

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 RESPONSE IN SUPPORT OF
DISCRETIONARY DENIAL
UNDER 37 C.F.R. § 42.107(a)**

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P.O. Box 1450
Alexandria, VA 22313-1450

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I. INTRODUCTION

On March 26, 2025, US Patent and Trademark Office (“USPTO”) Director Stewart issued a Memorandum on Interim Processes for Patent Trial and Appeal Board (“PTAB”) Workload Management describing a new bifurcated process for determining discretionary denials of *inter-parties* review (“IPR”). Under the new process, the USPTO Director will review the case for discretionary denial considerations separately from the merits. The parties are permitted to address all relevant considerations, including:

- Whether the PTAB or another forum has already adjudicated the validity or patentability of the challenged patent claims;
- Whether there have been changes in the law or new judicial precedent issued since issuance of the claims that may affect patentability;
- The strength of the unpatentability challenge;
- The extent of the petition’s reliance on expert testimony;
- Settled expectations of the parties, such as the length of time the claims have been in force;
- Compelling economic, public health, or national security interests;
and
- Any other considerations bearing on the Director’s discretion.

The Petition for IPR of U.S. Patent No. 11,660,376 (“Petition”), filed by RegenX Science, Inc. (“Petitioner”), should be denied institution because (1) the PTO has already adjudicated the validity of the challenged patent during prosecution using art that is superior to the, at best, cumulative art presented in the Petition; (2) the weakness of the unpatentability challenge due to the Petition failing to 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”; (3) the lack of the petition’s reliance on expert testimony to provide articulated reasoning with rational underpinnings as to why a person of ordinary skill in the art (“POSA”) would have modified the cited *eight* primary prior art references from disparate fields of endeavor, the dubious combinations of which are supported only by conclusory motivation and hindsight motivated contentions; (4) the settled expectations of the parties based on Petitioner’s substantive participation in the prosecution of U.S. Patent No. 11,660,376 (“the ’376 Patent”) (including direct input into the claim scope and financial support for the prosecution of the challenged claims and related divisional and foreign applications), and several pre-existing licenses to the ’376 Patent; and (5) compelling public policy, public health and economic interests.

Based on these considerations, it is clear that the Petition suffers from multiple fundamental flaws that warrant the PTAB in exercising its discretion to deny institution of an IPR.

II. DESCRIPTION OF THE STATE OF THE ART

The '376 Patent relates to methods and materials for using engineered biological tissue for wound treatment and skin repair. Any violation of live tissue integrity may be regarded as a wound. Skin is the largest organ of the human body and one of its key functions is to protect water-rich internal organs from the dry external environment. Maintaining skin integrity and possessing a robust wound healing capacity are key prerequisites for healthy survival. EX-1001, Abstract; EX-2005, p.148.

Wound healing presents a significant challenge and burden on health care systems. Poor or delayed wound healing can lead to increased healthcare costs, prolonged hospital stays, and reduced quality of life for patients. A conservative estimate of the staggering cost of caring for these wounds exceeded \$50 billion per year during 2012. The highest wound-related expenses were attributed to surgical wounds followed by diabetic foot ulcers. Thus, effective wound care is crucial for minimizing complications, accelerating healing, and improving patient outcomes. EX-2006, pp.10-11.

Thus, the ability to restore biomechanical function to damaged tissue, however, presents a true challenge. 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, many of such interactions are either not yet elucidated or fully understood. In biology, an ECM is a network of extracellular proteins and other macromolecules secreted by cells that provide, among other things, structural and biochemical support to cells and tissues in the body. EX-2007, pp.1-2.

The '376 Patent explains that “[b]y applying biological, chemical and engineering principles... tissue engineers have developed transplantable products for use in promoting the tissue repair and regeneration processes.” Using a variety of techniques, ECM and accompanying cutaneous tissue can be engineered into porous scaffolds and grafts that mimic the structural and compositional aspects of the native tissue or organ microenvironment. Tissue engineers have developed transplantable products comprising synthetic and biological scaffolds that to serve as a temporary replacement, both mechanically and functionally, for damaged, diseased or absent tissue. EX-1001, 2:6-2:56.

These engineered tissue implants can be categorized into three categories according to their source: xenograft implants (derived from heterologous animals), allograft implants (derived from another individual of the same species with a

different genotype), or autograft implants (derived from the same individual, and 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.

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). Prior to the invention of the '376 Patent, all bioengineered scaffolding products were almost exclusively made from either synthetic materials or mammalian tissue. Synthetic ECMs, as the name implies, were engineered from a variety of chemical compounds (such as fibrous polymers, gelatin, polymer/ceramic composites, and collagen). These scaffolds were designed to mimic the structure of the naturally occurring ECM and had a longer (if not indefinite) shelf life and minimal storage requirements. Moreover, 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.

In contrast, scaffolds made from mammalian starting materials (*e.g.*, mammalian dermis, urinary bladder, small intestine, mesothelium, pericardium, bone, etc.) naturally contain cells and other cell residues native to mammalian

tissues. These materials must first undergo extensive decellularization processes to devitalize and remove these cells, cell residues or donor antigens that will elicit immune responses in the host. While biological scaffolds made from mammalian tissue most closely mimic the natural structure of other mammalian ECMs, the '376 Patent explains, that the "use of conventional tissue scaffold products is not without drawbacks...." For example, "it may be difficult to obtain sufficient tissue components necessary to cover large areas of damaged tissue [and]... materials can be costly, not effective in many instances, and limited in availability." "Disease transmission risk and inter-sample variation are additional drawbacks associated with biological scaffold products." EX-1001, 3:7-40.

Moreover, key to long-term survival of the implants is biocompatibility, including avoiding severe immune-mediated tissue rejection and inflammatory responses inherent to these materials. For example, the proteoglycans and collagens of xenogeneic derived ECM have antigenic properties that can in some cases elicit immune responses in the host due to different sequences and bound carbohydrates of homologous proteins between human and heterogeneous animals such as pig. Cell residues caused by incomplete decellularization could further initiate immune rejection. As a result, although engineered implants using xenogeneic (belonging of different species) decellularized ECM was promising, immune rejection by the host was a serious concern for clinical use. Moreover,

common methods for treating ECMs, including antigen removal, and glutaraldehyde or formaldehyde treatment (that results in crosslinking) require tedious fabrication processes, sacrifice of regeneration effect, cause ill-effects in patients, and result in material unsuitable for use as a xenograft. EX-1001, 3:29-50; 4:44-5:3; EX-1004, 837-1049. Recent news has also reported efforts to remove the alpha-gal antigen from pig tissue to enable use as a source of xenografts. To date, such efforts have been met with limited success, making the success using the xenograft of the present invention all the more novel and nonobvious. EX-2015, 757; EX-2016, 369.

The '376 Patent provides several advantageous characteristics required of these transplantable scaffold products to support cell adhesion, proliferation and differentiation, while at the same time, avoiding rejection. For example, the scaffold materials should be “biocompatible, biodegradable and exhibit low antigenicity [the ability of an antigen (a substance that triggers an immune response) to bind specifically to antibodies or T cell receptors].” “The implant should degrade at a rate roughly equal to that of the new tissue formation.” Moreover, “[o]nce implanted, the scaffold must have the mechanical properties necessary to temporarily offer structural support until the new tissue has formed”, while also being porous so as to “provid[e] an appropriate path for nutrient transmission and tissue ingrowth.” To “promote fast healing”, implanted scaffold

products “should offer (i) bioactive stimulation... to encourage cell migration, proliferation and differentiation, and (ii) mechanical or structural support for these processes.” EX-1001, 2:16-35.

