

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

REGENX SCIENCE, INC.
Petitioner,

v.

NEXTGEN BIOLOGICS, INC.
Patent Owner.

Case No: IPR2025-00621
U.S. Patent No. 11,660,376

**PATENT OWNER'S PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107(a)**

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EX-2001	US Patent No. 6,485,969 (“Asem”)
EX-2002	Smith et al., “Collagens From the Skin and Cartilage of the Larval Salamander <i>Ambystoma tigrinum</i> ”, J of Exp Zoology, 220:243-250, 1982 (“Smith”)
EX-2003	Satoh. A., Hirata, A. & Makanae, A. Collagen reconstitution is inversely correlated with induction of limb regeneration in <i>Ambystoma mexicanum</i> . <i>Zoological science</i> 29, 191-197 (2012) (“Satoh”)
EX-2004	Seifert et al., “Skin Regeneration in Adult Axolotls: A Blueprint for Scar-Free Healing in Vertebrates”, PLoS One, www.plosone.org , Apr. 2012, vol. 7, Issue 4, e32875 (“Seifert”)
EX-2005	Swann G., The skin is the body’s largest organ. J Vis Commun Med. 2010;33(04):148–149. doi: 10.3109/17453054.2010.525439 (“Swann”)
EX-2006	Fife. E.C., et al., “Wound Care Outcomes and Associated Cost Among Patients Treated in US Outpatient Wound Centers: Data From the US Wound Registry”, WOUNDS 2012;24(1):10–17 (January 2012)
EX-2007	Diegelmann R., Wound healing: an overview of acute, fibrotic and delayed healing. <i>Front Biosci.</i> (2004) 9:283–9. doi: 10.2741/1184 (“Diegelmann”)
EX-2008	RegenxScience website (https://regenxscience.com)
EX-2009	Seifert, A. W. & Maden, M. New insights into vertebrate skin regeneration. <i>Int. Rev. Cell Mol. Biol.</i> 310, 129–69 (2014)
EX-2010	Denis, J.-F., Lévesque, M., Tran, S. D., Camarda, A.-J. & Roy, S. Axolotl as a Model to Study Scarless Wound Healing in Vertebrates: Role of the Transforming Growth Factor Beta Signaling Pathway. <i>Adv. Wound Care</i> 2, 250–260 (2013).

Exhibit No.	Reference
EX-2011	Block, L., Gosain, A. & King, T. W. Emerging Therapies for Scar Prevention. Adv. Wound Cblockbloare 4, 607–614 (2015)
EX-2012	Peck, M. D. Epidemiology of burns throughout the world. Part I: Distribution and risk factors. Burns 37, 1087–100 (2011)
EX-2013	Sen, C. K. et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen. 17, 763–71 (2009)
EX-2014	U.S. Patent No. 12,311,079
EX-2015	Megan Sykes, et al., “Progress in xenotransplantation: overcoming immune barriers”, Nat Rev Nephrol. 2022 December; 18(12): 745–761. doi:10.1038/s41581-022-00624-6
EX-2016	Asghar Ali, et al., Annual Review of Animal Biosciences, “Advances in Organ and Tissue Xenotransplantation”, Annu. Rev. Anim. Biosci. 2024. 12:369–90A
EX-2017	US Patent Appl. 2025/0134801 A1 assigned to Petitioner, REGENX
EX-2018	Written Opinion of International Phase Searching Authority issued in the International Phase prosecution of PCT/US2023/062398
EX-2019	US 2019 / 0255217 A1
EX-2020	Declaration Of Gerard H. Bencen in Support of Patent Owner’s Response in Support of Discretionary Denial Under 37 C.F.R. § 42.107(A)
EX-2021	Certified Prosecution History for US Patent No. 10,617,790
EX-2022	Farkas JE, Monaghan JR. “Housing and maintenance of Ambystoma mexicanum, the Mexican axolotl.” Methods Mol Biol. 2015;1290:27-46. doi: 10.1007/978-1-4939-2495-0_3. PMID: 25740475.

I. INTRODUCTION

Pursuant to 35 U.S.C. § 313 and 37 C.F.R. § 42.107, NextGen Biologics, Inc. (“NeXtGen” or “Patent Owner”) hereby provides this preliminary response to the Petition for *inter-parties* review (“IPR”) of U.S. Patent No. 11,660,376 B2 (“Petition”), filed by RegenX Science, Inc. (“Petitioner”). The Petition fails to establish a reasonable likelihood that any challenged claim of U.S. Patent No. 11,660,376 (“the ’376 Patent”) is unpatentable. The Board should deny institution.

NeXtGen developed and markets NEOMATRIX® Wound Matrix: a sterile acellular dermal membrane that is FDA-cleared as a device for use in management of wounds. NEOMATRIX® is fabricated from the dermal extracellular matrix (ECM) of urodeles (and, in particular, a type of salamander known as an “axolotl”) and provided as sheets of various sizes for placement on wound beds to help manage the wound environment. The challenged claims of the ’376 Patent cover NEOMATRIX®.

Petitioner’s obviousness case begins with mammalian ECM, which had been used for wound repair for decades before the priority date. During those decades, not a single piece of literature suggested that mammalian ECM could be improved by sourcing the material from urodeles. The ’376 Patent is based on the discovery that the skin and ECM of urodeles (and, in particular, axolotls) possess desirable

characteristics that, despite their small size, high cost and non-mammalian lineage, make them an ideal source of biomaterial for wound healing.

The '376 Patent reports that the resulting urodele-derived dermal membrane results in a faster healing process with less scarring compared to traditional dermal membrane manufactured from postnatal mammals. The claimed urodele-derived dermal membrane also enjoys an immunoprivileged status. EX-1001, 3:50-5:23.

Petitioner asserts that the challenged claims were obvious in view of combinations of *eight* different primary references and more than *eleven* secondary references from disparate fields of endeavor for the three Grounds in the Petition. As a threshold matter, the Board should exercise its discretion to deny institution pursuant to 35 U.S.C. § 325(d). Much of the art Petitioner cites and primarily relies upon (Badylak 2004 (EX-1005), Badylak 2009 (Ex-1008), Freyman (EX-1015), Van Dyke (EX-1023), Gilbert (EX-1032), McGann (EX-1026) and Keating (EX-1027)) is cumulative of the art already adjudicated by the Examiner during prosecution.

Petitioner fails to explain – and provides no expert testimony on – how its obviousness combinations are not the same or substantially the same as the arguments the Examiner already considered. To the contrary, the art cited by Examiner and overcome by the applicant during prosecution was *closer* to the claimed inventions than the art relied on in the Petition, demonstrating the futility of the Petition.

Petitioner's arguments also fail on the merits. Rather than identify with particularity the grounds on which each claim challenged are allegedly obvious, and provide detailed evidence that supports such grounds for challenge for each claim, Petitioner relies on undisclosed "cumulative teachings" of all *eight* primary prior art references for the three Grounds. Petitioner fails to convey either the specific combinations that allegedly render the challenged claims obvious or provide detailed evidence that supports such grounds for challenge for each claim.

Petitioner never performs the fundamental steps required of an obviousness evaluation, including analyzing the references against the claims as a whole, evaluating the differences therebetween, and then explaining why the subject matter of the claims would have been obvious to the person of ordinary skill in the art. Petitioner utterly fails to grapple with the extensive prior art or the disparate teachings contained in many of the relied-upon references. Moreover, apart from hindsight reasoning, Petitioner provides no alleged motivation that would have caused a person of ordinary skill in the art ("POSA") to combine those references in whatever combination Petitioner intended to convey. Even if these references are combined, it would not result in or suggest the patented invention.

Indeed, that the Petition-cited references are cumulative to the art cited and applied by the Examiner, that the Petition is futile, and that the Petition-cited references fail to establish a reasonable likelihood that any challenged claim of the

'376 Patent is unpatentable, are evinced by the grant of descendent U.S. Patent No. 12,311,079 B2 ("the '079 Patent"), with claims reciting "a decellularized extracellular matrix (ECM) derived from a Urodele", over both the art cited and applied during the prosecution of the '376 Patent, and also the herein-Petition, and Petition-cited references. EX-2014, claim 1.

Petitioner's request to institute *Inter Partes* Review should be denied.

II. DESCRIPTION OF THE STATE OF THE ART

Skin is the largest organ of the human body and is primarily made up of three layers: epidermis (upper layer), dermis (middle layer), and subcutaneous tissue (deepest layer). Skin contributes many important functions to the body, including protection, sensation, mobility, immunity, and water retention, among others. Maintaining skin integrity and possessing a robust wound healing capacity are key prerequisites for healthy survival. EX-1001, Abstract; EX-2005, p.148.

The structure of the skin is complicated and wound biology involves highly complex interactions between cells, growth factors, and extracellular matrix (ECM) components to reconstitute tissue following injury. The ECM is a network of extracellular proteins and other macromolecules secreted by cells that provides, among other things, structural and biochemical support to cells and tissues in the body. EX-2007, pp.1-2. It constitutes over 70% of the skin, and is the central hub for repair and regeneration of the skin. In view of this important role, tissue

engineers have developed a variety of techniques to engineer ECM and accompanying cutaneous tissue into porous scaffolds and grafts that mimic the structural and compositional aspects of the native tissue or organ microenvironment and that can be transplanted into damaged or diseased tissue. These transplantable products comprising synthetic and biological scaffolds that serve as a temporary replacement, both mechanically and functionally, for damaged, diseased or absent tissue during wound healing. EX-1001, 2:6-2:56.

These engineered tissue products can be categorized into three categories according to their source: xenografts (derived from heterologous animals), allografts (derived from another individual of the same species), or autografts (derived from the same individual), as well as synthetic biomaterials. The chemical, physical, and biological composition of these biological scaffolds can vary widely depending on the source of the starting material and, in turn, have a substantial impact on the material's ability to accelerate healing times, minimize scarring, and reduce pain. EX-1001, 2:6-2:56.

