United States Court of Appeals for the Federal Circuit

REGENERON PHARMACEUTICALS, INC.,
Plaintiff-Appellant

v.

MERUS N.V.,

Defendant-Appellee

2016-1346

Appeal from the United States District Court for the Southern District of New York in No. 1:14-cv-01650-KBF, Judge Katherine B. Forrest.

Decided: July 27, 2017

NEAL KUMAR KATYAL, Hogan Lovells US LLP, Washington, DC, argued for plaintiff-appellant. Also represented by CHRISTOPHER P. BORELLO, MICHAEL ENZO FURROW, BRENDAN M. O'MALLEY, ROBERT SETH SCHWARTZ, Fitzpatrick, Cella, Harper & Scinto, New York, NY.

PATRICIA A. CARSON, Kirkland & Ellis LLP, New York, NY, argued for defendant-appellee. Also represented by SAUNAK DESAI, AARON D. RESETARITS; JOHN C. O'QUINN, Washington, DC; PETER B. SILVERMAN, Merus US, Inc., Cambridge, MA.

KEVIN EDWARD NOONAN, McDonnell, Boehnen, Hulbert & Berghoff, LLP, Chicago, IL, for Amicus Curiae Seven Chicago Patent Lawyers. Also represented by JEFFREY PALMER ARMSTRONG, AARON VINCENT GIN, JAMES LEE LOVSIN, JEREMY E. NOE, ANDREW W. WILLIAMS, DONALD LOUIS ZUHN, JR.,

---

Before PROST, *Chief Judge,* NEWMAN and WALLACH, *Circuit Judges.*

Opinion for the court filed by *Chief Judge* PROST.

Dissenting opinion filed by *Circuit Judge* NEWMAN.

PROST, *Chief Judge*.

Regeneron Pharmaceuticals, Inc. ("Regeneron") appeals from a final judgment of the district court holding U.S. Patent No. 8,502,018 ("'018 patent") unenforceable because of Regeneron's inequitable conduct during prosecution. Regeneron also appeals the district court's construction of several claim terms and determination of indefiniteness. Because we conclude that Regeneron engaged in inequitable conduct during prosecution of the '018 patent, we affirm.

I

In March 2014, Regeneron filed suit in the Southern District of New York accusing Merus B.V. ("Merus") of infringing the '018 patent. The district court heard argument and expert testimony on claim construction and issued an opinion construing various terms. *See Regeneron Pharm., Inc. v. Merus B.V.*, No. 14-cv-1650, 2014 WL 6611510 (S.D.N.Y. Nov. 21, 2014). The court also declared one term indefinite. *Id.* at *23–24.

Merus asserted a counterclaim of unenforceability due to inequitable conduct. It argued that Regeneron's patent

prosecutors withheld four references (the "Withheld References") from the U.S. Patent and Trademark Office ("PTO") during prosecution of the '018 patent. According to Merus, these references were cited in a third-party submission in related U.S. patent prosecution and in European opposition briefs, were but-for material, and were withheld by Regeneron with the specific intent to deceive the PTO. There was no dispute that Regeneron knew of the Withheld References during prosecution of the '018 patent. Regeneron argues, however, that the references were not but-for material, that they were cumulative of references the PTO actually relied on during prosecution, and that Regeneron did not have any specific intent to deceive the PTO.

The district court scheduled a bench trial on Regeneron's inequitable conduct, but bifurcated the trials based on the two elements of inequitable conduct: a first bench trial on the materiality of the Withheld References, and a second bench trial regarding the specific intent to deceive the PTO. *See Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1287 (Fed. Cir. 2011) (en banc).

Following the first trial, the district court issued a lengthy opinion detailing the materiality of the Withheld References. *Regeneron Pharm., Inc. v. Merus B.V.*, 144 F. Supp. 3d 530 (S.D.N.Y. 2015) ("*Regeneron I*").[1] The district court, however, never held the scheduled second trial on Regeneron's specific intent to deceive the PTO. In-

---

[1] The district court also found that Regeneron had engaged in affirmative egregious misconduct—an alternative to but-for materiality—based on certain misleading statements Regeneron made to the PTO during prosecution of '018 patent. *Id.* at 582. Because we conclude that the Withheld References are but-for material, we do not discuss the district court's affirmative egregious misconduct determination.

stead, in its opinion following the first bench trial, the court exhaustively detailed Regeneron's discovery misconduct throughout litigation and sanctioned Regeneron by drawing an adverse inference of specific intent to deceive the PTO. In particular, the district court discussed Regeneron's repeated violations of the district court's discovery orders and improper secreting of relevant and non-privileged documents. Based on this misconduct, the district court drew an adverse inference that Regeneron's agents failed to disclose the Withheld References to the PTO with the specific intent to deceive the PTO. Having determined the but-for materiality of the Withheld References and drawn an adverse inference of Regeneron's specific intent to deceive the PTO, the district court concluded that Regeneron had committed inequitable conduct and held the '018 patent unenforceable.

Regeneron timely appealed the district court's claim construction order and final judgment of inequitable conduct. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

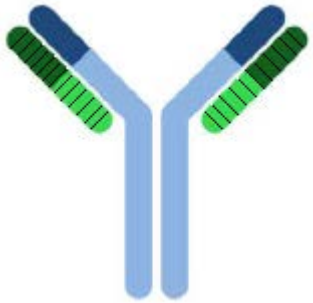
A

The '018 patent emerged from a family of applications that originated in December 2000. In February 2001, Regeneron filed a continuation-in-part from that original application, which ultimately issued as U.S. Patent No. 6,596,541 ("'541 patent"). Regeneron then filed a divisional of the '541 patent, and from that divisional filed several continuations including U.S. Application No. 13/164,176 ("'176 application") entitled "Method of Modifying Eukaryotic Cells." That continuation application issued as the '018 patent on August 6, 2013, to inventors Drs. Andrew J. Murphy and George D. Yancopoulos, who assigned it to Regeneron.

In general, the '018 patent relates to using large DNA vectors to target and modify endogenous genes and chromosomal loci in eukaryotic cells. '018 patent col. 1 ll. 17–

33. One practical use of this technology is that users may target and modify specific genes in mice so that the mice develop antibodies that can be used by humans.

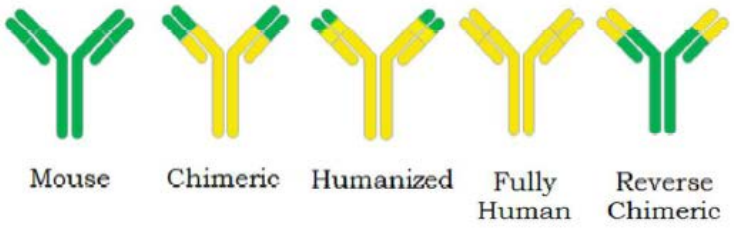
Antibodies are proteins that the body uses to counteract specific pathogens such as bacteria, viruses, and other foreign substances in the blood. Antibodies are typically represented by a "Y" shape consisting of four chains of amino acids: two longer "heavy" chains, and two shorter "light" chains. Each of the chains, in turn, consists of two regions: a "variable" region toward the top of the "Y," and a "constant" region toward the bottom. One such antibody is illustrated below:



Appellant's Br. 5 (stripes added). In this antibody, the light chains are striped and the heavy chains are solid. Further, the constant regions are represented in lighter shades, and the variable regions in darker shades.

Mouse DNA coding for antibodies can be modified using human DNA in various different ways. For example, mouse DNA can be manipulated to create chimeric antibodies that have mouse variable region DNA and human constant region DNA. Similarly, mice can be used to create humanized antibodies that have some mouse variable region DNA, some human variable region DNA, and human constant region DNA. Further, genetically modified mice can be used to create antibodies that have fully human DNA. Finally, mice can also be modified to

create reverse chimeric antibodies that have mouse constant region DNA and human variable region DNA. This spectrum of modified antibodies is illustrated below.



Claim 1 of the ʼ018 patent, the only claim at issue here, recites, in its entirety, "[a] genetically modified mouse, comprising in its germline human unrearranged variable region gene segments inserted at an endogenous mouse immunoglobulin locus." ʼ018 patent col. 29 ll. 24–26. As discussed in greater detail below, Regeneron contends that under the broadest reasonable construction, this claim is limited to mice that produce reverse chimeric antibodies. Merus, on the other hand, argues that under the broadest reasonable construction, claim 1 includes mice that can produce humanized, fully human, or reverse chimeric antibodies.[2]

B

As originally filed, claim 1 of the ʼ176 application recited "[a] genetically modified mouse, comprising in its germline human unrearranged variable gene region segments inserted at a mouse immunoglobulin locus."

---

[2] Because this opinion primarily focuses on inequitable conduct, the court applies the broadest reasonable construction to determine claim scope. *See Therasense*, 649 F.3d at 1291–92 ("[T]o establish inequitable conduct . . . the court should apply the preponderance of the evidence standard and give claims their broadest reasonable construction.").

J.A. 450. In January 2012, the PTO issued a Non-Final Office Action rejecting claims 1–19 of the '176 application as being anticipated by a U.S. Application No. 11/009,873 to Nils Lonberg and Robert Kay ("Lonberg"). J.A. 376–88.

In July 2012, Regeneron's Dr. Smeland, in-house counsel responsible for prosecuting the '176 application and others in the same family in the United States and Europe, replied to this Office Action. He argued that unlike the recited claims of the '176 application, Lonberg teaches random and not targeted insertion. In particular, Dr. Smeland argued that Lonberg did not teach inserting "human unrearranged variable region gene segments" in the mouse immunoglobulin ("Ig") locus. Instead, according to Dr. Smeland, Lonberg teaches genes that are "randomly inserted at (unknown) loci." J.A. 408–09.

In October 2012, the PTO mailed a Final Office Action, rejecting the pending claims of the '176 application, maintaining the rejection of claims 1–19 as anticipated by Lonberg.

In a January 2013 Reply to the Final Office Action, Regeneron amended claim 1 to include the additional limitation that the human unrearranged variable region gene segments would be inserted at "an endogenous" mouse immunoglobulin locus. Regeneron also sent a presentation to the PTO with the Reply. In that presentation, Regeneron asserted that it had developed a commercial embodiment of the claimed mouse with surprising results. It is undisputed that that assertion was false. J.A. 7563. Regeneron had not developed any such mouse at the time.

