the method of Walker would have yielded the desirable and predictable result of a soft tissue graft where the plasticizer is contained in the internal matrix and/or the plasticizer impregnates the internal matrix. (Ex.1034, ¶¶312-313.)

2. It would have been obvious to a POSITA that the soft tissue graft of Walker did not require refrigeration or freezing required and that it could be stored at room temperature

To the extent it is determined that Walker does not explicitly disclose that "no refrigeration or freezing is required," or that the tissue "can be stored at room temperature," those claim elements would have been obvious to a POSITA at the time of the alleged invention. (Ex.1034, ¶314.)

Nothing in Walker would have led a POSITA to understand that the plasticized soft tissue graft of Walker requires any special conditions for storage and a POSITA would have understood Walker to disclose a soft tissue graft that

could be stored at room temperature. (Ex.1034, ¶315.) But if it is determined that Walker does not explicitly disclose these claim limitations, a POSITA in February 1998 would have known that soft tissue grafts preserved with glycerol were considered "dried/dehydrated" grafts, and as such, did not require special conditions for storage and that they could be stored at room temperature. (Ex.1034, ¶¶316-318.) Walker discloses that the water is replaced with glycerol and that the tissue is thereafter dried to allow removal of any remaining water. (Ex.1005, 7:20-23.) A POSITA would have therefore understood that the resulting soft tissue product of Walker is dried/dehydrated and therefore would not require special conditions for storage and that it could be stored at room temperature. (Ex.1034, ¶319)

Thus, even if claims 1-3, 9, 13-15, and 23-25 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 "said plasticized soft tissue does not require refrigeration or freezing for storage," or "said plasticized soft tissue graft is suitable for storage at room temperature," a POSITA in February 1998 would have understood from Walker that a soft tissue graft preserved with glycerol would not require special conditions for storage and could be stored at room temperature, and (3) a POSITA in February 1998 would

have recognized that the method of Walker would have yielded the desirable and predictable result of a soft tissue graft which does not require refrigeration or freezing for storage and which could be stored at room temperature. (Ex.1034, ¶¶314-319.)

The additional subject matter of claims 3, 5, 9, 15, and 23-25 would also have been obvious to a POSITA in view of Walker.

Claims 3 and 15 require that "cellular elements [are] removed from the soft tissue graft." (Ex.1003, 24:52-54, 26:1-2.) Walker discloses a method in which the tissue product is stored in ethanol prior to treatment with glycerol. (Ex.1005, 7:19-20, 15:3-5.) A POSITA would have recognized that storing the biological tissue in ethanol would result in a cleaned, plasticized soft tissue graft in which "cellular elements are removed." (Ex.1034, ¶¶320, 323.)

Claim 5 recites "The plasticized soft tissue graft of claim 1, wherein said soft tissue graft comprises cadaveric skin, pericardium, dura mater, fascia lata, ligaments, or tendons." (Ex.1003, 24:58-60.) 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, ¶321.) Walker discloses examples of its method using bovine carotid and thoracic arteries, which a POSITA would have recognized are other types of load-bearing soft tissue. (Ex.1034, ¶321.) 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.1005, 25:1-2.) Therefore, Claim 5 would have been obvious to a POSITA in view of Walker. (Ex.1034, ¶321.)

Claims 9 and 24 require that the plasticizer is "selected from the group consisting of glycerol, adonitol, sorbitol. . . [among other compounds]." (Ex.1003, 25:4-11, 26:27-34.) Walker discloses that the use of glycerol is extremely advantageous and provides several examples using glycerol as the plasticizer and, therefore Walker discloses the additional limitation of Claims 9 and 24. (Ex.1005, 4:26-27, 7:20-23, 15:13-14; *see also* Ex.1034, ¶¶322, 325.)

Claim 23 recites "The method of claim 13, comprising impregnating the cleaned soft tissue graft with a plasticizer composition comprising one or more water-soluble plasticizers and one or more biocompatible solvents selected from the group consisting of water and alcohols." (Ex.1003, 26:22-26.) Walker Example 3 discloses that the samples were plasticized in a solution of 50% glycerol in 50% ethanol. (Ex.1005, 7:20-22.) Walker therefore discloses impregnating the cleaned soft tissue graft with a plasticizer composition comprising one or more plasticizers

(i.e., glycerol) and one or more biocompatible solvents selected from the group consisting of water and alcohols (i.e., ethanol). (Ex.1034, ¶324.)

