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Paper 49
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BAXTER HEALTHCARE CORP.,
APATECH, INC., and APATECH LIMITED
Petitioner

v.

MILLENIUM BIOLOGIX, LLC
Patent Owner

Case IPR2013-00590
Patent 6,585,992

Before MICHELLE R. OSINSKI, SCOTT E. KAMHOLZ, and BRIAN P. MURPHY, *Administrative Patent Judges.*

OSINSKI, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and *37 C.F.R. § 42.73*

I. INTRODUCTION

Baxter Healthcare Corp., ApaTech, Inc., and ApaTech Limited (collectively, "Petitioner") filed a Petition (Paper 1, "Pet.") requesting *inter partes* review of claims 1, 2, 4, 9, 11, 16–18, 20, 25, 26, 36, 38, 43, and 44 of U.S. Patent No. 6,585,992 (Ex. 1001, "the '992 patent"). On March 21, 2014, we instituted an *inter partes* review of the challenged claims on the following grounds of unpatentability asserted by Petitioner:

References	**Basis**	**Claim(s) Challenged**
Ruys '93a[1] and Lynch[2]	§ 103(a)	1, 2, 9, 11, 16, 18, 20, and 25
Ruys '93a, Bioceramics[3], and Ohgushi[4]	§ 103(a)	4, 36, 38
Ruys '93a, Bioceramics, Ohgushi, and Lynch	§ 103(a)	43
Ruys '93a, Lynch, and Chaki[5]	§ 103(a)	17 and 26
Ruys '93a, Bioceramics, Ohgushi, Lynch, and Chaki	§ 103(a)	44

Decision to Institute (Paper 9, "Dec.") 29.

[1] Ruys, *A Feasibility Study of Silicon Doping of Hydroxylapatite*, 42 INT'L CERAMIC REV. 372 (1993) (Ex. 1011).
[2] Lynch, US 5,306,303 (issued Apr. 26, 1994) (Ex. 1026).
[3] 1 INTRO. TO BIOCERAMICS (Hench et. al. eds., 1993) (Ex. 1021).
[4] Ohgushi et al., *Marrow Cell Induced Osteogenesis in Porous Hydroxyapatite and tricalcium phosphate: A comparative histomorphometric Study of Ectopic Bone Formation*, 24 J. BIOMED MAT. RES. 1563–1570 (1990) (Ex. 1073).
[5] Chaki and Wang, *Densification and Strengthening of Silver-Reinforced Hydroxyapatite-Matrix Composite Prepared by Sintering*, 5 J. MAT. SCI.: MAT. IN MED. 533–542 (1994) (Ex. 1130).

Millenium Biologix, LLC ("Patent Owner") filed a Patent Owner Response (Paper 21, "PO Resp."), and Petitioner filed a Reply (Paper 24, "Pet. Reply").

Patent Owner did not file a motion to amend claims, but Patent Owner did file a motion to exclude certain of Petitioner's evidence (Paper 29, "PO Mot. Excl."). Petitioner filed an Opposition (Paper 38) and Patent Owner filed a Reply (Paper 42). Petitioner filed a motion to exclude certain of Patent Owner's evidence (Paper 31, "Pet. Mot. Excl."). Patent Owner filed an Opposition (Paper 37) and Petitioner filed a Reply (Paper 43).

Petitioner relies on declarations of Dr. Antonios G. Mikos in support of its Petition (Ex. 1003) and Reply (Ex. 1134). Petitioner further relies on the declaration of Dr. Karin Hing (Ex. 1136) in support of its Reply. Patent Owner relies on the declaration of Dr. Joo L. (Anson) Ong in support of its Response (Ex. 2026). Petitioner relies on deposition testimony of Dr. Ong (Ex. 1133) in support of its Reply. Patent Owner relies on deposition testimony of Dr. Mikos (Ex. 2028; Ex. 2055), including its Motion for Observations on Cross-Examination of Dr. Mikos (Paper 34, "PO Obs."), to which Petitioner filed a Response (Paper 39).

We heard oral argument on November 14, 2014. A transcript is entered as Paper 48 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6(c). This final written decision is entered pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

We determine Petitioner has shown by a preponderance of the evidence that claims 1, 2, 4, 9, 11, 16–18, 20, 25, 26, 36, 38, 43, and 44 are unpatentable under 35 U.S.C. § 103(a).

Petitioner's Motion to Exclude Evidence and Patent Owner's Motion to Exclude Evidence are *dismissed as moot*.

A. Related Proceedings

The ’992 patent is the subject of a lawsuit in the Northern District of Illinois, *Millenium Biologix, LLC v. Baxter Healthcare Corp.*, Civil Action No. 1:13-cv-03084 (N.D. Ill.). Pet. 2; Ex. 1123; Paper 7 (Mandatory Notice by Patent Owner), 2. The ’992 patent is related to U.S. Patent No. RE41,251 (“the ’251 patent”), certain claims of which are the subject of the petition in IPR2013-00582 on which we instituted trial. *Id*. Our Final Written Decision in IPR2013-00582 is being entered concurrently with this Decision.

B. The ’992 Patent

The ’992 patent is directed to methods of using a synthetic biomaterial compound based on stabilized calcium phosphates and adapted for supporting bone cell activity. Ex. 1001, Title and Abstract, 33:59–38:28. The compound, an embodiment of which is referred to in the patent as “Skelite,” has treatment applications for the repair and restoration of natural bone compromised by disease, trauma, or genetic influences. *Id*. at 1:17–24. The compound can be made in different forms, one of which is a macroporous structure of interconnected voids having a pore size of approximately 50 to 1000 microns that can serve as a scaffold for the integration of new bone tissue. *Id*. at 20:48–54, 25:59–26:5. The compound is made by sintering a fine precipitate of a calcium phosphate material at high temperature (in the range from 800° C to 1100° C (*id.* at 27:53–58)) in the presence of a stabilizing additive having an ionic radius of a size that enables substitution into the Ca—P lattice. *Id*. at 4:52–56. The ’992 patent discloses that silicon, having an ionic radius of 0.40Å, is a preferred additive used to stabilize the claimed compound such that it “is essentially insoluble in biological media but is resorbable when acted upon by osteoclasts.” *Id*. at 4:64–66. The compound “can

be assimilated into natural bone during the natural course of bone remodeling through the activity of osteoclasts and osteoblasts." *Id*. at 4:67-5:2.

The challenged independent claims 1, 2, and 4 are illustrative of the claimed subject matter and are reproduced below.

> 1. A method for substituting natural bone at sites of skeletal surgery in human and animal hosts with a biomaterial compound comprising calcium, oxygen and phosphorous, wherein a portion of at least one of said elements is substituted with an element having an ionic radius of approximately 0.1 to 0.6 Å;
>
> said method comprising the steps of:
>
> > implanting said biomaterial compound at the site of skeletal surgery wherein such implantation promotes the formation of new bone tissue at the interfaces between said biomaterial compound and said host, the progressive removal of said biomaterial compound primarily through osteoclast activity, and the replacement of that portion of said biomaterial compound removed by further formation of new bone tissue by osteoblast activity, such progressive removal and replacement being inherent in the natural bone remodeling process.
>
> 2. A method for repairing large segmental skeletal gaps and non-union fractures arising from trauma or surgery in human and animal hosts using a biomaterial compound comprising calcium, oxygen and phosphorous, wherein a portion of at least one of said elements is substituted with an element having an ionic radius of approximately 0.1 to 0.6 Å;
>
> said method comprising the steps of:
>
> > implanting said biomaterial compound at the site of the segmental skeletal gap or non-union fracture wherein such implantation promotes the formation of new bone tissue at the interfaces between said biomaterial compound and said host, the progressive removal of said biomaterial compound primarily through osteoclast activity, and the replacement of that portion of said biomaterial compound removed by further formation of new bone tissue by osteoblast activity, such

> progressive removal and replacement being inherent in the natural bone remodeling process.

4. A method for providing tissue-engineering scaffolds for bone replacement in human or animal hosts using a biomaterial compound comprising calcium, oxygen and phosphorous, wherein a portion of at least one of said elements is substituted with an element having an ionic radius of approximately 0.1 to 0.6 Å;

said method comprising the steps of:

> forming said biomaterial compound as a macroporous structure comprising an open cell construction with interconnected voids, combining mature and/or precursor bone cells with said macroporous structure, and allowing the cells to infiltrate said structure in order to develop new mineralized matrix throughout said structure.

