United States Court of Appeals for the Federal Circuit

GENETICS INSTITUTE, LLC,
Plaintiff-Appellant,

v.

NOVARTIS VACCINES AND DIAGNOSTICS, INC.,
Defendant-Appellee.

2010-1264

Appeal from the United States District Court for the District of Delaware in Case No. 08-CV-0290, Judge Sue L. Robinson.

Decided: August 23, 2011

BRADFORD J. BADKE, Ropes & Gray LLP, of New York, New York, argued for plaintiff-appellant. With him on the brief were JEANNE C. CURTIS and MATTHEW A. TRAUPMAN. Of counsel was CHRISTOPHER J. HARNETT.

GEORGE A. RILEY, O'Melveny & Myers LLP, of San Francisco, California, argued for defendant-appellee. With him on the brief was GEORGE C. YU. Of counsel on the brief was JOHN C. KAPPOS, of Newport Beach, California. Also of counsel were POLAPHAT VERAVANICH, O'Melveny & Myers LLP, of Newport Beach, California,

and MARK S. DAVIES, Orrick, Herrington & Sutcliffe LLP, of Washington, DC.

Before LOURIE, PLAGER, and DYK, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* LOURIE.
Opinion concurring-in-part and dissenting-in-part filed by *Circuit Judge* DYK.

LOURIE, *Circuit Judge*.

Genetics Institute, LLC, ("Genetics") appeals from the decision of the United States District Court for the District of Delaware dismissing its action under 35 U.S.C. § 291 for lack of an interference in fact between certain claims of its U.S. Patent 4,868,112 (the "'112 patent") and certain claims of U.S. Patents 6,228,620 and 6,060,447 (the "'620 patent" and the "'447 patent"; collectively, the "Novartis patents"). Novartis asserts that the expiration of the '112 patent following the district court's entry of judgment renders us without jurisdiction over Genetics' appeal. Novartis also asserts that the district court lacked jurisdiction over certain claims of the '112 patent because its term extension under 35 U.S.C. § 156 applied only on a claim-by-claim basis. Because the district court did not err in dismissing Genetics' § 291 action for lack of an interference in fact, and because we disagree with Novartis's jurisdictional arguments, we affirm.

BACKGROUND

I

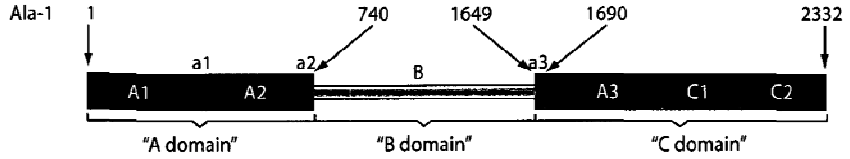
The district court's opinion summarizes the science underlying the patented technology in this case, which relates to truncated forms of a protein called Factor VIII. *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 687 F. Supp. 2d 486, 490-92 (D. Del. 2010). Factor

VIII is an essential blood-clotting protein that circulates freely in the blood in an inactive state. Factor VIII becomes activated as part of a chain of reactions called the "blood-clotting cascade," which causes the formation of a blood clot to stop bleeding from damaged blood vessels. Defects in the gene encoding Factor VIII result in hemophilia A, a genetic disorder associated with prolonged bleeding.

The human Factor VIII protein is stabilized in the bloodstream by binding to von Willebrand factor ("vWF"), a large blood protein that prevents the degradation of Factor VIII. *Id.* at 491. If Factor VIII is not able to form a complex with vWF, the half-life of Factor VIII in plasma is reduced about five-fold. Thus, while Factor VIII retains its procoagulant activity even without vWF binding, the association of Factor VIII with vWF is critical for the optimal regulation of blood coagulation. In addition, a Factor VIII protein that cannot bind vWF may cause unwanted clots in areas such as heart vessels because unbound Factor VIII can bind blood platelets even when no injury has been detected.

The full-length Factor VIII protein consists of 2,332 amino acid residues—the chemical building blocks of proteins. *Id.* The protein contains several regions, or "domains," each of which folds into a three-dimensional structure independent of the others. Factor VIII contains the following domains: A1, A2, B, A3, C1, and C2. The Figure below depicts the locations of these domains in the full-length Factor VIII protein. *See* Br. of Pl.-Appellant at 9; *see also* Def.-Appellee Br. at 10-11. The "heavy chain" or "A domain" portion of the protein consists of amino acids 1 to 740 and contains the A1 and A2 domains as

well as two acidic regions known as a1 and a2.[1] The B domain contains amino acids 741 to 1648. The "light chain" or "C domain" portion of the protein consists of amino acids 1649 to 2332. It contains a third acidic region, a3, as well as the A3, C1, and C2 domains. The a3 acidic region, of particular importance to the dispute in this case, contains amino acids 1649 to 1689. It is directly adjacent to the B domain.



Figure

Treating patients with hemophilia A traditionally involved administering partially purified Factor VIII derived from porcine or human plasma. In the 1980s, however, human plasma sources had become contaminated with viruses, such as HIV and hepatitis, making treatment with plasma-derived Factor VIII dangerous. Recombinant Factor VIII, produced from DNA cloning, offered a safer and more abundant new source of therapeutic material. Scientists raced to clone Factor VIII successfully for the first time. Yet cloning Factor VIII proved to be an enormous technical undertaking, because the Factor VIII protein was nearly ten times larger than

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[1] The amino acid numbering system used throughout this opinion, unless otherwise specified, is the system referred to as "ala-1," in which the 20-amino-acid region known as the "signal peptide" at the beginning of the N terminal of the protein is omitted for numbering purposes. The '620 and '447 patents use ala-1 numbering. The '112 patent follows the met-1 system; its amino acid numbers can be converted to the ala-1 system by subtracting 19 amino acids.

any protein previously cloned. The large size of the DNA sequence encoding the full-length Factor VIII protein also complicated the cloning process. *Id.* at 491-92.

Once the feat of cloning the full-length Factor VIII protein was achieved, researchers focused their efforts on finding a smaller, more easily cloned recombinant protein that mimicked the biological activity of Factor VIII in humans. *Id.* at 492. Those efforts formed the basis of the patents at issue in this appeal. As described below, scientists discovered that portions of the full-length Factor VIII protein were unnecessary for procoagulant activity, and they designed truncated Factor VIII proteins lacking these portions. Scientists further found that the a3 acidic region of Factor VIII is responsible for binding to vWF and is therefore critical to Factor VIII's performance.

II

The '112 patent is assigned to Genetics, a wholly owned subsidiary of Wyeth (which itself was recently acquired by Pfizer Inc.). *Genetics*, 687 F. Supp. 2d at 489-90. The '112 patent, which issued on September 19, 1989, claims priority from an application filed April 12, 1985, and names John J. Toole, Jr., as the sole inventor. The '112 patent was set to expire on September 19, 2006, at the end of its seventeen-year term. In 2000, however, Genetics obtained a patent term extension under 35 U.S.C. § 156 based on the time consumed by testing and regulatory review of its commercial recombinant Factor VIII protein, ReFacto®. The United States Patent and Trademark Office ("PTO") extended the term of the '112 patent to February 28, 2010.

At issue in this appeal are claims 1, 5, 9, and 10 of the '112 patent. These claim, respectively, a recombinant DNA whose expression results in a truncated Factor VIII protein; a host cell containing the recombinant DNA; a

method of producing the truncated Factor VIII protein by culturing the host cells; and a truncated human Factor VIII protein.

The truncated Factor VIII protein of claims 1, 5, and 9 has the amino acid sequence for human Factor VIII protein except that, in the region between amino acid 740 and amino acid 1690, a number of amino acids are deleted; the size of the deletion ranges from at least 581 to all 949 amino acids in this region.[2] The region eligible for deletion encompasses the inactive B domain (amino acids 741 to 1648) and the a3 acidic region in the light chain (amino acids 1649 to 1689). Claim 10 claims a truncated Factor VIII protein having one of three specific deletions: between amino acids 981 to 1563; 759 to 1640; or 759 to 1675.[3]

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[2] Using the met-1 numbering system, claim 1 of the '112 patent reads:

> 1. A recombinant DNA which upon expression results in a truncated Factor VIII protein which is an active procoagulant wherein the recombinant DNA encodes for a protein having the amino acid sequence of a human Factor VIII:C except for having a deletion corresponding to at least 581 amino acids within the region between Arg-759 and Ser.-1709, wherein the amino acid numbering is with reference to Met-1 of the human Factor VIII:C leader sequence.

See also Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc., No. 08-290-SLR, 2010 WL 677745, at *1 (D. Del. Feb. 24, 2010) (construing a "truncated Factor VIII protein which is an active procoagulant" as a "Factor VIII protein that promotes blood coagulation and lacks a portion of the amino acid sequence of the human Factor VIII protein").

[3] Using the met-1 numbering system, claim 10 of the '112 patent reads:

> 10. A truncated human Factor VIII:C protein which is an active procoagulant protein having a

Novartis Vaccines and Diagnostics, Inc., ("Novartis") is the assignee of the '620 and '447 patents. Both of the Novartis patents claim priority from an application filed January 27, 1986.

At issue in the '620 patent are claims 68, 74, and 83. Claim 68 claims a nucleic acid expressing a truncated recombinant Factor VIII protein in which all or part of the B domain is deleted. The claimed recombinant protein retains the amino acids in the heavy chain (amino acids 1 to 740) and the light chain (amino acids 1649 to 2332, including the a3 acidic region) with the requirement that these retained portions have at least 90% sequence identity to the native human Factor VIII protein. The protein also optionally retains certain amino acids in the B domain: up to 10 amino acids contiguous to amino acid 740, and up to 10 amino acids contiguous to amino acid 1649.[4]

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peptide sequence of human Factor VIII:C but lacking a peptide region selected from the group consisting of:

(a) the region between Pro-1000 and Asp-1582;

(b) the region between Thr-778 and Pro-1659; and,

(c) the region between Thr-778 and Glu-1694.