Claim 25 recites "The method of claim 13, further comprising washing the plasticized soft tissue graft to remove plasticizer from a surface of the plasticized soft tissue graft." (Ex.1003, 26:35-37.) Walker discloses that "[t]he material can, after being treated, be drained and/or washed to remove excess glycerol or other substance, prior to implantation." (Ex.1005, 4:33-36.) A POSITA would have understood from Walker that draining or washing the tissue to remove excess glycerol would remove glycerol from the surface of the graft. (Ex.1034, ¶326.)

C. Ground 3: Livesey anticipates claims 1-6, 9-20, and 23-24

Claim 1 can be divided into a preamble and five elements, 1 through 5 (*see* Ex.1003, 24:38-48), 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, ¶328.) 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, ¶62; 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, ¶328.)

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, leaving a cleaned soft tissue with an internal matrix. (Ex.1034, ¶¶61, 329.)

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

As noted, Livesey discloses a soft tissue graft incubated in a cryosolution that contains 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.1004, 12:33-37.) The "cryoprotectants" described in Livesey constitute the "plasticizer" described in the 986 patent. (Ex.1034, ¶¶62-64, 330.) Several examples of plasticizer components given in the 986 patent match the non-exclusive examples of cryoprotectant listed in Livesey. (*Compare* Ex.1004, 11:49-55 *with* Ex.1003, 7:54-63.) Therefore, Livesey discloses the recited one or more plasticizers contained in the internal matrix. (Ex.1034, ¶330.)

Claim 1, element 3: ***said one or more plasticizers not being removed from said internal matrix prior to packaging,***

Livesey discloses that the cryosolution is exposed to the soft tissue graft "until complete penetration of the components of the cryosolution is achieved." (Ex.1004, 12:33-37.) Livesey discloses that the tissue is packaged after incubation in the cryopreservation solution. (*Id.*, 5:27-30.) Livesey discloses no steps between incubation of the tissue in the cryopreservation solution and packaging of the tissue that would remove the cryoprotectant from the internal matrix of the tissue.

(Ex.1034, ¶331.) A POSITA would have understood that in order to remove the cryoprotectant from the internal matrix, extensive washing would be required. (Ex.1034, ¶331.) A POSITA would have understood from Livesey that the cryoprotectants would be contained within the internal matrix prior to packaging. (Ex.1034, ¶331.)

Claim 1, element 4: ***wherein said plasticized soft tissue graft does not require refrigeration or freezing for storage;***

Livesey discloses that the packaged dried tissue may be stored for extended time periods under ambient conditions and, therefore, Livesey discloses that the tissue graft does not require refrigeration or freezing for storage. (Ex.1004, 6:6-11; *see also* Ex.1034, ¶332.)

Claim 1, element 5: ***wherein the plasticized soft tissue graft has mechanical properties approximating mechanical properties of natural soft tissue.***

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, ¶¶65-66, 333; Ex.1004, 25:12-17.) A POSITA would have recognized that a soft tissue graft with the structural characteristics of natural soft tissue would also maintain the mechanical properties of natural soft tissue because function of a soft tissue is highly dependent on the structure. (Ex.1034, ¶¶74-81.)

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.)
2	and 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

Element	Claim 1	Livesey (Ex.1004)
		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: . . . sucrose . . . glycerol, sorbitol, fructose . . . and combinations thereof." (Ex.1004, 11:49-55.) See Example 1 where the plasticizers are dextran and sucrose. (Ex.1004, 24:10-19.) "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.)

Element	Claim 1	Livesey (Ex.1004)
3	said one or more plasticizers not being removed from said internal matrix prior to packaging	"After the tissue is decellularized, it is preferably incubated in a cryopreservation solution . . . this solution contains one or more cryoprotectants . . . . Following incubation in this cryopreservation solution, the tissue is packaged inside a sterile container . . . ." (Ex.1004, 5:15-30.) See also Example 1 showing that the cryoprotectants are not removed from the tissue prior to packaging. (Ex.1004, 5:27-30.)
4	wherein said plasticized soft tissue graft does not require refrigeration or freezing for storage	"the package dried tissue may be stored for extended time periods under ambient conditions. Transportation may be accomplished via standards carriers and under standard conditions relative to normal temperature exposure and delivery times." (Ex.1004, 6:6-11.)
5	wherein the plasticized soft tissue graft has mechanical properties approximating mechanical properties of natural soft tissue	"Treatment of the tissue with this processing solution must be at a concentration for a time duration such that degradation of the basement membrane complex is avoided and the structural integrity of the matrix is maintained including collagen fibers and elastin." (Ex.1004, 5:10-14.) "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.)