Following receipt of Dr. Smeland's Reply and presentation, the PTO issued an Advisory Action maintaining the rejection of claims 1–19 as anticipated by Lonberg, and claim 20 remained rejected in view of Lonberg and other references. Shortly thereafter, in February 2013, Regeneron retained Brendan Jones, Ph.D., to assist with

prosecution. Drs. Jones and Smeland together planned an in-person meeting with the Examiner during which they relied on the misleading presentation asserting that Regeneron had developed a commercial embodiment of the claimed mouse. That meeting occurred in March 2013.

Following that meeting, in April 2013, the PTO issued a Notice of Allowance for the '176 application. In the statement of reasons for allowance, the Examiner stated that "[t]he prior art does not teach or suggest a genetically modified mouse comprising, in its germline cells, human unrearranged variable region gene segments inserted at an endogenous mouse immunoglobulin locus." J.A. 531. The applicant transmitted the fee in June 2013, and the '018 patent issued on August 6, 2013.

C

Days before the PTO issued its notice of allowance for the '176 application, which would become the '018 patent, a third-party filed a submission in the parent application of the '018 patent, describing three references:

1. Marianne Brüggemann & Michael S. Neuberger, "Strategies for Expressing Human Antibody Repertoires in Transgenic Mice," 17(8) Review Immunology Today 391 (1996) ("Brüggemann");
2. Shinsuke Taki et al., "Targeted Insertion of a Variable Region Gene into the Immunoglobulin Heavy Chain Locus," 262 Science 1268 (1993) ("Taki"); and
3. Yong–Rui Zou et al, "Cre-loxP-mediated Gene Replacement: A Mouse Strain Producing Humanized Antibodies," 4(12) Current Biology 1099 (1994) ("Zou").

Dr. Rajewsky co-authored both the Taki and Zou refer-

ences. Further, Dr. Alt, another inventor, co-invented WIPO Patent Publication No. WO 91/00906 entitled "Chimeric and Transgenic Animals Capable of Producing Human Antibodies," credited to Clive Wood et al. ("Wood"). Collectively, the Brüggemann, Taki, Zou, and Wood references are the "Withheld References."[3]

Given their prior work, Regeneron recruited Drs. Alt and Rajewsky to its scientific advisory board to work on the claimed mouse before Regeneron filed the '018 patent. During prosecution, these individuals corresponded with Dr. Murphy, an '018 patent inventor, expressing concerns about his characterizations of the prior art in related publications.

Dr. Smeland knew of the third party submission as well as all four Withheld References during prosecution, yet withheld them from the '018 patent's examiner. Although Regeneron did not disclose the Withheld References during prosecution of the '018 patent, once the '018 patent had been allowed, Regeneron disclosed the Withheld References to the PTO in every related application having the same specification and similar claims. Merus contends that Regeneron's failure to disclose the Withheld References constituted inequitable conduct. Regeneron responds that Dr. Smeland was under no obligation to disclose these references because they were not but-for material.

---

[3] The district court also found that certain withheld litigation documents filed in European Opposition proceedings in 2013 were also but-for material. Regeneron argues that legal documents prepared for litigation cannot be but-for material. Appellant's Br. 48–49. Because we do not rely on these litigation documents for our holding, we need not address this issue.

II

"Inequitable conduct is an equitable defense to patent infringement that, if proved, bars enforcement of a patent." *Therasense*, 649 F.3d at 1285. Unlike validity defenses, which are claim specific, inequitable conduct regarding a single claim renders the entire patent unenforceable. *Id.* at 1288. Inequitable conduct has two separate requirements: materiality and intent. *Id.* at 1290.

"[A]s a general matter, the materiality required to establish inequitable conduct is but-for materiality." *Id.* at 1291. A prior art reference is "but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art." *Id.* In determining the materiality of a reference, the court applies the preponderance of the evidence standard and gives claims their broadest reasonable construction. *Id.* at 1291–92.

A reference is not but-for material, however, if it is merely cumulative. *See Dig. Control Inc. v. Charles Mach. Works,* 437 F.3d 1309, 1319 (Fed. Cir. 2006) ("However, a withheld otherwise material prior art reference is *not* material for the purposes of inequitable conduct if it is merely cumulative to that information considered by the examiner."). A reference is cumulative when it "teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO." *Regents of the Univ. of Calif. v. Eli Lilly & Co.,* 119 F.3d 1559, 1575 (Fed. Cir. 1997).

In addition to proving the materiality of withheld references, "the accused infringer must prove that the patentee acted with the specific intent to deceive the PTO." *Therasense*, 649 F.3d at 1290. "[A] court must weigh the evidence of intent to deceive independent of its analysis of materiality. Proving that the applicant knew of a reference, should have known of its materiality, and decided not to submit it to the PTO does not prove specific intent

to deceive." *Id.* (citing *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.,* 537 F.3d 1357, 1366 (Fed. Cir. 2008)). "In a case involving nondisclosure of information, clear and convincing evidence must show that the applicant *made a deliberate decision* to withhold a *known* material reference." *Id.* (quoting *Molins PLC v. Textron, Inc.,* 48 F.3d 1172, 1181 (Fed. Cir. 1995)) (internal quotation marks omitted).

Direct evidence of intent is not, however, required. A court may infer intent from circumstantial evidence. *Id.* An inference of intent to deceive is appropriate where the applicant engages in "a pattern of lack of candor," including where the applicant repeatedly makes factual representations "contrary to the true information he had in his possession." *Apotex Inc. v. UCB, Inc.,* 763 F.3d 1354, 1362 (Fed. Cir. 2014).

On appeal, Merus asserts that Drs. Smeland and Murphy violated their duty of candor and engaged in inequitable conduct. Regeneron does not contest that both of these individuals had a duty of candor to the PTO. Regeneron, however, argues that the duty was not violated because none of the Withheld References were but-for material and because the district court improperly concluded that the applicants possessed the necessary specific intent to deceive the PTO.

"[W]e review the district court's findings of materiality and intent for clear error." *Am. Calcar, Inc. v. Am. Honda Motor Co.*, 768 F.3d 1185, 1189 (Fed. Cir. 2014). A finding of inequitable conduct based on those facts is reviewed for an abuse of discretion. *Id.*

Further, "[w]hen reviewing the imposition of sanctions under a district court's inherent powers, we apply the law of the regional circuit in which the district court sits," here the Second Circuit. *Monsanto Co. v. E.I. Du Pont de Nemours & Co.*, 748 F.3d 1189, 1196 (Fed. Cir. 2014). The Second Circuit reviews a district court's

imposition of sanctions and an adverse inference for litigation misconduct for abuse of discretion. *Residential Funding Corp. v. DeGeorge Fin. Corp.*, 306 F.3d 99, 107 (2d Cir. 2002).

A

The first step in an inequitable conduct inquiry is determining whether the patentee failed to disclose but-for material information to the PTO. Determining but-for materiality requires that the court place itself in the shoes of a patent examiner and determine whether, had the reference(s) been before the examiner at the time, the claims of the patent would have still issued. *Therasense,* 649 F.3d at 1291–92.

As with an invalidity analysis, the first step in determining but-for materiality of a reference is determining the scope of the claims at issue. Thus, the court must first determine the broadest reasonable construction of the claims that the PTO would have applied during prosecution. Next, based on the broadest reasonable construction, the court must determine whether a reasonable patent examiner would have allowed the claims had she known of the Withheld References. *See Am. Honda Motor,* 768 F.3d at 1189.

1

The broadest reasonable construction of a claim term is one that is consistent with "the specification and the record evidence" and is "consistent with the one that those skilled in the art would reach." *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015). But "[a] construction that is unreasonably broad and which does not reasonably reflect the plain language and disclosure will not pass muster." *Id.* (internal quotation marks omitted).

Both Regeneron and Merus agree that the claimed mouse has, as recited in claim 1, "human unrearranged

variable region gene segments." But Regeneron argues that under the broadest reasonable construction of claim 1, the non-variable (constant) region of the claimed mouse's modified gene segments exclusively contains mouse genes. In other words, Regeneron argues that claim 1 is limited to a reverse chimeric mouse. Appellant's Br. 32–35. Merus, on the other hand, argues that the constant region of the gene segments in the claimed mouse may contain mouse genes or human genes, and may, therefore, be reverse chimeric, humanized, or fully human. Appellee's Br. 51.

Regeneron first relies on the claim language to support its position. As noted above, claim 1 recites "[a] genetically modified mouse, comprising in its germline human unrearranged variable region gene segments inserted at an endogenous mouse immunoglobulin locus." According to Regeneron, because claim 1 only recites modifying the mouse by inserting "human unrearranged variable region gene segments," it implies leaving the remainder of the mouse's DNA unmodified. This, however, is inaccurate. Because "comprise" is inclusive or open-ended, the use of the term does not exclude unrecited elements. *See Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) ("'Comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim."); *accord* MPEP § 2111.03 ("The transitional term 'comprising,' which is synonymous with 'including,' 'containing,' or 'characterized by,' is inclusive or open-ended and does not exclude additional, unrecited elements or method steps."). A germline that "comprises" human variable region gene segments may very well also include human constant gene segments. Thus, the "customary and ordinary" meaning of the language in claim 1 is not limited to a reverse chimeric mouse.

Regeneron further argues that the specification purportedly limits the claim to mice that produce "hybrid antibodies containing human variable regions and mouse constant regions." Appellant's Br. 33 (citing '018 patent col. 20 ll. 37–39). The patent, however, clearly teaches producing antibodies that "*compris[e] a human constant region*." '018 patent col. 7 ll. 19–23 (emphasis added). Regeneron argues that this disclosure is limited to reverse chimeric antibodies that are later modified to insert a human constant region. But Regeneron points to no portion of the specification to support its argument. In context, it is clear that the endogenously produced antibodies may comprise a human constant region. The specification thus does not limit the claims to mice with human variable regions and mouse constant regions.

Accordingly, we disagree with Regeneron and conclude that under the broadest reasonable construction, the district court correctly found that the claims are not limited to mice that solely comprise mouse constant region gene segments.

2

Under this broadest reasonable construction, the court next determines if the district court clearly erred in finding the Withheld References but-for material and not cumulative of prior art that the PTO considered during prosecution. We conclude that the district court properly found that the Withheld References were but-for material and were not cumulative.

During prosecution, Drs. Smeland and Murphy knew of the Withheld References and did not disclose them to the PTO. Merus argues, and the district court found, that each of these references was but-for material, i.e., the "PTO would not have allowed [the] claim had it been aware of" these references. *Therasense,* 649 F.3d at 1291. Regeneron disagrees. As noted above, the four Withheld References were Brüggemann, Wood, Taki, and Zou.