Historically, ECM-derived biological scaffolds were most often made from either mammalian tissue or synthetic materials. For example, because mammalian tissue grafts mostly share the mechanical properties (including strength, porosity and biodegradability) and biocompatibility with other mammal tissues, tissue engineers expected a reduced risk of immunogenicity and graft rejection. EX-1001, 2:16-35.

Moreover, ample supply of mammalian starting material is readily available through, *e.g.*, commercial slaughterhouses (including pig, bovine and horse), and can be decellularized using any number of known decellularization techniques. Thus, mammalian tissue was a common source of starting material.

Similarly, synthetic ECMs, as the name implies, were engineered from a variety of man-made chemical compounds (such as fibrous polymers and polymer/ceramic composites). Because synthetic scaffolds are engineered from man-made starting materials, they do not contain any living cells and can exhibit low antigenicity. EX-1001, 2:6-2:56. Moreover, these scaffolds have a longer (if not indefinite) shelf life, minimal storage requirements, are not limited by the availability of source materials, and essentially eliminate the risk of disease transmission and inter-sample variation. EX-1001, 3:7-40. Thus, synthetic materials were commonly pursued by tissue engineers as a starting source for scaffold materials. EX-1001, 3:7-40.

III. DESCRIPTION OF THE '376 PATENT

The '376 Patent teaches a novel non-mammalian biological scaffold biomaterial, and a method for making it, comprising intact ECM obtained from a urodele (*e.g.*, a salamander). The '376 Patent is grounded in Dr. Early's recognition that the skin and ECM of urodeles (*e.g.*, a type of salamander known as an "axolotl") possess desirable characteristics that, despite their small size, high cost and non-

mammalian lineage, make them an ideal source of biomaterial for xenograft production.

For example, Dr. Early recognized that, unlike the healing process used in adult mammals, the “axolotl process more closely resembles the scar-free healing process of fetal and embryonic wounds. Thus, such wounds likewise exhibit re-epithelialization and basement membrane reformation that occur at a faster rate (is ‘enhanced’) than do the corresponding events in postnatal mammals.” EX-1001, 4:29-35.

Axolotl skin also is rich in growth factors and antimicrobial peptides, similar to the amnionic membrane (AM) in mammals. Furthermore, axolotl ECM is immunoprivileged and contains collagen III and tissue inhibitors of metalloproteinases (TIMPs), also in resemblance to AM. EX-1001, 3:53-5:3.

Despite its amphibian roots, Dr. Early discovered that the urodele skin could be decellularized and the resultant urodele-derived biomaterial could be used to enhance restoration of skin homeostasis, to reduce the severity, duration and associated damage caused by post-surgical inflammation, and to promote progression of natural healing and regeneration processes in mammals. In addition, urodele-derived biomaterial promotes the formation of remodeled tissue that is comparable in quality, function, and compliance to undamaged human tissue. EX-1001, 5:4-23.

So, too, did Petitioner recognize the novelty and importance of Dr. Early's discovery. Even before the '376 Patent issued, Petitioner took a field-of-use license to the technology and retained its own counsel to assist with the prosecution of the application that issued as the '376 Patent and its foreign equivalents. Indeed, Petitioner directly engaged in substantive prosecution of the '376 Patent, including providing direct input into the claim language and amendments, and contributing financial support towards the prosecution of the now challenged claims. Petitioner further participated in the prosecution of related US and foreign applications, including the prosecution of a parent US application Serial No. 14/759,895 that matured into U.S. Patent No. 10,617,790 ("the '790 Patent") (which is the subject of PTAB case IPR2025-00620, also filed by Petitioner), as well as foreign equivalents of the '790 Patent. Indeed, Petitioner went so far as to file on its own a patent application (without Patent Owner's permission) descending from the '790 Patent claiming "A composition comprising decellularized Urodele extracellular matrix (ECM) having functional activity." EX-2019, claim 34; EX-2020 ¶9.

With Petitioner's prosecution assistance, the '376 Patent was granted on May 30, 2023 after more than four and half (4.5) years of prosecution of the parent '790 Patent, and more than three (3) additional years of prosecution of the application that issued as the '376 Patent. Notwithstanding that the axolotl, a Urodele, has been an intensively studied animal in the laboratory since at least the 1860's, no prior art has

been identified which disclosed, taught, or suggested using Urodele ECM to create a biological scaffold for use as a xenograft material. EX-2022, Abstract. Ultimately, the '376 Patent issued over numerous prior art references that are far more relevant to the claimed invention than the references cited by Petitioner, and that were applied by the Examiner more meaningfully than the application of references in the Petition.

A. The Challenged Claims.

The independent claims of the '376 Patent cover a tissue graft comprising ECM components derived from a Urodele. For example, independent claim 1 provides:

1. Decellularized extracellular matrix (ECM) derived from a Urodele
said decellularized ECM derived by:
 - a. obtaining a tissue sample from a urodele, which tissue sample comprises ECM; and
 - b. decellularizing said tissue sample to produce decellularized ECM by removing sufficient cellular components of the sample to reduce or eliminate antigenicity, making it suitable for use as a xenograft.

EX-1001, claim 1; *see also id.*, claim 31. The dependent claims add various other limitations describing certain tissue requirements, its composition, its source, various agents or growth factors that can be infused into the ECM, and select methods for making it. EX-1001, claims 2-30; 32.

B. Summary of the Relevant Prosecution History.

As discussed further in Section I below, the Petition's obviousness arguments are substantively the same as those considered and rejected during prosecution.¹ Thus, the Petition should be denied under 35 U.S.C. § 325(d).

The Examiner conducted four and half (4.5) years of careful and thorough prosecution of the parent '790 patent that included three (3) substantive Office Actions, two (2) RCEs, and three (3) expert Declarations based on these references and arguments, and more than three (3) additional years of prosecution of the application that issued as the '376 Patent. Beginning with a January 25, 2017 Non-Final Office Action (NFOA), the tissue graft claims were rejected on three grounds of anticipation under 35 USC 102(a) (*i.e.*, in view of Smith, Satoh, and Seifert), and one ground of obviousness under 35 USC 103 (*i.e.*, Asem in view of Siefert). In particular, the Examiner argued that the pending claims were anticipated because (i) Smith "teaches compositions comprising collagen (ECM components, decellularized ECM or fractions thereof) from *Ambystoma tigrinum* (a Urodele)"; (ii) Satoh

¹ Reference to the prosecution history in this Preliminary Response includes statements, amendments and art cited and overcome during prosecution of parent US application Serial No. 14/759,895, that matured into the '790 Patent (which is the subject of PTAB case IPR2025-00620, also filed by Petitioner). EX-2021.

“teaches acellular collagen sheets (ECM components, decellularized ECM or fractions thereof) from axolotl”; and (iii) Seifert “teaches an ECM from axolotl.” EX-2021, 584-587.

The Examiner further argued the claims were obvious based on Asem in view of Siefert asserting that “Asem teaches decellularized ECM comprising basement membranes” from, for example, amphibians, and that a POSA following Asem “would have been motivated to use any known functionally equivalent amphibian ECM” including axolotls because “Seifert teaches axolotl ECM and its basement membrane are useful for regenerative therapies and wound repair (abstract) as well as blueprints for healing in vertebrates.” EX-2021, 584-587.

In response, Patent Owner amended application claim 5 (which became patent claim 1), to recite that the graft is derived by a process that comprises obtaining a tissue sample from a urodele, which tissue sample comprises extracellular matrix and decellularizing said tissue sample to produce decellularized extracellular matrix by removing sufficient cellular components of the sample to reduce or eliminate antigenicity, which, with minor modifications, matured into the granted claim recitations. EX-2021, 630-658.

Nonetheless, in an October 18, 2017, Final Office Action (FOA), the Examiner maintained the Section 102 rejection based on Satoh, and the Section 103 rejection based on Asem in view of Seifert. EX-2021, 694-703. Patent Owner submitted an

expert declaration, by inventor Early, in response to the FOA and further amended pending claim 5 (issued claim 1) to state that the decellularizing that reduces or eliminates antigenicity makes the material therefrom suitable for use as a xenograft. The Examiner nonetheless maintained the grounds for final rejection, arguing that Asem in view of Seifert rendered the pending claims obvious because Asem disclosed a:

decellularized ECM comprising basement membranes (col. L, line 66 - col. 2, line 1-18, col. 5, line 23-39), derived from amphibians (col. 4, line 35-40); that the Asem ECM is said to be in the form of sheets that are adhered together (or laminated) (col. 6 line 20-32), powders (or particles) or reconstituted gels, made under alkaline conditions (col. 6, line 43-64); that the ECM compositions may be used as tissue grafts constructs (col. 4, line 30-35) or with cell culture comprising growth factors for culturing human (col. 11, line 40-45) cells (or are infused with, coated with, or attached to a growth factor) (col. 7-8) or as a coating wherein it is preferably sterilized prior to use (col. 7, line 30-45).”

EX-2021, 1040-42 (cleaned up).

Examiner acknowledged that “Asem does not teach the ECM wherein the amphibian is a Urodele, or axolotl”, but asserted that, “Seifert teaches axolotl ECM

and its basement membrane are useful for regenerative therapies and wound repair (abstract) as well as blueprints for healing in vertebrates (entire document)”. EX-2021, 1040-42.

As a result, Patent Owner submitted a second expert declaration from Ashley Seifert (the author of the Seifert publication discussed above), and further amended claim 5 (whereby it was placed in the form of granted claim 1) to affirmatively recite that the decellularizing produces decellularized extracellular matrix. Patent Owner explained that the process in Satoh does not result in removal of all cells from native axolotl skin, whereas the claims require decellularizing sufficiently to produce decellularized extracellular matrix that can be used as a xenograft. EX-2021, 837-1049.

Moreover, in response to the Examiner’s obviousness combination, Patent Owner’s expert, Dr. Seifert, explained that the reference teachings did not support the position that the Seifert material is a suitable substitute for the material used in Asem, including because there was no basis for believing that material from the species axolotl would be non-antigenic/immunogenic or suitable for use as a xenograft. Patent Owner’s expert asserted that prior art axolotl material was not processed adequately to remove cells and cellular debris, and that the Seifert process involved cross-linking, both compromising the immunoprivileged state of the extracellular matrix, rendering the material toxic and unusable as a xenograft. Also,

the Seifert reference was asserted to show that the axolotl ECM enhanced scarring and, thus, teach away from the invention. EX-2021, 1043-45. In response, the Examiner allowed the challenged claims. EX-2021, 1061-1067, 1110-1120, 1210-1263.