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 xenotransplantation. For example, 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 the 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 the parent application that matured into US Patent No. 10,617,790 ("the '790 Patent") which is the subject of related PTAB case IPR2025-00620, also filed by Petitioner, as well as foreign equivalents of the '376 and '790 Patents. Indeed, Petitioner went so far as to file on its own a patent application (without Patent Owner's permission) descending from '790 Patent, and is a sister application to the '376

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 eventually granted after more several years of prosecution before the USPTO on May 30, 2023. The independent claims of the ’376 Patent claim 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.*, claims 31, and 32. 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.

No prior art disclosed, taught, or suggested using Urodele ECM to create a biological scaffold for use as a xenotransplant material. Nonetheless, the ’376

Patent issued over numerous prior art references that were far more relevant to the claimed invention than the references cited by Petitioner.

IV. THE BOARD SHOULD EXERCISE ITS DISCRETION AND DENY INSTITUTION

A. The PTO has already adjudicated the validity of the Challenged Claims during prosecution using art in comparison to which the art presented in the Petition is merely, and at best, cumulative

The Board should deny institution under 35 U.S.C. § 325(d) because Petitioner relies solely on art and arguments that are the same or substantially the same as those considered by the Examiner during prosecution of the '376 Patent and related '790 Patent, and Petitioner does not meet its burden to demonstrate material error by the Examiner. Under the two-part framework from *Advanced Bionics*, the PTAB must first determine whether the art or arguments were previously presented (step one), and, if so, whether the Office materially erred in allowing the claims (step two). *See, e.g., Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GMBH*, IPR2019-01469, Paper 6, 10 (PTAB Feb. 13, 2020). The step two inquiry is guided by the non-exclusive factors articulated in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017) ("*Becton Dickinson*"), which address how the Examiner evaluated the art, how the petitioner's arguments differ from those made during prosecution, and whether other facts warrant reconsideration.

The record evidence in this case demonstrates that Petitioner’s “Section 103” Grounds 1-3 merely retread the same combination arguments that the Examiner fully addressed during prosecution of the parent application that issued as the ’790 Patent, and were again considered during prosecution of the ’376 Patent. *See* EX-1004; *see also* EX-1004 to IPR2025-00620 at 584, 585, 586, 586-87, 630-658, 694-703, 705-767, 799-822, 824-835, 837-49, 1061-67, 1110-1120, 1210-1263. Petitioner fails to explain – and provides no expert testimony on – how its “Section 103” Grounds 1-3 are not the same or substantially the same as the arguments the Examiner considered. The Petitioner cannot do so because the art cited by the Examiner and overcome by the applicant during prosecution was substantially more relevant to the claimed invention than the art relied on in the Petition. The Petition therefore fails to meet *Advanced Bionics*, step one, and, therefore, *per force*, step two.

Petitioner fails to demonstrate any material error by the Examiner, as it merely declares—again without any analysis or expert testimony—its own circular and incorrect conclusion that the Examiner failed to “consider and identify” the “Section 103 issues” raised in the Petition. In short, the Petition is a classic example of the type of recycled and rehashed arguments that *Advanced Bionics* and 35 U.S.C. § 325(d) warns against. Reviewing similar facts, the Board has denied institution on several occasions where the Examiner considered the

same § 103 arguments proffered by Petitioner (*e.g.*, both Examiner and Petitioner considered obviousness). *See, e.g., Advanced Bionics*, Paper 6, 10; *Novartis Pharms. Corp. v. Plexxikon, Inc.*, IPR2018-01287, Paper 17, at 6-16 (PTAB Jan. 16, 2019); *Triplet Therapeutics, Inc. v. Board of Supervisors of Louisiana State University and Agricultural and Mechanical College*, PGR2021-00059, Paper 12, at 33-39 (PTAB Sept. 8, 2021). Petitioner makes no mention of these decisions.

1. Petitioner’s art is, at best, cumulative to the art before the Examiner

Neither Petitioner nor its expert, Dr. Badylak, make any effort to explain how the Petition’s obviousness Grounds 1-3 are not the same or substantially the same arguments that were previously considered by the Examiner during prosecution. Petitioner feebly asserts, without more, that “none of the primary references presented here were before the Examiner during prosecution, nor were they considered.” Petition at 10. Neither did Dr. Badylak provide any testimony on this issue. EX-1002, ¶¶4-46. Rather, in spite of Dr. Badylak having himself applied for and been granted at least forty-one (41) ECM related US patents, Dr. Badylak essentially declares that an ECM is an ECM is an ECM, and that all things ECM related are known or obvious.

The application that issued as the ’376 Patent was filed on February 26, 2020, and is a continuation of U.S. application No. 14/759,895 (“the ’895 Parent Application”), filed January 9, 2014, now the ’790 Patent. After four and half (4.5)

years of careful and thorough prosecution of the '895 Parent Application that included three (3) substantive Office Actions, two (2) RCEs, and three expert Declarations, the USPTO granted the parent '790 Patent on April 14, 2020.

Moreover, all of the references examined during the prosecution of the '895 Parent Application were again before the USPTO during prosecution of the application that issued as the '376 Patent. During that lengthy prosecution of these two patents, the Examiner cited and substantively applied Smith (EX-2002), Satoh (EX-2003), and Seifert (EX-2004) in rejections under 35 USC § 102, and Asem (EX-2001) and Seifert in rejections under 35 USC § 103. *See* EX-1004; *see also* EX-1004 to IPR2025-00620 at 584, 585, 586, 586-87, 630-658, 694-703, 705-767, 799-822, 824-835, 837-49, 1061-67, 1110-1120, 1210-1263.

Hoping to second-guess the Examiner's detailed examination (an examination that Petitioner itself actively participated in!), the Petition purports to raise literally *dozens* of references without any connection amongst them in an effort to assert that Petitioner is presenting new issues and new art. As is often the case with the "everything but the kitchen sink" approach, in reality, Petitioner has done nothing more than cite numerous references in place of single references cited and applied by the Examiner and overcome by the Patentee during original prosecution. That the Petitioner has (now) been able to find and cite other references which disclose the same or similar information taught in the references

applied by the Examiner – and overcome during prosecution – does not render the claims any less valid. The documents cited in the Petition are cumulative of the references presented during prosecution, and the Petitioner has not shown otherwise.

It is relevant here to recall that the Patentee, even putting aside the combinatorial rejections based on 35 USC § 103, overcame a claim rejection for lack of novelty over Satoh (EX-2003). In particular, Satoh investigated collagen deposition and apical epithelial cap (AEC) formation during axolotl limb regeneration and, in the process, created an acellular collagen sheet derived from axolotl skin. Patentee successfully distinguished its claimed product from the axolotl skin derived material disclosed in Satoh on the grounds that the resulting collagen sheet in Satoh was heavily cross-linked, making the Satoh product more antigenic, and less suitable for use as a xenograft than even native axolotl tissue, not to mention the product according to the herein challenged patent. Tellingly, none of Petitioner's references purport to even come close to a § 102 rejection, much less do they compare to the references already cited and overcome during prosecution. EX-2003, at 191-193; EX-1004 to IPR2025-00620.