First, Regeneron argues that the district court improperly found Brüggemann to be but-for material. Brüggemann is a review paper that teaches the use of transgenic mice to express human antibodies. In particular, Brüggemann teaches that "[a]n attractive alternative [to the random integration of human genes into mouse genes] would be to replace the mouse Ig loci with the human Ig loci." J.A. 3917. Brüggemann further expands that in doing so, "much of the DNA of the mouse Ig loci" might be replaced with human DNA. J.A. 3918. Regeneron only contests Brüggemann's materiality because Brüggemann purportedly does not disclose a reverse-chimeric mouse. *See* Appellant's Br. 37–38 ("[Brüggemann] does not specify that the mouse constant region should be retained, or that any portion of the mouse locus should be retained at all."). As discussed above, however, claim 1 is not limited to reverse-chimeric mice. Claim 1 encompasses humanized, fully human, and reverse chimeric mice as well. We therefore are not persuaded by the distinction drawn by Regeneron and conclude that the district court did not clearly err in finding Brüggemann but-for material.

Second, Regeneron argues that the district court improperly found Wood to be but-for material. According to Regeneron, Wood does not teach inserting a human variable gene into a mouse by targeting the mouse Ig locus. Instead, Regeneron contends that Wood teaches "randomly integrating human transgenes" into a mouse genome with no such targeting. Appellant's Br. 40.

As Merus's expert Dr. Geoff Davis explained, however, Wood does disclose specific targeting of the mouse's Ig locus. For example, Wood teaches that "[t]he present invention relates generally to *immunoglobulin* rearrangement in chimeric and transgenic animals, and more specifically to a mouse containing in its germline . . . the ability to generate immunoglobulins . . . ." Wood at 1:4–9 (emphasis added); J.A. 2125–26. Wood further teaches

that when human DNA is combined with mouse DNA, the "constant region," i.e., the constant region of the DNA in the Ig locus, "is of exogenous or *endogenous* species origin" and that this constant region may be "from the animal itself." Wood at 6:17–20, 10:3–5 (emphasis added); J.A. 2126–28. Skilled artisans are therefore taught to specifically target the endogenous Ig locus when inserting human DNA into the mouse. The district court did not err in finding Wood but-for material.

The dissent argues that Wood is not material because it only teaches a "DNA fragment *construct*" but does not describe "any targeted insertion method described elsewhere in the prior art . . . ." Dissent at 17. As an initial matter, neither party argues this position and the district court did not make this factual finding. *See 3M Co. v. Avery Dennison Corp.*, 673 F.3d 1372, 1378 (Fed. Cir. 2012) ("[I]t is improper for us to determine factual issues in the first instance on appeal . . . finding those facts in the first instance would overstep our bounds as a reviewing court and we cannot resolve the parties' factual disputes on appeal."). Regardless, the dissent's argument is unavailing because the claim at issue does not recite a particular method of inserting DNA into a mouse. The claim simply recites a genetically modified mouse that comprises "human unrearranged variable region gene segments inserted at an endogenous mouse immunoglobulin locus." Wood teaches that "[t]he animals of this invention are designed by the integration into their germlines of DNA carrying unrearranged or only partially rearranged exogenous Ig gene segments." J.A. 2127. Wood thus teaches the elements of the claim at issue and is but-for material.

Third, Regeneron argues that the district court improperly found Taki to be but-for material. According to Regeneron, Taki only teaches inserting rearranged variable region DNA from one *mouse* into the genome of another mouse. Claim 1, on the other hand, recites inserting

unrearranged *human* variable region DNA into a mouse genome.

As the district court correctly noted, Taki teaches insertion of exogenous (i.e., foreign) "rearranged mouse variable region [DNA] into the Ig locus" to produce a transgenic mouse with good B-cell development and antibodies. *Regeneron I*, 144 F. Supp. 3d at 573. The development of a transgenic mouse with good B-cell development and antibodies is also an intended goal of the '018 patent. '018 patent col. 20 ll. 63–65 ("These interactions are important for a strong and specific immune response, for the proliferation and maturation of B cells, and for the affinity maturation of antibodies."). The fact that Taki teaches using exogenous mouse DNA instead of exogenous human DNA does not detract from the motivation Taki provides to target the mouse Ig locus with exogenous DNA, including human DNA. As the district court correctly found,

> Taki teaches targeting at the specific locus—the Ig locus—with operable linkage . . . taking advantage of the mouse regulatory and constant regions. Taki, in short, provides the motivation to target human variable region DNA into the mouse Ig locus.

Regeneron I, 144 F. Supp. 3d at 574. The district court did not err by finding Taki's disclosure of targeting insertion of exogenous variable region DNA to be but-for material.

Fourth, Regeneron argues that the district court improperly found Zou to be but-for material. Regeneron contends that Zou only teaches modifying a mouse's constant region whereas the '018 patent teaches modifying a mouse's variable region. According to Regeneron, "the '018 Patent discloses the insertion of human variable regions; Zou does not. Zou discloses the insertion of

human constant regions; the '018 Patent does not." Appellant's Br. 44.

As even Regeneron admits, Zou teaches specifically inserting human Ig DNA into the mouse Ig locus, preserving part of the mouse constant region, and discloses producing antibodies at the "same level and efficiency as wild-type mice." J.A. 2414–17. The district court properly found that Zou's teaching of inserting portions of human constant, rather than variable, DNA did not detract from its motivation to insert human variable regions in the mouse Ig locus. In fact, as Merus's expert Dr. Davis noted, Brüggemann cited Zou for this precise disclosure a few years later. J.A. 2123–24. Thus, the district court properly concluded that Zou was also but-for material.

In addition to arguing that the Withheld References are not but-for material individually, Regeneron also argues that the Withheld References are not but-for material in combination. We disagree. As noted above, the references both individually and in combination teach one of skill in the art to genetically modify mice by inserting exogenous, including human, variable region gene segments endogenously into a mouse immunoglobulin locus. The references, in particular Taki and Zou, also provide the motivation to combine these references to develop the genetically modified mouse.

Regeneron also argues that Brüggemann, Wood, and Taki are cumulative of references that the examiner considered during prosecution of the '018 patent.[4] In

---

[4] While Regeneron's opening brief states, in a heading, that Zou is "cumulative of Kucherlapati and Lonberg," Regeneron provides no further argument regarding these references. Appellant's Br. 44–46. We therefore do not address this point. The dissent, however, argues that Zou is cumulative of a different cited reference,

particular, Regeneron contends that Brüggemann is cumulative of U.S. Patent No. 6,114,598 issued to Raju Kucherlapati et al. on June 5, 1995 ("Kucherlapati"), Wood is cumulative of Lonberg, and Taki is cumulative of Kucherlapati and Lonberg. There is no dispute that the PTO considered both Lonberg and Kucherlapati during prosecution.

Kucherlapati relates generally to "the production of xenogeneic specific binding proteins in a viable mammalian host." Kucherlapati col. 1 ll. 20–21. Kucherlapati explains that in a modified mouse,

> the target [or mouse] locus may be substituted with the analogous xenogeneic [or human] locus. In this way, the xenogeneic locus will be placed substantially in the same region as the analogous host locus, so that any regulation associated with the position of the locus will be substantially the same for the xenogeneic immunoglobulin locus.

Id. at col. 10 ll. 50–55. Regeneron contends that this disclosure teaches targeted insertion of human DNA at the mouse Ig locus, Appellant's Br. 43, to achieve the "benefit of preserving normal regulatory sequences," *id*. at 39.

Jakobovits. Dissent at 15–16. Neither the parties nor the district court argued or found that Zou is cumulative of Jakobovits. The only relevant expert testimony suggests that Jakobovits is not cumulative of Zou. *See* J.A. 2184 (Merus's expert trial declaration) (Filed under seal). Because we cannot weigh expert testimony and factual assertions made by the dissent in the first instance, we limit our review to facts established in the record and arguments presented to us by the parties. *See 3M Co.*, 673 F.3d at 1378.

Lonberg relates generally to "transgenic non-human animals capable of producing heterologous antibodies . . . ." Lonberg at ¶ 002. As Regeneron explains, Lonberg teaches using a "'knockout plus transgene' method for genetically engineering mice. Under that method, human variable and human constant region gene segments are randomly integrated into the mouse genome, while the mouse's own antibody genes are 'knocked out' by targeted deactivation of the mouse immunoglobulin locus." Appellant's Br. 8.

Although Regeneron argues that Brüggemann is cumulative of Kucherlapati, we disagree. Brüggemann instructs to "retain and exploit any possible regulatory sequences in the mouse loci that are located distal to protein-coding regions," and cites Zou's method to accomplish this. J.A. 3917. In contrast, Regeneron represented both during prosecution of a related application and in litigation that Kucherlapati's discussion of a "xenogeneic locus" is not enabled and concerns wholesale replacement. J.A. 2178–80 (Regeneron's Non-Final Office Action Response, U.S. Patent Application No. 13/719,819) ("[O]ne of ordinary skill in the art would not have a reasonable expectation of successfully using the YAC-based method described in Kuncherlapati to generate the mice comprising the targeted insertion of human unrearranged variable region gene segments into the endogenous mouse immunoglobulin locus, as currently claimed."); J.A. 2193 (Dr. Jones's deposition transcript) ("Kucherlapati is primarily focused on adding the fully human transgene randomly in the genome and then inactivating the endogenous locus."). Further, Regeneron's technical expert testified that Kucherlapati's prophetic description would disrupt "important aspects of lymphoid development" and would prevent normal B cell development. J.A. 3188. Because Brüggemann teaches targeted gene replacement as compared to Kucherlapati's non-enabled wholesale

replacement, Brüggemann teaches a known technique to target the Ig locus, nowhere found in Kucherlapati.

Regeneron also unpersuasively argues that Wood is cumulative of Lonberg. As Dr. Smeland stated to the PTO during prosecution, "Lonberg does not disclose a mouse comprising in its germline human unrearranged variable region gene segments inserted at a mouse immunoglobulin locus. Instead, Lonberg discloses transgenes that are apparently randomly inserted at (unknown) loci." J.A. 408–09. Wood, as explained above, teaches skilled artisans to specifically target the mouse Ig locus and insert human variable DNA there. Thus, Wood is not cumulative of Lonberg.

