

REMARKS

This paper is being filed to accompany a Request for Continued Examination in response to the final Office Action, dated 04/20/2018 in the subject application. A Petition and Fee for a Three-Month Extension of Time is likewise provided with this Response and RCE.

Claims 1-4, 6-19, and 23-25 and 27-33 stand withdrawn from consideration as being drawn to non-elected subject matter. Rejoinder of method claims upon allowance of composition of matter claims is requested.

Claims 34, 35, and 39 are cancelled or have been previously cancelled.

Accordingly, the claims under consideration in this application prior to entrance of this Amendment were claims 5, 20-22, 26, 36-38, and 40-61; new claims 62-65 are introduced herein above.

New Claims 62-65, directed to a process of decellularization that does not involve cross-linking, are newly presented as a species of the claims from which they depend, explicitly excluding cross-linked product, and it is respectfully urged that the cited art, namely Satoh, Seifert, Asem, whether cited alone or in any reasonable combination, do not/does not teach or suggest such a process or resultant product and does not meet the positively recited limitations of these claims in which cross-linked material is excluded.

It is noted that throughout the entire specification there is significant written description and enabling disclosure regarding Urodele ECM, how to obtain it and how to decellularize it for purposes of this invention and claims (see, especially, e.g. paragraphs 0023-0040, the figures, their legends, paragraphs 0058-0092, 0094-0107 and the claims) with substantial emphasis on retention of natural architecture and function (which cross-linking constrains), without a single mention of a process including cross-linking or cross-linking agents..

It is urged that one of ordinary skill in the art would read the claims to exclude a cross-linked product and, as explained below, why the claims as amended must be read to exclude a cross-linked product.

There is but one mention of the concept of cross-linking in the entire patent disclosure - namely, at paragraph 0093 of US2015/0352257 (the USPTO's publication of the subject application). That mention does not relate to achieving the material of the present invention but

instead relates to a use to which the material of the invention may be directed. It is quoted below in its entirety with bolded emphasis added:

"Urodele decellularized ECM can be used also for sustained delivery of therapeutic molecules, proteins or metabolites, to a site in a host. See, for example, U.S. 2004/0181240, which describes an amniotic membrane covering for a tissue surface which may prevent adhesions, exclude bacteria or inhibit bacterial activity, or to promote healing or growth of tissue, and U.S. Pat. No. 4,361,552, which pertains to the preparation of cross-linked amnion membranes and their use in methods for treating burns and wounds. The ECMs of the invention can be used in the same manner."

In light of the above, it is respectfully urged that whatever the fate of the of the remaining pending claims in this application, claims 62-65 should be recognized as being free of the prior art.

I. 35 USC §112:

Claim 42 stands rejected under 35 U.S.C. §112(b) or pre-AIA 35 U.S.C. §112 second paragraph, as being indefinite. Claim 42 is rejected based on the phrase "a human agent" which is asserted to not be adequately defined by the claim language or specification.

To address and overcome this ground for rejection of claim 42, the claim was previously amended to recite "an agent found in a human, whether isolated, synthetically or recombinantly produced". This text is supported by the specification at paragraph 0029 which discloses: "a human agent (i.e., an agent found in a human, isolated, synthetically or recombinantly produced)." The claim has, however, been rejected again for indefiniteness. Since claim 42 merely narrows the claim from which it depends, claim 42 is herein amended to delete the "human agent" text to overcome this ground for rejection. Reconsideration and withdrawal of this ground for rejection is therefore respectfully requested. The withdrawal of rejections for indefiniteness of Claims 44 and 61 is gratefully acknowledged.

II. 35 USC §102 and 35 USC §103:

Claim(s) 5, 20-22, 36-38, 41, 44, and 47 stand rejected under 35 USC 102a1 as being anticipated by Satoh et al. (2012), and claims 5, 20-22, 26, 36-38, and 40-61, stand rejected under 35 U.S.C. 103 as being unpatentable over Asem et al. (US 6485969) in view of Seifert et al. (2012).

It is noted for the record that Claims 26, 40, 42-43, 45-46, and 48-61 are not rejected as anticipated by Satoh, and are therefore free of this ground for rejection, and are therefore only subject to the 35 U.S.C. 103 rejection discussed below as to obviousness in light of the combination of Asem and Seifert.

With respect to novelty and non-obviousness of the claims in this application, prior to introduction of this Amendment, arguments and Declaratory evidence in support of the patentability of the claims of record and under examination have been presented, essentially as follows:

1. It is unreasonable to assert that the prior art product "appears to be **identical with** or **slightly different than** the claimed product-by-process" product;
2. the intended use, and method of producing the currently claimed product, **does** create structural differences between the claimed composition and the composition of the prior art; and
3. the Declaration of Dr. Ashley Seifert supports the assertion that significant structural and functional differences exist between the claimed ECM and the product produced by Satoh as a result of the different methods of production.

In the outstanding Final Rejection, the Examiner has essentially reiterated the anticipation rejection previously made of record, stating that:

"Satoh teaches acellular collagen and ECM sheets (decellularized ECM) from axolotl (p192). Although Satoh does not teach each of the claimed process steps by which the collagen is produced, these limitations are considered to product by process type limitations. It is noted that the patentability of a product does not depend on its method of production. If the claimed product

is the same or obvious from a product in the prior art (i.e. the product disclosed in the cited reference), the claim is unpatentable even though the reference product was made by a different process. When the prior art discloses a product which reasonably appears to be identical with or slightly different than the claimed product-by-process, rejections under 35 U.S.C. 102 and/or 35 U.S.C. 103 are proper. (MPEP 2113) Regarding the intended use of decellularizing the ECM to retain structure and functional integrity of the ECM, this intended use of the claimed composition does not patentably distinguish the composition, *per se*, since such undisclosed use is inherent in the reference composition. In order to be limiting, the intended use must create a structural difference between the claimed composition and the composition of the prior art. **In the instant case, the intended use fails to create a structural difference, thus, the intended use is not limiting.** Please note that when applicant claims a composition in terms of function, and the composition of the prior art appears to be the same, the Examiner may make rejections under both 35 U.S.C. 102 and 103 (MPEP 2112). Regarding claim 22, the claim reads on the skin and cartilage samples containing the collagen, which is considered to be a material impregnated with or having attached thereto, the collagen. Therefore, the reference anticipates the claimed subject matter."