See also Genetics, 2010 WL 677745, at *1 (construing "having a peptide sequence of human factor VIII:C but lacking a peptide region selected from the group consisting of" as "[h]aving the amino acid sequence of the human Factor VIII protein lacking only the particular segment of the human Factor VIII protein in one of the specified alternatives (a), (b) or (c)").

[4] Claim 68 of the '620 patent reads:

68. A nucleic acid composition for introducing nucleic acid into a eukaryotic host cell to obtain expression of a recombinant protein lacking all or a portion of the B domain of human Factor VIII, wherein said recombinant protein consists of:

a first amino acid sequence which consists of an amino acid sequence having at least 90% sequence identity with the contiguous amino acid

Claim 74 claims a host cell containing nucleic acid capable of expressing the truncated recombinant Factor VIII protein, and claim 83 claims a method of producing the truncated recombinant Factor VIII protein by culturing the host cell.

The only claim at issue in the '447 patent is claim 1, which claims a composition comprising Factor VIII proteins consisting essentially of two polypeptides: a first comprising an amino acid sequence of the heavy chain (A domain), and a second comprising an amino acid sequence of the light chain (C domain). At least 90% sequence identity with each region is required.[5]

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sequence of amino acids 1 to 740 of the native, mature A domain of human Factor VIII and optionally up to 10 amino acids of the human Factor VIII B domain sequence contiguous to amino acid 740 as encoded by the polynucleotide present in plasmid pSVF8-200 (ATCC No. 40190); and

a second amino acid sequence which consists of an amino acid sequence having at least 90% sequence identity with the contiguous amino acid sequence of amino acids 1649 to 2332 of the native, mature C domain of human Factor VIII and optionally up to 10 amino acids of the human Factor VIII B domain sequence contiguous to amino acid 1649 as encoded by the polynucleotide present in plasmid pSVF8-200 (ATCC No. 40190);

wherein said nucleic acid encodes said first and second amino acid sequences, and further wherein said recombinant protein is capable of coagulation activity in a coagulation activity assay.

[5] Claim 1 of the '447 patent reads:

1. A composition comprising Factor VIII:C proteins, wherein the Factor VIII:C proteins consist essentially of a first polypeptide comprising an amino acid sequence of the A domain of human Factor VIII:C as encoded by the polynucleotide present in plasmid pSVF8-200 (ATCC No. 40190)

III

On May 16, 2008, Genetics sued Novartis in the United States District Court for the District of Delaware to determine priority of invention under 35 U.S.C. § 291. Genetics alleged that an interference in fact existed between the following claims: (1) claim 1 of the '112 patent and claim 68 of the '620 patent; (2) claim 5 of the '112 patent and claim 74 of the '620 patent; (3) claim 9 of the '112 patent and claim 83 of the '620 patent; and (4) claims 9 and 10 of the '112 patent and claim 1 of the '447 patent. Genetics asserted that all three patents are directed to the same subject matter, *viz.*, truncated Factor VIII proteins lacking all or part of the B domain while retaining procoagulant activity.

Novartis moved to dismiss, arguing that the court lacked subject matter jurisdiction because the extension of the '112 patent under 35 U.S.C. § 156 applied to fewer than all of that patent's claims. Novartis further argued that there was no interference in fact between the asserted claims because the Novartis patents—unlike the '112 patent—are directed to truncated Factor VIII proteins that preserve the functional a3 acidic region.

In a memorandum order dated February 24, 2010, the district court construed the disputed claim language of the '112 patent. *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, No. 08-290-SLR, 2010 WL 677745 (D.

> or an amino acid sequence that differs therefrom in having not more than 10 number % amino acid substitutions, and a second polypeptide comprising an amino acid sequence of the C domain of human Factor VIII:C as encoded by the polynucleotide present in plasmid pSVF8-200 (ATCC No. 40190) or an amino acid sequence that differs therefrom in having not more than 10 number % amino acid substitutions.

Del. Feb. 24, 2010). In a memorandum opinion of the same date, the district court held that the patent term extension under § 156 applied to all claims of the '112 patent. *Genetics*, 687 F. Supp. 2d at 497. The court also granted Novartis's motion to dismiss, holding that there was no interference in fact as to any of the allegedly interfering claims. *Id.* at 502. The court entered its final judgment on February 25, 2010. On March 12, 2010, Genetics filed a timely notice of appeal.

Under 28 U.S.C. § 1295(a)(1), we have jurisdiction over final judgments arising under the patent laws.

DISCUSSION

I. Appellate Jurisdiction

As noted, the district court entered final judgment on February 25, 2010, and the extended term of the '112 patent expired three days later, on February 28, 2010. On April 12, 2010, Novartis filed a motion in this court to dismiss Genetics' appeal for lack of subject matter jurisdiction in light of the expiration of the '112 patent. In an order dated December 1, 2010, we denied the motion to dismiss Genetics' appeal, dismissed Novartis's related cross-appeal, and directed the parties to present arguments in their briefs on the issue of jurisdiction. *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, No. 2010-1264, -1301, slip. op. at 3-4 (Fed. Cir. Dec. 1, 2010).

Novartis disputes our jurisdiction over Genetics' appeal. Novartis contends that we should dismiss Genetics' appeal because the expiration of the extended term of the '112 patent following the district court's entry of final judgment divested this court of jurisdiction. Relying on *Albert v. Kevex Corp.*, 729 F.2d 757 (Fed. Cir. 1984), Novartis argues that "invocation of Section 291 requires the rather unusual step of the court dismissing the action

for lack of jurisdiction after the filing of a well-pleaded complaint *whenever* it becomes apparent that there is no interference." Def.-Appellee Br. at 29.

Genetics argues in response that we have jurisdiction over its appeal despite the expiration of the '112 patent. Genetics contends that an interference action under § 291 may apply to any patent, including an expired patent. Genetics contrasts § 291 with an interference action under § 135, which by its terms is limited to unexpired patents. Genetics further contends that the holding in *Albert* is limited to disclaimed patents and does not extend to expired patents.

We have an independent obligation to determine whether subject matter jurisdiction exists over an appeal. *Litecubes, LLC v. N. Light Prods., Inc.*, 523 F.3d 1353, 1362 (Fed. Cir. 2008); *see also Arbaugh v. Y & H Corp.*, 546 U.S. 500, 514 (2006). As we explain below, we conclude that we possess jurisdiction over the present appeal.

The dispute over appellate jurisdiction in this case boils down to the parties' divergent interpretations of *Albert*, 729 F.2d 757. That case, like this one, involved an interfering patents action under 35 U.S.C § 291. Section 291 reads:

> The owner of an interfering patent may have relief against the owner of another by civil action, and the court may adjudge the question of the validity of any of the interfering patents, in whole or in part. The provisions of the second paragraph of section 146 of this title shall apply to actions brought under this section.

Albert asserted, among other causes of action, that claims in his patent interfered with claims of a patent owned by Kevex Corporation. *Albert*, 729 F.2d at 759. Albert also

asserted that the claims of the Kevex patent were invalid under 35 U.S.C. § 102(b). Subsequently, Kevex filed in the PTO a disclaimer of the claims in its patent that allegedly interfered with Albert's claims. The trial court held that the filing of the disclaimer mooted the interfering patents action. *Id.* at 760. Yet the trial court proceeded to evaluate Albert's invalidity contentions, ultimately granting Albert's motion for summary judgment of invalidity. *Id.*

Kevex argued on appeal that the existence of an interference in a § 291 action is jurisdictional, such that the district court was required to determine that the patents interfered before determining the validity of either. *Id.* We agreed and held that after the entry of Kevex's disclaimer there were no interfering patents to support jurisdiction for an action under § 291. *Id.* at 760-61. We therefore vacated and remanded to the district court with instructions to dismiss for lack of jurisdiction. *Id.* at 762.

Novartis seeks to enlarge our holding in *Albert* to reach patent expirations. We reject this expansive reading, and we decline to extend *Albert*'s holding beyond the effect of a patent disclaimer in a § 291 action. Disclaimers of patent claims are provided for under 35 U.S.C. § 253, which provides in part that:

> A patentee, whether of the whole or any sectional interest therein, may, on payment of the fee required by law, make disclaimer of any complete claim, stating therein the extent of his interest in such patent. Such disclaimer shall be in writing, and recorded in the Patent and Trademark Office; and it shall thereafter be *considered as part of the original patent* to the extent of the interest possessed by the disclaimant and by those claiming under him.

Id. (emphasis added). Disclaiming particular claims under § 253 "effectively eliminate[s] those claims from the original patent." *Vectra Fitness, Inc. v. TNWK Corp.*, 162 F.3d 1379, 1383 (Fed. Cir. 1998). In other words, upon entry of a disclaimer under § 253, we treat the patent as though the disclaimed claim(s) had "never existed." *Id.* ("This court has interpreted the term 'considered as part of the original patent' in section 253 to mean that the patent is treated as though the disclaimed claims never existed.").

We held in *Albert* that "the court has no jurisdiction under § 291 unless interference is established." 729 F.2d at 760-61 ("[I]nterference between patents is a sine qua non of an action under § 291."). Jurisdiction under § 291 thus requires the existence of an interference, and a claim that "never existed," *Vectra*, 162 F.3d at 1383, cannot form the basis for an interference. Because the disclaimer in *Albert* precluded any basis for an interference between the patents in suit, we held that it also eliminated jurisdiction under § 291.

Unlike a disclaimed claim, however, an expired patent is not viewed as having "never existed." Much to the contrary, "a patent does have value beyond its expiration date." *In re Morgan*, 990 F.2d 1230, 1232 (Fed. Cir. 1992). For example, an expired patent may form the basis of an action for past damages subject to the six-year limitation under 35 U.S.C. § 286. *See, e.g.*, *id.* (recognizing that an action for patent infringement may be filed up to six years after the patent's expiration). There is no comparable statute providing any such rights in a disclaimed claim.

