United States Court of Appeals for the Federal Circuit

INSTITUT PASTEUR & UNIVERSITE PIERRE ET MARIE CURIE,
Appellant,

v.

MARGARET A. FOCARINO,
Commissioner for Patents,
Appellee,

AND

PRECISION BIOSCIENCES, INC.,
Appellee.

2012-1485

Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences in Reexamination No. 95/000,443.

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2012-1487

Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences in Reexamination No. 95/000,491.

Decided: December 30, 2013

THOMAS H. JENKINS, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, of Washington, DC, argued for appellant. With him on the brief was KENNETH J. MEYERS, of Washington, DC and AMELIA F. BAUR, of Boston, Massachusetts.

MARY L. KELLY, Associate Solicitor, United States Patent and Trademark Office, of Alexandria, Virginia, argued for appellee Margaret A. Focarino, Commissioner for Patents. With her on the brief were NATHAN K. KELLEY, Acting Solicitor, and KRISTI L. R. SAWERT, Associate Solicitor.

MICHAEL J. TWOMEY, Wilmer Cutler Pickering Hale and Dorr, LLP, of Boston, Massachusetts, argued for appellee Precision BioSciences, Inc. Of counsel was ANDREJ BARBIC.

Before NEWMAN, CLEVENGER, and TARANTO, *Circuit Judges.*

TARANTO, *Circuit Judge.*

The Institut Pasteur owns U.S. Patent Nos. 7,309,605, 6,610,545, and 6,833,252, which claim methods and tools for the site-directed insertion of genes into eukaryotic chromosomes. Precision BioSciences requested *inter partes* reexamination of each of the patents, and the Patent and Trademark Office examiner rejected a number of Pasteur's claims for obviousness, under 35 U.S.C. § 103.

On appeal, the Board of Patent Appeals and Interferences (now the Patent Trial and Appeal Board) affirmed the rejections, concluding that the claimed inventions were obvious extensions of two prior-art references disclosing similar methods of targeting non-chromosomal DNA in prokaryotic cells. Pasteur appeals the Board's conclusions to this court. For the '605 patent, we dismiss Pasteur's appeal as moot, because Pasteur presented only substantively amended claims to the Board and to this court, and amended claims cannot be entered now that the patent has expired. For the '545 patent, we reverse the Board's conclusion as based on factual findings unsupported by substantial evidence and an erroneous obviousness analysis, including an improper discounting of Pasteur's objective indicia of non-obviousness. For the '252 patent, we vacate the Board's decision and remand for consideration of what motivation, if any, a skilled artisan at the relevant time would have had to pursue the claimed invention.

BACKGROUND

In the early 1990s, scientists at the Institut Pasteur made a series of inventions that allowed for the insertion, deletion, or modification of genes at targeted locations in the chromosomes of living cells. Specifically, Pasteur discovered a class of enzymes—group I intron-encoded (GIIE) endonucleases—that cleave both backbones of the DNA double helix at the location of a specific nucleotide sequence, called a recognition site. Pasteur established, first, that GIIE endonucleases can cleave DNA in the chromosomes of eukaryotic (nucleus-possessing) cells and, second, that eukaryotic cells can successfully repair such cleavages by initiating a process known as homologous recombination. This process uses a DNA template whose sequence is, in certain places, highly similar (*i.e.*, homologous) to that of the cleaved chromosomal DNA. It requires that the DNA template be homologous only at two portions, which must, respectively, match the regions of

the pieces of the broken DNA on either side of the break. When such matching occurs, the whole template sequence, including the nucleotides lying between the matching portions, gets copied to become part of a rejoined DNA molecule in a chromosome. The cell faithfully reproduces the DNA template, including the interior nucleotides, which need not match the broken DNA at all. In this way, it is possible to design a DNA template that adds a DNA sequence to the chromosome or makes specific alterations to its sequence.

GIIE endonucleases are particularly well suited for genetic engineering. Their recognition sites, *i.e.*, the nucleotide sequences at which they cleave DNA, are much longer than most other endonucleases. Whereas other classes of endonucleases recognize and bind to DNA sequences as short as four to eight nucleotides long, the recognition sites of GIIE endonucleases extend over eighteen nucleotides. This makes GIIE endonucleases much more discriminating in where they cleave a DNA molecule. By sheer probability, a given sequence of eight nucleotides occurs much more frequently than one of eighteen nucleotides. So whereas other endonucleases tend to cleave an organism's DNA at many different sites, GIIE endonucleases provide far superior specificity.

