

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

REGENX SCIENCE, INC.,
Petitioner,

v.

NEXTGEN BIOLOGICS, INC.,
Patent Owner.

Case IPR2025-00620

U.S. Patent No. 10,617,790

**PETITIONER'S OPPOSITION TO PATENT OWNER'S REQUEST FOR
DISCRETIONARY DENIAL OF INSTITUTION**

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TABLE OF EXHIBITS

Exhibit	Description
1001-1061	<i>Previously presented.</i>
1062	<i>Reserved.</i>
1063	September 23, 2014 ISE-Synogen License
1064	October 15, 2014 Synogen-NeXtGen License
1065	[REDACTED]
1066	[REDACTED]
1067	April 5, 2019 ISE Termination Letter
1068	September 16, 2019 Amended Demand for Arbitration
1069	October 15, 2019 Emergency Motion to Confirm Arbitration Award
1070	December 3, 2019 Final Arbitration Award
1071	January 6, 2020 Emergency Motion to Confirm Final Arbitration Award
1072	March 31, 2020 Final Judgment
1073	May 5, 2020 Notice of Bankruptcy
1074	August 7, 2020 Settlement Agreement
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1078	[REDACTED]
1079	[REDACTED]
1080	[REDACTED]
1081	U.S. Patent Application No. 16/399,068 Prosecution History (September 13, 2019 Power of Attorney)
1082	U.S. Patent Application No. 16/399,068 Prosecution History (July 31, 2020 Abandonment)
1083	Excerpted '790 Patent Prosecution History (October 22, 2018-January 10, 2019)

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Exhibit	Description
1084	Excerpted ’790 Patent Prosecution History (July 2, 2019-March 25, 2020)
1085	Excerpted ’376 Patent Prosecution History (February 26, 2020-January 24, 2023)
1086	July 16, 2019 Letter from ISE
1087	Declaration of Elisabeth Corson
1088	Memorandum on Interim Processes for Patent Trial and Appeal Board Workload Management
1089	U.S. Patent Application Publication No. US2025/0134801 A1 (U.S. Application No. 18/837,137), published May 1, 2025
1090	International Publication No. WO2023/154873 A2, “Novel methods for decellularizing extracellular matrix,” published August 17, 2023 (PCT/US2023/062398)
1091	House Report 112-98, Part 1 – America Invents Act (H.R. 1249) (June 1, 2011)
1092	October 9, 2019 Interim Injunctive Relief Award
1093	October 7, 2021 NeoMatriX 510(k) Approval Letter

I. INTRODUCTION

Patent Owner NeXtGen Biologics, Inc. (“NeXtGen” or “Patent Owner”) spends the majority of its discretionary denial brief arguing the merits of RegenX Science, Inc.’s (“RegenX” or “Petitioner”) Petition. That is not surprising given that most of the factors that typically factor into a discretionary denial analysis are not present. Most notably, there is no parallel district court litigation and therefore there are no concerns about duplicative proceedings.

Moreover, notwithstanding Patent Owner’s arguments to the contrary, denial under 35 U.S.C. § 325(d) is not appropriate here. As set forth in Section III, none of Petitioner’s prior art references—Badylak 2004, Badylak 2009, Freyman, McCusker, McGann, Keating, Van Dyke, and Gilbert 2005—were substantively considered during prosecution. Indeed, none of the six references that form the basis for Ground I were even before the Examiner.

In an attempt to shoehorn these undisclosed references into a Section 325(d) denial, Patent Owner declares, based solely on attorney argument, that all of these references are cumulative of prior art considered during prosecution. In doing so, Patent Owner repeatedly mischaracterizes the teachings of the cited prior art. As set forth in Section III, Petitioner’s references address the very gaps the applicant relied upon to obtain U.S. Patent No. 10,617,790 (the “790 patent”). They are not cumulative and instead provide a clear, rational basis for why a POSA would have

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combined these teachings to apply known ECM processing methods to urodele tissues to produce a urodele ECM xenograft with a reasonable expectation of success. That is dispositive under the *Advanced Bionics* framework and discretionary denial under 35 U.S.C. § 325(d) is not appropriate.

Under the guise of addressing the alleged weakness of the Petition, Patent Owner then makes numerous merits-based arguments. None of them have merit and, if anything, they simply confirm that institution is appropriate so that the Board can resolve the parties’ technical and factual disputes based on a complete record. As further detailed in Section IV.A, Patent Owner’s argument that the Petition lacks particularity under 35 U.S.C. § 312(a)(3) is unfounded. The Petition asserts three—and only three—clearly delineated grounds, each based on a single defined combination of references joined by “and”—rather than a set of interchangeable or optional permutations based on “and/or” and “one or more.” Pet. 6. Petitioner provides an element-by-element mapping of each challenged claim to specific disclosures in Petitioner’s prior art references, with separate subsections addressing the preamble and each claim element. *Id.*, 29-68. In each subsection, the Petition identifies where each claim element is disclosed and explains how and why a POSA would have combined the teachings with a reasonable expectation of success. *Id.* Patent Owner’s own analysis, which categorizes the references by subject matter and

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attempts to critique their content, only reinforces the clarity of Petitioner’s arguments, warranting institution under 35 U.S.C. § 312(a)(3).

Moreover, as discussed in Sections IV.B and IV.C, the Petition presents a strong unpatentability challenge and there was a strong motivation for a POSA to combine the cited art. Patent Owner contends that Petitioner’s references reflect fundamentally different approaches to regeneration and are therefore incompatible. But that argument misrepresents the teachings of the art and ignores the shared premise underlying all the references: using extracellular signals to stimulate regeneration in xenogeneic applications. A POSA would have viewed the references as complementary, not conflicting, and understood their combined teachings as supporting the development of urodele-derived ECM xenografts as claimed.

Next, as set forth in Section V, Patent Owner’s assertion that the parties operated under “settled expectations” regarding the ’790 patent is contradicted by the record. Petitioner’s licensing history, which involved two different license agreements with two different licensors, both of which were improperly terminated, is the antithesis of settled expectations. It was defined by instability, including shifting ownership, arbitration, bankruptcy, litigation, and disputes over enforceability and supply obligations. Petitioner spent years navigating a fractured and uncertain licensing regime, with no substantive role in prosecution and no assurance that its rights would be honored, culminating in Patent Owner’s unilateral

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termination of the license agreement in violation of its terms, just months before the Petition was filed. The Supreme Court has long rejected the notion that licensing precludes validity challenges, and Patent Owner itself included a provision anticipating such a challenge. There is no basis to infer that either Petitioner or Patent Owner maintained a settled belief in the validity of the ’790 patent.

Finally, as explained in Section VI, there are no compelling public interests that support discretionary denial. Patent Owner trumpets its NEOMATRIX product as a reason for discretionary denial, but that product has been a failure. Despite being cleared by the FDA in 2021, it has yet to reach full-scale commercial adoption. If anything, this failure supports institution. Likewise, Patent Owner’s “competitive interests” policy argument ignore that it was Patent Owner, not Petitioner, who unilaterally terminated the parties’ license agreement—an act that Petitioner believes is a breach of that agreement. Again, this is not a legitimate basis for discretionary denial.