Surprisingly, despite the lengthy prosecution history involving references far more relevant to patentability than those cited in the Petition, neither Petitioner nor its expert, Dr. Badylak, undertook any discussion of Asem, Seifert, Smith or Satoh, whatsoever. Neither Petitioner nor its expert address the teachings of these references, or purport to explain why the references cited in the Petition (which disclose the same, or less relevant, subject matter) are not cumulative of the references overcome during prosecution. Nor does the Petition or Petitioner's expert discuss the numerous expert declarations submitted during prosecution that addressed the state of the art, distinguished the references cited by the Examiner, and provided support in favor of the patentability of the pending claims. Indeed, the sum-total of both the Petitioner's and its expert's analysis is a cursory two-paragraph summary of the prosecution history that concludes that "I understand that the primary references presented here were neither before the Examiner during prosecution, nor were they considered. I understand that while Van Dyke was disclosed during prosecution, it was not substantively evaluated by the Examiner."

The law requires more than mere citation of references that were not before the Examiner during prosecution. Rather, Petitioner has the burden to demonstrate that a reasonable Examiner would have considered the references now cited to be as relevant or more relevant to the question of patentability than those cited, asserted, and overcome during prosecution. Petitioner has failed to make any such showing as to the newly cited references; its request for IPR should be denied.

ARGUMENT

IV. PETITIONER HAS NOT ESTABLISHED A REASONABLE LIKELIHOOD OF PREVAILING ON ANY GROUND.

Petitioner's three Grounds present highly overlapping arguments, which are addressed together in this Section. Specifically, as best as one can understand the Petition, Petitioner advances the following grounds:

Ground	Claims	References	Secondary References
1 - §103	1-6, 9-12, 18-23 and 26-34	Badylak 2004, Badylak 2009, Freyman, McCusker, McGann, and Keating	None formally identified by Petitioner; Ground 1, claim 1 discussion in Petition (pp 29-41) additionally cites: Hoshiba, EX-1009; Hayashi, EX-1059; Gilbert 2006 EX-1010; Stocum 2002, EX-1024; Levesque 2010, EX-1030; Roy, EX-1029; Seifert, EX-1031; Stocum 1998, EX-1028; Choi, EX-1060; Ota, EX-1018; Freytes, EX-1038; Teebken, EX-1057
2- §103	6-8	Badylak 2004, Badylak 2009, Freyman, McCusker, McGann, Keating, and Gilbert	None formally identified; Petitioner's discussion of Ground 2 continues from its Ground 1 discussion
3- §103	14-16 and 24-25	Badylak 2004, Badylak 2009, Freyman, McCusker, McGann, Keating, and Van Dyke	None formally identified; Petitioner's discussion of Ground 3 continues from its Ground 1 and 2 discussions

In each Ground, Petitioner argues that the POSA would have started with between three to five “Mammalian ECM” references (Badylak 2004, Badylak 2009, Freyman, Van Dyke, and Gilbert), combined them with two “Newt Extract” references (McGann and Keating), and then further combined that combination with a “Fibroblast” reference (McCusker) to arrive at the claimed Urodele-derived ECM scaffold. To that jumble of teachings, Petitioner seeks to backfill missing support through an even more nebulous combination of up to eleven, or more, additional

secondary references, often simply cited by reference only to the exhibit number, leaving it unknown as to what portion(s) of the exhibit is the basis for the citation.

Petitioner's three Grounds all suffer from the same three fundamental flaws:

First, Petitioner's references are cumulative of the art already considered by the Examiner during prosecution, including art that is (i) far more relevant than the instant references, and (ii) includes the *very references* and *Petition* now before the Board (through citation to, and allowance over this art and these Petitions, in a daughter application). In total, the Examiner has found the challenged claims patentable not just once, but on *three* separate occasions, including during prosecution of the '376 Patent; prosecution of the parent '790 patent; and most recently during prosecution of the related '079 patent (which included both *all of the references and the Petition* at issue in this proceeding). Petitioner fails to undertake any analysis whatsoever of the extensive prosecution history.

Second, Petitioner fails to identify with particularity the specific combinations that allegedly render the challenged claims obvious, the differences between the claimed invention and the prior art, or set forth sufficient articulated reasoning with rational underpinning to support their proposed obviousness challenge. Plaintiffs do not purport to present a unified understanding of the myriad of factors impacting the successful creation and use of mammalian ECMs, much less those derived from an entirely separate taxonomic Class of animals, such as amphibians, Urodeles, or

axolotls. Petitioner's mélange of references leaves the work of ferreting out the actual combinations and support for its arguments to the Board. Petitioner's muddled approach is not a proper § 103 analysis. There is no analysis of each claim as a whole together with differences between the claimed subject matter and the prior art including identification of teachings in the primary and secondary references and application of prior art teachings to show why the differences would have been obvious. The Petition is grossly inadequate.

Third, Petitioner fails to account for the disparate teachings contained in many of the relied-upon references and provides no alleged motivation that would have caused a POSA to combine those references in whatever combination Petitioner intended to convey. Petitioner's prior-art alphabet soup is comprised of non-analogous references plucked from three disparate arts without any teaching, suggestion or motivation as to why a POSA would select these references as a starting point.

Each of these issues apply across all three of Petitioner's Grounds, and each independently justifies denying institution.

A. The Office Substantively Considered Substantially the Same Prior Art Raised in the Petition.

As discussed in detail below, the Petition advances a scattershot of references that fall into three disparate categories that are both cumulative of the art overcome during prosecution and, when read in full, in fact teach away from the claimed

invention. A detailed discussion of those references follows. From there, Patent Owner explains their cumulative nature, before then discussing Petitioner's failure to make its obviousness combinations explicit, how the references teach away from the claimed inventions, and the lack of any alleged motivation to combine their disparate teachings. In short, Petitioner fails to show that the art either teaches or suggests the present invention as recited in the patented claims.

1. Petitioner's "Mammalian ECM References"

Referring back to claim 1 as an example, Petitioner argues that a first category of prior art comprising Badylak 2004, Badylak 2009 and Freyman (collectively, the "Mammalian ECM references") "are all from the same field of endeavor – the use of xenogeneic ECMs". Petition at 34. This first category of Petition-cited references discloses the unremarkable concept that mammalian ECM can be used as a biological scaffold in connection with surgical wound repair. Of course, Patent Owner never disputed this concept was well-known in the art prior to the filing date of the '376 Patent, as this was *expressly* discussed during prosecution of the '376 Patent.

a. Badylak 2004

The first of the Mammalian ECM references, Badylak 2004, was authored by Petitioner's expert, Stephen F. Badylak. Badylak 2004 describes a whole host of important considerations that influence the viability and host response to mammalian engineered ECM scaffolds, including the structure, function and 3D organization of

the “source material” and the phenotype of the resident cells at the injury site, the “method of preparation” of the ECM, any “biologic response mediators” contained in the source material, and even the “biologically active degradation products” inherent to the ECM of the source material. EX-1005, Abstract, 370-373. Badylak 2004 cautions that any number of variables falling within each of these categories – many of which are unknown – can drastically impact the safety, efficacy and therapeutic benefit of the ECM scaffold. EX-1005, Abstract, 370-373.

For example, Badylak 2004 teaches that there is an “interrelationship” between the function performed by the source material, and the resultant properties of the ECM scaffold. That is, “[t]he composition and ultrastructure” of the source ECM are determined by factors that influence the phenotype of the cells that excrete it, “including mechanical forces, biochemical milieu, oxygen requirements, pH and the inherent gene expression patterns.” EX-1005, 367. In turn, the type of ECM scaffold used for a xenograft “influences the behavior and phenotype of the resident cells. Cell attachment, migration, proliferation and three-dimensional spatial arrangement are strongly affected by matrix composition and structure” of the ECM scaffold xenograft. EX-1005, 367.

Badylak 2004 cautions that, “[i]n spite of the extensive measures taken to decellularize” ECM scaffolds, “the complete elimination of all cell membrane and nuclear materials is very difficult and perhaps impossible.” EX-1005, 373. And,

even when processed properly, “the ECM contains biologic response mediators of the immune system that affect the host response to injury.” EX-1005, 372. These immuno mediators are present in the ECM itself as well as in the degradation products that are released during the host remodeling process. EX-1005, 372-373. Badylak 2004 explains that as the host organism begins to enzymatically breakdown and adsorb the ECM scaffold during the remodeling process, specific growth factors, peptides, and other chemically active degradation products are released at the injury site that impact the risk of bacterial infection, stimulation of angiogenesis, and attraction of host cells for tissue repair and reconstruction. EX-1005, 372-373. These degradation products, both naturally occurring and those resulting from the method of preparation, are critical to the viability and host response to ECM scaffolds. EX-1005, 372-373. Thus, a POSA reading Badylak 2004 would have been dissuaded from using non-mammalian materials given the large number of unknown considerations that influence its viability, including increased risk of immune response rejection to dissimilar foreign cells. EX-1005, 373.

Finally, Badylak 2004 highlights several notable practical considerations when considering sources of scaffold material precursors, “such as shelf life, cell sourcing and regulatory approval” which can “limit the utility of these devices in human patients.” EX-1005, 371. These practical limitations are amplified with non-mammalian xenografts.

b. Badylak 2009

Badylak 2009 picks up where Badylak 2004 left off: highlighting the myriad of unpredictable challenges faced by tissue engineers when creating ECM scaffolds. Badylak 2009 reinforces Badylak 2004's teaching that "ECM scaffolds consist of the structural and functional molecules secreted by the resident cells of each tissue and organ from which they are prepared. Therefore, the specific composition and distribution of the ECM constituents will vary depending on the tissue source." EX-1008, 2. While these biological scaffolds "are perfectly suited to support the cellular processes necessary for optimal function of the tissue and organ *from which they are harvested*", Badylak 2009 expressly cautions that "[t]he ability of an ECM harvested from one tissue to function as a biological scaffold material for the same or different tissue may vary." EX-1008, 2-3.