Pasteur first encountered GIIE endonucleases in yeast mitochondria, which are membrane-enclosed structures found within most eukaryotic cells. Although most of an organism's DNA is contained in chromosomes located in the cell nucleus—a different membrane-enclosed cellular structure—mitochondria have a small amount of their own DNA. Pasteur identified a specific DNA sequence that is repeatedly copied from one location in the mitochondrial DNA to another location in that DNA, *i.e.*, a mobile genetic sequence. The mobile DNA sequence that Pasteur identified resided in the introns of mitochondrial genes, *i.e.*, those nucleotides in a gene that generally do not code for the protein that the gene ex-

presses. After analyzing this mobile intronic sequence, Pasteur determined that it coded for an endonuclease, an enzyme that cleaves DNA backbones. Pasteur named the newly discovered endonuclease "I-SceI," and the new class became known as group I intron-encoded endonucleases.

Pasteur recognized that GIIE endonucleases could be useful laboratory tools and set out to determine whether they could cleave DNA other than the yeast mitochondrial DNA that they naturally cleave. First, Pasteur inserted an artificial GIIE endonuclease recognition site into a yeast chromosome and demonstrated that the GIIE endonuclease cleaved yeast chromosomes *after* they had been extracted from yeast cells and purified. *See, e.g.*, '545 patent, col. 15, line 63, to col. 16, line 8. Next, Pasteur created a plasmid—a small DNA molecule that is separate from and can replicate independently of chromosomal DNA—containing an artificial GIIE endonuclease recognition site and injected the plasmid into the yeast nucleus. The GIIE endonuclease successfully cleaved the plasmid. *See, e.g., id.*, col. 18, lines 35-39. Finally, and of particular significance, Pasteur found that GIIE endonucleases could cleave chromosomes in living cells and that, if DNA homologous to the cleavage site was present or added, the cell could repair the break using homologous recombination. *See, e.g.*, *id.*, col. 18, lines 42-53.

Pasteur filed a series of patent applications relating generally to GIIE endonucleases and methods of using them to insert DNA at a targeted location in an organism's DNA. All of the patents at issue here—the '605, '545, and '252 patents—claim priority to the same patent application, which was filed on May 5, 1992, and is now abandoned. All three patents expired on May 6, 2012. The '605 and '252 patents have a common specification, which differs in only minor ways from the specification of the '545 patent. Each specification describes first introducing a GIIE recognition site into a cell's chromosomal DNA. *See, e.g.*, '545 patent, col. 18, line 43, to col. 19, line

64. By introducing into the cell both (a) a GIIE endonuclease and (b) a plasmid that is homologous to the cleavage site and contains the DNA sequence to be inserted, the Pasteur inventors taught, it is possible to achieve the "site specific insertion of a DNA fragment from a plasmid into a chromosome." *Id.*, col. 19, lines 42-44.

The '605 patent claims methods for using a GIIE endonuclease to cleave DNA at a specific location and (for some claims) the subsequent insertion of DNA. During reexamination, Pasteur proposed amendments to claim 1 and the dependent claim now at issue, claim 14. Specifically, the proposed amendments would limit the claims to targeting *chromosomal* DNA in *viable* cells. Claim 1 reads as follows, with the amendments underlined:

> 1. A method for inducing at least one site directed double-stranded break in the chromosomal DNA of an organism comprising:
>
> (a) providing an isolated, viable cell of said organism containing at least one Group I intron encoded endonuclease recognition site at a location in the chromosomal DNA of the cell,
>
> (b) providing said Group I intron encoded endonuclease to said cell by genetically modifying the cell with a nucleic acid comprising said Group I intron encoded endonuclease or by introducing said Group I intron encoded endonuclease protein into the cell such that the Group I intron encoded endonuclease cleaves said Group I intron encoded endonuclease site at the location in the DNA of the cell.

'605 patent, col. 69, lines 22-35; *see also* J.A. 79 (as amended). Although claim 1 does not claim the insertion of new DNA sequences into the cleaved DNA, dependent claim 14, the only claim now at issue, adds that element. It reads (also with a proposed amendment underlined):

> 14. The method of claim 1, wherein said method further comprises providing to said cell
>
> a plasmid comprising a DNA sequence homologous to the sequence of the chromosome, which allows homologous recombination, and
>
> a modified sequence,
>
> wherein said Group I intron encoded endonuclease cleaves the Group I intron encoded endonuclease recognition site,
>
> whereby said cleavage promotes the insertion of said modified sequence into said chromosomal DNA of said cell at a specific site by homologous recombination.

’605 patent, col. 70, lines 26-39; *see also* J.A. 4029 (as amended).

