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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CORNELIUS DIAMOND

Appeal 2019-005351
Application 14/391,883
Technology Center 1600

Before DONALD A. ADAMS, RACHEL H. TOWNSEND, and MICHAEL A. VALEK, *Administrative Patent Judges*.

VALEK, *Administrative Patent Judge.*

DECISION ON APPEAL

Appellant[1] submits this appeal under 35 U.S.C. § 134(a) involving claims to a rapid assay for the prediction of bleeding based on the level of human cellular fibronectin (c-Fn) that have been rejected for lack of written description under 35 U.S.C. § 112(a) and for obviousness under 35 U.S.C. § 103. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42(a). Appellant identifies Prediction Biosciences S.A.S. as the real party in interest. Appeal Br. 1.

STATEMENT OF THE CASE

"The present invention . . . relates to a rapid test that predicts bleeding events" by measuring c-Fn levels. Spec. 1. According to the Specification,

> Despite the previous data of the implication of c-Fn in determining disease management, until the instant invention, c-Fn's role in healthcare has been limited to research only as no assay has been created for measuring its level in human samples in a rapid, efficient, and accurate manner. Previous assay that have been created, such as BioHit Oyj's ELISA kit, are (1) only linear in a response over a small range (1-3 mg/mL0 compared to the full range of c-Fn variation in human blood plasma samples (0-20 mg/mL), (2) take specialized training to perform, and (3) require several hours to obtain a result.

Id. at 3–4. The Specification states that the "instant invention" provides "antibodies and methods . . . for producing a quantitative level of c-Fn concentration in blood plasma over the entire range of interest" and "that can be performed by a clinician in less than 20 minutes with no specialized training." *Id.* at 4. According to the Specification, "[t]hese antibodies immunoreact with a synthetic polypeptide of this invention and denatured human cellular fibronectin, and preferably also immunoreact with native, non-denatured human cellular fibronectin, but do not substantially immunoreact with human plasma fibronectin in either the denatured or native states." *Id.*

Claims 24–26, 42, 46, 47, 49, and 51–54 are on appeal and can be found in the Claims Appendix of the Appeal Brief. Claim 24 is illustrative and reads as follows:

> 24. A rapid assay for the prediction of bleeding in a human test subject that determines in 60 minutes or less the level of human cellular fibronectin (c-Fn) in a test sample taken from the human test subject;

wherein the test sample is selected from the group consisting of whole blood serum, and a plasma sample,

wherein said rapid assay comprises

(a) obtaining a test sample from the human test subject,

(b) mixing the test sample with an antibody and a reference epitope,

wherein the antibody is an isolated human monoclonal antibody, or an antigen-binding portion thereof, or both an antibody and its antigen-binding portion, wherein the antibody binds to c-Fn with an affinity at least 100 fold greater than it binds to plasma fibronectin and wherein the antibody binds to amino acid sequence 1631-1721 of the c-Fn molecule ("the EDA region"),

wherein the reference epitope is a synthetic polypeptide consisting essentially of an amino acid sequence, from left to right and in the direction from amino-terminus to carboxyterminus, selected from the group consisting of

(v) DGEEDTAELQGLRPGSEC (SEQ ID NO: 1),

(vi) ESPQGQVSRYRVTYSSPEDC (SEQ ID NO: 2),

(vii) HDDMESQPLIGTQSC (SEQ ID NO: 3), and

(viii) NIDRPKGLAFTDVDVDSIKIAWESPQGQVSRY RVTYSSPEDGIHELFPAPDGEEDTAELQGLRPGSEYTVSV VALHDDMESQPLIGTQSTA (SEG ID NO: 4)

wherein either (1) said antibody or an antigen-binding portion thereof are bound to magnetic particles and said reference epitope is labeled or (2) said reference epitope is bound to magnetic particles and said antibody or an antigen-binding portion thereof are labeled,

wherein said assay does not require the antibody to be fixed to a solid matrix to immunoreact with the EDA region of the c-Fn molecules or the reference epitope in said test sample, and

wherein said assay is a competitive assay, provided that said antibody binds the EDA region and the reference epitope, characterized in that the EDA region of the c-Fn antigen of the test sample competes with the reference epitope for the binding sites on said antibody,

(c) followed by forming a complex between the antibody and either said EDA region of the c-Fn of the test sample or the

> reference epitope of (i), (ii), (iii), or (iv), and measuring the amount of labeled epitope bound to the magnetic particles or labeled antibody or labeled antigen-binding portion thereof bound to the magnetic particles,
>
> wherein the amount of bound labeled antibody or bound labeled reference epitope is inversely proportional to the amount of human cellular fibronectin levels in the test sample, which is predictive of bleeding in a human test subject and
>
> wherein the obtaining, mixing, forming and measuring steps occur in 60 minutes or less.

