Trials@uspto.gov
Tel: 571-272-7822

Paper 8
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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
Petitioners

v.

MILLENIUM BIOLOGIX, LLC
Patent Owner

Case IPR2013-00582
Patent RE41, 251

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

MURPHY, *Administrative Patent Judge*.

DECISION

Institution of *Inter Partes* Review
37 C.F.R. § 42.108

Baxter Healthcare Corp., ApaTech, Inc., and ApaTech Limited ("Petitioners") filed a Petition requesting *inter partes* review of claims 1, 6, and 8-13 of U.S. Patent No. RE41, 251 ("the '251 patent") pursuant to 35 U.S.C. § 311. Paper 1 ("Pet."). Millenium Biologix, LLC ("Patent Owner") filed a Preliminary Response to the Petition. Paper 7 ("Prelim. Resp.").

I. INTRODUCTION

The standard for instituting an *inter partes* review is set forth in 35 U.S.C. § 314(a):

> THRESHOLD – The Director may not authorize an inter partes review to be instituted unless the Director determines that the information presented in the petition filed under section 311 and any response filed under section 313 shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.

Upon consideration of the Petition and Patent Owner's Preliminary Response, we conclude that Petitioners have shown a reasonable likelihood that they would prevail with respect to claims 1, 6, and 8-13 of the '251 patent. Accordingly, we institute an *inter partes* review of claims 1, 6, and 8-13 of the '251 patent.

A. Related Proceedings

The '251 patent is the subject of litigation 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. Petitioners were named as defendants and served with a complaint alleging infringement of the '251 patent in May 2013. Pet. 2. Claims 1, 6, and 8-13 of the '251 patent also are

the subject of the petition in IPR2013-583, filed concurrently with Petitioners' petition in this matter. *Id*.

B. The '251 Patent

The '251 patent is directed to a synthetic biomaterial compound based on stabilized calcium phosphates and adapted for supporting bone cell activity. Ex. 1001, Title and Abstract. 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 1:25-33. The compound can be manufactured 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 21:56-62, 27:1-13. The compound is made by sintering a fine precipitate of a calcium phosphate at high temperature (about 1000º C) in the presence of a stabilizing additive having an ionic radius of a size that enables substitution into the Ca-P lattice. *Id*. at 5:31-35. 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 5:39-41.

The '251 patent is a reissue of U.S. Patent No. 6,323,146. Claims 1, 6, and 8 are representative and reproduced below. Italicized text indicates language that was added to the claims during prosecution of the reissue application. Bracketed text indicates language that was removed.

> 1. An isolated bioresorbable 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**]** *Si^{4+}, wherein said compound has a microporous structure*.

6. The biomaterial compound as claimed in claim **[5]** *1* wherein said compound is formed as a macroporous structure comprising an open cell construction with interconnected voids having a pore size of approximately 50 to 1000 microns.

8. The biomaterial compound as claimed in claim **5**[1], wherein said compound has a nanoporous structure.

C. Prior Art Relied Upon in the Petition

Petitioners rely upon the following references, further supported by the Declaration of Antonios Mikos (Ex. 1003):

Pugh	WO97/09286	March 13, 1997	Ex. 1017
Davies	WO94/26872	Nov. 24, 1994	Ex. 1015
Ichitsuka	EPO267624	May 18, 1988	Ex. 1024
Qiu	3 CELLS & MATER. 351:360	1993	Ex. 1016
Ruys '93a	42 INT'L CERAM. REV. 372:374	Dec. 6, 1993	Ex. 1011
Bioceramics	1 INTRO. BIOCERAMICS 41:103; 139:21	1993	Ex. 1021
White	30 DENTAL CLIN. NA 49:67	Jan. 1986	Ex. 1022
Ruys '93b	29 J. AUST. CERAM. 71:80	1993	Ex. 1014

[1] Claim 8 depends from a claim canceled in reissue. Solely for purposes of this decision, we interpret claim 8 as depending from claim 1.

D. Proposed Grounds of Unpatentability

Petitioners assert that the challenged claims are unpatentable based on the following grounds:

Reference[s]	**Basis**	**Claims challenged**
Pugh	§ 102(a)	1, 6, and 8-13
Pugh and Ichitsuka	§ 103	8
Davies	§ 102(b)	1 and 8-13
Davies and Ichitsuka	§ 103	8
Qiu	§ 102(b)	1 and 8-13
Qiu	§ 103	8
Ruys ’93a	§ 102(b)	1 and 8-13
Ruys ’93a and Bioceramics	§ 103	6
Ruys ’93a and White	§ 103	6
Ruys ’93a and Ichitsuka	§ 103	8
Ruys ’93b	§ 102(b)	1 and 8-13
Ruys ’93b and Bioceramics	§ 103	6
Ruys ’93b and White	§ 103	6
Ruys ’93b and Ichitsuka	§ 103	8

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); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012). 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. "Isolated . . . compound"

Petitioners argue the broadest reasonable interpretation of "isolated . . . compound" consistent with the specification is "a multi-phasic mixture containing a substituted-TCP[2] phase, which has been separated from other starting materials used to synthetically or otherwise prepare that multi-phase compound." Pet. 15. Petitioners point out that the '251 patent specification does not use the word "isolated" to describe any calcium phosphate

[2] TCP stands for tricalcium phosphate, one of several calcium phosphate species. Ex. 1001, 3:4-15.

compound.[3] Pet. 14. Petitioners emphasize that the word "isolated" was added to the claim by amendment during prosecution of the original patent prior to reissue. *Id.*; Ex. 1009, 269, 274, 275. Patent Owner responds with a proposed construction of "any single phase or multiphase CaP compound where silicon is substituted consistently throughout." Prelim. Resp. 21, 22; Ex. 1009, 304.

