UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIFECELL CORPORATION
Petitioner,

v.

LIFENET HEALTH,
Patent Owner.

Case No. To Be Assigned
Patent No. 9,125,971

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,125,971 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *et seq.*

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

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

The real parties-in-interest for this petition for *Inter Partes* Review ("IPR") are LifeCell Corporation ("Petitioner"), Acelity Holdings, Inc., Acelity L.P. Inc., and Kinetic Concepts, Inc.

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

Related U.S. Patent No. 6,569,200 was the subject of litigation in the United States District Court for the Eastern District of Virginia, captioned *LifeNet Health v. LifeCell Corporation* (Civil Action No. 2:13-cv-486), presently on appeal to the United States Court of Appeals for the Federal Circuit (Appeal. No. 2015-1549).

C. Lead and Backup Counsel, and Service Information (37 C.F.R. §§ 42.8(b)(3) & (b)(4))

Lead counsel for Petitioner is Andrea G. Reister (Reg. No. 36,253); T: (202) 662-5141; F: (202) 778-5141; E: areister@cov.com. Back-up counsel are Gregory S. Discher (Reg. No. 42,488); T: (202) 662-5485; F: (202) 778-5485; E: gdischer@cov.com and Grant D. Johnson (Reg. No. 69,915); T: (202) 662-5867; F: (202) 778-5867; E: gjohnson@cov.com. The postal address for the foregoing counsel is: Covington & Burling LLP, One CityCenter, 850 Tenth St., NW, Washington, DC 20001. Service of any document may be made at the postal address of the lead and back-up counsel designated above. Petitioner consents to electronic service by email at the above listed email addresses.

II. FEES (37 C.F.R. § 42.103)

The undersigned authorizes the Office to charge $23,000 ($9,000 request fee and $14,000 post-institution fee) to Deposit Account No. 50-0740 for the fees set forth in 37 C.F.R. § 42.15(a) for this Petition for *Inter Partes* Review. The undersigned further authorizes payment for any additional fees that might be due in connection with this Petition to be charged to the above referenced Deposit Account.

III. REQUIREMENTS FOR INTER PARTES REVIEW UNDER 37 C.F.R. § 42.104

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

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '971 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

B. Prior Art Patents and Printed Publications Relied Upon

Exhibit	Reference	Publication or Filing Date	Availability as Prior Art
Ex. 1003	U.S. Patent No. 5,336,616 to Livesey *et al.* ("Livesey")	August 9, 1994	§ 102(b)
Ex. 1004	U.S. Patent No. 4,357,274 to Werner ("Werner")	November 2, 1982	§ 102(b)

Ex. 1005	U.S. Patent No. 4,776,853 to Klement *et al*. ("Klement")	October 11, 1988	§ 102(b)
Ex. 1006	International Patent Application Publication No. WO 98/07452 to Walker ("Walker")	February 26, 1998	§ 102(a)
Ex. 1007	U.S. Patent No. 5,558,875 to Wang ("Wang")	September 24, 1996	§ 102(b)

C. Claims and Statutory Grounds (37 C.F.R. §§ 42.104(b)(1) & (b)(2))

The relief requested by Petitioner is that claims 1-13 of the '971 patent be found unpatentable and cancelled from the '971 patent on the following grounds:

Ground	Claims	Basis
I	1, 4-9, 12-13	Unpatentable under 35 U.S.C. § 103 in view of Livesey
II	1, 4-9, 12-13	Unpatentable under 35 U.S.C. § 103 in view of Werner and Klement
III.	1-3, 9-11	Unpatentable under 35 U.S.C. § 103 in view of Walker and Wang

D. Relief Requested

Petitioner requests that the Patent Trial and Appeal Board cancel the challenged claims because they are unpatentable under 35 U.S.C. § 103.

E. Unpatentability of the Construed Claims (37 C.F.R. § 42.104(b)(4))

An explanation of how claims 1-13 of the '971 patent are unpatentable, under the statutory grounds identified above, is provided in Section VI., below.

F. Supporting Evidence (37 C.F.R. § 42.104(b)(5))

The exhibit numbers of the supporting evidence relied upon to support the challenge and the relevance of the evidence to the challenge raised, including identifying specific portions of the evidence that support the challenge, are provided below in the form of explanatory text and claim charts. An Exhibit List with the exhibit numbers and a brief description of each exhibit is set forth above.

IV. INTRODUCTION

U.S. Patent No. 9,125,971 ("the '971 patent"), titled "Plasticized Bone and Soft Tissue Grafts and Methods of Making and Using Same," issued on September 8, 2015. Its claims are directed to "soft tissue grafts" from which "cellular elements" have been "substantially removed" and which have been preserved by treatment with a "plasticizer composition" containing "one or more alcohols"—e.g., the sugar alcohol glycerol, a material the patent also defines as a "plasticizer."

Substantially removing cellular elements from a soft tissue graft was well-known in the prior art, as the Examiner recognized during prosecution. (Ex. 1002

at 141). Preserving a soft tissue graft with a plasticizer composition, such as a composition containing glycerol, was also a well-known, conventional process in the prior art. Patent Owner conceded that a prior art reference cited by the Examiner described how "[d]ermal matrices were prepared from normal human skin and sterilized via glycerol treatment." (Ex. 1002 at 106).

While plasticizer compositions containing the sugar alcohol glycerol were well-known in the prior art, the Examiner believed that claims reciting soft tissue grafts treated with a "plasticizer composition comprising **one or more *alcohols***," overcame the prior art rejections. (*See* Ex. 1002 at 86, 106 (emphasis added)). At the time, the pending dependent claims had recited that the "one or more alcohols" were "ethanol or isopropyl alcohol." (Ex. 1002 at 103-04).

The specification stated, however, that "[s]uitable alcohols useful in the plasticizer composition of the present invention preferably include C_1-C_{10} alcohols, and more preferably ethanol and isopropyl alcohol." (Ex. 1001, 5:52-58). And after the Examiner withdrew the prior art rejections, (Ex. 1002 at 86), Patent Owner proceeded to add a new dependent claim clarifying that the "one or more alcohols" could be (instead of ethanol or isopropyl alcohol) a *sugar alcohol* such as glycerol, propylene glycol, or any of numerous other materials also listed as "plasticizers" in the specification, (Ex. 1002 at 72, claim 69). Patent Owner thus added a new dependent claim to clarify that sugar alcohols such as glycerol—the same material

present in prior art plasticizer compositions previously cited by the Examiner—could constitute the "alcohol" in the claimed plasticizer composition. Yet, the Examiner did not raise any further prior art rejections.

The Examiner failed to appreciate the relevance of prior art references that disclosed a plasticizer composition including glycerol, which is both a "plasticizer" and an alcohol according to the '971 patent. The Examiner further failed to appreciate that the prior art had taught persons of ordinary skill in the art to use plasticizer compositions combining a "plasticizer" such as sucrose with an additional alcohol such as propylene glycol to preserve soft tissues. The Examiner also failed to appreciate that the prior art taught persons of ordinary skill in the art to use plasticizer compositions containing ethanol, the alcohol specifically recited in dependent claims 2-3 and 10-11.

In short, the '971 patent was issued by the Examiner based on a limitation which was not novel, and which had been disclosed by and well-known in the prior art literature for years. As discussed further below, the claims of the '971 patent are not (and were not) patentable over the prior art.

V. OVERVIEW OF THE '971 PATENT

A. Technological Background of the '971 Patent

The '971 patent relates to soft tissue grafts, such as skin, dura mater, or pericardium, derived from human or animal tissue. (Ex. 1001, 8:8-13, Ex. 1008,

¶ 42). Soft tissues are composed of cells as well as an internal matrix that includes collagen fibers, elastin fibers, and high molecular weight solutes. (Ex. 1001, 8:13-17, Ex. 1008, ¶ 42). Collagen is a load bearing component of a soft tissue graft. (Ex. 1001, 3:13-17; Ex. 1008, ¶ 42). The fibers of collagen, elastin, and other proteins in the internal matrix give structure to the cellular elements and other small-weight components of the soft tissue. (Ex. 1008, ¶ 42).

When implanted into a human patient, the internal matrix of a soft tissue graft is intended to serve as a "scaffold" upon which a patient may regenerate his or her own viable cells. (Ex. 1008, ¶ 14, citing Ex. 1003 at 1:26-30). While the internal matrix itself does not provoke a significant adverse response from the immune system of a recipient patient, if that patient's immune system detects foreign cellular material on an implanted soft tissue graft, it may recognize the graft as foreign, causing an adverse immunogenic reaction in a patient that manifests as inflammation. (Ex. 1008, ¶ 15, citing Ex. 1003 at 4:45-55; 3:38-40).

To help avoid such adverse immunogenic reactions, in preparing a soft tissue graft, persons of ordinary skill in the art have long known to process the tissue to substantially remove cellular elements. (Ex. 1008, ¶ 43). The soft tissue grafts as recited in the claims of the '971 patent are substantially free of cellular elements. (Ex. 1001, 24:21-22, 24:43-44; Ex. 1008, ¶ 43).

The soft tissue grafts claimed in the ’971 patent are also treated with a plasticizer composition that contains at least one alcohol, such as ethanol or a sugar alcohol. (Ex. 1001, 24:20, 24:45-47, 7:58-64; Ex. 1008, ¶ 44). Glycerol and propylene glycol are examples of non-toxic and naturally occurring sugar alcohols. (Ex. 1001, 24:38-41; Ex. 1008, ¶ 22). The ’971 patent also characterizes these materials, as well as other materials such as sucrose, as biocompatible, water-soluble plasticizers. (Ex. 1001, 7:35-55, 8:37-57, Ex. 1008, ¶¶ 13, 44). The soft tissue grafts of the ’971 patent’s claims are preserved for storage using a “plasticizer composition” that includes a plasticizer, such as glycerol, propylene glycol, or sucrose. (Ex. 1001, 24:20, 24:45-47, 7:58-64, Ex. 1008, ¶¶ 13, 44). The claims of the ’971 patent specify that glycerol and propylene glycol (among other materials), in addition to being plasticizers, may be the “one or more alcohols” in the plasticizer composition. (Ex. 1001, 24:38-41; Ex. 1008, ¶¶ 36, 60).

By June 30, 1998, there was an extensive body of literature teaching persons of ordinary skill in the art how to process and preserve soft tissues to make grafts suitable for transplantation into humans. (Ex. 1008, ¶¶ 13-33).

By 1981, harvested tissue was being processed to reduce the immunogenic response elicited in the recipient by removing cells. (Ex. 1008, ¶ 16, citing Ex. 1004 at 2:50-57). In the 1980s and early 1990s, improvements were made in processing techniques to render donor soft tissues of various types devoid of viable

cells and to remove cellular elements. (Ex. 1008, ¶¶ 17-21, citing Ex. 1010 at 2:32-35, 15:61-66; Ex. 1005 at 3:6-26, 3:37-50, 3:58-60, 4:13-28, 4:34-42; Ex. 1007 at 2:64-3:6, 3:10-13, 3:59-65; Ex. 1003 at 9:38-40; 23:62-68). It was well understood by the early 1990s that donor cells in a soft tissue graft could cause immunogenic reactions in the recipient upon implantation, and those of ordinary skill in the art understood that decellularization processes taught in the literature of the early 1990s would remove substantially all cellular elements from a soft tissue before it was preserved for later transplantation. *Id*. By 1998, such techniques were conventional in grafts for transplant into humans. *Id.*

In parallel with the development of decellularization techniques for soft tissue grafts described above, soft tissue grafts had been preserved for transplantation into humans with chemicals referred to by the ’971 patent as “plasticizers,” such as glycerol, since the 1950s. (Ex. 1008, ¶¶ 22-25, citing Ex. 1011 at 457-58; Ex. 1012 at 12; and Ex. 1013 at 268-277). Numerous of these “plasticizers,” including sugar alcohols such as glycerol, ethylene glycol, propylene glycol, and mannitol, are also classified chemically, and in the claims of the ’971 patent, as alcohols. (Ex. 1001, 24:38-41; Ex. 1008, ¶¶ 23, 60)

Use of glycerol, for example, was widespread by the mid-1990s, and its effects and benefits in preserving soft tissue were well documented. (Ex. 1008, ¶¶ 26-30, citing Ex. 1004 at 2:21-32; Ex. 1014 at 969, 971; Ex. 1015 at S43-46; Ex.