With respect to the obviousness rejection directed to claims 5, 20-22, 26, 36-38, and 40-61 as being unpatentable over Asem et al. (US 6485969) in view of Seifert et al. (2012), the Examiner has reiterated the rejection previously made of record, notwithstanding that in the prior response, the Applicant argued and presented Declaratory evidence in support of the following arguments:

1. Asem does not teach the ECM wherein the amphibian is a Urodele, or axolotl;
2. the Seifert et al. reference, if anything, teaches away from the combination proposed by the Examiner, and this was confirmed by Dr. Ashley Seifert in the Expert Declaration filed with the prior response;
3. the Declaration of Dr. Seifert establishes that Asem teaches, if anything, that follicular tissue, like placental tissue, **is unique**, found in small quantities and is relatively difficult to obtain from eggs, including eggs of reptiles, and one would not substitute the material of Seifert for that

of Asem. In addition, Seifert teaches that one would want to avoid the presence of ECM in promoting scar-free healing, teaching away from the combination suggested by the Examiner; and

4. Seifert's mention of ECM is all in the context of *in vivo* modelling of ECM production as it relates to scar tissue formation and there is no disclosure or suggestion in Seifert of production of anything like the ECM disclosed and claimed in the present application, and, therefore, much like the *ex vivo* tissue produced by Satoh, the Seifert material fails to meet the present claims' requirements of decellularization and reduced antigenicity.

Applicant believes that its prior showing was adequate to rebut the position taken by the Examiner, particularly when considering the Declaration by the very author of the paper cited by the Examiner, which author disagrees with the Examiner's interpretation and conclusions. Nonetheless, Applicant has further amended the claims to clearly distance the present claimed material from the material of the prior art.

III. CURRENT STATUS OF THE CLAIMS AS HEREIN AMENDED, COMPRISING (1) QUOTATION OF THE EXAMINER'S REASONS FOR MAINTAINING THE PRIOR-ART-BASED REJECTIONS AND (2) REBUTTAL REMARKS RELATING TO NEWLY INTRODUCED AMENDMENTS TO THE PENDING CLAIMS

The application provides:

"Decellularized ECM" means extra cellular matrix sufficiently free of cellular components to eliminate or reduce antigenicity of the extra cellular matrix to an extent where the matrix would be considered **non-toxic as a xenograft.**"

"Non-toxic" means that a composition, **when implanted in a subject, causes little or no adverse reaction or substantial harm to cells** and tissues in the body, and does not cause a substantial adverse reaction or substantial harm to cells and tissues in the body, for instance, the composition **does not cause** necrosis, an infection, **or a substantial immune response** resulting in harm to tissues from the implanted or applied composition."

Applicant cites to a reference, made of record in the attached PTO1449 IDS submission, in which it is concluded that **glutaraldehyde-treated bovine pericardium incites significant toxic, inflammatory, immune, and calcification responses** which is not desirable for a long-term function as an implant. Applicant notes that Satoh uses **glutaraldehyde** in Satoh's process, which would result in a material that "incites significant toxic, inflammatory, immune, and calcification responses". Such a process and the resulting product is excluded from the claims as amended.

As amended, claim 5 provides:

A tissue graft comprising extracellular matrix components derived from a Urodele, said tissue graft derived by:

- a. obtaining a tissue sample from a urodele, which tissue sample comprises extracellular matrix; and
- b. decellularizing said tissue sample to produce **decellularized extracellular matrix** by removing sufficient cellular components of the sample to reduce or eliminate antigenicity of the biomaterial making it suitable for use as a xenograft.

Decellularized extracellular matrix, as explicitly defined in the specification, **means** extra cellular matrix sufficiently free of cellular components to eliminate or reduce antigenicity of the extra cellular matrix **to an extent where the matrix would be considered non-toxic as a xenograft**.

Satoh teaches (and Applicant will shortly file a Declaration that confirms that Satoh teaches) use of **glutaraldehyde** and Satoh does not remove sufficient cellular components or reduce antigenicity to an extent where the matrix would be considered **non-toxic as a xenograft**. There are present in the material made by Satoh: DNA, glands, and nuclei. All these things are antigenic. In addition, the newly cited reference, Umashankar (and Declaration to be submitted) will confirm that **glutaraldehyde treatment of a graft material will result in a product that incites significant toxic, inflammatory, immune, and calcification responses**. Such a product is outside the scope of the claims as amended.

In contrast, there is evidence in the application to establish the disclosed and claimed product is free of cellular debris. Figure 5 of the published patent application, US2015/0352257, shows that the claimed product has no intact glands of the dermis and all cellular constituents are removed. Applicant believes the present claims address and overcome the reasons previously stated on the record as to why the claimed invention is anticipated and/or obvious in view of the cited art.

For the sake of completeness, the Examiner, at pages 5-8 of the outstanding Final Rejection, provides the following seven rationales for maintaining the rejections, each quoted in full below. After each rationale/basis for maintaining each rejection is *quoted (and italicized)*, Applicant provides rebuttal evidence and arguments.

1. *"Regarding Satoh the reference teaches a decellularized ECM sheet from a Urodele as claimed. The reference teaches an acellular ECM, or decellularized, which would inherently have the claimed retention of structural and functional integrity as claimed. Even if the ECM is crosslinked with glutaraldehyde, it would still retain sufficient structure and function to permit and support use of the matrix as a substrate for growth of cells in vivo or in vitro, as defined by the instant specification on page 12, thus inherently meeting the claimed limitations. **Absent clear evidence of a structural or functional difference between the claimed ECM and that of Satoh, the arguments are found unpersuasive.**"*

In response, Applicant has amended the claims (which implicitly excluded a glutaraldehyde cross-linking step and cross-linked graft) to include an explicit definition contained in the specification which necessarily excludes a glutaraldehyde cross-linking step and cross-linked graft. Applicant also will soon file a further Declaration of Dr. Ashley Seifert, to demonstrate that a product made by the Satoh method does not meet the limitations of the claims. Data will be presented to confirm clear structural and functional differences between the ECM prepared according to the Satoh process as compared to that which is presently claimed and described in the instant specification.