Petitioners and Patent Owner are attempting to read limitations into the claim term "isolated . . . compound," even though such limitations are not found in the claim language and are inconsistent with the specification. Such attempts violate fundamental principles of claim construction. *See, e.g., Translogic Tech.*, 504 F.3d at 1257-58; *Phillips*, 415 F. 3d at 1323 ("although the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments."). Neither party's proposed construction reflects the broadest reasonable interpretation of the '251 patent, consistent with the specification, and we decline to adopt either party's proposed construction.

Claim 1 claims a silicon-substituted compound "comprising calcium, oxygen and phosphorous." The silicon-substituted calcium, oxygen, and phosphorous compounds disclosed in the '251 patent are stabilized calcium phosphates synthesized and isolated as calcium phosphate "phases" or as a calcium phosphate "phase." Ex. 1001, Title,[4] 4:24-28, 5:4-5, 11:14-23,

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[3] The '251 patent uses the term "isolated" only in reference to an unrelated description of osteoclast cells isolated from bone marrow to permit *in vitro* observation of osteoclast activity. Ex. 1001, 3:41-4:8.

[4] "Synthetic Biomaterial Compound of Calcium Phosphate Phases Particularly Adapted for Supporting Bone Cell Activity."

13:40-61, and Figs. 9, 10, and 16. The '251 patent summary of invention states that a silicon-substituted calcium phosphate (silicon "substituted into the Ca—P lattice") "typically coexists with hydroxyapatite,[5] and is itself a novel stabilized calcium phosphate compound having a microporous morphology . . . ." *Id*. at 5:31-39. Although silicon-substituted TCP is identified and claimed as a preferred compound (*Id*. at 6:5-7 and 34:22-27), the '251 patent states that "[s]pecific compounds of the present invention include but are not limited to" silicon-substituted TCP. *Id*. at 6:5-7. The Pugh priority application[6] repeatedly and consistently refers to stabilized calcium phosphate phases, defined by Pugh "to include the various calcium phosphate species *in the sintered product* such as hydroxyapatite, [alpha]-TCP, [beta]-TCP, calcium octophosphate, tetracalcium phosphate and dicalcium phosphate." Ex. 1017, 12:17-20 (emphasis added); *see also* Ex. 1001, 20:62- 21:10. Silicon substitution stabilizes a calcium phosphate phase or phases such that they "maintain a consistent crystallographic and chemical structure when placed in ambient conditions or in a physiological environment *in vivo* or *in vitro*" (Ex. 1017, 12:6-9) and are "essentially insoluble in biological media . . . ." (Ex. 1001, 5:39-41).

In light of the above and contrary to Petitioners' argument, the claimed "isolated . . . compound" is not limited to compounds including a silicon-substituted TCP phase. Claim 1 uses the open-ended phrase

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[5] Hydroxyapatite, another calcium phosphate species also referred to as calcium hydroxyapatite or "HA," is the primary inorganic component of natural bone. Ex. 1001, 2:66-67.

[6] The '251 patent claims priority to Pugh through a chain of continuation-in-part applications.

"comprising calcium, oxygen and phosphorous," which includes several different calcium phosphate species in addition to TCP, as indicated in the '251 patent specification and Pugh priority document discussed above. The open-ended language of claim 1 also contrasts with the narrower Markush group language contained in independent claims 15 (Si-substituted TCP) and 22 (several Si-substituted calcium phosphate species). *See, e.g., Abbott Labs. v. Andrx Pharm., Inc.*, 473 F.3d 1196, 1210 (Fed. Cir. 2007) ("A Markush group is a form of drafting a claim term that is approved by the PTO to serve a particular purpose when used in a claim—to limit the claim to a list of specified alternatives.") (citations omitted). The'251 patent consistently refers to stabilized "calcium phosphate phases," without any indication of intending to limit the claimed invention solely to compounds including a silicon-substituted TCP phase.

We recognize that Patent Owner added the word "isolated" to distinguish claim 1 (among others) from Davies during prosecution and argued that applicants have developed "a stabilized calcium phosphate phase (claimed in WO 97/09286) from which the presently claimed biomaterial compound was then further isolated therefrom." Ex. 1009, 304. We do not read this as an intention to limit the claims to a silicon-substituted TCP phase or as providing a special definition for the claimed "isolated compound." *See In re Paulsen*, 30 F.3d at 1480. An interpretation limiting the claims only to compounds including a silicon-substituted TCP phase would contradict Patent Owner's repeated references to stabilized calcium phosphate phases isolated by the processes disclosed in the '251 patent. Ex. 1001, Title, 4:24-28, 5:4-5 and 31-39, 11:14-23, 13:40-61, 20:62-21:10, and Figs. 9, 10, and 16; Ex. 1017, 12:17-20. The open-ended claim language,

the deliberate use of more limiting language in other claims, the disclosures of the '251 patent and Pugh priority document, and the prosecution history all counsel against limiting claim 1 to compounds including a silicon-substituted TCP phase.

The plain meaning of the word "isolated" also should not be encumbered with inappropriate constraints. The word "isolated" in claim 1 is used in accordance with its plain and ordinary meaning to those skilled in the art—separated from all other substances. *See* Ex. 1005, 4 (right-hand column, "[1]isolate," definition "**2**"[7]). Patent Owner interprets the prosecution argument made in support of adding "isolated" to claim 1 as "distinguishing the fact that the claimed invention had Si substituted consistently throughout the compound, rather than the striated silicon content shown in Davies." Prelim. Resp. 21.[8] Patent Owner's interpretation of "isolated" is not supported by the claim language, the '251 patent specification, or the prosecution history, as detailed above.