With respect to second guessing the Examiner's vigorous § 103 obviousness rejections, Petitioner's "combinations" – to the extent they can be understood – attempt only to substitute many references in place of the most relevant references

cited by the Examiner that disclose the same information. For example, in place of one reference cited and applied by the Examiner, Asem (EX-2001), Petitioner substitutes five references that disclose the same information: Badylak 2004 (EX-1005), Badylak 2009 (Ex-1008), Freyman (EX-1015), Van Dyke (EX-1023), and Gilbert (EX-1032). Petitioner fails to explain what information was missing or misapplied from Asem that is somehow supplanted by the five references cited in the Petition that teach essentially the same thing.

All five substitute references (*i.e.*, Badylak 2004, Badylak 2009, Freyman, Gilbert and Van Dyke) (hereinafter the “ECM references”) relate to the same field of decellularized mammalian ECMs for use in xenogeneic wound repair. Thus, they teach methods for decellularizing (*i.e.*, removing) native cells and cell debris from various mammalian tissue sources, sterilizing the remaining ECM material, and using the sterile decellularized matrix as a scaffold for wound repair. EX-1005, Abstract; EX-1009, Abstract, EX-1015, 48:10-49:18.

By comparison, Asem seeks to solve the same technical problem only using ECM from a non-mammalian species which (while still not disclosing Urodele ECM) at least originates from ovarian follicular tissue from an avian or reptile source.¹ Like the numerous ECM references cited by Petitioner, Asem discloses

¹ The word “Amphibian” is mentioned once in Asem. EX-2001, 4:36-51.

methods for repairing and regenerating tissues and inducing the proliferation and growth of eukaryotic cells by administering decellularized ECM, including methods for producing bioscaffolds and ECM powders with controlled particle sizes, by decellularizing animal tissues. Unlike Petitioner's numerous ECM References, however, Asem discloses these methods in a single reference, and using a non-mammalian (i.e., avian, reptile or a list of other possible animals, including, without more, amphibian) tissue source, making Asem more closely related to the claimed subject matter in the '376 Patent than Petitioner's ECM References. Thus, all of Badylak 2004 (EX-1005), Badylak 2009 (Ex-1008), Freyman (EX-1015), Van Dyke (EX-1023), and Gilbert (EX-1032) are cumulative in view of Asem cited and applied by the Examiner in original prosecution. EX-2001, 8:27-21:52, 22:1-50.

Next, Petitioner cites to McCusker (EX-1025) (the "Fibroblast reference"), and McGann (EX-1026) and Keating (EX-1027) (collectively, the "Newt Extract references"), to demonstrate the well-known regenerative capabilities of the Mexican axolotl, and its role as a potential model for understanding tissue regeneration. Petition at 29-40. These same well-established concepts, however, were already before the Examiner, and were taught – and overcome – in references far more pertinent than Petitioner's art.

Take, for example, the Newt Extract references. The near identical disclosure contained in the Newt Extract references was previously cited and applied by the Examiner in the context of Smith (EX-2002). Smith teaches a method of creating a newt protein extract generated from degradation and centrifugation of larval salamander (*Ambystoma tigrinum*, a Urodele, hereafter, “*At*”) components. Specifically, in Smith, an acid soluble fraction of collagen from *At* skin was isolated, purified and characterized. Per the described process, any ECM present in the starting material was centrifuged and removed from the solution along with any other acid insoluble debris, resulting in a collagen-rich supernatant that can be used to stimulate tissue growth and repair. Accordingly, any ECM that existed in the starting material of Smith was completely destroyed and discarded by the extraction that Smith conducts. EX-2002, 244.

This is the near identical approach taken by the Newt Extract references. Like Smith, the Newt Extract references teach *homogenizing* the potential source tissue in a blender, and centrifuging the homogenate to *disassociate* and *remove* all ECM materials. Like Smith, only the liquid supernatant is retained containing certain cellular proteins that can be used to stimulate tissue growth and repair. EX-1026, 13699-700; EX-1027, [0010]; EX-2002, 244. Petitioner fails to establish how the teachings in the Newt Extract references are any different from the same experiments disclosed in Smith.

Petitioner's final reference, McCusker (EX-1025) (the "Fibroblast reference"), is cumulative of art cited during prosecution, such as Smith (EX-2002), Satoh (EX-2003) and Seifert (EX-2004) that were cited as to ECM, ECM components, decellularized ECM or fractions thereof from an axolotl or urodele, EX-1004, 585, 586; and Satoh recognized the importance of fibroblast growth factors (FGFs) that are expressed by nerves. EX-2003, 191. While cumulative in that regard, however, it is clear that McCusker, in fact, teaches the complete antithesis of the claimed invention. Rather than *decellularize* an axolotl-derived ECM matrix to remove cellular components and to reduce or eliminate antigenicity (as required by the claimed invention), McCusker explores the use of ***fibroblasts*** – a type of connective tissue cell that is capable of de-differentiating back to blastema cells in axolotls – as the "target for regeneration and rejuvenation therapies". EX-1025, 569. Therefore, McCusker's disclosure is unrelated to axolotl ECMs as disclosed and claimed in the subject patent. Moreover, "fibroblasts" are among the many types of cells that the '376 Patent teaches must be ***removed*** from ECM scaffolds in order to prevent adverse immunoresponses by the host. EX-1001, 5:26-27 ("The biomaterial of the invention is produced by *decellularizing* a tissue sample obtained from a urodele.") (emphasis added). Thus, McCusker is not only "cumulative", but when read in full, actually teaches away from the claimed invention. EX-1025, 569.

Indeed, the conclusion that Petitioner's cited art is cumulative of the references considered and overcome in original prosecution is further demonstrated by the fact that Petitioner's art was cited to the Examiner during Patentee's prosecution in a related pending application. The Examiner indicated consideration on the record of Petitioner's cited references, without rejection, and on May 27, 2025, the USPTO granted the Patentee a third related patent, US Patent No. 12,311,079 ("the '079 Patent") (EX-2014), based on a continuation application claiming priority back to the challenged patent. Claim 1 of the '079 Patent recites 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. In granting that claim, the Examiner considered and 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 '790 and '376 Patents. Nonetheless, 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).

In this case, the Examiner cited “better” art than that cited by the Petitioner, in clearly enunciated rejections that were overcome by the Patentee. The Petition should be dismissed for many reasons, not least, because it fails to clearly enunciate how the Petition-cited references are to be applied against the Challenged Claims, and are not cumulative of the art overcome during prosecution. Petitioner fails to raise any new issue of patentability warranting initiation of IPR proceedings and the allocation of resources by the PTAB, the Petitioner and Patentee.

2. Petitioner failed to identify any error, much less “material error” by the Examiner

Petitioner also cannot satisfy the second part of the *Advanced Bionics* test because they do 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. As Petitioner has not even attempted to address any of these factors, Petitioner has failed to establish that the Examiner erred and the Board should deny institution.

Petitioner offers only a *single* bald statement identifying the Examiner's alleged "material error": *i.e.*, that "the Examiner failed to make an obviousness rejection over, for instance, the Ground I References" cited in the Petition. Petition at 73. Petitioner's circular attempt to show material error is flatly deficient. Furthermore, it impugns the work product of an Examiner who, demonstrably, on the record, performed a diligent job in examining this related series of applications now issued to patents.