Further still, Badylak 2009 notes that "[t]he mechanisms by which biological scaffold materials promote site appropriate tissue reconstruction are not well understood and there is legitimate controversy concerning the relevant importance of the composition vs. structure of these materials." EX-1008, 2. Thus, in order to make an "[a]ccurate prediction[] of the biological functionality" of a particular ECM material, a POSA would first need to "understand[] the rate of scaffold degradation, the composition of the materials from which the biological scaffolds are constructed, and the nature of degradation products and their local and systemic distribution

following in vivo placement.” EX-1008, 10. These biological properties will vary not only from species to species, but even within the same species depending on the tissue type of the source material. EX-1008, 9-10.

Notably, despite being published five-years after Badylak 2004, Badylak 2009 identifies 28 different “commercially available biological scaffold materials” – *every one of which is from a mammalian source*:

Table 1
Commercially available biological scaffold materials

Product	Company	Material	Processing	Form
AlloDerm	Lifecell	Human skin	Natural	Dry sheet
AlloPatch®	Musculoskeletal Transplant Foundation	Human fascia lata	Natural	Dry sheet
Axis™ dermis	Mentor	Human dermis	Natural	Dry sheet
Bard® Dermal Allograft	Bard	Cadaveric human dermis	Natural	Dry sheet
CuffPatch™	Arthrotek	Porcine small intestinal submucosa (SIS)	Cross-linked	Hydrated sheet
DurADAPT™	Pegasus Biologicals	Horse pericardium	Cross-linked	Dry sheet
Dura-Guard®	Synovis Surgical	Bovine pericardium	Cross-linked	Hydrated sheet
Durasis®	Cook SIS	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet
Durepair®	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet
FasLata®	Bard	Cadaveric fascia lata	Natural	Dry sheet
Graft Jacket®	Wright Medical Tech	Human skin	Natural	Dry sheet
Oasis®	Healthpoint	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet
OrthADAPT™	Pegasus Biologicals	Horse pericardium	Cross-linked	Dry sheet
Pelvicol®	Bard	Porcine dermis	Cross-linked	Hydrated sheet
Peri-Guard®	Synovis Surgical	Bovine pericardium	Cross-linked	Dry sheet
Permacol™	Tissue Science Laboratories	Porcine skin	Cross-linked	Hydrated sheet
PriMatrix™	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet
Restore™	DePuy	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet
Stratasis®	Cook SIS	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet
SurgiMend™	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet
Surgisis®	Cook SIS	Porcine small intestinal submucosa (SIS)	Natural	Dry sheet
Suspend™	Mentor	Human fascia lata	Natural	Dry sheet
TissueMend®	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet
Vascu-Guard®	Synovis Surgical	Bovine pericardium	Cross-linked	Dry sheet
Veritas®	Synovis Surgical	Bovine pericardium	Cross-linked	Hydrated sheet
Xelma™	Molnlycke	ECM protein, PGA, water		Gel
Xenform™	TEI Biosciences	Fetal bovine skin	Natural	Dry sheet
Zimmer Collagen Patch®	Tissue Science Laboratories	Porcine dermis	Cross-linked	Hydrated sheet

EX-1008, 2, Table 1.

Indeed, Badylak 2009 contains no reference to any non-mammalian tissue source, much less an amphibian tissue source.

c. Gilbert

The third Mammalian ECM Reference, Gilbert, also includes Badylak as an author and, yet again, addresses the unpredictability of mammalian-sourced tissue

ECMs. Rather than sheet forms of ECM, Gilbert discloses “two methods to produce a particulate form of ECM from porcine urinary bladder.” EX-1032, Abstract.

Nonetheless, even with powdered ECMs (which are lyophilized and ground into 250 μm particles), Gilbert notes the impact of the source material on the end properties of the engineered ECM, stating that “the size, distribution and shape of the particles may differ depending on the source and composition of the ECM.” EX-1032, 1431.

Moreover, Gilbert again acknowledges the importance of “bioactive peptides... [and] active growth factors resident in” the source material “such as VEGF, bFGF, and TGF- β ” which are released into the wound area during the remodeling process. EX-1032, 1434. While Gilbert makes no reference to any non-mammalian source materials, a POSA would understand that the composition and relative concentration of these bioactive peptides and growth factors vary between mammalian and non-mammalian source tissue, and provide another level of uncertainty when trying to switch between the two, demonstrating the unpredictability of the art of ECM xenografts. EX-1032, 1431, 1434.

d. Freyman

Freyman teaches that “ECM is a complex structural entity surrounding and supporting cells... [that] affects cell function through mechanical and chemical signals.” EX-1015, 14. Freyman acknowledges that the decellularized ECM “provides a microenvironment and contains important biological materials that

promote the efficient and effective repair, regeneration and/or strengthening of cells, tissues or organs.” EX-1015, 13. As taught by the other ECM references, this microenvironment has a localized effect that directly impacts tissue reconstruction and healing at the wound site. EX-1015, 13-14.

Freyman discloses various methods of “biologically conditioning” the source tissue prior to harvesting in order to make the tissue over-express or under-express a particular biological property or material of interest. These “biologically conditioning” methods allow time for changes to the biochemical composition and histoarchitecture to occur. EX-1015, 23-29.

Contrary to Petitioner’s arguments, however, Freyman does not teach or suggest the use of amphibian tissue for xenographs. Petition at 18-21. Rather, Freyman’s singular reference to “amphibians” was made in context of allograph ECM wherein *both* the donor and recipient were of the *same species*:

Thus, the donor and the recipient can be of the same species. In other embodiments, donor ***and*** recipient are mammals, birds, reptiles, amphibians, or marsupials.

EX-1015, 16, ll. 26-34 (emphasis added). Freyman does not disclose using “amphibians” as a source of ECM tissue for xenographs, nor does Freyman contain any examples, discussion or disclosure of using amphibian tissue (much less specifically Urodele tissue) as a source for xenogeneic transplant into a human.

Rather, like Badylak 2004, Badylak 2009, Gilbert and the scores of references that came before, Freyman's focus remained on the use of domesticated mammalian sources for ECMs scaffolds (*e.g.*, cows, pigs, horses, cats, dogs, etc.). EX-1015, p.9 ll.1-5; p.20, ll. 24 - p.21, ll.6; p.47, ll.15- p.49, ll.18.

e. Van Dyke

Van Dyke is similar. Rather than exploring the potential to create decellularized ECM from alternative tissue sources, Van Dyke attempts to solve a perceived porosity problem related to bioscaffolds derived from "dense organ or tissue, such as muscle, tendons, ligaments... [and] cartilage." EX-1032, 2. Van Dyke explains that given the dense micro-architecture of these starting materials, the preparation and use of allogeneic grafts (*i.e.*, tissue taken from an animal of the same species but not the same genotype) and xenogeneic grafts (*i.e.*, tissue taken from an animal of a different species) for tissue regeneration "has shown that dense grafts with residual cells are difficult to seed *in vitro*, instigate prolonged inflammatory responses *in vivo*, and require longer times to incorporate into native tissue and remodel." EX-1032, 2. A similar problem, however, was not seen in autograft tissue (which is tissue taken from the same animal). EX-1032, 2.

While Van Dyke mentions in passing that "tissue that may be used to carry out the present invention may be from any suitable animal source, including human, other mammalian (*e.g.*, cat, dog, pig, cow, sheep, horse, monkey), avian (*e.g.*,

chicken, turkey, duck, good, etc.) reptile, amphibian”, Van Dyke contains no disclosure or teaching of any tissue scaffolds actually created from any avian, reptile, amphibian, not to mention Urodele tissue (which, in any event, is not dense and, thus, not the subject of Van Dyke). EX-1032, 8.

* * *

The ECM-related art cited by the Examiner – including Smith, Satoh, Asem and Seifert (discussed further below) – is far more relevant than Petitioner’s Mammalian ECM references and, yet, were expressly overcome during prosecution.

2. Petitioner’s “Newt Extract References”

The second category of references relied on by Petitioner – consisting of McGann (EX-1026) and Keating (EX-1027) – disclose a different, and unrelated, well-known concept: that certain animals, including the Urodele (*e.g.*, newts), Teleost Fish, Echinoderms and crustaceans, possess certain regenerative properties that allow them to re-grow certain amputated limbs or body parts. Again, the regenerative properties of these animals were well known in the art prior to the priority date of the ’376 Patent, *as was also discussed and overcome during prosecution.*

Apart from noting the well-known (but not well-understood) regenerative properties of these animals, Petitioner’s “Newt Extract references” teach the exact opposite of claimed inventions in the ’376 Patent. Rather than preserve intact ECM

for use as a tissue scaffold for xenotransplant (mammalian or otherwise) as claimed, the Newt Extract references seek to *digest* and *completely dispose* of any ECM material from the tissue source. That is, both of these references describe *protein extracts* that are obtained by *homogenizing* tissue, including axolotl tissue, in the presence of protease inhibitors and extracting and discarding any ECM components, to create a liquid extract containing cellular proteins. EX-1026, 13699-700; EX-1027, [0010]. These references have nothing to do with the present invention as they treat residual ECM as a waste product.

a. McGann

McGann sought to explore the undefined molecular and cellular mechanisms that govern epimorphic regeneration (*i.e.*, the ability to regenerate lost anatomical structures) by stimulating a mammalian mouse model with a liquid extract prepared from newt limb tissue. EX-1026, 13699. McGann begins by homogenizing and then *sterile-filtering* a sample of regenerating axolotl limb tissue. All “cell debris” from the axolotl limb tissue (which would include all components of the ECM) was “removed using two centrifugation steps.” EX-1026, 13699-700 (Preparation of Protein Extracts). The remaining supernatant was “filter sterilized through a 0.45-um filter” and assayed for protein concentration, while any and all components of the ECM (which comprise all the non-soluble collagens, fibrogens, and “cell debris” materials in the pellet) were *discarded*. EX-1026, 13699-700.