The ’545 patent similarly claims methods for the site-specific insertion of DNA sequences into the chromosomes of living cells. As amended during reexamination, Claim 7 reads:

> 7. A method for in vivo site directed genetic recombination in an organism comprising:
>
> (a) providing a transgenic eukaryotic cell having at least one Group I intron encoded endonuclease recognition site inserted at a unique location in a chromosome;
>
> (b) providing an expression vector that expresses said endonuclease in said transgenic cell;
>
> (c) providing a plasmid comprising a gene of interest and a DNA sequence homologous to the sequence of the chromosome, allowing homologous recombination;

> (d) transfecting said transgenic cell with said plasmid of step (c);
>
> (e) expressing said endonuclease from said expression vector in said cell; and
>
> (f) cleaving said at least one Group I intron encoded endonuclease recognition site with said endonuclease, whereby said cleavage promotes the insertion of said gene of interest into said chromosome of said organism at a specific site by homologous recombination.

’545 patent, col. 51, lines 14-33; *see also* J.A. 121 (as amended). Dependent claims 10 and 12, the only claims at issue in this appeal, limit the method to yeast and mammalian cells, respectively. ’545 patent, col. 51, lines 40-41; *id.*, col. 52, lines 3-4.

The ’252 patent claims a mammalian chromosome that contains a GIIE endonuclease recognition site. Its claims, unlike the claims of the ’605 and ’545 patents at issue here, do not require the targeted insertion of DNA through homologous recombination. Claim 1 reads:

> 1. A recombinant mammalian chromosome comprising an exogenous Group I intron encoded endonuclease site,
>
> wherein the endonuclease site is within an integrated nucleic acid sequence from a vector,
>
> wherein the site is selected from the group consisting of an I-SceIV site, an I-CsmI site, I-PanI site, I-SceII site, an I-CeuI site, an I-PpoI site, an I-SceIII site, an I-CreI site, an I-TevI site, an I-TevII site, an I-TevIII site, and an I-SceI site.

’252 patent, col. 67, lines 57-65. Pasteur did not amend claim 1 during reexamination.

In 2009, Precision BioSciences filed *inter partes* reexamination requests for the ’605, ’545, and ’252 patents and for related U.S. Patent No. 7,214,536. *See* 35 U.S.C. § 311 *et seq*. (2006). The PTO granted all four requests, and during the ensuing reexaminations, the Examiner rejected most claims as anticipated or obvious.

In each reexamination, Pasteur timely appealed the rejections to the Patent Trial and Appeal Board. On decisions dated the same day and before the same panel, the Board relied on the same prior-art references to conclude that the matter claimed in the claims now at issue would have been obvious to one skilled in the art as of May 1992. *See Precision BioSciences, Inc. v. Institut Pasteur*, No. 11-012285, 2012 WL 1050572 (B.P.A.I. Mar. 14, 2012) (’605 Board Decision); *Precision BioSciences*, No. 11-010715, 2012 WL 1050569 (B.P.A.I. Mar. 14, 2012) (’545 Board Decision); *Precision BioSciences*, No. 11-011261, 2012 WL 1050570 (B.P.A.I. Mar. 14, 2012) (’252 Board Decision); *Precision BioSciences*, No. 11-010572, 2012 WL 1050568 (B.P.A.I. Mar. 14, 2012) (’536 Board Decision).

The Board founded its analysis on two articles from scientific journals—the Quirk and Bell-Pedersen references—that disclosed using a GIIE endonuclease to transfer DNA from a plasmid to *non-chromosomal* DNA in bacterial (*i.e.*, *prokaryotic*) cells. *See* J.A. 12535 (Quirk reference); *id.* at 8508 (Bell-Pedersen reference). Relying on certain statements in the prior art, the Board found that there was “reason to substitute the [non-chromosomal prokaryotic] DNA described in Quirk and Bell-Pedersen with chromosomal DNA of a eukaryotic cell.” *’545 Board Decision*, at *6; *see ’605 Board Decision*, at *18; *’252 Board Decision*, at *5.

In its decisions on the ’605 and ’545 patents, the Board then considered if “one of ordinary skill in the art [had] a reasonable expectation that the teachings of Quirk

and Bell-Pedersen could be successfully applied to [chromosomal DNA in] yeast cells."[1] *'545 Board Decision*, at *7; *see '605 Board Decision*, at *17-18. In finding a reasonable expectation of success, the Board relied on two references—Frey and Dujon. *'545 Board Decision*, at *8 ("Frey and Dujon[] achieved cleavage of eukaryotic chromosomes using a GIIE[endonuclease], giving rise to a reasonable expectation of success that the claimed invention could be practiced successfully."). The Board characterized both references as disclosing cleavage of chromosomal DNA *in yeast cells*. *See id.* ("In sum, each of Frey and Dujon[] showed that a GIIE endonuclease cleaved yeast chromosomal DNA when expressed in yeast cells."); *id.* at *7 ("Frey and Dujon . . . both . . . describe results using GIIE endonucleases in yeast."). (For the Board's similar findings in its '605 ruling, see *'605 Board Decision*, at *17-18.) For the '545 and '252 patents, the Board considered Pasteur's evidence that the claimed inventions were praised, copied, and licensed by the industry, but concluded that the evidence did not outweigh "the strong case of obviousness." *'545 Board Decision*, at *10; *see also '252 Board Decision*, at *6-7.