To show material error, a petitioner must go beyond mere repetition of cumulative arguments addressed during prosecution and explain why the examiner's analysis was incorrect or incomplete. Here, Petitioner failed to identify any specific errors in failing to consider the most relevant art, or how the Examiner interpreted the prior art, or improperly applied the law in a way that impacts patentability. Petitioner fails to show that the Examiner overlooked key teachings, or misunderstood the scope of the claims or art. Petitioner fails to show that the Examiner relied upon materially false or incomplete statements during prosecution.

Petitioner also fails to present any arguments where the Examiner “inexplicably” changed her position. To further compound these deficiencies, Petitioner failed to support its assessment of the factual record with any expert testimony. Simply put, *Advanced Bionics* requires more of Petitioner than a blanket statement that the Examiner “failed to consider” alleged prior art. *Advanced Bionics*, Paper 6, at 10-11 (stating that “the petitioner’s required showing of material error must overcome persuasively [disagreement with a] ***specific finding*** of record” by the Office) (emphasis added); *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) (“generalized statements as to the strength of its [p]etition fail to identify sufficiently a material error.”).

The thorough and lengthy prosecution history underlying the ’376 Patent and related applications demonstrates that the Examiner possessed a firm understanding of relevant prior art and its subject matter, and meaningfully evaluated the teachings of those references. Petitioner’s failure to identify “material error” of any kind is a clear signal that the Petition is not likely to lead to a different outcome, and warrants denial of institution.

* * *

Because Petitioner's arguments are essentially the same as those that were before the Office, and because Petitioner has failed to establish any material error warranting reconsideration, the Board should deny institution under § 325(d).

B. The weakness of the unpatentability challenge warrants discretionary denial

35 U.S.C. § 312(a)(3) demands 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.” As the Federal Circuit emphasized in *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, “[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.’” 821 F.3d 1359, 1369 (Fed. Cir. 2016).

The Board should deny institution because Petitioner failed to 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.” *Id.* The Petition provides a panoply of *eight* primary prior art references for the three Grounds from disparate fields of endeavor, the dubious combinations of which are supported only by contentions which are conclusory in Petitioner's favor. Worse still, unable to arrive at the claimed invention through its combination of *eight* primary references, Petitioner has chosen to backfill missing

support, relying on countless secondary references that are described nowhere in the Petition.

Taking claim 1 as representative, Petitioner purports to combine six “primary” references with *eleven additional* references – *seventeen* in total – in an attempt to find support for omitted claim elements or missing factual or technical support – for a claim that only recites *two elements*. Holding together Petitioner’s mélange of prior art, Petitioner proffers only the *ipse dixit* of its purported expert (who, himself, either simply “declares” statements to be true or relies on yet additional secondary references to support his arguments). While a seventeen-reference obviousness combination is itself telling, Petitioner’s failure to particularly identify the evidence that supports the grounds for the challenge does not stop there.

Addressing claim 1, Petitioner argues that “[t]he *cumulative* teachings of the [six] Ground I References [which, also apparently includes the *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 each other and also with the eleven secondary references.

This type of mish-mash of references has been previously rejected by the Board for failing to meet the “with particularly” standard. *Ikea Supply AG v. Everlight Electronics Co., Ltd*, IPR2024-00988, Paper 6 (PTAB Dec. 12, 2024). In *Ikea*, the Board found that the IKEA petition failed the particularity requirement in several ways. Most notably, its Ground 3 relied on combining a primary reference (Shin) with “one or more of Terashima, Sugimoto, Uemura ’259, Uemura ’999 and/or Inoue (Collectively the ‘Thin Film Art’).” *Id.* at 28. The Board noted this created “potentially at least 25 different combinations of Shin with the cited Thin Film Art.” *Id.* at 25.

Making matters worse, IKEA then “compound[ed] the multiplicity of potential combinations” by further combining these 25 combinations with additional references in Grounds 4-11. *Id.* at 28. The Board found this approach particularly puzzling given IKEA’s own argument that “using thin film electrodes as taught in each of the Thin Film Art was well-understood, common knowledge, predictable, and routine in 2003.” *Id.* at 28.

Here, Petitioner makes the same perplexing argument as IKEA, only the number of potential combinations proposed by Petitioner is orders of magnitude greater. Like IKEA, the Petition asserts that “Petitioner provides an overview of ECM tissue grafts, the well-known regenerative properties of urodele tissues, and their conserved signaling pathways.” Petition at 11. In contrast to the 25 different

combinations identified in *Ikea*, Petitioner’s proposed combination of seventeen different references gives rise to **131,071** potential combinations of primary and secondary references to establish something the Petition asserts is “well-known.” IPR2024-00988, Paper 6, p.11.

C. Petitioner fails to provide articulated reasoning with rational underpinnings as to why a POSA would have modified the cited prior art references

1. Petitioner’s primary references cannot be combined

The Board should deny institution for the additional reason that Petitioner failed to meet its burden to demonstrate that a POSA would have had a reason to combine all eight primary references (in addition to untold secondary references) to arrive at the claimed inventions with a reasonable expectation of success.

As discussed above, Petitioner’s primary references fall into three categories each arising from an entirely different field of endeavor: the “ECM references” (*i.e.*, Badylak 2004, Badylak 2009, Freyman, Gilbert and Van Dyke), the “Fibroblast Repair reference” (*i.e.*, “McCusker”), and the “Newt Extract references” (*i.e.*, McGann and Keating). The ECM references relate to the field of decellularized mammalian ECMs for use in xenogeneic wound repair. Thus, they teach methods for decellularizing (*i.e.*, removing) native cells and cell debris from various mammalian tissue sources, sterilizing the remaining ECM material, and

using the sterile decellularized matrix as a scaffold for wound repair. EX-1005, Abstract; EX-1009, Abstract, EX-1015, 48:10-49:18.

In contrast, the Fibroblast reference teaches the opposite approach. Rather than *decellularizing* source tissue for use in wound repair, it teaches a process of *culturing* fibroblast cells from the source tissue, and using those cells as a target for regeneration and rejuvenation therapies. EX-1025, 569.

While in yet further contrast, the Newt Extract references describe an entirely unrelated third approach: namely, *homogenizing* the potential source tissue in a blender, to *disassociate* and *remove* all ECM materials from the sample, in order to create an extract containing only cellular proteins that can be used to stimulate tissue growth and repair. EX-1026, 13699-700; EX-1027, [0010]. Petitioner fails to establish any motivation why a POSA would look across these eight references arising from three very different (and irreconcilable) fields of endeavor.

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 would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.” 35 U.S.C. § 103(a). 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). It is Petitioner's burden to bring forth proper factual determinations for an obviousness ground, including identifying the differences between a claim and a prior art reference for the obviousness ground; or, have that ground denied. *See Liberty Mutual Ins. Co. v. Progressive Casualty Ins. Co.*, CBM2012-00003, Paper 7 at 2-3 (PTAB Oct. 25, 2012) ("A petitioner who does not state the differences between a challenged claim and the prior art, and relies instead on the Patent Owner and the Board to determine those differences based on the rest of the submission in the petition risks having the corresponding ground of obviousness not included for trial for failing to adequately state a claim for relief."). Petitioners must also set forth sufficient articulated reasoning with rational underpinning to support their proposed obviousness challenge. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007); *see also Naughty Dog, Inc. v. McRO, Inc.*, IPR2014-00197, Paper 11 at 20-21 (PTAB May 28, 2014) (explaining the requirements of a proper obviousness allegation).