Claims 9, 11, 16–18 depend, directly or indirectly, from claim 1; claims 20, 25, and 26 depend, directly or indirectly, from claim 2; and claims 36, 38, 43, and 44 depend, directly or indirectly, from claim 4. Claims 9, 18, and 36 specify various configurations for the biomaterial compound. Claims 11, 20, and 38 specify that the substituting element is silicon. Claims 16, 25, and 43 specify that the biomaterial compound comprises at least one other calcium phosphate material. Claims 17, 26, and 44 specify that the biomaterial compound comprises an additive to increase mechanical strength and toughness.

II. DISCUSSION

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the patent specification. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Tech., LLC*, No. 2014-1301, 2015 WL 448667, *7–*8 (Fed. Cir. Feb. 4, 2015). Claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in

the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). "The specification 'is the single best guide to the meaning of a disputed term.'" *Id.* (quoting *Phillips v. AWH Corp.*, 415 F. 3d 1303, 1312 (Fed. Cir. 2005). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. "wherein" clauses of claims 1 and 2

Independent claims 1 and 2 recite, "wherein such implantation promotes the formation of new bone tissue at the interfaces between said biomaterial compound and said host, the progressive removal of said biomaterial compound primarily through osteoclast activity, and the replacement of that portion of said biomaterial compound removed by further formation of new bone tissue by osteoblast activity, such progressive removal and replacement being inherent in the natural bone remodeling process." Ex. 1001, 33:67–34:9, 34:20–29 (claims 1 and 2).

a. Decision to Institute

In the Petition and Preliminary Response, the parties proposed constructions for various portions of the "wherein" clauses of claims 1 and 2. Pet. 17–18; Prelim. Resp. 20–21. In the Decision to Institute, we determined that "[t]hese clauses list various intended results of implanting the biomaterial compound at a specified site. They do not recite positive acts that are carried out as part of the claimed methods. Nor do they specify any limitation on the manner in which the 'implanting' step is to be carried out." Dec. 8. We determined, for purposes of the Decision to Institute, that the clauses were "to be given no patentable weight beyond requiring that the recited biomaterial compound be capable of producing the recited intended results when implanted at the specified site." *Id*. at 8–9 (citing *Minton v. Nat'l Ass'n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003)

(clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited) (citing *Tex. Instruments Inc. v. U.S. Int'l Trade Comm'n,* 988 F.2d 1165, 1172 (Fed.Cir.1993))).

b. The Petition, Patent Owner's Response, and Petitioner's Reply

With respect to the particular phrasing in the "wherein" clauses, namely, "the progressive removal of said biomaterial compound primarily through osteoclast activity," Petitioner contends that "'progressively' would be understood to mean incrementally, or over the course of time." Pet. 18. Petitioner further contends that the phrase refers to "cellular resorption by osteoclasts, which the patent admits is 'inherent in the natural bone remodeling process.'" *Id.* (citing Ex. 1003 ¶ 311; Ex. 1001, 34:1–29).

In its Response, Patent Owner explains that it agrees with the Board's claim construction in the Decision to Institute that the "'recited biomaterial compound <u>be capable of</u> producing the intended results when implanted at the specified site.'" PO Resp. 4 (quoting Dec. 8). Patent Owner argues, however, that the intended result of the "wherein" clauses is that the "progressive removal and replacement [of the biomaterial compound through osteoclast and osteoblast activity, respectively] must be in a biologically relevant time frame 'inherent in the natural bone remodeling process.'" PO Resp. 5 (citing Ex. 1001, 5:52–57). Patent Owner further argues that the intended result can be achieved only when the biomaterial compound has both microporosity and macroporosity. *Id.* at 5–6.

Petitioner replies that Patent Owner's arguments are an attempt to re-write independent claims 1 and 2 to require microporosity and macroporosity, although "[n]either claim says anything about morphology." Pet. Reply 2. Petitioner points out that in claim 1 of the related '251 patent, Patent Owner expressly recites a "microporous structure" and that in claim 4 of the '992 patent, Patent Owner

expressly recites a "macroporous structure." *Id*. Petitioner argues that although "[t]he inventors clearly knew how to describe these structural elements, [they] chose not to do so in claims 1 and 2." *Id*.

Petitioner further argues that if the biomaterial compound of independent claims 1 and 2 would be understood by those of ordinary skill in the art as inherently macroporous, it would be unnecessary to include the specific limitation of a macroporous structure in claims 9 and 18. Pet. Reply 2–3; *see Phillips v. AWH Corp*., 415 F.3d 1303, 1324–25 (Fed. Cir. 2005) (determining that (i) where a dependent claim recited a particular orientation of previously claimed "baffles," patentee likely did not contemplate reading "baffles" as requiring the particular orientation, and (ii) additional claim language reciting the function of baffles would be unnecessary if one of skill in the art understood "baffles" inherently to serve that function). Petitioner further asserts that the "thin films" and "coatings" recited in claims 9 and 18 (Ex. 1001, 35:38–41 (claim 9); 36:8–11 (claim 18)) are incapable of being macroporous, but are still described in the Specification as being bioresorbable and bioactive. Pet. Reply 3 (citing Ex. 1134 ¶ 175; Ex. 1001, 3:31–45, Ex. 1003 ¶¶ 74, 175). Petitioner relies on the deposition testimony of Dr. Ong, who testified that macroporosity is not necessary for bioactivity and bioresorption. Pet. Reply. 3 (citing Ex. 1133, 149:6–151:1, 282:2–284:21, 206:10–209:10; Ex. 1134 ¶¶ 173–180); *see, e.g.,* Ex. 1133, 283:1–6 ("Calcium phosphate materials would resorb, and it resorbs at different rates. And depending on what you want the intended application, the macroporosity just helps with increasing the surface area to help with the resorption.").

c. Analysis

The issue in dispute is whether the "wherein" clause of claims 1 and 2 should be interpreted to require the progressive removal and replacement of the

biomaterial compound *at the same pace as that found in the natural bone remodeling process*. "A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." *Minton v. Nat'l Ass'n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003). "However, when the 'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005). Determining whether to give a "whereby" or "wherein" clause patentable weight, if any, is done on a case-by-case basis. *Id.*; *Minton*, 336 F.3d at 1381; *see also In re Griffin v. Bertina*, 285 F.3d 1029, 1033–34 (Fed. Cir. 2002) (holding that the Board did not err by giving limited effect to the "wherein" clauses in an interference count because the wherein clauses "giv[e] meaning and purpose to the manipulative steps" rather than "merely stat[ing] the inherent result of performing the manipulative steps").

We maintain our determination that the "wherein" clauses in this case are "to be given no patentable weight beyond requiring that the recited biomaterial compound be capable of producing the recited intended results when implanted at the specified site." Dec. 8–9. Patent Owner is attempting to read in structural limitations of the biomaterial compound, such as microporosity and macroporosity, which Patent Owner chose not to recite in claims 1 and 2 of the '992 patent. *Compare* Claims 1 and 2 of the '992 patent, *with* claims 9 and 18 of the '992 patent, *and* claims 1 and 6 of the '251 patent (referring to "macroporous structure" or "microporous structure"). It is improper to import such structural limitations into a wherein clause that does nothing more than recite an intended result of a positively recited process step. A "macroporous structure," moreover, is not

necessary to achieve bioactivity and bioresorption. Pet. Reply. 3 (citing Ex. 1133, 149:6–151:1, 282:2–284:21, 206:10–209:10; Ex. 1134 ¶¶ 173–180).

The particular phrasing of the "wherein" clause, "such progressive removal and replacement being inherent in the natural bone remodeling process," does not give meaning and purpose to the method step of implanting the biomaterial compound at the site of skeletal surgery. Rather, that portion of the wherein clause states only that progressive removal and replacement is inherent in natural bone remodeling. The phrase itself does not require us to construe the claim so that the recited progressive removal and replacement of the biomaterial compound is at the pace of natural bone remodeling processes.

The Specification also does not require us to construe the claim so that the recited progressive removal and replacement of the biomaterial compound be at any particular pace. The Specification describes only that the compound be able to interface with osteoclast and osteoblast cells. For example, the Specification states that "[t]he stabilized artificial bioactive composition is the first such composition which supports both osteoclast and osteoblast activity and which allows for the reliable assessment of the physiological activities of both cell types as well as for the development of both diagnostic and therapeutic strategies." Ex. 1001, 3:65–4:3. The Specification further states that the claimed biomaterial compound was "well adapted for osteoclast and osteoblast activity." *Id*. at 9:48–49. In addition, the Specification states that "[a]ll of the applications in which the present synthetic biomaterial compound can be used have the advantage that both osteoclasts and osteoblasts function actively with the compound in any form thus providing natural cell-mediated remodeling much like that found in vivo." *Id*. at 26:24–28. Therefore, the broadest reasonable interpretation of the "wherein" clause, that is consistent with the Specification, requires the progressive removal and

replacement of the biomaterial compound through osteoclast and osteoblast activity, but does not require that such progressive removal and replacement be at the same pace as natural bone remodeling.