McGann then added an aliquot of the newt extract to cell medium of Mouse myotube cells growing in culture to measure whether the cells could be induced to revert back to less differentiated cells. EX-1026, 13699-700.

b. Keating

Keating contains the near identical disclosure as McGann. Keating is a published patent application filed by two of the same authors as McGann and is directed at “methods and compositions to induce cellular dedifferentiation and tissue regeneration *in vitro* and *in vivo*.” EX-1027, Abstract. Keating notes that the “molecular and cellular mechanisms that govern epimorphic regeneration are incompletely defined” and discusses the “significant disadvantages” arising from tissue engineering approach of the invention claimed in the ’376 Patent:

In addition, current bio-mediated tissue and organ replacement techniques also suffer from significant disadvantages. *Tissue engineering*, the approach of replacing tissue by culturing in vitro cells onto a biomaterial Substrate and then transplanting to an individual (a mammalian, preferably a human, Subject), *is hampered by cost, time, and the result is a structure that does not have all of the intrinsic functions and morphology of the tissue it replaces.*

EX-1027, [0005-0008] (emphasis added).

To solve these “significant disadvantages” with engineered ECM scaffolds (such as the claimed invention), Keating proposes “an *extract* from the newt, as well as *purified* components therefrom, can be used to achieve [dedifferentiating cells].” EX-1027, [0010]. Like McGann, the “protocol” in Keating describes the same process for creating a newt “regeneration extract” and includes homogenizing, removing, and discarding all ECM components:

Tissues are ground with a tissue homogenizer, hand homogenized, and then briefly sonicated. Cell debris [*e.g.*, all ECM components] is removed in two centrifugation steps. The nonsoluble lipid layer is aspirated and the remaining supernatant filter sterilized. The protein content is then assayed and the extract stored at -80 C.

EX-1027, [0130-0131].

* * *

Thus, the Newt Extract references are the antithesis of ECM xenograft use and production. Instead of exploring (or providing motivation to a POSA to explore) the use of axolotl ECM for tissue regeneration and repair, the Newt Extract references destroyed and discarded all ECM components resulting in a protein-rich supernatant that has nothing to do with the invention claimed in the '376 Patent.

3. Petitioner's "Fibroblast Reference"

The third category relied on by Petitioner – consisting solely of McCusker – stands alone in its disclosure. Unlike any of the Mammalian ECM References, the Newt Extract References, or the challenged claims – all of which seek to *remove* host cells and ECM either through a decellularization process (*i.e.*, the Mammalian ECM References and claimed invention) or cell lysis (*i.e.*, the Newt Extract references) – McCusker suggests that certain types of **cells** should be the “target for regeneration and rejuvenation therapies”. EX-1025, 569. Indeed, McCusker teaches that regeneration in axolotls “involves the spatial and temporal regulation of the behavior of fibroblast [cells] in order to balance the proliferation of undifferentiated blastema cells with the differentiation of these cell[s] to reform the connective tissues of the limb.” EX-1025, 570. Thus, rather than decellularized ECM materials of the claimed invention, McCusker teaches that use of axolotl fibroblast cells may be the key to successful limb regeneration and anti-aging. EX-1025, 569. Beyond acknowledging the well-known regenerative properties of axolotls – a concept recognized by the Examiner and never in dispute during prosecution or otherwise – McCusker teaches away from the invention claimed in the '376 Patent. EX-1025, 569.

* * *

In short, the three Mammalian ECM references (instructing the use of decellularized, intact *mammalian* ECMs), the two Newt Extract references (instructing the use of newt *protein extracts* that had ECM components *removed* therefrom), and the Fibroblast reference (instructing the use of *fibroblasts cells* to resist aging), disclose three different and conflicting approaches to tissue regeneration, which cannot be combined, and if combined, would not result in the invention disclosed and claimed in the '376 Patent.

B. The Office Substantively Considered Prior Art and Arguments Raised in the Petition and Petitioner Raises no New Patentability Issue Based on its Cited References

Discretionary denial is warranted because “the same or substantially the same prior art or arguments previously were presented to the Office,” and the Office did not err (materially or otherwise) in allowing the claims over the Petition’s asserted art. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020). The first part of the *Advanced Bionics* framework addresses whether the same prior art or arguments were previously presented to the Office. As relevant here, the Board considers “(a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination;” and “(d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on

the prior art.” *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (PTAB Dec. 15, 2017).

All three factors support denying institution, as prevailing on the merits based on settled law is not in Petitioner’s favor. In particular, (1) Petitioner’s primary references are substantially similar to the prior art involved during prosecution (and were the *same* references considered during subsequent prosecution, without the Examiner raising any new patentability concerns); (2) Petitioner’s primary references are at best cumulative of the references considered by the Examiner, and (3) Petitioner’s arguments overlap with the arguments made during examination.

1. Petitioner’s Mammalian ECM References Are Cumulative of Satoh, Smith, Asem and Seifert

All five of Petitioner’s Mammalian ECM references are cumulative of the art cited and applied by the Examiner during prosecution. Three out of the five Mammalian ECM references (*i.e.*, Badylak 2004, Badylak 2009, and Gilbert) exclusively describe ECM scaffolds derived from native *mammalian* ECMs. Badylak 2004 (EX-1005), Abstract (discussing the biologic response to mammalian ECM xenogeneic bioscaffolds); Badylak 2009 (EX-1009), Abstract (discussing “biological scaffold materials derived from the ECM of intact mammalian tissues”); Gilbert (EX-1032) at Abstract (discussing methods to produce “a particulate form of ECM from porcine urinary bladder”). While the two remaining ECM references, Freyman and Van Dyke, mention in passing the potential for non-mammalian source

materials, albeit in far less detailed disclosure than the art considered by the Examiner during prosecution.

The Examiner, however, had substantial literature before her related to ECM scaffolds not just from mammalian sources, but from more closely related amphibian sources, that was successfully overcome. Starting with the very first office action, the Examiner cited a litany of references (including Satoh, Smith, Seifert and Asem) concerning ECM derived from *axolotl* specifically. EX-2021, 584-587. The Examiner discussed Satoh, Smith and Seifert noting that they each “teach acellular collagen sheets (ECM components, decellularized ECM or factions thereof) from axolotl” and as such “anticipate the claimed subject matter.” EX-2021, 585. The Examiner further rejected the claims as obvious over Asem in view of Seifert. The Examiner noted that “Asem teaches decellularized ECM comprising basement membranes... derived from amphibians...[that] may be used as tissue graft[] constructs....” Moreover, while Asem generally disclosed “amphibian” source tissue, Seifert *specifically* “teaches axolotl ECM and its basement membrane are useful for regenerative therapies and wound repair....” EX-2021, 586-87. The Examiner argued that, “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... [and] it

would have been obvious to one of ordinary skill in the art to use ECM from axolotl in the compositions of Asem, since it was a known, functionally equivalent amphibian ECM and because of its known benefit in cellular regeneration.” EX-2021, 586-87.

The Examiner again cited and discussed these references in the three subsequent office actions on October 18, 2017, April 20, 2018, and January 10, 2019. The Examiner extensively discussed Satoh (EX-2003) for its teachings about “acellular collagen and ECM sheets (decellularized ECM) from axolotl (pg. 192)”, and reiterated her obviousness rejection over Asem in view of Seifert. As to the latter, the Examiner continued to rely on Asem “to teach decellularized ECM comprising basement membranes derived from amphibians... for use[] as tissue grafts constructs”, while “Seifert is relied upon to evidence that it would have been obvious to use Urodele or axolotl as a functionally equivalent amphibian ECM with a reasonable expectation of successfully obtaining a functional decellularized ECM.” EX-2021, 694-703, 824-835, 1061-1067.

Over the course of the next almost three years, the Examiner considered the scope, content and disclosures of these references at length, including consideration of an inventor declaration and two expert declarations, by the very same Dr. Seifert whose reference was relied on by the Examiner in rejecting the subject claims, discussing their teachings and the claimed invention. Ultimately, the Examiner

agreed with Patent Owner's arguments that the axolotl-derived ECM disclosed in Satoh was not sufficiently decellularized and resulted in a cross-linked ECM that did not "reduce or eliminate antigenicity of the biomaterial as a xenograft" as required by the claims. Moreover, the Examiner agreed that Patent Owner had demonstrated that the combination of Asem in view of Seifert did not render the claims obvious because Asem taught a specific type of tissue (follicular tissue collected from the eggs of amphibians) that was unique from other tissues in the prior art. Thus, the Examiner's assertion (repeated here by Petitioner) that "any known functionally equivalent ECM" could be substituted in its place was unsupported. Moreover, Seifert did not suggest anything to the contrary. Seifert teaches that one would avoid the presence of native ECM in promoting scar-free healing, teaching away from the combination suggested by the Examiner.

Thus, after years of thorough consideration of these references and the declaration evidence before her, the Examiner withdrew her rejections and issued the claims. As even a cursory review of the file history makes plain, the Examiner was well aware of the general principles underlying decellularizing amphibian tissues to create ECM scaffolds for wound repair, but nonetheless found the claims patentable over art that is far more on-point than the generic mammalian ECM materials disclosed in Badylak 2004, Badylak 2009, and Gilbert, or the passing-reference to potential non-mammalian source materials found in Freyman and Van Dyke. Indeed,

as discussed above, the references cited in the Petition – including many by their Declarant – in fact *support*, rather than call into question, the patentability of the challenged claims. Because Petitioner’s Mammalian ECM references “teach[] no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO,” those references are cumulative. *Roku Inc. v. Universal Electronics, Inc.* IPR2019-01619, Paper 11 at 16 (PTAB Apr. 2, 2020) (quoting *Regeneron Pharms. v. Merus N.V.*, 864 F.3d 1343, 1350 (Fed. Cir. 2017)).