Furthermore, the expiration of the '112 patent does not deprive this § 291 action of meaning. In *Kimberly-Clark Corp. v. Procter & Gamble Distributing Co.*, 973 F.2d 911, 914 (Fed. Cir. 1992), in determining that juris-

diction in a § 291 action existed following the parties' settlement of infringement liability issues, we noted in support of our holding that "a declaration of priority and the subsequent elimination of an invalid patent that claims the same subject matter as claimed in one's patent are 'relief' under [§ 291]." Similar reasoning applies here. Genetics points out that the outcome of this § 291 action "will have real-world consequences," because Genetics' corporate parent, Wyeth, has been sued for allegedly infringing the Novartis patents in a related case in the United States District Court for the Eastern District of Texas. Pl.-Appellant's Reply Br. at 10; *see also* Compl. at 1, *Novartis Vaccines & Diagnostics, Inc. v. Wyeth*, No. 2:08-cv-067 (E.D. Tex. Feb. 15, 2008), ECF No. 1. A determination that the '112 patent interferes with and has priority over the Novartis patents would directly affect the outcome of that infringement suit.

We also note an important distinction between § 291 and the statute governing interferences before the PTO, 35 U.S.C. § 135. Whereas an interfering patents action under § 291 involves two "interfering patents" without qualification, a § 135 action, in contrast, is declared between one pending application and "any pending application, or . . . any *unexpired* patent." 35 U.S.C. § 135 (emphasis added). This meaningful difference in statutory language indicates that § 291, unlike § 135, is not limited to "unexpired" patents. That is but one essential difference between these two statutes. *Compare Guinn v. Kopf*, 96 F.3d 1419, 1421-22 (Fed. Cir. 1996) (holding that the disclaimer of an allegedly interfering claim did not divest the PTO of jurisdiction over the § 135 interference), *with Albert*, 729 F.2d at 760-61 (holding that the disclaimer of the allegedly interfering claims divested the district court of jurisdiction over the § 291 interfering patents action).

In view of the substantial differences between a disclaimer and an expiration, we decline to extend the holding in *Albert* to patent expiration situations. Accordingly, we hold that the expiration of the '112 patent following the district court's final decision does not strip our court of jurisdiction over the present appeal.

II. District Court Jurisdiction

Novartis alleges that the district court lacked jurisdiction to decide whether certain claims of the '112 patent and the Novartis patents interfered. Novartis argues that claims 1 and 5 of the '112 patent are not entitled to an extended term because Genetics, in its patent term extension application under § 156(d)(1), identified only claims 9 and 10 of the '112 patent as relating to its commercial product ReFacto®. Because patent term extensions apply only on a claim-by-claim basis, Novartis argues, claims 1 and 5 expired on September 19, 2006, following the original seventeen-year patent term. Novartis also maintains that because claim 10, as construed by the district court, does not cover ReFacto®, it too is ineligible for patent term extension under § 156. Citing *Albert*, 729 F.2d 757, Novartis argues that because expired claims cannot support an interfering patents action under § 291, claims 1, 5, and 10 of the '112 patent were not properly before the district court.

Genetics argues in response that the district court correctly held that a patent term extension under § 156 applies to the term of the patent as a whole, *i.e.*, to all claims in the patent. Genetics asserts that the plain language of § 156 compels this statutory interpretation. Genetics further maintains that each of claims 1, 5, and 9 covers ReFacto®. Specifically, Genetics argues that because claim 9 of the '112 patent covers ReFacto® (a point conceded by Novartis), claims 1 and 5 must also

cover this commercial product, since claim 9 depends from claim 5, which in turn depends from claim 1.

We, like the district court, *Genetics*, 687 F. Supp. 2d at 497, reject Novartis's assertion that a patent term extension under § 156 applies on a claim-by-claim basis. The plain language of § 156 refutes Novartis's argument. The title of this section is "Extension of *patent term*." 35 U.S.C. § 156 (emphasis added). Subsection (a) dictates that the term of the patent, as opposed to specific claim(s), shall be extended:

> *The term of a patent* which claims a product, a method of using a product, or a method of manufacturing a product *shall be extended* in accordance with this section from the original expiration date of the patent . . . ."

§ 156(a) (emphases added).

The text of subsection (b), which sets forth "the rights derived from *any patent the term of which is extended* under this section," *id.* § 156(b) (emphasis added), is equally clear that § 156 applies to the term of the patent, not individual claim(s). The restrictions on the "rights derived" set forth in subsection (b) do not suggest otherwise. Subsection (b) was intended not to restrict the extension to particular claims, but rather to limit the effect of the extension. *Id.* (stating, for example, that for patents that claim a product, the rights in the extended term are "limited to any use approved for the product"). As the accompanying 1982 House Report explained: "[I]f a chemical is subjected to regulatory review for new drug uses, but is also marketed for other commercial uses, the patent term extension would apply only to the new drug uses for which regulatory review was required." H.R. Rep. No. 97-696, at 10 (1982).

Thus, neither § 156(a) nor § 156(b) supports Novartis's position that § 156 applies only to particular claims. A patent as a whole is extended even though its effect may be limited to certain of its claims. Novartis nonetheless contends that the extension must apply on a claim-by-claim basis because § 156(d)(1) requires an application for a patent term extension to identify each claim that claims the approved product or method of using or manufacturing the approved product. 35 U.S.C. § 156(d)(1)(B). Yet subsection (d)(1) merely lists the required contents of an application for a patent term extension. Subsections (a) and (b), on the other hand, set forth the legal effect of the patent term extension itself.[6]

In sum, in light of the plain language of § 156, and absent any indication that Congress intended that the extension should apply only to particular claims, we decline to adopt Novartis's arguments.

To the extent Novartis contends that the restrictions under § 156(b) on the rights derived from the extension of the '112 patent prevented Genetics from asserting claims 1, 5, and 10 in this § 291 action, we also disagree. Novartis concedes that claim 9 covers Refacto®, the approved product for which Genetics received the patent term extension. Because claim 9 depends from claims 1 and 5, those claims must also cover Refacto®. *See* 35 U.S.C. § 112 ¶ 4. Regarding claim 10, Novartis incorrectly asserts that "the district court construed claim 10 as not covering the active ingredient of ReFacto®." Def.-Appellee's Br. at 63. In fact, the district court noted that,

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[6] In *Boehringer Ingelheim International GMBH v. Barr Laboratories, Inc.*, 592 F.3d 1340, 1349 (Fed. Cir. 2010), a case involving obviousness-type double patenting, we suggested in passing that a patent term extension might apply only to specific claims. That dictum was not cited in support of either party's position in this case.

under its claim construction, "ReFacto® *may* not be encompassed by claim 10." *Genetics*, 687 F. Supp. 2d at 497 n.14 (emphasis added). The court thus did not make a factual finding on the issue of whether claim 10 of the '112 patent covers ReFacto®, and we decline to do so for the first time on appeal. *See Sage Prods., Inc. v. Devon Indus., Inc.*, 126 F.3d 1420, 1426 (Fed. Cir. 1997).

Finally, we also reject Novartis's related argument that no patent extended under § 156 can form the basis of a § 291 interfering patents action. The statutory text does not suggest that rights afforded by § 156 are so limited. And, as the district court correctly noted, *Genetics*, 687 F. Supp. 2d at 497, the legislative history advises against Novartis's interpretation: the 1984 House Report discussing the Hatch-Waxman Act provides that "*all provisions of the patent law apply* to the patent during the period of extension." H.R. Rep. No. 98-857, pt. 1, at 39 (emphasis added).

III. Interference In Fact

The patent laws recognize two types of actions involving interfering claims. An "interference" action under 35 U.S.C. § 135 can be declared by the PTO "[w]henever an application is made for a patent which . . . would interfere with any pending application, or with any unexpired patent." An "interfering patents" action under 35 U.S.C. § 291 permits "[t]he owner of an interfering patent [to seek] relief against the owner of another by civil action." This case is an appeal from an interfering patents suit under § 291 to determine the priority of invention between certain issued patents. *See Slip Track Sys., Inc. v. Metal Lite, Inc.*, 159 F.3d 1337, 1341 (Fed. Cir. 1998).

The first step in a § 291 interfering patents action is the determination whether an interference in fact exists between claims of the two patents. *Medichem, S.A. v.*

Rolabo, S.L., 353 F.3d 928, 934 (Fed. Cir. 2003). This requires application of a "two-way test," which, as discussed below, involves underlying questions of anticipation and obviousness under 35 U.S.C. §§ 102, 103. *Id.* at 932. Accordingly, the standards of review for an interference in fact mirror those of anticipation and obviousness inquiries. *Id.*

Anticipation and obviousness require the court to compare the properly construed claims to the available prior art. *Oakley, Inc. v. Sunglass Hut Int'l*, 316 F.3d 1331, 1339 (Fed. Cir. 2003). If "each and every limitation is found either expressly or inherently in a single prior art reference," then the claim is invalid under § 102 for anticipation. *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1375 (Fed. Cir. 2006) (internal quotation marks omitted). We review a finding of anticipation for clear error. *Zenon Envtl., Inc. v. U.S. Filter Corp.*, 506 F.3d 1370, 1377 (Fed. Cir. 2007). Obviousness under § 103 is a question of law based on underlying factual determinations. *Oakley*, 316 F.3d at 1339. We review the legal conclusion of obviousness *de novo* and the underlying findings of fact for clear error. *Id.*

An interference in fact under § 291 requires that the two patents claim "the same or substantially the same subject matter." *Slip Track*, 304 F.3d at 1263. Interfering subject matter is defined by courts in the same manner as in the PTO—by using the "two-way test." *Medichem*, 353 F.3d at 934. Under the PTO's regulations, "[a]n interference exists if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party and vice versa." 37 C.F.R. § 41.203(a). In other words, for two claims to interfere, each claim must anticipate or render obvious the other; failure of either claim to anticipate or render obvious the other defeats the test for

interfering patents. *Medichem*, 353 F.3d at 935 ("[T]here can be no interference-in-fact without satisfaction of each leg of the two-way test.").