Finally, Regeneron argues that Taki is cumulative of Kucherlapati and Lonberg. As noted above, even Regeneron's technical expert testified that Kucherlapati's prophetic description would disrupt "important aspects of lymphoid development" and would prevent normal B cell development. Taki, which teaches inserting "rearranged mouse variable region [DNA] into the Ig locus" to produce a transgenic mouse with good B-cell development and antibodies, would not. *Regeneron I*, 144 F. Supp. 3d at 573. Further, Lonberg teaches targeting a mouse Ig locus with a marker gene to inactivate the locus whereas Taki teaches targeting functional exogenous variable region DNA to produce normal antibodies. J.A. 2187–88. Thus, Taki is not cumulative of Kucherlapati and Lonberg.

In sum, we conclude that the district court did not clearly err in finding each of the Withheld References but-for material.

B

As noted earlier, the district court never held a second trial to determine if Regeneron acted with the specific intent to deceive the PTO during prosecution. Instead, the court sanctioned Regeneron for its litigation miscon-

duct by drawing an adverse inference of specific intent. Contrary to Regeneron's arguments, we determine that the district court did not abuse its discretion by sanctioning Regeneron in this manner.

Regeneron's behavior in district court was beset with troubling misconduct. In its November 2015 opinion, the district court extensively detailed Regeneron's litigation misconduct and exercised its discretion to sanction Regeneron. *See Regeneron I*, 144 F. Supp. 3d at 585–96. On appeal, Regeneron argues that the district court abused its discretion by sanctioning Regeneron, but does not meaningfully dispute any of the factual findings underlying the district court's decision. Accordingly, we largely repeat, and adopt, the district court's factual findings regarding Regeneron's litigation misconduct below.

1

According to the district court, Regeneron's misconduct began at a relatively early stage in litigation. The district court's local patent rules required Regeneron to disclose its infringement contentions, broken down by element, to Merus. Regeneron claimed that it could not comply. Instead, Regeneron provided a chart with infringement contentions that listed each claim as consisting of a single limitation—that is, a single element. Merus moved to compel—seeking developed infringement contentions. In that same motion, Merus also moved to compel production of documents as required by the district court's rules relating to the conception and reduction to practice of the '018 patent. Regeneron claimed to have few such documents and did not include in its production a key document written by Dr. Murphy, one of the inventors of the '018 patent, setting forth the '018 patent's conception and reduction to practice.

The district court issued a written decision in response to Merus's motion to compel. Discovery Order #6, *Regeneron Pharm., Inc. v. Merus B.V.*, No. 14-cv-1650

(S.D.N.Y. July 22, 2014), Dkt. No. 82. At a later conference, the district court discussed its concerns regarding Regeneron's conduct and gave Regeneron an opportunity to correct its contentions. Regeneron chose not to do so. In both its order and at that conference, the district court noted that the infringement claim that Regeneron had asserted—as with all infringement claims—required an element-by-element identity between the accused product and the '018 patent. The district court stated explicitly, both in its written decision on the issue and at a hearing held soon thereafter, that it was troubled by Regeneron's refusal. At that time, experienced patent counsel (later replaced by Regeneron's trial and appellate counsel here) asserted that he did not understand what the district court was asking for or how to break a claim down into elements. The district court determined that this obfuscation made no sense and was a tactical choice—seeking to shift the plaintiff's burden in an infringement case to define the elements of a claim to the defendant.

During claim construction, Regeneron again chose tactics over substance. Because Regeneron was the plaintiff, the district court's rules required that Regeneron first propose its claim constructions, and that the defendant then respond. Regeneron took the position that no terms required construction. The district court issued an order expressing its concern that Regeneron was attempting to "game" the system by shifting the burden to Merus to propose constructions and then to take shots at those proposals. Discovery Order #5, *Regeneron Pharm., Inc. v. Merus B.V.*, No. 14-cv-1650, 2014 WL 3865366, at *1 (S.D.N.Y. July 22, 2014), Dkt. No. 81. To avoid this potential gamesmanship, the district court required Regeneron to live by its plain language constructions. *Id.* at *2.

The district court also detailed Regeneron's litigation misconduct relating to the "Jones Memo." Although this misconduct was not the primary basis for the district

court's decision to impose sanctions, the district court explained that Regeneron's behavior with respect to the Jones Memo was relevant for multiple reasons. First, Regeneron's behavior followed the pattern of misconduct described above. Second, Regeneron sought to use the memo as a cloak for its later misconduct that was the primary basis for the district court's sanctions decision.

The Jones Memo was created during prosecution of the '018 patent. While he was prosecuting the patent, Regeneron's in-house counsel Dr. Smeland retained Dr. Jones. Dr. Jones was an outside patent attorney, as noted above, retained to help with Regeneron's patent prosecution. During prosecution of the '018 patent, Dr. Jones drafted a chart and memo in connection with his review of whether to disclose the Withheld References to the PTO.

During litigation in district court, Regeneron listed the chart and memo on its privilege log based on attorney-client privilege. On the eve of Dr. Jones's deposition, however, Regeneron disclosed both the chart and the memo. Merus asserted that this disclosure resulted in a broad privilege waiver and brought a motion to compel.

The evidence presented to the district court on that motion demonstrated that on November 7, 2013, Dr. Jones had attached the chart to an email to Dr. Smeland, and wrote, "[w]hile we discussed this analysis in numerous calls, I don't know if I have ever sent you this document. For your records, I have also attached a memo I drafted regarding the third-party disclosures made in the other U.S. case." *Regeneron I*, 144 F. Supp. 3d at 586. That email was forwarded to Regeneron's then outside-counsel on the same day. On November 11, 2014, Regeneron's outside counsel wrote an email to Regeneron stating, "I believe Brendan [Jones] also discussed his analysis with Tor [Smeland] around the time that Brendan prepared these memos." *Id.* That same e-mail notes that Dr. Jones "was asked to analyze[] whether certain references

that came up in the European Opposition and the Third Party Submission should be disclosed to the PTO," and that "[t]here are several documents that he prepared on this subject in late June 2013." *Id.* (internal quotation marks omitted).

The memo, written by Dr. Jones on June 28, 2013, appeared in all respects to contain the formatting and content of a legal memo to Regeneron—though it is designated as a memo to file. Printed on a law firm letterhead and beginning with entry lines for "to", "cc", "from", and "regarding", the memo read "Privileged and Confidential," began with a summary section, contained footnotes, and was organized under formal headings. It described basic standards for the duty to disclose prior art, and analyzed the materiality of three publications. The memo amounted to an elucidation of the rationale underlying the charts and is inextricably connected to the charts. The district court concluded that the document was plainly one created in connection with Dr. Jones's provision of legal advice to Regeneron. *Id.* at 586–87.

The references to discussions of the chart and analysis made clear that Dr. Jones analyzed the prior art and arrived at a legal conclusion about disclosure obligations as part of his advisory role to Regeneron. He contemporaneously communicated the substance of the very same advice to his client.

Regeneron argued that by disclosing the memo and the chart, Regeneron had not waived any privilege because the documents were not privileged. According to Regeneron, Dr. Jones had merely used these documents to assist himself in connection with his professional obligations unrelated to his advisory role. The district court found that Regeneron's argument was "seriously incorrect." *Id.* at 587.

As part of its inquiry into this waiver, the district court decided to conduct an *in camera* review of the doc-

uments related to the memo and the chart. In particular, the district court ordered that Regeneron provide it with "[a]ll documents relating to groups or individuals who at the time of creation or subsequently thereto received a copy of the chart or memo" and "[a]ll documents and communications . . . referring or relating *in any way* to Dr. Jones's chart and memo." *Id.*

In response, Regeneron provided the district court a single binder containing what it represented was the universe of such materials. As it turned out, this was false. Instead of providing the district court the documents that the court ordered, Regeneron applied its own conditions and only provided documents that *directly* related to the chart and memo. Regeneron did not inform the district court of this self-imposed limitation. The district court thus believed the binder provided insight into all that was at issue and ruled on the motion.

Because Regeneron affirmatively produced the Jones Memo and accompanying chart to Merus, the district court found that Regeneron waived the attorney-client privilege as to its subject matter. The district court ordered that Regeneron produce all relevant documents concerning the decision to not disclose prior art during the patent prosecution to Merus ("Order"). *Id.* at 587–88.

Subsequently, disputes arose as to the scope of the waiver. Regeneron represented that it had produced:

> all documents and communications related to any decision, analysis or advice by Dr. Jones or anyone at Regeneron on whether or not to disclose references from Dr. Jones' charts and memo during prosecution of the '018 Patent. In searching for this information, Regeneron: searched documents from Messrs./ Drs. . . . Smeland . . . Murphy . . . .

Id. at 588. Regeneron also asserted that it had produced all of its communications or attachments thereto from the

time period of the prosecution of the '018 patent "that even mentioned the content of any of the references cited" in the chart and memo. *Id.* Regeneron argued against Merus's request to impose sanctions for non-compliance with the Order by stating that it had explained to Merus that its production was tailored to the subject matter of the Jones documents. Regeneron also argued that broader disclosure could result in serious prejudice as it could impact a pending European patent appeal.

The district court determined that Regeneron needed to produce any documents which reflected *additional thoughts, concerns, and considerations given to whether certain references should have been disclosed.* The district court's broad Order included any other memos or communications related to whether such references should have been disclosed to the PTO. Included within the Order would have been drafts of Dr. Jones's chart or memo, which might have contained a different conclusion, memos of others who questioned Dr. Jones's conclusion, and the like. To remove all ambiguity, the district court required Regeneron to confirm to Merus that it had produced or would produce:

> 1. All documents from anyone involved directly or indirectly in prosecuting the '018 Patent, *relating to* whether prior art should be or should have been disclosed as part of the prosecution of the '018 Patent . . . .
>
> 2. To avoid any doubt, the following documents are included within the scope of the above directive:
>
> a. All documents of any kind from the files of Dr. Jones and others with whom he worked on the prosecution of the '018 Patent regarding whether or not to disclose prior art to the PTO. All documents of any kind from the files of anyone else who was involved (directly or indirectly) in the

> prosecution of the '018 Patent and who may not be captured in paragraph 1 above, who gave consideration to the relevance or applicability of prior art to the '018 Patent.

Id. at 589. Regeneron confirmed it had produced what was required.

