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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GREEN CROSS CORPORATION,
Petitioner,

v.

SHIRE HUMAN GENETIC THERAPIES, INC.,
Patent Owner.

Case IPR2016-00258
Patent 9,051,556 B2

Before LORA M. GREEN, RAMA G. ELLURU, and
ROBERT A. POLLOCK, *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge*.

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

I. INTRODUCTION

Green Cross Corporation ("Petitioner") filed a Petition (Paper 2; "Pet.") to institute an *inter partes* review of claims 1–3, 9–13, 16, and 17 of US 9,051,556 B2 (Ex 1001; "the '556 Patent"). Shire Human Genetic Therapies, Inc. ("Patent Owner" or "Shire") filed a Patent Owner Preliminary Response ("Prelim. Resp."). Paper 10.

On May 25, 2016, we instituted an *inter partes* review of claims 1–3, 16, and 17 ("the challenged claims") based on our determination that the information presented in the Petition demonstrated a reasonable likelihood that Petitioner would prevail in challenging these claims as unpatentable under 35 U.S.C. § 103(a). Paper 12 ("Dec. on Inst."). Thereafter, Patent Owner filed a Response (Paper 39 ("PO Resp.")), and Petitioner filed a Reply (Paper 58 ("Reply")).

Petitioner relies on the Declarations of Mark Sands (Ex 1010 ("Sands Declaration"), Ex 1049 ("Sands II Declaration")), Doo-Hong Park (Ex 1035 (Park Declaration")), Chul-Soo Cheong (Ex 1039 ("Cheong Declaration")), Andrew C. Webb (Ex 1041 (Webb Declaration")), and Ruben G. Carbonell (Ex 1051 (Carbonell Declaration")).

Patent Owner relies on the Declarations of Zhaohui Sunny Zhou (Ex 2012 ("Zhou Declaration")), Chester B. Whitley, (Ex 2013 ("Whitley Declaration")), Dave Nichols (Ex 2014 ("Nichols Declaration")), Paulina Andzie-Quainoo (Ex 2015 ("Andizie-Quanoo Declaration")), Romit Thakore (Ex 2016 ("Thakore Declaration")), Randall Morin (Ex 2018 ("Morin Declaration")), and Yiming Yang (Ex 2017 ("Yang Declaration")).

Patent Owner filed Motions for Observations regarding the cross–examination testimony of Drs. Carbonell and Webb (Papers 71 and 72, respectively), to which Petitioner responded (Papers 80 and 82, respectively). The parties also briefed whether certain exhibits should be excluded from the record. *See* Papers 75, 77, 81, 83, 87, 89. We address separately the parties' motions to seal (Papers 38, 73, and 84).

Oral hearing was held on February 10, 2017. A transcript of the hearing is included in the record (Paper 88, "Tr.").

We have jurisdiction under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons that follow, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–3, 16, and 17 of the '556 Patent are unpatentable.

A. The '556 Patent

The '556 Patent, entitled "Purification of Iduronate-2-Sulfatase," and naming Dave Nichols as the sole inventor, issued from Application No. 13/829,706, filed March 14, 2013, and claims the benefit of priority to Provisional Application No. 61/666,733, filed June 29, 2012. Ex 1001, (54), (72), (21), (22), (60).

Iduronate-2-sulfatase ("I2S") is a lysosomal enzyme responsible for removing the terminal 2-O-sulfate moieties from glycosaminoglycans such as heparin sulfate and dermatan sulfate. *Id*. at 1:23–32. Hunter syndrome or Mucopolysaccharidosis type II is a progressively debilitating condition resulting from a deficiency of I2S activity and the resulting cellular accumulation of sulfated glycosaminoglycans. *Id.* at 1:23–24, 33–51. "Enzyme replacement therapy (ERT) is an approved therapy for treating

Hunter syndrome (MPS II), which involves administering exogenous replacement I2S enzyme to patients with Hunter syndrome." *Id.* at 52–55.

The '556 Patent discloses methods for isolating recombinant human I2S, which may have an amino acid sequence identical to SEQ ID NO: 1. *Id.* at 4:56–58, Abstract. According to the Specification, SEQ ID NO:1 corresponds to "a typical wild-type or naturally-occurring human I2S protein." *See id*. at 10:27–40, Table 1. A closely related polypeptide, SEQ ID NO:2, corresponds to the intracellular precursor of the 525 amino acid SEQ ID NO:1 prior to removal of the 25 amino acid N-terminal signal peptide. *Id*.; *see id* at 31:7–9 ("After synthesis of the full length I2S enzyme, the 25 amino acid signal peptide is removed and a soluble mature I2S enzyme is secreted from the cell."); *see also* columns 38–46 (sequence listing showing amino acid sequence of SEQ ID NO:1 and SEQ ID NO:2).