In sum, Patent Owner’s arguments rest on a selective and misleading portrayal of the record. They misrepresent the prior art, ignore or misstate critical disclosures, misapply the law, and distort the licensing history to manufacture support for their request. Accordingly, institution is appropriate for the reasons detailed further below.

II. BACKGROUND

Petitioner seeks cancellation of claims 1-12, 14-16, and 18-34 (the “Challenged Claims”) of the ’790 patent (Ex.1001), assigned to NeXtGen.

The independent claims (claims 1, 20, and 32) of the ’790 patent are product by process claims directed to a tissue graft, medical implant, or material for use comprising decellularized urodele extracellular matrix (“ECM”) produced by obtaining, decellularizing, and sterilizing a urodele tissue. The dependent claims (2-12, 14-16, 18-19, 21-31, and 33-34) set forth additional limitations for the claimed biomaterials, including their physical forms (e.g., powder, mesh, gel, paste, or sheet), types and sources of the ECM, additives (e.g., growth factors, human cell, or anti-microbial agents), method of production, and further processing steps.

The Petition identifies three clearly defined grounds. The Ground I References—Badylak 2004, Badylak 2009, Freyman, McCusker, McGann, and Keating—form the basis for the unpatentability of all Challenged Claims. Ground II adds Gilbert 2005 for claims relating to ECM particle size. Ground III further includes Van Dyke for claims concerning additives to the urodele-derived ECM xenograft.

As discussed in Section IV.B, Petitioner presents a straightforward and well-supported unpatentability challenge. By January 2013, decellularization and related processing methods for ECM scaffolds were well studied and, as admitted by the

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applicant, had become standard practice for producing functional xenogeneic ECM scaffolds. Ex.1002, ¶55; Ex.1001, 2:43-59, 9:55-11:53; Ex.1004, 847; Ex.1010, 3681; Ex.1023; Ex.1015. The prior art taught that regenerative signaling pathways were conserved across species, and as a result, xenogeneic ECMs from a wide range of species (e.g., dog, rat, pig, boar, monkey, horse, and cow) were successful, confirming that the use of ECM xenografts was not limited to specific animal sources. Pet., 14-16.

In line with these teachings, the applicant conceded that “removing cells to produce a non-toxic graft [was] straight forward” and that the ’790 patent “did not invent a new process of decellularization,” identifying its sole purported invention as “a new graft material”—ECM derived from urodele tissue. Ex.1004, 847. Accordingly, by the applicant’s own account, the only purported invention of the ’790 patent is the use of urodele tissue, in particular axolotl, as the source material for ECM xenografts.

That choice, however, was itself obvious. Urodeles were well known for their exceptional regenerative capabilities, and the prior art recognized that the signaling pathways responsible for these properties in urodeles, specifically, axolotl, were also conserved in humans. For example, the art taught that “[t]he remarkable regenerative abilities of salamanders demonstrate what can reasonably be expected in enhancing human regenerative potential...[t]hus, *we can expect to stimulate*

regeneration in a human by the same mechanisms used by the axolotl.” Ex.1025,

566. Given these teachings, a POSA would have been motivated to select urodele, including axolotl, as a source for xenogeneic ECM.

III. DISCRETIONARY DENIAL UNDER § 325(d) IS NOT APPROPRIATE HERE

None of references relied upon in Ground I were before the Examiner and only the Van Dyke reference, cited in Ground II, was cited in an IDS; however, that reference was never substantively addressed by the Examiner. Notwithstanding these facts, Patent Owner (at 11) argues that discretionary denial under 35 U.S.C. § 325(d) is appropriate because “Petitioner relies solely on art and arguments that are the same or substantially the same as those considered by the Examiner during prosecution.” That assertion is without merit. As noted above, none of the Ground I References are the same as those considered by the Examiner as none of these references were cited in IDS. Moreover, Petitioner’s cited art is not substantially the same as the art considered by the Examiner. The art cited in the Petition discloses distinct subject matter concerning ECM xenografts never raised during prosecution, provides a motivation and rationale for selecting axolotl-derived ECM, and fills the very gaps the applicant identified as a basis for allowance of the ’790 patent. Petitioner’s references are not cumulative, and the Examiner’s failure to substantively consider this art and the teachings therein warrants institution.

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First, Patent Owner argues (at 17) that “all of Badylak 2004 (EX1005), Badylak 2009 (EX1008), Freyman (EX1015), Van Dyke (EX1023), and Gilbert (EX1032) are cumulative in view of Asem cited and applied by the Examiner in original prosecution.” However, Asem discloses a narrow, highly specific composition “directed to the basement membrane of avian and reptile follicles and the use of same to support the growth and differentiation of eukaryotic cells cultured in vitro.” Ex.2001, Asem, 1:12-19. Critically, Asem does not disclose or suggest using follicular ECM in xenogeneic applications, nor does it address whether its compositions could be derived from urodele or axolotl tissues. Indeed, the applicant during prosecution explicitly distinguished Asem on these very grounds. The applicant stated that “Asem’s intended use is not as a xenograft” and that follicular tissue is “unique,” such that a POSA would have no reason to “substitute the material of [axolotl ECM] for that of Asem.” Ex.1004, 726, 743, 841-842, 849.

Petitioner’s references teach exactly what Asem does not. Badylak 2004, Badylak 2009, Freyman, Van Dyke, and Gilbert (collectively, the “ECM Xenograft References”) reflect the state of the art as of the priority date that xenogeneic ECMs were routinely derived from a wide range of tissues and animal species for use in cross-species applications. Exs.1005, 1008, 1015, 1023. For example, they report that, by January 2013, more than 200,000 patients had received ECM-based grafts from a variety of different animal sources, each tailored to specific clinical needs

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using a variety of known ECM sources, decellularization techniques, additives, and processing methods. Ex.1008, 1–8, Table 1; Ex.1005, 369–374.

These references also explain why xenogeneic ECMs from diverse species were effective: because the signaling pathways involved in tissue repair and regeneration are conserved across species. Ex.1005, 367; Ex.1008, 4–5. Moreover, they provide detailed protocols for decellularization tailored for different uses, aimed at minimizing immune rejection while preserving bioactivity—precisely the type of teaching Asem lacks. *Id.* Collectively, these references confirm to a POSA that xenogeneic ECMs and their manufacturing methods were well-established and could be successfully applied to a variety of animal tissues, including axolotl, to produce xenogeneic ECM grafts as claimed.

Patent Owner’s argument that Petitioner’s xenograft-focused references are cumulative of Asem is therefore incorrect. Petitioner’s references disclose materially distinct subject matter, including the use of ECMs in xenograft applications across species and the general applicability of ECM processing methods beyond a single tissue type or species. As noted above, these are precisely the gaps the applicant identified during prosecution as reasons for allowance. If, as the applicant argued, Asem fails to teach xenograft use or its applicability to other animal sources, then references that do teach those concepts cannot, by definition, be cumulative. Moreover, Petitioner’s prior art goes even further by providing a

rationale for success of xenogeneic ECMs: conservation of regenerative signaling pathways across species. The ECM Xenograft References provide both a motivation and a reasonable expectation of success in selecting another animal source, e.g., urodele, for ECM xenograft applications. Asem contains no such teachings and offers no basis for making that leap.