3

These events lead up to trial. A bench trial on Merus's claim of inequitable conduct was scheduled to commence on June 8, 2015. Under the local rules, the district court required the parties' witnesses to testify by declaration/affidavit on direct examination. Regeneron submitted trial affidavits from Drs. Smeland and Jones, both attorneys acting as attorneys. At this time, Regeneron's privilege log indicated that it had withheld many documents from Dr. Smeland's files that he had authored or received on the basis of the attorney/client privilege and/or work product doctrine. The same was true for Dr. Jones except for the binder of documents that Regeneron had earlier disclosed pursuant to the district court's Order.

Merus cried foul. Merus argued that Regeneron was again engaging in a sword/shield use of the attorney client privilege and moved to strike these affidavits based on, *inter alia,* the assertion that Regeneron had shielded privileged documents from disclosure that were now directly implicated by the trial declarations. According to Merus, Dr. Jones's trial affidavit relied heavily on information that Regeneron failed to disclose during fact discovery and in response to the district court's prior Order. In particular, Merus cited Dr. Jones's deposition testimony that apart from a phone call that he had made to the PTO to schedule a meeting, he could not recall a single other communication with the Examiner during the '018 patent prosecution. Late-produced billing records

referenced in Dr. Jones's trial affidavit, however, suggested otherwise.

Things were worse with respect to Dr. Smeland. Merus argued that Dr. Smeland was proposing to testify about his views on the meaning of claim language and his subjective understanding of the Withheld References. During discovery, however, Regeneron had withheld numerous documents on precisely those topics on the basis of privilege.

The district court reviewed each of the trial affidavits and concluded that a comparison of these affidavits with entries on Regeneron's privilege logs raised a number of concerns. In his affidavit, Dr. Smeland made dozens of assertions regarding topics about which Regeneron had not disclosed documents by placing those documents on its privilege log. In particular, Dr. Smeland made statements about his understanding of the scope of the invention in the '176 application, his state of mind, and what he knew and thought about each of the Withheld References at the time of patent prosecution continuing up to the present. The district court provided a lengthy list of Dr. Smeland's problematic assertions to emphasize the seriousness of the issue. In particular, Dr. Smeland stated that:

- "*I firmly believed—and still believe today*—that Brüggemann, Taki, Zou and Wood were not material to patentability because they were substantially different from the mice claimed in the '176 application . . . and were cumulative of other information before the Patent Examiner."
- Dr. Smeland's description of his understanding of what a materiality analysis for inequitable conduct involves: "Regardless of whether I satisfied the minimum requirements of being an ordinary skilled artisan, I felt comfortable

evaluating the art from that perspective during the prosecution of the '176 application. When I did have questions, however, I did not hesitate to reach out to those with more experience and knowledge."

- "I routinely made Regeneron inventors aware of the foregoing obligations when providing them with invention declarations."
- With regards to Brüggemann and Zou, "*I was generally familiar with* the subject matter of those two references . . . *[a]t no time did I consider* these references to be material to patentability to the claims pending in the '176 application."
- "Because of this experience [prosecuting the '176 application as well as the '287 Patent], *I was readily familiar* with both prior art that was before the Examiner in the '176 application and the pending claims of the '176 application."
- "I viewed the analysis [relating to the Withheld References] as straightforward."
- "*I concluded* that [the Withheld References], alone or combined with other prior art of which I was aware, were cumulative of information already before the Examiner. Furthermore, *it was my view that* the skilled artisan would not have viewed them as teaching the reverse chimeric inventions that the Examiner had allowed in the '176 application."

Id. at 590–93.[5]

These statements and others implicated Dr. Smeland's knowledge and state of mind regarding the Withheld References directly—both during prosecution and continuing through to trial. During litigation, Regeneron made a choice to maintain the attorney-client privilege as to Dr. Smeland's knowledge and thoughts about the Withheld References during prosecution of the '176 application. In maintaining its assertion of privilege, Regeneron shielded Dr. Smeland's documents relating to his knowledge and thoughts about the Withheld References during prosecution from disclosure. As with any affirmative disclosure of information otherwise protected by the attorney-client privilege, however, once the disclosure of the trial affidavit was made, as it was not inadvertent, the waiver was complete. *See In re von Bulow*, 828 F.2d 94, 102–03 (2d Cir. 1987) ("'[S]ubject matter waiver' . . . allows the attacking party to reach all privileged conversations regarding a particular subject once one privileged conversation on that topic has been disclosed."); *see also Fort James Corp. v. Solo Cup Co.*, 412 F.3d 1340, 1349 (Fed. Cir. 2005) ("The widely applied standard for determining the scope of a waiver of attorney-client privilege is that the waiver applies to all other communications relating to the same subject matter.").

Thus, on the day that Regeneron disclosed Dr. Smeland's trial affidavit, it waived the privilege as to the subject matter of each of the topics the affidavit addressed. In particular, Regeneron waived privilege as to Dr. Smeland's views on the broadest reasonable construction of the claim language, understanding of the technolo-

---

[5] The full list of problematic assertions the district court highlighted can be found in *Regeneron I*, 144 F. Supp. 3d at 590–93.

gy, and materiality (including cumulativeness) of each of the Withheld References.

Regeneron argued that it had fully complied with its disclosure requirements throughout litigation. Merus, on the other hand, pointed to entries on Regeneron's privilege log that seemed inconsistent with Regeneron's representations. To resolve this dispute, the district court conducted an *in camera* review of a subset of the "many thousands" of documents on Regeneron's log. *Regeneron I*, 144 F. Supp. 3d at 594. According to the district court, the log turned out to be a "Pandora's Box." *Id.* The district court's *in camera* review revealed that there were dozens of "Smeland documents" that were not disclosed during litigation but as to which privilege had now been waived. The district court's *in camera* review revealed additional serious discovery issues including a number of relevant *non-privileged* documents that had been withheld on the basis of privilege and documents that should have been produced pursuant to the Order regarding the Jones Memo issue that had not been disclosed.

In all, the district court concluded that there were three categories of documents that presented serious concerns of discovery misconduct:

1. Non-privileged documents that were not produced and instead resided throughout litigation on the privilege log (e.g., numerous Excel spreadsheets with scientific test results, third party filings to the PTO, and fact statements by non-lawyers not seeking legal advice).

2. Previously privileged documents as to which Regeneron affirmatively waived the privilege by disclosing the "Jones Memo" and that the district court ordered be produced pursuant to its Order.

3. Documents on the privilege log relating to precisely those topics waived by Regeneron when Regeneron filed trial declarations of Drs. Smeland and Jones.

The district court determined that Regeneron's failure to make full and adequate production of documents in the first two categories during the period of fact discovery independently of the trial misconduct warranted serious sanction. But the third category was the most egregious. According to the district court, the production failure was undoubtedly larger than the few exemplars revealed by the court's *in camera* review. Given the thousands of documents on Regeneron's privilege log, the district court concluded that it could not possibly learn the full extent of the problem.

As to the first category, there were spreadsheets related to scientific tests, published articles, correspondence with third parties—all of which were relevant to issues in the case and should have been disclosed. Although the ultimate value of the documents in this category was unclear, it was clear that Merus should have received them well before trial.

In the second category, the district court concluded that there were a number of documents on the log involving Dr. Jones discussing his communication with the PTO during prosecution of the '018 patent. These should have been produced as part of the "Jones Memo" waiver issue.

The third category was most troubling. In the third category, the district court concluded that many documents on the log were directly relevant to the topics as to which privilege has been waived. In particular, these documents were directly relevant to Drs. Smeland and Murphy's mental impressions of the Withheld References during prosecution of the '018 patent. The documents would therefore have been relevant to determining if Regeneron specifically intended to deceive the PTO by

failing to disclose the Withheld References during prosecution of the '018 patent.

Based on its review of the privilege log and its *in camera* review of some of the documents on the log, the district court concluded that Regeneron's behavior warranted sanctioning. Before imposing its sanction, the district court considered several alternate options including allowing the trial declarations into evidence. To do so, however, the district court would have had to wholesale reopen discovery requiring "a top-to-bottom re-review of the Regeneron privilege log," "additional document production, fact depositions, and revised expert reports and depositions." *Regeneron I*, 144 F. Supp. 3d at 594–95. Additionally, the district court noted that given its "concerns with Regeneron's process to date, the [c]ourt would require that any such process only occur with the direct oversight of a special master." *Id.* This would have significantly increased the time and cost for both Merus and the district court. As the district court noted, "[a]t this point in the litigation, this is not a fair burden for Merus or this [c]ourt." *Id.*

The district court also considered whether striking the trial affidavits and precluding Drs. Smeland and Murphy from testifying at trial would be a sufficient remedy. The court concluded that it would not because doing so would not address the problems caused by the first two categories of undisclosed documents and would not address the delay and disruptions caused by Regeneron's behavior throughout litigation.

The district court ultimately concluded that it would be unfair to Merus to reopen discovery on the eve of trial and inject further delay in the case entirely due to Regeneron's behavior. The court also concluded that doing so would impose an unfair burden on the court and require expending substantial additional judicial resources. Further, because Regeneron's behavior suggested "a

pattern" of misconduct, simply reopening discovery, striking the problematic affidavits, and/or shifting costs would not ensure fairness. *Id.* at 595–96. Accordingly, the district court sought an alternative remedy and concluded that it was appropriate to draw an adverse inference against Regeneron from the undisclosed documents. In particular, the district court concluded that Regeneron failed to disclose the Withheld References to the PTO during prosecution of the '018 patent with the specific intent to deceive the PTO.

4

Regeneron contends that it was improper for the district court to apply an adverse inference here. According to Regeneron, under Second Circuit law, a district court may only apply an adverse inference when *a particular piece of evidence* is missing, destroyed, or untimely produced. Appellant's Br. 57–58 (citing *Residential Funding*, 306 F.3d at 106).[6] Because the district court did not apply the adverse inference to any particular piece of evidence, Regeneron argues that the district court abused its discretion. We disagree.

Although Regeneron relies on *Residential Funding* for its argument, that case does not support Regeneron's position. There, the Second Circuit explained that a district court may properly draw an adverse inference when a party engages in discovery abuses even when no *particular piece of evidence* is missing, destroyed, or untimely produced. *Residential Funding*, 306 F.3d at 107. In fact, the Second Circuit goes on to clarify that when "the alleged breach of a discovery obligation is the

---

[6] We apply the law of the relevant regional circuit with respect to privilege disputes that do not implicate substantive patent law. *See GFI, Inc. v. Franklin Corp.*, 265 F.3d 1268, 1272 (Fed. Cir. 2001).

non-production of evidence, a district court has broad discretion in fashioning an appropriate sanction, including the discretion to . . . proceed with a trial and give an adverse inference instruction." *Id.* (emphasis added). *Residential Funding* confirms the broad discretion of district courts in sanctioning parties for violating discovery obligations, and never limits the power of the district court to only apply adverse inferences against specific pieces of evidence that are missing, destroyed, or untimely produced.