The disclosed methods employ "as few as four chromatography columns," and may involve "purifying recombinant I2S protein from an impure preparation using a process based on one or more of anion-exchange chromatography, cation-exchange chromatography, mixed-mode chromatography, and hydrophobic interaction chromatography" (*id.* at Abstract, 2:16–21). In some embodiments, the resultant I2S composition "contains less than 100 ng/mg Host Cell Protein (HCP)." *Id* at 2:26–34; *see also id*. at 31:66–32:2 ("Typically, using a process described herein, the HCP concentration of drug substance (DS) was <100 ppm, meeting the <100 ppm specification required in many markets including the US."). The Specification further provides that "recombinant I2S enzyme purified according to the present invention retains high percentage of Ca-formylglycine (FGly) . . . which is important for the activity of I2S enzyme,"

in particular, the purified enzyme has " at least about 70% . . . conversion of the cysteine residue corresponding to Cys59 of human I2S (SEQ ID NO: 1) to Ca-formylglycine." *Id*. at 2:5–8, 5:16–21; *see* Ex. 2013 ¶ 24.

With respect to an exemplary scheme for the production of recombinant human I2S in animal free media (*see id*. at 30:17– 32:17 (Example 1)), the Specification discloses that:

> A cell line stably expressing an iduronate-2-sulfatase enzyme (I2S) and formylglycine generating enzyme (FGE) was developed. Generation and characterization of exemplary cell lines are described in the U.S. Provisional Application entitled "Cells for Producing Recombinant Iduronate-2-Sulfatase" filed on even date herewith, the entire contents of which is hereby incorporated by reference. Briefly, a human cell line was engineered to co-express human I2S protein with the amino acid sequence shown in SEQ ID NO:2[1] and human formylglycine generating enzyme (FGE) with the amino acid sequence shown in SEQ ID NO:6.

Id. at 30:26–36 (footnote added). Examples 2–4 of the Specification disclose the purification and subsequent characterization of recombinant human I2S from the 2D[2] cell line. *See id*. at 32:18–40:40.

B. Challenged Claims

Claim 1, the sole independent claim at issue, recites:

> 1. A composition comprising purified recombinant iduronate-2-sulfatase (I2S) having the amino acid sequence of SEQ ID NO:1, wherein the purified recombinant I2S comprises at least 70% conversion of the cysteine residue corresponding to Cys59 of

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[1] As noted above, SEQ ID NO:2 corresponds to the precursor of SEQ ID NO:1 prior to signal peptide processing.

[2] We note that Example 4 relates the characterization of "recombinant I2S protein [] generated using the 2D *and* 4D human cell lines, in two separate serum-free cell culture reactions." *See id*. at 36:22–24 (emphasis added).

> SEQ ID NO:1 to Cα-formylglycine (FGly), wherein the purified recombinant I2S contains less than 150 ng/mg Host Cell Protein (HCP).

Claims 2 and 3 further require 75% and 85% conversion of Cys59 to FGly ("FGly59"), respectively; claims 16 and 17 further limit the HCP content of the composition to 100 ng/mg and 80 ng/mg, respectively.

C. Reviewed Ground of Unpatentability

The Board instituted trial to determine whether claims 1–3, 16, and 17 of the '556 Patent were shown to be obvious over the combination of Jin[3] and any one of Wolter,[4] CEBER,[5] ICH,[6] Champion,[7] and Wang,[8] and further

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[3] Jin et al. US 2014/0242059 Al, published Aug. 28, 2014. Ex. 1002 ("Jin").

[4] Wolter and Richter, *Assays for Controlling Host-Cell Impurities in Biopharmaceuticals*, BIOPROCESS INT'L 40–46 (Feb. 2005). Ex. 1011 ("Wolter").

[5] U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use*, Docket No. 94D-0259 (February 28, 1997). Ex. 1012 ("CEBER").

[6] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products Q6B* (March 10, 1999). Ex. 1013 ("ICH")

[7] Champion, et al., *Defining Your Product Profile and Maintaining Control Over It, Part 2*, BIOPROCESS INT'L 52–57 (Sept. 2005). Ex. 1014 ("Champion").

[8] Wang, et al., *Host Cell Proteins in Biologics Development: Identification, Quantitation and Risk Assessment*, 103(3) BIOTECHNOLOGY AND BIOENGINEERING 446–458 (Apr. 2009). Ex. 1-15 ("Wang").

in view of the general knowledge in the art as reflected in Jin and any one of Wolter, Champion, Wang, and Mihara.[9] Dec. on Inst. 22.

II. ANALYSIS

A. Person of Ordinary Skill in the Art.

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). With respect to the identity a person of ordinary skill in the art, the parties' propose similar, albeit non-identical, definitions that are consistent with the high level of ordinary skill as demonstrated by the prior art of record. *See* Pet. 23–24; PO Resp. 35; *see also* Prelim. Resp. 11–12 (declining to contest Petitioner's definition for the purposes of the Preliminary Response). Discerning no conflict between the parties' proposed definitions that impacts our ultimate determination, we rely on the level of ordinary skill demonstrated by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) (finding that the Board of Patent Appeals and Interferences did not err in concluding that the level of ordinary skill in the art was best determined by the references of record).

[9] Mihara et al., WO 2012/101671 Al, published August 2, 2012. Ex. 1016 ("Mihara").

B. Claim Construction

In an inter partes review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard). Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); *see also Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history."). Only claim terms which are in controversy need to be construed, and then only to the extent necessary to resolve the controversy. *See, e.g. Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

For purposes of this Decision, we agree with the parties that no term requires express construction and all claim terms should be accorded their plain and ordinary meaning. *See* Pet. 24; Prelim. Resp. 11–12; PO Resp. 35.