1016 at S4; Ex. 1017 at 391-96). From the 1970s through the 1990s, researchers published numerous articles teaching, for example, that preserving soft tissue using glycerol was inexpensive and safe and permitted storage of soft tissue at room temperature. *Id*. By 1998, it was well-known by those skilled in the art that aqueous glycerol solutions could be used to preserve soft tissue. (Ex. 1008, ¶¶ 33, 39, citing Ex. 1004 at 2:1-20, 2:30-32).

It was well-known by 1998 that other chemicals, including other sugar alcohols, were also effective in preserving soft tissues, and many preservation solutions containing alcohols had been taught in the art. (Ex. 1008, ¶¶ 31-33, citing Ex. 1003 at 11:17-23, 11:49-55, 12:15-30, 16:30-40, 26:19-27; and Ex. 1006 at 4:33-36, 19:17-23, 20:3-8, 24:8-10, 24:19-21, 24:26-35). For example, publications taught multi-component preservation solutions using an alcohol (e.g., a sugar alcohol or ethanol) in combination with another chemical that is a plasticizer, to preserve soft tissue. (Ex. 1008, ¶¶ 31-32, citing Ex. 1003 at 11:17-23; 11:49-55; 12:15-30; 16:30-40; Ex. 1006 at 19:17-23; 20:3-8).

B. The Alleged Invention of the ’971 Patent

The ’971 patent claims (1) methods for producing a soft tissue graft by “substantially removing cellular elements” from the soft tissue and treating the soft tissue with a “plasticizer composition” that includes “one or more alcohols,” and (2) the resultant grafts. (Ex. 1001, 24:18-23, 24:42-47). The patent defines

"plasticizer composition" to mean "any composition which includes one or more plasticizers and one or more biocompatible solvents." (Ex. 1001, 7:58-61). The patent further explains that "[s]uitable solvents include for example: water, and alcohols." (Ex. 1001, 7:61-62).

The '971 patent lists eighteen "suitable plasticizers," including glycerol, propylene glycol, and sucrose, and states this list is not exhaustive. (Ex. 1001, 7:47-55, 8:49-57). The '971 patent further notes that "[e]xamples of acceptable plasticizers include . . . members of the polyol family (sugar alcohols) of compounds including C_2 to C_7 polyols." (Ex. 1001, 8:39-41). The '971 patent's specification states that "suitable alcohols" that can be used in a "plasticizer composition . . . preferably include C_1-C_{10} alcohols, and more preferably ethanol and isopropyl alcohol." (Ex. 1001, 5:55-58). The patent's claims state the "one or more alcohols" in "a plasticizer composition" can include "glycerol, adonitol, sorbitol, … ethylene glycol, triethylene glycol, propylene glycol, mannitol, xylitol, or mesoerythritol." (Ex. 1001, 24:38-41). These alcohols are all among the materials listed in the '971 patent as plasticizers. (Ex. 1001, 7:47-55, 8:49-57).

The '971 patent describes soft tissue grafts as being composed of collagen and elastin fibers bound together by proteoglycans and polysaccharides to form a matrix, as well as cellular elements and other small-weight components of the soft tissue. (Ex. 1001, 3:12-17, 8:13-17). According to the patent's specification, there

are two basic steps in preparing the soft tissue graft. First, the graft undergoes processing that removes some of the cellular elements from the soft tissue. (Ex. 1001, 10:37-42, 24:43-44, Ex. 1008, ¶ 43). Second, the graft is treated with a "plasticizer composition." (Ex. 1001, 10:42-45, 24:45-47, Ex. 1008, ¶ 44).

The '971 patent states that various types of soft tissues can be processed and preserved in this way, including pericardium, fascia lata, dura mater, skin, ligaments, and tendons. (Ex. 1001, 8:10-13). Yet, the patent contains only two examples of soft tissues treated with a plasticizer composition, in which the source tissues are fascia lata and pericardium, respectively. (Ex. 1001, 22:32-23:17, 23:18-24:11, Ex. 1008, ¶¶ 43, 44). In both examples, the tissue is first processed by soaking in a dilute solution of Allowash for at least 15 minutes followed by rinsing to remove any residual detergent, then is placed in a solution of 30% glycerol and 70% isopropyl alcohol for 2-5 minutes, and soaked for at least 20 minutes in a plasticizer composition of 30% glycerin in water. (Ex. 1001, 22:44-23:3, 23:31-58).

C. Prosecution History Summary of the '971 Patent

The '971 patent issued from an application filed on March 15, 2013, as application number 13/836,803. Petitioner summarizes here the actions most relevant to the grounds of unpatentability set forth in this Petition.

Claims 1-7 and 9-13 of the '971 patent were first introduced in an amendment filed by applicants on November 26, 2013. (Ex. 1002 at 283-84). After these claims were rejected by the Examiner in an April 9, 2014 Office Action, applicants filed a response arguing the references applied by the Examiner failed to "teach or suggest a plasticizer composition comprising one or more alcohols." (Ex. 1002 at 106). Applicants acknowledged that *A Comparison of Methodologies for the Preparation of Human Epidermal-Dermal Composites* by Ghosh *et al*. disclosed how "[d]ermal matrices were prepared from normal human skin and sterilized via glycerol treatment," but argued this failed to "teach or suggest a plasticizer composition comprising one or more alcohols." (Ex. 1002 at 106). Applicants similarly argued that *The use of glycerol-preserved homologous dura mater grafts in cardiac surgery: the Southampton experience* by Osinowo *et al*. "does not teach or suggest a plasticizer composition comprising one or more alcohols." (Ex. 1002 at 106). At the time, the only dependent claims directed to the "one or more alcohols" limitation stated the one or more alcohols "comprise ethanol or isopropyl alcohol" or merely "ethanol." (Ex. 1002 at 103-04).

On April 15, 2015, however, after the Examiner had indicated the then-pending claims overcame the prior art rejections, applicants added a new dependent claim reciting the "one or more alcohols" in the "plasticizer composition" could be "glycerol, adonitol, sorbitol, … ethylene glycol, triethylene

glycol, propylene glycol, mannitol, xylitol, or mesoerythritol." (Ex. 1002 at 72). On July 30, 2015, without commenting on this new dependent claim, the Examiner issued a Notice of Allowance allowing all pending claims. (Ex. 1002 at 9).

The Examiner did not, however, apply Livesey or Werner in a rejection, or otherwise discuss or analyze the subject matter disclosed in these references, during prosecution of the '971 patent. The Examiner also did not consider Walker during prosecution. As discussed in Sections V.F. and VI.A.–D. below, Livesey, Werner, and Walker each disclose the feature the Examiner believed was missing in the prior art—a "plasticizer composition comprising one or more alcohols."

D. Person of Ordinary Skill in the Art

The '971 patent claims priority to an application filed June 30, 1998. A person of ordinary skill in the art of the '971 patent at the time of the alleged invention ("POSA") would typically have had at least a Master of Science degree in biology, biochemistry, physiology, pathology, toxicology, biomaterials engineering, biomedical engineering, or a related field, and approximately at least five years of professional experience related to processing tissue for implantation into humans or animals, or the equivalent. (Ex. 1008, ¶ 4).

E. Claim Construction (37 C.F.R. § 42.104(b)(3))

A claim subject to IPR is given its "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b);

Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,764, 48,766 (Aug. 14, 2012); *In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271, 1281 (Fed. Cir. 2015), *reh'g en banc denied*, 2015 WL 4100060 (Fed. Cir. July 8, 2015).

Claim terms are given their ordinary and customary meaning as would be understood by a person of ordinary skill in the art at the time of the invention and in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). If an inventor acts as his or her own lexicographer and provides an explicit definition of a term, that explicit definition will control interpretation of that term in the claim, including under the broadest reasonable construction standard. *See In re ICON Health and Fitness, Inc.*, 496 F.3d 1374, 1379 (Fed. Cir. 2007).

1. Expressly Defined Terms

In a section of the specification entitled "Definitions," the '971 patent expressly defines several terms. (Ex. 1001, 5:49-51). Patent Owner has acted as its own lexicographer for the following pertinent terms:

- "alcohol" is defined as "one of a series of organic chemical compounds in which a hydrogen attached to carbon is replaced by a hydroxyl. Suitable alcohols useful in the plasticizer composition of the present invention preferably include C_1-C_{10} alcohols, and more preferably ethanol and isopropyl alcohol." (Ex. 1001, 5:52-58).

- "plasticizer" is defined as "any biocompatible compounds which are soluble in water and can easily displace/replace water in 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." (Ex. 1001, 7:35-57).

- "plasticizer composition" is defined as "any composition which includes one or more plasticizers and one or more biocompatible solvents. Suitable solvents include for example: water, and alcohols, including for example C_1-C_{10} alcohols, and more preferably ethanol and isopropyl alcohol." (Ex. 1001, 7:58-64).

- "soft tissue graft" is defined as "load-bearing and non-load-bearing soft tissue products" that "are composed of an internal matrix which includes collagen, elastin and high molecular weight solutes where during cleaning cellular elements and small molecular weight solutes are removed." (Ex. 1001, 8:8-17).

2. "Plasticizer Composition Comprising One or More Alcohols"

Patent Owner expressly defined the term "plasticizer composition" as "any composition which includes one or more plasticizers and one or more biocompatible solvents." (Ex. 1001, 7:58-61). Patent Owner's definitions further expressly state that water and alcohols are "suitable solvents" for a plasticizer composition, (Ex. 1001, 7:61-64), and that the listed plasticizers, including glycerol and propylene glycol, are "biocompatible," (Ex. 1001, 7:35-55).

Despite this definition, Patent Owner argued during prosecution that Ghosh, which Patent Owner described as disclosing "glycerol treatment" of "human skin," did not teach a "plasticizer composition comprising one or more alcohols," and that Osinowo *et al*. ("*The use of glycerol-preserved homologous dura mater grafts in cardiac surgery: the Southampton experience"*) also "does not teach or suggest a plasticizer composition comprising one or more alcohols." (Ex. 1002 at 106). Yet six months later, on April 15, 2015, Patent Owner added a new dependent claim expressly reciting that the "one or more alcohols" in the "plasticizer composition" may "comprise ***glycerol***, adonitol, sorbitol, ribitol, galactitol, 1,3-dihydroxypropanol, ethylene glycol, triethylene glycol, propylene glycol, mannitol, xylitol, or mesoerythritol." (Ex. 1002 at 72 (emphasis added)).