Regeneron also argues that the district court's sanction was not an adverse inference but was, in fact, a dismissal which should have required a predicate finding of bad faith. Appellant's Br. 57–63. As explained above, however, the district court's sanction was not a dismissal but was a properly drawn adverse inference against Regeneron. Even Regeneron admits that bad faith is not required for such a sanction. *See* Reply Br. 27 ("That matters because, although an ordinary adverse inference does not require a finding of bad faith, more punitive sanctions do."); *accord Residential Funding*, 306 F.3d at 101 ("[D]iscovery sanctions, including an adverse inference instruction, may be imposed where a party has breached a discovery obligation not only through bad faith or gross negligence, but also through ordinary negligence.").[7]

---

[7] Although neither party addressed this issue, *Residential Funding* may have been superseded in part by the 2015 Amendment to the Federal Rule of Civil Procedure Rule 37(e). As the Advisory Committee Notes to the rule state, the new Rule 37(e) "rejects cases such as *Residential Funding* . . . that authorize the giving of adverse-inference instructions on a finding of negligence or gross negligence." Rule 37(e), however, only applies to sanctions based on a party's "failure to preserve electroni-

The dissent relies heavily on *Aptix Corp. v. Quickturn Design Systems, Inc.*, 269 F.3d 1369 (Fed. Cir. 2001), for the proposition that litigation misconduct cannot support a finding of unenforceability of a patent for inequitable conduct. Dissent at 3–6. Neither the parties nor the district court relied on *Aptix*, and for good reason. *Aptix* is inapposite.

In *Aptix*, the district court declared a patent unenforceable as a "penalty" because Aptix engaged in litigation misconduct under the doctrine of unclean hands. 269 F.3d at 1378. We reversed that decision holding that "the doctrine of unclean hands [does not] provide a suitable basis for the district court's judgment, as this equitable doctrine is not a source of power to punish." *Id.* We did so because "the relief for unclean hands targets specifically the misconduct, without reference to the property right that is the subject of the litigation." *Id.* at 1376. Essentially, we held that courts may not punish a party's post-prosecution misconduct by declaring the patent unenforceable.

Here, Regeneron is accused not only of post-prosecution misconduct but also of engaging in inequitable conduct *during* prosecution. *Cf.* Dissent at 4 ("[I]n order to invalidate the patent, the inequitable conduct must have occurred in patent prosecution."). Regeneron's litigation misconduct, however, obfuscated its prosecution misconduct. In particular, Regeneron failed to disclose documents directly related to its prosecuting attorneys' mental impressions of the Withheld References during prosecution of the '018 patent. The district court drew an adverse inference to sanction this litigation misconduct. The district court did not punish Regeneron's litigation

---

cally stored information." For sanctions based on other discovery misconduct, *Residential Funding* remains good law in the Second Circuit.

misconduct by holding the patent unenforceable. Only after Merus proved the remaining elements of inequitable conduct did the district court hold the patent unenforceable. In light of Appellant's widespread litigation misconduct, including Appellant's use of sword and shield tactics to protect Drs. Smeland and Murphy's thoughts regarding disclosure of the Withheld References to the PTO during prosecution of the '018 patent, we conclude that the district court did not abuse its discretion by drawing an adverse inference of specific intent to deceive the PTO.

C

Substantial evidence supports the district court's finding of but-for materiality of the Withheld References. Further, the district court did not abuse its discretion by drawing an adverse inference of Regeneron's specific intent to deceive the PTO. Thus, the district court did not abuse its discretion in holding the '018 patent unenforceable due to Regeneron's inequitable conduct. Because we conclude that Regeneron's inequitable conduct renders the '018 patent unenforceable, we do not address Regeneron's remaining claim construction and indefiniteness challenges.

AFFIRMED

United States Court of Appeals for the Federal Circuit

REGENERON PHARMACEUTICALS, INC.,
Plaintiff-Appellant

v.

MERUS N.V.,

Defendant-Appellee

2016-1346

Appeal from the United States District Court for the Southern District of New York in No. 1:14-cv-01650-KBF, Judge Katherine B. Forrest.

NEWMAN, *Circuit Judge,* dissenting.

The only issue decided by the panel majority is the district court's ruling of inequitable conduct during patent prosecution.[1] I respectfully dissent, for my colleagues apply incorrect law and add confusion to precedent.

---

[1] *Regeneron Pharmaceuticals v. Merus B.V.,* 144 F. Supp. 3d 530 (S.D.N.Y. 2015) ("Dist. Ct. Op.").

To establish "inequitable conduct" in patent prosecution, both materiality and deceptive intent must be proved

"Inequitable conduct" arises when material references were intentionally withheld by the patent applicant in order to deceive or mislead the examiner into granting the patent. Both materiality and intent must be proved by clear and convincing evidence. *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1287 (Fed. Cir. 2011). Intent to deceive cannot be inferred; yet here, the district court inferred intent to deceive during prosecution and invalidated the patent, as a sanction for purported attorney misconduct during this litigation.

The district court found that certain uncited references were "but-for material" to patentability—although the court did not find the '018 patent claims invalid on the substantive content of these references. The district court then declined to decide the question of specific intent to deceive the patent examiner. Instead, the court cancelled the scheduled trial on the question of intent, adopted an "inference" of intent, and held the '018 patent unenforceable on grounds of inequitable conduct as a sanction for Regeneron's "litigation misconduct" relating to discovery and the privilege log during this litigation.

The panel majority acknowledges that "the district court never held a second trial to determine if Regeneron acted with the specific intent to deceive the PTO during prosecution." Maj. Op. at 21. This absence of trial and trial findings on this critical issue cannot be substituted by inference.

Nor is the appellate role to scour the Appendix to fill the gap and make our own appellate finding of "intent to deceive." Here, no evidentiary record was developed on intent to deceive, with no testimony and no opportunity for examination and cross-examination of witnesses. The panel majority instead engages in innuendo based on its

careful selections from documents not admitted into evidence. The panel majority thus convicts Regeneron, its counsel, and its scientists, with no trial, no evidence, and no opportunity to respond in their defense.

Materiality does not establish intent; deliberate withholding of but-for invalidating prior art, with the intent to deceive the examiner, must be established by clear and convincing evidence. The majority's mechanism whereby dispositive facts are found for the first time on appeal, with no right of traverse by the affected party, is contrary to fundamental fairness and judicial process. If the panel majority indeed believes that the four "uncited" references are but-for material to patentability, we should at least require trial of the question of intent.

Whether or not counsel's discovery and privilege disputes were justifiable, invalidation of the patent is not an available remedy for such disputes

Instead of requiring proof of intent to deceive the examiner during patent prosecution, the panel majority upholds the district court's "adverse inference" in light of "widespread litigation misconduct." Maj. Op. at 38. Misconduct during litigation—as the district court viewed counsel's actions concerning discovery and the privilege log—cannot substitute for evidence of intent to deceive by withholding but-for material prior art during patent prosecution.

Precedent is long-standing, unambiguous, and binding. In *Keystone Driller Co. v. General Excavator Co.*, 290 U.S. 240 (1933), the Court established that litigation misconduct can support the dismissal of the suit, whereas patent invalidity or unenforceability must be established on the law of validity or enforceability. Applying *Keystone Driller*, in *Aptix Corp. v. Quickturn Design Systems, Inc.*, 269 F.3d 1369 (Fed. Cir. 2001), this court held that:

> [T]he remedies for litigation misconduct bar the malfeasant who committed the misconduct. The property right itself remains independent of the conduct of a litigant.

Id. at 1375. This court elaborated:

> Leaving the patent right intact, the Supreme Court repeatedly stressed that litigation misconduct bars the litigant. Again in *Hazel–Atlas Glass Co. v. Hartford–Empire Co.*, 322 U.S. 238 (1944), *overruled on other grounds by Standard Oil Co. v. United States*, 429 U.S. 17, 18 (1976), another instance of extreme litigation misconduct, the Supreme Court "require[d] that Hartford be denied relief," but left the patent right intact. *Id.* at 251.

Id. We continued to explain that in order to invalidate the patent, the inequitable conduct must have occurred in patent prosecution:

> Litigation misconduct, while serving as a basis to dismiss the wrongful litigant, does not infect, or even affect, the original grant of the property right.

Id. We concluded:

> No case law from the Supreme Court or this court provides a basis for nullifying property rights granted by the United States when such property rights did not themselves accrue through inequitable conduct.

Id. at 1377.

The *Aptix* holding has been applied in trial forums across the nation. *E.g.*, *Kimberly-Clark Worldwide, Inc. v. First Quality Baby Prod., LLC*, 2011 WL 679337, at *6 (E.D. Wis. Feb. 16, 2011) ("[A]lleged litigation misconduct is not sufficient to support a counterclaim of unenforceablity of a patent."); *MedPointe Healthcare Inc. v. Hi-Tech*

Pharmacal Co., 380 F. Supp. 2d 457, 467 (D.N.J. 2005) ("[B]ecause the alleged misconduct involved conduct before the court and not before the patent office during the procurement of the patent, it does not taint the property right *ab initio* to render the patent unenforceable."); *Honeywell Int'l, Inc. v. Universal Avionics Sys. Corp.*, 398 F. Supp. 2d 305, 311 (D. Del. 2005) ("If the wrongdoing occurs during the prosecution of the patent, in the furtherance of obtaining a patent right, then it can render the patent unenforceable. Alternatively, if unclean hands occurs during litigation, it bars any recovery by the offending party.").

The panel majority dismisses *Aptix* as "inapposite," Maj. Op. at 37, because Regeneron was "accused . . . of engaging in inequitable conduct *during* prosecution," *id.* Our system of justice is bottomed upon proof, not upon bare accusation. Intent to deceive is not established by accusation and innuendo. It is only established by evidence. That evidence "must be sufficient to *require* a finding of deceitful intent in the light of all the circumstances." *Therasense,* 649 F.3d at 1290 (quoting *Kingsdown Med. Consultants Ltd. v. Hollister Inc.*, 863 F.2d 867, 873 (Fed. Cir. 1988) (emphasis original)).