In support of its construction, Patent Owner points to the Specification's characterization of prior art calcium phosphate materials as being biocompatible, but not participating in natural bone remodeling. PO Resp. 5 (citing Ex. 1001, 2:1–15). Patent Owner states that, in contrast, "the claimed biomaterial 'promotes organic bone matrix deposition by osteoblasts and can be assimilated into natural bone during the natural course of bone remodeling through the activity of osteoclasts and osteoblasts.'" *Id*. (citing Ex. 1001, 4:66–5:2). Such a statement, however, does not establish the rate at which the progressive removal and replacement of the biomaterial compound takes place, but reasonably may be construed to mean that the claimed biomaterial compound participates in natural bone remodeling through interaction with osteoclast and osteoblast cells, regardless of the rate at which this occurs.

Patent Owner's reference to the characterization of the biomaterial compound as having both a unique chemical composition and a unique morphology (PO Resp. 5 (citing Ex. 1001, 20:41–45, 58–65)) also does not establish that the progressive removal and replacement must take place at any particular rate or that the biomaterial compound must be microporous and/or macroporous to achieve the intended result of participating in progressive removal and replacement. We decline to import microporosity or macroporosity into claims 1 and 2 when Patent Owner did not recite these structural limitations.

Finally, Patent Owner's argument that the Specification characterizes the biomaterial compound as having to "be provided in a macroporous configuration such that the cells required for bone remodeling can enter and work throughout the

structure" (PO Resp. 6 (citing Ex. 1001, 22:26–34, 25:59–66))[6] is not supported by the Specification. The Specification does not require that the claimed implanted biomaterial compound participate in progressive removal and replacement at any particular pace or that it must be macroporous to achieve the intended result. We decline to import the specific macroporous configuration as a limitation of claims 1 and 2 when the claim language is broader than a particular embodiment described in the Specification.

We determine the broadest reasonable interpretation consistent with the Specification is that the implanted biomaterial compound be capable of promoting the progressive removal and replacement of the implanted biomaterial compound primarily through osteoclast and osteoblast activity.

2. Other Claim Terms

In our Decision to Institute, we determined that construction of several other claim terms[7] were not material to our decision. Dec. 8. The parties do not argue further in Patent Owner's Response or Petitioner's Reply that construction or consideration of any additional claim terms need be undertaken. We maintain our initial determination that all other claim terms in the '992 patent are not material to our decision.

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[6] *See also* Ex. 2026 ¶¶ 96–97 (Patent Owner's expert explaining that osteoclast cells are in a range of 20–30 microns and osteoblast cells are in a range of 10–20 microns, such that one of skill in the art would understand the claims to require both microporosity and macroporosity in order to facilitate natural bone remodeling).

[7] These other claim terms include: "biomaterial," "compound," "comprising calcium, oxygen and phosphorous wherein a portion of at least one of said elements is substituted with an element having an ionic radius of approximately 0.1 and 0.6 Å," "implanting said biomaterial compound at the site of skeletal surgery," and "implanting said biomaterial compound at the site of the segmental skeletal gap or nonunion fracture." Pet. 11–18.

B. Obviousness of Claims 1, 2, 9, 11, 16, 18, 20, and 25 over Ruys '93a (Ex. 1011) and Lynch (Ex. 1026)

1. Overview of Ruys '93a

Ruys '93a, titled "A Feasibility Study of Silicon Doping of Hydroxylapatite," discloses an approach to enhancing "the relatively low bioactivity of hydroxylapatite" (Ex. 1011, Abstract) by using silicon doping to form a silicon-doped calcium phosphate compound. Ex. 1011, 3 (left column).[8] Ruys '93a discloses a two-solution sol-gel process to make finely divided (20 nm) stoichiometric HA[9] suspended in ethanol. Ex. 1003 ¶ 383 (citing Ex. 1011, 3 (right column)). Ruys '93a discloses the addition of ethyl silicate to the suspended HA, then excess water, to form colloidal silica. *Id*. The precipitated HA and silica powder are pressed into pellets and sintered at 1100°C for one hour in air. *Id*. Ruys '93a discloses 11 experimental compositions with varying silicon:HA molar ratios. Ex. 1003 ¶ 385 (citing Ex. 1011, 3 (right column)).

Ruys '93a further discloses analytical data for the sintered material, a multi-phase, silicon-substituted calcium phosphate compound that includes TCP as one of "two new apatite phases." Ex. 1003 ¶ 385 (citing Ex. 1011, 4 (right column)). Ruys '93a discloses lattice expansion data supporting the author's conclusion that "silicon substitution probably occurred . . . at the phosphorous site since ionic radii restrictions favour this site to the exclusion of the three alternatives – the calcium, oxygen, and hydroxyl sites." Ex. 1011, 4 (right column); Ex. 1003 ¶ 384. Ruys '93a further states that "[t]he formation of $Ca_{10}(PO_4)_4$ $(SiO_4)_2$ shows that *silicon*

[8] Hydroxylapatite or hydroxyapatite (HA) has the empirical formula $Ca_5(PO_4)_3(OH)$, but can also be written as the molecular formula $Ca_{10}(PO_4)_6(OH)_2$. Ex. 1001, 2:40; Ex. 1011, 3.

[9] Stoichiometric HA has a Ca:P ratio of 1.67 "consistent with the chemical formula of HA which includes 10 calcium atoms for every 6 phosphorous atoms." Pet. 43 (citing Ex. 1003 ¶ 393).

substitution into the phosphorous site can be induced by the sol-gel synthesis method used in the present work." Ex. 1011, 4 (right column) (emphasis added). Ruys '93a also discloses data demonstrating the "apparent porosity"[10] of the compound as a function of the silicon:HA molar ratios tested. Ex. 1011, 4 (left column), Fig. 2.

2. Overview of Lynch

Lynch discloses "[a] method of inducing bone growth . . . [that includes] implanting . . . [a] ceramic consisting of a calcium phosphate which is at least partially resorbable, and leaving the ceramic in place until new bone growth is induced." Ex. 1026, Abstr. Lynch further discloses:

> It is known that ceramics, especially calcium hydroxyapatite and other calcium phosphates and mixtures thereof, are osteoconductive (i.e., when placed next to viable bone they provide a framework for the rapid incorporation of connective tissue and subsequent bone ingrowth).

Id. at 1:14–19.

3. Obviousness of Claims 1 and 2

Petitioner asserts that claims 1 and 2 would have been obvious to a person of ordinary skill in the art over Ruys '93a and Lynch. Pet. 40–45. Petitioner argues that Ruys '93a (Ex. 1011) discloses a silicon-substituted calcium phosphate compound made by a very similar process to the sol-gel/sintering process described in examples of the '992 patent and, therefore, "necessarily resulted in products having the same physical, chemical, and biological properties, including

[10] Apparent porosity is a measure of the porosity of a material using a hydrostatic weighing technique where the material is immersed in water or kerosene. Ex. 1011, 4 (Fig. 2); *see also* Ex. 1003 ¶ 134 ("[I]ncomplete sintering of HA ceramics, which is what was observed in Ruys 1993a, was known to result in pores."); Ex. 2026 ¶ 38 (measuring apparent porosity "does indicate some pores that are accessible to fluid in contact with the outside of the pellet.").

'biomaterial properties.'" Pet. 41. Petitioner also argues that incomplete sintering in Ruys '93a confirms the microporosity of the biomaterial compound. Pet. Reply 6–8. With respect to the claimed method steps of "implanting" the biomaterial compound, Petitioner argues that Lynch "describes a method of inducing bone growth by implanting a restorable Ca-P ceramic." Pet. 24 (citing Ex. 1003 ¶ 552). Petitioner argues that:

> Given the known properties of Ca-P materials such as TCP and HA . . . and the guidance provided in [Lynch]—which discloses implantation of Ca-P material at the site of skeletal surgery in place of bone—the person of ordinary skill in the art would have been motivated to use the biomaterial compounds described in Ruys 1993a in methods that involved "substituting natural bone at sites of skeletal surgery in human and animal hosts" where the methods further involved "implanting said biomaterial compound at the site of skeletal surgery." . . . The person of ordinary skill in the art would have had a reasonable expectation of success given the extensive literature describing the clinical and surgical uses of Ca-P compounds.