2. Petitioner’s Newt Extract References Are Cumulative of Smith

While Petitioner’s Newt Extract references have little to do with the challenged claims, they too are cumulative of the art and arguments previously before the Examiner. Specifically, the Examiner explored the same arguments and approach that Petitioner relies on these references for in the context of the Smith reference during original prosecution. Thus, to the extent they have any relevance, the Newt Extract references are entirely cumulative of Smith.

Indeed, in the very first office action, the Examiner rejected the claims under §102 as anticipated by Smith. The Examiner (incorrectly) argued that “Smith teaches compositions comprising collagen (ECM Components, decellularized ECM or fractions thereof) from *Ambystoma tigrinum* (a Urodele)” which the Examiner considered to also include any product by process type limitations in the claims. In response, Patent Owner explained that the Examiner’s reliance on Smith was

mistaken; rather than teach a decellularized ECM matrix, Smith, in fact, teaches the use of a *collagen protein extract* derived from isolating and purifying Urodele tissue that is completely devoid of any ECM components. Specifically, the “Materials and Methods” section of Smith discloses that “the skins and cartilage dissected from other tissues” on the newt and “were subsequently extracted in 0.4 ionic strength phosphate buffer, pH 7.6, and three changes of 0.5 M acetic acid. Each extract was clarified by centrifugation, and *the collagen in the supernatant was purified.*” EX-2002, 244. Accordingly, Patent Owner explained that any ECM that existed in the starting material of Smith is actually completely destroyed and discarded by the extraction that Smith conducts. EX-2021, 647-648.

In response, the Examiner withdrew any rejections over Smith and, thus, acknowledged its lack of relevance to the challenged claims. EX-2021, 695-703; 706-758. The same result is warranted here. Petitioner’s reliance on the Newt Extract references – which disclose the same collagen protein extract derived from isolating and purifying Urodele tissue that is disclosed in Smith – is no different than the art already before the Examiner and overcome during prosecution, and has no relevance to the patentability of the challenged claims.

3. All of Petitioner's References Are Cumulative of Art Considered During Prosecution of Family-Member Patent Applications

The art relied on by Petitioner is not only *cumulative* of the references considered and overcome in prosecution of the '376 Patent but, in fact, was directly cited during Patent Owner's prosecution of a related pending application before the same Examiner, and issued to patent without rejection. Indeed, in connection with the prosecution of the '079 Patent (which issued from a continuation application claiming priority back to the challenged patent), Patent Owner made of record not only the Petitioner's references, but also the full IPR Petition in this case, the IPR Petition in related IPR2025-00620, and all of the references cited in both IPR Petitions, along with the references of record in the '376 and '790 Patents. The Examiner indicated consideration on the record of Petitioner's cited references, and Petitions, without rejection, and on May 27, 2025, the USPTO granted the '079 Patent. EX-2014, pg. 2 (references cited).

The claims of the newly issued '079 Patent recite a similar invention to that of the '376 Patent that includes, *inter alia*, "a decellularized extracellular matrix (ECM) derived from a Urodele." EX-2014, claim 1. The Examiner signed off as considered and made of record all of the art underlying the Petition, and granted the claims of the '079 Patent, demonstrating the Examiner's opinion that the herein Petition-cited art is cumulative to that already considered and overcome during prosecution. *See*

e.g., *Advanced Bionics*, Paper 6 at pg. 10 (holding that, although *Becton, Dickinson* factors (a), (b) and (d) “pertain to art evaluated ‘during examination,’ these factors more broadly provide guidance as to whether the art [and arguments] presented in the petition are ‘the same or substantially the same’ as the prior art [and arguments] previously presented to the Office during *any* proceeding.”) (emphasis original).

C. The Petitioner Cannot Demonstrate that the Office Erred in a Manner Material to the Patentability of the Challenged Claims

Petitioner cannot satisfy the second part of the *Advanced Bionics* test because it does not demonstrate that the Office erred in a manner material to patentability in allowing the challenged claims. Under *Becton Dickinson*, the Board looks to

(c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; . . . (e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson, IPR2017-01586, Paper 8 at 17-18. These factors weigh against institution, as the cited art was evaluated closely during examination, and Petitioner has failed to establish that the Examiner erred.

1. Petitioner's Art and Arguments Were Closely Evaluated

As shown above, the Examiner had art more relevant than Petitioner's Mammalian ECM, Newt Extract and Fibroblast related art before her, and highlighted precisely the same points in those references that Petitioner now raises. *Supra* Section IV.B. The Examiner also had extensive literature related to axolotl ECMs, the regenerative abilities of axolotls, and extracts from homogenized axolotl tissue, and thoroughly considered the purported combinations now urged by Petitioner. *Id.* The Examiner addressed those references extensively, particularly the Satoh, Smith, Asem and Seifert references that thoroughly discuss axolotl and amphibian-based ECMs. As such, there is every indication that Petitioner's arguments were considered carefully during examination, and not found persuasive. This weighs against institution. *Puma N. America v. Nike, Inc.*, IPR2019-01042, Paper 10 at 11 (PTAB Oct. 31, 2019).

2. Petitioner Fails to Identify Any Material Error that Warrants Reconsideration.

It has been well established that the Board may exercise its discretion to deny institution in circumstances where a petitioner does not address whether the Office materially erred. *See Wolfspeed, Inc. v. The Trustees of Purdue Univ.*, IPR2022-00761, Paper 9 at 14-15 (PTAB Nov. 8, 2022) (denying institution when petitioner did not address whether the Office materially erred); *see also Darfon Elecs. Corp. v. Michael Shipman*, IPR2022-01008, Paper 11 at 14 (PTAB Dec. 2, 2022) (same).

Yet, in addressing the second prong of *Advanced Bionics*, the sum-total of Petitioner’s analysis of *Becton Dickinson* Factors (c), (e) and (f) amounts to a single incorrect allegation that “the Examiner failed to make an obviousness rejection over, for instance, the Ground I References” cited in the Petition. Petition at 72-73. Even putting aside the fact that Petitioner does not even mention any alleged “error” pertaining to its Ground II and III References (which should be dispositive of those Grounds), Petitioner’s sole conclusory statement regarding the Ground I References cannot satisfy its burden to show material error. *See, e.g., ABS Global, Inc. v. Cytonome/ST, LLC*, IPR2021-00306, Paper 13 at 13-14 (PTAB June 7, 2021) (Argument that “the Examiner did not apply [a] reference” was insufficient because petitioner did “not point[] out any specific disclosure from [the reference] that was overlooked by the Office.”); *Vital Connect, Inc. v. Bardy Diagnostics, Inc.*, IPR2023-00381, Paper 7 at 19 (PTAB July 11, 2023) (Argument that grounds were “not previously considered and/or applied by the Examiner..., without any further analysis, cannot persuade us of material error.”).

Here, Petitioner fails to even make the bare allegation that the purported error was material, much less identify in its § 325(d) analysis what teachings purportedly were misapprehended or overlooked. Indeed, neither Petitioner (nor its expert) makes any attempt to discuss or distinguish any of many references cited during prosecution. The Acting Director, in *Ecto World*, rejected a similar invitation—to

search Petitioner’s discussion of the grounds for an argument in this regard—determining that petitioner’s “generalized statements as to the strength of its [p]etition fail to identify sufficiently a material error.” *Ecto World, LLC and SV3, LLC v. RAI Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 at 4-6 (PTAB, May 19, 2025) (predental as to Section A). *Ecto World* clarifies that “a petitioner must explain, with reference to *Becton Dickinson* factors (c), (e), and (f), how the Examiner erred in overlooking the prior art.” *Id.*, Paper 13 at 5. Cf. *Ecto World*, Paper 13 at 6 n.2 (“Petitioner’s suggestion that the Board should have scoured the Petition to cobble together an argument under the second part of *Advanced Bionics* improperly shifts Petitioner’s burden to demonstrate material error onto the Board.”); *Advanced Bionics*, IPR2019-01469, Paper 6 at 8-9 (where “the petitioner fails to make a showing of material error, the Director generally will exercise discretion not to institute *inter partes* review”); see also *Becton, Dickinson*, IPR2017-01586, Paper 8, at 17-18 (factor (e), relating to “whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art”).

Even if the Board were to “scour” the Petition, no alleged “material error” would be found. In fact, Petitioner’s only alleged “error” by the Examiner was *not* material at all, because there was no error. Under *Becton, Dickinson* factor (e), no “error” occurs where the Examiner considered equivalent references for the

purported disclosure of elements known in the art. *Sony Interactive Entm't LLC v. Terminal Reality, Inc.*, No. IPR2020-00711 (PTAB Oct. 13, 2020).

In *Sony*, the Board denied institution despite the fact that one of the asserted references was not considered during examination. *Id.* at *5. This is because in the petition, the previously unused reference was “relied on for simply teaching an ‘accumulation buffer.’” *Id.* As the Board explained, the Examiner had relied on another, equivalent reference disclosing an accumulation buffer. *Id.* Because the Examiner relied on this equivalent reference, the Board found that the Examiner’s lack of consideration of the new reference was not a material error. *Id.*

The Board reached the same result applying the same rationale in *Gardner Denver, Inc. v. Utex Indus., Inc.*, IPR2020-00333, Paper 12 (PTAB Aug. 5, 2020). There, the Board acknowledged that references in the petition “were not presented to the Office during prosecution.” *Id.* at 8. The Board denied institution anyway because “other disclosed references containing substantially similar teachings” were presented (*id.* at 8) and the Petition did not identify material errors in the Examiner’s consideration of those substantially similar references. *Id.* at 16-17.

Here, as in *Sony* and *Gardner*, the Examiner did not “err” by not considering the “Ground I References” — she simply relied on equivalent references for the same teachings. As set forth above, the Examiner relied on Satoh, Smith, Asem and Seifert for disclosure concerning amphibian-based decellularized ECM scaffolds for

wound repair. These references are not just “equivalent”, but in fact more relevant, to the claimed invention than the Mammalian ECM references relied on in the Petition.