A. There is no interference in fact between the asserted claims of the '112 patent and the '620 patent

Genetics argues that the district court erred by failing to find that an interference in fact existed between the allegedly interfering claims. According to Genetics, the court erroneously determined that all of the allegedly interfering claims of the Novartis patents require binding to vWF, when in fact that is not an explicit claim limitation. Moreover, Genetics asserts, the court incorrectly applied the two-way test in finding no interference in fact.

Regarding the allegedly interfering claims in the '112 and '620 patents in particular, Genetics maintains that the amino acid deletion claimed by the '620 patent is subsumed entirely by the deletion claimed by the '112 patent; thus, the '620 patent's claims would have been *prima facie* obvious over the allegedly interfering claims of the '112 patent. Genetics further contends that the district court misunderstood the testimony of its expert, Dr. Phillip Fay, who stated that with knowledge of the deletion points claimed in the '112 patent (*i.e.*, amino acids 740 and 1690) it would have been obvious to select the deletion points claimed in the '620 patent (*i.e.*, amino acids 740 and 1649) because the latter points were known *in vivo* cleavage points of the full- length Factor VIII protein. Genetics does not allege error in the district court's determination that the '112 patent's claims would not have anticipated the '620 patent's claims. As for the second leg of the two-way test, Genetics contends that the district court erred by failing to find that the '620 patent's claims anticipate the '112 patent's claims.

Novartis responds that there is no interference in fact between the allegedly interfering claims of the '112 patent and the Novartis patents. Novartis contends that the two-way test is not satisfied because the broader range of deletions permitted by the claims of the '112 patent does not anticipate or render obvious the narrower range claimed in the Novartis patents. Novartis asserts that only the claimed Novartis proteins retain the a3 region and possess the increased stability associated with vWF binding, and even if this increased stability was not known as of the priority dates of the Novartis patents, that property may nonetheless support the claimed proteins' nonobviousness. Novartis then proceeds on a claim-by-claim basis to demonstrate why, in its view, the district court correctly concluded that the claims of the '112 patent do not interfere with the claims of the Novartis patents.

As we shall explain, we agree with the district court's determinations that (1) claim 1 of the '112 patent would not have rendered obvious claim 68 of the '620 patent; (2) claim 5 of the '112 patent would not have rendered obvious claim 74 of the '620 patent; and (3) claim 9 of the '112 patent would not have rendered obvious claim 83 of the '620 patent. We therefore affirm the district court's conclusion that the two-way test is not satisfied and that there is no interference in fact between these claims.

The district court started (and ultimately ended) by examining the first leg of the two-way test, *i.e.*, whether the claims of the '112 patent, if prior art, would invalidate the claims of the '620 patent. *Genetics*, 687 F. Supp. 2d at 497-500. The court noted that these claims differ in terms of the nature of the truncated Factor VIII proteins encoded by the nucleic acids. *Id.* at 498. The court then proceeded to analyze the differences between the groups of proteins claimed in the two patents.

To summarize the district court's analysis, the claimed truncated Factor VIII proteins in the '112 and '620 patents differ in terms of the size of the permitted amino acid deletions, the location of the permitted amino acid deletions, and the degree of allowable amino acid substitutions. In particular, the deletion in claim 1 of the '112 patent (and, by extension, claims 5 and 9) ranges in size from 581 to 949 amino acids and is located between amino acids 740 and 1690,[7] whereas the deletion in claims 68, 74, and 83 of the '620 patent ranges in size from 889 to 909 amino acids and is located between amino acids 740 and 1649. The '620 patent's claims permit substitution of up to 10% of the amino acids, whereas the '112 patent's claims do not. Importantly, it is undisputed that the '112 patent permits deletion of amino acids in the 1649-1689 region, whereas the '620 patent does not.

In view of these structural differences between the proteins claimed in the '112 and '620 patents, the district court correctly required as part of the *prima facie* obviousness inquiry the identification of some reason that would have prompted a researcher to modify the prior art compounds in a particular manner to arrive at the claimed compounds. *Id.* at 500; *see also Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007); *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc) ("[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, *where the prior art gives reason or motivation to make the claimed compositions*, creates a *prima facie* case of obviousness." (emphasis added)); *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985) (To establish *prima facie* obviousness, "there must

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[7] As the district court found, this deletion range forms a group of protein variants numbering about 68,000. *Genetics*, 687 F. Supp. 2d at 498.

be adequate support in the prior art for the . . . change in structure."); *In re Lalu*, 747 F.2d 703, 705 (Fed. Cir. 1984) ("In determining whether a case of prima facie obviousness exists, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the claimed substitution or other modification."). This principle was reaffirmed by the Supreme Court's opinion in *KSR International Co. v. Teleflex Inc.*, which acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." 550 U.S. 398, 418 (2007).

The district court correctly found that Genetics failed to establish any such reason for modifying the group of proteins claimed in the '112 patent to produce the group claimed in the '620 patent. *Genetics*, 687 F. Supp. 2d at 500. As of the 1986 priority date of the '620 patent, those of skill in the art understood the inactive B domain of the Factor VIII protein to be "essentially delimited by residues 740 and 1689"—*i.e.*, to include the amino acids in the a3 region. *Id.* (quoting J.A. 6117, John J. Toole et al., *A Large Region (≈95 kDa) of Human Factor VIII Is Dispensable for In Vitro Procoagulant Activity*, 83 Proc. Nat'l Acad. Sci. 5939, 5939 (1986)). Indeed, as the district court noted, Dr. Randal Kaufman, a former Genetics scientist, confirmed this fact. During his deposition, he stated that, in 1986, the 1649-1689 amino acid region was understood to be part of the B domain. *Id.*

Genetics argues that amino acid 1649 was one of the known *in vivo* cleavage sites on the Factor VIII protein, and, on account of this fact, it "would be readily apparent" to make a truncated Factor VIII protein that retained amino acids in the 1649-1689 region, contrary to the teachings of the '112 patent. Br. of Pl.-Appellant at 35.

In support of its position, Genetics cites two articles published in 1984 that disclosed a number of *in vivo* cleavage cites on the Factor VIII protein. J.A. 5181-86, 5195-200; *see also* J.A. 3781-83. Yet Genetics concedes that it was not known prior to the filing of the '620 patent that amino acids 1649-1689 were critical to maintain vWF binding. Br. of Pl.-Appellant at 35. And Genetics offers no basis for its assertion that the mere existence of *in vivo* cleavage points between particular amino acid residues would have provided one of ordinary skill with a reason or motivation to make the particular truncated proteins claimed in the '620 patent. *Genetics*, 687 F. Supp. 2d at 500.

Indeed, those same *in vivo* cleavage sites were known as of the 1985 priority date of the '112 patent, but the proteins claimed in the '112 patent do not require retention of amino acids 1649-1689. That indicates the weakness of Genetics' position and supports the district court's conclusion that mere knowledge of *in vivo* cleavage sites on Factor VIII would not have provided a sufficient reason for making the proteins claimed in the '620 patent. *Id.*

Genetics' arguments also run contrary to the research objectives of those in the field of truncated Factor VIII proteins. The district court found that research in the Factor VIII field focused on "finding a *smaller* recombinant protein that mimicked the biological activity of Factor VIII in humans." *Id.* at 492 (emphasis added). That is consistent with the disclosure of the '112 patent, which is focused on making "proteins which have procoagulant activity similar to that of factor VIII:C and also have substantially lower molecular weight." '112 patent col.2 ll.10-13; *see also id.* col.20 ll.9-14 ("I contemplate that my compounds may be produced by recombinant DNA techniques at a much lower cost than is possible for production of human factor VIII. The host organisms

should more efficiently process and express the *substantially simpler molecules of this invention*." (emphasis added)). Genetics fails to explain why, with knowledge of the claimed range of proteins in the '112 patent, one of ordinary skill would have sought out a range encompassing *larger* recombinant proteins (*i.e.*, proteins having smaller amino acid deletions), such as the range of proteins claimed in the '620 patent. Thus, contrary to Genetics' arguments, the mere existence of an *in vivo* cleavage point, without more, would not have provided the requisite "reason or motivation," *Dillon*, 919 F.2d at 692, to manipulate the claimed proteins of the '112 patent at that cleavage point to make those claimed in the '620 patent.

The dissent, in arguing for obviousness, relies on those claimed proteins of the '112 patent that retain the a3 region. Dissent Op. at 8-9. But the dissent selectively parses the prior art disclosure with impermissible hindsight. Each disputed claim of the '112 patent teaches deletion of the a3 region in some variants, thus leading away from a requirement that that region be retained. Viewed as a whole, the prior art would not have prompted one of ordinary skill to require retention of the a3 region. *See Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987) ("[A] prior patent must be considered in its entirety, i.e., as a *whole*, including portions that would lead away from the invention in suit[.]").

Further, the dissent challenges well-established law requiring the identification of some reason that would have prompted a researcher to substantially modify a prior art compound to produce the claimed compound. Dissent Op. at 3-5. While the dissent accepts that the prior art here provided "no suggestion or stated need for further experimentation" and "no motivation to optimize for some value within the range" of proteins disclosed by the '112 patent, *id.* at 8, the dissent nonetheless contends

that, because of "structural similarity" in the patented proteins, no reason for chemical modification need be shown. The dissent vastly oversimplifies the differences in the claimed proteins, however. One of ordinary skill would appreciate that the claimed truncated proteins vary enormously in structure: for example, the a3 region alone contains 40 amino acid residues and has a relative molecular mass of about 4,500. J.A. 5199. In contrast, the homologs, analogs, and isomers referenced by the dissent typically differ, at most, by only a few atoms—and even in cases involving such ostensibly minor chemical differences, *prima facie* obviousness is by no means inevitable. *See, e.g.*, *Grabiak*, 769 F.2d at 730 (reversing the PTO's finding of *prima facie* obviousness even though the prior art compound differed from the claimed compound "only by the presence . . . of a sulfur atom instead of a particular oxygen atom"). The dissent's oversimplification violates our longstanding admonition that "generalization is to be avoided insofar as specific structures are alleged to be *prima facie* obvious one from the other." *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992) (citing *Grabiak*, 769 F.2d at 731). On the facts of this case, the nontrivial differences in the proteins at issue compel the requirement of identifying a reason for the chemical modification.