The product of claim 5 as herein amended (and claims 20 and 22 have been likewise amended) is prepared by a process in which the active affirmative step of "decellularizing" is

characterized as producing “a decellularized ECM” As defined in the specification, this means reducing antigenicity to an extent where the matrix would be considered non-toxic as a xenograft. The newly cited reference makes clear that the glutaraldehyde treatment of Satoh will result in a product that “incites significant toxic, inflammatory, immune, and calcification responses”, which is outside the scope of the claims.

Based on the clear structural and functional differences shown between the ECM prepared as disclosed and claimed in the present application, and the material produced according to the Satoh process, it is urged that the Applicant has met its burden of demonstrating the novelty of the claimed subject matter and has also limited the scope of the rejected claims to be commensurate with the scope of novelty by excluding from the scope of the rejected claims products produced in the prior art by a cross-linking step in the decellularization of the ECM material, whether that be a mammalian ECM, an amphibian ECM, or an Urodele or axolotl ECM. Reconsideration and withdrawal of this ground for rejection is therefore respectfully requested.

2. *"Regarding the argument that the prior art does not teach the claimed process steps, it is noted that **the claim fails to recite active process steps** as argued. Rather, **the claims only recite functional descriptive language**, without any specific step to meet the limitations. The claims do not require any step for removing cellular debris, any amount of ECM, **nor do they exclude crosslinking**. Thus, the argument is not commensurate in scope with the claimed invention."*

Applicants disagree, particularly in view of the claims as amended. The claims require decellularization to a degree where the ECM is sufficiently free of cellular components to eliminate or reduce antigenicity of the extra cellular matrix to an extent where the matrix would be considered non-toxic as a xenograft. The specification cites many methods for accomplishing this, which methods are known in the art. Satoh, however, does not employ such methods because Satoh employs a glutaraldehyde cross-linking step which prevents removal of cellular materials and also results in a toxic graft.

The Examiner is urged to keep in mind the *entire disclosure* and thrust of the present invention. Applicant discovered that if cellular material is removed from certain Urodel tissue, then the remaining native material is *immunoprivileged*. The application is based on that novel and

unexpected discovery. The unequivocal thrust of the application is to eliminate the cells to yield that immunoprivileged material. Satoh not only does not eliminate the cells, because Satoh cross-links cellular organelles like nuclei in place, but Satoh also cross-links the material in a manner to destroy the immunoprivileged state in same manner as is described in the newly cited reference. Satoh's process is the antithesis of that described and presently claimed, as would be understood by one of ordinary skill in the art.

As stated in the application:

"Moreover, the cutaneous and subcutaneous structures of an axolotl resemble that of the amniotic/chorionic interface, in the sense that axolotl skin is composed of fused ectoderm and mesoderm. Axolotl skin also is rich in growth factors and antimicrobial peptides, similar to the AM. Furthermore, **axolotl ECM is immunoprivileged and contains collagen III and tissue inhibitors of metalloproteinases (TIMPs), inter alia, also in resemblance to AM. Of particular importance for transplantation purposes, more generally, is the immunologically privileged state of the human neonate (e.g., fetal dermis) and the AM, a state mirrored by axolotl ECM, whereby immogenicity is rarely manifested.**"

Accordingly, it is urged that the claims as amended should be sufficient to distinguish the Satoh process and product, which includes a glutaraldehyde cross-linking step, destroying immunoprivilege and retaining cellular components. Glutaraldehyde treatment interferes with Applicant's decellularization step. This will be further supported in a further Declaration of Dr. Ashley Seifert.

3. *"Regarding applicant's assertion that the examiner has not proven the ECM of the prior art has eliminated antigenicity and is suitable for xenograft, it is maintained that the prior art teaches acellular collagen, acellular ECM, and decellularized basement membranes, which means the ECM are free of cellular components. As defined by applicant on page 12, being free of cells and cellular components eliminates or reduces antigenicity as well as makes the material suitable for xenograft. Further, as the claimed invention fails to recite any specific step for making the graft, the claims neither require nor exclude any step in achieving such a decellularized ECM. As such, the claims read on the prior art. It is noted that the burden is on applicant to provide arguments and evidence establishing that the claimed product is different from that of the prior art, and that such arguments and evidence must be commensurate in scope with the claimed invention."*

Again, carrying out the invention is straight forward, once the initial unexpected discovery is made. Once it is known that the native cell-free material is immunoprivileged, then removing cells to produce a non-toxic graft is straight forward. It is black letter law that the office should take into account the unexpected discovery which forms the basis of the invention. Applicant believes it has met its burden to show its product is different from a glutaraldehyde treated product, and will submit a further Declaration to further support this view.

4. *"Regarding the intended use of the compositions, it is noted that intended use of the claimed composition does not patentably distinguish the composition, per se, **since such undisclosed use is inherent in the reference composition.** In order to be limiting, the intended use must create a structural difference between the claimed composition and the composition of the prior art. In the instant case, the intended use fails to create a structural difference, thus, the intended use is not limiting. Please note that when applicant claims a composition in terms of function, and the composition of the prior art appears to be the same, the Examiner may make rejections under both 35 U.S.C 102 and 103 (MPEP 2112). **Furthermore, the claimed process does not recite any active steps that must be practiced to arrive at a product with structural or physical differences. It is reiterated that the claims only recite functional descriptive language, without any specific step to meet the limitations. As such, the claims encompass any decellularized ECM with structural/functional integrity and has been decellularized. Thus, the argument is not commensurate in scope with the claimed invention.**"*

As discussed above, as amended, the claims in the present application have been rendered commensurate in scope with a product produced by a process wherein treatment with an agent like glutaraldehyde is excluded. Applicant did not invent a new process of decellularization. Applicant invented a new graft material, based on the discovery that such material is immunoprivileged, as would be understood by one of ordinary skill in the art reading the instant specification. The claim scope, as amended, clearly does not read on the Satoh product.

5. *Regarding the combination of Asem and Seifert, it is noted that it is the combination of references that is relied upon. Asem teaches decellularized ECM derived from amphibians in the form of sheets that can be adhered together (or laminated), powders (or particles) or reconstituted gels, which are made under alkaline conditions. Asem teaches the ECM*

compositions may be used as tissue grafts constructs, with cell culture, or culturing human cells wherein it is preferably sterilized prior to use. Seifert is relied upon to demonstrate that Urodele, specifically axolotl, was a known amphibian source from which a decellularized ECM may be obtained. Moreover, Seifert provides evidence of a functionally equivalent amphibian source of ECM that can be decellularized and used in the compositions of Asem with a reasonable expectation for success.