Similarly, the Examiner considered Smith for its disclosure of a protein extract derived from newt tissue, and determined that it was not relevant to the claimed invention. Smith is almost identical to the disclosures in the Newt Extract references cited by Petitioner. The mere fact that the Examiner did not explicitly consider (unknown combinations) of the Ground I references in connection with the various claim elements was not material error, and does not warrant institution.

This is particularly true where, here, Petitioner argues that all of the claim elements were generally known in the art. *See e.g.*, Petition at 14 (“decellularization and related processing methods for ECM scaffolds were well studied and had become standard practice for producing functional xenogeneic ECM scaffolds by January 2013.”), 17 (Due to their exceptional regenerative capacity, urodeles have been widely studied for potential applications in regenerative medicine.... One of the most well-studied urodele species is axolotl (*Ambystoma mexicanum*), which by January 2013 had become a model organism for understanding the molecular and cellular mechanisms of regeneration.). Petitioner does not identify any error in the Examiner’s analysis of Satoh, Smith, Asem or Seifert with respect to the scope of the

challenged claims, much less any error that would be addressed by considering (again, unknown combinations of) the Ground I References instead.

Finally, as noted above, the Examiner *did* consider the Petitioner's art, purported combinations, and its Petition during prosecution of the related '079 patent, and nonetheless found similar claims patentable. Thus, because the Petition does not establish the unpatentability of any claim, it follows that the Examiner committed no error in declining to apply the asserted Ground I prior art during prosecution of the '376 Patent and institution should, therefore be denied.

D. Petitioner Fails to Make its Obviousness Combinations Explicit

The Board should deny institution for the additional reason that Petitioner failed to make its obviousness evaluation explicit. Both the Patent Statute and established Federal Circuit law emphasize that “[i]t is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify ‘with particularity’ the ‘evidence that supports the grounds for the challenge to each claim.’” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016); 35 U.S.C. § 312(a)(3) (requiring that IPR petitions identify “with particularity, each claim challenged, the grounds on which the challenges to each claim are based, and the evidence that supports the grounds for challenge to each claim.”). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any

differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). The four *Graham* factors are not alternatives; all four factors must be analyzed. *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012).

The statutory requirement for particularity in a petition for IPR takes on heightened importance when considered in conjunction with *SAS*'s "all-or-nothing" approach. *See SAS Institute Inc. v. Iancu*, 138 S. Ct. 1348, 1355 (2018). Under 35 U.S.C. § 314(a) and *SAS*, an IPR can be instituted only if there is a reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314(a). Thus, the Board is required to make "a binary choice—either institute review or don't." *SAS*, 138 S. Ct. at 1355; *see also* Guidance on the Impact of *SAS* on AIA Trial Proceedings (April 26, 2018) (explaining that "the PTAB will institute as to all claims or none" and "if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition").

Because the Board's practice, in light of *SAS*, is to institute on all grounds asserted in a petition, the Board may consider whether a lack of particularity as to one or more of the asserted grounds justifies denial of an entire petition. For example, where a petition contains voluminous or excessive grounds, Office guidance indicates "[t]he panel will evaluate the challenges and determine whether, in the

interests of efficient administration of the Office and integrity of the patent system (*see* 35 USC § 316(b)), the entire petition should be denied under 35 USC 314(a).” *SAS* Q&As (June 5, 2018) (“*SAS* Q&As”), 11 at Part D, Effect of *SAS* on future challenges that could be denied for statutory reasons, Question D2.

Yet, despite these hornbook requirements, and the implications of *SAS*, Petitioner does not perform any of the requisite analysis. Petitioner does not identify with any specificity what limitations are missing from any of the six to eight primary references relied upon, or how a person of ordinary skill in the art would have modified those references to supply those missing elements.

Take, for example, claim 1. Petitioner argues that “[t]he *cumulative* teachings of the [six] Ground I References [which, also apparently includes the more than *eleven* additional secondary references]... would have motivated a POSA to select urodeles, and axolotl in particular, as a source of xenogeneic ECM.” Petition at 34. Petitioner never articulates which of the six primary references discloses each of the claim elements or how, or why, a POSA would combine these references with the more than eleven secondary references. Nor does Petitioner explain what is missing from each of the references that would lead a POSA to a second, and then a third, and then a fourth, and then a fifth, to ultimately needing six primary references and eleven or twelve secondary references.

Instead, Petitioner relies on the overarching “cumulative teachings of the Ground I References” to suggest that if *any* element of a claim is missing from any reference, that element could be readily substituted by the disclosure of anyone of the other five references, without more. Petitioner seems to mix and match references at-will, without articulating specific reasons to combine the references in any particular combinations proposed. Critically, however, the Petition fails to specify what Petitioner regards as the difference(s) between any of the six “Ground I References” and the challenged claims. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966) (requiring that the differences between the prior art and the claims at issue be ascertained as part of an obviousness analysis). Petitioner’s whack-a-mole approach glosses over the full context of their teachings, and fails to identify which reference Petitioner purports to rely on to provide support for the specific limitations in the challenged claims.

The lack of particularity and volume of issues raised by the Petition is further aggravated by Petitioner’s so-called “secondary references.” While the extent to which these additional documents may be relied upon to fill gaps in the asserted references with respect to the claimed subject matter is unknown from the Petition, it is nonetheless clear that such undefined reliance turns the Petition into an empty invitation for the Board and Patent Owner to search the record for evidence that might support the full breadth of Petitioner’s contentions. Petitioner’s “catch-all”

approach attempts to require both the Board and Patent Owner to address whether each and every claim limitation is taught not only by each of six Ground I references, but by each of these six references in combination with one or more of the other eleven or twelve secondary reference asserted in the proceeding. In this way, Petitioner's "catch-all" ground is not reasonably bounded in scope and unduly burdensome for both Patent Owner and the Board to address.

Moreover, the lack of particularity is not limited to Petitioner's "Ground I" challenge. Petitioner's second and third obviousness grounds also suffer from a lack of particularity that results in voluminous and excessive grounds. For each of Petitioner's Grounds II and III, Petitioner separately relies on yet another "primary reference" on top of the six "Ground I" references (eight in total), in addition to the large number of secondary references sprinkled throughout. As such, Petitioner's Grounds II and III result in a multiplicity of grounds for the same reasons discussed above. Nor does Petitioner explain why it needs to assert so many grounds and references to show unpatentability of relatively limited number of distinct challenged claims, which confirms that the Petition imposes an undue burden on Patent Owner and the Board.

Having failed to identify the specific combinations being proffered, Petitioner demands that the Board (and Patent Owner) take it upon themselves to intuit the differences between the challenged claims and the references based on the Petition's

conditional assertions and various exhibits. Petitioner’s attempt to shift the burden on the Patent Office to articulate unstated arguments, rather than evaluate the soundness of a few well supported arguments, fails to adhere to the foundational requirement to identify “‘with particularity’ the ‘evidence that supports the grounds for the challenge to each claim’” (*Intelligent Bio-Sys.*, 821 F.3d at 1369) and, thus, “fail[s] to adequately state a claim for relief” (*Liberty Mut. Ins. Co. v. Progressive Casualty Ins. Co.*, Case CBM2012-00003, slip op. at 3 (PTAB Oct. 25, 2012) (Paper 7) (representative)). *See also KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007) (“[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). Therefore, the Petition should be denied for failing to establish that Petitioner is entitled to relief. 35 U.S.C. § 312(a)(3); 37 C.F.R. § 42.20(c).

E. Petitioner Fails to Address the References as a Whole

As the Board is well-aware, an obviousness determination is based on whether “the differences between the claimed invention and the prior art are such that the claimed invention as a whole....” 35 U.S.C. § 103(a). Thus, focusing the §103 inquiry on a particular aspect of the invention that differs from the prior art improperly disregards the “as a whole” statutory mandate. MPEP §2141.02; *see*

Jones v. Hardy, 727 F.2d 1524, 1530 (Fed. Cir. 1984); *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004) (The “as a whole” instruction in title 35 prevents evaluation of the invention part by part. ... This form of hindsight reasoning, using the invention as a roadmap to find its prior art components, would discount the value of combining various existing features or principles in a new way to achieve a new result - often the very definition of invention.”); *Princeton Biochemicals, Inc. v. Coulter, Inc.*, 411 F.3d 1332, 1337 (Fed. Cir. 2005); *Allergan, Inc. v. Apotex, Inc.*, 754 F.3d 952 (Fed. Cir. 2014).

Similarly, in ascertaining whether the claimed subject matter as a whole would have been obvious, the Examiner must also determine the content of the prior art “as a whole.” *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550-1552 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984); *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965) (“It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.”); *see also Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 449-49 (Fed. Cir. 1986) (holding that the district court, by failing to consider a prior art reference in its entirety, ignored portions of the reference that led away from obviousness).

Despite these statutory cannons prohibiting hindsight reasoning, Petitioner engages in textbook hindsight, picking and choosing “helpful” statements from references in isolation from their full context and using the claims as an instruction manual to reconstruct the invention. Apart from a few select statements, Petitioner ignores the full teachings of these references which teach away from the claimed invention.

1. Petitioner Ignores the Teachings of the Mammalian ECM References

Petitioner asserts that “based on Badylak 2004, Badylak 2009, and Freyman, a POSA would have known that xenogeneic ECMs from a wide variety of sources had been successfully used in humans and that these varied xenogeneic ECMs were efficacious because the components of ECMs are conserved across species.” Rather than suggest that a “wide variety of sources” can be used for xenogeneic ECMs, these references focus on mammalian ECMs and highlight the uncertainty and potential problems of using other ECM source materials.