Appeal Br. 18–19.

Appellant seeks review of the following rejections:

I. Claims 24–26, 42, 46, 47, 49, and 51–54 under 35 U.S.C. § 112(a), for failure to meet the written description requirement ("Written Description Rejection");

II. Claims 24–26, 49, and 52 under 35 U.S.C. § 103 as unpatentable over Davalos,[2] Ylätupa,[3] and Peters,[4] as evidenced by UniProtKB[5];

III. Claim 42 under 35 U.S.C. § 103 as unpatentable over Davalos, Ylätupa, Peters, UniProtKB, and Gorell[6];

IV. Claim 46 under 35 U.S.C. § 103 as unpatentable over Davalos, Ylätupa, Peters, UniProtKB, and Maxfield[7];

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[2] US 2005/0130230 A1, published June 16, 2005 ("Davalos").
[3] S. Ylätupa et al., *Cellular Fibronectin in Serum and Plasma: a Potential New Tumour Marker?*, 71 British J. of Cancer, 578–82 (1995) ("Ylätupa").
[4] US 5,108,898, issued Apr. 28, 1992 ("Peters").
[5] UniProtKB – P02751 (FINC_HUMAN), https://www.uniprot.org/uniprot/PO2751. ("UniProtKB").
[6] Jay M. Gorell et al., *Parkinson's Disease and its Comorbid Disorders*, 44 Neurology 1865 (1994) (abstract only) ("Gorell").
[7] US 5,780,319, issued July 14, 1998 ("Maxfield").

V. Claim 47 under 35 U.S.C. § 103 as unpatentable over Davalos, Ylätupa, Peters, UniProtKB, and Pujuguet[8]; and

VI. Claims 51, 53, and 54 under 35 U.S.C. § 103 as unpatentable over Davalos, Peters, Maxfield, as evidenced by Harlow.[9]

Appeal Br. 4–16.

I. WRITTEN DESCRIPTION REJECTION

Issue

The issue for this rejection is whether a preponderance of the evidence supports Examiner's finding that claims 24–26, 42, 46, 47, 49, and 51–54 fail to comply with the written description requirement.

Analysis

> Examiner determines that the claims recite a
>
> broad genus of antibodies, where the "antibody is an isolated human monoclonal antibody, or an antigen-binding portion thereof, or both an antibody and its antigen-binding portion, wherein the antibody binds to c-Fn with an affinity at least 100 fold greater than it binds to plasma fibronectin and wherein the antibody binds to amino acid sequence 1631-1721 of the c-Fn molecule ('the EDA region')."

Non-Final Action mailed July 30, 2018 ("Non-Final Act.") 6–7.[10] Examiner finds that the limited number of antibodies the Specification identifies as meeting these binding criteria are insufficient to demonstrate possession of

[8] Phillippe Pujuguet et al., *Expression of Fibronectin Ed-A$^+$ and ED-B$^+$ Isoforms by Human and Experimental Colorectal Cancer*, 148 Am. J. of Pathology 579–92 (1996) ("Pujuguet").
[9] Ed Harlow et al., Antibodies A Laboratory Manual 23–26, 321–323, 584–585, 591–592 (1988) ("Harlow").
[10] Examiner makes the same finding regarding the similarly–recited genus of antibodies in independent claim 51. Non-Final Act. 7.

the full scope of the broadly recited genus. *See id.* at 7–8. According to Examiner,

> the MPEP indicates that all of the limitations in a claim must be sufficiently described in order to satisfy written description. Here, a significant feature of the claimed assay is the antibody that is used in the assay. This antibody is only described by its binding. No structure is given which correlates with this binding. Moreover, it appears that only one antibody (P4F6) works in the assay, and Applicant admits that these antibodies are difficult to obtain. *See* Spec. at 10-11. This further indicates that it is not clear what structure correlates with this function and that Applicant did not have possession of the genus of antibodies with the claimed function.