Here, however, Petitioner does none of the required analysis to meet its burden of proof. Simply put, Petitioner fails to analyze the references against the claims as a whole, evaluate the differences therebetween, and then explain why the

subject matter of the claims would have been obvious to the person of ordinary skill in the art. Rather, Petitioner resorts to cobbling together support from an array of different disclosures and then opting for the Board to work out for itself proposed combination(s) to somehow arrive at the claimed invention. When one does examine the teachings of the cited references and the claims as a whole, it is apparent that substantial differences exist therebetween and that the claimed invention would not have been obvious to a person of ordinary skill in the art.

Referring back to claim 1 as an example, Petitioner argues that a first category of prior art comprising “Badylak 2004, Badylak 2009 and Freyman are all from the same field of endeavor – the use of xenogeneic ECMs”. Petition at 34. To the extent these three references can be considered in the “same field of endeavor”, however, Petitioner’s statement tacitly admits that the *other* three primary references relied on for claim 1 (*i.e.*, McCusker, McGann and Keating) are ***not*** from the “same field of endeavor.” *See id.* Petitioner never explains why a POSA would look to combine three references from one field of endeavor, with three additional references from different fields of endeavor that are unrelated to the “use of xenogeneic ECMs”. Petitioner’s analytical leap is particularly glaring given that technical approaches disclosed in these six references are not only dissimilar but technologically incompatible.

Like many references in the prior art, the xenogeneic ECM scaffolds described in Badylak 2004 and Badylak 2009 are 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”). Thus, neither Badylak reference discloses or suggests a xenogeneic ECM scaffold made from non-mammalian source tissue, much less amphibian source tissue, or Urodele tissue, as claimed in the ’376 Patent.

Contrary to Petitioner’s argument, neither does Freyman. Petitioner relies on Freyman to suggest that “ECM material can be derived from any suitable animal body tissue of xenogeneic origin... includ[ing]... amphibians.” Petition at 31. Freyman, however, contains no such disclosure. The sole reference to “amphibians” in Freyman’s fifty-three-page specification is made in the context of an *allogenic* ECM (*i.e.*, ECM wherein the donor and the recipient are the *same* species), not a *xenogeneic* ECM scaffold, as claimed in the ’376 Patent:

A more detailed discussion of the source and preparation of the ECM is presented in the following sections of the present application. 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. In a specific embodiment, said mammals are domestic mammals. In a more specific embodiment, said

domestic mammal is a canine or a feline. In another more specific embodiment, said domestic mammal is an equine, bovine, porcine species. In yet further embodiments, the recipient is a primate. In one embodiment, the recipient is a human.

EX-1015, 17:26-34. Petitioner's characterization of Freyman is simply incorrect; Freyman makes no suggestion of a xenogeneic transplant of amphibian ECM, but instead generally relates to the same field of mammalian ECMs discussed in the Badylak references.² Indeed, the only example disclosed in Freyman was an experiment involving a porcine (*i.e.*, mammalian) ECM. EX-1015, 48:10-49:18. Thus, to the extent that the three ECM references can be combined to teach anything, they stand for the unremarkable idea that mammalian ECMs can be used as xenogeneic bioscaffolds (an idea that was squarely before the Examiner and, in any event, has little to do with the claimed invention).

In contrast, Petitioner's fourth reference, McCusker, relates to an entirely different field of endeavor. Rather than using "decellularized" ECM for tissue repair, McCusker explores the use of *fibroblasts* – a type of connective tissue cell that is capable of de-differentiating back to a type of stem cell in axolotls – as the "target for regeneration and rejuvenation therapies". EX-1025, 569. Not only does

² As discussed above, even if Freyman did disclose amphibian-based *xenogeneic* ECM scaffolds – it does not – such limited disclosure is far less detailed than the Asem reference cited and overcome during prosecution. *Supra*, Section IV (A)(1).

McCusker's hypothesis have nothing to do with axolotl ECMs, "fibroblasts" are among the many types of cells that the '376 Patent teaches must be *removed* from ECM scaffolds in order to prevent adverse immunoresponses by the host. EX-1001, 5:26-27 ("The biomaterial of the invention is produced by *decellularizing* a tissue sample obtained from a urodele.") (emphasis added). Thus, McCusker teaches away from the inventions claimed in the '376 Patent. EX-1025, 569.

Moreover, far from providing a reliable reference from which a POSA would draw meaningful motivation, McCusker acknowledges 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"). Thus, the only "conclusion" a POSA would draw from McCusker, is that McCusker has nothing to do with the claimed invention, it in fact teaches away.

Finally, Petitioner's "Newt Extract references" are even less on point. Rather than attempting to preserve intact ECM for use as a tissue scaffold for xenotransplant (mammalian or otherwise), 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 (i.e., grinding) 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].

For example, in McGann, following homogenization of the axolotl tissue, all “cell debris” (which would include all components of the ECM) were “removed using two centrifugation steps.” EX-1026, 13699-700 (Preparation of Protein Extracts). “The homogenate [*i.e.*, the ground-up tissue] was first spun at 2000 x g for 25 min and then the supernatant was spun again at 100,000 x g for 60 min.” *Id.* 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*. *Id.*

Keating, filed by two of the McGann authors, contains a nearly identical disclosure to McGann. Keating states that “the present inventors have now discovered that 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].

Further still, rather than teach the use of axolotl ECM for xenotransplant, Keating expressly discredits such an approach, arguing the “significant disadvantages” of transplanting engineered tissues:

Tissue engineering, the approach of replacing tissue by culturing in vitro cells onto a biomaterial substrate [such as an ECM] 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 the intrinsic functions and morphology of the tissue it replaces.

EX-1027, [0008].

Thus, the Newt Extract references are the antithesis of ECM xenotransplant. 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.

2. Petitioner fails to articulate how the primary references could be combined

In short, the three ECM references (instructing the use of decellularized, intact *mammalian* ECMs), the Fibroblast reference (instructing the use of *fibroblasts cells* to resist aging), and the two Newt Extract references (instructing the use of *newt protein extracts* removed from ECM components), disclose three different and conflicting approaches to tissue regeneration, which cannot be combined.

Nor does Petitioner actually articulate how such disparate references could be combined to create the inventions of the '376 Patent. At best, Petitioner picks isolated statements out of context from the three categories of references, and then declares that a POSA would somehow combine these isolated statements to derive the actual invention. However, an invention “composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. 418. A determination of unpatentability on a ground of obviousness must also include ““articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.”” *Id.* (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). The obviousness evaluation “should be made explicit,” and it “can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *Id.*

Here, Petitioner’s rationale is premised on a bare recitation of disparate claim elements scattered throughout multiple prior art references stitched together with flawed logic and unsound conclusions. Petitioner’s arguments lack any reason, absent impermissible hindsight, why one skilled in the art would have combined and applied six different references that each disclose incompatible approaches arising from three distinct fields of endeavor to arrive at the inventions claimed in the ’376 Patent. 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 KSR*, 550 U.S. at 421 (“A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.”).