Second, Patent Owner’s assertion (at 17-18) that McGann (Ex.1026) and Keating (Ex.1027) are cumulative of Smith (Ex.2002) is likewise without merit. Smith merely characterizes the collagen types present in salamander skin and cartilage; it says nothing about the use of urodele ECM in xenogeneic regenerative applications. Moreover, as the applicant noted during prosecution, Smith disclosed “no decellularization,” and “no isolation, purification, or characterization of ECM.” Ex.1004, 647. Instead, “[t]he ECM...[in] Smith [was] actually completely destroyed.” *Id.*, 647-648.

In contrast, McGann and Keating provide experimental support for the use of urodele ECM in xenogeneic applications. McGann demonstrates that regeneration extracts derived from newt tissues—containing extracellular proteins—can reactivate the cell cycle in mammalian cells, causing them to dedifferentiate and divide into regenerative cell types. McGann attributes this effect to soluble extracellular ligands likely present in the newt ECM. Ex.1026, 13704.

Keating reinforces and extends these findings by disclosing methods for promoting mammalian tissue regeneration using regenerating newt limb extracts (RNLE). Keating teaches that these extracts can induce dedifferentiation across species, including in mammalian tissues such as humans. Moreover, both McGann and Keating prepared their extracts by removing cellular debris, resulting in materials that were decellularized, and those extracts retained extracellular components, including growth factors.¹ *See, e.g.*, Ex.1026, 13699-13700; Ex.1027, [0131].

¹ Patent Owner’s argument that “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” mischaracterizes Keating and McGann. Both references expressly teach that their extracts contain ECM components, including growth factors, and reflect the use of xenogeneic material, as set forth further below. Pet. 33-37; Ex.1027, Table C1 (listing “extracellular” components in the regenerating extract), [0010], [0017], [0021]-[0027], [0122]-[0131], [0215],[0341]-[352], Tables III and IV; Ex.1002, ¶¶109-111; Ex.1026, 13704.

Together, Keating and McGann provide experimental evidence and rationale supporting the use of urodele ECM components—disclosures directly relevant to a POSA’s motivation and reasonable expectation of success. Smith, by contrast, contains no disclosure of decellularization, ECM characterization, or xenogeneic regenerative applications. Patent Owner wrongly equates Smith with McGann and Keating despite these fundamental differences.

Finally, Patent Owner argues (at 18-19) that McCusker is cumulative of Smith (Ex.2002), Satoh (Ex.2003), and Seifert (Ex.2004) with respect to teachings regarding the regenerative potential of urodeles. But Smith, Satoh, and Seifert focus narrowly on biochemical or localized mechanisms of salamanders, and say nothing about the relevance of those mechanisms to human regeneration or the suitability of axolotl as a model for developing human therapies—precisely the connection that McCusker makes and that Petitioner relies on. *See, e.g.*, Pet., 2-3, 35-36, 44-45.

Specifically, Smith reports on the characterization of collagen types in salamander skin and cartilage, primarily to enable the study of collagen metabolism during regeneration, but does not address conserved regenerative signaling pathways in salamander or how these conserved pathways can be extrapolated to humans. Ex.2002, 243. Satoh focuses on the accessory limb model to study limb regeneration in axolotls, emphasizing collagen’s inhibitory effects on nerve-epidermis interactions and apical epithelial cap formation, but does not discuss molecular

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conservation across species or implications for xenogeneic grafting. Ex.2003, 191-192. Seifert describes scar-free skin healing in axolotls, attributing it to reduced inflammation and ECM remodeling, yet makes no mention of signaling pathway conservation or suitability for use in human xenograft applications. Ex.2004, 1.

In contrast, McCusker explicitly identifies axolotl as a “model organism for identifying the relevant signaling pathways and factors” involved in regeneration. Ex.1025, 565; Ex.1002, ¶137. McCusker also teaches that “the mechanisms of regeneration involve many basic biological processes regulated by conserved signaling pathways,” and that “***we can expect to stimulate regeneration in a human by the same mechanisms used by the axolotl.***” Ex.1025, 565–566; Ex.1002, ¶137. These disclosures—absent from Smith, Satoh, or Seifert—would have further motivated a POSA to investigate axolotl ECM for xenograft applications. Ex.1002, ¶137. McCusker draws the straightest line from axolotl biology to the expectation of regenerative benefit through xenograft applications—exactly the kind of motivation a POSA would have needed to choose urodele tissue as a source of ECM xenograft.

Moreover, Patent Owner suggests (at 21-23) that Petitioner was required to “demonstrate that the Office erred in a manner material to patentability in allowing the Challenged Claims” and “cannot satisfy the second part of the *Advanced Bionics* test.” But, the law is clear that the second prong of *Advanced Bionics* needs to be

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considered only if the same or substantially same art was before the Examiner. *Advanced Bionics, LLC v. Med-el Elektromedizinische Geräte GmbH*, 2020 WL 740292, at *8 (Patent Tr. & App. Bd., 2020) (the Board reaches the second prong only if “condition of the first part of the framework is satisfied.”); *Apple Inc. v. Carbyne Biometrics, LLC*, 2024 WL 3432614, at *6 (PTAB 2024) (“Since the first prong of the *Advanced Bionics* framework is not satisfied, we need not reach the second prong”; granting institution under 35 U.S.C. § 325(d)); *Godbersen-Smith Constr. Co. v. Guntert & Zimmerman Const. Div., Inc.*, 2021 WL 2036531, at *4 (PTAB 2021) (same); *Oticon Medical Ab v. Cochlear Limited*, 2019 WL 5237817, at *8 (Patent Tr. & App. Bd., 2019) (same). As discussed above, the Petition does not rely on the same or substantially the same art as the Examiner and thus there is no need to demonstrate material error during prosecution.

Even if these references and arguments were deemed substantially similar (they are not), the Examiner materially erred by failing to consider the breadth of established xenograft applications at the time, the well-known conservation of regenerative signaling pathways across species, including between axolotl and human, and the recognized use of urodeles in xenogeneic applications. These teachings would have provided a POSA with a clear motivation and reasonable expectation of success in applying existing ECM processing methods to urodele tissues to produce a urodele based ECM xenograft. In view of this art, the Examiner

made a material error in failing to find that the claimed use of axolotl ECM as a xenograft was obvious.

IV. THE ALLEGED WEAKNESS OF THE UNPATENTABILITY CHALLENGE IS PREMISED UPON PATENT OWNER’S MISCHARACTERIZATIONS OF THE PETITION

A. The Petition Complies With 35 U.S.C. § 312(a)(3) and Identifies the Obviousness Grounds and Evidence With Particularity

Patent Owner next argues (at 24-25) that discretionary denial is appropriate under 35 U.S.C. § 312(a)(3) because the Petition allegedly does not articulate “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.” In particular, according to Patent Owner (at 24-25), Ground I is based on a “mélange” of seventeen different prior art references—six “primary” and eleven “secondary” references—and that “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.” In making this argument, Patent Owner repeatedly mischaracterizes the Petition to create a strawman upon which to base its Section 312(a)(3) challenge.