C. Brief Overview of Petitioner's Argument

Petitioner argues that Jin discloses a purification method used to obtain a recombinant human I2S composition having "the same amino acid sequence and the same or substantially the same percentage conversion of cysteine to Cα-formylglycine at the Cys59 position as is claimed in the '556 Patent. Pet. 2; *see generally, id*. at 25–45. Although Petitioner admits that

Jin does not quantify the exact amount of host cell protein in the composition (Pet. 40), Petitioner argues that one of ordinary skill in the art would understand that Jin discloses highly pure I2S that meets or exceeds the purity limitations of the '556 Patent (*id*. at 40–45; Reply 28–30). In support, Petitioner presents experimental and testimonial evidence, which it contends shows that recombinant I2S purified according to Jin satisfies all limitations of the challenged claims, including the purity limitation. Reply 34 (citing Ex 1035 (Park Declaration); Ex 1039 (Cheong Declaration); Exs. 1036, 1037, 1038); *see* Ex 1049 ¶¶ 19 (Sands II Declaration); Ex 1051 ¶¶ 52 (Carbonell Declaration).

Petitioner further relies on Wolter, CEBER, ICH, Champion, Wang, and Mihara as evidence that, in light of Jin, one of ordinary skill in the art at the time of the invention would had reason to minimize the HCP content of an I2S composition within the scope of the challenged claims, and would have had a reasonable expectation of success of doing so. *See generally* Pet. 13.

We address below the threshold question of whether Jin qualifies as prior art.

D. Whether Jin Qualifies as Prior Art under 35 U.S.C. § 102(e)

Jin issued from the U.S. national stage entry of PCT application No. KR2012/004734, filed on June 15, 2012, which, in turn, claims priority to its U.S. Provisional Application No. 61/500,994, filed on June 24, 2011. Ex 1002, (21), (86).

Petitioner asserts that Jin qualifies as prior art under § 102(e).[10] Pet. 4, 25. With respect to the effective date of this reference, Patent Owner argues that Petitioner waived its right establish the date of Jin's Provisional Application as the 102(e) date. PO Resp. 65, n7; *see* Prelim. Resp. 9, 47–48. Petitioner appears to concede that it does not, in fact, rely on this earlier date. *See* Reply 4 (stating that "[i]n order to antedate Jin, Shire bears the burden to produce evidence supporting, at a minimum, a date of invention before Jin's filing date of June 15, 2012"). In our Decision on Institution, we determined that, "[f]or the purposes of institution, we have no need to determine priority with respect to Jin's provisional application." Dec. on Inst. 8.

Subsequent to our institution decision, Patent Owner asserts that Jin fails to qualify as prior art because Dave Nichols, the inventor of the '556 Patent, reduced to practice the invention described by the challenged claims "as of at least April 2011" —and, thus, prior to the dates of both the Jin PCT application, and its U.S. Provisional Application. PO Resp. 64–91. Because, as set forth below, we find that Patent Owner has demonstrated adequately an actual reduction to practice "as of at least April 2011" (and thus prior to the earliest effective date that Jin might be accorded), we again have no need to determine whether Petitioner is entitled to rely on the date of the Jin Provisional application.

[10] The relevant sections of the Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29 took effect on March 16, 2013. Because the application from which the '556 Patent issued was filed before that date, our citations to Title 35 are to its pre-AIA version.

E. Evidence of Reduction to Practice Prior to the Effective Date of Jin

Petitioner bears the burden of persuasion that the challenged claims are unpatentable, which includes the burden of establishing that any reference upon which it relies constitutes prior art under 35 U.S.C. § 102. 35 U.S.C. § 316(e); *see Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996) (holding that the challenger "bore the burden of persuasion . . . on all issues relating to the status of [the asserted reference] as prior art"). However, because Petitioner offered Jin into evidence, which qualifies on its face as prior art under §102(e), Patent Owner bears the burden of producing evidence supporting a date of invention prior to the critical date of Jin. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378–80 (Fed. Cir. 2015). As discussed below, Patent Owner elected to antedate, and thereby remove, Jin as prior art by showing that the inventor actually reduced the claimed invention to practice prior to Jin's 102(e) priority date(s). As a result, the burden of production returned to Petitioner to demonstrate that the invention set forth in the challenged claims was not actually reduced to practice as of the date alleged. *Id*. at 1380.