Ans. 22.

Appellant argues that the claims "are not directed to antibodies per se," but rather recite methods that "rely on the function of an antibody as recited in claims 24 and 51 and described in the specification on page 4, lines 21-24, page 7, lines 10-12, and page 10, lines 6-7." Appeal Br. 5. Appellant urges that "Examples I and II [in the Specification] illustrate a reduction to practice of the methods claims," i.e., both "a competitive assay and a sandwich assay," and therefore describe a representative number of species sufficient to show possession of the claimed genus. *Id.* According to Appellant,

> [t]he specification identifies five antibody development methods used to generate antibodies and identifies four antibodies generated from these methods and a commercially available antibody that meet the criteria recited in the claim of binding to c-Fn with an affinity at least 100 fold greater than it binds to plasma fibronectin, [and] an amino acid sequence 1631-1721 of the c-Fn molecule ("the EDA region"). Four of these were screened further as capture antibodies in Example 1 to obtain a quality antibody. These disclosures, with or without

> the details within the Examples, provide a representative number of antibodies for one skilled in the art to conclude that the Appellants were in full possession of the methods as claimed with the antibodies defined therein by their function.

Id. at 6.

We determine that Examiner has the better argument and, as explained below, that Appellant's written description does not demonstrate possession of the full scope of the genus of antibodies recited in Appellant's claims. Appellant does not argue the claims separately with respect to this rejection. We focus on claim 24 as representative.

An adequate written description must contain enough information about the actual makeup of the claimed products—"a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials," which may be present in "functional" terminology "when the art has established a correlation between structure and function." *Ariad Pharm., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc). This is true even where the claim at issue is focused on a method that uses a genus of products, rather than on the products *per se*. *See Ariad* at 1354–55 ("Regardless whether the asserted claims recite a compound, Ariad still must describe some way of performing the claimed methods . . . the specification must demonstrate that Ariad possessed the claimed methods by sufficiently disclosing molecules capable of reducing NF-κB activity so as to 'satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed.'") (internal citation omitted); *see also Univ. of Rochester v. G.D.*

Searle & Co., Inc., 358 F.3d 916, 918 (Fed.Cir.2004) (applying the same analysis to assess whether claims to a "method for selectively inhibiting" a particular enzyme by administering a functionally defined compound, i.e., a "non-steroidal compound that selectively inhibits activity" of the gene product for that enzyme).

We agree with Examiner that Appellant's claims recite a broad genus of functionally defined monoclonal antibodies and antigen-binding portions thereof for use in the claimed methods. Claim 24 sets forward three functional requirements for a species within this genus: (1) it must bind to amino acid sequence 1631-1721 of the c-Fn molecule, i.e., the "EDA region;" (2) it must bind an epitope consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 1 – 4;[11] and (3) it must bind c-Fn with an affinity at least 100 fold greater than they bind plasma fibronectin. The Specification broadly defines the term "antibody" to include "fragments or portions as well as single chain forms." Spec. 7. It further indicates "[a]n antibody may be derived from a single copy or clone, including e.g., any eukaryotic, prokaryotic, or phage clone" and produced using "e.g., recombinant technologies, phage display technologies, synthetic technologies or combinations of such technologies or other technologies readily known in the art." *Id.*

The Specification identifies five antibodies as "passing screening" because they "show[ed] strong positive binding to the c-Fn whole molecule

[11] Examiner found, and Appellant does not dispute, that the amino acid sequence in SEQ ID NO: 4 is contained in c-Fn. Non-Final 12. In fact, SEQ ID NO: 4 appears to correspond to the complete "EDA region" as defined in claim 24, i.e., "amino acid sequence 1631–1721 of the c-Fn molecule." *See* UniProtKB, 17 (amino acids 1631–1721).

and zero binding to p-Fn." Spec. 10. The Specification identifies these antibodies as follows: "P4F6, P3A3, P1H11, 19B12-3H5," and "commercially available IST-9 Ab." *Id.* There is no description of the structure or amino acid sequence of any of these five antibodies. The Specification indicates that the first four of these antibodies were generated by "five different antibody development methods," two involving "panning" of an "ABD Serotect HUCAL library" and three involving "immunization of mice." *Id.* at 9–10. It does not indicate which of these five methods produced the particular antibodies that passed screening, nor does it indicate whether any of these antibodies were deposited in a public depository. Appellant presents no evidence, nor argument, that a skilled artisan could identify the structure of these antibodies based on the names in the Specification or that the disclosure of the methods by which these antibodies were generated and screened discloses anything about their structure.