With the prior response, the Expert Declaration of Dr. Ashley Seifert was provided in which he stated on the record his opinion that, as an expert in the field, and as principal author of the Seifert reference being cited in combination with the Asem reference, that he contests the Examiner's assertion that the Seifert reference teaches or suggests use of Urodele or axolotl as a functionally equivalent amphibian ECM to the material used in Asem. Dr Seifert opined that one skilled in the art reading Asem and Seifert together would not have had a reasonable expectation for successfully obtaining a functional decellularized ECM.

First, there is no teaching in Asem (or in Seifert et al.) that there is any tissue (other than placental tissue) that is the "functional equivalent" to follicular ECM. By contrast, as noted in the Declaration of Dr. Seifert, Asem teaches, if anything, that follicular tissue, like placental tissue, is unique.

Dr. Seifert's expert testimony is directly contradictory to the Examiner's assertion that *"Seifert is relied upon to demonstrate that Urodele, specifically axolotl, was a known amphibian source from which a decellularized ECM may be obtained."* The Examiner has failed to show that Seifert may properly be relied on for the teaching asserted by the Examiner. The Examiner has failed to show how or where Seifert provides such evidence. It is also directly contradictory to what Dr. Seifert, a person skilled in the art and the author of the Seifert reference, has stated. Seifert is directed to studying wound healing in the axolotl as a model for wound healing in mammals. Any "ECM" material produced is a cross-linked material, much as is the Satoh material, produced for the purpose of analysis, and is excluded from the scope of the present claims as amended and the newly introduced claims.

6. *Regarding a teaching away, it is acknowledged that Seifert teaches different outcomes than applicant. However a different outcome is not a teaching away from functionality*

*of the ECM. Seifert is not cited to motivate one in the art to use a crosslinked ECM from Urodele in the compositions of Asem, but rather **to evidence it was a known source of amphibian ECM that can be decellularized and used as the amphibian ECM in the compositions of Asem with a reasonable expectation for success.** Please note that the instant claims do not exclude or require any step for producing the decellularized ECM, nor do they require or exclude any particular type or source of ECM other than being any tissue from a Urodele. Thus, the arguments are not commensurate in scope with the claimed invention."*

The Applicant and the author of the Seifert reference itself contests the Examiner's assertion that Seifert may properly be used "**to evidence it was a known source of amphibian ECM that can be decellularized and used as the amphibian ECM in the compositions of Asem with a reasonable expectation for success**". Asem teaches, if anything, that follicular tissue, like placental tissue, is unique. The Examiner has not shown anything to the contrary. The Examiner has not shown or provided a reasoned basis for why someone would ever substitute the material of Seifert for that of Asem with an expectation of success. There has been no showing on the record of any teaching or suggestion in the Seifert reference of the production of decellularized ECM as claimed. The entire reference is directed to the study of ECM and its role *in vivo* in wound healing. It is only through hindsight extrapolation from the present disclosure that the Examiner boot-straps the Seifert reference, over the objection of the Author himself, into a rejection of the present claims. Further, just as in Satoh and in Seifert, Asem provides for a cross-linked product, which is excluded from the present claims.

7. *"In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170USPQ 209 (CCPA 1971)."*

Simply stating that "*obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning*", the Examiner does not demonstrate the permissibility of the hindsight at

play in the present situation. Here, all of the cited and relied upon art relates to cross-linked products and processes using cross-linking. This is explicitly excluded from the pending claim set as amended, and from the newly introduced claim set. In addition, in this instance, the Examiner ignores the main teaching in the Asem reference that the tissue used by Asem is unique and ignores the declaration by the Author of Seifert as to the meaning of the Seifert reference.

Reconsideration and withdrawal of this ground for rejection is respectfully requested.

SUMMARY:

All grounds for objection or rejection of claims asserted in the outstanding Office Action have been addressed and overcome herein by Amendment of the claims and by the remarks, arguments, and evidence, including that provided by Dr. Ashley Seifert. The objections/rejections under 35 USC 112 have been addressed by claim amendments. The rejection of claims under 35 USC 101 as being drawn to ineligible subject matter has been withdrawn. Likewise, it is urged, the rejection of claims under 35 USC 102 and 103 have been overcome by claim amendments and by the arguments and evidence provided herein and in the Declaration of Dr. Seifert.

It is respectfully urged that all claims pending in this application are in condition for allowance.

In the event a telephonic or in-person interview would assist in bringing prosecution in this application to a successful conclusion, the Examiner is invited to contact the undersigned to arrange such an interview.

Dated: October 22, 2018

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**CLEAN LISTING OF ALL CLAIMS PENDING (ALBEIT SOME ARE WITHDRAWN
BUT NOT CANCELED) IN THIS APPLICATION:**

1. A decellularized biomaterial produced by the process that comprises (A) obtaining a tissue sample from a urodele, which tissue sample comprises extracellular matrix, and (B) decellularizing the sample to retain structural and functional integrity while removing sufficient cellular components of the sample to reduce or eliminate antigenicity of the biomaterial as a xenograft.
2. The decellularized biomaterial of claim 1, wherein said decellularizing comprises subjecting said tissue sample to an alkaline treatment.
3. The decellularized biomaterial of claim 1, wherein said process further comprises subjecting said sample to sterilization.
4. The decellularized biomaterial of claim 1, further comprising devitalized cells.
5. A tissue graft comprising extracellular matrix components derived from a Urodele, said tissue graft derived by:
 - a. obtaining a tissue sample from a urodele, which tissue sample comprises extracellular matrix; and
 - b. decellularizing said tissue sample to produce decellularized extracellular matrix by removing sufficient cellular components of the sample to reduce or eliminate antigenicity of the biomaterial making it suitable for use as a xenograft.
6. An isolated, decellularized Urodele ECM.
7. The isolated ECM of claim 6, wherein the ECM is derived from Axolotl tissue.
8. The isolated ECM of claim 6, wherein the ECM includes basement membrane.