In order to establish an inventor's actual reduction to practice, Patent Owner must show: (1) construction of an embodiment meeting all limitations of the challenged claims; (2) that the invention would work for its intended purpose, and (3) sufficient evidence to corroborate the inventor's testimony. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1169 (Fed. Cir. 2006). "Sufficiency of corroboration is determined by using a 'rule of reason' analysis, under which all pertinent evidence is examined when determining the credibility of an inventor's testimony." *Id*. at 1170 (citation omitted). "[I]t is not[, however,] necessary to produce an actual

over-the-shoulder observer. Rather, sufficient circumstantial evidence of an independent nature can satisfy the corroboration requirement. Furthermore, an actual reduction to practice does not require corroboration for every factual issue contested by the parties." *Cooper v. Goldfarb*, 154 F.3d 1321, 1330 (Fed. Cir. 1998) (internal citations omitted). "[E]ach corroboration case must be decided on its own facts with a view to deciding whether the evidence as a whole is persuasive." *Id*. at 1331 (citation omitted),

Patent Owner presents documentary evidence (Exs. 2101, 2102, 2104–2110, 2113, 2115, 2120) and supporting declarations (Exs. 2014–2017) intended to show that (1) by 2004, and prior to its acquisition by Patent Owner, the named inventor Dave Nichols ("Mr. Nichols") worked for a company known as TKT that created a stable, recombinant human cell line containing an expression cassette (pXI2S6) for the secretion of mature human I2S having the amino acid sequence of SEQ ID NO:1; (2) in October 2010, Mr. Nichols and his team used the 2D cell line to purify a batch of I2S ("Run 80"); (3) in November 2010, they used peptide mapping and ELISA testing, respectively, to show that the purified I2S of Run 80 had 87.4% FGly59 conversion and an HCP concentration of ≤25 ng/mg; and (4) in March 2011 Mr. Nichols and his team again used the 2D cell line to purify a batch of I2S ("Run 92"), which in April 2011 they found to have 94.68% FGly59 conversion and 6 ng/mg HCP. *See* PO Resp. 70–85.[11] Patent Owner further relies on Exhibits 2100, 2103, 2018 in arguing that

[11] Although not addressed here in detail, Patent Owner provides evidence of additional runs within the scope of the invention to show that the reduction to practice of the claimed invention was "consistent and reliable." *See id*. at 80–81 (citations omitted).

Mr. Nichols timely recognized the significance of the invention, as well as providing additional corroborating evidence. *Id*. at 85–91.

In light of the above, and as discussed below in response to Petitioner's arguments, we conclude that Patent Owner has satisfied its burden of producing evidence sufficient to support a date of invention prior to the critical date of Jin. Accordingly, the burden shifts to Petitioner to establish by the preponderance of the evidence that Patent Owner has *not* shown possession of each element of the challenged claims as of the critical date. In *Dynamic Drinkware* our reviewing court instructs:

> In an inter partes review, the burden of persuasion is on the petitioner to prove "unpatentability by a preponderance of the evidence," 35 U.S.C. § 316(e), and that burden never shifts to the patentee. Failure to prove the matter as required by the applicable standard means that the party with the burden of persuasion loses on that point—thus, if the fact trier of the issue is left uncertain, the party with the burden loses.

800 F3d 1375 at 1378–79 (internal citations omitted). We, therefore, turn to Petitioner's evidence and arguments that the invention set forth in the challenged claims was not actually reduced to practice as of the critical date, as Patent Owner contends. *See* Reply 6–17.

Petitioner argues that Patent Owner's evidence is insufficient to establish reduction to practice because the purported embodiments (e.g., Run 80 and Run 92) fail to meet all limitations of the challenged claims, most particularly, that the purified recombinant I2S has "the amino acid sequence of SEQ ID NO:1," as required by the challenged claims. Reply 6–16. In sum, Petitioner argues that

> Shire provides no evidence whatsoever that it had reduced to practice the required SEQ ID NO:1 at any time, let alone prior to the filing and priority dates of Jin . . . . Shire's various declarations are devoid of any test data showing the amino acid

> sequence of the recombinant I2S ("r-I2S") enzyme Shire alleges to have possessed prior to the filing of Jin.

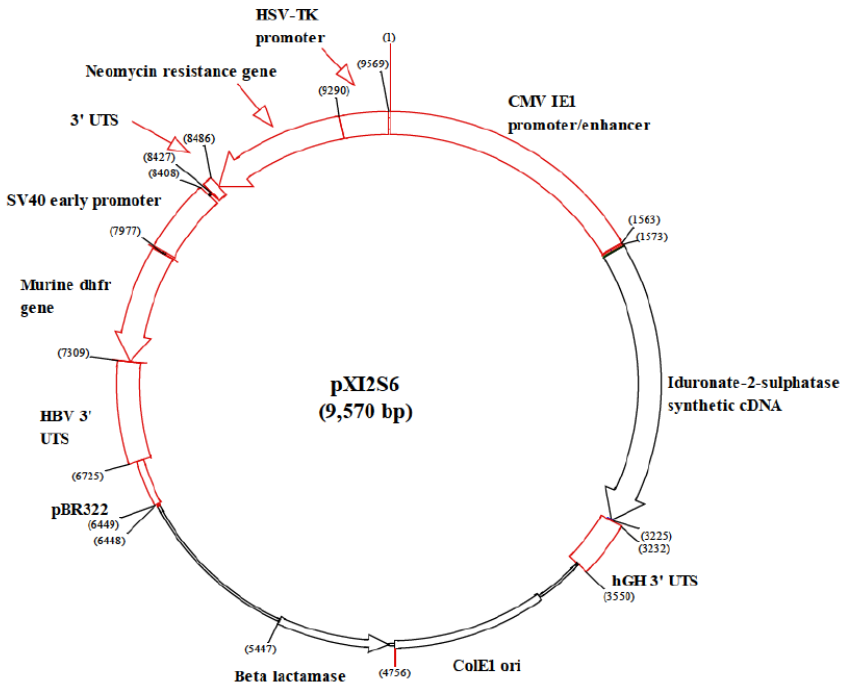
Id. at 1–2 (emphasis omitted).[12] For the reasons set forth below, we do not find Petitioner's arguments persuasive.