Genetics asserts that the district court's conclusion of nonobviousness is contrary to *In re Peterson*, 315 F.3d 1325 (Fed. Cir. 2003). According to Genetics, *Peterson* holds that a broad range necessarily renders obvious a narrower range falling within that broader range. That is incorrect. In *Peterson*, we stated that "[a] *prima facie* case of obviousness *typically* exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art." *Id.* at 1329 (emphasis added). The facts here do not present the "typical[]" case contemplated in *Peterson*, however.

First, we noted in *Peterson* that "we do not have here any assertion that the disclosed range is so broad as to encompass a very large number of possible distinct compositions," and that our reasoning did not necessarily extend to "a disclosed range of such breadth." *Id.* at 1330 n.1. In this case, in contrast, about 68,000 protein variants are encompassed by the claims of the '112 patent. *Genetics*, 687 F. Supp. 2d at 498. Genetics fails to acknowledge this important distinction.

Moreover, in *Peterson* our holding was based on the recognition that "[t]he normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." 315 F.3d at 1330. As noted above, however, the only evidence of motivation in the present record is that of researchers to make smaller, truncated proteins to solve the cloning difficulties associated with the large size of Factor VIII. That motivation would not have supplied researchers with a reason to make the group of proteins claimed in the '620 patent encompassing larger truncated proteins than those claimed in the '112 patent. Simply put, the typical desire of scientists to find an optimum value within a narrow disclosed range, *id.*, does not apply to the facts of this case.

The dissent also attempts to shoehorn the facts of this case into our holding in *Peterson*. But the Novartis inventors did not simply "[s]elect[] a narrow range from within a somewhat broader range," as did the *Peterson* inventors when selecting the range of "about 1–3%" rhenium from the prior art range of "0–7%" rhenium. *Peterson*, 315 F.3d at 1329-30. As noted, the '112 patent contains 68,000 truncated variants of a protein made up of 2,332 amino acids, and the allegedly interfering inventions differ in terms of the size of the permitted amino acid deletions,

the location of those deletions, and the degree of allowable amino acid substitutions. The facts here present a case where the "disclosed range is so broad as to encompass a very large number of possible distinct compositions" thus "requir[ing] nonobvious invention," not a case, as in *Peterson*, where prior art "ranges that are not especially broad invite routine experimentation to discover optimum values." *Id.* at 1330 n.1. On this point the dissent appears to agree, conceding not only that the prior art '112 patent claims a "large breadth of possible protein variants," but also that "there was no motivation to optimize for some value within the range" disclosed by prior art. Dissent Op. at 8. Viewed in context, our holding in *Peterson* does not extend to the facts of this case.

We therefore hold that the district court did not err in concluding that the '620 patent's claims would not have been *prima facie* obvious over the '112 patent's claims.

We also reject Genetics' contention that the district court erred by crediting the unexpected results of the claimed invention in the '620 patent as part of its obviousness analysis. Genetics maintains that, because the importance of the a3 region to vWF binding was not known as of the filing date of the '620 patent, the retention of the a3 region in the claimed proteins of the '620 patent and their corresponding ability to bind vWF may not be relied upon to demonstrate the unexpected results of those proteins. We disagree. Our case law is clear that the structure of a claimed compound and its properties are inseparable for purposes of § 103. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("For chemical compounds, the structure of the compound and its properties are inseparable considerations in the obviousness determination."); *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963) ("From the standpoint of patent law, a

compound and all of its properties are inseparable; they are one and the same thing.").

Our law is equally clear that every property of a claimed compound need not be fully recognized as of the filing date of the patent application to be relevant to nonobviousness. *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) ("There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack."). For those reasons, we have held that evidence of unexpected results may be used to rebut a case of *prima facie* obviousness even if that evidence was obtained after the patent's filing or issue date. *Id.* ("Evidence [of unexpected results] developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application."); *In re Khelghatian*, 364 F.2d 870, 876 (CCPA 1966) (holding the claimed invention nonobvious in view of post-filing evidence of an unexpected property not disclosed in the specification, while noting that the evidence "[wa]s directed to that which 'would inherently flow' from what was originally disclosed" (quoting *In re Zenitz*, 333 F.2d 924, 927 (CCPA 1964)); *see also Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006) ("This court will not ignore a relevant property of a compound in the obviousness calculus." (citing *Lalu*, 747 F.2d at 707)).

The dissent, like Genetics, misstates our precedent regarding secondary considerations of nonobviousness. Dissent Op. at 10-17. Although the § 103 analysis remains properly focused "at the time the invention was

made," it would be error to prohibit a patent applicant or patentee from presenting relevant indicia of nonobviousness, whether or not this evidence was available or expressly contemplated at the filing of the patent application. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Relevant secondary considerations often are not manifest even until well after the issuance of a patent. The dissent would require either an express prediction of unexpected properties in the patent specification or a showing of the inventors' contemporaneous knowledge of such properties before the PTO or any court could consider such probative evidence. Our precedent contains no such requirement. *See, e.g.*, *In re Chu*, 66 F.3d 292, 298-99 (Fed. Cir. 1995) (noting that evidence supporting nonobviousness need not be contained within the specification, and holding that the PTO erred by failing to consider unexpected results even though the specification was "virtually silent on the matter"); *see also KSR*, 550 U.S. at 406 ("The analysis is objective[.]"). Even so, the dissent's supposed requirement is an incorrect basis for rejecting the evidence in this case, where the patents expressly disclose the claimed proteins' high stability and ability to bind vWF, *e.g.*, '447 patent col.2 ll.29-31, col.8 ll.19-22; '620 patent col.2 ll.30-32, col.8 ll.25-29, and where the parties do not dispute that the Novartis inventors' development of the claimed proteins used a technique that excluded any protein that did not bind vWF, J.A. 3707-08.

Consequently, the district court did not err in its nonobviousness analysis by considering, as evidence of unexpected results, the ability of the claimed proteins to bind vWF, even if, as Genetics contends, the role of the a3 region was not appreciated as of the '620 patent's priority date. *Genetics*, 687 F. Supp. 2d at 500.

Genetics alleges yet another error in the district court's nonobviousness determination. Genetics contends that Novartis's proffered unexpected results are not commensurate with the full scope of its claims because the Novartis patents permit amino acid substitution that may reduce or eliminate vWF binding. Again, we disagree. Whether an invention has produced unexpected results is a question of fact, *In re Harris*, 409 F.3d 1339, 1341 (Fed. Cir. 2005), and we do not perceive clear error in the district court's decision to credit Novartis's evidence of vWF binding. The district court explicitly recognized that the claims of the Novartis patents permit substitution (*i.e.*, replacement of one amino acid with another) in up to 10% of the protein's amino acids. *Genetics*, 687 F. Supp. 2d at 499, 501. Notwithstanding that finding, Genetics points to an article published by Leyte in 1991 demonstrating that the substitution of the amino acid phenylalanine for tyrosine at position 1680 in the a3 region eliminated vWF binding but retained procoagulant activity in the resulting B-domain deleted protein. *See* Anja Leyte et al., *Sulfation of Tyr^{1680} of Human Blood Coagulation Factor VIII Is Essential for the Interaction of Factor VIII with von Willebrand Factor*, 266 J. Biological Chem. 740, 744 (1991); J.A. 6084-90. Based on this information, Genetics asserts that the unexpected result of improved stability through vWF binding is not commensurate in scope with the claims of the '620 patent, and therefore must be ignored.

The district court's opinion did not explicitly address the Leyte article. Even taking Genetics' assertions as true, however, the Leyte article demonstrates at most that one particular amino acid substitution at one particular position eliminates vWF binding—in a claimed truncated protein of between 1,424 and 1,444 total amino acids. This solitary fact does not undermine the district

court's decision to credit the vWF binding properties of the proteins claimed in the Novartis patents—properties that Genetics itself concedes are possessed by truncated Factor VIII proteins retaining the a3 region.

While we have held that unexpected results must be commensurate in scope with the claims, we have not required absolute identity of scope; rather, we have rejected unexpected results where the evidence was plainly disproportionate to the scope of the claim. *See, e.g.*, *Peterson*, 315 F.3d at 1331 (affirming obviousness where the applicant claimed an alloy with 1–3% rhenium, yet presented unexpected results only for 2% rhenium, and evidence suggested that 3% rhenium possessed inferior properties); *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983) (concluding that unexpected results "limited to sodium only" were not commensurate in scope with claims to a catalyst having "an alkali metal"); *In re Greenfield*, 571 F.2d 1185, 1189 (CCPA 1978) (affirming the obviousness of a genus containing "several hundred compounds," where unexpected results were proved for "only one" such compound); *cf. In re Glatt Air Techniques, Inc.*, 630 F.3d 1026, 1030 (Fed. Cir. 2011) (stating that objective evidence of commercial success relating "only to a single embodiment" should be considered even if claim covers "multiple embodiments"). Indeed, a rigid requirement of absolute identity that ignores relevant properties of claimed compounds would defy the mandate of § 103 requiring consideration of the claimed "subject matter as a whole." On the facts of this case, it was not improper for the district court, in its nonobviousness analysis, to weigh Novartis's proffered evidence of unexpected results.