Pasteur timely sought this court's review of the Board's decisions. The PTO then moved to dismiss Pasteur's appeal with respect to the '536 patent, the '605 patent, and all claims of the '545 patent except dependent claims 10 and 12. The PTO argued that, because all of the patents had expired since the Board issued its decisions, and because the Board could not enter amendments

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[1] The Board's analysis of the '252 patent did not include a similar consideration, because "[c]laim 1 is directed to a mammalian chromosome with a [GIIE endonuclease] cleavage site" only. *'252 Board Decision*, at *6. Thus, the Board found that "the claims do not require endonuclease activity." *Id.*

to claims in expired patents, the challenges to the rejection of all claims that Pasteur had proposed to amend during reexamination were moot. Pasteur did not oppose the PTO's motion with respect to the '536 patent and to certain claims of the '545 patent, but did oppose dismissing its appeal of claim 14 of the '605 patent. This court dismissed Pasteur's appeal with respect to the '536 patent, as all parties agreed, but not with respect to the '605 patent, explaining that the parties should address the mootness of the '605 patent claims in their briefing. Order, *Institut Pasteur*, No. 12-1484 (Fed. Cir. Nov. 27, 2012).

This court has jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

Pasteur challenges the Board's determinations of obviousness as to claim 14 of the '605 patent, claims 10 and 12 of the '545 patent, and all claims of the '252 patent. We find Pasteur's appeal moot as to the '605 patent, and we address the merits of the '545 and '252 patents.

A

The '605 patent has expired since the Board's decision. Pasteur does not dispute that the PTO cannot issue amended claims for an expired patent if the amendments change the claim's scope. 37 C.F.R. § 1.530(j), (k). We conclude, contrary to Pasteur's contention, that the amendments it proposed during reexamination of the '605 patent did substantively narrow claim 1 and dependent claim 14. It follows that there is no live controversy over the Board's rejection of amended claim 14: even if the Board erred, the claim cannot issue.

Pasteur proposed amendments both to independent claim 1 and to dependent claim 14 that limited the targeted "DNA of an organism" to chromosomal DNA only. While agreeing that the amendments changed the scope

of claim 1, which is not at issue, Pasteur argues that they did not change the scope of claim 14, because the unamended claim 14 itself was implicitly limited to chromosomal DNA. Specifically, Pasteur argues that the original claim's requirement that the targeted DNA undergo homologous recombination with a newly introduced plasmid whose sequence is "homologous to the sequence of [a] chromosome," '605 patent, col. 70, lines 28-29, limited the claim to targeting chromosomal DNA.

Pasteur's reasoning is flawed. That homologous recombination occurs between the targeted DNA and an introduced plasmid that is homologous to a chromosome does not require that the targeted DNA actually be chromosomal DNA. It requires only that the targeted DNA be homologous to chromosomal DNA. Non-chromosomal DNA, such as mitochondrial DNA or DNA in an additional plasmid, can be homologous to chromosomal DNA. Thus, the original claim covered situations where non-chromosomal DNA is the targeted DNA. The amendment substantively narrowed the claim in requiring chromosomal DNA as the target.

Because amending the claim to target only "chromosomal" DNA substantively altered (narrowed) its scope, the PTO may not issue the amended claim now that the patent has expired, as stated in applicable provisions of a PTO regulation, 37 C.F.R. § 1.530(j), (k). That rule follows from the relevant statutory provisions. Looking backward, if the claim were to issue on reexamination, Pasteur could not enforce it for the period before issuance of the reexamination certificate. That is because, for *inter partes* reexaminations under the pre-2013 version of 35 U.S.C. § 316(b) applicable here, as for reissues under 35 U.S.C. § 252, when a claim is substantively amended, the analysis of intervening rights after issuance, considering pertinent references and prosecution history, treats the amendment as raising an irrebuttable presumption that the original claim was materially flawed, so there can be

no liability for acts of infringement before the amended claim issues. *See Bloom Eng'g Co., v. N. Am. Mfg. Co.*, 129 F.3d 1247, 1249 (Fed. Cir. 1997); *Tennant Co. v. Hako Minuteman, Inc.*, 878 F.2d 1413, 1417 (Fed. Cir. 1989) ("Claims amended during reexamination are entitled to the date of the original patent if they are without substantive change or are legally 'identical' to the claims in the original patent."). Looking forward, the PTO may not grant Pasteur a patent right extending beyond the statutorily authorized term, which has already ended. *See* 35 U.S.C. §§ 154 (term), 271(a) (limiting infringement to acts that occur "during the term of the patent").