None of these characterizations of the Petition are accurate. First, Ground I relies on six and only six references, which are explicitly identified in the Petition. Pet., 6, 29-61. And notably, the Petition does not use “and/or” language for Ground

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I; Ground I is based on the combination of all six references. Ground I does not rely on any secondary references and the Patent Owner never identifies what it considers to be the eleven “secondary” references that allegedly are included in Ground I. The mere fact that an exhibit is cited in the Detailed Grounds of Invalidity does not mean that it is part of the ground. For example, the Petition cites a paper, Stocum 2002, to support the factual statement that urodeles “can regenerate entire limbs, spinal cords, and even portions of the heart.” Pet., 32. Patent Owner appears to be taking the position that by citing Stocum 2002 to support this factual statement, Stocum 2002 became a “secondary” reference that is part of Ground I. Yet, Patent Owner cites no authority to support this argument. The Petition is clear that Ground I is based on six specifically enumerated prior art references, not seventeen references, as Patent Owner alleges.

Second, Patent Owner’s criticisms that the Petition fails to explain where the six Ground I references disclose each claim element are similarly misplaced. For each of the three independent claims—claims 1, 20, and 32—the Petition has separate subsections for the preamble and the two substantive claim elements. Pet., 29-41, 54-55, and 59-61. In each subsection, the Petition cites to the specific portions of the Ground I prior art references that disclose each claim element and explain why a POSA would have been motivated to combine these references with

a reasonable expectation of success. *Id.* A similar analysis follows for each of the challenged dependent claims. *Id.*, 41-54, 55-60, 61-68.

Petitioner thus provides a detailed, element-by-element mapping of each challenged claim to the cited prior art references, identifies the specific disclosures relied on, and articulates the rationale for combining them. This includes clear citations to the relevant portions of the prior art and explanations of how each reference addresses the corresponding claim limitation. Under the Board’s case law, this satisfies the particularity requirement under § 312(a)(3). *FanDuel, Inc. v. Cg Tech. Development, LLC*, 2018 WL 5269266, at *29 (Patent Tr. & App. Bd., 2018) (“The Petition’s clause-by-clause analysis of each challenged claim, and citation to the specific portions of the prior art that disclosed the recited element or limitation fully complied with the applicable statutory and regulatory requirements.”).

Third, utilizing its factually inaccurate characterization of Ground I as including seventeen prior art references, Patent Owner cites *Ikea Supply AG v. Everlight Elecs. Co., Ltd*, IPR2024-00988, Paper 6 (PTAB Dec. 12, 2024) to argue (at 26) that “Petitioner’s proposed combination of seventeen different references gives rise to **131,071** potential combinations.” Beyond its mischaracterization of Ground I as including seventeen reference, Patent Owner’s reliance on *Ikea* is misplaced. In that proceeding, the petitioner relied on a primary reference combined with “one or more of” multiple secondary references listed with “and/or,” creating

ambiguous, undefined combinations across *twelve* separate grounds. *Ikea Supply AG v. Everlight Elecs. Co., Ltd*, IPR2024-00988, Paper 6, 10-12, 29. No such ambiguity, or excessive number of grounds, exists here. The Petition includes only three grounds and, unlike the petition in *Ikea*, it does not use “one or more” or “and/or” language. It uses “and” language. Thus, each ground presents only a single combination of references, not 131,071 as Patent Owner alleges.

In fact, Patent Owner implicitly acknowledges the clarity of structure and substance of Petitioner’s references and combinations. It categorizes the cited references by subject matter and attempts—albeit incorrectly as discussed above—to critique them, confirming that the Petition clearly identifies the role of each reference and how a POSA would have understood their collective teachings. *Philip Morris Products, S.a. v. Rai Strategic Holdings, Inc.*, 2021 WL 3438555, at *16 (Patent Tr. & App. Bd., 2021) (granting institution under § 312(a)(3) where patent owner’s response “demonstrat[ed] that it fully comprehends the scope and content of Petitioner’s challenges.”). Petitioner satisfied the particularity requirement under 35 U.S.C. § 312(a)(3).

B. The Unpatentability Challenge is Strong

Contrary to Patent Owner’s assertion (at 23), the Petition is not weak. Petitioner presents a strong and straightforward unpatentability challenge that warrants institution.

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Claims 1, 20, and 32—the only independent claims among the Challenged Claims—each recite only two elements beyond their preambles. First, they require “obtaining a tissue sample from a urodele, which tissue sample comprises extracellular matrix” and second they require “decellularizing” or “decellularizing and sterilizing” “to produce decellularized extracellular matrix.” But, the applicant candidly admitted during prosecution that “Applicant did not invent a new process of decellularization.” Ex.1004, 847. This statement is amply supported by Badylak 2004, Badylak 2009, and Freyman, three of the six references cited in Ground 1, which show that decellularization processes were well known and applied broadly across a broad range of species.

Accordingly, by the applicant’s own account, the only purported inventive aspect of the ’790 patent is the use of urodele tissue—including axolotl—as the source material for producing ECM xenografts: “A key aspect of the present invention is the inventor’s recognition that the growth factor profile, connective tissue matrix constituents, and immunoprivileged status of urodele ECM and accompanying cutaneous tissue, plus the presence of antimicrobial peptides therein, render urodele-derived tissue an ideal source for biological scaffolds for xenotransplantation.” Ex.1001, 4:64-5:3. But as demonstrated by McCusker, McGann, and Keating—the other three references included in Ground 1—the choice

of urodele ECM would have been obvious because the prior art already recognized its properties as well-suited for xenogeneic use. Pet., 32-37.

Specifically, McCusker taught that the mechanisms of regeneration in axolotl “involve many basic biological processes regulated by conserved signaling pathways,” and scientists “*expect[ed] to stimulate regeneration in a human by the same mechanisms used by the axolotl.*” Ex.1025, 566; Ex.1028, 277; Ex.1029, 20 (“[B]ased on our knowledge that genes and their functions are highly conserved between species, the idea of using the axolotl... to uncover the mechanisms leading to ... regeneration in mammals is an excellent approach.”). In other words, McCusker taught that just as the conserved ECM components enabled the success of xenogeneic ECM grafts, the conserved regeneration signaling pathways in urodeles suggested that their ECM could similarly facilitate tissue regeneration in other species (e.g., humans) without causing adverse reactions. Ex.1002, ¶108.

Keating further reinforced these findings. Keating describes a composition and an experimental method for promoting tissue regeneration in mammalian cells using regenerating newt limb extracts (“RNLE”). See, e.g., Ex.1027, [0010], [0017], [0021]-[0027], [0122]-[0131], [0215], [0341]-[352]; Ex.1002, ¶¶88-89, 110-111. Consistent with McGann, Keating discloses that RNLE “induced the dedifferentiation of ... murine myotubes in culture,” confirming that “mammalian (murine) myotubes are capable of dedifferentiating in response to dedifferentiation

signals received from regenerating newt limbs.” Ex.1027, [0027]; Ex.1002, ¶¶88-89, 110-111. Keating teaches that these findings support the use of RNLE to “dedifferentiate tissue from, for example, humans.” Ex.1027, [0027]; Ex.1002, ¶¶110-111. Importantly, Keating discloses that regenerating extracts can be prepared from “any animal that regenerates, for example, urodeles (newt or *axolotl*),” and states that such extracts would likely include ECM components. *See*, Ex.1027, [00129] and Table C1 (listing “extracellular” components in the regenerating extract); *see also, id.*, [0010], [0017], [0021]-[0027], [0122]-[0131], [0215], [0341]-[352], Tables III and IV; Ex.1002, ¶111. Keating further reinforces urodele ECM’s potential use as a xenograft source material. *Id.* Ex.1002, ¶111.