Because on appeal Genetics challenges only the district court's conclusion of nonobviousness, we need not review the court's determination that the '112 patent's claims would not, if prior art, anticipate the '620 patent's

claims, *Genetics*, 687 F. Supp. 2d at 499. In view of our conclusion that the claims of the '112 patent would not invalidate the claimed subject matter of the '620 patent, we also need not consider whether the reverse is true. Because the two-way test was not met, we conclude that the district court did not err in holding that there was no interference in fact between claims 68, 74, and 83 of the '620 patent and claims 1, 5, and 9 of the '112 patent, respectively.

B. There is no interference in fact between the asserted claims of the '112 patent and the '447 patent

Genetics maintains that the district court erred by finding no interference in fact between the allegedly interfering claims of the '112 and '447 patents. Genetics argues in general that the court committed the same errors as with the allegedly interfering claims of the '112 and '620 patents. As explained above, we reject those arguments.

Regarding claim 9 of the '112 patent and claim 1 of the '447 patent, Genetics additionally asserts that it would have been obvious to use the method of claim 9 to make the composition of claim 1, because there is no patentable distinction between a method of making a protein and the protein itself. We need not address this argument, however, because it is premised on Genetics' flawed assertion (the basis for which we rejected above) that the court erred by finding a patentable distinction between the proteins of claim 9 of the '112 patent and those of claim 1 of the '447 patent. Genetics does not contend on appeal that claim 9 of the '112 patent would anticipate claim 1 of the '447 patent. Accordingly, at least the first leg of the two-way test fails for the alleged interference in fact between claim 9 of the '112 patent and

claim 1 of the '447 patent. *Genetics*, 687 F. Supp. 2d at 501.

Regarding claim 10 of the '112 patent and claim 1 of the '447 patent, Genetics contends that the district court erred because each claim, as prior art, would render the other obvious. We disagree. Taking claim 1 of the '447 patent as prior art to claim 10 of the '112 patent, Genetics again asserts that "it would be readily apparent" to one of ordinary skill in the art to modify the protein of claim 1 of the '447 patent to make the three proteins of claim 10 of the '112 patent. Br. of Pl.-Appellant at 43. As an initial matter, Genetics, which describes the necessary modifications as "smaller deletions," *id.*, misconstrues the scope of claim 10. As the district court correctly determined, whereas claim 1 of the '447 patent deletes the complete B domain (909 amino acids), claim 10 of the '112 patent claims three specific proteins, two of which have smaller deletions (581 and 880 amino acids) and one of which has a *larger* deletion (915 amino acids) than the B domain. *Genetics*, 687 F. Supp. 2d at 501. The larger deletion ranges from amino acid 759 to 1675, which includes part of the a3 acidic region.

As the district court noted, Genetics failed to present evidence showing why one of ordinary skill would modify the protein of claim 1 of the '447 patent to make the three different proteins of claim 10 of the '112 patent. *Id.* at 502. Genetics alleges that obviousness of a chemical compound does not require evidence of some reason for modification. As we explained above, however, this reflects a misunderstanding of the law. Moreover, Genetics' position is belied by the testimony of Debra Pittman, a Genetics scientist who worked with Toole on Factor VIII proteins. As explained by Pittman, a researcher intent on designing a new truncated Factor VIII protein would first identify the amino acid regions he or she wished to delete,

and only then would consider particular protein design strategies:

> Q. What steps were involved in going about making the deletion variants of Factor VIII that Dr. Toole had in mind?
>
> A. Well, *first*, was to identify the regions that he wanted to delete, and *then* devising a scheme to make those deletions, using either restriction sites or oligonucleotides.

J.A. 3612 (emphases added). Common sense dictates that "want[ing] to delete" a particular amino acid region implies that a reason must exist for that deletion. Pittman's testimony thus corroborates what our case law requires for proving that a claimed compound would have been obvious: the identification of some reason why one of ordinary skill would make the necessary chemical modifications to arrive at the claimed compound. *Takeda*, 492 F.3d at 1357; *Dillon*, 919 F.2d at 692.

We therefore affirm the district court's conclusion that claim 1 of the '447 patent would not have rendered obvious claim 10 of the '112 patent. Moreover, Genetics does not contend that claim 1 would have anticipated claim 10. Because one leg of the two-way test fails, we need not consider the second leg. *Medichem*, 353 F.3d at 935.

Accordingly, we agree with the district court's determinations that there is no interference in fact between claims 9 and 10 of the '112 patent and claim 1 of the '447 patent.

CONCLUSION

For the foregoing reasons, we affirm the district court's order granting Novartis's motion to dismiss due to the absence of an interference in fact between the alleg-

edly interfering claims. In particular, we conclude that the expiration of the '112 patent following the district court's entry of final judgment did not divest our court of appellate jurisdiction; that the patent term extension of the '112 patent applied to all of the allegedly interfering claims; and that there is no interference in fact between (1) claim 1 of the '112 patent and claim 68 of the '620 patent, (2) claim 5 of the '112 patent and claim 74 of the '620 patent, (3) claim 9 of the '112 patent and claim 83 of the '620 patent, and (4) claims 9 and 10 of the '112 patent and claim 1 of the '447 patent.

AFFIRMED.

United States Court of Appeals for the Federal Circuit

GENETICS INSTITUTE, LLC,
Plaintiff-Appellant,

v.

NOVARTIS VACCINES AND DIAGNOSTICS, INC.,
Defendant-Appellee.

2010-1264

Appeal from the United States District Court for the District of Delaware in Case No. 08-CV-0290, Judge Sue L. Robinson.

DYK, *Circuit Judge*, concurring-in-part and dissenting-in-part.

I join Parts I and II of the majority's opinion, but I respectfully dissent from Part III. In my view, the majority erred in holding that the asserted claims of the '112 patent would not render obvious the asserted claims of the '620 and '447 patents (collectively the "Novartis patents") and in holding that there was, accordingly, no interference-in-fact.

In the mid-1980s, the '112 patent and the Novartis patents were co-pending before the Patent and Trademark Office ("PTO"). At the time, there was concern that pathogens, like the HIV and hepatitis virus, were con-

taminating the supply of hemophilia treatments made from human Factor VIII proteins. Genetics and Novartis thus competed to clone safer, synthetic forms of Factor VIII. Because of the large size of Factor VIII, however, yields from the host cells expressing the gene were very low. The patents-in-suit were directed to solving this problem by producing truncated forms of Factor VIII that would nonetheless maintain the same procoagulant (i.e. blood-clotting) activity of the full-length protein.

By comparing human Factor VIII to porcine Factor VIII, Genetics discovered that, while significant regions of human and porcine Factor VIII were homologous, the large B domain of human Factor VIII diverged greatly from the B domain of porcine Factor VIII. Because porcine Factor VIII was nonetheless effective in treating human hemophilia patients, Genetics deduced that the B domain was superfluous and could be excised without compromising Factor VIII's procoagulant activity. This discovery led to the innovations of the '112 patent. The truncated Factor VIII proteins of the '112 patent have a "substantially lower molecular weight," '112 patent col.2 ll.10–12, but have "similar procoagulant activity" to the full-length version of human Factor VIII, *id.* col.1 ll.8–9. These "simpler molecules" were advantageous because they could "be produced . . . at a much lower cost." *Id.* col.20 ll.9–14. Around the same time, Novartis scientists were researching a more efficient way to clone Factor VIII. The objective of the Novartis patents was, similarly, to design a truncated protein with "activity equal to that of cloned full-length Factor VIII[ ]." '447 patent col.2 ll.18–19; '620 patent col.2 ll.18–19.

All of the patents-in-suit are directed to truncated Factor VIII proteins in which the B domain is either partially or completely deleted. These proteins differ mainly in one respect: while the Novartis proteins retain

the a3 region, the proteins of the '112 patent permit (but do not require) deletions in that region. As it turned out, years later, independent researchers discovered that the a3 region had the previously unforeseen benefit of being able to bind to von Willebrand Factor ("vWF"). Though it had been known since the late 1970s that vWF had a stabilizing effect on Factor VIII, the location of vWF binding in the a3 region was not known until at least 1988, years after the Novartis patents were filed, as the Novartis witnesses themselves described. One Novartis expert admitted that there was "nothing in the scientific literature by April 1986 suggesting the importance of [the a3 region] to interactions between Factor VIII and vWF." J.A. 2683. And one of the inventors testified that the Novartis patents "do[ ] not specifically tell you [the location of the vWF binding sites within the Factor VIII protein], [because] that was not the intention of the patent, to specify the binding to von Willebrand Factor." J.A. 3732. The majority does not dispute this, stating that "Genetics concedes that it was not known prior to the filing of the '620 patent that [the a3 region] was critical to maintain vWF binding." Maj. Op. at 24.

In my view, there are four fundamental flaws with the majority's conclusion of non-obviousness. First, the majority holds that the Novartis patents could not be obvious over the '112 patent unless Genetics could identify "some reason that would have prompted a researcher to modify" the '112 patent to retain the a3 region. *Id.* at 21. However, a requirement for a motivation to retain the a3 region should not be the test where, from an objective standpoint, no inventor—including the Novartis inventors themselves—could have been aware of the benefits of retaining the a3 region at the time of the invention. Rather, we should look to whether there was enough structural similarity between the patents-in-suit to make

a prima facie case of obviousness, given what was known to the inventors at the time of the invention.