In sum, the compounds disclosed in the '251 patent are stabilized calcium phosphates synthesized and isolated as calcium phosphate "phases" or as a calcium phosphate "phase." Therefore, for purposes of this decision, we determine that the broadest reasonable interpretation of "isolated . . .

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[7] "to separate (as a chemical compound) from all other substances: obtain pure or in a free state"

[8] Patent Owner relies on figures 5A-5C of Pugh (not Davies) in an effort to illustrate the asserted "heterogeneous" silicon substitution of Davies' quartz thin films. Prelim. Resp. 35, 36. Patent Owner's argument is not persuasive, and we note figures 5A-5C of Pugh appear to be identical to figures 6(c)(i)-(iii) of the '251 patent on which Patent Owner relies, in part, as disclosing the quartz thin film embodiment of the claimed invention. Ex. 1001, 12:16-23.

compound" in the context of the claimed invention, consistent with the '251 specification, is "a stabilized single phase or multi-phase calcium phosphate compound separated from all other substances."

2. "bioresorbable biomaterial"

The isolated compound is claimed as a "bioresorbable biomaterial" in the preamble. The '251 patent describes how osteoblast cells synthesize organic components necessary for bone growth and osteoclast cells resorb or degrade bone as part of the natural process of bone remodeling. Ex. 1001, 1:45-54, 6:22-31. The '251 patent further describes the claimed "biomaterial" in terms of its bioactivity. *Id*. at 10:9-14. Such functional claim language merely describes properties that are inseparable from the claimed compound prepared according to the methods described in the '251 patent. *See In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990) (finding it reasonable to infer that polymerization of the same monomers using the same or similar techniques would produce polymers having the identical composition) (citing *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963) (a chemical compound and its properties are inseparable)). Therefore, we determine that no express interpretation of "bioresorbable biomaterial" is required for purposes of this decision.

3. "compound comprising calcium, oxygen and phosphorous, wherein a portion of at least one of said elements is substituted with an element Si^{4+}*"*

The parties dispute the broadest reasonable interpretation of the above-quoted claim phrase, reprising their arguments to the first two disputed claim phrases discussed above. Pet. 16-19; Prelim. Resp. 24-26.

We determine that no express interpretation is required, and the claim phrase is to be given its ordinary and customary meaning to those skilled in the art.

4. "microporous structure"

The parties agree that the claim phrase "microporous structure" means a structure having pore sizes of about a micron or less, or pores having diameters smaller than the diameters of the macropores on the same material. Pet. 19-20; Prelim. Resp. 27. This construction is not the broadest reasonable interpretation consistent with the specification. The '251 patent and Pugh priority application both describe a fine precipitate of a calcium phosphate, prepared using a sol-gel process, as central to the formation of a compound having a microporous structure. Ex. 1001, Col. 5:31-39; Ex. 1017, 17:12-20. Pugh describes the fine precipitate as "fine particles in suspension, the size of which is . . . about 0.3μm to over 1 μm when aging the sol-gel substance for 24 hours after preparation." Ex. 1017, 13:26-29. The '251 patent describes the formation of "inter-connected particles of average size 0.2-1.0μm with a large degree of local porosity" and adds that varying the preparation conditions "permits the formation of a range of microporous structures comprised of particles of size range 0.1-2.0 μm." Ex. 1001, Col. 13:61-66. The '251 patent does not discuss micropore sizes relative to macropore diameters.

In view of the above disclosures, and for purposes of this decision, the broadest reasonable interpretation of "microporous structure" in the context of the claimed invention, consistent with the '251 specification, is "a porous structure of interconnected particles having pore sizes of about 2 microns or less in diameter." Ex. 1001, 5:31-39, 13:61-66; Ex. 1017, 13:26-29 and 17:12-20.

5. "macroporous structure"

The parties dispute the meaning of the phrase "macroporous structure," which appears in claim 6. Pet. 19; Prelim. Resp. 27. Petitioners ask the Board to adopt the language of claim 6 as the broadest reasonable interpretation, while Patent Owner interprets "macroporous structure" more broadly, outside the confines of claim 6. Claim 6 defines "macroporous structure" with clarity and precision: "comprising an open cell construction with interconnected voids having a pore size of approximately 50 to 1000 microns." No further express interpretation is required.

6. "nanoporous structure"

The phrase "nanoporous structure" appears in claim 8 but otherwise is not found in the '251 patent. Unlike claim 6, claim 8 does not provide a definition of the subject structure. The parties agree that a person of ordinary skill in the art of synthetic bone material would understand nanoporosity to mean a pore size of less than about 0.1 micron (100 nanometers), an interpretation supported by the Mikos Declaration. Ex. 1003 ¶ 334. Therefore, for purposes of this decision, the broadest reasonable interpretation of "nanoporous structure" in the context of the claimed invention is "a porous structure of interconnected particles having pore sizes of less than about 0.1 micron (100 nanometers) in diameter."

The parties discuss other claim phrases, none of which is material or necessary to this decision.