Patent Owner fails to address the full scope of these teachings and constructs a strawman by mischaracterizing the references and taking them out of context to argue (at 23) that “[t]he weakness of the unpatentability challenge warrants discretionary denial.” But the prior art is clear, consistent, and compelling. It would have provided a POSA ample motivation to select axolotl ECM with a reasonable expectation of success for use as ECM xenografts as claimed.

C. A POSA Would Have Had a Strong Motivation to Combine Petitioner’s References

Patent Owner argues (at 27-40) that discretionary denial is appropriate because a POSA would not have been motivated to combine Petitioner’s references,

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which Patent Owner claims reflect fundamentally different approaches to cellular regeneration. As a threshold matter, Patent Owner never explains how this argument relates to discretionary denial. Patent Owner’s brief contains a different subsection on the alleged weakness of the unpatentability challenge. Instead, Patent Owner presents several merits arguments regarding the alleged teachings of the prior art all based on attorney argument and without expert testimony. But, the Director’s Memorandum on Interim Processes for Patent Trial and Appeal Board Workload Management makes clear that merit-based issues are distinct from discretionary considerations. Ex.1088, 1. Indeed, the fact that Patent Owner spends over a dozen pages disputing the technical teachings of the prior art only highlights why it is appropriate for the Board to institute the petition and resolve these disputes based on a full record.

In any event, Patent Owner’s characterizations of the prior art are wrong. Patent Owner contends (at 27-35) that McCusker, McGann, and Keating are “irreconcilable” with the xenograft-based strategies disclosed in the ECM Xenograft References. But this argument rests on a mischaracterization of the references, which Patent Owner selectively frames to create the appearance of conflict where none exists. In fact, the references describe related approaches that rely on the same biological principle: that the signaling mechanisms for tissue repair are highly conserved across species such that regenerative signals derived from axolotl tissue

can be used to stimulate mammalian tissue repair. Pet., 3, 31, 33-37. A POSA would not have seen these approaches as conflicting, but as compatible strategies that could be used together to successfully develop an ECM xenograft using axolotl tissue. *Id.*

Patent Owner concedes (at 27) that the ECM Xenograft References “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.” It then claims (at 27-28) that McCusker “teaches the opposite approach...[of] *culturing* fibroblast cells from the source tissue, and using those cells as a target for regeneration and rejuvenation therapies.”

That is simply wrong. McCusker says nothing about culturing fibroblasts for transplantation or therapeutic use—much less suggest that as an “opposite approach” to ECM scaffolds. McCusker explains that fibroblasts are the endogenous cells within the axolotl that *respond* to regenerative signaling after injury. Ex.1025, 569-570. McCusker teaches that regeneration is initiated by signals from the nerve and wound epithelium (“WE”) that cause resident dermal fibroblasts near the wound to dedifferentiate and form a blastema—not that fibroblasts are cultured, manipulated, or administered as therapy. *Id.* Specifically, McCusker explains, “[i]n response to injury, connective tissue fibroblasts within a few hundred micrometers of the wound are induced to dedifferentiate and migrate to form the blastema,” and that “signaling

between the nerves and the WE is critical for inducing and maintaining the blastema, and it is the fibroblasts that are the target cells of those signals.” Ex.1025, 569.

McCusker further explains that these regenerative mechanisms are driven by “highly conserved” signaling pathways and concludes that “humans have the potential to regenerate structures in the same way as salamanders.” *Id.* at 565. The point is not to transplant fibroblasts—but to understand and harness the conserved signaling processes that govern them for application in humans. *Id.*, 565-571.

A POSA would have therefore recognized that McCusker reinforces the use of signaling-rich xenogeneic ECM scaffolds to stimulate endogenous regeneration—not the culturing or transplantation of cells, as Patent Owner wrongly asserts. McCusker emphasizes that regeneration is governed by conserved signaling pathways that act on resident fibroblasts, and never suggests culturing or delivering fibroblasts as a therapeutic product. Ex.1025, 565-566, 569-570. The concept of using extracellular signals to activate a host’s regenerative program is entirely consistent with the teachings of the ECM Xenograft References, which describe the use of decellularized ECM scaffolds to deliver such signals.

Patent Owner additionally contends (at 35) Keating and McGann, the so-called “Newt Extract references,” “are the antithesis of ECM xenotransplant” because they allegedly “destroyed and discarded all ECM components resulting in a protein-rich supernatant that has nothing to do with the invention claimed in the ’790

patent.”² Patent Owner again misrepresents what these references actually teach. Keating and McGann do not reject ECM-based regeneration; on the contrary, both disclose that their regenerative extracts included extracellular matrix proteins—such as collagens and glycoproteins. For example, Keating teaches that ECM components such as growth factors are present in the regenerating extract. *See, e.g.*, Ex.1027, [0215], Table C1 (listing “extracellular” components present in the regenerating extract); *see also id.*, [0010], [0017], [0021]–[0027], [0122]–[0131], [0341]–[0352], Tables III and IV; Ex.1002, ¶¶88–89, 110. Keating further teaches that regenerating extracts containing these extracellular components “induced the dedifferentiation of ... murine myotubes in culture,” confirming that “mammalian (murine) myotubes are capable of dedifferentiating in response to dedifferentiation signals received

² Patent Owner specifically faults Keating and McGann (at 33) for “homogenizing” newt tissue, but the ’790 patent explicitly discloses that the claimed ECM xenograft “can take on any variety of shapes, as the material can be formed, laminated, **homogenized**, gelled, etc.” Ex.1001, 6:61-62; *see also* claim 6 (“wherein the ECM is a powder”), and claim 20 (“implant comprising...sterile urodele fraction”). Thus, far from being contrary to the ’790 patent, Keating and McGann reflect precisely the types of ECM processing and forms the ’790 patent teaches and claims.

from regenerating newt limbs.” Ex.1027, [0027]; Ex.1002, ¶110. McGann similarly teaches that the extract contains “soluble extracellular proteins acting as ligands to activate receptors that transduce dedifferentiation signals through receptive cells, such as myotubes.” Ex.1026, 13704. A POSA would have understood both references as affirming—rather than undermining—the biological relevance of urodele ECM components in promoting regenerative responses across species.