Pet. 43–44 (citations omitted).

Patent Owner responds that "the differences in Ruys' method and the methods of the '992 patent" mean that "the two methods cannot possibly be equivalent and cannot with any certainty inherently produce a biomaterial capable of being removed by osteoclasts and replaced by osteoblasts in a biologically relevant time frame inherent in the natural bone remodeling process." PO Resp. 3–4; *see also id.* at 33 ("the method employed by Ruys differs in important process parameters from that provided by the '992 patent, and thus no conclusion can be drawn on whether the materials generated would inherently have the same properties."). Patent Owner points to differences, such as smaller starting particle size, the application of a pressing step before sintering, and higher sintering temperatures. PO Resp. 3–4, 33, 35, 37–41. Patent Owner also responds that reference in Ruys '93a to incomplete sintering does not establish that the Ruys

'93a compound is inherently microporous and capable of achieving the intended result recited in the wherein clause. We have also considered Patent Owner's observations, which are directed to the cross-examination testimony of Dr. Mikos (Ex. 2055), who was deposed after Petitioner filed its Reply. In particular, we have considered Patent Owner's observations, and Petitioner's response, regarding the dispute over whether Ruys '93a discloses a "microporous structure" and the assertion of "misleading" positions by Petitioner and Dr. Mikos. PO Obs. 1–5.

Patent Owner's arguments are not persuasive. Patent Owner effectively concedes that a biomaterial compound having the right chemistry, whether or not the compound exhibits interconnected microporosity or macroporosity, would be capable of at least "slowly and progressively remov[ing] the material from the outside." PO Resp. 7 (citing Ex. 2026 ¶ 97) (emphasis added) ("If the biomaterial features only the right chemistry but lacks interconnected microporosity and macroporosity, osteoclasts and osteoblasts would be confronted with a solid dense surface for osteoblast and osteoclast activities only on the surface but would not allow these cells to penetrate within the biomaterial. As such, for a dense biomaterial, the cells could only *slowly and progressively remove the material from the outside* and such process would not be analogous to that occurring with natural bone.").

As we have construed the "wherein" clause, Petitioner does not have to establish that the progressive removal and replacement of the biomaterial compound necessarily occurs at the same pace as natural bone remodeling. Petitioner's evidence is sufficient to support the finding that Ruys '93a's implanted biomaterial compound would be capable of promoting the progressive removal and replacement of the implanted biomaterial compound primarily through osteoclast

and osteoblast activity because of the right chemistry (*see* Pet. 41–43). Patent Owner's observations (PO Obs. 1–5) do not change our findings or conclusions.

Patent Owner also argues that Ruys '93a teaches away from the porosity which is required for the biomaterial compound to be capable of progressive removal and replacement in a time frame consistent with natural bone remodeling. PO Resp. 33 (citing Ex. 2026 ¶¶ 94–97), 47–49 (citing Ex. 1003 ¶ 368; Ex. 2026 ¶¶ 64–65). More specifically, Patent Owner argues that Ruys '93a disparages the properties of porous HA as having low compressive strength, and desires a means for enhancing the bioactivity of HA other than porosity control. *Id*. at 48 (citing Ex. 1011, 3; Ex. 1014, 5, Ex. 2026 ¶¶ 77–78). Patent Owner argues that "one of skill in the art reading Ruys would have been discouraged from taking the SiCaP of Ruys and adding the structural features that the '992 inventors determined were required to make the biomaterial capable of bioresorption and rebuilding according to the process of natural bone." PO Resp. 49 (citing Ex. 2026 ¶¶ 66, 79). Petitioner's position, however, is not based on modification of the biomaterial compound of Ruys '93a to render it capable of progressive removal and replacement of the biomaterial compound. Rather, Petitioner's position is based on Ruys '93a inherently being capable of such progressive removal and replacement, due to its silicon-substituted CaP chemistry. Accordingly, the focus of Ruys '93a on silicon doping rather than porosity control to improve bioactivity is immaterial to the obviousness determination in this case.

Patent Owner also argues that Petitioner has failed to show that the methods of claims 1 and 2 could be obtained by the combination of Ruys '93a and Lynch, let alone with a reasonable expectation of success. PO Resp. 50. Patent Owner argues that Petitioner's reasoning "that 'the person of ordinary skill in the art would have had a reasonable expectation of success given the extensive literature

describing the clinical and surgical uses of Ca-P compounds, which included the very use claimed'" is "mere argument, and is unavailing." *Id*. at 51 (quoting Pet. 44). Patent Owner describes the combination of Ruys '93a and Lynch as mere "hindsight." *Id*. We do not agree with Patent Owner, because Petitioner relies on Lynch to show it was known to implant calcium phosphates and related compounds during skeletal surgery (Pet. 43–44), not to remedy any purported deficiency of Ruys '93a with respect to the capability of supporting normal bone remodeling processes. PO Resp. 52.

Petitioner also points out that calcium phosphate materials "were well known to have utility in 'skeletal surgery' (claim 1) and for 'repairing large segmental skeletal gaps and non-union fractures' (claim 2)." Pet. Reply. 11 (citing Ex. 1133, 262:10–264:6) ("Q. Now it was known that calcium phosphate materials could be implanted at the [s]ite of skeletal surgery, correct? A. Yes. . . . Q. And it's a 'method comprising the steps of: implanting said biomaterial compound at the site of the segmental skeletal gap or nonunion fracture.' . . . That was also a known use of calcium phosphate materials, correct?" . . . "A. Yes.").

4. Secondary Considerations

Patent Owner argues that objective indicia, including, long-felt but unmet need (PO Resp. 14–15), the failure of Petitioner to arrive at the invention until many years later (*id*. at 15–21), the length of intervening time between the prior art and the claimed invention (*id*. at 21–23), unexpected results (*id*. at 23–26), wide acclaim in the industry (*id*. at 26–28, 31–32), and commercial success (*id*. at 28–31) "are convincingly present and are tied to the novel elements of the claims . . . [and] compel a determination that the invention was non-obvious." *Id*. at 10. In support, Patent Owner relies on, *inter alia*, the Declaration of Dr. Ong (Ex. 2026).

Patent Owner cites evidence of the success of Patent Owner's bone graft material, sold under the trade name Skelite, and Petitioner's bone graft material sold under the trade name Actifuse, in support of Patent Owner's argument. PO Resp. 11. Patent Owner states that Skelite is a "calcium-phosphate bone material that contains silicon substitution" and "result[s] in resorption by osteoclasts and deposition of new bone by osteoblasts according to the natural course of bone remodeling on the basis of its interconnected micro- and macroporosity." *Id*. at 12 (citing Ex. 1001, 22:6–1332:15–45; Ex. 2030, 2; Ex. 2026 ¶ 83). Patent Owner states that Actifuse is a "silicon substituted calcium-phosphate bone material having properties that . . . result in resorption by osteoclasts and deposition of new bone by osteoblasts according to the natural course of bone remodeling on the basis of its interconnected micro- and macroporosity." *Id*. at 13 (citing Ex. 2026 ¶ 85; Ex. 2032, 1).

It is not sufficient for Patent Owner to establish that a product or its use is within the scope of a claim. Patent Owner must establish a causal relationship, a "nexus," between the asserted secondary consideration and the unique characteristics of the claimed invention. *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Where the offered secondary consideration evidence is not due to novel elements of the claim at issue, the evidence will not suffice to establish the required nexus to the claimed invention. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

a. Long-Felt but Unmet Need

Patent Owner contends that the claimed invention met a long-felt but unsolved need. PO Resp. 14. Patent Owner contends that, prior to the '992 patent priority date, only autologous bone could provide biocompatibility and bioresorption to match that of natural bone rebuilding, but autologous bone had the

disadvantage of requiring at least two surgical interventions (one to harvest and one to implant). *Id*. at 14–15 (citing Ex. 2026 ¶¶ 86–87; Ex. 2034, 1)). Patent Owner also argues that Petitioner has acknowledged the long-felt need and prior failure of others. *Id*. at 15 (citing Ex. 2001, 2; Ex. 2025, 2).