For example, in order to combine the ECM references with the Newt Extract references, a POSA would be forced to choose between two diametrically opposed solutions: using a mammalian ECM as a xenograft scaffold for tissue repair, or homogenizing and disposing of all ECM material in favor of a liquid protein extract. *Compare* EX-1005, Abstract; EX-1009, Abstract, EX-1015, 48:10-49:18 *with* EX-1026, 13699-700; EX-1027, [0010]. Furthermore, to combine the ECM references with the Fibroblast reference, a POSA would need to choose between decellularizing and removing all cell debris from the potential ECM material, or

alternatively *seeding* ECM materials with living Fibroblast cells to promote tissue repair. *Compare* EX-1005, Abstract; EX-1009, Abstract, EX-1015, 48:10-49:18 *with* McCusker EX-1025, 569. Petitioner fails to specify where each element of the challenged claims is suggested in the prior art, and never explains how, or why, a POSA would combine these teachings in a way to arrive at the claimed inventions. Worse yet, Petitioner never articulates how all six ECM, Fibroblast and New Extract references could be combined. Indeed, a reasoned reading of these references demonstrates that none of the Challenged Claims are rendered obvious by the Petitioner's proposed references, at least because the discrepant teachings of these six references cannot be combined.

3. Petitioner's secondary references further complicate its obviousness combinations

Petitioner's purported six-reference combination of primary references for claim 1 alone, is rendered all the more unconvincing when read in view of the *eleven* additional secondary references Petitioner is forced to rely upon to backfill missing support. By way of brief example, Petitioner relies on Seifert [EX-1031] to argue that axolotls were "widely studied as a model organism for understanding the molecular and cellular mechanisms of regeneration." Petition at 32. Petitioner ignores, however, that Seifert teaches that the production of new ECM in response to injury in axolotls is *delayed* during scar-free healing. Thus, Seifert teaches that

the use of axolotl ECM runs counter to scar-free healing during wound repair. EX-1031 at 1.

Similarly, Petitioner cites Hoshiba [EX-1009] for the proposition that, prior to the invention of the '376 Patent, the use of “xenogeneic ECM tissue grafts” derived from a “wide variety of animal sources” had become “standard practice” for wound healing in humans. Petition at 30. Not only does Hoshiba only disclose mammalian-based ECM materials, but the authors conclude that the “optimal methods” for novel biomaterial scaffolds are those made by “cultured autologous cells”, not ECMs. EX-1009, 1725.

Petitioner also cites Hayashi [EX-1059] to argue that “even ECM components from fish—an entirely different vertebrate class – had demonstrated good biocompatibility, low antigenicity, and cell growth potential suitable for xenograft applications.” Petition at 30. Yet again, Petitioner’s partial characterization of Hayashi, however, ignores the author’s conclusion. After discussing the differences in amino acid composition and degeneration temperatures between fish collagens and humans, Hayashi concludes that “the initial inflammatory reactions associated with [fish ECM components]... need to be controlled before it can be considered for clinical application as scaffold. Further, as it takes too long for biodegradation of implanted [fish ECM components] in vivo, generally [they are] concluded to be *not suitable for the*

scaffold for degenerative medicine....” EX-1059, Abstract. Thus, Hayashi, like Seifert and Hoshiba, actually teach away from the inventions claimed in the ’376 Patent.

In short, by demanding 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 “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)). Petitioner provides no explanation why a POSA would be motivated to combine teachings from such disparate references to arrive at the claimed invention, all the while ignoring the full scope of what the references actually teach. Therefore, the Petition should be denied for failing to establish that Petitioners are entitled to relief. 37 C.F.R. § 42.20(c).

D. The Petition should be denied under 35 U.S.C. § 314(a) in view of Petitioner’s long-standing license and the settled expectations of the Parties

1. Petitioner helped prosecute the ’376 Patent and has benefited from a license thereunder for seven years

While not disclosed in the Petition, Petitioner is not a third party with no prior relationship to the patent. It is a sophisticated entity that helped prosecute the very claims it now seeks to invalidate and that has entered into several arms-length

license agreements involving the '376 Patent from which it has profited over many years. EX-2020, ¶¶5-25.

From the very beginning, Petitioner has sought to exploit the inventions claimed in the '376 Patent and drape itself under the cloak of their protection. Under the auspices of a field-of-use license dating back to as early as 2017 – i.e., more than three-years prior to the issuance of the '376 Patent – Petitioner was directly engaged in substantive prosecution of the '376 Patent. As a licensee, Petitioner provided direct input into the claim language and other amendments prosecuted before the Examiner, and contributed financial support towards the prosecution of the Challenged Claims. Petitioner further sought to expand the scope and protection of the '376 Patent, assisting with the filing and prosecution of related US and foreign patent applications. For example, Petitioner participated in the prosecution of parent US application Serial No. 16/801,956 that matured into US Patent No. 11,660,790 (which is the subject of PTAB case IPR2025-00620 also filed by Petitioner). Petitioner further participated in the prosecution of foreign equivalents of the '376 Patent. Finally, Petitioner even sought to obtain patent protection on its own, without permission from Patent Owner, by filing an application seeking to patent “[a] composition comprising decellularized Urodele extracellular matrix (ECM) having functional activity.” Petitioner’s efforts to advocate for the patentability of the claims of the '376 Patent, as well as other

patents US and abroad claiming similar subject matter, unquestionably gave rise to a settled expectation that the challenged patent was novel, non-obvious, and valid.

EX-2020, ¶¶6-9.

So too, did the Parties' lengthy licensing history. Indeed, even prior to the issuance of the '376 Patent, the rights to the then-pending patent application (i.e., Application No. 14/759,895 ("the '895 Application")) were recognized by many in the field, including Petitioner, and subject to numerous license agreements. For example, the rights to the '895 Application were first assigned from the inventor (Dr. Ryanne Early) to her predecessor company, ISE Professional Testing & Consulting Services, Inc. ("ISE"), and later exclusively licensed to a second company, Synogen Management, Inc. ("Synogen"), in 2014. Synogen, in turn, subsequently sublicensed certain rights to the '895 Application to both Petitioner and Patent Owner. In particular, Petitioner received a field-of-use license covering the field of "cosmeceutical" products, while all "other" fields of use were licensed to Patent Owner. EX-2020, ¶¶6-11.

In 2019, ISE sought to terminate the original license it had accorded to Synogen and, as a result, the two sublicenses that Synogen had entered into with Petitioner and Patent Owner. As a result, arbitration ensued between Patent Owner and Synogen, on the one hand, and ISE and Ryanne Early, on the other hand, (Case No, 2019-CA-012605-O (Circuit Court, 9th Judicial Circuit, Orange County,

Florida)), which finally concluded in 2020 with the execution of a Settlement Agreement. Consistent with the terms of the Settlement Agreement, ownership of the '376 Patent was ultimately transferred to Patent Owner, on the condition that Petitioner be allowed to enter into a sublicense to certain fields of use. Thereafter followed several years of negotiations between Petitioner and Patent Owner, which concluded with Petitioner accepting a second license to the '376 Patent on August 15, 2022. In accordance with the second license, Petitioner was again accorded an exclusive field-of-use license to develop a “cosmetic” product utilizing the claimed inventions of the '376 Patent, with extended milestone deadlines under the license from Synogen to Petitioner. EX-2020 ¶¶9-10.