Indeed, Appellant does not dispute Examiner's finding that the antibodies are described only by their binding and "[n]o structure is given which correlates with this binding." Ans. 22. Instead, Appellant asserts the application "need not disclose the structure of the antibodies to show possession" because it names five antibodies that "meet the criteria recited in the claim (1 commercially available and 4 developed from disclosed methods)" one of which "was used to reduce the methods claimed to practice." Reply Br.[12] 4; *see also* Appeal Br. 6. We are not persuaded. Our reviewing court has "repeatedly stated that actual 'possession' or reduction

[12] Appellant's Reply Brief is not paginated, therefore, all reference to page numbers refer to this document as if it were numbered consecutively starting with the first page.

to practice outside of the specification is not enough." *Ariad*, 598 F.3d at 1352. It may be that the invention was actually reduced to practice. But the written description requirement must be met by what is actually disclosed within the "four corners of the specification." *See id* at 1351.

Here, the only description the Specification provides for the five antibodies that Appellant says are representative of the recited genus is a functional one, i.e., they "show[ed] strong positive binding to the c-Fn whole molecule and zero binding to p-Fn." Spec. 10. While the Federal Circuit has recognized that "the written description requirement can in some cases be satisfied by functional description," it has made clear that "such functional description can be sufficient only if there is also a structure-function relationship known to those of ordinary skill in the art." *In re Wallach*, 378 F.3d 1330, 1335 (Fed. Cir. 2004); *see also Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1378 (Fed. Cir. 2017) (holding that an "adequate written description must contain enough information about the actual makeup of the claimed products").

The record here does not demonstrate the requisite structure-function relationship. At most, the Specification identifies peptide sequences or epitopes to which the claimed antibodies must bind. However, as Examiner notes, merely describing the antigen to which an antibody binds does not demonstrate possession of the antibody itself, much less the full scope of the genus of antibodies recited here. *See* Non-Final Act. 5 (citing *Amgen*, 872 F.3d at 1378–79 and USPTO Memorandum dated Feb. 22, 2018 clarifying written description examination guidance in light of *Amgen*).

Appellant argues that *Amgen* does not apply here because its claims "are not directed to antibodies per se." Appeal Br. 5. We disagree. Claim

24 recites a functionally described genus of monoclonal antibodies for use in the claimed method. As such, Appellant's claims present the same issue as the claims in *Amgen*, i.e., whether the written description provides a "precise definition" of the claimed genus either by disclosing a representative number of species or common structural features "so that one of skill in the art can 'visualize or recognize' the members of the genus." *Amgen*, 872 F.3d at 1373 (quoting *Ariad*, 598 F.3d at 1350). As explained above, the written description of the present application does neither. Accordingly, we determine that Examiner's rejection is supported by a preponderance of the evidence and therefore affirm.

II. OBVIOUSNESS REJECTIONS OF CLAIMS 24–26, 42, 46, 47, 49, and 52

Issue

The issue for these rejections is whether the preponderance of evidence of record supports Examiner's conclusion that the cited prior art renders Appellant's claims obvious.

Examiner entered four obviousness rejections for these claims, each of which is premised on the same base references, i.e., Davalos, Ylätupa, and Peters. Regarding the first rejection, Appellant does not argue claims 25, 26, and 52 separately from claim 24. Appeal Br. 8–12. Likewise, Appellant relies on the same arguments for the rejection of claim 42, the rejection of claim 46, and the rejection of 47 that it does for claim 24. *See id.* at 13–14. Accordingly, we analyze the rejections together with claim 24 being representative. We address Appellant's additional argument concerning claim 49 (*see id.* at 13) separately in our analysis below.