Patent Owner does not explain how a nexus exists between the asserted long-felt need for a synthetic bone graft material to replace autologous bone and the features of claims 1 and 2. In particular, Patent Owner does not identify to what it attributes the effectiveness of Skelite and/or Actifuse and whether that feature is (i) found in the claims and (ii) a novel element not in the prior art. To the extent that the effectiveness may be attributed to the substitution of silicon, for example, this feature was already present in the prior art as evidenced by Ruys '93a. To the extent that the effectiveness may be attributed to a macroporous structure, for example, this feature is not claimed in independent claims 1 and 2. Consequently, we are not persuaded by Patent Owner's contentions in relation to long-felt but unmet need.

b. Failure of ApaTech to Arrive at the Invention Until Many Years Later

Patent Owner argues that Petitioner's position that one of ordinary skill in the art would have combined the silicon substituted CaP of Ruys '93a with the implantation of HA of Lynch to arrive at the claimed invention is counter to Petitioner's "own admissions as to its prolonged path to discovery." PO Resp. 16. Patent Owner explains that Petitioner's team spent years of study to conclude that silicon was a correct substituent. *Id*. (citing Ex. 2026 ¶ 70; Ex. 2001, 2–3).

The length of time it took to determine the propriety of the substitution of silicon, however, is irrelevant to the obviousness analysis since a silicon-substituted compound was found in the prior art, and the Petitioner's obviousness analysis extended only to implantation of the compound at the site of skeletal

surgery in connection with independent claims 1 and 2. Consequently, we are not persuaded by Patent Owner's contentions in relation to ApaTech's failure to arrive at the invention. We have also considered Patent Owner's observations, and Petitioner's response, regarding the dispute over ApaTech's development history. PO Obs. 4. Patent Owner's observations (PO Obs. 4) do not change our findings or conclusions.

c. Unexpected Results

Patent Owner contends that the claimed silicon-substituted micro and macro-porous calcium phosphate "was very surprisingly able to greatly exceed the performance of porous HAP as evidenced by studies conducted using both Skelite and Actifuse, and according to studies conducted on Actifuse, was able to meet or exceed the performance of autologous bone." PO Resp. 23 (citing Ex. 2026 ¶ 88). For example, Patent Owner contends that the osteoclastic resorpotion rate of Skelite greatly exceeded that of HA. *Id*. (citing Ex. 2036, 1; Ex. 2026 ¶ 90). Patent Owner further contends that Actifuse "was biomechanically, radiographically, and histologically equivalent to autograft in the ovine model." *Id*. at 24. Patent Owner also contends that Actifuse "promote[d] rapid bone formation and an elevated volume of bone ingrowth compared with traditional calcium phosphates of similar structure." *Id*.

Patent Owner fails to explain how the asserted unexpected results are attributable to features that are (i) recited in claims 1 and 2 and (ii) novel elements not found in the prior art. To the extent that Patent Owner may be arguing that silicon substitution might account for the asserted unexpected results, the use of silicon was already present in the prior art as evidenced by Ruys '93a, such that modification to include silicon was not part of the obviousness analysis. To the extent that Patent Owner may be arguing that macroporosity might account for the

asserted unexpected results, this feature is not claimed in independent claims 1 and 2. Consequently, we are not persuaded by Patent Owner's contentions in relation to unexpected results.

d. Industry Acclaim

The evidence cited by Patent Owner suggests the benefits from Skelite and Actifuse are attributable to silicon substitution, previously disclosed in Ruys '93a, and the use of the claimed macroporous "scaffolds" to promote bone growth. PO Resp. 26–28 (citing Ex. 2039, 2–3 ("we have uncovered the role of trace elements that are found in normal bone that were thought to be benign and have no effect. . . [and] if you incorporate these elements in synthetic bone graft scaffolds, you actually get a unique biological effect")); Ex. 2040, 4 ("[T]he company has successfully received FDA approval for clinical use of Skelite™ scaffolds."); Ex. 2041;[11] Ex. 2043, 1–2; Ex. 2044[12]. Again, Patent Owner fails to explain how the asserted industry acclaim is attributable to features that are recited in claims 1 and 2 and are novel elements not found in the prior art. Consequently, we are not persuaded by Patent Owner's contentions in relation to industry acclaim.

[11] "Current products range from powders and granules, which are designed to fill small, irregular bone voids at common fracture sites, to large porous synthetic scaffolds that can repair problems such as badly damaged limbs or collapsing spines. . . . Because it can be manufactured at low cost in various function-specific configurations, Skelite satisfies critical needs in a variety of medical and biotechnology applications." Ex. 2041, 7.

[12] "ApaTech has introduced a novel silicate substituted calcium phosphate bone graft material, Actifuse globally. The company believes that Actifuse is the first of a new class of synthetic bone graft material that combines osseo-conductive and osseo-stimulatory activities. Actifuse has been shown to accelerate the rate and quality of bone formation and is available as a range of granule and microgranule formulations . . . combining the biological benefits of Actifuse scaffold with placement and mouldability benefits."

e. Commercial Success

Patent Owner argues that in 2009, after only four years on the market, annual sales of Actifuse were $90 million, and in March 2010, Baxter acquired ApaTech for $330 million, specifically to acquire Actifuse. PO Resp. 29 (citing Ex. 2049, 1; Ex. 2001, 6). Gross sales figures, in the absence of evidence as to market share or what sales would normally be expected in the market, do not support an inference that the sales represent a substantial share of any definable market. *Cable Elec. Prod., Inc. v. Genmark, Inc.*, 770 F.2d 1014, 1027 (Fed. Cir. 1985) (reversed on other grounds); *see also* Pet. Reply 14 (stating that "because the sales figures for Actifuse that are provided omit any analysis of relative market share, they are fatally defective") (citing *In re Applied Materials, Inc.*, 692 F.3d 1289, 1300 (Fed. Cir. 2012)).

Patent Owner further argues that Petitioner avoided the cost of clinical trials in connection with Actifuse by utilizing Patent Owner's Skelite as a predicate device when seeking FDA approval, gaining "considerable commercial benefit" and that Petitioner more quickly gained market acceptance through Patent Owner's already public showing that "silicon-stabilized calcium phosphate coatings and bulk ceramics manifest the critical property of osteoclast resorption, which was not observed with HA." PO Resp. 29–30 (citing Ex. 2050, 2, 11). Both of these further arguments tend to indicate that the success of Actifuse was at least partly due to extraneous factors other than the patented invention itself. Based on the record before us, we find evidence of nexus in relation to commercial success to be tenuous and do not accord the cited evidence of commercial success significant weight.

5. Conclusion

In considering the entirety of the record, we are persuaded that Ruys '93a's compound is capable of promoting the progressive removal of the biomaterial compound primarily through osteoclast activity and the replacement of that portion of the biomaterial compound removed by further formation of new bone tissue by osteoblast activity, such progressive removal and replacement being inherent in the natural bone remodeling process, as we have construed that term. *See* Pet. 41–42 (citing Ex. 1003 ¶¶ 369–370, 612–613); PO Resp. 7 (citing Ex. 2026 ¶ 97). We also are satisfied that one of ordinary skill in the art would have appreciated Ruys '93a's compound would be suitable for use in skeletal surgery given the clinical and surgical uses of Ca-P compounds as described in Lynch. In that respect, Petitioner has articulated sound reasoning with rational underpinnings in urging that an ordinarily skilled artisan would have incorporated Ruys '93a's compound in skeletal surgery because it is known that calcium phosphates are osteoconductive as taught in Lynch and because Ruys '93a itself suggests subjecting its composition to clinical trials. Pet. 25, 43–45; Ex. 1026, 1:14–19; Ex. 1011, 5. In full consideration of the evidence advanced by the parties in this challenge, we determine that the balance of the evidence supports a finding of obviousness. We conclude that Petitioner has proved, by a preponderance of the evidence, that claims 1 and 2 are unpatentable under 35 U.S.C. §103(a) for obviousness over the combination of Ruys '93a and Lynch.