B

Pasteur appeals the Board's conclusion that claims 10 and 12 of the '545 patent are invalid for obviousness.[2] As the Board correctly identified, the key issue in making that determination is whether the relevant skilled artisan–after reading Quirk's and Bell-Pedersen's disclosure that a GIIE endonuclease can promote targeted gene transfer into *non-chromosomal* DNA in *prokaryotic* cells–would have expected that a GIIE endonuclease would successfully promote targeted gene transfer into the chromosomal DNA of eukaryotic cells, and thus had good reason to pursue that possibility. The Supreme Court summarized the analysis that is relevant here:

[2] During reexamination, Pasteur proposed an amendment to narrow the method of independent claim 7 to eukaryotes. J.A. 121. Pasteur proposed no amendments specifically for dependent claims 10 and 12. Because those claims were already limited to eukaryotes (*i.e.*, yeast and mammals, respectively), '545 patent, col. 51, lines 40-41; *id.*, col. 52, lines 3-4, their scope was not altered by Pasteur's proposed amendment to claim 7.

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007). The Supreme Court's reference to "predictable solutions" and "anticipated success" accords with this court's longstanding focus on whether a person of ordinary skill in the art would, at the relevant time, have had a "reasonable expectation of success" in pursuing the possibility that turns out to succeed and is claimed. *E.g.*, *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1375 (Fed. Cir. 2013); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

The obviousness assessment depends on what the prior art teaches and on what non-prior-art evidence of "secondary considerations" (or objective indicia) may indicate about whether the invention would have been obvious at the relevant time. *KSR*, 550 U.S. at 406-07. Here, in ascertaining the scope and content of the prior art, the Board made factual determinations that were not supported by substantial evidence. The Board also failed to give proper consideration to at least two categories of evidence–(1) teachings in the prior art that targeting a cell's chromosomal DNA could be toxic to the cell and (2) industry praise and licensing of Pasteur's invention–that are important to the obviousness evaluation.

Those errors were prejudicial. Under a proper reading of the prior art, and with the appropriate consideration given to clear teachings that the claimed method could have been toxic to cells and to Pasteur's objective indicia of non-obviousness, we conclude that one of ordi-

nary skill in the art would not have reasonably predicted the successful adaptation of Quirk and Bell-Pedersen to target chromosomal DNA in eukaryotic cells. *See KSR*, 550 U.S. at 421. We therefore reverse the Board's determination that claims 10 and 12 of the '545 patent would have been obvious.

1

Applying the deferential "substantial evidence" standard of review, *see, e.g., Smith & Nephew, Inc. v. Rea*, 721 F.3d 1371, 1380 (Fed. Cir. 2013), we conclude that the Board erred in finding that two references in the prior art, Frey and Dujon, "showed that a GIIE endonuclease cleaved yeast chromosomal DNA when expressed in yeast cells." *'545 Board Decision*, at * 7. In fact, neither reference discloses a GIIE endonuclease cleaving yeast chromosomes while those chromosomes are in yeast cells.

Frey discloses cleaving yeast chromosomes that had already been extracted from yeast cells and purified, not chromosomes still "in yeast cells." The reference, a 1992 article from the Journal of Analytical Chemistry, expressly states that "[p]urified, intact chromosomes from the resulting strain [of yeast] were digested [*i.e.*, cleaved] with" a GIIE endonuclease. J.A. 9345. Thus, contrary to the Board's finding that the reference "describe[s] results using GIIE endonucleases in yeast," *'545 Board Decision*, at *7, the reference discloses only that a GIIE endonuclease could cleave yeast chromosomes extracted from yeast cells.

Nor does Dujon disclose cleaving yeast chromosomes in yeast cells; the reference is silent about what type of DNA is cleaved. Dujon is a two-page abstract that lists some of the '545 patent co-inventors as authors. *See* J.A. 11785-86. It teaches that a GIIE endonuclease "can be expressed in the yeast nucleus from artificial constructs and the protein is able to cleave efficiently both its natural site within mitochondria and an artificially placed site

within the nucleus." J.A. 11786. Nowhere else does the reference clarify what is meant by cleaving "an artificially placed site within the nucleus." As the PTO bears the burden of demonstrating a prima facie case of obviousness, *see, e.g.*, *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993), Dujon's language is insufficient to establish that the GIIE endonuclease targeted chromosomal DNA.