Petitioner’s references are therefore not “irreconcilable.” Instead, they share the common focus on extracellular matrix materials in regenerative medicine. Patent Owner, instead of addressing the full scope of these disclosures, constructs a strawman—deliberately mischaracterizing the references and taking them out of context to artificially manufacture contradictions in support of a purported lack of motivation—despite the references being compatible and complementary. Patent Owner’s assertion runs “afoul of KSR’s basic mandate in a number of ways” by “fail[ing] to consider the interrelated teachings of multiple references, the background knowledge possessed by a person having ordinary skill in the art, or the inferences and creative steps that a person of ordinary skill in the art would employ.” *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 97 F.4th 915, 929 (Fed. Cir. 2024); *see also, Elekta Ltd. v. ZAP Surgical Sys., Inc.*, 81 F.4th 1368, 1374 (Fed. Cir. 2023)(“The inquiry into the existence of a motivation to combine assumes that a skilled artisan is a person of ordinary creativity with common sense, common

wisdom, and common knowledge.”); *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 420-421 (2007) (“A person of ordinary skill is also a person of ordinary creativity, not an automaton.”).

Petitioner’s references make clear that applying known decellularization techniques for making xenogeneic ECMs to axolotl was not just a logical choice—it was an expected one. The ECM Xenograft References established the viability of cross-species ECM xenografts, McCusker identified axolotl’s conserved regenerative pathways present in humans, and Keating and McGann confirmed the bioactivity of urodele ECM components in xenogeneic applications. A POSA would have seen axolotl as a natural next step for xenogeneic ECM graft development and found the ’790 patent obvious.

Patent Owner’s assertion (at 38) that Petitioner’s “secondary” references—such as Seifert, Hoshiba, and Hayashi—“further complicate its obviousness combinations” and render Petitioner’s grounds “more unconvincing” is premised on Patent Owner’s strawman argument that these “secondary” references are part of the obviousness grounds. As discussed in Section IV.A, these references are not part of the obviousness grounds; they are cited solely to provide context and reflect the state of the art. The Petition does not rely on them to meet any claim limitations or as part of any asserted combination. Rather these “secondary” references were cited to support factual assertions in the Petition. For example, Seifert is cited to show that

axolotls were widely studied for their regenerative biology, not for any disclosure regarding decellularized ECMs. Pet. 17-18. Hoshiba is cited to reflect the general understanding that decellularized ECM xenografts, derived from a range of animal sources, were widely used in tissue engineering, not to provide any specific disclosure about the claimed elements. Pet., 13, 16. And Hayashi is cited to show that the field had explored xenogeneic ECMs from diverse animal tissues, including fish-derived collagens, illustrating the breadth of known sources at the time. Pet., 15. Because none of these references are part of any combination of prior art relied on to meet the claim limitations, there is nothing for them to “complicate” Petitioner’s obviousness grounds, as Patent Owner alleges. Patent Owner’s attempt to treat these contextual references as if they are part of the asserted grounds is incorrect and reflects a fundamental misrepresentation of both the Petition and the references themselves.

V. YEARS OF LICENSING INSTABILITY AND PETITIONER’S LIMITED ROLE IN PROSECUTION PRECLUDE ANY SETTLED EXPECTATIONS REGARDING THE ’790 PATENT

Patent Owner (at 40-48) contends that the licensing history of the ’790 patent gave rise to settled expectations that Petitioner would not challenge the ’790 patent’s validity following Patent Owner’s unilateral termination of the license agreement in 2024. As a threshold matter, Patent Owner does not cite to any authority that entering into a patent license creates a settled expectation that the licensee will not

challenge the validity of patent. To the contrary, in *Lear, Inc. v. Adkins*, 395 U.S. 653, 670 (1969), the Supreme Court rejected the doctrine of licensee estoppel and expressly held that the public interest weighs in favor of a licensee being able to challenge the validity of licensed patents:

[T]he equities of the licensor do not weigh very heavily when they are balanced against the important public interest in permitting full and free competition in the use of ideas which are in reality a part of the public domain. ***Licensees may often be the only individuals with enough economic incentive to challenge the patentability of an inventor’s discovery. If they are muzzled, the public may continually be required to pay tribute to would-be monopolists without need or justification.***

(emphasis added). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] This is the antithesis of a settled expectation that licensee would not challenge these patents. Moreover, Patent Owner’s public policy arguments (at 48) in “licensing and contractual stability” are directly foreclosed by *Lear*, which recognizes that there is an “important public

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interest in permitting full and free competition in the use of ideas which are in reality a part of the public domain” and that this interest outweighs the “equities of the licensor.” *Lear*, 395 U.S. at 670.

In any event, even if licensor-licensee relationship could give rise to settled expectations, that is not what happened in this situation. The parties’ history here, which Patent Owner repeatedly mischaracterizes, was anything but settled. Rather, it was defined by shifting ownership, repeated terminations, litigation, bankruptcy, and prolonged uncertainty over Petitioner’s licensing rights. That instability, together with Petitioner’s lack of any substantive involvement in prosecution, undermines any reasonable expectation that the patent’s validity would go unchallenged. Ex.1087, ¶¶1-40.

The licenses to the ’790 patent involved four separate entities: ISE Professional Testing & Consulting Services, Inc. (“ISE”), Synogen Management, Inc. (“Synogen”), Patent Owner NeXtGen Biologics, Inc., and Petitioner RegenX Science, Inc. Ex.1087, ¶7. In 2014, ISE, the original assignee of the patent portfolio that includes the ’790 patent, entered into a license agreement with Synogen (the “Synogen License”) in which Synogen was granted (i) an exclusive license to the urodele ECM patent portfolio, which included the application that matured into the ’790 patent (“Licensed Patents”); and (ii) a non-exclusive license to trade secret decellularization technology defined as “Licensed Know-How” (collectively, the

“Licensed Technology”). Ex. 1063, September 23, 2014 Synogen License, §2.2.1; Ex.1087, ¶8. Under the license, Synogen was to commercialize ISE’s urodele ECM technology, and as part of that endeavor, was responsible for “prosecut[ing] and maintain[ing]” the Licensed Patents. Ex. 1063, § 9.1; Ex.1087, ¶9. The Synogen License specified that Synogen was not permitted to “delegate this responsibility to a Third Party or an Affilliate.” *Id.* ISE was to “cooperate in all respects with [Synogen]’s efforts in preparing and prosecuting the Licensed Patents” and retained the right to “comment on prosecution.” *Id.* The Synogen License also provided that “in the event of termination...by [ISE], any Sublicense [e.g., Petitioner and Patent Owner] shall, at the Sublicensee’s option survive such termination...provided that Sublicensee and [ISE] enter into a direct license on substantially the same terms as the sublicense.” Ex. 1063, § 2.2; Ex.1087, ¶10.

In 2014, Synogen sublicensed the Licensed Patents to Patent Owner, granting it exclusive rights to develop diagnostic and therapeutic medical device applications. Ex. 1064, October 15, 2014 NeXtGen License; Ex.1087, ¶11. Synogen retained prosecution rights but required Patent Owner to cover certain prosecution-related costs (“NeXtGen License”). Ex.1064, § 9.1; Ex.1087, ¶11. [REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

But before any Licensed Patents had even issued,³ the licensing arrangement began to unravel, casting doubt over whether any sublicensees—including Petitioner—would retain any of the rights to the Licensed Patents that they were previously granted. Ex.1087, ¶14. In April 2019, ISE sent Synogen a notice of termination of the Synogen License, alleging breach of contract for, among others, deficiencies in reporting obligations. Ex. 1067, April 5, 2019 Termination Letter; Ex.1087, ¶15. Synogen and Patent Owner initiated arbitration in response, asserting that ISE obstructed prosecution of the Licensed Patents, withheld promised manufacturing know-how, and refused to acknowledge Patent Owner’s right of survival as a sublicensee upon termination of the Synogen License. Ex. 1068, September 16, 2019 Amended Demand for Arbitration; Ex.1087, ¶16.