6. Dependent Claims 9, 11, 16, 18, 20, and 25

Patent Owner directs no arguments specifically to any of claims 9, 11, 16, 18, 20, and 25 with regard to the challenge for obviousness over Ruys '93a and Lynch. We address these claims in turn.

a. Claims 9 and 18

These dependent claims specify various configurations in which the biomaterial compound of claim 1 can exist, reciting that the biomaterial compound "exists as a fine or coarse powder, pellets, three-dimensional shaped pieces, macroporous structures, thin films, and coatings." Ex. 1001, 35:38–41, 36:8–11. Petitioner argues that Ruys '93a discloses that the material therein "was made as a powder (*i.e.*, a dried colloidal mixture) that was then tabletted." Pet. 46 (citing Ex. 1003 ¶ 709 (citing Ex. 1011, 3)). We credit Dr. Mikos's testimony and are persuaded that Petitioner presents sufficient evidence to support a finding that the combination of Ruys '93a and Lynch renders obvious the claimed subject matter.

b. Claims 11 and 20

These dependent claims specify that the substituting element is silicon. Ex. 1001, 35:45, 36:15. Petitioner argues that "the compound in Ruys 1993a necessarily includes Si-TCP, wherein silicon has 'substituted' for phosphorus in the TCP structure." Pet. 46 (citing Ex. 1003 ¶ 613). We credit Dr. Mikos's testimony and are persuaded that Petitioner presents sufficient evidence to support a finding that the combination of Ruys '93a and Lynch renders obvious the claimed subject matter.

c. Claims 16 and 25

These dependent claims specify that the biomaterial compound additionally comprises at least one other calcium phosphate material, reciting that the "biomaterial compound is provided as a composition additionally comprising at least one calcium phosphate material selected from the group consisting of calcium hydroxyapatite, α-TCP, β-TCP, ostacalcium phosphate, tetracalcium phosphate, dicalcium phosphate and calcium oxide." Ex. 1001, 35:66–36:4, 36:38–43. Petitioner argues that it would have been "an obvious design choice" to combine

the biomaterial compound with an additional Ca-P component "given that Ca-P materials having more than one Ca-P component (*e.g.*, both TCP and HA) were well known, and routinely used in clinical applications." Pet. 47 (citing Ex. 1003 ¶¶ 76–78, 89, 93, 147–148, 550–562, 722). In particular, Petitioner points out that Lynch "identifies the benefits of, for example, a TCP/HA combination." *Id*. (citing Ex. 1003 ¶ 724) ("According to the patent, the benefits of having a TCP component and a HA component are that TCP provides 'a soluble phase . . . which initiates the giant cell response, is resorbed and may initiate osteoblast differentiation, and that it provides local calcium phosphate to form calcified woven bone. The remaining hydroxyapatite appears to provide an appositional interface and scaffold for the new bone formation.'") (quoting Ex. 1026, 4:33–39). We credit Dr. Mikos's testimony and are persuaded that Petitioner presents sufficient evidence to support a finding that the combination of Ruys '93a and Lynch renders obvious the claimed subject matter.

D. Obviousness of Claims 4, 36, and 38 over Ruys '93a, Bioceramics (Ex. 1021), and Ohgushi (Ex. 1073)

1. Overview of Bioceramics

Chapter 10 of Bioceramics is directed to a discussion of porous HA. Ex. 1021, 108. Figure 4 in chapter 10 of Bioceramics illustrates an "idealized microstructure for cancellous bone regeneration." *Id*. at 110–111.[13] Bioceramics also discloses that "[a]n ideal cancellous bone graft substitute would mimic osteon-evacuated cancellous bone and have a thin lattice interconnected by pores of 500-

[13] A visual comparison of Bioceramics Figure 4 (Ex. 1021, 111) to Figure 23 of the '992 patent (Ex. 1001) shows the strong similarity between the idealized macroporous structure illustrated in Bioceramics and the macroporous structure of the preferred Skelite embodiment described in the '992 patent.

600 μm" and that "[p]orosity and interconnectivity are key determinants of amount and type of ingrowth." *Id*. at 110, 116–117.

2. Overview of Ohgushi

Ohgushi discloses the beneficial effect of marrow cells with respect to bone formation when utilized with porous HA and tricalcium phosphate implants. Ex. 1073, 1. Ohgushi discloses that "[i]mplants without marrow cells . . . did not show bone formation, whereas implants with marrow cells showed bone formation in the pores of the ceramics." *Id*. More particularly, Ohgushi discloses that "all implants with marrow cells showed bone formation in the pore regions" and "the bone formation was active and progressive." *Id*. at 3–4.

3. Obviousness of Claim 4

Petitioner asserts that claim 4 would have been obvious over Ruys '93a, Bioceramics, and Ohgushi. Pet. 45; Pet. Reply 14–15. With respect to forming the biomaterial compound as a macroporous structure (Ex. 1001, 34:59–60), Petitioner argues that "[m]ethods of making a biomaterial compound having a macroporous structure . . . were well known." Pet. 32 (citing Ex. 1003 ¶¶ 147–64, 699). Petitioner points to the "widespread use of macroporous CaP in a variety of bone implant applications by the mid-1990s." Pet. Reply 9 (citing Ex. 1133, 208:3–13, 260:5–261:12, 207:12–15) (deposition testimony supporting that a majority of commercially available calcium phosphate bone implant products are porous, and specifically macroporous, in order to facilitate cellular activity, fluid flow, vascularization, and rapid osteointegration, despite a corresponding reduction in strength).

Petitioner also argues that forming Ruys '93a's compound "as an open cell structure with interconnected voids would have been an obvious design choice in order to facilitate bone ingrowth and vascularization within the implant material."

Pet. 45 (citing Ex. 1003 ¶697). Petitioner provides evidence supporting that it was well known that a macroporous structure was important to promote vascularization and bone ingrowth in Ca-P materials. *See* Ex. 1136 ¶¶ 8–18 (explaining Dr. Hing's awareness that macropores were important to promote vascularization and bone ingrowth in Ca-P materials); Ex. 1140, 64–65, 105–06, 129–31 (Dr. Hing's 1996 doctoral dissertation at Queen Mary University referencing various porous bone implant materials having pore sizes ranging from 50–500 microns); Ex. 1139, 18 (Dr. Shaw's doctoral dissertation discussing early work of researchers noting that "bony ingrowth initiated with pores of greater than 75μm in size. The rationale expressed by [these researchers] behind developing porous implants was to encourage ingrowth of tissue, in order to provide a mechanical bond between the implanted component and the surrounding tissue.").

With respect to the claimed step of "combining mature and/or precursor bone cells with said macroporous structure," (Ex. 1001, 34:61–63), Petitioner argues that "it would have been obvious to pretreat Ca-P material comprising an open cell structure with interconnected voids with precursor and mature bone cells in a manner that would allow the cells to infiltrate the structure in order to develop new mineralized matrix throughout the structure." Pet. 33; Ex. 1003 ¶¶ 700–702.

Patent Owner argues that "the teachings of Ruys could not have provided a recognition of the suitability of SiCaP as a 'lead compound' for further development such as by addition of macroporosity, because Ruys provided absolutely no biocompatibility or bioresorption data." PO Resp. 52. Patent Owner posits that the compound of Ruys '93a might have less biocompatibility or be more brittle than HA due to the addition of silicon. *Id*. at 52–53 (citing Ex. 2026 ¶ 99). Patent Owner argues that there is nothing in Ruys '93a that would indicate that the addition of silicon "changed the biocompatible properties of CaP, thus enabling the

claimed development of a new mineralized matrix throughout the structure." *Id*. at 53 (citing Ex. 2026 ¶ 100). Patent Owner also argues that prior work "showed that [the] addition of macroporosity does nothing to improve the bioresorbability of a CaP material and indeed, the finding that Si changed the biocompatible properties of CaP was not known until the work of the '992 [patent] inventors." *Id*. (citing Ex. 2026 ¶ 100).

Even in the absence of Ruys providing biocompatibility or bioresorption data or recognizing the effect of silicon on the biocompatibility or bioresorption properties, Ruys '93a discloses a calcium phosphate biomaterial compound stated to be suitable for clinical trials. Ex. 1011, 5; Ex. 1003 ¶ 617; *see* Pet. 43; Pet. Reply 1, 9, 11. Petitioner emphasizes the Bioceramics disclosure that "[a]n ideal cancellous bone graft substitute would mimic osteon-evacuated cancellous bone and have a thin lattice interconnected by pores of 500–600 μm" (Ex. 1021, 110) and that "[p]orosity and interconnectivity are key determinants of amount and type of ingrowth" of CaP bone implant material (*id*. at 116–17). Pet. 46–47 (citing Ex. 1003 ¶¶ 155, 528–530, 685–87). Petitioner asserts that one of ordinary skill in the art would have been motivated by the teachings of Bioceramics to form the silicon-substituted CaP compound disclosed in Ruys '93a into a macroporous open cell structure with interconnected voids having pore sizes within the claimed range of 50 to 1000 microns. *Id*. at 47–48 (citing Ex. 1003 ¶¶ 689–90).