Findings of Fact

FF1. Davalos teaches that c-FN is a marker for hemorrhage in a human patient. Davalos ¶ 190. According to Davalos, increased levels of plasma c-FN have been reported in "patients with vascular injury secondary to vasculitis, sepsis, acute major trauma, diabetes, and patients with ischemic stroke." *Id.* Davalos explains there is a "need . . . for a rapid, sensitive and specific differential diagnostic assay for stroke, stroke subtype, and stroke mimic that can also identify those individuals at risk for hemorrhagic transformation." *Id.* ¶ 23. According to Davalos, "[b]y correlating the subject's marker level(s)," including c-Fn levels, "to the diagnostic marker level(s), the presence or absence of stroke, and also the probability of future adverse outcomes . . . may be rapidly and accurately determined." *Id.* ¶ 27.

FF2. Davalos teaches assays for determining the presence of c-FN and other markers in blood samples. Davalos ¶ 311. According to Davalos, "[t]he presence or amount of a marker is generally determined using antibodies specific for each marker and detecting specific binding." *Id.* ¶ 193. Davalos teaches that "various sandwich, competitive or non-competitive assay formats" can be used for such assays and that the antibodies used in such can be immobilized on magnetic particles. *Id.* ¶ 194.

FF3. Davalos teaches that "[i]n a preferred embodiment, the assay is in a format that permits multiple markers to be tested from one sample, such as the Luminex platform.TM, and/or in a rapid fashion, defined to be under 30 minutes and in the most preferred enablement of the instant invention, under 15 minutes." Davalos ¶ 307. Davalos claims a kit "capable of determining the levels of cellular fibronectin . . . within 20 minutes." *Id.*, 42 (claim 22).

FF4. Davalos describes results of c-FN assays in which c-FN levels ranged from 4.8 μg/mL to 1.3 μg/mL. Davalos ¶ 317, Fig. 2.

FF5. Ylätupa teaches there are "two major groups" of fibronectin—plasma (p-Fn) and cellular (c-Fn), the latter of which differs from p-FN because it has "extra domain (ED) sequences A or B in the molecule." Ylätupa 578. Ylätupa further teaches that "specific antibodies [have] made it possible to study the cellular form of FN containing the EDA sequence." *Id.*

FF6. Ylätupa describes results from "competitive enzyme immunoassay" for c-FN. *See* Ylätupa 579–81. According to the protocol described in Ylätupa, serum and plasma samples were incubated with "peroxidase-conjugated DH1 antibody against EDAcFN" before being transferring to "microtitration strips coated with cFN." *Id.* at 579. The strips are then incubated for 1 hour, washed, and then incubated for an additional 30 minutes before measuring absorbance to determine c-FN levels. *Id.*

FF7. Peters describes detecting and monitoring "toxemias of pregnancy, particularly preeclampsia and eclampsia, by the use [of] a marker, human fibronectin having a variably included Type III repeat sequence, ED1." Peters, Abstr. Peters teaches that the ED1 region is "unique to cellular fibronectins." *Id.* at 3:1–6.

FF8. Peters teaches that "[a]ntibodies specific for the ED1 region of fibronectin have been produced" and that such antibodies may be "induced by a polypeptide whose sequence corresponds" to portions of the ED1 domain. Peters, 6:59–7:13.

FF9. Peters describes determining c-Fn levels in a serum or plasma sample by admixing the sample "with an antibody that immunoreacts with fibronectin" having the EDA region, i.e., (ED+ Fn), but does not immunoreact with plasma fibronectin (pFn)." Peters, 6:9–13. Peters explains that the "admixture is maintained for a time period sufficient for any

[c-Fn] present in the sample to immunoreact with the antibody to form an immunoreaction product." *Id.* at 6:13–16; *see also id.* at 7:25–33.

FF10. Peters teaches that the assay can be employed in a variety of formats, including "competitive" and "non-competitive" assays. Peters, 6:21–29. Peters teaches that the antibodies used in such assays may be "polyclonal or monoclonal." *Id.* at 6:34–35.

FF11. UniProtKB discloses an amino acid sequence for c-FN, including the EDA region thereof. UniProtKB 16–17. The sequence for c-FN contains SEQ ID NO: 4 as recited in Appellant's claims 24 and 51.

FF12. Maxfield teaches the use of "magnetically attractable particles" as the "solid phase in assays." Maxfield, 8:22–30. Maxfield teaches that such particles "allow the separation step to be done through magnetic separation and thus avoids the necessity of centrifuging or waiting for the particles to settle out of solution." *Id.* at 8:27–30.