That license agreement remained in effect until shortly prior to the filing of the Petition. Having been given a milestone for first commercial sale of a licensed product in the US by August 2024, Petitioner failed to meet the milestone or to extend its license Agreement, but now attempts to challenge, via the subject Petition, the very patent rights that Petitioner had willingly licensed for the past seven years. The parties' extensive course of performance reasonably gave rise to legitimate expectations on the part of Patent Owner that Petitioner would not suddenly reverse course and challenge the patent's validity, or to operate outside of its licensed field, while having had the option of continuing to benefit from the license's protections. Petitioner's attempt to now attack the very patent rights it

has long enjoyed through a belated IPR petition disrupts this reliance and undermines the integrity of negotiated licensing arrangements. EX-2020 ¶¶11-12.

The doctrine of settled expectations recognizes that long-term commercial relationships under a patent license typically involve substantial investments and strategic decisions by both the licensee and licensor based on the presumed validity and enforceability of the licensed patent. These investments may include directing research opportunities and developing products, establishing supply chains, and building brand recognition around the licensed technology. For the licensor, continued performance by the licensee without objection reinforces the perception that the license is stable and that the licensed rights are being respected. In exchange, the licensor agrees to forego developing the licensed technology itself, or licensing the patent to other potential licensees and, thus, exploring such opportunities with different or perhaps more lucrative terms.

When, as here, the Petitioner/licensee initiates an IPR proceeding after years of reaping the benefits of the license, it disrupts this balance. For almost seven years, Petitioner was licensed to operate under the patents issuing from the '895 Application (including the '790 and '376 patents), it did or could have derived substantial commercial benefit from the use of the patented technology. They were given the opportunity to develop and market products incorporating the patented technology, and they made contractually required minimum annual royalty

payments, showing that Petitioner respected and appreciated the validity and value of the '376 Patent. During that same period of time, Patent Owner respected the license accorded to Petitioner and has forborne from developing a “cosmeceutical” or cosmetic product. Indeed, settled expectations included that the cosmetic products market is a multi-billion-dollar market, that there are far less regulatory hurdles to bring a cosmetic product to market than there are to bring a medical device to market, and that Petitioner would commercialize a cosmetic product that would have provided a percentage of sales as royalty revenue back to the Patent Owner.

Petitioner has relied on the license to develop its core technologies, raise revenue and research financing, and position itself in the marketplace as a “leader” in bio-sourced tissue engineered products, all while enjoying the shield of a license that avoided litigation risk. Indeed, outside of this IPR, Petitioner actively touts its axolotl-based tissue ECM product as “a proprietary regenerative biomaterial inspired by one of nature’s most remarkable healing organisms.” EX-2008; EX-2020 ¶¶13-15.



Innovative Regenerative Technology

At RegenX Science, we have developed a proprietary regenerative biomaterial inspired by one of nature's most remarkable healing organisms. This technology harnesses cutting-edge molecular biology and regenerative medicine techniques to create products that transform patient care. Our research-driven approach focuses on accelerating tissue regeneration and optimizing cellular repair for injuries and wounds. Our team is pioneering new solutions in wound healing and tissue regeneration to support faster, more effective recoveries. The bioactive microenvironment provided by our product promotes cell adhesion, proliferation, and differentiation, fostering robust tissue regrowth in damaged skin and open wounds. This approach jumpstarts the body's natural healing processes, aiming to reduce scarring and improve outcomes for patients.

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Petitioner asserts that the technology in these materials “harnesses cutting-edge molecular biology and regenerative medicine techniques to create products that transform patient care.” EX-2008. Indeed, Petitioner has itself filed for several patents directed at accelerating tissue regeneration and optimizing cellular repair for injuries and wounds using engineered Axolotl-tissue based ECMs, while Patent Owner’s ’376 Patent lies at the heart of that “cutting-edge” technology. EX-2020 ¶16.

For example, US application No. 18/837,137 (“the ’137 Application”) is a patent publication filed by Petitioner claiming priority to national phase of PCT/US2023/062398 filed on February 11, 2022. Like Patent Owner’s ’376 and ’790 Patents, Petitioner’s ’137 Application, entitled “Novel Methods for Decellularizing Extracellular Matrix” describes method for decellularizing amphibian extracellular matrix to obtain an isolated ECM that is substantially free

of cellular and nuclear debris and “various methods of using the isolated ECM”.

Indeed, the first reference cited in the text of Petitioner’s ’137 App. (at page 12) is Patent Owner’s related ’790 Patent. EX-2020 ¶¶16-17.

On July 26, 2023, the International Phase Searching Authority issued a Written Opinion in the International Phase prosecution of the PCT/US2023/062398 application deny the inventive step as to Petitioner’s pending claims in view of the publication of the ’376 Patent. Thus, these materials demonstrate not only Petitioner’s awareness of the relevance of Patent Owner’s ’376 and ’790 Patents for a long time prior to filing it the instant Petition, but also help highlight the contradictory positions Petitioner is taking before the two different patent tribunals with respect to the patentability of the amphibian extracellular matrix. Worse yet, despite Petitioner’s position with respect to the alleged “material relevance” of the art cited in the Petition, Petitioner has not disclosed – and the Examiner has not cited – *any of the art* cited in the Petition during prosecution of Petitioner’s related ’137 Application. Thus, contrary to Petitioner’s assertions in the Petition, Petitioner either does not consider the art cited in the Petition to be pertinent to the claimed amphibian extracellular matrix, or Petitioner has deliberately chosen not to disclose such “material” prior art to the ISA during prosecution of its related ’137 Application. Either way, Petitioner’s statements and patent filings outside of this

Petition directly contradict its commercially-inspired positions in this case. *See e.g.*, EX-2017; EX-2018, pg. 5-7; EX-2020 ¶¶17-19.

This is particularly relevant given that Petitioner helped prosecute the Challenged Claims and has licensed the patent for such a significant duration without contesting its validity, thus creating an implied recognition of the patent's validity, or at minimum, an equitable estoppel against late-stage challenges. Indeed, Petitioner's delay in raising any validity challenge—despite full knowledge of the patent's claims, scope, and application—suggests that the IPR is being used not to promote patent quality, but as a litigation tactic or as leverage in ongoing business negotiations. Petitioner was aware of, or could have reasonably located, the references relied upon in the Petition to submit to the Examiner before the '376 Patent issued, or in the nine months immediately after the patent was granted (making a PGR possible). Despite this knowledge, Petitioner makes no attempt to explain why it failed to disclose these references, helped prosecute the claims, and agreed to license and commercially benefit from the technology, until the instant Petition.

Thus, this tension between Petitioner's conduct prior to the IPR petition – help procuring the patent claims, silence regarding patent validity, continued royalty payments, its own aggressive patent portfolio development, and opportunity to actively develop products under the license – and Petitioner's

current IPR posture demonstrates implicit recognition of the patent's value and validity, and amply informs the Board's discretionary denial considerations.

Indeed, the facts in this case parallel the facts supporting the June 6, 2025 Decision Granting Patent Owner's Request for Discretionary Denial and Denying Institution of *Inter Partes* Review in *Irhythm v. Welch Allyn, Inc.*, IPR2025-00363, -00374, -00376, -00377, and -00378, Paper 10 (PTAB June 6, 2025). Patentee respectfully urges the PTAB to follow *Irhythm v. Welch Allyn, Inc.* and deny institution of IPR proceedings in this case.