Claims 2 and 14 add the limitation that the "plasticized soft tissue graft is suitable for storage at room temperature." (Ex.1003, 24:49-51, 25:55-56.) Livesey teaches that the packaged dried tissue may be stored for extended time periods under ambient conditions, therefore, a POSITA would have recognized that Livesey discloses a plasticized soft tissue graft is "suitable for storage at room temperature." (Ex.1034, ¶¶334, 367; Ex.1004, 6:6-11.)

Claims 3 and 15 add the limitation that "cellular elements have been removed from the soft tissue graft." (Ex.1003, 24:52-54, 26:1-2.) Livesey discloses a method wherein the tissue is decellularized by treatment with a sodium dodecyl sulfate detergent solution. (*Id.*, 23:65-67.) A POSITA would have recognized that treatment of the tissue with a detergent as disclosed in Livesey would result in a cleaned, plasticized soft tissue graft that is "essentially free from cellular elements," and that is "produc[ed] by removing cellular elements." (Ex.1034, ¶¶335, 368.)

Claims 4, 6, 16, 18, and 20 add the limitations that the "soft tissue graft comprises cadaveric skin and said one or more plasticizers comprise glycerol." (Ex.1003, 24:55-57, 24:61-63, 26:3-5, 26:8-10, 26:14-16.) Livesey provides an example of its method using cadaveric skin. (Ex.1004, 23:5-25:42.) Livesey also teaches the use of glycerol as a cryoprotectant. (*Id.* 12:24-30.) Livesey, therefore,

discloses the subject matter of claims 4, 6, 16, 18, and 20. (Ex.1034, ¶¶336, 338, 369, 371, 373.)

Claims 5 and 19 add the limitation that the soft tissue graft "comprises cadaveric skin, pericardium, dura mater, fascia lata, ligaments, or tendons." (Ex.1003, 24:58-60, 26:11-13.) Livesey provides an example of its method using cadaveric skin. (Ex.1004, 23:5-25:42; *see also* Ex.1034, ¶¶337, 372.)

Claims 9 and 24 add the limitation that the "one or more plasticizers is selected from the group consisting of glycerol, adonitol, sorbitol . . . [among other compounds]." (Ex.1003, 25:4-11, 26:27-34.) Livesey teaches use of one or more cryoprotectants (Ex.1004, 5:15-24) providing examples such as glycerol, sorbitol, fructose, and propylene glycol and, therefore, Livesey discloses the subject matter of claims 9 and 24. (*Id.*, 11:49-55; *see also* Ex.1034, ¶¶339, 375.)

Claim 10 can be divided into a preamble and five elements, 1 through 5 (*see* Ex.1003, 25:12-23), and Livesey discloses every element. (*See* Ex.1034, ¶¶340-348.)

Element	**Claim 10**	**Livesey (Ex.1004)**
Preamble	A plasticized soft tissue graft suitable for transplantation into a human, comprising:	See Claim 1 Table, Preamble.

Element	Claim 10	Livesey (Ex.1004)
1	a cleaned soft tissue graft comprising cadaveric skin having an internal matrix	See Claim 1 Table, Element 1. "Donor skin is harvested under aseptic conditions with a dermatome" (Ex.1004, 23:5-43.)
2	wherein cellular elements have been removed from the soft tissue graft	See Claim 1 Table, Element 1.
3	and one or more plasticizers comprising glycerol contained in said internal matrix	See Claim 1 Table, Element 2.
4	said one or more plasticizers not being removed from said internal matrix prior to packaging;	See Claim 1 Table, Element 3.
5	wherein said plasticized soft tissue graft is suitable for storage at room temperature and has strength and tensile properties of natural tissue.	See Claim 1 Table, Elements 4 and 5.

Claim 11 can be divided into a preamble and five elements, 1 through 5 (*see* Ex.1003, 25:24-32), and Livesey discloses every element. (*See* Ex.1034, ¶¶349-355.)

Element	Claim 11	Livesey (Ex.1004)
Preamble	A soft tissue graft, comprising:	See Claim 1, Preamble.

Element	Claim 11	Livesey (Ex.1004)
1	soft tissue obtained from a human or animal donor;	"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.)
2	and a plasticizer,	See Claim 1, Element 2.
3	wherein cellular elements are substantially removed from said soft tissue,	See Claim 1, Element 1.
4	said plasticizer is contained in said soft tissue,	See Claim 1, Elements 2 and 3.
5	and the plasticized soft tissue has mechanical properties approximating mechanical properties of natural soft tissue	See Claim 1, Element 5.