4. Secondary Considerations

a. Long-Felt but Unmet Need

As explained above in connection with independent claims 1 and 2, Patent Owner contends that the claimed invention met a long-felt but unmet need. PO Resp. 14. Patent Owner does not explain how a nexus exists between the asserted long-felt need for a synthetic bone graft material to replace autologous bone and

the features of claim 4. In particular, Patent Owner does not tie the effectiveness of Skelite and/or Actifuse to any asserted novelty of the claimed macroporous structure. For example, Dr. Ong admitted he did not perform a comparative analysis of Actifuse or Skelite with autologous bone grafts or macroporous bone graft substitutes that were available on the market or reported in the prior art. Pet. Reply 13 (citing Ex. 1133, 248:22–250:17, 253:7–258:21; Ex. 2031, 5; Ex. 2026 ¶ 83). Consequently, we are not persuaded by Patent Owner's contentions in relation to long-felt but unmet need.

b. Failure of ApaTech toAarrive at the Invention Until Many Years Later

Patent Owner argues that Petitioner had in hand both Ruys '93a and Lynch,[14] but "did not leap to the conclusion that they should add macroporosity to their silicon substituted dense CaP." PO Resp. 18 (citing Ex. 2026 ¶ 75; Ex. 2001, 3). As an initial matter, Petitioner's challenge to independent claim 4 includes Bioceramics for its teachings regarding the use of macroporous structures; that is, Petitioner does not rely on Ruys '93a and Lynch in connection with challenging any claims reciting macroporous structures. Patent Owner also argues that Petitioner's "prolonged path to discovery" regarding Actifuse reflects the non-obviousness of combining the silicon substituted CaP of Ruys '93a with the porous HA of Bioceramics. *Id*. at 16. Patent Owner continues that Petitioner's team finally filed a patent application directed to a process of creating macroporosity in October 1998, but did not reference silicon substitution and that their technical papers and patent applications support that it took years for them to determine the "crucial" nature of interconnecting porosity. *Id*. at 18–20 (citing Ex. 2026 ¶¶ 74, 76; Ex. 2024, 2:61, 5:10; Ex. 2001, 2–3).

[14] Patent Owner states that Ruys '93a and Lynch were published in 1993 and 1994, respectively. PO Resp. 15.

We do not find Patent Owner's contentions regarding Petitioner's purported failure to derive its desired bone replacement product until years after it "had the very same information in hand then that it asserts today would have rendered the instant claims obvious" to be persuasive. *Id*. at 20. To the extent Patent Owner relies on the Declaration of Dr. Ong to establish ApaTech's development timeline, Dr. Ong admitted "he had no personal knowledge of ApaTech's development of Actifuse." Pet. Reply 12 (citing Ex. 1133, 49:22–51:14, 11:17–22, 221:15–222:2). Dr. Ong also admitted the ApaTech patent (Ex. 2024) on which he relied in his Declaration (i) recognizes that the concept of interconnected macropores was known, and (ii) is directed to a process for making a "specific macroporous structure." Pet. Reply 12 (citing Ex. 1133, 217:14–218:2, 219:7–11). As noted earlier, Dr. Hing testified that the benefits of interconnected macroporosity and methods for incorporating macroporosity were known well before the August 1996 priority filing date of the '992 patent. Ex. 1136 ¶¶ 8–20. Dr. Hing further testified that the ApaTech patent referenced in Dr. Ong's Declaration (Ex. 2024) is directed to a foamed ceramic technique intended to be "used commercially, for reproducibly introducing macroporosity into any bioceramic material." *Id.* ¶¶ 21–22.

In short, Patent Owner conflates Petitioner's efforts to develop a particular technique for reliably forming a CaP biomaterial into a macroporous structure, with the more general claim 4 limitation of "forming said biomaterial compound as a macroporous structure comprising an open cell construction with interconnected voids." Therefore, the evidence of record does not support Patent Owner's argument that Petitioner's asserted failure to arrive at its bone replacement product was due to the non-obviousness of forming a silicon-substituted CaP biomaterial into a macroporous structure.

c. Length of Intervening Time Between Prior Art and Claimed Invention

Patent Owner also points out that "both macroporosity and the ability to chemically generate at least some form of Si substituted CaP were present in a very crowded and rapidly moving art for years prior to Millenium's invention of micro- and macroporous SiCaP in 1996 and ApaTech's description of dense SiCaP in 1996 followed by macroporous carbonated HaP in 1998." PO Resp. 21. Patent Owner argues that the length of time before these elements were put together "is an objective indicator that the combination was not in fact obvious." *Id*. Patent Owner points out several references teaching elementally-substituted HAP that were *not* modified to add macroporosity, suggesting that "macroporosity was not a routine design choice and was not considered desirable." *Id*. at 22. Patent Owner continues that there is no evidence that any others apart from Patent Owner and Petitioner were working to create SiCaP ceramics, much less micro- and macroporous SiCaP bioceramics.

The length of time before the known prior art elements of silicon substituted CaP and macroporosity were combined is not persuasive of the unobviousness of the combination, in the absence of accompanying evidence that there were attempts and failures in the art in solving the problem. *See In re Wright*, 569 F.2d 1124, 1127 (CCPA 1977) ("The mere age of the references is not persuasive of the unobviousness of the combination of their teachings, absent evidence that, notwithstanding knowledge of the references, the art tried and failed to solve the problem."). Consequently, we are not persuaded by Patent Owner's contentions in relation to the length of intervening time between the prior art and claimed invention.

d. Unexpected Results

As explained above in connection with independent claims 1 and 2, Patent Owner contends that the claimed invention provided unexpected results. PO Resp. 23 (citing Ex. 2026 ¶ 88). Patent Owner fails to explain how the asserted unexpected results are attributable to features that are (i) recited in claim 4 and (ii) novel elements not found in the prior art. More particularly, Patent Owner has not provided comparative tests or analysis of the claimed invention relative to prior art silicon-substituted CaP biomaterials, such as those disclosed in Ruys '93a, to establish that formation of the silicon-substituted biomaterial into a macroporous structure is the reason for the asserted unexpected results. *See In re De Blauwe*, 736 F.3d 699, 705 (Fed. Cir. 1984) (explaining that reliance on comparative tests to rebut a *prima facie* case of obviousness requires comparison of the claimed invention to the closest prior art).

Petitioner contends that Patent Owner could have compared Skelite or Actifuse "to numerous bone substitute products on the market in the mid-1990s, such as Endobon and Pro Osteon" as opposed to the "autologous bone and generic hydroxyapatite material [Patent Owner] does compare." Pet. Reply 13 (citing Ex. 1133, 248:22–250:17, 253:7–258:1; Ex. 2031, 5; Ex. 2026 ¶83). Having considered the evidence presented, we are not persuaded by Patent Owner's contentions in relation to unexpected results, because it does not provide evidence of unexpected results relative to the closest prior art.

e. Industry Acclaim

Patent Owner contends that the development of Skelite "resulted in considerable industry recognition and success for the young company [Millenium]" and that there was also significant industry praise and recognition for ApaTech's Actifuse product. PO Resp. 26–28. As explained above in connection

with independent claims 1 and 2, the evidence cited by Patent Owner suggests the benefits from Skelite and Actifuse are attributable to silicon substitution, previously disclosed in Ruys '93a, and the use of the claimed macroporous "scaffolds" to promote bone growth. PO Resp. 26–28 (citing Ex. 2039, 2–3; Ex. 2040, 4; Ex. 2041; Ex. 2043, 1–2; Ex. 2044. The cited evidence, however, must be read in the context of the Bioceramics disclosure of an idealized cancellous bone graft substitute having an interconnected macroporous structure (Ex. 1021, 110–11) and Dr. Hing's unrebutted testimony regarding the benefits of interconnected macroporosity and prior art methods for incorporating macroporosity (Ex. 1136 ¶¶ 9–20), which was confirmed by Dr. Ong (Ex. 1133, 226:7–233:18). On balance, we are not persuaded that Patent Owner's industry acclaim evidence is sufficient to overcome Petitioner's strong evidence of the obviousness of claim 4.

f. Commercial Success

As explained above in connection with independent claims 1 and 2, Patent Owner contends that the commercial success of Actifuse compels a finding of non-obviousness. PO Resp. 29 (citing Ex. 2049, 1; Ex. 2001, 6). For the same reasons as described above, based on the record before us, we find evidence of nexus in relation to commercial success to be tenuous and, thus, do not accord the cited evidence of commercial success significant weight.