ISE responded by threatening to “undermine, abandon, or invalidate” the Licensed Patents if the arbitration moves forward. Ex. 1069, October 15, 2019

³ The ’790 patent was the first to issue on April 14, 2020.

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Emergency Motion to Confirm Arbitration Award, at 5; Ex.1087, ¶17. It then revoked Synogen’s power of attorney before the USPTO and took control over prosecution. *Id.*; Ex. 1092, October 9, 2019 Interim Arbitration Award, 4-5; Ex. 1070, December 3, 2019 Final Arbitration Award, at 10-11; Ex. 1086, July 16, 2019 Letter from ISE. Synogen and Patent Owner subsequently won arbitration awards for injunctive relief against ISE, which enjoined ISE from “directly or indirectly, interfering with or impeding Synogen[]’s prosecution and preparation of the Licensed Patents.” Ex. 1070, at 27–28; Ex.1092; Ex.1087, ¶18.

The dispute did not stop there. ISE continued to violate the terms of the injunction, and Synogen and Patent Owner filed a separate lawsuit to enforce the arbitration award in the Circuit Court of the Ninth Judicial Circuit in and for Orange County, Florida. (Case No. 2019-CA-012605-O). Exs.1069-1071; Ex.1087, ¶19. Through extensive motions practice, Synogen and Patent Owner ultimately prevailed against ISE in 2020. Ex. 1072, March 31, 2020 Final Judgment; Ex.1087, ¶20. As a result of this proceeding, ISE filed for bankruptcy. Ex. 1073, May 5, 2020 Notice of Bankruptcy; Ex.1087, ¶20.

ISE, Synogen, and Patent Owner subsequently entered into a settlement. Ex. 1074, August 7, 2020 Settlement Agreement; Ex. 1075, September 5, 2020 Order Approving Settlement; Ex.1087, ¶21. As part of the settlement, Synogen acquired the rights to the Licensed Patents from ISE and assigned them to Patent Owner. *Id.*;

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Ex. 1076, October 5, 2020 Synogen Assignment; Ex.1087, ¶22. Petitioner was excluded from negotiating the terms of the settlement agreement, despite having a sublicense to the Licensed Patents. Ex.1087, ¶23. The settlement agreement required that “the Prior Agreements[, including the RegenX License] [were] ... terminated and cancelled, in all respects with no further or surviving obligations.” Ex. 1074, August 7, 2020 Settlement Agreement, at 8-9; Ex.1087, ¶24. Petitioner thus lost all rights to the Licensed Patents and was forced to renegotiate a new license on substantially different terms—a process that took nearly two more years. Ex.1087, ¶25.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Patent Owner’s assertion that RegenX operated under “settled expectations” of the ’790 patent’s validity thus misrepresents the actual licensing history. The fact that Petitioner entered into licensing agreements does not establish reliance on the validity of the patent—particularly when Petitioner was repeatedly blocked from developing its licensed product due to Patent Owner’s failure to supply required materials. Petitioner did not initiate or benefit from prosecution of the patent claims and received no meaningful value from the agreements that it bargained for. Indeed, far from relying on the patent’s validity, Petitioner spent years navigating conflicting obligations, involuntary terminations, and disputes over ownership and

enforceability—all while being deprived of the supply of urodele ECM it needed to fulfill its obligation under the license. Patent Owner glosses over these facts, providing no objective evidence—let alone the actual agreements defining the parties’ respective rights—and instead relies solely on a conclusory, self-interested declaration from its own counsel to manufacture a narrative of supposed stability and reliance that is contradicted by the record. Patent Owner’s claim of settled expectation should be rejected.

Patent Owner further alleges (at 40-41) that “[a]s 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.” But, that assertion is incorrect in a number of ways and Patent Owner offers no record evidence to support this assertion. Ex.1087, ¶¶33-39.

First, at no point between 2017 and 2024, did Petitioner have the right under the agreements to prosecute the Licensed Patents—Synogen and Patent Owner did.

Moreover, as Patent Owner agrees (at 9, 41), Petitioner was not permitted to file new claims. In 2019, Petitioner submitted a continuation

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application directed to cosmetic uses of urodele ECM⁴—a field exclusively licensed to RegenX under the Synogen License—to protect its interests. Ex.1087, ¶35. But ISE’s counsel promptly assumed control before any office action issued, and the application was later expressly abandoned by Synogen’s counsel. Ex. 1081, U.S. Patent Application No. 16/399,068 Prosecution History (September 13, 2019 Power of Attorney); Ex. 1082, U.S. Patent Application No. 16/399,068 Prosecution History (July 31, 2020 Abandonment); Ex.1087, ¶35. This limited and temporary involvement does not support any settled expectation that Petitioner had a role in shaping the patent claims or affirming their validity. Ex.1087, ¶35.

Second, it was not until 2019—five years after the ’790 patent was filed—that Petitioner’s counsel communicated in any way regarding the prosecution of Licensed Patents. Ex.1087, ¶36. By then, the majority of the claims of the ’790 patent already had been allowed with no involvement from Petitioner. Ex. 1083, January 10, 2019 Non-Final Rejection, 22-30, 32-39; Ex.1087, ¶37. The remaining

⁴ As noted above, when the application was filed in 2019, Synogen had the sole responsibility to prosecute and maintain the Licensed Patents and was not allowed to “delegate this responsibility to a Third Party or an Affiliate” under the Synogen License. Ex.1062, September 23, 2014 Synogen License, § 9.1; *see also*, Ex.1064.

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claims were allowed shortly thereafter, following a reorganization in which certain claims were rejoined and rewritten as dependent claims to the allowed claims. Ex. 1084, Excerpted ’790 Prosecution History, 9-11, 20-23; Ex.1087, ¶37. Thus, Petitioner had no substantive role in drafting the claims of the ’790 patent. Likewise, for U.S. Application No. 16/801,956, a child application to the ’790 patent issued as U.S. Patent No. 11,660,376 (the “’376 patent”), Synogen and Patent Owner were responsible for drafting and filing the claims, as the agreements require. Ex.1087, ¶38. Thereafter, the only substantive office actions—a double patenting rejection and a restriction requirement—were resolved through a terminal disclaimer and withdrawal of certain claims, without a substantive response and without any meaningful input from RegenX. Ex. 1085, Excerpted ’376 Patent Prosecution History, 8-12, 18-31; Ex.1087, ¶39. Notably, Patent Owner offers no record evidence that Petitioner or its representatives had any substantive involvement in the drafting of any claims or in formulating any substantive response to an Office Action.