The panel majority also states that "the district court did not punish Regeneron's litigation misconduct by holding the patent unenforceable." Maj. Op. at 37–38. However, the district court stated that it "impose[d] the sanction of an adverse inference as to the intent of Smeland and Murphy with regard to inequitable conduct during patent prosecution." Dist. Ct. Op. at 595. A sanction, by definition, is punishment; here, in holding the patent unenforceable. This is a further departure from binding precedent, as equitable doctrines are not a source of a power to punish. *Feltner v. Columbia Pictures Television, Inc.*, 523 U.S. 340, 352–53 (1998); *Tull v. United States*, 481 U.S. 412, 422 (1987) ("Remedies intended to punish culpable individuals, as opposed to those

intended simply to extract compensation or restore the status quo, were issued by courts of law, not courts of equity.").

In its attempt to the Supreme Court precedent or principles of equity underlying the holding. Nor does the panel majority cite a single case—at any level of the federal system—in which litigation misconduct was part of a finding of inequitable conduct. An unbroken line of precedent strictly limits the inequitable conduct inquiry to a patentee's conduct before the examiner.

Aptix instructs that litigation misconduct in the infringement suit "does not infect, or even affect" the patent right. 269 F.3d at 1375. The panel majority errs in "infecting" its analysis of inequitable conduct with counsel's purported litigation misconduct years later in the infringement trial.

I also review the court's treatment of the four purportedly withheld references, for they do not impart unpatentability to the claims, and thus are not but-for material.

The references cited by the examiner were fully explored during patent prosecution; the additional references do not add invalidating information

The '018 patent is one of a family of patents directed to Regeneron's VelociGene technology, which uses quantitative assays to screen for DNA recombination events. During prosecution the examiner cited seven references, including U.S. Application 11/009,873 ("Lonberg") and U.S. Patent No. 6,114,598 ("Kucherlapati"), and considered U.S. Patent No. 6,130,364 ("Jakobovits"). The examiner rejected all the claims of the '018 application as anticipated by Lonberg, and obvious over Lonberg in combination with three other references, including a

Brüggemann reference dated four years after the allegedly withheld Brüggemann reference, discussed *post*.

Lonberg was the examiner's primary reference, and teaches the introduction of immunoglobulin transgenes into mouse cells. Lonberg specifically discloses "constructing" a transgene composed of at least one variable gene segment, one joining gene segment, and one constant region gene segment, preferably of human origin. Lonberg, [0031][2]. These segments are "unrearranged" in that they are not "rearranged as to encode a functional immunoglobulin light or heavy chain," but are not in germline configuration. *Id.* The Lonberg transgene constructs may include regulatory sequences from either the host (i.e., murine) or a related animal, or from the exogenous (i.e., human) species. *Id.* at [0033]. These transgenes are randomly integrated into the host (mouse) genome, *id.* at [0292], and the resulting animals are then crossed with "knockout" mice—i.e., mice with a disrupted immunoglobulin locus, *id.* at [0296]. The result is that the crossbred mice produce heterologous (i.e., non-host) antibodies.

Kucherlapati teaches methods of producing transgenic animals in which the host endogenous immunoglobulin locus is "substituted by a portion of, or an entire, xenogeneic immunoglobulin locus, or may have a xenogeneic immunoglobulin locus inserted into a chromosome of the host cell and an inactivated endogenous immunoglobulin region." Kucherlapati, col. 3, ll. 51–55. Kucherlapati teaches both random integration and targeted insertion of the immunoglobulin locus. Such xenogeneic immunoglobulin loci are described as "human, constant and/or variable regions." *Id.* at col. 5, ll. 51–54. Kucherlapati teaches that the xenogeneic locus "will be placed in substantially the same position as the analogous host locus,

---

[2] The bracketed paragraph citation format is retained from the reference.

so that any regulation associated with the position of the locus will be substantially the same for the xenogeneic locus." *Id.* at col. 10, ll. 51–55. As an example, Kucherlapati teaches retaining promoter and regulatory regions of the host DNA. *Id.* at col. 10, l. 64–col. 11, l. 2.

The district court referred to Regeneron's arguments before the European Patent Office about whether Kucherlapati was enabled. Dist. Ct. Op. at 577–78 (citing Merus's expert). The panel majority cites Regeneron's arguments about Kucherlapati's enablement in the prosecution of a different patent application, U.S. Application No. 13/719,819.[3] Maj. Op. at 20. However, argument of Kucherlapati's enablement does not appear in the prosecution record of the '018 application. "United States patents—even those only asserted as prior art in an invalidity defense—are presumed enabled." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003). Kucherlapati was thus presumed enabled before the examiner.

The Jakobovits reference teaches the "use of *Cre*-mediated site-specific recombination for modifying immunoglobulin loci, for instance, to replace all or a part of either the constant region or variable region of an antibody molecule." Jakobovits, col. 1, ll. 11–14. That is, Jakobovits teaches a method for targeted insertion at an immunoglobulin locus.

The examiner in the "reasons for allowance" stated that "the prior art does not teach or suggest a genetically modified mouse comprising, in its germline cells, human unrearranged variable region gene segments inserted at an endogenous mouse immunoglobulin locus." J.A. 531. No error has been ascribed to this finding.

---

[3] I note that this application was recently allowed over both Kucherlapati and Taki.

The purportedly withheld references were not more material than the cited references

None of the purportedly withheld references provides teachings more material than in the cited references. No purportedly withheld information was identified by the district court or the panel majority to teach a missing limitation or provide a motivation missing in the art.

Despite this failure, the district court held that the following uncited references and information were material to patentability:

1. Marianne Brüggeman & Michael S. Neuberger, "Strategies for Expressing Human Antibody Repertoires in Transgenic Mice," 17(8) *Review Immunology Today* 391 (1996) ("Brüggeman")
2. Shinsuke Taki et al., "Targeted Insertion of a Variable Region Gene into the Immunoglobulin Heavy Chain Locus," 262 *Science* 1268 (1993) ("Taki")
3. Yong-Rui Zou et al., "Cre-loxP-mediated Gene Replacement: A Mouse Strain Producing Humanized Antibodies," 4(12) *Current Biology* 1099 (1994) ("Zou")
4. WO 91/00906 ("Wood")
5. Certain opposition briefs filed by third parties in the European Patent Office contesting patentability of EP No. 1 360 287 (EP '287)

The test for materiality is not whether references are directed to similar subject matter; the test is whether "the PTO would not have allowed a claim had it been aware of the undisclosed prior art." *Therasense*, 649 F.3d at 1291. That standard is not met here.

Neither the district court nor my colleagues find that any uncited reference was closer to the claimed subject matter than the cited references, or filled gaps in the cited references, or related to additional limitations in the claims. Nor did the district court find invalidity based on the uncited references; invalidity was based on the court's finding of indefiniteness, not on obviousness over cited or uncited prior art.[4]

The uncited references do not provide additional information of but-for materiality with respect to the claimed technology. My colleagues suggest that because these four references were later cited by Regeneron in the prosecution of related cases, this is an admission that the references are material. Surely it was prudent for Regeneron to submit these citations to the examiner for consideration in any still-pending applications, and Regeneron states that it also submitted the district court's opinion. That action cannot be taken as an admission of but-for materiality.

The parties debate several aspects of the broadest reasonable interpretation of claim terms, but neither the district court's nor my colleagues' analysis shows that any "withheld reference" is more material than the cited references. Under the district court's "broadest reasonable interpretation," the '018 claims require a genetically modified mouse, the genes of which have been modified using the particular large targeting vector method described in the specification, by the insertion of human

---

[4] The references, cited and uncited, all recognize the goal of providing antibodies for utility in human therapies—a goal not achieved. The district court recognized that the references state the motivation for development of the science, but it appears undisputed that the problem was not solved until the Regeneron scientists succeeded, as reported in the '018 patent.

variable region DNA in its germline configuration into or next to the endogenous mouse immunoglobulin locus. Dist. Ct. Op. at 564–67. The "withheld references" indeed relate to genetic modification, but they are not but-for material as compared with the references before the examiner.

The district court does not establish that the allegedly withheld references lead to unpatentability. Instead, the district court states that the references disclose motivations, benefits, and cumulative teachings. That is correct; but the references do not provide but-for materiality, whether taken alone, or with the cited references.

The VelociGene project arose in a field of complex and unpredictable science, with no consensus on how to produce therapeutically effective antibodies. The predictability of the state of the science relates to the materiality determination, as the court has explained:

> The methodology of science and the advance of technology are founded on the investigator's educated application of what is known, to intelligent exploration of what is not known. Each case must be decided in its particular context, including the characteristics of the science or technology, its state of advance, the nature of the known choices, the specificity or generality of the prior art, and the predictability of results in the area of interest.

Abbott Labs. v. Sandoz, Inc., 544 F.3d 1341, 1352 (Fed. Cir. 2008). Recognition of the value of providing a murine source of antibodies with therapeutic effect in humans does not render the achievement obvious when it is ultimately successful. *See Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 381 F.3d 1371, 1377 (Fed. Cir. 2004) ("Recognition of a need does not render obvious the achievement that meets that need.").

Nonetheless, my colleagues find that these four cumulative references are but-for material and were intentionally withheld in order to deceive the examiner. That is insupportable, as review demonstrates:

i. Brüggemann

Brüggemann is a 1996 review paper that collects the then-published methods of integrating immunoglobulin transgenes into murine genomes. Brüggemann concludes with a statement of hope for future achievement:

> [A]n attractive alternative would be to replace the mouse Ig loci with the human Ig loci; in this way it might also be possible to retain and exploit any possible regulatory sequences in the mouse loci that are located distal to protein-coding regions. While such ambitions have not yet been realized, successful replacement of small portions of the mouse genome have been described.

Brüggemann at 394. Brüggemann also states:

> [I]t is far from clear whether this [Ig loci replacement] will be the best way to create a mouse strain giving rise to a wide-range of high-affinity antibodies.

Id. at 397. The district court found that Brüggemann taught (1) replacing "much of" the mouse Ig locus with human DNA; (2) an "explicit motivation" to exploit endogenous regulatory sequences; and (3) retaining an entirely human gene segment and an entirely murine gene segment. Dist. Ct. Op. at 572, 575. The district court ignored Brüggemann's statements that these results had not been achieved, as well as that these elements are not required by the claims. *See SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1121 (Fed. Cir. 1985) (en banc) ("It is the claims that measure the invention.").