As noted above, Patent Owner contends that I2S batches of Run 80 and Run 92 were prepared from recombinant human cell line 2D, created at TKT before it was acquired by Patent Owner. *See* PO Resp. 70–71 (citing Exs. 2014, 2017, 2115, 2117). Patent Owner presents Exhibit 2115, entitled "TKT RESEARCH & DEVELOPMENT REPORT: Development of I2S Manufacturing Cell Line, 2D," ("the TKT report") as evidencing the development of the 2D cell line. *Id*. at 70–73 & n.9.

The TKT report discloses the construction of expression plasmid pXI2S6, illustrated in Figure 2.3.2-2 below.

[12] Although Petitioner further asserts that Patent Owner fails to establish that it was in possession of I2S having the claimed levels of FGly59 conversion and HCP content, these contentions are expressly premised on Petitioner's primary argument that Patent Owner did not have possession of I2S of SEQ ID NO:1 prior to the critical date of Jin (Reply, 17) and, accordingly, we need not consider them separately.

Figure 2.3.2-2. The Expression Construct pXI2S6



Ex 2115, 4. Figure 2.3.2-2 shows expression construct pXI2S6. The TKT report discloses that plasmid pXI2S6 was "constructed for the expression of I2S" in a human cell line and contains key features including "[a] coding sequence for I2S (550 amino acids long including 25 amino acids of signal peptide)." *Id*. at 1. The report also states that nucleotide sequencing of the entire pXI2S6 plasmid confirmed "all of the sequences designed to produce I2S in [human] cells were correctly assembled." *Id*. at 7.

Figure 2.3.2–7 of the TKT report presents the DNA sequence of pXI2S6. *See id*. at 8–14. The unredacted portion of this sequence also indicates the predicted amino acid sequence of the I2S precursor polypeptide, SEQ ID NO:2, as set forth in the '556 Patent, aligned with the corresponding DNA sequence. We note that the terminal Proline ("Pro" or "P") of the I2S amino acid sequence shown in Figure 2.3.2-7 appears to be covered by a redaction. The unredacted portion of DNA sequence, however,

indicates that terminal amino acid is proline (encoded by the triplet CCC and followed by the termination codon TAG). Moreover, Petitioner does not dispute that pXI2S6 had the nucleotide sequence encoding the predicted amino acid sequence of I2S. See Tr. 16:24–17:17. Accordingly, we find that the DNA sequence of Figure 2.3.3-7 encodes SEQ ID NO:2, which may be processed to SEQ ID NO:1 with the removal of the N–terminal 25 amino acid signal peptide as Patent Owner contends. *See* PO Resp. 72–73, 87; Ex 2014 ¶¶ 11–13.

Consistent with the above, Yiming Yang, a co-worker of Mr. Nichols during the relevant period, testified that

> An engineered human cell line referred to as the "2D" cell line was used to produce recombinant I2S to be purified by the process we were developing. The 2D cell line had been generated as of 2004. It contains a plasmid construct called pXI2S6, which encodes a wild-type human I2S protein. I understand the amino acid sequence listed as SEQ ID NO: 1 in the '556 Patent is identical to the wild-type mature human I2S protein (without the signal peptide).

Ex 2017 ¶ 11.

Neither Petitioner nor Petitioner's declarants appear to contest that pXI2S6 encodes SEQ ID NO:2, which may be processed to SEQ ID NO:1 by the cellular machinery. To the contrary, Petitioner's declarant, Dr. Webb, testified that pXI2S6 "might end up producing the predicted amino acid sequence if processed correctly by the cell that it was transfected into." Ex 2203, 125:11–126:14. Rather, Petitioner argues that

> without amino acid sequencing . . . . [t]here would be no way to rule out rearrangements during integration or errors in transcription, translation, or post-translational modification. . . . In other words, the mere fact that a protein obtained by Shire had a high FGly conversion ratio, or high enzymatic activity, cannot provide corroborative evidence that Shire actually

> possessed the specific amino acid SEQ ID NO:1 required by the challenged claims.

Reply 16 (emphasis omitted). Petitioner does not, however, provide any evidence suggesting that that "rearrangements during integration" occurred, or were likely to have occurred, in connection with the 2D cell line.

Petitioner also does not convince us that "errors in transcription, translation, or post-translational modification" were likely to have prevented the isolation of I2S having the claimed characteristics in Run 80 and Run 92. Drummond,[13] for example, estimates that amino acid misincorporation during translation occurs "once in every 1,000 to 10,000 codons translated," such that about "15% of average-length protein molecules will contain at least one misincorporated amino acid." Ex. 1044, 715. Although Dr. Webb implies that the rate of misincorporation may be higher for the expression of recombinant proteins (*see* Ex. 2203 95:7–98:10), he presents no evidence to suggest that all, or even a majority, of I2S molecules in batch Runs 80 and 92 did not have the amino acid sequence of SEQ ID NO:1, nor explain how such, presumably random, misincorporation should be analyzed (*see e.g.*, Ex. 1041 ¶¶ 24–26).