Claim 12 can be divided into a preamble and four elements, 1 through 4 (*see* Ex.1003, 25:33-43), and Livesey discloses every element.

Claim 12, preamble: ***A method for producing a soft tissue graft, comprising:***

To the extent the preamble is limiting, Livesey discloses a method for producing a soft tissue graft. (Ex.1034, ¶357.) Livesey describes a method for processing and preserving collagen-based biological tissues for transplantation.

(Ex.1004, 4:39-42.) Therefore, a POSITA would have recognized that Livesey discloses a method for producing a soft tissue graft. (Ex.1034, ¶357.)

Claim 12, element 1: ***substantially removing cellular elements from soft tissue obtained from a human or animal donor;***

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, leaving a cleaned soft tissue with an internal matrix. (Ex.1034, ¶¶61, 358.) Livesey also discloses that the tissues are derived from humans and animals for transplantation into humans or other animals and, therefore, Livesey discloses soft tissue obtained from a human or animal donor. (Ex.1004, 1:17-21; *see also* Ex.1034, ¶358.)

Claim 12, element 2: ***impregnating the soft tissue with a biocompatible, water-soluble plasticizer,***

As noted, Livesey discloses a soft tissue graft incubated in a cryosolution that contains 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.1004, 12:33-37.) The "cryoprotectants" described in Livesey constitute the "plasticizer" described in the 986 patent. (Ex.1034, ¶¶62-64, 359.) Several examples of plasticizer components given in the 986 patent match the non-exclusive examples of cryoprotectant listed in Livesey. (*Compare* Ex.1004, 11:49-55 *with* Ex.1003, 7:54-63.) A POSITA would have recognized that the cryoprotectants identified in Livesey are biocompatible and water-soluble and, therefore, Livesey discloses impregnating the soft tissue with a biocompatible, water-soluble plasticizer. (Ex.1034, ¶359)

Claim 12, element 3: ***said plasticizer not requiring substantial removal prior to packaging of the soft tissue graft,***

Livesey teaches that the cryosolution is exposed to the soft tissue graft "until complete penetration of the components of the cryosolution is achieved." (Ex.1004, 12:33-37.) Livesey discloses that the tissue is packaged after incubation in the cryopreservation solution. (*Id.*, 5:27-30.) Livesey discloses no steps between incubation of the tissue in the cryopreservation solution and packaging of the tissue that would remove the cryoprotectant from the internal matrix of the tissue. (Ex.1034, ¶360.) A POSITA would have understood that in order to remove the cryoprotectant from the internal matrix, extensive washing would be required. (*Id*.) A POSITA would have understood this to mean that the cryoprotectants would be contained within the internal matrix prior to packaging. (*Id*.)

Claim 12, element 4: *wherein the plasticized soft tissue has mechanical properties approximating mechanical properties of natural soft tissue.*

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, ¶¶65-66, 361; Ex.1004, 25:12-17.) A POSITA would have recognized that a soft tissue graft with the structural characteristics of natural soft tissue would also maintain the mechanical properties of natural soft tissue because function of a soft tissue is highly dependent on the structure. (Ex.1034, ¶361.)

Element	Claim 12	Livesey (Ex.1004)
Preamble	A method for producing a soft tissue graft, 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.)

Element	Claim 12	Livesey (Ex.1004)
1	substantially removing cellular elements from soft tissue obtained from a human or animal donor	"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.) "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 12	Livesey (Ex.1004)
2	impregnating the soft tissue with a biocompatible, water-soluble plasticizer	"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: . . . sucrose . . . glycerol, sorbitol, fructose . . . and combinations thereof." (Ex.1004, 11:49-55.) See Example 1 where the plasticizers are dextran and sucrose. (Ex.1004, 24:10-19.) "In general, cryopreservation is performed as a continuous sequence of events. The

Element	Claim 12	Livesey (Ex.1004)
		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.)
3	said plasticizer not requiring substantial removal prior to packaging of the soft tissue graft,	“After the tissue is decellularized, it is preferably incubated in a cryopreservation solution . . . this solution contains one or more cryoprotectants . . . . Following incubation in this cryopreservation solution, the tissue is packaged inside a sterile container . . . .” (Ex.1004, 5:15-30.) See also Example 1 showing that the cryoprotectants are not removed from the tissue prior to packaging. (Ex.1004, 5:27-30.)
4	wherein the plasticized soft tissue has mechanical properties approximating mechanical properties of natural soft tissue.	“Treatment of the tissue with this processing solution must be at a concentration for a time duration such that degradation of the basement membrane complex is avoided and the structural integrity of the matrix is maintained including collagen fibers and elastin.” (Ex.1004, 5:10-14.) “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.)