The Board relied on its misreading of both references, and nothing more, to conclude that "one of ordinary skill in the art [had] a reasonable expectation that the teachings of Quirk and Bell-Pedersen could be successfully applied to yeast cells." *'545 Board Decision*, at *7; *see also id.* at *8 ("Frey and Dujon[] achieved cleavage of eukaryotic chromosomes using a GIIE[endonuclease], giving rise to a reasonable expectation of success that the claimed invention could be practiced successfully."). Because no other references identified by the Board show a GIIE endonuclease cleaving chromosomal DNA in a eukaryotic cell, its errors were highly material to whether the '545 patent claims would have been obvious.

2

The Board compounded its erroneous findings by ignoring teachings that targeting a GIIE endonuclease to chromosomal DNA in a living cell could be highly toxic to the cell. The sole prior-art reference identified by the Board that discloses such a method warns of such dangers: a 1990 article in Nucleic Acids Research specifically teaches that introducing a GIIE endonuclease could be "highly toxic" to the cell, which might not be able to repair double-stranded breaks in the chromosome using homologous recombination. J.A. 10314. Such a teaching counts significantly against finding a motivation to take the claimed steps with a reasonable expectation of success. *See, e.g.*, *In re Rosuvastatin Calcium Patent Litig.*, 703 F.3d 511, 517 (Fed. Cir. 2012); *Takeda Chem. Indus., Ltd.*

v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1361-62 (Fed. Cir. 2007).

The Board's disregard of the toxicity teaching was not harmless. The Board stated that "[t]he claims [of the '545 patent] do not expressly require that the cells remain viable," *'545 Board Decision*, at *8, but it did not deny that continuing viability was implicit in the claims at issue, and the Director here does not say otherwise. In any event, the Board identified no reason at all that a skilled artisan would have pursued a method toxic to cells. It relied, rather, on the interest stated by the prior-art reference Old: "[i]t would be a great advance if such alterations could be engineered into copies of a chosen gene *in situ* within the chromosomes *of a living animal cell*." J.A. 10075 (second emphasis added). Toxicity would bear heavily on whether a skilled artisan would have a reasonable expectation of success in achieving that objective. The Board thus erred by disregarding evidence of toxicity of the method at issue.

In short, the prior art confirmed the great potential payoff of a method that produced a particular result. The desire for that payoff could motivate pursuit of the method, but "knowledge of the goal does not render its achievement obvious," *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008), and obviousness generally requires that a skilled artisan have reasonably expected success in achieving that goal. Importantly, without a sound explanation for doing otherwise, which is not present here, the expectation-of-success analysis must match the highly desired goal, not switch to a different goal that may be a less challenging but also less worthwhile pursuit. *See KSR*, 550 U.S. at 421 (asking if there is "a design need or market pressure to solve" a problem and if that same problem is one having "identified, predictable solutions").

Under a proper reading of the Frey and Dujon references, none of the prior art disclosed using a GIIE endonuclease to target gene transfer into chromosomal DNA without the potential for severe, toxic effects on the cell. In Frey, the process of extracting and purifying the chromosomes invariably kills the yeast cell; thus, in Frey, toxicity was not at issue. Dujon, like Quirk and Bell-Pedersen, did not disclose cleaving chromosomal DNA. There simply was no teaching that using a GIIE endonuclease to cleave eukaryotic chromosomes would successfully initiate the cell's reparative homologous-recombination machinery. To the contrary, the prior art teaches only that such cleavages could be highly toxic to the cell. The Board erred in concluding that one of ordinary skill in the art had a reasonable expectation that the teachings of Quirk and Bell-Pedersen could be successfully applied to chromosomal DNA in yeast and mammalian cells. *See '545 Board Decision*, at *7.

3

Confirming the non-obviousness of the claims at issue, Pasteur presented compelling evidence that the industry has licensed, praised, and copied its inventions. The Board did not properly weigh this evidence, because it applied too stringent a standard and misread the Dujon reference.

Objective indicia of non-obviousness "can be the most probative evidence of non-obviousness in the record, and enables the court to avert the trap of hindsight." *Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010). Objective indicia of non-obviousness "may often establish that an invention appearing to have been obvious in light of the prior art was not." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). To be afforded substantial weight, the objective indicia of non-obviousness must be tied to the novel elements of the claim at issue. *See, e.g.*, *In re Kao*, 639 F.3d 1057, 1068

(Fed. Cir. 2011). Objective indicia "need only be reasonably commensurate with the scope of the claims." *Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013).