Thus, as we understand the argument, Petitioner would require Patent Owner to conduct amino acid sequencing, or similar analysis, on the I2S batches Run 80 and Run 92. According to Dr. Webb,

> The exact amino acid sequence of a produced recombinant protein may be determined by a variety of well-established techniques, all of which were in common use during the 2010-2011 time period. These teachings include N-terminal amino acid analysis, C-terminal amino acid analysis, and various

[13] Drummond and Wilke, *The evolutionary consequences of erroneous protein synthesis*," 10(10) NAT. REV. GENET. 715–24 (2009). Ex. 1044.

> forms of mass spectrometry (MS). . . . All of these sequencing techniques are directly applicable to the protein in question, or derived fragments thereof, to yield a primary amino acid sequence. It is imperative, however, to perform the analysis such that one knows the order in which the constituent fragments should be connected to provide the complete amino acid sequence of the protein.

Ex 1041 ¶ 21. Moreover, Dr. Webb opines "the only way a scientist can unambiguously confirm that a particular protein has been made by a recombinant cell is by peptide sequencing of the expressed protein following its isolation". *Id*. at ¶ 22.

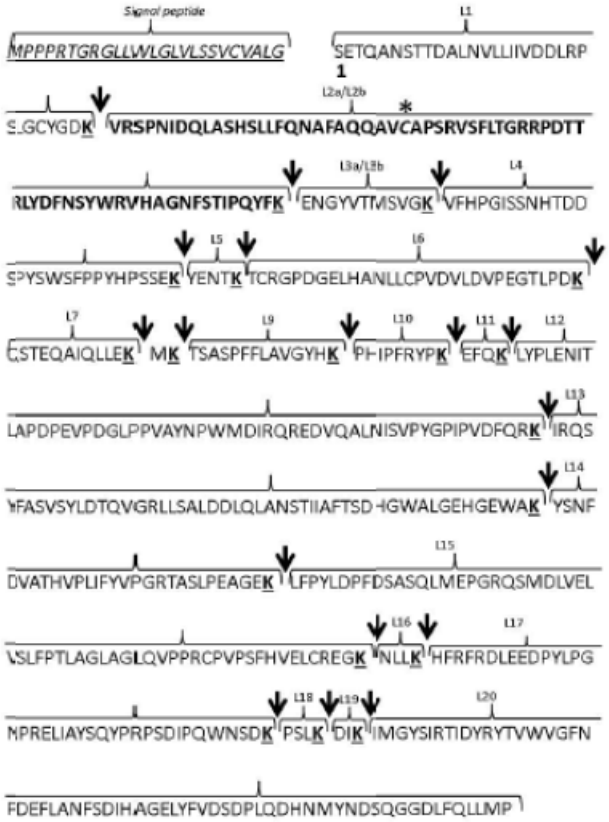
Although the above techniques may be applicable in some contexts, we conclude that such rigorous analysis is not required under our evidentiary standard. To the contrary, Dr. Webb admits that "*the likely amino acid sequence* of a recombinant protein *can be predicted* (using the genetic code) from the DNA sequence of a plasmid incorporating the gene for the protein in question." *Id*. at 22 (emphasis added); *see also* Ex 2203 at 42:5–12, 45:3–18 (indicating that prior to the critical date it "was well known in the art" that the amino acid sequence of a protein is determined by the DNA sequence). We similarly note that when asked: "So if you made I2S using the 2D cell line, once its secreted out [of the 2D cell], you would expect to have the 525 amino acids that correspond to that coding region, right?", Dr. Webb responded: "You would expect to see a protein, a polypeptide that is reduced by its [25 amino acid] signal sequence. *Id*. at 174:11–24.

We further note that Dr. Webb's own patent, US 5,998,578 (Ex 2204), claims specific IL-1 polypeptides based on their predicted amino acid sequences. Ex. 2204 8:35–37, claim 2; *see* Ex 2203 45:3–48:25, 49:5–8 (stating with reference to Ex. 2204: "I mean, we had information which was a genetic sequence from which one could deduce the amino acid

sequence."); *id*. at 179:12–22. Accordingly, we find that the state of the art did not require the complete or partial sequencing techniques indicated by Dr. Webb to reasonably ascertain that a recombinant protein would likely have amino acid sequence predicted by the DNA sequence of its expression construct.