In light of the specification's definition of "plasticizer composition," and the dependent claim Patent Owner added in April 2015 reciting that the "one or more alcohols" in the "plasticizer composition" comprise, among other things, glycerol or propylene glycol (which are sugar alcohols), Petitioner submits that the broadest reasonable construction of "a plasticizer composition comprising one or more alcohols" is any composition containing at least two chemicals in which (a) one chemical is a plasticizer and the second chemical is a solvent (*e.g.*, water), and (b) either the plasticizer or the solvent is an alcohol (*e.g.*, glycerol or propylene glycol). A narrower construction would be that the plasticizer composition must contain a

first substance that is a plasticizer (such as sucrose) and a different second substance that is an alcohol (such as propylene glycol). Petitioner believes this second construction would be inconsistent with the '971 patent's definitions and dependent claims and would not be the broadest reasonable construction. In any event, as explained in Sections V.F. and VI. below, regardless of which construction is adopted, the prior art cited in the present petition discloses "a plasticizer composition comprising one or more alcohols."

F. Prior Art

1. Summary of the Prior Art

There is nothing new or non-obvious in Patent Owner's claims, as shown below. Substantially removing cellular elements from a soft tissue graft and using a plasticizer composition containing a sugar alcohol such as glycerol or propylene glycol, or another alcohol such as ethanol, to preserve a soft tissue graft were both well known. (Ex. 1008, ¶¶ 21, 33). At most, the Patent Owner chose new words (*e.g.*, describing a preservation solution as a "plasticizer composition" that contains an "alcohol"), (Ex. 1001, 24:20), to describe what was already known, and further provided dependent claims that are obvious (*e.g.*, "soft tissue comprises cadaveric skin"), (Ex. 1001, 24:31-32).

2. Livesey (Ex. 1003)

Livesey issued on August 9, 1994. It therefore qualifies as prior art to the '971 patent under 35 U.S.C. § 102(b). Although Livesey is listed among many

items submitted to the Office in the Information Disclosure Statements filed during the original examination of the '971 patent, it was not applied in a rejection, and there was no discussion of its disclosure.

Livesey (Ex. 1003) describes techniques for the preservation of soft tissue grafts including cadaveric skin derived from human or animal tissue and intended for transplantation into human patients. (Ex. 1003, 23:9-18; Ex. 1008, ¶ 45). The human skin grafts are first decellularized by treating the skin graft with a sodium dodecyl sulfate detergent solution, which removes essentially all of the cellular material from the skin graft while maintaining the extracellular collagen matrix of the dermis. (Ex. 1003, 7:36-51. 23:65-67; Ex. 1008, ¶ 46).

After decellularization, the soft tissues (e.g., skin) are "incubat[ed]" in a preservation solution. (Ex. 1003, 11:17-23; Ex. 1008, ¶ 47). The preservation solution is a "cryosolution" containing one or more "cryoprotectants," such as the dry protectant sugar sucrose or the organic solvent sugar alcohols propylene glycol or glycerol. (Ex. 1003, 11:17-23, 11:49-55, 12:3-7, 12:27-30, Ex. 1008, ¶ 47). Livesey discloses multiple examples of "cryosolutions" or "vitrification solutions" containing both sucrose and propylene glycol to preserve a variety of soft tissues. (Ex. 1003, 16:33-40, 16:45-51, 26:17-27, 28:8-13; Ex. 1008, ¶ 48). As explained further below, a POSA would have recognized that Livesey's sucrose and propylene glycol cryosolutions were biocompatible, water-soluble "plasticizer

composition[s] comprising one or more alcohols" and were suitable for preserving the decellularized soft tissue grafts, including the human cadaveric skin grafts, disclosed by Livesey. (Ex. 1008, ¶¶ 37, 48, 51, 53, 55-56 citing Ex. 1003 at 11:46-55, 12:19-30, 16:33-40; 16:45-51, 23:9-18, 23:65-68, 24:10-14, 26:17-27, 28:8-13).

Livesey instructs that the decellularized tissue should be incubated in the cryosolution "until complete penetration of the components of the cryosolution is achieved." (Ex. 1003, 12:31-37; Ex. 1008, ¶ 56). Livesey further explains its preserved grafts are "easily stored and transported at ambient temperatures" (Ex. 1003, 4:43-55; Ex. 1008, ¶ 57). A POSA would have recognized that Livesey's freeze-dried grafts were suitable to be stored at room temperature before being transplanted into a human patient. (Ex. 1008, ¶ 57, citing Ex. 1003 at 4:29-31, 4:43-55, 6:6-11, 25:30-42).

3. Werner (Ex. 1004)

Werner issued on November 2, 1982. It therefore qualifies as prior art to the '971 patent under 35 U.S.C. § 102(b). Although Werner is listed among many items submitted to the Office in the Information Disclosure Statements filed during the original examination of the '971 patent, it was not applied in a rejection, and there was no discussion of its disclosure.

Werner (Ex. 1004) discusses techniques for preparing soft tissue grafts, such as dura mater grafts, that are composed of proteins such as collagen, keratin, and/or

elastin, which Werner describes as "sclero proteins." (Ex. 1004, 1:6-10; Ex. 1008, ¶ 58). Werner teaches that these grafts can be processed, preserved, and implanted into human patients. While Werner describes dura mater as an example of soft tissue made up of sclero proteins, (Ex. 1004, 2:21-24), a POSA would have understood that numerous other types of soft tissue, such as skin, are also composed of sclero proteins such as collagen, keratin, and/or elastin. (Ex. 1008, ¶ 58, citing Ex. 1003 at 2:4-44; 7:46-51 and Ex. 1005 at 2:32-38), and that Werner's techniques could be used to preserve these other soft tissues, such as human skin (Ex. 1008, ¶ 62). Werner provides an example of preparation of soft tissue grafts from human dura mater (Ex. 1004, 2:21-24; Ex. 1008, ¶ 58), a type of tissue the '971 patent describes as having a "similar" "structural organization" to the fascia lata in example 9 of the '971 patent. (Ex. 1001, 3:17-25, 22:32-23:17).

Werner discloses processing in which the dura mater grafts are soaked in saline for 24 hours, then soaked in a 5% hydrogen peroxide solution for 48 hours, and then "degreas[ed]" in an acetone-diethylether solution for 4 hours. (Ex. 1004, 2:50-57, Ex. 1008, ¶ 59). The dura mater is then rinsed in water for 12 to 24 hours. (Ex. 1004, 2:55-57, Ex. 1008, ¶ 59). A POSA, understanding that cellular membranes are made up of "greasy" lipids (among other components), would recognize that Werner's "degreasing" disrupts and lyses cellular membranes in the graft, and that the subsequent rinse would rinse away some cellular material from

the dura mater. (Ex. 1008, ¶ 59). Werner expressly states that other "conventional procedural steps of purifying and antigen separation" can alternatively be used to process grafts before preservation in glycerol. (Ex. 1004, 2:1-4).

Werner explains that after rinsing in water for 12 to 24 hours, the dura mater graft is stirred in an aqueous 30% glycerol solution for 4 hours. (Ex. 1004, 2:58-59; Ex. 1008, ¶ 60). A POSA would have recognized that Werner's solution of glycerol in water is an example of a "plasticizer composition" as recited by the claims of the '971 patent, where glycerol is a plasticizer and an alcohol and water is a biocompatible solvent. (Ex. 1008, ¶ 60). Indeed, the 30% glycerol solution contains the same concentration of the same plasticizer (which is a sugar alcohol) in the same solvent (water) that the '971 patent uses in both of its examples of methods for making plasticized soft tissues. (Ex. 1001, 22:65-23:2, 23:51-56).

Werner discloses that soaking the dura mater in a glycerol solution causes the glycerol to "impregnate[]" the graft and to replace water in the graft. (Ex. 1006, 2:4-8; Ex. 1008, ¶ 61). After being "impregnated" with glycerol, the glycerolized soft tissue graft is "dried at room temperature in the open air" for 12 hours. (Ex. 1006, 2:61-64; Ex. 1008, ¶ 61, citing Ex. 1013 at 273 and Ex. 1014 at 969). POSAs knew that human skin, like dura mater, is composed of collagen, keratin, and elastin (the "sclero proteins" discussed by Werner), and that aqueous glycerol

solutions, such as Werner's glycerol in water solution, could be used to preserve human skin. (Ex. 1008, ¶ 62).

4. Klement (Ex. 1005)

Klement issued on October 11, 1988. It therefore qualifies as prior art to the '971 patent under 35 U.S.C. § 102(b). Although Klement is listed among many items submitted to the Office in the Information Disclosure Statements filed during the original examination of the '971 patent, it was not applied in a rejection, and there was no discussion of its disclosure.

Klement (Ex. 1005) discloses techniques for processing various types of soft tissue—including dura mater and skin—to prepare the soft tissues for transplantation by "complete removal" of all "cell membranes, cytoplasm, nuclear material," and other cellular components which "could initiate an immunological rejection response." (Ex. 1005, 3:6-26, 4:34-42; Ex. 1008, ¶ 63). A POSA would have recognized that Klement's "complete removal" of cellular elements meant cellular elements had been substantially removed from that graft. (Ex. 1008, ¶ 64).

Klement discloses a technique for preparing a soft tissue graft for transplantation by decellularizing the soft tissue with a non-ionic detergent, such as Triton X-100, and an anionic detergent, such as sodium dodecyl sulfate. (Ex. 1005, 2:32-38, 3:37-40, 3:58-60, 4:13-28; Ex. 1008, ¶¶ 63-64). Klement explains that this process results in a graft that has its "collagenous and elastic fraction . . . retained

intact and in its natural state," so that "the mechanical properties would be essentially the same." (Ex. 1005, 3:6-26, 4:43-68). Klement describes the resulting decellularized graft as being free of "soluble small and high molecular weight substances from natural tissue . . . while retaining the insoluble, collagenous and elastic 'backbone' of the natural tissue." (Ex. 1005, 2:23-28; Ex. 1008, ¶ 64).

5. Walker (Ex. 1006)

Walker was published on February 26, 1998. It therefore qualifies as prior art to the '971 patent under 35 U.S.C. § 102(a). Walker was not cited, applied, or discussed by the Examiner or Patent Owner during prosecution of the '971 patent.

Walker (Ex. 1006) discusses techniques for "plasticization" of bovine pericardium (Ex. 1006, 19:17-23; Ex. 1008, ¶ 69). Pericardium is defined as a type of soft tissue in the '971 patent. (Ex. 1001, 8:11-13). Walker teaches that "plasticization" is performed by incubating the pericardium in a solution of 50% ethanol and 50% glycerol for at least 16 hours. (Ex. 1006, 20:3-8; Ex. 1008, ¶ 69). A POSA would have recognized Walker's "plasticization" solution is a "plasticizer composition" as recited by the '971 patent, and that incubating the pericardium would result in the pericardium graft being impregnated with and containing the "plasticization" composition in which the graft was incubated. (Ex. 1008, ¶ 69).

Walker explains this "plasticization" prepares soft tissue "for implantation in a human or animal body," and produces tissues that had "no significant decrease in

physical strength after treatment" and "were not rigid" and "felt more natural." (Ex. 1006, 4:33-36; 24:8-10; 24:19-21; 24:26-35; Ex. 1008, ¶ 70).

6. Wang (Ex. 1007)

Wang issued on September 24, 1996. It therefore qualifies as prior art to the '971 patent under 35 U.S.C. § 102(b). Although Wang is listed among many items submitted to the Office in the Information Disclosure Statements filed during the original examination of the '971 patent, it was not applied in a rejection, and there was no discussion of its disclosure.