Our precedent has established that "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995). Moreover, such structural similarity (i.e., an established structural relationship between a prior art compound and the claimed compound) can give rise to a case of prima facie obviousness. *Id.* Thus, "a known compound may suggest its [homologs,] analogs, or isomers" because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* In *In re Jones*, 958 F.2d 347, 349 (Fed. Cir. 1992), we acknowledged that "particular types or categories of structural similarity[,] without more[,] have, in past cases, given rise to prima facie obviousness." (citing *In re Dillon*, 919 F.2d 688, 692–94 (Fed. Cir. 1990) (tri-orthoesters and tetra-orthoesters), cert. denied, 500 U.S. 904 (1991)); *In re May*, 574 F.2d 1082 (CCPA 1978) (stereoisomers); *In re Wilder*, 563 F.2d 457 (CCPA 1977) (adjacent homologs and structural isomers); *In re Hoch*, 428 F.2d 1341 (CCPA 1970) (acid and ethyl ester)).[1] In this case, the truncated Factor VIII

[1] *See also In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997) (finding a claimed enterokinase recognition sequence containing the amino acid sequence Phe-Pro-Leu was merely "an obvious functional equivalent" to prior art sequences that included arrangements of Phe-Pro-Ile and Leu-Pro-Leu); *In re Dillon*, 919 F.2d 688, 693 (Fed. Cir. 1990) (finding a prima facie case of obviousness where the prior art tri-orthoester compound was found to be equivalent to the claimed tetra-orthoester compound and the use of the tri-orthoester as a fuel additive was expected to produce essentially the same result as the use

proteins of the '112 patent and the truncated Factor VIII proteins of the Novartis patents are not merely homologs, analogs, or isomers—they are all variants of the *exact same* protein, exhibiting the *exact same* procoagulant functions. Here, the majority found that the patents-in-suit differed in terms of the size of the permitted amino acid deletions, the location of the deletions, and the degree of allowable amino acid substitutions. However, these differences are of no consequence to the core procoagulation function of the proteins. This is so because the main innovation of the patents-in-suit is the discovery that the B domain is completely unnecessary to procoagulation. Consequently, it does not matter whether the deletions are large or small or whether the deletions begin at one amino acid or another. Any deletion in the B domain, ipso facto, would retain the procoagulation function of Factor VIII. The similarities in structure and function would provide the requisite motivation to modify the proteins of the '112 patent to obtain the proteins of the Novartis proteins. *See In re Dillon*, 919 F.2d 688, 696 ("[T]he fact that the claimed and the prior art compounds possessed the same activity were added factors in the establishment of a prima facie case.").

Second, under our prior authority, a prima facie case of obviousness can also exist if the range of an earlier patent incorporates the range of later patents.[2] That is

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of the tetra-orthoester); *In re Payne*, 606 F.2d 303, 313–15 (CCPA 1979) (discussing the presumption of obviousness based on close structural similarity).

[2] Though the majority does not appear to dispute that the broader range of deletions in the '112 patent subsumed the narrower range of deletions in the Novartis patents, I think the proper focus should be on the range of retentions, not the range of deletions. This is so because we are concerned with whether the Novartis patents can be differentiated based on what they retain rather than

the case here where it is clear that the range of retentions in the '112 patent fall within the range of retentions of the Novartis patents, as discussed above. Our case law has held that "[a] prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art." *In re Peterson*, 315 F.3d 1325, 1329–30 (Fed. Cir. 2003). "[E]ven a slight overlap in range establishes a prima facie case of obviousness." *Id.* at 1329; *see also In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (finding prima facie obviousness where range of prior art reference (100–600 Angstroms) overlapped the claimed range (50–100 Angstroms)); *In re Woodruff*, 919 F.2d 1575, 1578 (CCPA 1990) (holding a claimed invention obvious because claimed range ("more than 5% to about 25%" carbon monoxide) abutted range of prior art ("about 1–5%" carbon monoxide)); *In re Malagari*, 499 F.2d 1297, 1303 (CCPA 1974) (finding prima facie obviousness where the claimed range of the prior art reference (0.020–0.035% carbon) overlapped the claimed range (0.030–0.070% carbon)). Significantly, when "the claimed ranges are completely encompassed by the prior art, the conclusion [of obviousness] is even more compelling than in cases of mere overlap." *Peterson*, 315 F.3d at 1330.[3] Here, as in

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what they delete. Nonetheless, whether the focus is on deletions or retentions, there is still an overlap.

[3] We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." *Peterson*, 315 F.3d at 1329; *see Titanium Metals Corp. v. Banner*, 778 F.2d 775, 776, 783 (Fed. Cir. 1985) (concluding that a claim directed to an alloy containing "0.8% nickel, 0.3% molybdenum, up to 0.1% maximum iron, balance titanium" would have been prima facie obvious in view of a reference disclosing alloys containing 0.75% nickel, 0.25% molybdenum, balance

Peterson, the range of retentions or deletions in the Novartis patents overlap significantly with the range of the '112 patent, and are, in my view, prima facie obvious.

The majority, nevertheless, concludes that the compound here was not the "'typical[ ]' case" contemplated in *Peterson*, Maj. Op. at 26 (quoting 315 F.3d at 1329), pointing to a footnote in *Peterson* that opined:

> Although ranges that are not especially broad *invite routine experimentation to discover optimum values*, rather than require nonobvious invention, *we do not have here any assertion that the disclosed range is so broad as to encompass a very large number of possible distinct compositions*. We thus do not need to decide whether a disclosed range of such breadth *might* present a situation analogous to our cases involving the failure of a very broad disclosed genus of substances to render prima facie obvious specific substances within its scope.

315 F.3d at 1330 n.1 (emphases added). Because the majority found that the '112 patent claims encompassed a very large number of possible distinct compositions—nearly "68,000 truncated variants"—it declined to extend the reasoning in *Peterson* to a "disclosed range of such breadth." Maj. Op. at 27.

However, as the court in *Peterson* made clear, it is the facts of a particular case that will render it "typical" or not. 315 F.3d at 1329. An expansive range of variants should not per se defeat a prima facie case of obviousness. Moreover, the court's concern in *Peterson* was less the breadth of the claims, than the ability to conduct "routine

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titanium and 0.94% nickel, 0.31% molybdenum, balance titanium).

experimentation to discover optimum values." *Id.* at 1330 n.1. Narrower ranges would presumably invite more routine experimentation and "motivate[ ] [scientists] to determine where in a disclosed set of . . . ranges is the optimum combination," *see id.* at 1330, while broader ranges would presumably discourage such experimentation. Here, there is no suggestion or stated need for further experimentation to discover some "optimum range." As the majority acknowledges, the "typical desire of scientists to find an optimum value within a narrow disclosed range, *does not apply to the facts of this case*" because "the only evidence of motivation in the present record is that of researchers [trying] to make smaller, truncated proteins to solve the cloning difficulties associated with the large size of Factor VIII." Maj. Op. at 27 (emphasis added; internal citations omitted). Because there was no motivation to optimize for some value within the range of possible retentions, the large breadth of possible protein variants is of no consequence. In sum, I would find that the claims of the Novartis patents are prima facie obvious in view of the overlapping ranges of the '112 patent. The burden of proving nonobviousness should thus have shifted to the holder of the later-developed patent, in this case, Novartis. *Peterson*, 315 F.3d at 1330.

Third, the majority appears to suggest that the "ret[ention] of amino acids in the [a3] region" was "contrary to the teachings of the '112 patent." Maj. Op. at 23. This is wrong on the facts. The majority ignores that some variants of the '112 patent actually retain the a3 region and therefore have the ability to bind to vWF. For instance, claim 10 of the '112 patent claims a truncated Factor VIII protein having one of three specific deletions, two of which are the deletions of amino acids 981–1563 and 759–1640. *See* col.26 ll.28–34. These two deletions

clearly retain the a3 region (amino acids 1649–1689). Retention of the a3 region is also within the scope of retentions allowed by claim 1 of the '112 patent.[4] Therefore, many of the variants claimed in the '112 patent actually conserve the a3 region necessary for vWF binding. If, as the majority concludes, "the structure of a claimed compound and its properties are inseparable for purposes of § 103," it seems inconsistent to credit the a3 region in the Novartis compounds for giving rise to vWF binding while not doing the same for the compounds of the '112 patent. Maj. Op. at 28 (citing *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("For chemical compounds, the structure of the compound and its properties are inseparable considerations in the obviousness determination."); *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963) ("From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing.")).

The majority also urges that some variants of the '112 patent teach away from retaining the a3 region. The majority, however, ignores the fact that certain variants of the Novartis patents also teach away from keeping the a3 region intact, with the result that vWF binding is not achieved. In particular, the Novartis patents allow up to 10 percent of the amino acids in the Factor VIII protein to be substituted, including substitutions in the a3 region:

> [U]sually not more than 10, more usually not more than 5[%], preferably not more than about 1[%] of the amino acids in the chains will differ from the amino acids naturally present in the

[4] For example, claim 1 of the '112 patent teaches deletions that range from 581 to 949 amino acids. A more conservative deletion in this range could still leave intact the a3 region critical to vWF binding.

> Factor VIII[ ] . . . C domain[ ] . . . . Conservative substitutions include: . . . Phe[nylalanine] ←→ Tr[yptophan] ←→ Tyr[osine].

'620 patent col.4 ll.39–53. With the substitution of phenylalanine for tyrosine in the a3 region—that is, a "conservative substitution" expressly taught in the Novartis patents—vWF binding would be "completely abolished." *See* Anja Leyte et al., *Sulfation of Tyr-1680 of Human Blood Coagulation Factor VIII Is Essential for the Interaction of Factor VIII with von Willebrand* Factor, 266 J. Biological Chem. 740, 744 (1991), *available at* J.A. 6084–90 ("vWF binding was completely abolished" when "Tyr[osine]-1680 [in the a3 region] . . . was replaced by phenylalanine."). In this respect, the '112 patent and the Novartis patents all teach some variants that retain the a3 region and some variants that teach away from retaining the a3 region necessary for vWF binding.