Claim 13 can be divided into a preamble and three elements, 1 through 3 (*see* Ex.1003, 25:44-54), and Livesey discloses every element. (*See* Ex.1034, ¶¶362-366.)

Element	**Claim 13**	**Livesey (Ex.1004)**
Preamble	A method for producing a plasticized soft tissue graft suitable for transplantation into a human, comprising:	Claim 12 Table, Preamble "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 having an internal matrix with a biocompatible, water-soluble plasticizer to produce the plasticized soft tissue graft;	Claim 12 Table, Elements 1 and 2

Element	Claim 13	Livesey (Ex.1004)
2	wherein the plasticized soft tissue graft has mechanical properties approximating mechanical properties of natural soft tissue;	See Claim 12 Table, Element 4.
3	and packaging the plasticized soft tissue graft without refrigeration or freezing or removal of the plasticizer from the internal matrix of the soft tissue graft.	See Claim 12 Table, Element 3 "In the preferred embodiment, the packaged dried tissue may be stored for extended time periods under ambient conditions." (Ex.1004, 6:6-11.)

Claim 17 recites "The method of claim 13, further comprising cleaning said soft tissue graft with a detergent composition." (Ex.1003, 26:6-7.) Livesey discloses a method wherein the tissue is decellularized by treatment with a sodium dodecyl sulfate detergent solution, therefore, disclosing the subject matter of Claim 17. (Ex.1004, 23:65-67; *see also* Ex.1034, ¶370.)

Claim 23 recites "The method of claim 13, comprising impregnating the cleaned soft tissue graft with a plasticizer composition comprising one or more water-soluble plasticizers and one or more biocompatible solvents selected from the group consisting of water and alcohols." (Ex.1003, 26:22-26.) 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, ¶374.)

D. Ground 4: Claims 1-6, 9-20, and 23-24 are obvious over Livesey

Claims 1-6, 9-20, and 23-24 are obvious over Livesey. The explanation of Ground 3 (§VII.C.) details how Livesey anticipates these claims. 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 in view of Livesey's disclosure. (*See* Ex.1034, ¶¶376-377.)

To the extent it is determined that Livesey does not explicitly disclose that "said plasticizer is contained in said soft tissue," the subject matter of the claims reciting that element 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, Livesey discloses that the plasticizer is contained in the internal matrix. (Ex.1004, 11:17-23.) Livesey explicitly discloses that the soft tissue graft is exposed to the cryosolution for a time long enough to obtain complete penetration of the cryoprotectants. (Ex.1004, 12:33-37.) But if it is determined that Livesey does not explicitly disclose that the plasticizer is contained in the internal matrix or that the plasticizer impregnates the soft tissue graft, a POSITA in February 1998 would have understood from Livesey that small chemical compounds, such as the

cryoprotectants in Livesey, act by replacing free and loosely bound water within the tissue thereby incorporating themselves within the internal matrix. (Ex.1034, ¶377.)

Thus, even if claims 1-6, 9-20, and 23-24 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 "one or more plasticizers [are] contained in said internal matrix," or that the soft tissue graft is "impregnat[ed] . . . with . . . a plasticizer," a POSITA in February 1998 would have understood from Livesey that small chemical compounds such as the ones disclosed in Livesey act by penetrating the soft tissue graft and replacing free and loosely bound water within the internal matrix, and (3) a POSITA in February 1998 would have recognized that the method of Livesey would have yielded the desirable and predictable result of a soft tissue graft where the plasticizer is contained in the internal matrix and/or the plasticizer impregnates the internal matrix. (Ex.1034, ¶¶376-377.)

E. Ground 5: Claims 1-10, 13-25, and 27 are obvious over Walker in view of Livesey

Claims 1-10, 13-25, and 27 are obvious over Walker in view of Livesey. Livesey and Walker are both directed to methods for preparing soft tissue grafts for

implantation into a human or animal. (Ex.1004, Abstract; Ex.1005, Abstract.) Walker discloses many of the elements of the 986 patent. To the extent that Walker does not disclose the following claim elements, they are taught by Livesey as disclosed above in Ground 3:

- "plasticized soft tissue graft does not require refrigeration or freezing for storage,"
- "the plasticized soft tissue graft is suitable for storage at room temperature,"
- "the soft tissue graft comprises cadaveric skin," and
- "cleaning said soft tissue graft with a detergent solution."