9. The isolated ECM of claim 6, wherein the ECM is infused with, coated with, or attached to an agent xenogenic to a Urodele that is a growth factor, a cytokine, a chemokine, a protein, a carbohydrate, a sugar, a steroid, an antimicrobial agent, a synthetic polymer, an adhesive, a drug or a human agent.
10. The isolated ECM of claim 6, wherein the agent is a cell, optionally a human cell.
11. The isolated ECM of claim 6, wherein the ECM is a sheet.
12. The isolated ECM of claim 11, wherein the sheet includes perforations.
13. The isolated ECM of claim 6, wherein the ECM is a dry powder.
14. The isolated ECM of claim 6, wherein the ECM is a reconstituted gel.
15. The isolated ECM of any one of claims 6-13, therein the ECM is sterile.
16. A package containing sterile, isolated, decellularized Urodele ECM or a Urodele fraction derived from the sterile, isolated, decellularized Urodele ECM.
17. The package of claim 17, wherein the sterile, isolated, decellularized Urodele ECM or a Urodele fraction derived from the sterile, isolated, decellularized Urodele ECM is a sheet of isolated, decellularized Urodele ECM.
18. The package of claim 17, wherein the sterile, isolated, decellularized Urodele ECM or a Urodele fraction derived from the sterile, isolated, decellularized Urodele ECM is a dry powder.
19. The package of claim 17, wherein the sterile, isolated, decellularized Urodele ECM or

a Urodele fraction derived from the sterile, isolated, decellularized Urodele ECM is a gel.

20. A sterile medical implant comprising sterile, isolated, decellularized Urodele Extracellular Matrix (ECM) or a sterile Urodele fraction derived from the isolated, decellularized Urodele ECM produced by a process comprising:

- a. obtaining a tissue sample from a urodele, which tissue sample comprises extracellular matrix;
- b. decellularizing and sterilizing said tissue sample to produce decellularized extracellular matrix by removing sufficient cellular components of the sample to reduce or eliminate antigenicity of the biomaterial making it suitable for use as a xenograft; and sterilizing said tissue.

21. The sterile medical implant of claim 20, wherein the implant is a biocompatible sheet, mesh, gel, graft, tissue or device.

22. A material coated with, impregnated with, encapsulating, or having attached thereto isolated, decellularized Urodele ECM wherein said isolated, decellularized Urodele ECM is produced by a process comprising:

- a. obtaining a tissue sample from a urodele, which tissue sample comprises extracellular matrix;
- b. decellularizing said tissue sample to produce decellularized extracellular matrix by removing sufficient cellular components of the sample to reduce or eliminate antigenicity of the biomaterial making it suitable for use as a xenograft; and sterilizing said tissue.

23. A tissue culture system comprising (a) an isolated Urodele decellularized ECM, (b) tissue culture medium, and (c) cells xenogenic to the Urodele.

24. The tissue culture system of claim 22, wherein the cells are human cells.

25. Tissue culture medium conditioned with isolated Urodele decellularized ECM or a Urodele fraction derived from isolated, decellularized Urodele ECM.
26. A device comprising at least two sheets of isolated Urodele decellularized ECM laminated to one another.
27. A product prepared by isolating Urodele ECM from a Urodele, decellularizing the ECM, and sterilizing the decellularized ECM.
28. A method of preparing a biologic material comprising (A) obtaining a tissue sample from a urodele, which tissue sample comprises extracellular matrix, and (B) decellularizing the sample forming a decellularized ECM to remove sufficient cellular components of the sample to reduce or eliminate antigenicity of the biomaterial as a xenograft.
29. The method of claim 28, wherein the method further comprises performing the decellularization in a manner to retain structural and functional integrity of the decellularized ECM sufficient to permit the decellularized ECM to be useful as a matrix upon and within which cells can grow.
30. The method of claim 29, further comprising homogenizing the decellularized ECM to form a powder.
31. The method of claim 30, further comprising reconstituting the powder as a gel.
32. The method of claim 29, further comprising sterilizing the decellularized ECM.
33. The method of claim 29, further comprising attaching the decellularized ECM to an agent xenogenic to a Urodele.

36. The tissue graft of claim 5, wherein said decellularizing comprises subjecting said tissue sample to an alkaline treatment.

37. The tissue graft of claim 36, wherein said process further comprises subjecting said sample to sterilization.

38. The tissue graft of claim 5, wherein the Urodele is an Axolotl.

40. The sterile medical implant of claim 20, wherein the Urodele ECM includes basement membrane.

41. (Previously presented) The sterile medical implant of claim 20, wherein the Urodele ECM is derived from Axolotl tissue.

42. The sterile medical implant of claim 20, wherein the Urodele ECM is infused with, coated with, or attached to an agent xenogenic to a Urodele that is a growth factor, a cytokine, a chemokine, a protein, a carbohydrate, a sugar, a steroid, an antimicrobial agent, a synthetic polymer, an adhesive, or a drug.

43. The sterile medical implant of claim 20, further comprising a human cell and wherein the Urodele ECM is infused with, coated with, or attached to the human cell.

44. The sterile medical implant of claim 20, wherein the Urodele extracellular matrix (ECM) or a sterile Urodele fraction derived from the isolated, decellularized Urodele ECM is a sheet.

45. The sterile medical implant of claim 20, wherein the Urodele ECM is in the form of Urodele ECM particles.

46. The sterile medical implant of claim 20, wherein the Urodele ECM is a reconstituted gel.
47. The material of claim 22, wherein the Urodele ECM is Axolotl ECM.
48. The device of claim 26, wherein the Urodele ECM is Axolotl ECM.
49. A tissue graft according to claim 5 comprising sterile, isolated, decellularized Urodele extra cellular matrix (ECM), wherein the ECM is a powder, a paste, a gel, a sheet, or a mesh, and wherein the ECM is parietal ECM, mesothelial ECM, thoracic cavity ECM, abdominal cavity ECM, pericardium ECM or dermal tissue ECM.
50. The tissue graft of claim 49, wherein the ECM is a powder.
51. The tissue graft of claim 50, wherein the powder has a particle size between 125 and 850 microns.
52. The tissue graft of claim 50, wherein the powder has a particle size of less than 250 microns.
53. The tissue graft of claim 49, wherein the ECM is a paste.
54. The tissue graft of claim 49, wherein the ECM is a gel.
55. The tissue graft of claim 54, wherein the gel comprises a synthetic polymer.
56. The tissue graft of claim 49, wherein the ECM is a mesh.
57. A tissue graft according to claim 5 comprising sterile, isolated, decellularized Urodele extra cellular matrix (ECM), wherein the ECM is a sheet, wherein the ECM is parietal ECM, mesothelial

ECM, thoracic cavity ECM, abdominal cavity ECM, pericardium ECM or dermal tissue ECM, and the sheet of ECM is infused with, coated with, or attached to an agent xenogeneic to a Urodele that is a growth factor, a cytokine, a chemokine, a protein, a carbohydrate, a sugar, a steroid, an antimicrobial agent, a synthetic polymer, an adhesive, or a drug.