Finally, the majority found that the later-discovered, undisclosed benefits of retaining the a3 region qualified as unexpected results to help defeat the prima facie case of obviousness, even though the role of the a3 region was not appreciated as of the Novartis patents' priority date. I disagree. The majority's finding of nonobviousness is based entirely on hindsight and happenstance, and not on what the inventors knew at the time the Novartis patents were filed. *See* 35 U.S.C. § 103(a) (stating that an invention cannot be patented if "the subject matter as a whole would have been obvious *at the time the invention was made*") (emphasis added). The Supreme Court has never suggested that it is permissible to look beyond the inventor's knowledge at the time of patent filing in determining unexpected results. To the contrary, the Supreme Court has characterized such after-acquired knowledge as an "afterthought," *Ball & Socket Fastener Co. v. Kraetzer*, 150 U.S. 111, 117, 116–17 (1893), and has declined to give

it weight in determining patent validity. For example, in *Graham v. John Deere Co.*, 383 U.S. 1, 25 (1966), the Supreme Court rejected the patentee's argument that his patented plow had the unexpected result of additional "flex" over the prior art, noting that "[n]o 'flexing' argument was raised in the Patent Office." *See also Lincoln Eng'g Co. v. Stewart-Warner Corp.*, 303 U.S. 545, 550 (1938) ("If this [new feature] were so vital an element . . . it is strange that all mention of it was omitted [in the specification].").

Similarly, our court and our predecessor court have rejected later-acquired knowledge as supporting unexpected results. Early cases from the Court of Customs and Patent Appeals ("CCPA") have gone so far as to hold that unexpected results must be described in the specification itself.[5] Contrary to the majority's suggestion, Maj. Op. at 30, I do not propose such a stringent requirement.

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[5] *See In re Herr*, 304 F.2d 907, 909 (CCPA 1962) ("[If] an [unexpected advantage] is not disclosed in appellant's application, he is not in a favorable position to urge it as a basis for the allowance of claims.") (internal quotation marks omitted) (citing *In re Lundberg*, 253 F.2d 244, 247 (CCPA 1958)); *In re Crawford*, 250 F.2d 370, 373 (CCPA 1957) ("[T]here is no disclosure in appellant's application that the glass of which the casing is made has the property recited in [the claim] of 'substantially complete disintegration at a vibration frequency corresponding to that of the shock wave generated by detonation of the explosive body' and accordingly patentability cannot be predicated on that feature."); *In re Stewart*, 222 F.2d 747, 754 (CCPA 1955) ("[U]nexpected results sufficient to spell out patentability must be disclosed, not in briefs or affidavits filed in support of such patentability, but instead in the specification itself. In adjudging, in the first instance, a patent applicant's right to a patent, we are guided in our determination by that which is taught in the application and not by some subsequent undisclosed discovery.").

But I do think that unexpected properties must either be set forth in the specification or contemporaneously known to the inventors, rather than being discovered long after the fact.

In more recent CCPA cases, the court has suggested that a new, undisclosed feature must "inherently flow from the *indicated use*" of the invention. *In re Zenitz*, 333 F.2d 924, 927 (CCPA 1964) (emphasis added); *see also In re Khelghatian*, 364 F.2d 870, 876 (CCPA 1966) (allowing an unexpected result to overcome an obviousness rejection where the improved result "'inherently flow[ed]' *from what was originally disclosed* [in the patent application]") (emphasis added). Here, the sole "indicated use" of the truncated Factor VIII proteins was the ability to procoagulate blood—not the ability to bind to vWF. In fact, the parties do not dispute that the protein's ability to procoagulate blood was completely independent of its ability to bind to vWF. Thus, the ability to bind to vWF was a wholly new and undisclosed function that did not "inherently flow from the *indicated use*" of the invention—the procoagulation of blood. *See Zenitz*, 333 F.2d at 927. This later-discovered advantage should not have been allowed to defeat a finding of obviousness.

Nonetheless, the majority concludes that *Sanofi*, 550 F.3d at 1086, *Knoll Pharmaceutical Co. v. Teva Pharmaceuticals USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004), and *Papesch*, 315 F.2d at 391, support its decision to ignore that the inventors here knew nothing about the benefits of retaining the a3 region at the time its patents were filed. However, *Sanofi*, *Knoll*, and *Papesch* are quite different. In contrast to the present case, in each of these cases, it was shown that, as of the time of the invention, the inventor had contemplated that a particular claimed structure would confer a special and unanticipated advantage, even if the full scope of that advantage was un-

known. While it may have been known at the time of the Novartis patent that binding to vWF helped increase the stability of Factor VIII, there was no indication that the structure proposed in the Novartis patent (i.e., the retention of the a3 region) was any more effective in doing this than the structure of the '112 patent. Nor were the differences in the Novartis patents designed to achieve any such objective.

In *Sanofi*, we affirmed the district court's holding that the unpredictable and unusual properties of a claimed structure and the therapeutic advantages provided by that structure weighed in favor of nonobviousness. 550 F.3d at 1090. Unlike the prior art, the claimed compound "provide[d] all of the antiplatelet activity and none of the adverse neurotoxicity" of the prior art. *Id.* at 1087. At the time of the invention, it was known that scientists were "seeking optimum anti-platelet aggregation properties with minimal undesirable effects." *Id.* at 1079. Thus, it was clear that the evidence of unexpected results was based on the knowledge of what the inventor wanted to achieve at the time of the invention.

In *Knoll*, the district court refused to consider evidence showing the greater analgesic effect of a combination of drugs over the prior art, concluding that "the unexpected benefits or results were discovered after the . . . patent had been issued." 367 F.3d at 1384 (internal quotation marks omitted). We reversed, finding that, "[c]ontrary to the district court's perception, the specification expressly acknowledge[d] that the efficacy of the combination [was] 'surprising'" and stated that the combination of the drugs obtained "an analgesic effect greater than that obtained by increasing the dose of either [analgesic] alone." *Id.* To demonstrate the unexpected activity of the claimed combination, the patentee submitted additional data from experiments conducted after the

patent had been filed. *Id.* at 1385. In concluding that the district court erred in rejecting this after-acquired data, we simply held that it was "not improper to obtain *additional* support *consistent* with the patented invention" because "understanding of the *full* range of an invention [was] not always achieved at the time of filing the patent application." *Id.* at 1385 (emphases added). Thus, where there was already support showing that the inventor contemplated the unexpected result at the time the patent was filed, it was not improper to supplement this evidence of unexpected results with evidence obtained at a later time. *Knoll* is therefore consistent with a requirement that unexpected results be tied to what the inventor knew at the time of the invention.

In *Papesch*, the Board of Patent Appeals and Interferences ("Board") had rejected the claims for a chemical compound containing three ethyl groups as obvious over prior art homologs that contained three methyl groups. 315 F.2d at 383. The applicant responded with an affidavit showing that the claimed compound was an active anti-inflammatory agent while the prior art was inactive in that respect, but the Board rejected the affidavit. *Id.* Our predecessor court reversed, finding that, in addition to comparing the structural similarities and differences between a claimed compound and the prior art, a court should also "tak[e] into consideration their biological and pharmacological properties." *Id.* at 391. The court therefore accepted the affidavit and reversed the decision of the Board. *Id.* at 392. The specification in *Papesch* clearly underscored the advantageous property of the drugs, expressly stating that the "compounds of this invention have been found to possess unexpectedly potent anti-inflammatory activity in contrast to the related trimethyl compound." *Id.* at 382. This unexpected result was a

property contemplated by the inventor at the time of the invention.

Thus, the cases cited by the majority actually support a requirement that an unexpected result be either contained in the specification or contemporaneously known to the inventors. This rule is consistent with the written description requirement, which demands that the invention be in possession of the inventor as of the time the patent was filed. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (holding that our written description requirement requires that a specification "reasonably convey[ ] to those skilled in the art" that the inventor "actually invented" and "had possession of the claimed subject matter as of the filing date [of the invention]") (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562–63 (Fed. Cir. 1991)); *see also Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985). While, as the majority points out, certain secondary considerations, such as evidence of commercial success, can depend on after-acquired knowledge, such evidence must be directed to the significance of the invention and its scope. Those factors can not expand the scope of the invention beyond what was known to the inventors at the time of the patent filing.

The majority rule—dispensing with any requirement that an inventor possess knowledge of the unexpected results at the time the patent was filed—is not only unsupported by the cases it cites, it is also contrary to common sense. An applicant should not be able to avoid an obviousness determination merely by claiming additional, undifferentiated structure, like the a3 region, without any showing that this structure conferred any known benefit over the prior art at the time the invention was made. Just as a challenger to a patent must rely on a known motivation to combine existing prior art to achieve

what the invention was designed achieved,[6] so too the patent holder must prove that he actually contemplated the unexpected results at the time the patent was filed and not at some later time.

It is significant that if Genetics had brought this action at an earlier time—before it was discovered that vWF binding resided in the a3 region—the Novartis patents would likely have been found obvious. Instead, by happenstance and on hindsight, Novartis can now claim an advantage over the '112 patent based on information it did not know at the time of filing and based on research that was conducted by other parties.

My fear is that the majority's rule could ultimately stifle the important incentives for innovation that drive our patent system. Even though Novartis did not foresee the significance of the a3 region to vWF binding at the

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[6] As we discussed in *Eisai Co. Ltd v. Dr. Reddy's Labs, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008), obviousness must be judged from the knowledge of one skilled in the art at the time of invention:

> First, *KSR* assumes a starting reference point or points in the art, *prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions*. Second, *KSR* presupposes that the *record up to the time of invention would give some reasons*, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. . . . Third, . . . *KSR* presumes that the record *before the time of invention* would supply some reasons for narrowing the prior art universe to a finite number of identified, predictable solutions.

(internal citations and quotation marks omitted) (emphases added).

time its patent was filed, the majority has effectively allowed Novartis to broaden the scope of its claims to usurp the fruits of research by the subsequent, independent inventors who actually discovered the location of vWF binding in the a3 region. By ruling that a patentee can have a monopoly on the later-discovered properties of a structure merely by claiming the structure itself, the majority's decision would discourage others from investing in future research into that very structure.

I would therefore hold that the asserted claims of the '112 patent would render the asserted claims of the Novartis patents prima facie obvious, satisfying the first prong of the two-way interference test. I would not reach the question of whether the second prong would be satisfied, that is, whether the asserted claims of the Novartis patents would render obvious or anticipated the asserted claims of the '112 patent. It seems to me likely that they would, but that is an inquiry I would leave to the district court on remand.