A POSITA would have been motivated to combine Livesey with the teachings of Walker to add these elements with a reasonable expectation of success. (Ex.1034, ¶378.)

1. The soft tissue graft of Livesey did not require refrigeration or freezing and Livesey disclosed that it could be stored at room temperature

Claims 1-10, 13-25, and 27 require either that the plasticized soft tissue graft does not require refrigeration or freezing for storage or that the tissue is suitable for storage at room temperature. Nothing in Walker would indicate to a POSITA that the tissue required special conditions for storage and, as explained above in Ground 2, a POSITA in February 1998 would have understood Walker to disclose

a soft tissue graft that could be stored at room temperature. (*See* Ground 2, *supra;* Ex.1034, ¶379.) But if it is determined that Walker does not disclose these claim elements, Livesey discloses such claim elements. (Ex.1034, ¶380.) Livesey states that "the package dried tissue may be stored for extended time periods under ambient conditions." (Ex.1004, 6:6-11.)

A POSITA in February 1998 would have been motivated to combine the teaching in Livesey, that the tissue can be stored for extended periods of time under ambient conditions, with the method of Walker to provide a plasticized soft tissue graft that would not require special conditions for storage. (Ex.1034, ¶¶380-382.) Such a soft tissue graft that does not require refrigeration or freezing and that is able to be stored at room temperature is desirable because it would be less expensive to keep in storage and less expensive to transport. (Ex.1034, ¶381.) A POSITA would have had a reasonable expectation of success in combining the process of Walker with these teachings of Livesey because Livesey teaches the same processing steps as Walker and even lists glycerol, the pre-sterilizing substance used in Walker, as an alternative substance that can be used with its own process. (Ex.1034, ¶382.)

2. Livesey disclosed a soft tissue graft that comprises cadaveric skin

Claims 4-8, 10, 16, 18-22, and 27 require that the soft tissue comprise cadaveric skin. Walker discloses its method using vascular tissue and provides an example of its process using bovine carotid and thoracic arteries which are load-bearing soft tissue according to the 986 patent. (Ex.1005, 4:17-18, 7:19-20; Ex.1003, 8:19-21.) To the extent Walker does not specifically disclose a soft tissue that comprises cadaveric skin, that claim element is disclosed in Livesey. (Ex.1034, ¶¶383-384.) Livesey provides an example of its method using transplantable cadaveric skin. (Ex.1004, 23:5-25:42.)

A POSITA in February 1998 would have been motivated to extend the method disclosed in Walker to other types of soft tissue including cadaveric skin to provide a method that can be used to treat all types of soft tissue both load-bearing and non-load-bearing. (Ex.1034, ¶¶385-386.) A POSITA would have had a reasonable expectation of success in combining the process of Walker with these teachings of Livesey because the method disclosed in Livesey is very similar to the method disclosed in Walker and even lists glycerol, the pre-sterilizing substance used in Walker, as an alternative substance that can be used with its own process. (Ex.1034, ¶¶385-386.) Furthermore, Walker discloses that its method of

plasticization can be used on biological materials and cadaveric skin falls within that category.

3. Livesey disclosed that the soft tissue graft is cleaned using a detergent solution

Claims 17, 18, and 27 require that the tissue is cleaned using a detergent solution. Walker teaches a cleaned soft tissue graft by disclosing that the tissue is stored in ethanol prior to treatment with glycerol. (Ex.1005, 7:19-20, 15:3-5.) To the extent Walker does not explicitly use a detergent solution for cleaning, Livesey discloses a detergent solution for cleaning. (Ex.1034, ¶¶387-388.) Livesey discloses that the soft tissue grafts are decellularized by treatment with a sodium dodecyl sulfate detergent solution. (Ex.1004, 23:65-67.)

A POSITA by February 1998 would have sought to modify the cleaning procedure of Walker with the cleaning procedure of Livesey that utilizes detergent. (Ex.1034, ¶¶389-391.) A POSITA by February 1998 would have understood the importance of tissue cleaning and would have been motivated to use detergent, as taught by Livesey, in combination with the process taught by Walker since a POSITA would know that detergent is effective in removing cellular elements from the tissue. (*See* §V.C.1., *supra*; Ex.1004, 9:40-52.) A POSITA would have had a reasonable expectation of success in combining the process of Walker with

the cleaning method of Livesey because both references include a cleaning step that results in a cleaned soft tissue graft. (Ex.1034, ¶391.)