58. The tissue graft of claim 57, wherein the agent is an anti-microbial agent.

59. The tissue graft of claim 57, wherein the agent is a growth factor.

60. The tissue graft of claim 57, wherein the sheet is at least two sheets of isolated Urodele decellularized ECM laminated to one another.

61. The tissue graft according to claim 49 wherein the Urodele ECM is Axolotl ECM and is in a form selected from the group consisting of: a powder; a paste; a gel; a mesh; a sheet of parietal ECM, mesothelial ECM, thoracic cavity ECM, abdominal cavity ECM, pericardium ECM or dermal tissue ECM, and wherein the sheet of ECM is infused with, coated with, or attached to an agent xenogeneic to a Urodele that is a growth factor, a cytokine, a chemokine, a protein, a carbohydrate, a sugar, a steroid, an antimicrobial agent, a synthetic polymer, an adhesive, or a drug; and at least two sheets of isolated Urodele decellularized ECM laminated to one another.

62. The tissue graft according to claim 5 wherein said
(ii) removing sufficient cellular components of the sample, is carried out without cross-linking,
to reduce or eliminate antigenicity of the biomaterial making it suitable for use as a xenograft.
63. The tissue graft according to claim 5 which is not cross-linked.
64. The sterile medical implant according to claim 20 wherein said decellularization is carried
out without cross-linking.
65. The material coated with, impregnated with, encapsulating, or having attached thereto
isolated, decellularized Urodele ECM according to claim 22 produced without cross-linking.

IN THE CLAIMS:

Please replace all prior listings of claims in this application with the following listing of claims.

A clean set of claims, as herein amended, is provided as an attachment at the conclusion of this paper.

1. (Withdrawn) A decellularized biomaterial produced by the process that comprises (A) obtaining a tissue sample from a urodele, which tissue sample comprises extracellular matrix, and (B) decellularizing the sample to retain structural and functional integrity while removing sufficient cellular components of the sample to reduce or eliminate antigenicity of the biomaterial as a xenograft.
2. (Withdrawn) The decellularized biomaterial of claim 1, wherein said decellularizing comprises subjecting said tissue sample to an alkaline treatment.
3. (Withdrawn) The decellularized biomaterial of claim 1, wherein said process further comprises subjecting said sample to sterilization.
4. (Withdrawn) The decellularized biomaterial of claim 1, further comprising devitalized cells.
5. (Currently amended) A tissue graft comprising extracellular matrix components derived from a Urodele, said tissue graft derived by:
 - a. obtaining a tissue sample from a urodele, which tissue sample comprises extracellular matrix; and
 - b. decellularizing said tissue sample to produce decellularized extracellular matrix by a process comprising (i) retaining the structural and functional integrity of said tissue sample; and
(ii) removing sufficient cellular components of the sample to reduce or eliminate

antigenicity of the biomaterial making it suitable for use as a xenograft.

6. (Withdrawn) An isolated, decellularized Urodele ECM.
7. (Withdrawn) The isolated ECM of claim 6, wherein the ECM is derived from Axolotl tissue.
8. (Withdrawn) The isolated ECM of claim 6, wherein the ECM includes basement membrane.
9. (Withdrawn) The isolated ECM of claim 6, wherein the ECM is infused with, coated with, or attached to an agent xenogenic to a Urodele that is a growth factor, a cytokine, a chemokine, a protein, a carbohydrate, a sugar, a steroid, an antimicrobial agent, a synthetic polymer, an adhesive, a drug or a human agent.
10. (Withdrawn) The isolated ECM of claim 6, wherein the agent is a cell, optionally a human cell.
11. (Withdrawn) The isolated ECM of claim 6, wherein the ECM is a sheet.
12. (Withdrawn) The isolated ECM of claim 11, wherein the sheet includes perforations.
13. (Withdrawn) The isolated ECM of claim 6, wherein the ECM is a dry powder.
14. (Withdrawn) The isolated ECM of claim 6, wherein the ECM is a reconstituted gel.
15. (Withdrawn) The isolated ECM of any one of claims 6-13, therein the ECM is

sterile.

16. (Withdrawn) A package containing sterile, isolated, decellularized Urodele ECM or a Urodele fraction derived from the sterile, isolated, decellularized Urodele ECM.

17. (Withdrawn) The package of claim 17, wherein the sterile, isolated, decellularized Urodele ECM or a Urodele fraction derived from the sterile, isolated, decellularized Urodele ECM is a sheet of isolated, decellularized Urodele ECM.

18. (Withdrawn) The package of claim 17, wherein the sterile, isolated, decellularized Urodele ECM or a Urodele fraction derived from the sterile, isolated, decellularized Urodele ECM is a dry powder.

19. (Withdrawn) The package of claim 17, wherein the sterile, isolated, decellularized Urodele ECM or a Urodele fraction derived from the sterile, isolated, decellularized Urodele ECM is a gel.

20. (Currently amended) A sterile medical implant comprising sterile, isolated, decellularized Urodele Extracellular Matrix (ECM) or a sterile Urodele fraction derived from the isolated, decellularized Urodele ECM produced by a process comprising:

a. obtaining a tissue sample from a urodele, which tissue sample comprises extracellular matrix;

b. decellularizing and sterilizing said tissue sample to produce decellularized extracellular matrix by ~~a process which comprises:~~

~~(i) retaining the structural and functional integrity of said tissue sample; and (ii) removing sufficient cellular components of the sample to reduce or eliminate antigenicity of the biomaterial making it suitable for use as a xenograft; and (iii) sterilizing said tissue.~~

21. (Original) The sterile medical implant of claim 20, wherein the implant is a

biocompatible sheet, mesh, gel, graft, tissue or device.