For the first category—evidence that competitors or customers had licensed the '545 patent—Pasteur presented the declaration of Dr. Choulika, one of the named inventors of the patent and the chief executive officer of Cellectis S.A., the exclusive licensee. According to Dr. Choulika, the license permitted Cellectis to enter sub-license agreements, and since 2002, "Cellectis has entered into more than a dozen agreements to allow third parties access to the invention described and claimed in the '545 patent." J.A. 13490. Dr. Choulika stated that "[a]ll of the agreements . . . grant access to a method for *in vivo* site directed genetic recombination in an organism as claimed in the '545 patent." J.A. 13491. He listed eight press releases detailing sub-license agreements that granted access to Cellectis's technology for using a GIIE endonuclease and homologous recombination to target and modify a gene of interest in live cells. J.A. 13489, 13491-92. Among the sub-licensees were BASF Plant Science, Bayer CropScience, Biogen Idec, Monsanto, and Pioneer Hi-Bred International. *Id.*

The Board too finely parsed Pasteur's licensing activities. It rejected the evidence because "Dr. Choulika did not establish that the third parties specifically licensed the patent family to gain access to the subject matter *claimed* in the '545 patent, rather than other technology *described* in the patent but not claimed or claimed in related patents." *'545 Board Decision*, at 10. But that theoretical possibility does not undermine the strong probative value of the licensing of the '545 patent. The central success described in the patent is the one prior art hoped for and is captured in the claims at issue: a method that uses GIIE endonucleases and homologous recombination to achieve the targeted modification of chromosomal DNA in living cells, specifically in yeast and, indeed, in

mammals. *See* '545 patent, col. 51, lines 14-33. Pasteur's licensing activities provide "probative and cogent evidence" of non-obviousness of the claims at issue. *Stratoflex*, 713 F.2d at 1538.

The Board also erred in dismissing Pasteur's second category of objective indicia—industry praise—based on its misreading of the Dujon reference, as detailed above. The Board acknowledged that Pasteur established a connection between "the praise by the industry and the homologous recombination step which is claimed," but it found that step "was possessed by the prior art" and, thus, "not a proper basis to rebut the prima facie case of obviousness." *'545 Board Decision*, at *11. That finding, however, simply repeats the Board's misreading of Dujon. *See supra* B.2. Under a correct reading of the reference, a method that uses GIIE endonucleases and homologous recombination to achieve the targeted modification of chromosomal DNA was not "possessed by the prior art." Thus, industry praise, like others' licensing of Pasteur's invention, provides probative and cogent evidence that one of ordinary skill in the art would not have reasonably expected that a GIIE endonuclease could successfully modify chromosomal DNA in eukaryotic cells.

A final point is worth noting, though it does not affect the conclusion. The Board stopped its analysis of Pasteur's evidence of copying prematurely. Copying requires duplication of features of the patentee's work based on access to that work, lest all infringement be mistakenly treated as copying. *See Iron Grip Barbell Co., v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004). Pasteur publicized its method for gene transfer into the chromosomal DNA of eukaryotic cells in an article, co-authored by Dr. Choulika, published in Molecular and Cellular Biology in the spring of 1995. S*ee* J.A. 8965. During reexamination, Pasteur presented excerpts of more than twenty scientific articles, all published after the Choulika article, to demonstrate that other scientists

adopted the same method for targeted gene transfer. *See* J.A. 14001-12. The Board discounted that evidence, stating (without further analysis) that Pasteur "did not show that the cited publications referenced Choulika's method or that of [the] '545 patent [whose great grand-parent, U.S. Patent No. 5,474,896, issued in late 1995], rather than following another publication." *See '545 Board Decision*, at *11.

We have no reason to doubt the Board's statement that Pasteur did not supply the cited publications and trace the references cited in those publications, either directly or indirectly, to the 1995 Choulika article or the '545 patent's specification. But the Board did not analyze whether Pasteur's showing of the similarities of its method to the content of the cited publications, *e.g.*, their use of the same specific GIIE endonuclease, indicated that the publications' authors had access to, and borrowed from, the Pasteur sources. We need not pursue the point further, however, ourselves or through a remand. A finding that Pasteur had persuasive evidence of copying would only support the non-obviousness conclusion we reach independently of such evidence.