Analysis

Examiner determines that Davalos teaches "a rapid assay for the prediction of bleeding . . . in a human test subject that can determine in 60 minutes or less the level of human cellular fibronectin . . . wherein the test sample is plasma." Non-Final Act. 11. Examiner further finds Davalos teaches "using an immunoassay, which uses antibodies to measure cellular fibronectin" and that the assay may be a competitive assay with labelled antibodies "immobilized on magnetic particles." *Id.* Examiner finds that Ylätupa and Peters both teach competitive assays that use antibodies specific for the EDA or ED1 region of c-FN and "that the ED1 domain can be used to distinguish cellular fibronectin from plasma fibronectin." *Id.* at 11–12. According to Examiner,

> [i]t would have been *prima facie* obvious before the effective filing date of the claimed invention for one of ordinary skill in the art to have performed a competitive immunoassay, as taught by Ylatupa and Peters (b), with an immobilized reference epitope for measuring c-FN, as taught by Ylatupa, where the sample is mixed with the solid phase containing the immobilized cellular fibronectin and an antibody which binds to cellular fibronectin, where the assay does not require the antibody to be fixed to a solid matrix to immunoreact with the EDA region of c-FN molecules or the reference epitope in the solid phase, and wherein the assay is a competitive assay, provided that the antibody binds the EDA region and the reference epitope, followed by forming a complex between the antibody and either the EDA region or the reference epitope, as taught by Ylatupa, with the antibodies of Peters (b), in the assay of Davalos.

Id. at 12. Examiner determines a skilled artisan would be motivated to perform a competitive assay in this manner because such "steps are routinely used in competitive assays and because it is routine to immobilize the analyte in a competitive ELISA." *Id.* at 13.

After considering Examiner's rejections and Appellant's arguments, we adopt Examiner's findings of fact and reasoning regarding the scope and content of the prior art (Non-Final Act. 10–17; FF 1–11) and agree that claims 24–26, 42, 46, 47, 49, and 52 are rendered obvious by the cited prior art. We address Appellant's arguments below.

Appellant argues that none of the cited references disclose the "synthetic polypeptides" (i.e., SEQ ID NOS: 1–4) used as the "reference epitope" in claim 24. We disagree. As Examiner found, Ylätupa teaches the use of synthetic c-Fn produced from cell culture as a reference epitope in its competitive assay and c-Fn contains the sequence in SEQ ID NO: 4. Non-Final Act. 11–12; FF6. The Specification teaches that full-length c-FN may

be used as the reference epitope in a competitive assay. Spec. 14, 19. Indeed, Specification Example 1 states that "the cFn native whole molecule was chosen [over the EDA-Fc peptide] in the final assay configuration due to the improvement in the ability of cFn in 'sample' to displace labeled whole molecule cFn versus labeled EDA-Fc peptide." *Id.* at 19. Thus, Ylätupa teaches a competitive assay using the same reference epitope as the preferred embodiment in the Specification.

Appellant attempts to distinguish the c-Fn used in Ylätupa, urging that it is not a "synthetic" polypeptide because it is not produced by chemical synthesis or constructed according to recombinant DNA techniques. Reply Br. 6–7. We are unpersuaded. First, Appellant's claim construction is premised on a sentence in the Specification referring to "[s]ynthesized antigens," not the claim language in question. *See* Spec. 8. Moreover, this sentence merely states that such antigens "include" those constructed by chemical synthesis and recombinant techniques; it does not purport to define or otherwise limit the term to such. *Id.* Thus, Appellant's construction does not reflect the broadest reasonable interpretation of "synthetic peptide." Second, Appellant's construction relates only to the process for making the epitope and does not distinguish the structure of the recited "reference epitope" from that taught in Ylätupa. *See SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1315 (Fed. Cir. 2006) ("[O]nce a product is fully disclosed in the art, future claims to that same product are precluded, even if that product is claimed as made by a new process.").

We are also unpersuaded by Appellant's argument that the cited prior art does not teach an assay that may be performed in "60 minutes or less," as recited in claim 24. *See* Appeal Br. 8–12. Davalos teaches that its assays

are rapid and can test for multiple markers in less than 30 minutes. FF3. Indeed, Davalos claim 22 is specifically directed to a kit that "is capable of determining the levels of cellular fibronectin and said additional markers within 20 minutes." Davalos 42.