B. Anticipation of Claims 1, 6, and 8-13 by Pugh; Obviousness of Claim 8 over Pugh and Ichitsuka

Petitioners argue that, although the '251 patent claims the benefit of Pugh's filing date, Pugh should be considered prior art to the challenged

claims because Pugh fails to support the claims with adequate written description. Pet. 7-9. The '251 patent claims priority to Pugh through a chain of continuation-in-part applications. Ex. 1001, 1:12-22. Pugh was filed August 30, 1996 and published March 13, 1997. Ex. 1017. Application 09/044,749, which led to the issuance of U.S. Patent No. 6,323,146 prior to the '251 patent reissue, was filed on March 19, 1998. Ex. 1001.

Claim 1 requires a portion of at least one of the compound elements (Ca, O, or P) to be "substituted" with silicon. Petitioners argue that because Pugh does not disclose silicon substitution *per se,* but rather discloses silicon stabilization, the challenged '251 patent claims are not entitled to Pugh's August 30, 1996 priority date. Pet. 8, 9. Petitioners rely on evidence that Patent Owner distinguished Pugh from then-pending claim 1 during prosecution by arguing that Pugh did not teach or suggest "substitution," but only taught "stabilization" of an alpha-TCP compound. *Id*. (citing Ex. 1009, 202; Ex. 1003 ¶¶ 337-352). Petitioners argue that because the concept of "substitution" was not included in Pugh, Pugh does not provide sufficient written description support for an August 30, 1996 priority date and should be considered § 102(a) art that anticipates the challenged claims. *Id*. at 8, 9, and 21-25.

Patent Owner emphasizes that Petitioners do not challenge Patent Owner's unbroken chain of claimed priority. Prelim. Resp. 1. With regard to its supposed admission during prosecution that Pugh does not disclose "substitution," Patent Owner explains that the claims then pending were materially different from those now challenged. *Id*. at 1, 2, 29-33. In

particular, then-pending claim 1 was broad enough to include substitution "with an element having an ionic radius of approximately 0.1 to 1.1Å," and this claim limitation included a range of stabilizing elements beyond those disclosed in Pugh. Ex. 1009, 62, 182-84; Prelim. Resp. 12-13; *cf*. Ex. 1001, 33:10-40, Table 2. Patent Owner also argues that statements made during prosecution are irrelevant to an inquiry into adequate written description, which is limited to the four corners of the application as of the filing date. Prelim. Resp. 31-32 (citing *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351(Fed Cir. 2010) (en banc) ("[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.")).

Petitioner's argument and evidence do not persuade us that it is likely to prevail in showing that claims 1, 6, 8, and 10-13 of the '251 patent are not entitled to the benefit of Pugh's filing date.

As a first matter, we do not understand how Pugh could be an anticipatory reference that discloses each and every limitation in claims 1, 6, and 8-13, yet also fails to disclose the substitution limitation required by independent claim 1. We also are persuaded by Patent Owner's argument. The claims at issue at the time of the prosecution argument in question were of materially broader scope than the claims now challenged, were rejected on a basis different than the grounds of unpatentability proffered by Petitioners, and were amended during subsequent prosecution of the '749 application and during reissue proceedings. Therefore, even if we were to consider such evidence outside the four corners of the Pugh application, it

would be of little probative value given the materially different claim scope and basis for rejection of the prosecution claims.

For the foregoing reasons, we conclude that Petitioners have not demonstrated that Pugh is prior art to the '251 patent under 35 U.S.C. § 102(a). Accordingly, we decline to institute *inter partes* review of claims 1, 6, and 8-13 for anticipation by Pugh, or of claim 8 for obviousness over Pugh and Ichitsuka.

C. Anticipation of Claims 1 and 8-13 by Davies; Obviousness of Claim 8 over Davies and Ichitsuka

Petitioners argue the quartz thin-film coating and sintering process of Davies (Ex. 1015) is identical to the process described in the '251 patent for preparing the quartz thin-film embodiment of the claimed compound and, therefore, inherently anticipates claims 1 and 8-13 under 35 U.S.C. § 102(b). Pet. 32-33; Ex. 1003, 244-45 (App. B). Petitioners further argue the obviousness of claim 8 over Davies and Ichitsuka. Pet. 35-37. Patent Owner opposes. Prelim. Resp. 34-37.

1. Overview of Davies

Davies discloses synthetic calcium phosphate based thin films on which bone cells may be cultured to permit evaluation of bone cell functional properties, such as osteoclast activity. Ex. 1015, Abstract, 6:30-35. Davies's Procedure 1 describes the preparation of hydroxyapatite (HA) using a two-solution sol-gel process, where Solution A (pH 12) is made with 4.722 grams of calcium nitrate and Solution B (pH 12) is made with 1.382 grams of ammonium dihydrogen phosphate. Ex. 1015, 25:8-26:29; Ex. 1003, 244. After mixing Solutions A and B followed by centrifugation, a colloidal sol-gel of hydroxyapatite (HA or $Ca_5(OH)(PO_4)_3$) is formed. *Id.*

Davies's Procedure 3 describes cleaning a quartz (Si) substrate, and Procedure 4 describes dip coating the cleaned quartz substrate with the colloidal HA sol-gel prepared in Procedure 1. Ex. 1015, 28:17-29:9; Ex. 1003, 244. Procedure 5 describes sintering the HA-coated quartz substrate at 1000ºC for one hour. Ex. 1015, 29:11-19; Ex. 1003, 245. X-ray diffraction analysis reveals that, when sintered at 1000ºC, "the film has a majority of tricalcium phosphate and a ratio of approximately 10:90 of calcium hydroxyapatite [HA] to tricalcium phosphate." Ex. 1015, 29:20-35.