2. Institution would undermine policy interests in licensing and contractual stability

Petitioner's tactical use of the IPR process now—at a time when the patent and its license under that umbrella has already served as the backbone of Petitioner's product development—undermines the purpose of the IPR system and prejudices Patent Owner's settled expectations. Patent law encourages private parties to resolve disputes and allocate rights through licensing. The enforceability of such agreements depends in part on the reasonable expectation that counterparties will not use the IPR process as a belated and strategic tool to circumvent their own contractual obligations. Granting institution here would send a message that licensees may wait until they have fully exploited a patent's commercial value—then turn around and attack its validity under the guise of public interest. This would chill future licensing and disincentivize innovation.

The Board itself has discretion to decline institution based on the settled expectations of the parties. Given Petitioner’s extended course of conduct, including help prosecuting the Challenged Claims, years of compliance with the license and unchallenged use of the patent, the Board should find that institution is not warranted under the totality of the circumstances. The settled expectations of the parties—reinforced by the passage of time and the parties’ business dealings—strongly support discretionary denial under § 314(a).

E. Compelling public policy, public health and economic interests warrant discretionary denial

1. The claimed ECM bioscaffolds are mission-critical technologies with compelling public health value

The Challenged Claims are directed to pioneering regenerative ECM bioscaffolds used in surgical reconstruction, chronic wound treatment, and tissue regeneration. This technology is currently marketed under the brand name “NEOMATRIX®” and has been deployed in clinical settings, including in hospitals, where it has already demonstrated significant therapeutic benefit. The continued commercial availability and development of this patented technology are essential to meeting growing public health needs. EX-2020, ¶¶19-20.

Even with the advances in engineered skin, biological skin, and extensive resources allocated to research, a large unmet clinical need remains, and currently, no technology has been developed that satisfies the lofty goal of scar free healing.

EX-2009. In the United States, chronic wounds affect more than 6.5 million people annually at a cost of more than \$25 billion. EX-1010. An additional 12 million lacerations needed treatment each year in American emergency rooms and another ~480,000 burns needed treatment of which ~50,000 required hospitalization. EX-2011, EX-2012. Worldwide, the need is even more pressing. Each year, there are more than 250 million surgical incisions, and an additional 11 million burns that require treatment. EX-2011, EX-2012. Additionally, as the population continues to age, disabling diseases and injuries will continue to rise, increasing the number of patients that are undergoing soft tissue repair surgeries, which often require skin substitutes and replacement scaffolds to support damaged tissue and close wounds. EX-2013.

Patent Owner's NEOMATRIX[®] product is uniquely positioned to help address these urgent medical needs, while full-scale commercial adoption is still underway and will require additional financial support by future investors. Institution of IPR under these circumstances could introduce substantial uncertainty and risks, chilling future investment, disrupting patient access, and undermining the policy goals underlying the U.S. patent system. This disruption may result in reduced patient access to this technology and introduce hesitation among providers causing real and immediate consequences for patients, providers, and health systems. EX-2020, ¶21.

In contrast, denying institution protects investment-driven innovation in a nascent field. The development of new ECM bioscaffold technologies requires substantial investment in R&D, regulatory approval, clinical trials, and manufacturing scale-up. The commercial viability of these products is often predicated on enforceable patent rights that protect years of research and substantial capital. The market uncertainty that would result from subjecting this patent to IPR challenge at this pivotal commercialization stage could discourage further investment in regenerative medicines—a field that still faces major technical and clinical hurdles. EX-2020, ¶22.

2. The Petition is intended to serve only Petitioner's competitive interest, not the public's interest

The timing and context of the Petition appears to be a strategic, bad-faith attempt by the Petitioner to avoid the restrictions in the license it had freely accepted, as well as avoid paying royalties and/or meeting milestones, and disrupt the Patent Owner's market position, rather than a genuine challenge to patent validity. After failing to commercialize a product under its prior field-of-use license, the Petitioner has failed to extend its license to the '376 Patent that would cover its ECM product in development and, instead, filed this Petition. The timing of this Petition—aligned with the Patent Owner's own commercial expansion into its former licensor's field of operations – namely wound healing as shown on Petitioner's website – reflects both Petitioner's attempt to sidestep its future

licensing obligations and well as its intent to inflict commercial harm on Patent Owner by ignoring the Patent Owner's patent rights. The IPR process, however, should not be used as a tool for market disruption, especially in areas with significant public health importance. EX-2020, ¶¶23-24.

Moreover, Patent Owner has forborne opportunities to advance its own cosmetic product based upon its patented technology in respect to the license Patent Owner provided and respected in favor of Petitioner. The missed opportunity costs to Patent Owner having not developed that commercial segment under its own patent is enormous. That Petitioner not only failed to provide sales royalties but also to meet the commercial milestones in its license agreement with Patent Owner, should not be rewarded by granting the Petitioner's brazen entrance into its former licensor's field of operation under the challenged patent. EX-2020, ¶25.

This warrants discretionary denial by the Board.

3. Discretionary denial would align with USPTO policy and legislative intent

Congress designed the America Invents Act (AIA) to improve patent quality while promoting innovation—not to undermine viable, life-improving technologies. The claimed Urodele-derived ECM bioscaffolds are not only novel and unique but address substantial unmet medical needs, reduce costs to the healthcare system, and offer alternatives for soft tissue repair surgeries. The

claimed bioscaffolds represent more than simply a new proprietary product—they support life-changing therapies with a clear and compelling public value, including improved wound care outcomes and reduced long-term healthcare costs. The claimed bioscaffolds embody a class of innovations deserving of heightened policy protection. EX-2020, ¶26.

Allowing an IPR to proceed in this case would risk chilling innovation in a critical medical domain and undermine the very purpose of the patent system. Moreover, discouraging investment in such areas through institution of a disruptive IPR would, in turn, undermine the public’s interest in the advancement of regenerative medicine and conflict with broader legislative and public health goals, including the promotion of regenerative medicine.

For the foregoing reasons, the public interest, the critical role of ECM bioscaffold technologies in medicine, and the competitive context of the Petition all weigh strongly against proceeding. Patent Owner respectfully requests that the Board deny institution of *Inter Partes* Review under 35 U.S.C. § 314(a).

Respectfully submitted,

DUANE MORRIS LLP

By: /Patrick D. McPherson/

Patrick D. McPherson

Reg. No. 46,255

901 New York Avenue Suite 700 East
Washington, D.C. 20001

Dated: June 13, 2025

CERTIFICATION OF SERVICE

I hereby certify that on June 13, 2025, a copy of Patent Owner's Request for Discretionary Denial of Institution was filed by filing this document through the PTACT's System as well as delivering a copy via electronic mail upon the following:

Matthew A. Traupman
matthewtraupman@quinnemanuel.com
Elliot Choi
elliotchoi@quinnemanuel.com
Landon Andrew Smith
landonsmith@quinnemanuel.com

Respectfully submitted,

DUANE MORRIS LLP

By: /Patrick D. McPherson/
Patrick D. McPherson
Reg. No. 46,255
901 New York Avenue Suite 700 East
Washington, D.C. 20001

Dated: June 13, 2025

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 11,575 words as calculated by the “Word Count” feature of Microsoft 365, the word processing program used to create it.

Respectfully submitted,

DUANE MORRIS LLP

By: /Patrick D. McPherson/
Patrick D. McPherson
Reg. No. 46,255
901 New York Avenue Suite 700 East
Washington, D.C. 20001

Dated: June 13, 2025