> Appellant argues that Davaolos claim 22 "is not enabled" because
>
> [t]he only assays performed [in Davalos] are described in Example 1 where Plasma MMP-9 and c-Fn levels were measured with commercially available quantitative sandwich enzyme-linked immunoabsorbent assay kits obtained from Biotrack, Amersham Pharmacia UK, and Adeza Biomedical, respectively. There is no indication that these assays took less than 20 minutes and there is no indication these assays were performed in a device as defined in claim 22.

Appeal Br. 9.

We are not persuaded by Appellant's argument. Prior art is presumed to be enabled. *See In re Morsa*, 713 F.3d 104, 109 (Fed. Cir. 2013) ("[A] prior art printed publication cited by an examiner is presumptively enabling barring any showing to the contrary by a patent applicant or patentee."). Thus, Appellant must show that Davalos' teachings concerning rapid c-Fn assays are not enabled.

Appellant relies on Castellanos[13] as evidence that "conventional assays prior to the invention were too slow." Appeal Br. 10. Castellanos states that "ELISA kits can only be either accepted or are valid as screening analytic tests, because these technique are slow and expensive and are therefore not applicable in daily clinical practice." Castellanos 6. But

[13] Mar Castellanos et al., *Serum Cellular Fibronectin and Matrix Metalloproteinase-9 as Screening Biomarkers for the Prediction of Parenchymal Hematoma After Thrombolytic Therapy in Acute Ischemic Stroke*, 38 Stroke 1855-59 (2007) ("Castellanos").

Appellant has not shown that Castellanos is referring to the assays taught in Davalos. In particular, Davalos refers to rapidly testing multiple markers on the "Luminex platform.TM" as well as a "quantitative sandwich enzyme-linked immunoabsorbent assay kit" obtained from Adeza Biomedical. Davalos ¶¶ 307, 311. Neither of these assays are discussed in Castellanos, which instead involved kits from other manufacturers. *See* Castellanos 3. Accordingly, Castellanos does not show that Davalos' teaching of rapid c-Fn assays is not enabled.

Appellant also relies on the Declaration of Cornelius Allen Diamond dated September 25, 2017 ("Diamond Declaration"). According to the Diamond Declaration, "[t]he only methods/kits mentioned in Davalos with any specificity for measuring c-Fn are commercially available quantitative sandwich enzyme-linked immunoabsorbent assay kits obtained from Adeza Biomedical. In fact, all the data that were obtained and disclosed in the Davalos patent is from hours-long ELISA." Diamond Decl. ¶ 11. Davalos' teachings, however, are not limited to the particular kit used to obtain the data in its examples. As explained above, Davalos specifically refers to other platforms and rapid testing. *See* FF3. While the Diamond Declaration notes that Davalos "is silent as to the antibodies and the specific antibody/synthetic polypeptide combinations that would determine the levels of c-Fn in less than 60 minutes," both Ylätupa and Peters indicate that c-Fn can be measured using antibodies that specifically bind to peptides within the EDA region of c-Fn because the EDA region is not present in p-Fn. *See* FF5, FF7. Importantly, this is the same criteria used to screen antibodies for the assays described in the Specification. Moreover, as explained above, Ylätupa teaches a competitive assay using the same reference epitope as the

preferred embodiment in the Specification. Appellant has not shown that a skilled artisan would be unable to combine these teachings to perform the assay in less than 60 minutes as taught in Davalos. FF3.

Finally, we are not persuaded by Appellant's separate argument regarding claim 49. Appellant contends that claim 49 requires "determining the level of c-FN over a wide range" and that the values determined in Davalos do "not suggest assays with a broad operating range, such as that encompassed by claim 49, could be achieved." Appeal Br. 12. We disagree. Claim 49 recites "[t]he rapid assay according to claim 24, wherein c-Fn is determined in said test sample in the range of 0 — 20 mg/ml." Appeal Br. 19. Examiner found that Davalos teaches determining concentrations of c-Fn within the recited range and therefore teaches this limitation. Non-Final Act. 14. We agree the record supports Examiner's finding. FF4. Appellant has not pointed to evidence to overcome the presumption the recited range is obvious over Davalos' teaching of overlapping c-Fn values. *See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("[W]e and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness.").