2. Analysis of asserted anticipation by Davies

The issue raised by Petitioners, albeit without any supporting case citations, is one of inherent anticipation. *See, e.g., Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) ("[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference."); *SmithKlineBeecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44 (Fed. Cir. 2005) (patent challenger must demonstrate "that 'the disclosure [of the prior art] is sufficient to show that the natural result flowing from the operation as taught [in the prior art] would result in' the claimed product.") (citations omitted). Anticipation is a question of fact, and "the doctrine of inherent anticipation applies to the entire claimed subject matter just as it does to a single claimed feature." *SmithKline Beecham*, 403 F.3d at 1343. We therefore address the evidence in support of the facts alleged by Petitioners to establish inherent anticipation of claims 1 and 8-13 of the '251 patent by Davies.

The detailed description of preferred embodiments in the '251 patent begins by stating that the morphology of the stabilized calcium phosphate

compound "is provided in accordance with that method described in the Applicant's co-pending published PCT application WO94/26872 [Davies], the subject matter of which is incorporated herein by reference. The preferred embodiment for making the compound of the present invention is described herein in the accompanying examples." Ex. 1001, 9:66-10:8. Examples 1 and 3 of the '251 patent repeat, almost verbatim, the quartz thin-film coating and sintering process of Davies' Procedures 1 and 3-5. *Compare* Ex. 1015, 25:8-26:29, 28:17-29:19 *with* Ex. 1001, 27:55-28:39, 29:7-38. The '251 patent includes multiple figures of analytical data taken from quartz thin films prepared using the Davies method. Ex. 1001, Figs. 2-6, 20-22. The analytical data confirms the presence of silicon in the calcium phosphate thin films as well as the microporosity and nanoporosity of the isolated compound. *Id*. at 4:24-36, 11:13- 12:23, Figs. 2-6; Ex. 1003 ¶¶ 434-439, 449, 450, 610, 617, 725, 729-731; *see* Ex. 1015, 29:11-30:28. The analytical data also confirms the bioresorption capability and bioactivity of Davies' quartz thin-film compounds. Ex. 1001, 4:9-23, 16:58-17:32, Figs. 20-22(b); Ex. 1015, 7:32-37, 9:24-10:9, 30:7-28; Ex. 1003 ¶¶ 439, 611-613.

Patent Owner does not contest the above facts, but rather reargues its proposed claim constructions for "isolated . . . compound," "bioresorbable," and "macroscopic." Prelim. Resp. 34-37. Patent Owner attempts to distinguish the quartz thin films of Davies as not having "a consistent mixture of silicon substituted throughout the material," but rather having "stratified" or "heterogeneous" silicon substitution. *Id*. at 35-36. Patent Owner relies on figures 5A-5C of Pugh (not Davies) in an effort to illustrate this asserted heterogeneous silicon substitution of Davies' quartz thin films. *Id*.

Patent Owner's argument is not persuasive, not only because we have determined there is no requirement for a consistent mixture of silicon substituted throughout the claimed "isolated compound," but also because figures 5A-5C of Pugh appear to be identical to figures 6(c)(i)-(iii) of the '251 patent on which Patent Owner relies, in part, as disclosing the silicon-substituted thin-film embodiment of the claimed invention. Ex. 1001, 12:17-23. As for Patent Owner's argument regarding Davies' asserted absence of a bioresorbable/macroporous structure (Prelim. Resp. 36-37), while we agree with Patent Owner that Davies does not disclose, expressly or inherently, a macroporous structure, we reiterate that a macroporous structure is not a limitation of claims 1 and 8-13 of the '251 patent.[9]

Claims 8-13 of the '251 patent depend from claim 1 and add structural features (claims 8, 9, and 13) and functional properties (claims 10-12) inherent to Davies's silicon-substituted quartz thin films. Pet. 35-39; Ex. 1003 ¶¶ 735, 736, 781-785, 788-791. In particular with regard to claim 9, silicon-substituted TCP produced by Davies' quartz thin-film process exhibits monoclinic pseudo-rhombic symmetry and is in the monoclinic space group $P2_1/a$. Ex. 1009, 261; Ex. 1001, 7:41-48, 11:14-23, and Fig. 2; Ex. 1003 ¶ 781**.** In particular with regard to claim 13, the formation of silicon-substituted TCP results in a calcium-to-phosphorous ratio less than 1.67. Ex. 1001, 18:28-30; Ex. 1003 ¶ 791.

[9] A macroporous structure of open cell construction with interconnected voids having a pore size of approximately 50 to 1000 microns is claimed in claim 6. Ex. 1001, 27:1-41, 30:53-31:19, 33:59-63.

For the foregoing reasons, on the present record we conclude that Petitioners have demonstrated a reasonable likelihood that claims 1 and 8-13 of the '251 patent are unpatentable for anticipation by Davies.

3. Analysis of asserted obviousness of claim 8 by Davies and Ichitsuka

Petitioners rely on the combination of Davies and Ichitsuka for the asserted obviousness of claim 8, which depends from claim 1 and recites a compound that "has a nanoporous structure." Pet. 35-37. Petitioners emphasize that the sintered quartz thin films of Davies contain HA and TCP phases, are bioresorbable biomaterials having a microporous structure, and are "similar to materials implanted in the body." *Id*. at 36 (quoting Ex. 1015, 30:16-23); Ex. 1003 ¶¶ 436-439. Petitioners state that Ichitsuka discloses a porous calcium phosphate based bone prosthesis having pores within the nanoporous size range, which prevents encapsulation of bone implant material and permits the clinician to "work" or shape the bone prosthesis as necessary during surgery. Pet. 36-37; Ex. 1003 ¶¶ 555-57, 740-43. Petitioners argue that a person of ordinary skill in the art would have thought to use Davies's silicon-substituted, calcium phosphate thin film material in the porous calcium phosphate bone prosthesis taught by Ichitsuka with a reasonable expectation of success, given that both references teach the utility of calcium phosphate materials in bone implants and given the clinical benefits of using Ichitsuka's open pore (0.01-2.00 μm) and closed pore (0.01-30 μm) structure. Pet. 37; Ex. 1003 ¶¶ 740-43; Ex. 1024, 3:7-58.