Wang (Ex. 1007) teaches methods of decellularization for various types of soft tissue, including skin and pericardium, derived from a human or animal and intended for transplantation into humans. (Ex. 1007, 3:28-40, 3:48-50; 6:43-36; Ex. 1008, ¶ 71). The soft tissue is decellularized by soaking in an ionic detergent such as sodium dodecyl sulfate, which "remove[s] the cellular elements" from the tissue. (Ex. 1007, 2:64-67, 3:28-36; Ex. 1008, ¶ 71). It would be readily apparent to a POSA that Wang's detergent treatment would substantially remove cellular elements from the skin or pericardium. (Ex. 1008, ¶ 71). After the cellular elements are removed, Wang discloses that the soft tissue is preserved in an alcohol solution, such as a 70% ethyl alcohol solution. (Ex. 1007, 4:36-48; Ex. 1008, ¶ 71).

VI. THERE IS A REASONABLE LIKELIHOOD THAT PETITIONER WILL PREVAIL WITH RESPECT TO AT LEAST ONE CLAIM

The subject matter of claims 1-13 of the '971 patent is disclosed or

suggested to one of ordinary skill in the art by the prior art, as explained above in §§ V.F.2.–V.F.6. As set forth below in Sections VI.A.–D., the combination of references utilized in Grounds I, II, and III render each of claims 1-13 unpatentable under 35 U.S.C. § 103, and thus provide a reasonable likelihood that the Petitioner will prevail on at least one claim. *See* 35 U.S.C. § 314(a).

A. Explanation of the Grounds

Grounds I, II, and III, as described in detail below, are each based on a different prior art method for removing cellular elements from soft tissue and treating that soft tissue with a plasticizer composition that contains alcohol. They should not be considered cumulative, because the approaches to preservation solutions underlying each ground is different, and represent approaches that were known to POSAs at the time of the ’971 patent.

Ground I, the disclosure of Livesey, taught or suggested to those skilled in the art techniques for substantially removing cellular elements from soft tissues such as human cadaveric skin and treating the decellularized human cadaveric skin or other soft tissues using a plasticizer composition that contains both (i) a substance expressly defined in the ’971 patent as a plasticizer (sucrose); and (ii) an alcohol expressly listed in the claims (propylene glycol—a sugar alcohol). (Ex. 1008, ¶¶ 45-57). Thus, Livesey discloses “a plasticizer composition comprising one or more alcohols” under either construction set forth in Section V.E.2. above.

Ground II, the combination of the disclosures of Werner and Klement, teaches or suggests to those skilled in the art techniques for removing cellular elements from a soft tissue (*e.g.*, dura mater or skin) and then treating that decellularized soft tissue using a plasticizer composition containing glycerol, which the '971 patent describes as both an alcohol and a plasticizer, in water, which the '971 patent identifies as a suitable solvent. (Ex. 1008, ¶¶ 58-68). Thus, the combination of Werner and Klement discloses "a plasticizer composition comprising one or more alcohols" under the broadest reasonable construction in light of the '971 patent's definitions and the dependent claim added by Patent Owner in April 2015, as set forth in Section V.E.2. above.

Ground III, the combination of the disclosures of Walker and Wang, teaches or suggests to those skilled in the art techniques for removing cellular elements from a soft tissue, *e.g.*, cadaveric pericardium, and treating that decellularized tissue using a plasticizer composition made up of ethanol, as specifically recited in claims 2-3 and 10-11, and glycerol, which the '971 patent identifies as a suitable plasticizer. (Ex. 1008, ¶¶ 69-76).

B. Ground I: Claims 1, 4-9, and 12-13 are Unpatentable Under 35 U.S.C. § 103 in view of Livesey

As explained above, and as shown in the claim charts below, Livesey taught or suggested all of the limitations of claims 1, 4-9, and 12-13, and establishes a *prima facie* case of obviousness for these claims. In particular, Livesey discloses

substantially removing cellular elements from soft tissues such as human cadaver skin and further discloses the very feature argued by the applicant to be missing from the prior art: a "plasticizer composition" containing one or more alcohols used to treat a soft tissue graft. (Ex. 1008, ¶¶ 47-55).

Livesey describes techniques for preserving soft tissue grafts such as cadaveric skin derived from human or animals for transplantation into human patients. (Ex. 1003, 23:9-18; Ex. 1008, ¶ 45). The human skin grafts are decellularized by treatment with a sodium dodecyl sulfate detergent solution. (Ex. 1003, 23:65-67; Ex. 1008, ¶ 46). It would have been apparent to a POSA that Livesey's decellularization procedure results in cellular elements being substantially removed from the skin graft (Ex. 1003, 7:36-51; Ex. 1008, ¶ 46).

After decellularization, Livesey discloses that a skin graft or other soft tissue graft is "incubat[ed]" in a preservation solution. (Ex. 1003, 11:17-23; Ex. 1008, ¶ 47). Livesey discloses multiple examples of "cryosolutions" or "vitrification solutions" according to its invention, which contain both sucrose and propylene glycol to preserve decellularized soft tissues. (Ex. 1003, 16:33-40, 16:45-51, 26:17-27, 28:8-13; Ex. 1008, ¶ 48). Livesy also instructs that glycerol can be used in a cryosolution. (Ex. 1003, 11:49-55, Ex. 1008, ¶ 47). The '971 patent expressly lists sucrose, propylene glycol, and glycerol as examples of biocompatible, water-soluble "plasticizers," and identifies propylene glycol and glycerol as examples of

alcohols that may be used in the claimed "plasticizer composition." (Ex. 1001, 7:35-55, 8:37-57, 24:38-41; Ex. 1008, ¶ 48). Although Livesey used different terminology than the '971 patent to describe these materials, it would be readily apparent to a POSA that Livesey's cryosolutions and vitrification solutions containing sucrose and propylene glycol are examples of a "plasticizer composition containing one or more alcohols" (Ex. 1008, ¶ 48).

A POSA would have recognized that Livesey's sucrose and propylene glycol cryosolutions were useful to preserve the various decellularized soft tissue grafts discussed by Livesey, including human cadaveric skin grafts. (Ex. 1008, ¶¶ 51-55 citing Ex. 1003 at 11:46-55, 12:19-30, 16:33-40; 16:45-51, 23:9-18, 23:65-68, 24:10-14, 26:17-27, and 28:8-13). Indeed, Livesey provides specific examples of using these solutions to preserve human cadaver veins and porcine heart valve leaflets for transplant into humans, (Ex. 1003, 26:16-27, 28:8-13), and a POSA would have understood these solutions could equally be used to preserve the human cadaver skin and porcine skin that Livesey teaches how to decellularize for transplant into humans (Ex. 1008, ¶¶ 51-55, citing Ex. 1003 at 11:46-55, 12:19-30, 16:33-40; 16:45-51, 23:9-18, 23:65-68, 24:10-14, 26:17-27, and 28:8-13).

A POSA would have had reasons to apply these solutions to human cadaver skin. (Ex. 1008, ¶¶ 49-55, citing Ex. 1003 at 11:46-55, 12:19-30, 15:26-30, 16:15-51, 23:9-18, 23:65-68, 24:10-14, and 28:8-13). For example, after incubation in the

cryosolution, Livesey's decellularized, cryoprotected skin grafts are freeze-dried. (Ex. 1003, 5:45-59). Livesey teaches the sugar alcohol propylene glycol prevents "cracking" during freeze drying. (Ex. 1003, 12:19-30; Ex. 1008, ¶ 50). Livesey further explains that "heart valves following implantation are subject to repetitive stress and hence will tolerate *less* ice crystal damage than, for example, dermis." (Ex. 1003, 11:46-55; Ex. 1008, ¶ 51). A POSA would have understood that the sucrose/propylene glycol solution suitable for use with comparatively delicate heart valve tissue would be similarly suited to preserving skin (dermis), especially to prevent ice crystal damage during freeze-drying in applications where the skin tissue would be subject to repetitive stress. (Ex. 1008, ¶¶ 49-55, citing Ex. 1003 at 11:46-55, 12:19-30, 15:26-30, 16:15-51, 23:9-18, 23:65-68, 24:10-14, and 28:8-13).

Livesey instructs that the decellularized tissue should be incubated in the cryosolution "until complete penetration of the components of the cryosolution is achieved." (Ex. 1003, 12:31-37; Ex. 1008, ¶ 56). It would have been apparent to a POSA that this incubation would result in the decellularized graft being impregnated with the biocompatible plasticizer composition, whose components are water soluble. (Ex. 1008, ¶ 56)

Livesey explains its decellularized, freeze-dried grafts are "easily stored and transported at ambient temperatures" (Ex. 1003, 4:43-55; Ex. 1008, ¶ 57). As Livesey states, "the packaged dried tissue may be stored for extended time periods

under ambient conditions" (Ex. 1003, 6:6-8; Ex. 1008, ¶ 57). A POSA would have recognized that Livesey's freeze-dried grafts were suitable to be stored at room temperature before being transplanted into a human patient. (Ex. 1008, ¶ 57, citing Ex. 1003 at 4:29-31, 4:43-55, 6:6-11, 25:30-42).

Thus, Livesey discloses all limitations of claims 1, 4-9, and 12-13, and establishes a *prima facie* case of obviousness for these claims. Accordingly, it is submitted that the present petition establishes a reasonable likelihood that the Petitioner will prevail on at least one claim. 35 U.S.C. § 314(a).

Claim 1	**Livesey (Ex. 1003)**
A soft tissue graft, comprising:	"A method for processing and preserving an acellular collagen-based tissue matrix for transplantation is disclosed." Livesey, Abstract. "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." Livesey, 1:17-21. "Human donor skin is routinely harvested from cadavers and stored under refrigerated or frozen conditions at a number of tissue banks throughout the nation…. This same skin is also available for processing by the methods described below." Livesey, 23:9-18; *see also id.* at 23:19-25:42 (Example 1).
soft tissue obtained from a human or animal donor; and	"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." Livesey, 1:17-21. "Human donor skin is routinely harvested from cadavers and stored under refrigerated or frozen conditions at a number of tissue banks throughout the nation…. This same skin is also available for processing by the methods described below." Livesey, 23:9-

	18; *see also id.* at 23:19-25:42 (Example 1).
a plasticizer composition comprising one or more alcohols, wherein	"The initial steps of cryopreserving the decellularized tissue includes incubating the tissue in a cryosolution prior to the freezing step. The cryosolution comprises one or more cryoprotectants and/or dry protectants with or without an organic solution . . ." Livesey, 11:17-22. "Various cryoprotectants can be used in the present invention. These include: dimethylsulfoxide (DMSO), detxran, sucrose, 1,2 propanediol, glycerol, sorbitol, fructose, trehalose, raffinose, propylene glycol, 2-3 butane diol, hydroxyethyl starch, polyvinylpyrrolidone (PVP), proline …, human serum albumin and combinations thereof." Livesey, 11:49-55. "A modified vitrification solution (Vs2) has also been developed which comprises a mixture of: Dimethyl Sulfoxide (DMSO) 0.5 M Propylene glycol 0.5M 2-3 butanediol 0.25M Raffinose 10% (w/v) Trehalose 6% (w/v) Sucrose 6% (w/v) PVP 12% (w/v) (Ave. M.W. ≈ 40,000) Dextran 12% (w/v) (Ave. M.W. ≈ 40,000-70,000)" Livesey, 16:30-40; *see also id.*, 16:42-52. "The Cryosolution consists of the following: 0.5M Dimethyl Sulfoxide (DMSO) 0.5M Propylene Glycol 0.25M 2-3 Butanediol 2.5% (w/v) Raffinose 12.0% (w/v) Sucrose 15.0% (w/v) Polyvinylpyrrolidone (PVP) 15.0% Dextran" Livesey, 26:19-27. "Upon receipt of tissue, the discs were transferred to a cryosolution comprising 0.5M DMSO, 0.5M propylene glycol, 0.25M 2-3 butanediol, 2-5% raffinose, 15% polyvinyl pyrrolodone, 15% Dextran and 12% sucrose . . . ."