22. (Currently amended) A material coated with, impregnated with, encapsulating, or having attached thereto isolated, decellularized Urodele ECM wherein said isolated, decellularized Urodele ECM is produced by a process comprising:

- a. obtaining a tissue sample from a urodele, which tissue sample comprises extracellular matrix;
- b. decellularizing said tissue sample to produce decellularized extracellular matrix by a process which comprises: (i) ~~retaining the structural and functional integrity of said tissue sample; and~~ (ii) removing sufficient cellular components of the sample to reduce or eliminate antigenicity of the biomaterial making it suitable for use as a xenograft; and ~~(iii)~~ sterilizing said tissue.

23. (Withdrawn) A tissue culture system comprising (a) an isolated Urodele decellularized ECM, (b) tissue culture medium, and (c) cells xenogenic to the Urodele.

24. (Withdrawn) The tissue culture system of claim 22, wherein the cells are human cells.

25. (Withdrawn) Tissue culture medium conditioned with isolated Urodele decellularized ECM or a Urodele fraction derived from isolated, decellularized Urodele ECM.

26. (Original) A device comprising at least two sheets of isolated Urodele decellularized ECM laminated to one another.

27. (Withdrawn) A product prepared by isolating Urodele ECM from a Urodele, decellularizing the ECM, and sterilizing the decellularized ECM.

28. (Withdrawn) A method of preparing a biologic material comprising (A)

obtaining a tissue sample from a urodele, which tissue sample comprises extracellular matrix, and (B) decellularizing the sample forming a decellularized ECM to remove sufficient cellular components of the sample to reduce or eliminate antigenicity of the biomaterial as a xenograft.

29. (Withdrawn) The method of claim 28, wherein the method further comprises performing the decellularization in a manner to retain structural and functional integrity of the decellularized ECM sufficient to permit the decellularized ECM to be useful as a matrix upon and within which cells can grow.

30. (Withdrawn) The method of claim 29, further comprising homogenizing the decellularized ECM to form a powder.

31. (Withdrawn) The method of claim 30, further comprising reconstituting the powder as a gel.

32. (Withdrawn) The method of claim 29, further comprising sterilizing the decellularized ECM.

33. (Withdrawn) The method of claim 29, further comprising attaching the decellularized ECM to an agent xenogenic to a Urodele.

34-35. (Canceled)

36. (Previously presented) The tissue graft of claim 5, wherein said decellularizing comprises subjecting said tissue sample to an alkaline treatment.

37. (Previously presented) The tissue graft of claim 36, wherein said process further comprises subjecting said sample to sterilization.

38. (Previously presented) The tissue graft of claim 5, wherein the Urodele is an Axolotl.

39. (Canceled)

40. (Previously presented) The sterile medical implant of claim 20, wherein the Urodele ECM includes basement membrane.

41. (Previously presented) The sterile medical implant of claim 20, wherein the Urodele ECM is derived from Axolotl tissue.

42. (Currently amended) The sterile medical implant of claim 20, wherein the Urodele ECM is infused with, coated with, or attached to an agent xenogenic to a Urodele that is a growth factor, a cytokine, a chemokine, a protein, a carbohydrate, a sugar, a steroid, an antimicrobial agent, a synthetic polymer, an adhesive, or a drug ~~or an agent found in a human, whether isolated, synthetically or recombinantly produced.~~

43. (Previously presented) The sterile medical implant of claim 20, further comprising a human cell and wherein the Urodele ECM is infused with, coated with, or attached to the human cell.

44. (Previously presented) The sterile medical implant of claim 20, wherein the Urodele extracellular matrix (ECM) or a sterile Urodele fraction derived from the isolated, decellularized Urodele ECM is a sheet.

45. (Previously presented) The sterile medical implant of claim 20, wherein the Urodele ECM is in the form of Urodele ECM particles.

46. (Previously presented) The sterile medical implant of claim 20, wherein the Urodele ECM is a reconstituted gel.

47. (Previously presented) The material of claim 22, wherein the Urodele ECM is Axolotl ECM.

48. (Previously presented) The device of claim 26, wherein the Urodele ECM is Axolotl ECM.

49. (Previously presented) A tissue graft according to claim 5 comprising sterile, isolated, decellularized Urodele extra cellular matrix (ECM), wherein the ECM is a powder, a paste, a gel, a sheet, or a mesh, and wherein the ECM is parietal ECM, mesothelial ECM, thoracic cavity ECM, abdominal cavity ECM, pericardium ECM or dermal tissue ECM.

50. (Previously presented) The tissue graft of claim 49, wherein the ECM is a powder.

51. (Previously presented) The tissue graft of claim 50, wherein the powder has a particle size between 125 and 850 microns.

52. (Previously presented) The tissue graft of claim 50, wherein the powder has a particle size of less than 250 microns.

53. (Previously presented) The tissue graft of claim 49, wherein the ECM is a paste.

54. (Previously presented) The tissue graft of claim 49, wherein the ECM is a gel.

55. (Previously presented) The tissue graft of claim 54, wherein the gel comprises a synthetic polymer.

56. (Previously presented) The tissue graft of claim 49, wherein the ECM is a mesh.

57. (Previously presented) A tissue graft according to claim 5 comprising sterile, isolated, decellularized Urodele extra cellular matrix (ECM), wherein the ECM is a sheet, wherein the ECM is parietal ECM, mesothelial ECM, thoracic cavity ECM, abdominal cavity ECM, pericardium ECM or dermal tissue ECM, and the sheet of ECM is infused with, coated with, or attached to an agent xenogeneic to a Urodele that is a growth factor, a cytokine, a chemokine, a protein, a carbohydrate, a sugar, a steroid, an antimicrobial agent, a synthetic polymer, an adhesive, or a drug.

58. (Previously presented) The tissue graft of claim 57, wherein the agent is an anti-microbial agent.

59. (Previously presented) The tissue graft of claim 57, wherein the agent is a growth factor.

60. (Previously presented) The tissue graft of claim 57, wherein the sheet is at least two sheets of isolated Urodele decellularized ECM laminated to one another.

61. (Previously presented) The tissue graft according to claim 49 wherein the Urodele ECM is Axolotl ECM and is in a form selected from the group consisting of: a powder; a paste; a gel; a mesh; a sheet of parietal ECM, mesothelial ECM, thoracic cavity ECM, abdominal cavity ECM, pericardium ECM or dermal tissue ECM, and wherein the sheet of ECM is infused with, coated with, or attached to an agent xenogeneic to a Urodele that is a growth factor, a cytokine, a chemokine, a protein, a carbohydrate, a sugar, a steroid, an antimicrobial agent, a synthetic polymer, an adhesive, or a drug; and at least two sheets of isolated Urodele decellularized ECM laminated to one another.