Patent Owner relies on evidence of secondary indicia of nonobviousness in the form of published reports by Petitioner Apatech containing asserted admissions during Apatech's development of its own

macroporous (not nanoporous) silicon-calcium phosphate bone material. Prelim. Resp. 38-44. Patent Owner has not established, on the present record, a sufficient nexus between that evidence and the "nanoporous structure" of claim 8. *Id*. at 57-58; *see, e.g., Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) ("For objective evidence … to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention.") (citations omitted); *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1363 (Fed. Cir. 2012)("[F]or commercial success to be probative evidence of nonobviousness, a nexus must be shown between the claimed invention and the evidence of commercial success.").

Patent Owner also argues that neither Ichitsuka nor Davies's "SiCaP" thin films provides any teaching or suggestion of silicon substitution or macroporosity. Prelim. Resp. 57-58. The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness. *In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995) (affirming 35 U.S.C. § 103 rejection based, in part, on inherent disclosure in one of the references). The question of obviousness is "based on underlying factual determinations including . . . what th[e] prior art teaches explicitly and inherently . . . ." *In re Zurko*, 258 F.3d 1379, 1383 (Fed. Cir. 2001) (citations omitted). Given our analysis of Davies's inherent disclosure of porous, silicon-substituted calcium phosphate, and the express reference to its potential use as a bone implant material, and Ichitsuka's explicit teaching of the benefits of using microporous and nanoporous calcium phosphate as a bone implant material to improve its clinical utility, we are persuaded by Petitioners' argument. The rationale provided in the Mikos Declaration for

combining Davies and Ichitsuka to achieve the claimed "nanoporous structure" of claim 8 is logical, specific, and supported by sufficient evidence. *See* Pet. 35-36; Ex. 1003 ¶¶ 725, 735-743. We conclude, on this record, that Petitioners have demonstrated a reasonable likelihood that claim 8 of the '251 patent would have been obvious to a person of ordinary skill in the art over Davies and Ichitsuka.

D. Anticipation of Claims 1 and 8-13 by Ruys '93a

Petitioners argue the silicon-substituted calcium phosphate material of Ruys '93a (Ex. 1011) is made by a very similar process to the sol-gel sintering process described in Examples 1 and 2 of the RE'251 patent and, therefore, inherently anticipates claims 1 and 8-13 under 35 U.S.C. § 102(b). Pet. 42-45, 51, 53-54; Ex. 1003 ¶¶ 622-632 and App. D. Patent Owner opposes. Prelim. Resp. 37, 38, 49-55.

1. *Overview of Ruys '93a*

Ruys '93a discloses an approach to enhancing "the relatively low bioactivity of hydroxyapatite (HAP)" by using silicon doping as an alternative to porosity control to form a new silicon-substituted calcium phosphate compound. Ex. 1011, 3, 4. Ruys '93a pursues this alternative approach because "the low strength of porous HAP limits its use to bioactive coatings, or to monolithic implants in non-load-bearing sites. The manufacture of HAP, characterized by both high strength and high bioactivity, is . . . difficult to achieve in practice." *Id*. at 3. Ruys '93a describes a two-solution sol-gel process to make finely divided (20 nm) stoichiometric hydroxyapatite (HA) suspended in ethanol. *Id*. Ruys '93a adds ethyl silicate to the suspended HA, then excess water, to form colloidal

silica. *Id*. The precipitated HA and silica powder is pressed into pellets and sintered at 1100ºC for one hour in air. *Id*.

Ruys '93a analyses the sintered product and describes a multi-phase, silicon-substituted calcium phosphate compound, including tricalcium phosphate (TCP) as one of "two new apatite phases." *Id*. at 4. Ruys '93a further 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." *Id*. With regard to porosity and density, Ruys '93a discloses that "addition of very small amounts of silicon (as colloidal SiO_2) reduced the sintering efficiency" (increased apparent porosity, decreased apparent density) of the compound. *Id*., Fig. 2.

2. *Analysis of asserted anticipation by Ruys '93a*

On January 5, 2009, during reissue proceedings, the Examiner rejected then-pending claims 1, 2, 4, and 10-12 as anticipated by Ruys '93b,[10] finding that the Ruys article "teaches silicon doped hydroxyapatite, which is an isolated bioresor[b]able biomaterial compound. The article teaches the silicon substituted for a portion of the phosphorous atoms in the compound. . . . [The compound] must inherently have the properties of claims 10-12, absent any showing to the contrary." Ex. 1002, 138. A telephonic interview was conducted on March 31, 2009. *Id*. at 151. The Interview Summary indicates discussion of a proposed amendment that "will overcome the objections to the specification and the art rejection." *Id*. On

[10] Ruys '93b contains substantially the same disclosure as Ruys '93a.

May 5, 2009, applicants canceled dependent claims 4 and 5 and wrote the limitations into an amended claim 1 to specify substitution with "Si^{4+}" and "wherein said compound has a microporous structure."