Moreover, Patent Owner's evidence that it was in possession of SEQ ID NO:1 is not limited to a prediction of amino acid sequence based on DNA sequence of the pXI2S6 expression construct. Patent Owner also presents peptide mapping data that provides further information concerning the amino acid sequence of I2S batches Run 80 and Run 92. *See* PO Resp. 73–83; Ex 2203, 81:22–83:5. Although Mr. Nichols indicated that the purpose of this step was to determine the amount FGly59 conversion in each batch (Ex 1029, 151:19–153:3) the use of these results are not so limited. *See e.g.*, Ex. 2203 81:22–83:5 (agreeing that a peptide map provides some idea as to the identity of a protein beyond that ascertainable by the nucleic acid sequence). In particular, Romit Thakore, who trained and supervised those responsible for the peptide mapping, testified that "[w]e used this map to confirm protein identity by verifying the presence of specific peptides at given retention times and intensities in comparison to a reference standard peptide map." Ex 2016 ¶¶ 4, 5, 9; *see also* Ex 1042, 258 (stating, "at the IND stage, a peptide map should be used as an identity test capable of yielding a 'fingerprint' of the protein under consideration").

Mr. Thakore explained Shire's peptide mapping results with reference to Figure 1, reproduced below.



See Ex 2016, ¶ 7. Figure 1 illustrates the full-length I2S protein (SEQ ID. NO:2) encoded by pXI2S6, wherein the first 25 amino acids constitute a signal peptide, which is cleaved after secretion from the 2D host cells to form SEQ ID NO:1. *See Id*.; Ex 2014 ¶¶ 11, 12; Ex. 2115 1, 8–14; Ex. 1001, 10:27–40, Table 131:7–9, columns 38–46 (sequence listing showing amino acid sequence of SEQ ID NO:1 and SEQ ID NO:2). The downward-facing arrows mark the position of cleavage sites for the protease used in the peptide mapping protocol. Ex 2016 ¶7; Ex 2014 ¶ 11.

Mr. Thakore testified that in accord with a standard operating procedure, samples of purified I2S were subject to enzymatic digestion and deglycosylation. Ex, 2016 ¶¶ 6–8. The deglycosylated peptide fragments

were separated and quantified using HPLC chromatography using a reference standard. Ex 2016 ¶ 1, 8–14. Mr. Thakore presents Figure 2, reproduced below, as exemplary of Shire's peptide mapping results. *Id*. ¶ 9.

Peptide	Amino Acids	Approx. RT	Range of %Area
L1	1-32 (N-Terminus)	102	5.1 – 8.2%
L2a	33-99 (Formylglycine)	81	---
L2b	33-99 (Non-Modified Cysteine)	82	---
L3a	100-110	46	---
L3b	100-110 (Pyro Glu)	48	---
L4	111-139	64	---
L5	140-144	6.8	---
L6	145-174	74	---
L7	175-186	57	---
L9	189-202	66	---
L10	203-211	53	2.5 - 3.5%
L11	212-215	25	---
L12	216-270	86	11.3 – 13.1%
L13	271-322	109	7.2 – 10.2%
L14	323-351	76	5.8 – 7.0%
L15	352-411	107	---
L16	412-415	40	---
L17	416-454	71	10.2 – 12.0%
L18	455-458	28	---
L20	462-525 (C-Terminus)	101	4.8 – 9.0%

Figure 2.

Figure 2 is a table summarizing the peptide mapping results for run 92. *See id*. ¶¶ 5–7. We note that the Figure 2 identifies all but the two shortest predicted peptides, L8 (amino acids 187–188) and L19 (amino acids 459–461).

Petitioner does not argue, nor do we discern in the evidence of record any suggestion that the peptide mapping results for runs 80 and 92 differed from that of the reference standard. Nor does Petitioner allege that the absence of peptides L8 and L19 in the peptide map summaries indicates that the I2S produced from the D2 cell line was defective (rather than indicative of some technical limitation such as the resolution limits of the HPLC step).

Nor does Petitioner argue that any of Patent Owner's evidence is inconsistent with its possession of SEQ ID NO:1. *See* Ex 2203, 113:11–114:16; 174:24–179:11.

In addition to its argument that Patent Owner had not shown sufficiently that the I2S purified from the 2D cell line had the amino acid sequence of SEQ ID NO:1, Petitioner further argues that there is a "disconnect between the I2S produced in cell line '2D' (as described in the '556 Patent) and the I2S-containing plasmid described in Exhibit 2115, which cannot be related to cell line '2D' (because it does not describe both I2S and FGE constructs)." Reply 12; *see generally*, *id*. at 7–14.

We do not find Petitioner's arguments persuasive for several reasons. First, because the claims are not limited to the use of a cell line containing a FGE construct, Patent Owner had no need to document the use of an FGE construct (if any) in demonstrating that it possessed the claimed subject matter prior to the critical date of Jin. We find that Patent Owner's peptide mapping data and associated testimonial evidence, however, reasonably evidences such possession and Petitioner does not, by a preponderance of the evidence, convince us otherwise. *See* 35 U.S.C. § 316(e) (burden of proving invalidity during *inter partes* review).

Second, Petitioner presents no credible evidence that the 2D cell line used to generate I2S batches Run 80 and Run 92 did not contain the pXI2S6 expression construct. And despite Petitioner's numerous hypotheticals describing ways in which the predicted I2S polypeptide sequence of pXI2S6 *might* not result in a purified I2S composition having SEQ ID NO:1, as indicated above, we find that Petitioner has not demonstrated that such failures are more likely than not. *See e.g.*, Ex 1041 ¶ 22 ("the likely amino

acid sequence of a recombinant protein can be predicted (using the genetic code) from the DNA sequence of a plasmid incorporating the gene for the protein in question"); Ex 2203 at 42:5–12, 45:3–48:20; Ex 2204, 8:35–37. To the contrary, we find that Patent Owner's peptide mapping data experiments support a finding that that the I2S of Run 80 and Run 92 had the amino acid sequence of SEQ ID NO:1.