	Livesey, 28:8-13. *See* Ex. 1008, ¶¶ 47-55.
cellular elements are substantially removed from said soft tissue, and	"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. 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." Livesey, 1:17-26. "In its preferred form, the method of this invention includes the steps of processing biological tissues including treatment with a stabilizing solution to reduce procurement damage, treatment with a processing solution to remove cells and other antigenic tissue components …." Livesey, 4:20-35. "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." Livesey, 5:1-6. "The intent of this invention is to ultimately remove the cellular component and to optimally preserve the extracellular matrix, therefore the stabilizing solution is formulated to minimize the initial cellular and subsequently the extracellular matrix damage." Livesey, 7:36-51. "In the practice of this invention, it is essential that the harvested tissue be processed to remove antigenic cellular components." Livesey, 9:38-40. "Decellularization can be accomplished using a number of chemical treatments, including incubation in certain salts, detergents or enzymes. The use of the detergent Triton X-100 … has been demonstrated to remove cellular membranes, as detailed

	in U.S. Pat. No. 4,801,299." Livesey, 9:41-47. "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)." Livesey, 23:65-69. *See also* Livesey, 30:22-33 (claim 1). *See* Ex. 1008, ¶ 46.
said plasticizer composition is contained in said soft tissue.	"After the tissue is decellularized, it is preferably incubated in a cryopreservation solution." Livesey, 5:15-16. "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 solution . . ." Livesey, 11:17-22. "The biological samples are incubated in the cryosolutions for a period of a few minutes to a few hours before they are rapidly cooled. 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 . . . ." Livesey, 12:31-37. *See* Ex. 1008, ¶¶ 47-56.

Claim 4	**Livesey (Ex. 1003)**
The graft of Claim 1, wherein said soft tissue comprises one of cadaveric skin, pericardium, dura mater, fascia lata, ligaments, or tendons.	"Human donor skin is routinely harvested from cadavers and stored under refrigerated or frozen conditions at a number of tissue banks throughout the nation…. This same skin is also available for processing by the methods described below." Livesey, 23:9-18; *see also id.* at 23:19-25:42 (Example 1). "For example, with human cadaver skin Dispase II at 1.0 units/ml for 90 minutes at 37° C. will remove all keratinocytes except the basal layer …." Livesey, 10:3-5.

	"Heart valves following implantation are subject to repetitive stress and hence will tolerate less ice crystal damage than, for example, dermis." Livesey, 11:46-48. *See* Ex. 1008, ¶¶ 49-55.

Claim 5	**Livesey (Ex. 1003)**
The graft of Claim 1, wherein said soft tissue comprises cadaveric skin.	"Human donor skin is routinely harvested from cadavers and stored under refrigerated or frozen conditions at a number of tissue banks throughout the nation…. This same skin is also available for processing by the methods described below." Livesey, 23:9-18; *see also id.* at 23:19-25:42 (Example 1). "For example, with human cadaver skin Dispase II at 1.0 units/ml for 90 minutes at 37° C. will remove all keratinocytes except the basal layer …." Livesey, 10:3-5. "Heart valves following implantation are subject to repetitive stress and hence will tolerate less ice crystal damage than, for example, dermis." Livesey, 11:46-48. *See* Ex. 1008, ¶¶ 49-55.

Claim 6	**Livesey (Ex. 1003)**
The graft of Claim 1, wherein said soft tissue comprises human cadaveric skin.	"Human donor skin is routinely harvested from cadavers and stored under refrigerated or frozen conditions at a number of tissue banks throughout the nation…. This same skin is also available for processing by the methods described below." Livesey, 23:9-18; *see also id.* at 23:19-25:42 (Example 1). "In the practice of this invention, it is fundamental that suitable tissues are obtained prior to processing. Human cadaver tissues are obtainable through approximately 100 tissue banks." Livesey, 7:21-25. "For example, with human cadaver skin Dispase II at 1.0 units/ml for 90 minutes at 37° C. will remove all keratinocytes except the basal layer …." Livesey, 10:3-5. "Heart valves following implantation are subject to repetitive

	stress and hence will tolerate less ice crystal damage than, for example, dermis." Livesey, 11:46-48. *See* Ex. 1008, ¶¶ 49-55.

Claim 7	**Livesey (Ex. 1003)**
The graft of Claim 1, wherein said soft tissue graft is suitable to be stored at room temperature prior to transplantation into a human recipient.	"In its preferred form, the method of this invention includes the steps of . . . storage in the dry state at above freezing temperatures . . . ." Livesey, 4:20-35. "The processing and preservation method is designed to generate a transplantable biological tissue graft that specifically meets the following criteria: … (e) can be easily stored and transported at ambient temperatures." Livesey, 4:43-55 "In the preferred embodiment, the packaged dried tissue may be stored for extended time periods under ambient conditions. Transportation may be accomplished via standard carriers and under standard conditions relative to normal temperature exposure and delivery times." Livesey, 6:6-11. "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." Livesey, 1:17-21. "The processed dermis . . . has a number of clinical applications in full thickness skin injury. These include, but are not limited to, burn patients, patients suffering from venous, diabetic, or pressure ulcers, and patients who undergo reconstructive surgery, or skin replacement following excision of skin lesions. Processed human and porcine skin have been shown to undergo fibroblast infiltration and neovascularization in human burns patients . . . ." Livesey, 25:30-41. *See* Ex. 1008, ¶ 57.

Claim 8	**Livesey (Ex. 1003)**
The method of Claim 1, wherein	Various cryoprotectants can be used in the present invention. These include: dimethylsulfoxide (DMSO), detxran, sucrose,

said one or more alcohols comprise glycerol, adonitol, sorbitol, ribitol, galactitol, 1,3-dihydroxypropanol, ethylene glycol, triethylene glycol, propylene glycol, mannitol, xylitol, or mesoerythritol.	1,2 propanediol, glycerol, sorbitol, fructose, trehalose, raffinose, propylene glycol, 2-3 butane diol, hydroxyethyl starch, polyvinylpyrrolidone (PVP), proline …, human serum albumin and combinations thereof." Livesey, 11:49-55. "A modified vitrification solution (Vs2) has also been developed which comprises a mixture of: Dimethyl Sulfoxide (DMSO) 0.5 M Propylene glycol 0.5M 2-3 butanediol 0.25M Raffinose 10% (w/v) Trehalose 6% (w/v) Sucrose 6% (w/v) PVP 12% (w/v) (Ave. M.W. ≈ 40,000) Dextran 12% (w/v) (Ave. M.W. ≈ 40,000-70,000)" Livesey, 16:30-40; *see also id.* 16:42-52. "The Cryosolution consists of the following: 0.5M Dimethyl Sulfoxide (DMSO) 0.5M Propylene Glycol 0.25M 2-3 Butanediol 2.5% (w/v) Raffinose 12.0% (w/v) Sucrose 15.0% (w/v) Polyvinylpyrrolidone (PVP) 15.0% Dextran" Livesey, 26:19-27. "Upon receipt of tissue, the discs were transferred to a cryosolution comprising 0.5M DMSO, 0.5M propylene glycol, 0.25M 2-3 butanediol, 2-5% raffinose, 15% polyvinyl pyrrolodone, 15% Dextran and 12% sucrose . . . ." Livesey, 28:8-13. *See* Ex. 1008, ¶¶ 47-48.

Claim 9	**Livesey (Ex. 1003)**
A method for producing a soft tissue graft,	"A method for processing and preserving an acellular collagen-based tissue matrix for transplantation is disclosed." Livesey, Abstract.

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." Livesey, 1:17-21. "Human donor skin is routinely harvested from cadavers and stored under refrigerated or frozen conditions at a number of tissue banks throughout the nation…. This same skin is also available for processing by the methods described below." Livesey, 23:9-18; *see also id.* at 23:19-25:42 (Example 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. 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." Livesey, 1:17-26. "In its preferred form, the method of this invention includes the steps of processing biological tissues including treatment with a stabilizing solution to reduce procurement damage, treatment with a processing solution to remove cells and other antigenic tissue components …." Livesey, 4:20-35. "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." Livesey, 5:1-6. "The intent of this invention is to ultimately remove the cellular component and to optimally preserve the extracellular matrix, therefore the stabilizing solution is formulated to minimize the initial cellular and subsequently the extracellular matrix damage." Livesey, 7:36-51. "In the practice of this invention, it is essential that the harvested

	tissue be processed to remove antigenic cellular components." Livesey, 9:38-40. "Decellularization can be accomplished using a number of chemical treatments, including incubation in certain salts, detergents or enzymes. The use of the detergent Triton X-100 … has been demonstrated to remove cellular membranes, as detailed in U.S. Pat. No. 4,801,299." Livesey, 9:41-47. "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)." Livesey, 23:65-69. *See also* Livesey, 30:22-33 (claim 1). *See* Ex. 1008, ¶ 46.
impregnating the soft tissue with a biocompatible, water-soluble plasticizer composition comprising one or more alcohols.	"After the tissue is decellularized, it is preferably incubated in a cryopreservation solution." Livesey, 5:15-16. "The initial steps of cryopreserving the decellularized tissue includes incubating the tissue in a cryosolution prior to the freezing step. The cryosolution comprises one or more cryoprotectants and/or dry protectants with or without an organic solution . . ." Livesey, 11:17-22. "Various cryoprotectants can be used in the present invention. These include: dimethylsulfoxide (DMSO), detxran, sucrose, 1,2 propanediol, glycerol, sorbitol, fructose, trehalose, raffinose, propylene glycol, 2-3 butane diol, hydroxyethyl starch, polyvinylpyrrolidone (PVP), proline (or other protein stabilizers), human serum albumin and combinations thereof." Livesey, 11:49-55. "The biological samples are incubated in the cryosolutions for a period of a few minutes to a few hours before they are rapidly cooled. 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 . . . .” Livesey, 12:31-37. “A modified vitrification solution (Vs2) has also been developed which comprises a mixture of: Dimethyl Sulfoxide (DMSO) 0.5 M Propylene glycol 0.5M 2-3 butanediol 0.25M Raffinose 10% (w/v) Trehalose 6% (w/v) Sucrose 6% (w/v) PVP 12% (w/v) (Ave. M.W. ≈ 40,000) Dextran 12% (w/v) (Ave. M.W. ≈ 40,000-70,000)” Livesey, 16:30-40; *see also id.*, 16:42-52. “The Cryosolution consists of the following: 0.5M Dimethyl Sulfoxide (DMSO) 0.5M Propylene Glycol 0.25M 2-3 Butanediol 2.5% (w/v) Raffinose 12.0% (w/v) Sucrose 15.0% (w/v) Polyvinylpyrrolidone (PVP) 15.0% Dextran” Livesey, 26:19-27. “Upon receipt of tissue, the discs were transferred to a cryosolution comprising 0.5M DMSO, 0.5M propylene glycol, 0.25M 2-3 butanediol, 2-5% raffinose, 15% polyvinyl pyrrolodone, 15% Dextran and 12% sucrose . . . .” Livesey, 28:8-13. *See* Ex. 1008, ¶¶ 47-56.