C

Our disposition of Pasteur's challenge to the Board's rejection of the final patent at issue, the '252 patent, follows from our discussion of the '545 patent. In reversing the Board's rejection of claims 10 and 12 of the '545 patent, we conclude, considering all the evidence, that achieving the ultimate goal of targeted gene transfer into the chromosomal DNA of eukaryotic cells was not so likely to succeed as to render the claims obvious. We now vacate the Board's conclusion as to the '252 patent claims, which concern just the first step in that process. We remand for consideration of whether one of ordinary skill would have been motivated simply to create a recombinant chromosome with a GIIE endonuclease recognition

site—without having the reasonable expectation (as the claims of the ’545 patent but not those of the ’252 patent require) that the GIIE endonuclease could successfully cleave the recognition site and that homologous recombination could successfully repair the break.

All agree that the claims of the ’252 patent require less than claims 10 and 12 of the ’545 patent. The claims of the ’252 patent cover “[a] recombinant mammalian chromosome comprising an exogenous Group I intron encoded endonuclease site,” ’252 patent, col. 67, lines 57-58, whereas the ’545 patent claims at issue also require that a GIIE endonuclease cleave an equivalent chromosome “whereby said cleavage promotes the insertion of said gene of interest into said chromosome of said organism at a specific site by homologous recombination,” ’545 patent, col. 51, lines 31-33. Effectively, the claims of the ’252 patent serve as the first step to practicing the method recited by claim 12 of the ’545 patent (or, for that matter, claim 10, which covers yeast—because neither party argues that the distinction matters for present purposes).

The Board identified only a single reason that one of ordinary skill in the art would have attempted to make a recombinant chromosome containing a GIIE endonuclease recognition site: to apply the homologous recombination method disclosed by Quirk and Bell-Pedersen to chromosomal DNA in mammalian cells. *See ’252 Board Decision*, at *5 (finding that the prior art “provided express reason to use [Quirk and] Bell-Pedersen’s homologous recombination method in mammal cells”). That is the same motivation, however, that the Board identified as giving a skilled artisan good reason to pursue the methods of the ’545 patent. *See ’545 Board Decision*, at *6. We have held the evidence insufficient to support that determination.

Because it mistakenly thought that there was sufficient motivation for the ’545 patent, the Board has never considered whether other motivations would have made

the subject matter claimed in the ’252 patent obvious. Specifically, the Board has not made a finding about whether a skilled artisan would have introduced a GIIE endonuclease recognition site into a mammalian chromosome even without reasonably expecting its successful use for the site-directed insertion of DNA.

At oral argument, the parties briefly discussed what uses such recombinant chromosomes would have other than as a first step for successful targeted gene transfer. Pasteur admitted that, currently, there are other uses for the chromosomes, including as laboratory tools or as aids in gene mapping. Oral Argument at 16:33-17:14 (Pasteur’s counsel acknowledging that the recombinant chromosomes “could have some utility in the laboratory” without “necessarily hav[ing] to proceed” to targeted DNA insertion). But obviousness is determined at the time the invention was made, *see* 35 U.S.C. § 103, so current uses for the recombinant chromosomes, without more, would not establish a sufficient motivation at the time of invention. The issue of motivation at the relevant time has not been fully explored. The Board should address it on remand in the first instance. *See, e.g., In re Chapman*, 595 F.3d 1330 (Fed. Cir. 2010) (remanding after correcting error in obviousness analysis).

Finally, although the Board may have to reconsider objective-indicia evidence for the ’252 patent when it addresses the motivation question, we note that one argument that Pasteur makes about such evidence is not sound. Pasteur presented evidence similar to that used to support the patentability of the ’545 patent—others in the industry licensed, praised, and copied Pasteur’s method of targeted gene transfer that cleaves chromosomal DNA at a specific location and uses homologous recombination to repair the break. In seeking to rely on that evidence for the ’252 patent, Pasteur acknowledges that “double-stranded breaks and homologous recombination are not mentioned in the [’252 patent] claims,” but it argues that

"neither would be possible without a GIIE endonuclease site inserted into the chromosome." Br. of Appellants at 65. That the '252 patent claims serve as a necessary first step for a method that others in the industry licensed, praised, and copied, however, does not demonstrate that they licensed, praised, and copied the method because of that first step. Pasteur's argument does not meet its burden to show that the praise and adoption were due to that first step. *Cf. Rambus*, 731 F.3d at 1256 (objective indicia of non-obviousness support patentability if "due to" the claimed features).

CONCLUSION

For the foregoing reasons, we dismiss Pasteur's appeal with respect to the '605 patent, reverse the Board's rejection of claims 10 and 12 of the '545 patent, and vacate the Board's conclusion for the '252 patent and remand for further consideration.

No costs.

DISMISSED IN PART, REVERSED IN PART, VACATED IN PART, AND REMANDED