The issue, then, is whether Petitioners have established a reasonable likelihood that Ruys'93a inherently discloses a compound that necessarily has the claimed "microporous structure" and, regarding claim 8, the claimed "nanoporous structure." Petitioners rely on the Mikos Declaration[11] to demonstrate the asserted inherency. Pet. 44-45.

Mikos explains that some of the known processes for making HA were understood to result in a microporous structure, and that micropores are caused by "among other things, incomplete sintering of Ca-P granules," which leave open voids in the material. Ex. 1003 ¶ 70. Mikos acknowledges that "the porosity of the HA (e.g., size and quantity) could be manipulated simply by altering the reaction conditions or adding additives to the reaction" (*Id*. ¶ 71), but he emphasizes that Ruys '93a's two-solution sol-gel and sintering process is "equivalent" to the process disclosed in Examples 1 and 5 of the '251 patent. *Id*. ¶ 625. Mikos further reasons that because Ruys '93a indicates "reduced" or "retarded" sintering efficiency at very low levels of silicon addition, resulting in "restraining the green structure of the HAP," one of skill in the art would have understood that the pores were micropores. *Id*. ¶¶ 389-391, 631, 632. Regarding nanoporosity, Mikos relies on the equivalence of the Ruys '93a process to Examples 1 and

[11] Mikos is the Louis Calder Professor of Bioengineering and Chemical and Bimolecular Engineering at Rice University in Houston, Texas. Ex. 1003 ¶ 1.

5 in the '251 patent to conclude the Ruys '93a process necessarily would have produced a nanoporous structure. *Id*. ¶¶ 750, 751.

Patent Owner acknowledges Ruys '93a as the closest prior art teaching the introduction of silicon into the crystal lattice of calcium phosphate compounds. Prelim. Resp. 37, 38. Patent Owner attempts to distinguish Ruys '93a from all of the '251 patent claims being challenged on the grounds that Ruys '93a does not disclose bioactivity data and does not teach macroporosity. *Id*. at 38. Patent Owner does not challenge or discuss the Examiner's reissue rejection or Mikos's conclusions that the Ruys '93a process necessarily will produce an isolated, silicon-substituted compound comprised of calcium phosphate phases having a microporous structure and a nanoporous structure.

Given the detailed process steps disclosed in Ruys '93a, particularly the precipitation and sintering of "[f]inely divided (approx. 20nm) HAP"[12] in the presence of silicon, the Ruys '93a analytical data (e.g., Fig. 2 porosity and X-ray diffraction analysis), and Mikos's explanation of the analytical data, we are persuaded that Petitioners have provided sufficient evidence, on this record, to establish that the Ruys '93a process necessarily produces the claimed compound having a "microporous structure" and a "nanoporous structure." We are further persuaded that Petitioners have provided sufficient evidence to establish, on this record, that the Ruys '93a process necessarily produces an isolated, bioresorbable, silicon-substituted calcium phosphate biomaterial having the structural features and functional

[12] This is very similar to the description in the Pugh priority application that "the [HA] substance is originally prepared in the sol-gel process as very fine particles." Ex. 1017, 17:12-16.

properties claimed by Patent Owner in claims 1 and 8-13 of the ’251 patent. As stated previously, macroporosity is not a limitation of claims 1 and 8-13 of the ’251 patent. For the foregoing reasons, we conclude that Petitioners have established a reasonable likelihood that claims 1 and 8-13 of the ’251 patent are unpatentable for anticipation by Ruys ’93a.

E. Obviousness of Claim 6 over Ruys ‘93a and Bioceramics

1. Claim 6 of the ’251 patent

Claim 6 of the ’251 patent depends from claim 1 and requires the compound to be “formed as a macroporous structure,” with an “open cell construction” and “interconnected voids having a pore size of approximately 50 to 1000 microns.” Ex. 1001, 33:59-63. The ’251 patent describes using a silicon-substituted microporous calcium phosphate material to form a “bulk ceramic having a globular microporous structure, an underlying internal microporous structure and an internal macroporous structure allowing cells to migrate and function throughout the entire bulk ceramic unit.” *Id*. at 27:16-21. The open cell structure of interconnected macropores, best illustrated in Figure 23, “encourages bone growth and subsequent remodeling in a system more closely resembling physiological iii [in] vivo bone.” *Id*. at 27:5-8. Example 8 describes the use of sintered, silicon-substituted calcium phosphate powder to form an aqueous slurry in which a piece of open cell (reticulated) polyurethane foam is immersed. *Id*. at 30:53-62. The slurry-coated foam is dried and sintered at 1000ºC for one hour, during which time the foam decomposes and is removed by pyrolysis, leaving a silicon-substituted calcium phosphate product that replicates the

shape and open-cell structure of the foam as a macroporous structure. *Id*. at 30:62-67.

2. Analysis

Petitioners acknowledge Ruys '93a does not teach the formation of a macroporous, open-cell structure, but Petitioners argue that formation of such a structure using Ruys '93a's silicon-substituted calcium phosphate material would have been an "obvious design choice" for one skilled in the art in view of the Bioceramics reference. Pet. 45. Petitioners, relying on the Mikos Declaration, assert that methods of making a biomaterial compound having a macroporous structure were well known. *Id*. at 48 (citing Ex. 1003 ¶¶ 147-164, 690). Petitioners emphasize 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" (*Id*. at 116-117). Pet. 46, 47. Petitioners assert that one of ordinary skill in the art would have been motivated by Bioceramics to form the compounds disclosed in Ruys '93a into a macroporous open cell structure with interconnected voids having pore sizes of 50 to 1000 microns. *Id*. at 47, 48 (citing Ex. 1003 ¶¶ 689, 690).