Claim 12	**Livesey (Ex. 1003)**
The method of Claim 9, wherein the graft is suitable for transplantation after storage at	“In its preferred form, the method of this invention includes the steps of . . . storage in the dry state at above freezing temperatures . . . .” Livesey, 4:20-35. “The processing and preservation method is designed to generate a transplantable biological tissue graft that specifically meets the following criteria: … (e) can be easily stored and transported at

room temperature.	ambient temperatures." Livesey, 4:43-55 "In the preferred embodiment, the packaged dried tissue may be stored for extended time periods under ambient conditions. Transportation may be accomplished via standard carriers and under standard conditions relative to normal temperature exposure and delivery times." Livesey, 6:6-11. "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." Livesey, 1:17-21. "The processed dermis . . . has a number of clinical applications in full thickness skin injury. These include, but are not limited to, burn patients, patients suffering from venous, diabetic, or pressure ulcers, and patients who undergo reconstructive surgery, or skin replacement following excision of skin lesions. Processed human and porcine skin have been shown to undergo fibroblast infiltration and neovascularization in human burns patients . . . ." Livesey, 25:30-41. *See* Ex. 1008, ¶ 57.

Claim 13	**Livesey (Ex. 1003)**
The method of Claim 9, wherein said soft tissue comprises cadaveric skin, pericardium, dura mater, fascia lata, ligaments, or tendons.	"Human donor skin is routinely harvested from cadavers and stored under refrigerated or frozen conditions at a number of tissue banks throughout the nation…. This same skin is also available for processing by the methods described below." Livesey, 23:9-18; *see also id.* at 23:19-25:42 (Example 1). "For example, with human cadaver skin Dispase II at 1.0 units/ml for 90 minutes at 37° C. will remove all keratinocytes except the basal layer …." Livesey, 10:3-5. "Heart valves following implantation are subject to repetitive stress and hence will tolerate less ice crystal damage than, for example, dermis." Livesey, 11:46-48. *See* Ex. 1008, ¶¶ 49-55.

C. Ground II: Claims 1, 4-9, and 12-13 are Unpatentable Under 35 U.S.C. § 103 in view of Werner and Klement

One of ordinary skill in the art would have had reason to combine the teachings of Werner and Klement in June 1998, with such a combination yielding the claimed inventions of claims 1, 4-9, and 12-13. Werner and Klement are both directed to methods for preparing soft tissue grafts—in particular, dura mater grafts—for transplant into a recipient patient. (Ex. 1004, 2:21-24; Ex. 1005, 4:34-42). As discussed above, Werner discloses a method for preserving soft tissue grafts made up of proteins such as collagen and elastin (which Werner refers to as sclero proteins) such as dura mater or skin (Ex. 1008, ¶ 58), with a plasticizer composition containing the plasticizer and sugar alcohol glycerol in a biocompatible solvent, water. (Ex. 1008, ¶ 60). Indeed, Werner teaches soaking soft tissue in a solution of 30% glycerol in water, (Ex. 1004, 2:58-59), the same concentration (30%) of the same plasticizer and sugar alcohol (glycerol) in the same solvent (water) that the '971 patent uses for a plasticizer composition to treat both of its examples of soft tissue grafts, (Ex. 1001, 22:65-23:2, 23:51-56).

Werner is a patent filed in 1981. It explained "[t]he desired characteristics can be achieved by introducing the sclero protein material into a glycerin solution, after prior *conventional procedural steps of purifying and antigen separation*." (Ex. 1004, 2:1-6 (emphasis added)). As discussed above, Klement discloses a later-

developed, and improved, prior art technique for removing essentially all cellular material from a soft tissue graft without altering the collagen and elastin internal matrix of that graft. (Ex. 1005, 2:23-28, 3:6-26). While Werner discloses processing techniques that would remove some cellular material, (Ex. 1008, ¶ 59), Klement (which was filed years after Werner) recognizes the benefits of "complete removal" of all cellular material that "could initiate an immunological rejection response" and discloses improved processes to achieve this. (Ex. 1005, 3:13-17).

Further, Werner was expressly directed to improving the preservation of soft tissues processed using then-conventional cell-removal techniques, stating that its improvement was impregnating the processed tissue with a plasticizer composition. (Ex. 1008, ¶¶ 59-60; Ex. 1004, 4:3-9; Abstract). By June 30, 1998—years after Werner—a POSA would have had reason to combine the glycerol-preservation technique taught in Werner with the improved cellular removal methods taught in Klement to remove as much cellular material as possible from the soft tissue graft before treatment with glycerol, thereby minimizing any immunogenic reaction upon transplant of Werner's soft tissue grafts into a patient. (Ex. 1008, ¶¶ 64-66).

In addition, Werner teaches that glycerol preservation takes place following the processing of the soft tissue to lyse and rinse cells. (Ex. 1008, ¶ 60, citing Ex. 1004 at 2:58-59, 2:1-6). Thus, a POSA would have recognized that substituting the known decellularization method of Klement for this aspect of Werner's processing

would require no modification of the glycerol preservation technique taught in Werner, as the graft would already have undergone the processing to remove cells. (Ex. 1008, ¶¶ 67-68). Accordingly, a POSA would have reasons to utilize Klement's improved cellular removal techniques for dura mater or skin with Werner's plasticization techniques for dura mater or skin in order to produce a less immunogenic soft tissue graft, and would have expected such a combination to succeed without modifying either Klement's decellularization methods or Werner's plasticizer composition treatment. (Ex. 1008, ¶¶ 67-68).

As explained above, and as shown in the claim charts below, the combination of Werner and Klement discloses all the limitations of claims 1, 4-9, and 12-13, and establishes a *prima facie* case of obviousness for these claims. Accordingly, it is submitted that the present petition establishes a reasonable likelihood that the Petitioner will prevail on at least one claim. 35 U.S.C. § 314(a).

Claim 1	**Werner and Klement (Exs. 1004, 1005)**
A soft tissue graft, comprising:	"In a process for the manufacture of sclero protein transplants in which raw sclero protein from human or animals is watered, treated with H_2O_2, degreased, rinsed, dried and sterilized, the improvement in which the sclero protein, after rinsing and prior to drying, is treated with glycerin or polyetheylene glycol." Werner, Abstract; 4:4-9. "The process is carried out in that one first wets the sclero proteins as, for example, collagen, keratin, elastin from humans or animals and, in particular, raw dura matter from humans . . ." Werner, 2:21-24. "It has been well known that some sclero proteins as, for example,

	collagen, keratin, and elastin can be transplanted homologously as well as heterologously in humans." Werner, 1:6-9. "The soft dura matter obtained according to the invention can be used as transplants in various areas of medical use which are well known to those skilled in the art." Werner, 3:26-28. "It is appreciated that the treatment of this invention may be applied to a variety of sources of suitable tissue extracted from appropriate donors, including bovine, ovine, caprine, porcine, and human sources. The tissue samples may include veins, arteries, pericardium, dura mater, ligaments, tendons, trachea and skin. Such components, when treated, may be used for prostheses to replace arteries, veins, heart valves, ligaments, and tendons, trachea and skin." Klement, 4:34-42. *See* Ex. 1008, ¶¶ 58, 62.
soft tissue obtained from a human or animal donor; and	"The process is carried out in that one first wets the sclero proteins as, for example, collagen, keratin, elastin from humans or animals and, in particular, raw dura matter from humans . . ." Werner, 2:21-24. "It has been well known that some sclero proteins as, for example, collagen, keratin, and elastin can be transplanted homologously as well as heterologously in humans." Werner, 1:6-9. "The soft dura matter obtained according to the invention can be used as transplants in various areas of medical use which are well known to those skilled in the art." Werner, 3:26-28. "It is appreciated that the treatment of this invention may be applied to a variety of sources of suitable tissue extracted from appropriate donors, including bovine, ovine, caprine, porcine, and human sources. The tissue samples may include veins, arteries, pericardium, dura mater, ligaments, tendons, trachea and skin. Such components, when treated, may be used for prostheses to replace arteries, veins, heart valves, ligaments, and tendons, trachea and skin." Klement, 4:34-42. *See* Ex. 1008, ¶¶ 58, 62.

a plasticizer composition comprising one or more alcohols, wherein	"Water is removed from the material in the glycerin. Simultaneously, glycerin impregnates the transplant by a diffusion process. During the subsequent drying process the percentage content of glycerin increases substantially." Werner, 2:1-8. "The dura matter treated in this way was stirred for 4 hours in a 30% glycerin solution in water." Werner, 2:58-59. *See* Ex. 1008, ¶ 60.
cellular elements are substantially removed from said soft tissue, and	"The process is carried out in that one first wets the sclero proteins as, for example, collagen, keratin, elastin from humans or animals and, in particular, raw dura matter from humans, with water in the usual way. Then one treats it with H_2O_2, thereafter one degreases it, rinses it with water . . . ." Werner, 2:24-26. "Raw dura matter which was supplied in concentrated NaCl was watered for 24 hours. Thereupon it was put into 2% to 20%, preferably 5%, H_2O_2 for 48 hours. Then the dura matter was degreased in a Soxhlet apparatus in acetone-diethylether 1:1 for 4 hours. The degreased dura matter was rinsed for 12 to 24 hours with water." Werner, 2:50-57. "Accordingly, the invention removes soluble small and high molecular weight substances from natural tissue . . . while retaining the insoluble, collagenous and elastic 'backbone' of the natural tissue." Klement, 2:23-27. "All other components including cell membranes, cytoplasm, nuclear material and serum components could initiate an immunological rejection response and, therefore, necessitate complete removal." Klement, 3:13-17. *See also* 2:32-28. "According to a preferred embodiment of this invention, the non-ionic detergent may be selected from the following group TRITON X-100 (trademark), am octylphenoxy polyethoxyethanol, manufactured by Rohm and Haas; BRIJ-35 (trademark), a polyethoxyethanol lauryl ether, manufactured by Atlas Chemical Co.; TWEEN 20 (trademark), a polyethoxyethanol sorbitan monolaureate, manufactured by Rohm and Haas; and LUBROL-PX (trademark), a polyethylene lauryl ether, manufactured by Rohm

	and Hass. Suitable anionic detergents include those selected from the group consisting of a salt of a sulfated higher aliphatic alcohol, sulfonated alkane and sulfonated alkylarene containing from 7 to 22 carbon atoms in a branched or unbranched chain. The preferred anionic detergent is sodium dodecyl sulphate." Klement, 4:13-28. *See* Ex. 1008, ¶ 59.
said plasticizer composition is contained in said soft tissue.	"Water is removed from the material in the glycerin. Simultaneously, glycerin impregnates the transplant by a diffusion process. During the subsequent drying process the percentage content of glycerin increases substantially." Werner, 2:1-8. "The dura matter treated in this way was stirred for 4 hours in a 30% glycerin solution in water." Werner, 2:58-59. *See* Ex. 1008, ¶ 61.