F. Ground 6: Claim 26 is obvious over Walker in view of Livesey and Werner

Claim 26 is obvious over Walker in view of Livesey and Werner. Claim 26 recites "The method of claim 25, further comprising surgically washing the plasticized soft tissue graft to remove plasticizer from a surface of the plasticized soft tissue graft into a patient without rehydration." (Ex.1003, 26:38-40.)

If neither Walker nor Livesey discloses that the plasticized soft tissue graft that 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, Abstract.) Werner discloses that the resulting tissue product is soft and that no rehydration of the product is necessary before implantation. (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, ¶¶392-394, 174-175.)

A POSITA in February 1998 would have been motivated to simplify the steps for the processing of a soft tissue graft at the time of implantation and would

have explored avenues for doing so. (Ex.1034, ¶¶395-400, 176-180.) A POSITA by February 1998 would have sought to modify the method of Walker and Livesey by following Werner's teaching in order to simply the processing of the soft tissue graft during implantation. (*Id.*) Doing so would achieve the known advantage of allowing for direct implantation of the plasticized soft tissue graft instead of requiring rehydration before implantation. (*Id.*) Indeed, Werner teaches the same processing steps as Walker, and its further teaching to implant the graft without first rehydrating the graft would have been recognized as desirable by a POSITA. It would therefore have been evident to a POSITA that Werner's teaching could be advantageously incorporated into the method of Walker and Livesey. (*Id.*) Further, a POSITA would have expected a similar result for the soft tissue grafts referenced in Walker by utilizing the processing steps of Werner. (Ex.1034, ¶¶392-400.)

Claim 26 depends from claims 25 and 13 which are obvious over Walker in view of Livesey as explained in Ground 5. Therefore, Claim 26 would have been obvious to a POSITA at the time of the alleged invention.

VIII. Consideration under 35 U.S.C. §325(d) Supports Institution

Although Livesey was considered during prosecution, applicants mischaracterized Livesey and the Examiner accepted and relied on applicants' mischaracterization to allow the then-pending claims. Additionally, key portions of Livesey were *not* considered during prosecution and thus, Petitioner's Grounds

3 and 4 do not "present the same or substantially the same prior art or *arguments* previously [] presented to the [Patent] Office." 35 U.S.C. §325(d) (emphasis added).

The Board considers several non-exclusive factors under 35 U.S.C. §325(d) when evaluating whether the same or substantially the same prior art or arguments were previously presented to the Office. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, Case IPR2017-01586, slip op. at 17–28 (PTAB Dec. 15, 2017) (Paper 8) (informative). Relevant here are (i) "the manner in which . . . Patent Owner distinguishes the prior art;" (ii) "how the Examiner erred in its evaluation of the asserted prior art;" and (iii) "additional evidence and facts [that] warrant reconsideration of the prior art or arguments." (*Becton* factors d, e, and f.)

During prosecution of the 986 patent, the claims were rejected as being anticipated by Livesey and obvious over Livesey in view of Werner. (Ex. 1027 at 2-3.) The Examiner noted that Livesey disclosed all of the elements of many of the claims, and, for those that were not anticipated by Livesey, Werner disclosed the remaining limitations (i.e., certain weight percent limitations). (*Id*.)

To overcome the rejection based on Livesey, applicants amended the claims to include the following limitation: "wherein the plasticized soft tissue has mechanical properties approximating mechanical properties of natural soft tissue." (Ex. 1028 at page 2.) They then argued that Livesey did not disclose a plasticized

soft tissue graft having mechanical properties approximating those of natural soft tissue:

> freezing and drying the soft tissue, as taught by Livesey, will cause the soft tissue to have different mechanical properties than those of soft tissue, even once the tissue is returned to ambient temperature. Thus, *Applicants respectfully submit that Livesey does not disclose, teach, or suggest a plasticized soft tissue graft having mechanical properties approximating those of natural soft tissue*.

(Ex. 1028 at 7 (emphasis added).) The Examiner allowed the claims based on this amendment and argument.