62. (New) The tissue graft according to claim 5 wherein said
(ii) decellularization is carried out without cross-linking .
63. (New) The tissue graft according to claim 5 wherein said decellularization is
carried out without cross-linking.
64. (New) The sterile medical implant according to claim 20 wherein said
decellularization is carried out without cross-linking.
65. (New) The material coated with, impregnated with, encapsulating, or having
attached thereto isolated, decellularized Urodele ECM according to claim 22 produced without
cross-linking.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Ryanne Early
Application No.: 14/759,895
Confirmation No.: 3358
Filed: July 8, 2015
For: DECELLULARIZED BIOMATERIAL FROM NON-MAMMALIAN
TISSUE
Examiner: R. A. Davis
Art Unit: 1651

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I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office's electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: October 22, 2018

Electronic Signature for: /Eileen M. MacKenzie/

MAIL STOP RCE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO ACCOMPANY A REQUEST FOR CONTINUED EXAMINATION ("RCE")

The claims pending in this application are Claims 1-33, 36-38, and 40-61; Claims 1-4, 6-19, 23-25, and 27-33, stand withdrawn from consideration; Claims 34-35 are cancelled herein below; leaving claims 5, 20-22, 26, 36-38 and 40-61 under examination. Per the Final Office Action mailed in the subject application on 04/20/2018, all claims under consideration stand rejected under 35 U.S.C. §§ 102 and 103. Claims 5, 20, 21, and 42 are amended herein below and new claims 62-65 are introduced, leaving claims 5, 20-22, 26, 36-38, and 40-65 under examination. The Independent Claims are Claims 5, 20, 22, and 26 (four independent Claims).

Amendments to the claims begin on page 2 of this paper, and Remarks and Arguments in support of the patentability of the claims, as herein amended, begin on page 10 herein below.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/759,895	07/08/2015	Ryanne Early	S1860.70000US01	3358
23628	7590	01/10/2019		
WOLF GREENFIELD & SACKS, P.C. 600 ATLANTIC AVENUE BOSTON, MA 02210-2206			EXAMINER DAVIS, RUTH A	
			ART UNIT	PAPER NUMBER
			1651	
			NOTIFICATION DATE	DELIVERY MODE
			01/10/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 22, 2018 and December 7, 2018 have been entered.

Claims 62 – 65 are added; claims 1 – 33, 36 – 38 and 40 – 65 are pending; claims 1 – 4, 6 – 19, 23 – 25 and 27 – 33 are withdrawn; claims 5, 20 – 22, 26, 36 – 38 and 40 – 65 have been considered on the merits. All arguments and the affidavit have been fully considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person

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skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62 – 65 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 62 – 65 recite a tissue graft that is decellularized without cross-linking. While the specification teaches methods of decellularizing while maintaining natural properties, the specification fails to identify the process without crosslinking. It is noted that mere absence of a positive recitation is not the same as a basis for an exclusion (MPEP 2173.05 (i)).

Claim Rejections - 35 USC § 112

Rejections under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, are withdrawn due to amendment.

Claim Rejections - 35 USC § 102

Rejections under 35 U.S.C. 102a1 are withdrawn due to applicant's amendment and reply.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 26 and 48 are rejected under 35 U.S.C. 103 as being unpatentable over Asem et al. (US 6485969) in view of Seifert et al. (2012).

Asem teaches decellularized ECM comprising basement membranes (col.1 line 66 - col.2 line 1-18, col.5 line 23-39), derived from amphibians (col.4 line 35-40) that are adhered together (or laminated) (col.6 line 20-32)

Asem does not teach the ECM wherein the amphibian is a Urodele, or axolotl. However, at the time the instant claims were filed, in following the teachings of Asem, one of ordinary skill in the art would have been motivated to use any known functionally equivalent amphibian ECM in the compositions of Asem with a reasonable expectation for successfully obtaining a decellularized ECM. At the time the instant claims were filed, axolotls were known amphibian sources of ECM and components derived therefrom. In support, Seifert teaches axolotl ECM and its basement membrane (abstract). As such, at the time the claims were filed, it would have been obvious to one of ordinary skill in the art to use ECM from axolotl in the in the compositions of Asem, since it was a known, functionally equivalent amphibian ECM.

Thus, the claims are rendered obvious.

Response to Arguments

Applicant argues that the references do not teach Urodele or axolotl ECM; that Seifert teaches away from using Urodele ECM by way of disclosing models only; that the references do not teach a decellularized ECM with reduce antigenicity; that there is no teaching or suggestion to modify or substitute one source for the other, that the examiner uses inappropriate hindsight; and that the prior art crosslinks the ECM.

However, these arguments fail to persuade for the following reasons. It is first noted that the rejection is based on the combination of references and not any one alone. Asem teaches decellularized ECM derived from amphibians in the form of sheets that can be adhered together (or laminated) while Seifert is relied upon to demonstrate that Urodele, specifically axolotl, was a known amphibian source from which a decellularized ECM may be obtained. Moreover, Seifert provides evidence of a functionally equivalent amphibian source of ECM that can be decellularized and used in the compositions of Asem with a reasonable expectation for success.

Regarding a teaching away, it is acknowledged that Seifert teaches different outcomes than applicant. However a different outcome is not a teaching away from functionality of the ECM. Seifert is evidence that Urodele/axolotl was a known source of amphibian ECM that can be decellularized and used as the amphibian ECM in the compositions of Asem with a reasonable expectation for success. Please note that the instant claims do not exclude or require any step for producing the decellularized ECM, nor do they require or exclude any particular type or source of ECM other than being any tissue from a Urodele. Thus, the arguments are not commensurate in scope with the claimed invention.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on

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obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Allowable Subject Matter

Claims 5, 20 – 22, 36 – 38, 40 – 47, 49 – 61 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RUTH A DAVIS whose telephone number is (571)272-0915. The examiner can normally be reached on Monday - Friday (8am - 4pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Renee Claytor can be reached on 571-272-8394. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/RUTH A DAVIS/

Primary Examiner, Art Unit 1651