For example, Badylak 2004 cautions that, even among the known category of mammalian engineered ECM scaffolds, there is a sea of important considerations that impact the safety, efficacy and therapeutic benefit of the ECM scaffold, including the structure, function and 3D organization of the “source material”, the phenotype of the resident cells at the injury site, the “method of preparation” of the ECM, any “biologic response mediators” contained in the source material, and even the

“biologically active degradation products” inherent to the ECM of the source material, among others. EX-1005, Abstract, 370-373. Badylak 2004 warns that, “[i]n spite of the extensive measures taken to decellularize” ECM scaffolds, “the complete elimination of all cell membrane and nuclear materials is very difficult and perhaps impossible.” EX-1005, 373. Even if cellular material could be completely removed, Badylak 2004 teaches that the ECM itself “contains biologic response mediators of the immune system that affect the host response to injury” including growth factors, peptides, and other chemically active degradation products are released as the host organism begins to break down and absorb the ECM during the remodeling process. EX-1005, 372. Badylak 2004 cautions that these degradation products, both naturally occurring and those resulting from the method of preparation, impact the risk of bacterial infection, stimulation of angiogenesis, and attraction of host cells for tissue repair and reconstruction in ways that are critical to the viability and host response to ECM scaffolds. EX-1005, 372. Petitioner, however, ignores all of these considerations.

Petitioner’s reliance on Badylak 2009 only further highlights its incomplete analysis. Badylak 2009 was published five years later by the same author of Badylak 2004, yet reinforces the myriad of unpredictable challenges still faced by tissue engineers. Badylak 2009 expressly acknowledges that “[t]he mechanisms by which biological scaffold materials promote site appropriate tissue reconstruction are not

well understood...” EX-1008, Abstract. Badylak 2009 highlights a host of considerations a POSA would need to understand in order to make an “[a]ccurate prediction[] of the biological functionality” of a particular ECM material, including “understand[ing] the rate of scaffold degradation, the composition of the materials from which the biological scaffolds are constructed, and the nature of degradation products and their local and systemic distribution following in vivo placement.” EX-1008, 10. Badylak 2009 explains that these biological properties will vary not only from species to species, but even within the same species depending on the tissue type of the source material. EX-1008, 5.

Yet, despite the litany of considerations that Petitioner’s own expert identified as essential to understand, Petitioner fails to address *any* of these considerations in its Petition, much less demonstrate that all of those variables were resolved and known in the art by a POSA prior to the priority date of the ’376 Patent. Moreover, Petitioner further ignores Badylak 2009’s ultimate conclusion that “[i]t is now recognized that mammalian extracellular matrix represents an excellent scaffold material suitable for many therapeutic applications.” EX-1008, 10. In short, nothing in Badylak 2009 suggests that amphibian source tissue would be better, would be worth trying, and if tried, that there would be any expectation of success.

Similarly, Freyman provides Petitioner no shelter. Contrary to Petitioner’s argument that “Freyman discloses that the ECM material can be derived from any

suitable animal body tissue of xenogeneic origin [including].... amphibians”, nowhere does Freyman teach or suggest the use of amphibian tissue for xenographs. Petition at 31. The singular reference to “amphibians” in Freyman was made in context of allograph ECM wherein *both* the donor and recipient were of the *same species*:

Thus, the donor and the recipient can be of the same species. In other embodiments, donor *and* recipient are mammals, birds, reptiles, amphibians, or marsupials.

EX-1015, ll. 26-34 (emphasis added). Freyman focuses instead on the “localized effects” resulting from the “microenvironment” that the ECM creates, and discloses various methods of “biologically conditioning” the source tissue prior to harvesting in order to make the tissue over-express or under-express a particular biological property or material of interest. EX-1015 [Field of Invention] (“The present invention relate generally to... injecting or implanting decellularized extracellular matrix of *conditioned* body tissue directly into the site where treatment or therapy is desired.”) (emphasis added). Petitioner ignores the teachings of Freyman as a whole because Freyman’s focus on *preconditioning* mammalian body tissue has nothing to do with the claimed invention. Instead, Petitioner focused (incorrectly) only on Freyman’s passing reference to an “amphibian” allograph because it cannot explain how Freyman’s actual teachings could possibly apply in the asserted combination (to

the extent it can be understood). This “pick and choose” analysis has been rejected time and time again. *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965) (“It is impermissible [under section 103] to pick and choose from any one reference only so much of it as will support a given position.”); *In re Hedges*, 763 F.2d 1038, 1041 (Fed. Cir. 1986).

2. Petitioner Ignores the Teachings of the Newt Extract References

Petitioner’s *a la carte* reasoning continues in its application of the Newt Extract references; ignoring their teachings as a whole in favor of select statements that Petitioner takes out of context to create the appearance of a cohesive ground for obviousness. Not only does Petitioner erroneously pick and choose its support, but the Newt Extract references teach the exact opposite approach from the claimed inventions.

Petitioner relies on McCusker, McGann and Keating to supply support for the “known superior regenerative properties of urodeles” and that “the signaling pathways involved in axolotl regeneration were conserved across species, including humans.” Petition at 35. Not only were these properties known in the art (and considered by the Examiner during prosecution), but they have little to do with the full teachings of these references.

Indeed, while McCusker speculates that “many of the biological processes and the signaling pathways that control [regenerative processes] are highly conserved

among all tetrapods”, the full context of McCusker raises more questions than it answers and ultimately suggests an approach – seeding with Fibroblast cells – that has nothing to do with the claimed inventions. EX-1025, 565.

As an initial matter, McCusker focuses on aging; not tissue regeneration and, thus, explores an entirely different subject matter from wound healing. EX-1025, 565 (focusing on how the axolotl regeneration mechanisms “could be utilized to reverse the aging process”). Nonetheless, to the extent McCusker comments on regeneration, it begins by acknowledging that the mechanisms of axolotl regeneration are neither understood nor have they “led to the anticipated and desired breakthroughs in terms of inducing regeneration in humans.” EX-1025, 566 (further cautioning that “it is not surprising that attempts to induce regeneration in a non-regenerating animal with a single factor or treatment have been unsuccessful”). Notably, McCusker notes that “[i]ronically, studying animals that can regenerate also has failed to provide useful insights into potential therapies.” *Id.* Nowhere does McCusker discuss, much less suggest, the use of ECM derived from an axolotl for wound repair. To the contrary, McCusker teaches that “Fibroblasts are the target for regeneration and rejuvenation therapies”, not ECMs.

Nor do either McGann or Keating attribute the regenerative ability of the axolotl to its ECM. Instead, both McGann and Keating focus on the axolotl’s ability to dedifferentiate their cells (*i.e.*, the ability of a differentiated cell to revert back to a

less differentiated state). EX-1026, 13699 (exploring whether “mouse myotubes can dedifferentiate when stimulated with an extract prepared from newt regenerating limb tissue”); EX-1027, Background (“The present invention is directed to compositions that promote cellular dedifferentiation and tissue regeneration.”). These references investigated the suspected causes underlying the lack of cellular plasticity in mammalian cells by examining the effect of a liquid extract derived from newt regenerating limbs on terminally differentiated mouse cells in culture. The authors ultimately concluded that the “dedifferentiation signal is comprised of protein”; not ECM. EX-1026, 13702; EX-1027, [00270].

Not only are the newt homogenates taught in McGann and Keating centrifuged and filtered to remove any and all components of the ECM (and, thus, have nothing to do with the claimed invention), but Keating goes a step further, expressly noting the “significant disadvantages” arising from tissue engineering approach of the invention claimed in the ’376 Patent:

In addition, current bio-mediated tissue and organ replacement techniques also suffer from significant disadvantages. *Tissue engineering*, the approach of replacing tissue by culturing in vitro cells onto a biomaterial Substrate and then transplanting to an individual (a mammalian, preferably a human, Subject), *is hampered by cost, time,*

and the result is a structure that does not have all of the intrinsic functions and morphology of the tissue it replaces.

EX-1027, [0005-0008] (emphasis added).

Petitioner makes no effort to address this disclosure in Keating – or any of the teachings in the Newt Extract references – apart from the already well-known concept that axolotls are one of many animals (including *e.g.*, teleost fish, starfish, flatworms, hydra, crustaceans and salamanders) capable of regenerating limbs. This type of reasoning—where relevant parts of the reference are disregarded for the proposed combination without sufficient explanation of why a person of ordinary skill would do so—is precisely the type of hindsight reasoning that must be rejected. *See e.g., Grain Processing Corp. v. Am. Maize-Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988) (“Care must be taken to avoid hindsight reconstruction by using ‘the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.’”) (quoting *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed. Cir. 1983)).

Petitioner has not explained why a POSA, without the claims in front of them, would have been motivated to take the mammalian ECM materials disclosed in Badylak 2004, Badylak 2009, and Freyman, and merge them with the newt extracts disclosed in Keating and McCann, and the fibroblast cells taught in McCusker, in

any manner that would result in a decellularized ECM scaffold derived from an Urodele, as claimed. To the extent that any rationale can be derived from the Petition for its proposed combinations, at best Petitioner suggests is that a POSA *could* have done it, but “[t]his type of piecemeal analysis is precisely the kind of hindsight that the Board must not engage in.” *In re NTP, Inc.*, 654 F.3d 1279, 1299 (Fed. Cir. 2011); *see also Belden, Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (“Obviousness concerns whether a skilled artisan not only could have made but would have been motivated to make the combinations or modifications of prior art to arrive at the claimed invention.”).

Petitioner’s analysis of Grounds II and III all rely on the same principles, and fail to show by a preponderance of the evidence that challenged claims are obvious for the same reasons. Petitioner fails to meet its burden to demonstrate that a POSA would have had a reason to combine Badylak 2004, Badylak 2009, Freyman, McCusker, McGann, and Keating (Ground 1) or ***all six*** of those reference additionally in view of Gilbert 2005 (Ground 2), or ***all six*** of those reference additionally in view of Van Dyke (Ground 3), with a reasonable expectation of success. Petitioner simply provides no explanation of how (or why) a POSA would be motivated to combine ***eight*** different references that each disclose incompatible approaches arising from three distinct fields of endeavor to arrive at the inventions claimed in the ’376 Patent.

CERTIFICATION OF SERVICE

I hereby certify that on July 14, 2025, a copy of Patent Owner's Preliminary Response was filed by filing this document through the PTACT's System as well as delivering a copy via electronic mail upon the following:

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24 *et seq.*, the undersigned certifies that this document complies with the type-volume limitations. This document contains 13,439 words as calculated by the “Word Count” feature of Microsoft 365, the word processing program used to create it.

Respectfully submitted,

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