In short, Patent Owner’s claim of “settled expectations” is unsupported by the record. The history of the ’790 patent is not one of stable licensing and reliance, but rather one of fractured rights, shifting ownership, and prolonged uncertainty. Petitioner’s limited and frustrated role throughout both the prosecution and licensing history—combined with Patent Owner’s refusal to fulfill contractual obligations to

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supply urodele ECM—undermines any inference that Petitioner’s actions or inactions reflect a settled belief in the patent’s validity. Ex.1087, ¶¶1-40.

Patent Owner’s additional argument (at 46–47) that Petitioner’s prosecution of its own pending patent applications—filed years after the ’790 patent issued and directed to newly developed decellularization methods—“highlight[s] the contradictory positions Petitioner is taking ... with respect to the patentability of the amphibian extracellular matrix” and somehow supports the settled expectation regarding the ’790 patent is without merit and irrelevant.

As a threshold matter, Patent Owner fails to explain how the prosecution of entirely different patent applications—with different inventors, different technology, and developed independently by Petitioner—is relevant to any purported settled expectations regarding the validity of the ’790 patent. Petitioner’s pending applications—U.S. Patent App. No. 18/837,137 and PCT/US2023/062398 (Exs. 1089-1090)—are expressly titled “*Novel Methods for Decellularizing Extracellular Matrix*” and, as the title indicates, disclose and claim newly developed decellularization techniques that Petitioner developed after Patent Owner failed to deliver on its promise to supply decellularized urodele ECMs under the license agreements. These applications describe specific, stepwise decellularization protocols—including treatment with detergents, proteases (e.g., dispase II), and nucleases—combined with defined processing parameters and analytical

benchmarks to reduce cellular and DNA content while preserving ECM integrity. Exs.1089-1090.

The subject matter of Petitioner’s pending applications directed to new decellularization process is distinct and unrelated to the ’790 patent, which by the applicant’s own admission, does not disclose “a new process of decellularization.” Ex.1004, 847. The ’790 patent expressly relies on conventional techniques known in the art without providing or claiming any defined steps, reagents, or performance criteria. Ex.1001, 4:64-5:3; 5:25-6:64, 9:55-11:53. In contrast, Petitioner’s applications disclose and claim detailed process innovations that address specific technical challenges associated with decellularizing amphibian tissue, including ensuring reproducibility, minimizing residual DNA, and preserving scaffold function. Ex.1089, [0008]-[0012], [0044]-[0096]; Ex.1090.

Therefore, the fact that Petitioner is pursuing patent protection for these later-developed and distinct technologies has no bearing on whether there were settled expectations about the validity of the unrelated ’790 patent. Patent Owner’s reliance on the prosecution of Petitioner’s later-filed and independently developed decellularization method patents in support of its claim of settled expectations should be rejected.

Finally, Patent Owner’s assertion (at 48) that “the facts in this case parallel the facts ... in *Irhythm v. Welch Allyn, Inc.*, IPR2025-00363, -00374, -00376, -

00377, and -00378” is wrong. In *Irhythm*, there was no licensing relationship between the parties, and the petitioner was under no restriction that would have prevented or discouraged an earlier challenge. Yet the petitioner in *Irhythm* waited more than a decade after becoming aware of the patents to file its petitions. Here, by contrast, Petitioner operated under a complex licensing structure that, at various points, left its rights unclear and its ability to proceed uncertain. Once Patent Owner made its intentions clear by unilaterally terminating the license agreement, Petitioner promptly filed the instant Petition. Moreover, prosecution of the Licensed Patents directed to the same subject matter remains ongoing, further undermining any claim of undue delay. The decision in *Irhythm* does not apply here.

For the reasons set forth above, Petitioner respectfully requests that the Director deny Patent Owner’s request for discretionary denial.

VI. THERE ARE NO COMPELLING PUBLIC POLICY, PUBLIC HEALTH OR ECONOMIC INTERESTS THAT SUPPORT DISCRETIONARY DENIAL

Patent Owner (at 50-54) raises a number of policy issues that it alleges support discretionary denial. None of them have any merit.

First, Patent Owner argues (at 50) that “[t]he continued commercial availability and development of th[e] patent technology are essential to meeting growing public health needs.” However, as Patent Owner admits (at 51), “full-scale commercial adoption [of its product] is still underway and will require additional

financial support by future investors,” but Patent Owner fails to mention that its product was cleared by the FDA on October 7, 2021—almost four years ago (Ex. 1093). In other words, NEOMATRIX® was a commercial failure despite the benefit of an issued patent and years of exclusivity. The lack of commercial success merely underscores that the claimed invention offered no meaningful advancement over what was already known in the art and weighs in favor of institution.

Second, Patent Owner further asserts (at 52-53) that this Petition is driven by Petitioner’s “competitive interest” in “bad faith” because Petitioner “has failed to extend its license to the ’790 Patent that would cover its ECM product in development” and “brazen[ly] ent[ered] into its former licensor’s field of operation,” causing “market disruption.” But that again distorts the record. [REDACTED]

[REDACTED]

[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Accordingly, to the extent there is any “market disruption” as Patent Owner alleges, it was of Patent Owner’s own making. Patent Owner cannot have both ways – unilaterally stripping away Petitioner’s license rights while insisting those same rights should bar a validity challenge.

Third, Patent Owner (at 53) alleges that that “[a]llowing 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.” Patent Owner cites no authority to support this argument. Indeed, the same argument can be made with respect to virtually every patent that relates to any other “medical domain.” In effect, Patent Owner is advocating for special rules for discretionary denial for an entire class of patents. There is nothing about the legislative history of the AIA or the Director’s Interim Guidance that supports this. Congress intended IPR to provide a cost-effective, expert-driven mechanism for reassessing patents that should not have issued in the first place—especially those that create artificial barriers to competition. *See, e.g., Thryv, Inc v. Click-To-Call Techs., LP*, 590 U.S. 45, 54 (2020) (“Congress, concerned about overpatenting and its diminishment of competition, sought to weed out bad patent claims efficiently.”). Congress identified as the primary goals of the AIA: “establish[ing] a more efficient and streamlined patent system that will improve patent quality and limit unnecessary and counterproductive litigation costs.” Ex.1091, 40. That policy supports institution here.

VII. CONCLUSION

Patent Owner has identified no legitimate basis for the Director to deny institution based on any discretionary factors. Institution should be granted.

U.S. Patent No. 10,617,790 – Petitioner’s Opposition to Patent Owner’s Request for
Discretionary Denial of Institution

DATED: July 14, 2025

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certify that the foregoing Petitioner’s Opposition to Patent Owner’s Request for Discretionary Denial of Institution complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(1)(i) and (b)(1)(i) permitting a petition of up to 14,000 words because, exclusive of the exempted portions, it contains 9,469 words as counted by the word processing program used to prepare the paper.

Date: July 14, 2025

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CERTIFICATE OF SERVICE

In accordance with 37 C.F.R. §§ 42.6(e) and 42.105, I hereby certify that true and correct copies of Petitioner’s Power of Attorney, Petitioner’s Opposition to Patent Owner’s Request for Discretionary Denial of Institution and Exhibits 1063-1093 were served on July 14, 2025 via electronic mail on Patent Owner at:

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