Patent Owner argues that, without any testing or data regarding the bioactivity or biocompatibility of the silicon-substituted calcium phosphate compounds disclosed in Ruys '93a (Prelim. Resp. 45-47), one of ordinary skill in the art would not have had a reason to create the "SiCaP micro and macroporous compound of the claimed invention." Id. at 47. Patent Owner contends that without bioactivity testing or data in Ruys '93a, it would constitute impermissible hindsight to conclude otherwise. *Id*. at 46-48.

Patent Owner further contends, in contrast to the ’251 patent, Bioceramics teaches that forming HA into a macroporous structure does nothing to improve bioresorbability of the compound in a clinically relevant time frame. *Id*. at 51. Patent Owner reasons that failure to recognize properties of a prior art compound necessarily prevents a skilled artisan from having a reasonable expectation of success when modifying such compounds (e.g., forming a microporous SiCaP compound into a macroporous open cell structure), even where the type of modification already was known. *Id*. at 52.

Patent Owner’s argument, however, does not explain why Petitioners’ stated reasoning for forming the compounds disclosed in Ruys ’93a into an open cell, macroporous structure to promote bone ingrowth and vascularization (Pet. 46-48 (citing Ex. 1003 ¶¶ 685-697)) lacks a rational underpinning or is based on hindsight. In particular, Patent Owner’s argument does not address adequately why Petitioners’ stated reasoning lacks a rational underpinning in light of the Bioceramics disclosure that a thin lattice interconnected by pores in the macroporous range of 500-600 μm would be “ideal” (Pet. 46 (citing Ex. 1021, 110)) and would “mimic osteon-evacuated cortical bone” (Ex. 1021, 108). This reasoning is comparable to Patent Owner’s reasoning in the ’251 patent for forming the claimed silicon-substituted calcium phosphate compound into an open cell, macroporous structure (macropores of 50 to 1000 μm) so that it “encourages bone growth and subsequent remodeling in a system more closely resembling

physiological iii [in] vivo bone." Ex. 1001, 27:2-13. Therefore, we are not persuaded by Patent Owner's argument.[13]

Patent Owner also argues that the additional two years Petitioner Apatech required to generate a macroporous structure for its SiCaP compound is evidence of unexpected results, satisfaction of an unmet need, failure of others, commercial success, successful licensing, and praise of others. Prelim. Resp. 38-41, 46 (citing Exs. 2001, 2003, 2006, and 2017). We have considered Patent Owner's argument and evidence in this regard, but detailed review of the secondary indicia evidence may not be undertaken until after Patent Owner has had an opportunity to introduce new testimonial evidence, and Petitioners have had an opportunity to conduct cross-examination.

In conclusion, we determine that on the present record Petitioners have demonstrated a reasonable likelihood that claim 6 of the '251 patent is unpatentable for obviousness over Ruys '93a and Bioceramics. Accordingly, we institute *inter partes* review of claim 6 on the ground of obviousness over Ruys '93a and Bioceramics.

[13] Patent Owner's challenge to the qualifications of Professor Mikos is not persuasive. Prelim. Resp. 41, 42. An expert need not have worked in precisely the same field as the subject matter in question to give credible evidence as to the knowledge and level of skill in the relevant art. Professor Mikos's curriculum vitae indicates a degree of familiarity with calcium phosphates sufficient to satisfy us that he has the qualifications and experience necessary to give expert testimony in this case.

F. Other Challenges

Upon review of the other challenges asserted by Petitioners against claims 1, 6, and 8-13 of the '251 patent, we conclude they are redundant to the grounds that form the basis on which we institute *inter partes* review.

III. CONCLUSION

For the foregoing reasons, based on the present record, we conclude that there is a reasonable likelihood that Petitioners would prevail in showing that claims 1, 6, and 8-13 of the '251 patent are unpatentable. The Board has not made a final determination with respect to the patentability of these claims.

IV. ORDER

For the reasons given, it is

ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review is instituted as to claims 1, 6, and 8-13 based on the following grounds of unpatentability:

A. Claims 1 and 8-13 as anticipated by Davies under 35 U.S.C. § 102(b);

B. Claim 8 as obvious over Davies in view of Ichitsuka under 35 U.S.C. § 103;

C. Claims 1 and 8-13 as anticipated by Ruys '93a under 35 U.S.C. § 102(b); and

D. Claim 6 as obvious over Ruys '93a and Bioceramics under 35 U.S.C. § 103;

FURTHER ORDERED that *inter partes* review is commenced on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial;

FURTHER ORDERED that the trial is limited to the grounds of unpatentability listed above, and no other grounds of unpatentability are authorized for *inter partes* review;

FURTHER ORDERED that an initial conference call with the Board is scheduled for 11:00 am Eastern Time on Tuesday April 8, 2014. The parties are directed to the Office Trial Practice Guide, 77 Fed. Reg. 48,756, 48,765-66 (Aug. 14, 2012), for guidance in preparing for the initial conference call. The parties should be prepared to discuss any proposed changes to the Scheduling Order entered herewith and any motions the parties anticipate filing during the trial.

PETITIONERS:

Jeffrey P. Kushan
Peter S. Choi
Sidley Austin LLP
1501 K Street NW
Washington, DC 20005
jkushan@sidley.com

PATENT OWNER:

Keith A. Rutherford
Wong Cabello Lutsch Rutherford
& Brucculeri, L.L.P.
20333 SH 249, Suite 600
Houston, TX 77070
mbipr@counselip.com