Claim 4	**Werner and Klement (Exs. 1004, 1005)**
The graft of Claim 1, wherein said soft tissue comprises one of cadaveric skin, pericardium, dura mater, fascia lata, ligaments, or tendons.	"In a process for the manufacture of sclero protein transplants in which raw sclero protein from human or animals is watered, treated with H_2O_2, degreased, rinsed, dried and sterilized, the improvement in which the sclero protein, after rinsing and prior to drying, is treated with glycerin or polyetheylene glycol." Werner, Abstract; 4:4-9. "The process is carried out in that one first wets the sclero proteins as, for example, collagen, keratin, elastin from humans or animals and, in particular, raw dura matter from humans . . ." Werner, 2:21-24. "It has been well known that some sclero proteins as, for example, collagen, keratin, and elastin can be transplanted homologously as well as heterologously in humans." Werner, 1:6-9. "The soft dura matter obtained according to the invention can be used as transplants in various areas of medical use which are well known to those skilled in the art." Werner, 3:26-28. "It is appreciated that the treatment of this invention may be applied

	to a variety of sources of suitable tissue extracted from appropriate donors, including bovine, ovine, caprine, porcine, and human sources. The tissue samples may include veins, arteries, pericardium, dura mater, ligaments, tendons, trachea and skin. Such components, when treated, may be used for prostheses to replace arteries, veins, heart valves, ligaments, and tendons, trachea and skin." Klement, 4:34-42. *See* Ex. 1008, ¶ 58, 62.

Claim 5	**Werner and Klement (Exs. 1004, 1005)**
The graft of Claim 1, wherein said soft tissue comprises cadaveric skin.	"In a process for the manufacture of sclero protein transplants in which raw sclero protein from human or animals is watered, treated with H_2O_2, degreased, rinsed, dried and sterilized, the improvement in which the sclero protein, after rinsing and prior to drying, is treated with glycerin or polyetheylene glycol." Werner, Abstract; 4:4-9. "It has been well known that some sclero proteins as, for example, collagen, keratin, and elastin can be transplanted homologously as well as heterologously in humans." Werner, 1:6-9. "The process is carried out in that one first wets the sclero proteins as, for example, collagen, keratin, and elastin from humans or animals . . . ." Werner, 3:26-28. "It is appreciated that the treatment of this invention may be applied to a variety of sources of suitable tissue extracted from appropriate donors, including bovine, ovine, caprine, porcine, and human sources. The tissue samples may include veins, arteries, pericardium, dura mater, ligaments, tendons, trachea and skin. Such components, when treated, may be used for prostheses to replace arteries, veins, heart valves, ligaments, and tendons, trachea and skin." Klement, 4:34-42. *See* Ex. 1008, ¶¶ 58, 62.

Claim 6	**Werner and Klement (Exs. 1004, 1005)**
The graft of Claim 1, wherein said soft	"In a process for the manufacture of sclero protein transplants in which raw sclero protein from human or animals is watered, treated with H_2O_2, degreased, rinsed, dried and sterilized, the improvement in which the sclero protein, after rinsing and prior to drying, is treated

tissue comprises human cadaveric skin.	with glycerin or polyetheylene glycol." Werner, Abstract; 4:4-9. "It has been well known that some sclero proteins as, for example, collagen, keratin, and elastin can be transplanted homologously as well as heterologously in humans." Werner, 1:6-9. "The process is carried out in that one first wets the sclero proteins as, for example, collagen, keratin, and elastin from humans or animals . . . ." Werner, 3:26-28. "It is appreciated that the treatment of this invention may be applied to a variety of sources of suitable tissue extracted from appropriate donors, including bovine, ovine, caprine, porcine, and human sources. The tissue samples may include veins, arteries, pericardium, dura mater, ligaments, tendons, trachea and skin. Such components, when treated, may be used for prostheses to replace arteries, veins, heart valves, ligaments, and tendons, trachea and skin." Klement, 4:34-42. *See* Ex. 1008, ¶¶ 58, 62.

Claim 7	**Werner and Klement (Exs. 1004, 1005)**
The graft of Claim 1, wherein said soft tissue graft is suitable to be stored at room temperature prior to transplantation into a human recipient.	"It has been well known that some sclero proteins as, for example, collagen, keratin, and elastin can be transplanted homologously as well as heterologously in humans." Werner, 1:6-9. "[I]t became evident that the freeze drying can be substituted by air drying at room temperature without adversely affecting the resistance with the sclero protein has against decomposition in a living organism." Werner, 2:16-20. "As an alternative, the moist dura mater was dried at room temperature in the open air." Werner, 2:61-62. *See* Ex. 1008, ¶ 61.

Claim 8	**Werner and Klement (Exs. 1004, 1005)**
The graft of Claim 1, wherein said one or more alcohols comprise glycerol,	"In a process for the manufacture of sclero protein transplants in which raw sclero protein from human or animals is watered, treated with H_2O_2, degreased, rinsed, dried and sterilized, the improvement in which the sclero

adonitol, sorbitol, ribitol, galactitol, 1,3-dihydroxypropanol, ethylene glycol, triethylene glycol, propylene glycol, mannitol, xylitol, or mesoerythritol.	protein, after rinsing and prior to drying, is treated with glycerin or polyetheylene glycol." Werner, Abstract; 4:4-9. "Water is removed from the material in the glycerin. Simultaneously, glycerin impregnates the transplant by a diffusion process. During the subsequent drying process the percentage content of glycerin increases substantially." Werner, 2:1-8. "The dura matter treated in this way was stirred for 4 hours in a 30% glycerin solution in water." Werner, 2:58-59.

Claim 9	**Werner and Klement (Exs. 1004, 1005)**
A method for producing a soft tissue graft, comprising:	"In a process for the manufacture of sclero protein transplants in which raw sclero protein from human or animals is watered, treated with H_2O_2, degreased, rinsed, dried and sterilized, the improvement in which the sclero protein, after rinsing and prior to drying, is treated with glycerin or polyetheylene glycol." Werner, Abstract; 4:4-9. "The process is carried out in that one first wets the sclero proteins as, for example, collagen, keratin, elastin from humans or animals and, in particular, raw dura matter from humans . . ." Werner, 2:21-24. "It has been well known that some sclero proteins as, for example, collagen, keratin, and elastin can be transplanted homologously as well as heterologously in humans." Werner, 1:6-9. "The soft dura matter obtained according to the invention can be used as transplants in various areas of medical use which are well known to those skilled in the art." Werner, 3:26-28. "It is appreciated that the treatment of this invention may be applied to a variety of sources of suitable tissue extracted from appropriate donors, including bovine, ovine, caprine, porcine, and human sources. The tissue samples may include veins, arteries, pericardium, dura mater, ligaments, tendons, trachea and skin. Such components, when treated, may be used for prostheses to replace arteries, veins, heart valves, ligaments, and tendons,

	trachea and skin." Klement, 4:34-42. *See* Ex. 1008, ¶¶ 58, 62.
substantially removing cellular elements from soft tissue obtained from a human or animal donor;	"The process is carried out in that one first wets the sclero proteins as, for example, collagen, keratin, elastin from humans or animals and, in particular, raw dura matter from humans, with water in the usual way. Then one treats it with H_2O_2, thereafter one degreases it, rinses it with water . . . ." Werner, 2:24-26. "Raw dura matter which was supplied in concentrated NaCl was watered for 24 hours. Thereupon it was put into 2% to 20%, preferably 5%, H_2O_2 for 48 hours. Then the dura matter was degreased in a Soxhlet apparatus in acetone-diethylether 1:1 for 4 hours. The degreased dura matter was rinsed for 12 to 24 hours with water." Werner, 2:50-57. "Accordingly, the invention removes soluble small and high molecular weight substances from natural tissue . . . while retaining the insoluble, collagenous and elastic 'backbone' of the natural tissue." Klement, 2:23-27. "All other components including cell membranes, cytoplasm, nuclear material and serum components could initiate an immunological rejection response and, therefore, necessitate complete removal." Klement, 3:13-17. *See also* 2:32-28. "According to a preferred embodiment of this invention, the non-ionic detergent may be selected from the following group TRITON X-100 (trademark), am octylphenoxy polyethoxyethanol, manufactured by Rohm and Haas; BRIJ-35 (trademark), a polyethoxyethanol lauryl ether, manufactured by Atlas Chemical Co.; TWEEN 20 (trademark), a polyethoxyethanol sorbitan monolaureate, manufactured by Rohm and Haas; and LUBROL-PX (trademark), a polyethylene lauryl ether, manufactured by Rohm and Hass. Suitable anionic detergents include those selected from the group consisting of a salt of a sulfated higher aliphatic alcohol, sulfonated alkane and sulfonated alkylarene containing from 7 to 22 carbon atoms in a branched or unbranched chain. The preferred anionic detergent is sodium dodecyl sulphate." Klement, 4:13-28.

	See Ex. 1008, ¶ 59.
impregnating the soft tissue with a biocompatible, water-soluble plasticizer composition comprising one or more alcohols.	"Water is removed from the material in the glycerin. Simultaneously, glycerin impregnates the transplant by a diffusion process. During the subsequent drying process the percentage content of glycerin increases substantially." Werner, 2:1-8. "The dura matter treated in this way was stirred for 4 hours in a 30% glycerin solution in water." Werner, 2:58-59. *See* Ex. 1008, ¶¶ 60, 61.

Claim 12	**Werner and Klement (Exs. 1004, 1005)**
The method of Claim 9, wherein the graft is suitable for transplantation after storage at room temperature.	"It has been well known that some sclero proteins as, for example, collagen, keratin, and elastin can be transplanted homologously as well as heterologously in humans." Werner, 1:6-9. "[I]t became evident that the freeze drying can be substituted by air drying at room temperature without adversely affecting the resistance with the sclero protein has against decomposition in a living organism." Werner, 2:16-20. "As an alternative, the moist dura mater was dried at room temperature in the open air." Werner, 2:61-62. *See* Ex. 1008, ¶ 61.

Claim 13	**Werner and Klement (Exs. 1004, 1005)**
The method of Claim 9, wherein said soft tissue comprises cadaveric skin, pericardium, dura mater, fascia lata,	"In a process for the manufacture of sclero protein transplants in which raw sclero protein from human or animals is watered, treated with H_2O_2, degreased, rinsed, dried and sterilized, the improvement in which the sclero protein, after rinsing and prior to drying, is treated with glycerin or polyetheylene glycol." Werner, Abstract; 4:4-9. "The process is carried out in that one first wets the sclero proteins as, for example, collagen, keratin, elastin from humans or animals and, in particular, raw dura matter from humans . . ." Werner, 2:21-

ligaments, or tendons.	24. "It has been well known that some sclero proteins as, for example, collagen, keratin, and elastin can be transplanted homologously as well as heterologously in humans." Werner, 1:6-9. "The soft dura matter obtained according to the invention can be used as transplants in various areas of medical use which are well known to those skilled in the art." Werner, 3:26-28. "It is appreciated that the treatment of this invention may be applied to a variety of sources of suitable tissue extracted from appropriate donors, including bovine, ovine, caprine, porcine, and human sources. The tissue samples may include veins, arteries, pericardium, dura mater, ligaments, tendons, trachea and skin. Such components, when treated, may be used for prostheses to replace arteries, veins, heart valves, ligaments, and tendons, trachea and skin." Klement, 4:34-42. *See* Ex. 1008, ¶¶ 58, 62.

D. Ground III: Claims 1-3 and 9-11 are Unpatentable Under 35 U.S.C. § 103 in view of Walker and Wang

One of ordinary skill in the art would have had reason to combine the teachings of Walker and Wang in June 30, 1998, with such a combination yielding the claimed inventions of dependent claims 2-3 and 10-11 (as well as independent claims 1 and 9). Walker and Wang are both directed to preservation techniques for soft tissue grafts to be transplanted into a human, and both Walker and Wang disclose that their techniques for preserving the soft tissue consist of soaking the soft tissue in an alcohol solution, which results in the preserved tissue retaining its mechanical properties. (Ex. 1008, ¶¶ 72, 75).