Applicants' characterization of Livesey was incorrect and the Examiner erroneously relied on applicants' characterization in allowing the claims. A POSITA would have understood that the cryopreservation method taught by Livesey would not "cause the soft tissue to have different mechanical properties than those of soft tissue" as applicants argued. To the contrary, a POSITA would have understood that Livesey's cryoprotectants would function in the same way as the claimed plasticizers (Ex.1034, ¶¶78-79) and that Livesey expressly disclosed that its method of introducing cryoprotectants provided a method for cryopreservation "without causing structural and functional damage" to the soft tissue (Ex.1034, ¶79; Ex.1004, 14:59-63). In direct contrast to applicants' characterization, Livesey states 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.) Notably, neither the Examiner nor the applicants addressed this disclosure in Livesey.

A POSITA would have understood that the presence of collagen bundles and the preservation of the lamina densa and anchoring fibrils evidences that the treated tissue was structurally the same as natural tissue. (Ex.1034, ¶80.) Furthermore, a POSITA would have understood that a soft tissue graft with the structural characteristics of natural soft tissue would also maintain the mechanical properties of natural soft tissue because the function of soft tissue is dependent on its structure. (Ex.1034, ¶81.) Livesey, therefore, does disclose that the treated soft tissue maintains the mechanical properties of natural soft tissue. (Ex.1034, ¶81.)

Furthermore, applicants' argument to the Examiner that "freezing and drying the soft tissue, as taught by Livesey, will cause the soft tissue to have different mechanical properties than those of soft tissue, even once the tissue is returned to ambient temperature," contradicts the specification of the 986 patent. The 986 patent states that a plasticizer can be introduced at any number of steps during processing, and the resulting tissue will still maintain the mechanical and use properties of natural tissue:

> The plasticizer can be introduced into the . . . soft tissue matrix at any number of steps in the processing procedures . . . [t]he result(s) of plasticization of . . . soft tissue products are . . . soft tissue products which are similar to traditionally dehydrated bone and soft tissue products in residual moisture but are not subject to fractures or micro fractures like such dehydrated products, yet do not need to be rehydrated prior to use. The mechanical and use properties or a plasticized . . . soft tissue product are similar to those of natural [soft tissue].

(Ex.1003, 9:18-32.)

Further, the 986 patent explicitly discloses introducing the plasticizer *prior* to freeze-drying (as disclosed in Livesey) to provide a tissue with the mechanical and use properties of natural tissue:

> When processing using these methods *the graft is plasticized by adding one or more plasticizers or a plasticizer composition to processing steps after bone cleaning is essentially completed, and prior to freeze-drying*. Under 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 . . . [t]hus, the bone or soft tissue is dehydrated *yet the materials properties of the bone tissue will be similar to the materials properties of normal bone or soft tissue*.

(Ex.1003, 10:26-42 (emphasis added).) Therefore, Livesey's method of introducing the cryoprotectants prior to freeze-drying will, consistent with the specification of the 986 patent, result in the cryoprotectants remaining within the tissue and replacing the free and bound water thereby providing a dehydrated tissue that maintains the materials properties of natural soft tissue.

In sum, applicants' argument to the Examiner during prosecution that the method of Livesey will cause the soft tissue to have mechanical properties different from those of soft tissue was wrong and fails to account disclosure in Livesey that specifically teaches that the treated tissue maintains the mechanical properties of natural soft tissue. Furthermore, the applicants' argument is contradicted by the 986 patent itself. Thus, the considerations under 35 U.S.C. §325(d) support institution of *inter partes* review because, (1) the applicants distinguished Livesey on incorrect grounds during prosecution, (2) the Examiner erred in his evaluation of Livesey, and (3) additional disclosures from Livesey and evidence from Dr. McQuillan (Ex.1034, ¶¶74-81) warrant reconsideration of Livesey. Finally, consideration of Walker and Werner, the other two main references on which this petition relies, supports institution. Although Werner was cited during prosecution in an obviousness rejection, it was not discussed substantively. Walker was cited in an information disclosure statement, but was not

discussed at all during prosecution. In view of these additional references, institution is warranted.

IX. Secondary Considerations

Petitioner is not aware of any secondary considerations that would tend to show non-obviousness that have a provable nexus with claims 1-27 of the 986 patent. There is nothing in those claims that is not already taught in the prior art.

X. Conclusion

Petitioner has established a reasonable likelihood of prevailing as to each of claims 1-27 of the 986 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

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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

Pursuant to 37 C.F.R. §§42.6(e)(4) and 42.105, the undersigned certifies on this date, a true and correct 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. 9,585,986:

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