5. Conclusion

In considering the entirety of the record, we are persuaded that one of ordinary skill in the art would have appreciated Ruys '93a's biomaterial compound would be suitable for forming as a macroporous structure, given that making calcium phosphate materials in a macroporous structure was well known (Pet. 32 (citing Ex. 1003 ¶¶ 147–164, 699); Pet. Reply 9), as well as Bioceramics's disclosure that "[a]n ideal cancellous bone graft substitute would mimic osteon-

evacuated bone and have a thin lattice interconnected by pores of 500–600 μm" (Ex. 1021, 110), and that "[p]orosity and interconnectivity are key determinants of amount and type of ingrowth" (*id*. at 116–17). Pet. 45. In that respect, Petitioner has presented sound reasoning with rational underpinnings in urging that an ordinarily skilled artisan would have incorporated Ruys '93a's compound into a macroporous structure to facilitate bone ingrowth and vascularization within the implant material. Pet. 45 (citing Ex. 1003 ¶ 697).

We are also satisfied that one of ordinary skill in the art would have appreciated that the macroporous structures would be suitable for being combined with mature and/or precursor bone cells to allow the cells to infiltrate the macroporous structure in order to develop new mineralized matrix throughout the structure. Pet. 33, 45 (citing Ex. 1073, 3, 1566; Ex. 1003 ¶700–702). In that respect, Petitioner has presented sound reasoning with rational underpinnings in urging that an ordinarily skilled artisan would have combined the macroporous structure with mature and/or precursor bone cells because of Ohgushi's disclosure of combining porous calcium phosphate materials with bone cells to enhance implantation outcomes. *Id*.

In full consideration of the evidence advanced by the parties in this challenge, we determine that the balance of the evidence supports a finding of obviousness. We conclude that Petitioner has proved, by a preponderance of the evidence, that claim 4 is unpatentable under 35 U.S.C. §103(a) for obviousness over the combination of Ruys '93a, Bioceramics, and Ohgushi.

6. Dependent Claims 36 and 38

Patent Owner directs no arguments specifically to claims 36 and 38 with regard to the challenge for obviousness over Ruys '93a, Bioceramics, and Ohgushi. We address these claims in turn. Dependent claim 36 recites that the biomaterial

compound "exists as a fine or coarse powder, pellets, three-dimensional shaped pieces, macroporous structures, thin films, and coatings." Ex. 1001, 37:18–21. Petitioner argues that Ruys '93a discloses that the material therein "was made as a powder (*i.e.*, a dried colloidal mixture) that was then tabletted." Pet. 46 (citing Ex. 1003 ¶ 709 (citing Ex. 1011, 3)). We credit Dr. Mikos's testimony and are persuaded that Petitioner presents sufficient evidence to support a finding that the combination of Ruys '93a, Bioceramics, and Ohgushi renders obvious the claimed subject matter.

Dependent claim 38 specifies that the substituting element is silicon. Ex. 1001, 35:26. Petitioner argues that "the compound in Ruys 1993a necessarily includes Si-TCP, wherein silicon has 'substituted' for phosphorus in the TCP structure." Pet. 46–47 (citing Ex. 1003 ¶ 613). We credit Dr. Mikos's testimony and are persuaded that Petitioner presents sufficient evidence to support a finding that the combination of Ruys '93a, Bioceramics, and Ohgushi renders obvious the claimed subject matter.

E. Obviousness of Claim 43 over Ruys '93a, Bioceramics, Ohgushi, and Lynch

Claim 43 depends directly from claim 4 and recites that "said biomaterial compound is provided as a composition additionally comprising at least one calcium phosphate material selected from the group consisting of calcium hydroxyapatite, α-TCP, β-TCP, ostacalcium phosphate, tetracalcium phosphate, dicalcium phosphate and calcium oxide." Ex. 1001, 38:16–21. Upon reviewing the unchallenged contentions and supporting evidence regarding dependent claim 43 that were presented by Petitioner in its Petition (Pet. 47–48 (citing Ex. 1003 ¶¶ 588, 744–745); *see also* Pet. 36 (citing Ex. 1026, 4:33–39; Ex. 1003 ¶ 724–726) (Petitioner pointing out that Lynch identifies the benefits of a TCP/HA combination)), we are persuaded that Petitioner presents sufficient evidence to

support a finding that the combination of Ruys '93a, Bioceramics, Ohgushi, and Lynch renders obvious the claimed subject matter recited in dependent claim 43.

F. Obviousness of Claims 17 and 26 over Ruys '93a, Lynch, and Chaki and Obviousness of Claim 44 over Ruys '93a, Bioceramics, Ohgushi, Lynch, and Chaki

Claims 17, 26, and 44 recite that "said composition additionally comprises an additive to increase the mechanical toughness and strength of said compound." Ex. 1001, 36:5–7, 44–46, 38:22–24. Petitioner points out Chaki's recognition of the need to increase mechanical strength and toughness of Ca-P implant materials and Chaki's disclosure of the use of silver to reinforce HA. Pet.48–50 (citing Ex. 1003 ¶¶ 581–584, 747–750; Ex. 1021, 86; Ex. 1026, 2:45–3:9; Ex. 1130, 1–2, 8–9). Petitioner argues that "[g]iven that it was known that increasing the mechanical strength and toughness of Ca-P implant materials was desirable in certain applications, the person of ordinary skill in the art would have been motivated to introduce additives . . . [and] would have had a reasonable expectation of success." *Id*. at 49. We are persuaded that Petitioner presents sufficient evidence to support a finding that the combination of Ruys '93a, Lynch, and Chaki renders obvious the claimed subject matter recited in dependent claims 17 and 26 and that the combination of Ruys '93a, Bioceramics, Ohgushi, Lynch, and Chaki renders obvious the claimed subject matter of claim 44.

III. MOTIONS TO EXCLUDE EVIDENCE

The party moving to exclude evidence bears the burden of proof to establish that it is entitled to the relief requested, namely that the material sought to be excluded is inadmissible under the Federal Rules of Evidence. *See* 37 C.F.R. §§ 42.20(c), 42.62(a).

A. Petitioner's Motion

Petitioner moves to exclude Exhibit 2003 (a "timeline" of patent filings by Petitioner and Patent Owner, prepared by Patent Owner) for lack of authentication and foundation and Exhibits 2039–2041 (various publications found on the Internet) for lack of authentication and foundation and as containing inadmissible hearsay. Pet. Mot. Excl. 2–8.

We dismiss Petitioner's motion as moot, because we do not rely on the objected-to timeline in our final Decision and because, even without excluding Patent Owner's additional evidence, we have determined that Petitioner has demonstrated, by a preponderance of the evidence, that claims 1, 2, 4, 9, 11, 16–18, 20, 25, 26, 38, 38, 43, and 44 of the '992 patent are unpatentable.

B. Patent Owner's Motion

Patent Owner moves to exclude paragraphs 20, 21, 23–28, 35, 96–103, 108–140, 170–172 of Exhibit 1134 (reply declaration testimony of Petitioner's expert, Dr. Mikos) as irrelevant, likely to confuse the issues and mislead the panel, not based on sufficient facts or data and/or not the product of reliable principle and methods, and constituting new belatedly presented evidence which should be excluded as improperly included with the reply. PO Mot. Excl. 1–9.

Patent Owner also moves to exclude certain testimony by Patent Owner's expert, Dr. Ong, at pages 116–117 and 161 of his deposition, as being obtained pursuant to objectionable and/or misleading questioning. *Id*. at 10–13. Patent Owner also moves to exclude paragraphs 33–34 of Exhibit 1134 (reply declaration testimony of Petitioner's expert, Dr. Mikos) as relying on an improper basis. *Id*. at 13.

We dismiss Patent Owner's motion as moot, because we do not rely on any of the objected-to evidence in our final Decision.

IV. CONCLUSION

We determine Petitioner has established by a preponderance of the evidence that, under 35 U.S.C. § 103(a): claims 1, 2, 9, 11, 16, 18, 20, and 25 are unpatentable over Ruys '93a and Lynch; claims 4, 36, and 38 are unpatentable over Ruys '93a, Bioceramics, and Ohgushi; claim 43 is unpatentable over Ruys '93a, Bioceramics, Ohgushi, and Lynch; claims 17 and 26 are unpatentable over Ruys '93a, Lynch, and Chaki; and claim 44 is unpatentable over Ruys '93a, Bioceramics, Ohgushi, Lynch, and Chaki.

V. ORDER

In consideration of the foregoing, it is

ORDERED that claims 1, 2, 4, 9, 11, 16–18, 20, 25, 26, 36, 38, 43, and 44 of the '992 patent are determined to be unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude Evidence is *dismissed as moot*; and

FURTHER ORDERED that Patent Owner's Motion to Exclude Evidence is *dismissed as moot*.

This is a final written decision. Parties to this proceeding seeking judicial review of our decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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