Third, as counsel for Petitioner established at Mr. Nichols deposition, the application that issued as US Patent No. 9,150,841 ("the '841 Patent") is incorporated by reference into the '556 Patent. Ex 1029 71:6–76:13; *see* Exs. 1001, 30:26–36; 1024, 1025. The incorporated application lists Shire as the assignee (Ex 1024, 7), and both the '841 Patent and the '556 Patent list Patent Owner Shire as "Applicant." Ex 1001 (71); Ex 1025 (71). As described in the Abstract of the '841 Patent, the incorporated material is directed to "methods and compositions for production of recombinant I2S protein with improved potency and activity using cells [that] co-express I2S and FGE protein. In some embodiments, cells according to the present invention are engineered to simultaneously over-express recombinant I2S and FGE proteins." Ex 1025, Abstract. Of particular relevance here, Example 2 of the '841 Patent and the underlying application, "Evaluation of Stable Cell Lines Co-Expressing I2S and FGE," disclose the results of "experiments [] carried out to characterize two cells lines 2D and 4D co-expressing I2S and FGE." *Id*. 36:55–38:52; Ex 1024 ¶¶ 133–141.

That the '556 Patent on its face discloses the characterization of highly-purified, functional I2S "generated using the 2D and 4D human cell lines" (*see e.g.*, Ex 1001, 36:22–23) and incorporates by reference a co–owned application describing cell lines 2D and 4D "co-expressing I2S and

FGE," is strong circumstantial evidence that the 2D cell line Shire used to generate I2S batches Run 80 and Run 92 was the same 2D cell line discussed in the '556 and '841 Patents, and, thus, co-expressed I2S and FGE. Petitioner presents no evidence consistent with Shire's use of a different I2S cell line bearing the name "2D" which did not express FGE.

Considering the record as a whole, we find that Patent Owner has provided sufficient evidence to show that it reduced to practice an embodiment encompassing all elements of the challenged claims prior to the critical date of Jin, and Petitioner does not convince us otherwise. Accordingly, we find that Jin is not § 102(e) prior art, as Petitioner contends. Because Petitioner's ground for challenging the '556 Patent as obvious depends on Jin, we conclude that Petitioner has not proven by a preponderance of the evidence that the challenged claims are unpatentable.

F. Motions

i. Patent Owners Motion to Exclude Evidence (Paper 74)

Patent Owner moves to exclude Exhibits 1035, 1036, 1037, 1038, 1039, 1400, 1049, and 1051, each of which relates to Petitioner's obviousness case. As discussed above, Petitioner has failed to satisfy the threshold issue of demonstrating that Jin, the primary reference relied upon in its obviousness ground, is prior art to the '556 Patent. Accordingly, we do not address the substance of Petitioner's obviousness arguments and, thus, do not rely on the challenged exhibits in our analysis. Accordingly, we deny Patent Owner's Motion as moot.

ii. Petitioner's Motion to Exclude Evidence (Paper 75)

Petitioner moves to exclude Exhibit 2207 ("Webb Exhibit 4") which is purportedly an unredacted version of the TKT report (Exhibit 2115). *See*

Paper 81, 1. As we have no need to rely on the challenged exhibit or associated testimony in our analysis, Petitioner's motion is denied as moot.

iii. Petitioner's Request for Expungement of Papers 71 and 72

In its Response to Patent Owner's Motions for Observations Regarding Cross-Examination of Drs. Carbonell and Webb, Petitioner requests that we expunge, or accord no weight to, Patent Owner's Motions for Observations because Patent Owner "made no effort to faithfully quote any testimony, and its 'observations,' which are often crammed with multiple citations, improperly narrate and mischaracterize the testimony cited, are rife with legal argument, and include references to unauthorized exhibits." Paper 80, 1–3 (footnotes omitted); Paper 82, 1–3 (same). Although we are not convinced that Patent Owner "color[s] so far outside the lines" as Petitioner contends, we do not rely in our analysis on Patent Owner's Motions for Observations. Accordingly, Petitioner's request is denied as moot.

III. CONCLUSION

For the reasons given, we conclude that Petitioner has not shown by a preponderance of the evidence that claims 1–3, 16, and 17 of the '556 Patent are unpatentable under 35 U.S.C. § 103.

IV. ORDER

In consideration of the foregoing, it is

ORDERED that Petitioner has not shown by a preponderance of the evidence that claims 1–3, 16, and 17 of the '556 Patent are unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Exclude Evidence is denied as moot;

FURTHER ORDERED that Petitioner's Motion to Exclude Evidence is denied as moot;

FURTHER ORDERED that Petitioner's requests that the Board expunge, or accord no weight to, Patent Owner's Motions for Observations of Drs. Webb and Carbonell are denied as moot; and

FURTHER ORDERD that, because this is a final written decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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