For these reasons, we determine that the preponderance of the evidence supports Examiner's rejection of claims 24–26, 42, 46, 47, 49, and 52 and therefore affirm the obviousness rejections of these claims.

III. OBVIOUSNESS REJECTIONS OF CLAIMS 51, 53, and 54

Issue

The issue for this rejection is whether the preponderance of evidence of record supports Examiner's conclusion that the cited prior art renders claims 51, 53, and 54 obvious.

Appellant does not argue claims 53 and 54 separately from claim 51, therefore claims 53 and 54 stand or fall with claim 51.

Analysis

As Appellant points out, claims 51 "encompass[es] sandwich assays" that use a capture antibody that selectively binds c-Fn and at least one of the sequences in SEQ ID NOS: 1–4. Appeal Br. 3–4. "A complex is formed between the capture antibody and the c-Fn in the test sample and the complexes are mixed with coated paramagnetic particles that bind to the capture antibody." *Id.* at 4 (citations omitted). The amount of complex formed indicates the level of c-Fn in the sample. *Id.*

Examiner finds that Davalos teaches "using a sandwich immunoassay, which uses a monoclonal capture antibody to measure cellular fibronectin and naturally involves mixing the test sample with an isolated monoclonal antibody and then forming complexes between the capture antibody and c-FN in the test sample and detecting the complexes in the test sample" and performing the assay "in a rapid manner." Non-Final Act. 18. Examiner determines that Peters teaches a sandwich assay for c-Fn using a "monoclonal antibody that binds to a sequence ELFPAPDGEEDTAELQC contained in SEQ ID NO: 4 with a terminal" cysteine residue and therefore "it is reasonable to expect that it can bind to SEQ ID NO:4," particularly because the sequences overlap "over a length that is much longer than the length that typically defines an antibody epitope." *Id.* at 19 (citing Harlow 23–24). Examiner finds it would be obvious to use "a sandwich assay with a monoclonal antibody that binds [c-Fn] with an affinity at least 100 fold times that of plasma fibronectin, and binds without being attached to the

solid phase, as taught by Peters . . . where the magnetic particles are paramagnetic, as taught by Maxfield" in the rapid assay method of Davalos. *Id.* at 20.

After careful consideration of Appellant's arguments, we again adopt Examiner's findings of fact and reasoning regarding the scope and content of the prior art (Non-Final Act. 17–21; FF 1–4, 7-10, and 12) and agree that claims 51, 53, and 54 are rendered obvious by the cited prior art. We address Appellant's arguments below.

As it did for the other obviousness rejections, Appellant argues that the cited references do not teach "a rapid assay for the detection of cellular fibronectin which is completed in 60 minutes or less" because Davalos does not enable such. *See* Appeal Br. 14–15. We are not persuaded by that argument for the same reasons explained above.

Appellant additionally argues that Examiner has not "provide[d] sufficient reasons or explanation [for] why one of skilled in the art would combine" the cited references "when all of the assays described in these references take hours to prepare." Appeal Br. 16. We disagree. As Examiner determined, Davalos teaches rapid assays for c-Fn that are performed in less than 60 minutes. Non-Final Act. 18; FF3. Further Examiner explains that "one would be motivated [to perform a rapid assay] for all the reasons that Davalos says that a rapid assay for cellular fibronectin is important (e.g. rapid diagnosis of stroke, etc.)." Ans. 27–28; FF1. Accordingly, Examiner has articulated a sufficient, evidence–backed rationale for combining the cited references.

For these reasons, we determine the preponderance of the evidence supports the obviousness rejection of claims 51, 53, and 54 and therefore affirm the rejection.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
24–26, 42, 46, 47, 49, 51–54	112(a)	Written Description	24–26, 42, 46, 47, 49, 51–54	
24–26, 49, 52	103	Davalos, Ylätupa, Peters, UniProtKB	24–26, 49, 52	
42	103	Davalos, Ylätupa, Peters, UniProtKB,Gorell	42	
46	103	Davalos, Ylätupa, Peters, UniProtKB, Maxfield	46	
47	103	Davalos, Ylätupa, Peters, UniProtKB, Pujuguet	47	
51, 53, 54	103	Davalos, Peters, Maxfield, Harlow	51, 53, 54	
Overall Outcome			24–26, 42, 46, 47, 49, 51–54	