As discussed above, Walker discloses methods for "plasticization" of soft tissue, such as pericardium, by incubating the tissue in a 50% glycerol/50% ethanol solution. (Ex. 1006, 19:17-23, 20:3-11). Walker explains that this "plasticization" preserves the tissue "for implantation into a human or animal body." (Ex. 1006, 4:33-36). Wang, which also discloses preservation of soft tissue, such as pericardium, in an alcohol solution, discusses the importance of "remov[ing] the cellular elements" from the soft tissue before preservation by soaking the tissue in sodium dodecyl sulfate or another known organic detergent. (Ex. 1007, 2:64-67, 3:28-36). Such cellular removal is important, Wang explains, because it "reduce[s] antigenicity and rejection after implantation [into a patient]." (Ex. 1007, 3:9-13).

One skilled in the art would have had reason to use the rigorous cellular removal techniques of Wang to decellularize a soft tissue graft before incubating the graft according to Walker's glycerol and ethanol solution. (Ex. 1008, ¶ 73). In particular, a POSA would have had reason to incorporate Wang's cellular removal techniques into Walker's process to minimize any immunogenic reaction upon implantation of Walker's plasticized soft tissue grafts in a patient. (Ex. 1008, ¶ 74).

In addition, Wang teaches that soaking the soft tissue graft in an alcohol solution takes place after the removal of cellular elements from the soft tissue using detergent. (Ex. 1007 at 4:36-48). Thus, a POSA would have recognized that using the cellular removal techniques of Wang before incubating the graft in

Walker's glycerol and ethanol solution would have merely entailed the substitution of Walker's glycerol/ethanol "plasticization" solution for the "preservation with alcohol" step that Wang discloses for its soft tissue grafts, without modification of the cellular removal techniques taught by Wang. (Ex. 1008, ¶¶ 75-76). A POSA would have expected such a combination to successfully produce a decellularized soft tissue graft containing both plasticizer and alcohol, (Ex. 1008, ¶ 75), which, as Walker states, would produce soft tissue grafts having "no significant decrease in physical strength after treatment" and that are "not rigid" and "fe[el] more natural." (Ex. 1006, 4:33-36, 24:8-10, 24:19-21, 24:26-35).

As explained above, and as further shown below, the combination of Walker and Wang discloses all the limitations of claims dependent claims 2-3 and 10-11, as well as claims 1 and 9, and establishes a *prima facie* case of obviousness for these claims. Thus, it is submitted that the present petition establishes a reasonable likelihood that the Petitioner will prevail on at least one claim. 35 U.S.C. § 314(a).

Claim 1	**Walker and Wang (Exs. 1006, 1007)**
A soft tissue graft, comprising:	"It is possible to plasticize and sterilize bovine pericardium in the same way as bovine arteries." Walker, 25:1-2. "Example 5: Plasticization of Bovine Pericardium The physical characteristics of samples of bovine pericardium were assessed, before and after sterilisation, to assess the affect, if any, of the plasticization - sterilisation process on the pericardium." Walker, 19:17-23. "The processed tissue is suitable not only for small-diameter blood vessel implants, but for other tissue implants including heart valve,

	venous valve, skin and cornea." Wang, 3:3-6. "Therefore it is the objective of the present invention to prepare a biological collagenous tissue by removal of the cellular membrane proteins from the tissue therefore to reduce antigenicity and rejection after implantation." Wang, 3:9-13. "The tissue, such as blood vessel, skin, heart valve, venous valve, and cornea are removed from either a human or animal . . . ." Wang, 3:48-50. "The process according to claim 1, wherein said tissue is selected from the group consisting of blood vessels, venous valves, heart valves, skin, tendon, bone, pericardium, cornea, and umbilical cord." Wang, 6:43-36.
soft tissue obtained from a human or animal donor; and	"It is possible to plasticize and sterilize bovine pericardium in the same way as bovine arteries." Walker, 25:1-2. "Example 5: Plasticization of Bovine Pericardium The physical characteristics of samples of bovine pericardium were assessed, before and after sterilisation, to assess the affect, if any, of the plasticization - sterilisation process on the pericardium." Walker, 19:17-23. "The tissue, such as blood vessel, skin, heart valve, venous valve, and cornea are removed from either a human or animal . . . ." Wang, 3:48-50. "The process according to claim 1, wherein said tissue is selected from the group consisting of blood vessels, venous valves, heart valves, skin, tendon, bone, pericardium, cornea, and umbilical cord." Wang, 6:43-36.
a plasticizer composition comprising one or more alcohols, wherein	"Plasticization The following glycerol (PROLABO) solutions were prepared in 50% ethanol (BDH); 50%, 60%, 70%, 80%, 90%, and 100%. Plasticization was performed according to the established procedure i.e. at least 16 hours incubation with at 37°C with agitation." Walker, 20:3-8. "It is possible to plasticize and sterilize bovine pericardium in the

	same way as bovine arteries." Walker, 25:1-2. "As stated above, the substance may be water-soluble sugars such as sorbitol or glycerol. Suitable solutions range from 5% to 100%, usually in 50% ethanol or in water. Where water is used as a solvent it should preferably be RO grade. Preferred solution concentrations are 30% to 70%, particularly 40% to 60%. Generally, the material is incubated in the substance for at least 12 hours at above ambient temperature." Walker 3:17-24. *See* Ex. 1008, ¶ 69.
cellular elements are substantially removed from said soft tissue, and	"In the present invention, the biological collagenous tissue is processed by extensive detergent soaking and washing to remove the cellular elements … and to maintain the mechanical property of the tissue . . . ." Wang, 2:64-67. "The present invention provides a preparation process for making collagenous tissue comprising the following consecutive steps: (1) soaking the tissue in an organic detergent, such as sodium dodecyl sulfate (SDS), to solubilize the cell membrane proteins in the collagenous tissue; (2) washing and removing the cellular membrane proteins from the tissue by mechanical shaking and stirring . . . ." Wang, 3:28-36; *see also id.*, 3:47-4:35. *See* Ex. 1008, ¶ 71.
said plasticizer composition is contained in said soft tissue.	"<u>Plasticization</u> The following glycerol (PROLABO) solutions were prepared in 50% ethanol (BDH); 50%, 60%, 70%, 80%, 90%, and 100%. Plasticization was performed according to the established procedure i.e. at least 16 hours incubation with at 37°C with agitation." Walker, 20:3-8. "It is possible to plasticize and sterilize bovine pericardium in the same way as bovine arteries." Walker, 25:1-2. "As stated above, the substance may be water-soluble sugars such as sorbitol or glycerol. Suitable solutions range from 5% to 100%, usually in 50% ethanol or in water. Where water is used as a solvent it should preferably be RO grade. Preferred solution concentrations are 30% to 70%, particularly 40% to 60%.

	Generally, the material is incubated in the substance for at least 12 hours at above ambient temperature." Walker 3:17-24. *See* Ex. 1008, ¶ 69.

Claim 9	**Walker and Wang (Exs. 1006, 1007)**
A method for producing a soft tissue graft, comprising:	"It is possible to plasticize and sterilize bovine pericardium in the same way as bovine arteries." Walker, 25:1-2. "Example 5: Plasticization of Bovine Pericardium The physical characteristics of samples of bovine pericardium were assessed, before and after sterilisation, to assess the affect, if any, of the plasticization - sterilisation process on the pericardium." Walker, 19:17-23. "The processed tissue is suitable not only for small-diameter blood vessel implants, but for other tissue implants including heart valve, venous valve, skin and cornea." Wang, 3:3-6. "Therefore it is the objective of the present invention to prepare a biological collagenous tissue by removal of the cellular membrane proteins from the tissue therefore to reduce antigenicity and rejection after implantation." Wang, 3:9-13. "The tissue, such as blood vessel, skin, heart valve, venous valve, and cornea are removed from either a human or animal . . . ." Wang, 3:48-50. "The process according to claim 1, wherein said tissue is selected from the group consisting of blood vessels, venous valves, heart valves, skin, tendon, bone, pericardium, cornea, and umbilical cord." Wang, 6:43-36.
substantially removing cellular elements from soft tissue obtained from a	"The tissue, such as blood vessel, skin, heart valve, venous valve, and cornea are removed from either a human or animal . . . ." Wang, 3:48-50. "In the present invention, the biological collagenous tissue is processed by extensive detergent soaking and washing to remove the cellular elements … and to maintain the mechanical property of the tissue . . . ." Wang, 2:64-67.

human or animal donor;	"The present invention provides a preparation process for making collagenous tissue comprising the following consecutive steps: (1) soaking the tissue in an organic detergent, such as sodium dodecyl sulfate (SDS), to solubilize the cell membrane proteins in the collagenous tissue; (2) washing and removing the cellular membrane proteins from the tissue by mechanical shaking and stirring . . . ." Wang, 3:28-36; *see also id.* at 3:47-4:35. *See* Ex. 1008, ¶ 71.
impregnating the soft tissue with a biocompatible, water-soluble plasticizer composition comprising one or more alcohols.	"Plasticization The following glycerol (PROLABO) solutions were prepared in 50% ethanol (BDH); 50%, 60%, 70%, 80%, 90%, and 100%. Plasticization was performed according to the established procedure i.e. at least 16 hours incubation with at 37°C with agitation." Walker, 20:3-8. "It is possible to plasticize and sterilize bovine pericardium in the same way as bovine arteries." Walker, 25:1-2. "As stated above, the substance may be water-soluble sugars such as sorbitol or glycerol. Suitable solutions range from 5% to 100%, usually in 50% ethanol or in water. Where water is used as a solvent it should preferably be RO grade. Preferred solution concentrations are 30% to 70%, particularly 40% to 60%. Generally, the material is incubated in the substance for at least 12 hours at above ambient temperature." Walker, 3:17-24. *See* Ex. 1008, ¶ 69.

With respect to dependent claims 2-3 and 10-11, the combination of Walker and Wang discloses that in the graft of claim 1, and the method of claim 9, the one or more alcohols in the plasticizer composition comprises ethanol. *E.g.*, Walker, 19:17-20:8 ("Plasticization[:] The following glycerol (PROLABO) solutions were prepared in 50% ethanol (BDH); 50%, 60%, 70%, 80%, 90%, and 100%.

Plasticization was performed according to the established procedure i.e. at least 16 hours incubation with at 37°C with agitation."); Walker 3:17-24 ("As stated above, the substance may be water-soluble sugars such as sorbitol or glycerol. Suitable solutions range from 5% to 100%, usually in 50% ethanol or in water.").

VII. CONCLUSION

Petitioner respectfully submits that, for the reasons set forth above, there is a reasonable likelihood that Petitioner will prevail on at least one claim. Accordingly, Petitioner respectfully requests that this Petition be granted and claims 1-13 of the '971 patent be found to be unpatentable.

Date: September 8, 2015

Respectfully submitted,

By _____

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6 and 42.105, I hereby certify that on this 8th day of September 2015, the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,125,971 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq.*, together with Petitioner's Exhibits Nos. 1001-1018, was served by FedEx, a means at least as fast and reliable as Priority Mail Express®, on the following correspondence address of record for patent owner:

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Date: September 8, 2015

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