Brüggemann does not teach unrearranged variable region gene segments in the germline configuration, nor does it teach any method—much less the LTVEC method required by the claims. Indeed, the district court's finding of materiality of Brüggemann is in conflict with the district court's rejection of Regeneron's arguments that the claims require retaining the murine constant region and require functional murine regulatory elements. Brüggemann's statement of "unrealized ambitions" of targeted replacement of the immunoglobulin locus does not impart invalidating materiality when the ambitions are accomplished by Regeneron.

The Jakobovits reference teaches "replac[ing] all or a part of either the constant region or variable region of an antibody molecule." Jakobovits, col. 1, ll. 11–14. Kucherlapati, also cited by the examiner, teaches retaining promoter and regulatory regions of the host DNA. Kucherlapati, col. 10, l. 64–col. 11, l. 2. The district court found that Kucherlapati and Brüggemann were not cumulative, stating:

> Brüggemann teaches the benefits of targeted insertion as taking advantage of the regulatory regions distal to the protein-coding regions and the expectation that mouse regulatory sequences distal to the protein coding regions will remain intact. In contrast, Kucherlapati states that "the xenogeneic locus will be placed substantially in the same region as the analogous host locus, so that any regulation associated with the position of the locus will be substantially the same for the xenogeneic locus."

Dist. Ct. Op. at 578 (internal citations omitted). The district court does not explain how this distinction converts Brüggemann into an invalidating reference.

The panel majority adopts different and flawed reasoning, finding that Brüggemann shows "targeted gene

replacement" while Kucherlapati shows "wholesale replacement." Maj. Op. at 20. These "unrealized ambitions" are not teachings of this long-sought result, as the references readily demonstrate. Moreover, Kucherlapati states that the host endogenous immunoglobulin locus is "substituted by a portion of, or an entire, xenogeneic immunoglobulin locus," Kucherlapati, col. 3, ll. 55, and describes the inserted DNA as "human, constant and/or variable regions," *id.* at col. 5, ll. 51–54, as does Brüggemann.

The panel majority also incorrectly states that Brüggemann suggests the method of Zou to accomplish retaining and exploiting regulatory elements. The method of Zou is cited only as an example of the "successful replacement of small portions of the mouse genome," as opposed to a method to accomplish the "possibility" of inserting larger portions of the immunoglobulin loci. Brüggemann at 394. The panel majority's statement that Zou is described as a method to retain and exploit regulatory sequences is a misreading of both Zou and Brüggemann.

ii. Taki

Taki is a 1993 article describing the then-knowledge of targeted insertion of a rearranged murine variable region construct at the immunoglobulin locus. The rearranged gene inserted in the Taki reference, V_H15, is derived from a murine antibody to phosphorylcholine. Taki at 1268. In that early work, the Taki transgenic mouse produced fully murine antibodies to this particular antigen. The goal of this research was "exploration of immunoregulatory mechanisms," *id.*, not the development of therapeutically useful human antibodies.

The district court found that Taki taught "the motivation to target human variable region DNA into the mouse Ig locus." Dist. Ct. Op. at 574. Taki indeed mentions this long-sought ambition. The panel majority agrees, stating

that the "fact that Taki teaches using exogenous mouse DNA instead of exogenous human DNA does not detract from the motivation Taki provides to target the mouse Ig locus with exogenous DNA." Maj. Op. at 17. However, a "motivation" to solve a known scientific problem is not a teaching of how to achieve that solution. "Knowledge of the goal does not render its achievement obvious." *Abbott Labs.*, 544 F.3d at 1352.

The claims of the '018 patent require human DNA, not mouse DNA or any exogenous DNA. Neither the district court nor the panel majority addresses the enormous difference between Taki's use of a single rearranged variable region gene and the unrearranged variable region gene segment in the '018 patent. Taki does not teach a mouse with unrearranged variable region DNA capable of recombination to create innumerable immune responses. Taki does not teach the LTVEC method or human unrearranged variable region gene segments in their germline configuration. At most, Taki teaches targeted insertion of a single gene of mouse DNA at the immunoglobulin locus.

The district court recognized that Taki "provides different motivations" than Kucherlapati. Dist. Ct. Op. at 578. Taki reflects the early work in this field; it has been superseded by the teachings of Kucherlapati and the other cited references. The record does not support the district court's finding of materiality. The panel majority errs in holding otherwise.

iii. Zou

Zou teaches the targeted insertion of a human constant region gene segment, and uses the *Cre-loxP* system to "replace the mouse gene, Cγ1, which encodes the constant region of the heavy chain of IgG1 antibodies, with its human counterpart." Zou at 1099. The district court found Zou to be but-for material because it "provides significant motivation to target the mouse Ig locus with

human Ig DNA." Dist. Ct. Op. at 575. The district court's error was in equating the motivation to solve a known problem with teaching the solution to the problem.

The district court found that Zou, along with Taki, taught a "method" for inserting human unrearranged variable region gene segments into an endogenous mouse immunoglobulin locus. Dist. Ct. Op. at 575. Zou is cumulative of at least Kucherlapati, as well as Jakobovits who teaches the same *Cre-loxP*-mediated targeting of the immunoglobulin locus as utilized by both Zou and the '018 patent.[5] Jakobovits, col. 1, ll. 11–14. Kucherlapati teaches that the xenogeneic (human) locus is "substituted" in "substantially the same region as the analogous host locus." Kucherlapati, col. 10, ll. 50–55. Zou does not add but-for material information to these references. Zou and Jakobovits use the same method of targeted insertion; Zou is not alleged to teach a missing limitation, but only to provide a "motivation" to target the immunoglobulin locus. Again, "[k]nowledge of the goal does not render its achievement obvious." *Abbott Labs.*, 544 F.3d at 1352. The district court's contrary ruling is incorrect, as is the panel majority's endorsement of that ruling.[6]

---

[5] Although the district court found that Jakobovits taught targeting only for the insertion of lox sites, that is incorrect, for Jakobovits refers to the "use of Cre-mediated site-specific recombination for modifying immunoglobulin loci, for instance, to replace all or a part of either the constant region or variable region of an antibody molecule." Jakobovits, col. 1, ll. 11–14.

[6] The district court referred in a footnote to Regeneron's internal email discussion of citation to Zou in preparing a scientific publication, and found these conversations "relevant" to materiality. Dist. Ct. Op. at 557 n.21. This discussion has no bearing on the status of Zou as but-for material prior art.

iv. Wood

Wood describes a transgenic mouse having unrearranged human DNA fragments incorporated into its germline. Wood teaches the use of either constructed unrearranged gene fragments or the use of contiguous unrearranged human DNA. Wood, col. 16, ll. 14–22. Wood does not describe how such gene fragments are "introduced" or "integrated" into the germline of the described mouse; Wood does not teach targeted insertion.

The district court found that Wood teaches the "insertion of human variable region gene segments upstream of an endogenous mouse constant region, to produce a genetically modified mouse" and "motivates a person of ordinary skill to use an endogenous mouse constant μ (mu) region for purposes of allelic exclusion." Dist. Ct. Op. at 572–73. Both the district court and the panel majority misread Wood.

Wood teaches a "DNA fragment *construct*" with murine constant regions upstream from the human variable region gene segments. Building a DNA construct in a particular order to be later inserted is not the same as describing the targeted insertion of that construct into germline DNA. Wood does not describe any targeted insertion method described elsewhere in the prior art, such as *Cre-loxP*. The district court excuses this absence, because Wood "is appropriately understood as including but not limiting insertion at the Ig locus." Dist. Ct. Op. at 573.

Wood's teaching of a "DNA construct" was misread as teaching the targeted insertion of that construct at a particular portion of the endogenous locus. The Wood teaching of "integration" into the genome is cumulative of Lonberg and other references which broadly teach "integration" into the genome. Lonberg, [0292]. There is no support in Wood for the leap from a broad, unspecified disclosure of "integration" somewhere into the genome, to

the district court's finding of disclosure of targeted insertion at the Ig locus.

Neither my colleagues nor the district court explains how an examiner would have tied together the conflicting approaches and unrealized ambitions of the four purportedly omitted references to render obvious the method described and claimed in the '018 patent.

v. European Opposition Briefs

The European Opposition Briefs were filed in the European Patent Office, in an opposition proceeding associated with EP '287, a counterpart of the Regeneron technology. The Merus opposition brief cited the references cited by the United States examiner, and additional references in this busy field of science, including the same Brüggeman, Taki, Zou, and Wood references. The district court stated that the "faithful" "description" of the allegedly withheld references in the European opposition would "have led inexorably to an understanding of their relevance and but-for materiality." Dist. Ct. Op. at 577.

It is noteworthy that the European Technical Board of Appeals ruled that EP '287 was patentable over these allegedly withheld references. *See* Decision in Appeal No. T2220/14-3.3.08, at 67–68 (Taki); 71–72 (Brüggemann); 72–77 (Wood); and 77–78 (Zou), *available at* http://www.epo.org/law-practice/case-law-appeals/pdf/t-142220eu1.pdf. These determinations negate but-for materiality, as well as the district court's analysis. Perhaps this is why the panel majority chose not to discuss the European Opposition. Maj. Op. at 9 n.3.

There is no support—legally or factually—for the district court's reliance on the European opposition briefs to find these four references material to patentability. The European tribunal, with these references before it, did not find the claims unpatentable. Nor did the district court. The panel majority upholds a finding of but-for materiali-

ty without finding the claims invalid based on these purported but-for material references. It is not disputed that the information in those references did not solve the problem that was ultimately solved by the '018 patent.

CONCLUSION

The controlling precedent of *Aptix v. Quickturn*, *supra*, and *Keystone Driller*, *supra,* cannot be ignored by this panel. Although my colleagues make much of the purported "litigation misconduct" relating to the privilege log and discovery in this infringement litigation, this has no relation to whether there was inequitable conduct in the prosecution before the patent examiner. Intent to deceive the examiner cannot be inferred from purported litigation misconduct several years later.

The premises of the law of inequitable conduct have not been established by clear and convincing evidence. Intent to withhold material references in order to deceive the examiner was not found by the district court, and cannot be inferred. These four additional references were not but-for material to patentability, and specific intent to deceive was not shown. From my colleagues' contrary ruling, I respectfully dissent.