United States Court of Appeals for the Federal Circuit

99-1604
(Interference No. 102,416)

RONALD A. HITZEMAN, ARTHUR D. LEVINSON, and DANIEL G. YANSURA,

Appellants,

v.

WILLIAM J. RUTTER, PABLO D.T. VALENZUELA, BENJAMIN D. HALL and GUSTAV AMMERER,

Appellees.

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Appellees.

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Debra A. Shetka, Morrison & Foerster, L.L.P., of Palo Alto, California, argued for appellees in 99-1604. Gladys H. Monroy, Morrison & Foerster, L.L.P., of Palo Alto, California, argued for appellees in 99-1605. With them on the brief were Emily A. Evans, and Catherine M. Polizzi. Of counsel was Karl J. Kramer. Of counsel on the brief were P. Martin Simpson, Jr., and Sandra S. Schultz, The University of California, Office of General Counsel, of Oakland, California.

Appealed from: Patent & Trademark Office
Board of Patent Appeals and Interferences

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DECIDED: March 21, 2001

Before MICHEL, LINN, and DYK, Circuit Judges.

MICHEL, Circuit Judge.

This is a patent interference case. Ronald Hitzeman, Arthur Levinson, and Daniel Yansura (collectively, "the Hitzeman inventors" or "Hitzeman") are the junior parties in the two interferences at issue. William Rutter, Pablo Valenzuela, Benjamin Hall, and Gustav Ammerer (collectively, "the Rutter inventors" or "Rutter") are the senior parties. On July 30, 1990, the United States Patent and Trademark Office ("PTO") declared Interference No. 102,416 ("the '416 interference") between U.S. Application Serial No. 07/209,504 by Rutter, entitled to a filing date of August 4, 1981 ("the '504 Rutter application"), and U.S. Patent No. 4,803,164 to Hitzeman, entitled to a filing date of August 31, 1981 ("the '164 Hitzeman patent"). On October 22, 1992, the PTO declared Interference No. 102,989 ("the '989 interference") between U.S. Patent No. 4,769,238 to Rutter, entitled to a filing date of August 4, 1981 ("the '238 Rutter patent"), and U.S. Application Serial No. 07/248,863 by Hitzeman, entitled to a filing date of August 31, 1981 ("the '863 Hitzeman application"). On June 30, 1999, the Board of Patent Appeals and Interferences ("Board") issued separate Final Decisions in each of the interferences, awarding priority in both interferences to Rutter. On August 27, 1999, Hitzeman filed a timely notice of appeal to this court. We have jurisdiction pursuant to 35 U.S.C. § 141 (West Supp. 2000). We heard oral arguments in this case on January 9, 2001. The issues raised on appeal are nearly identical in the two interferences, and so we address both interferences in this opinion, with distinctions noted between the two interferences where appropriate. Because we conclude that the Board properly determined that the particle size and sedimentation rate

limitations recited in both counts are material limitations, and because substantial evidence supports the Board's conclusion that Hitzeman had not conceived of the particle size and sedimentation rate limitations prior to Rutter's reduction to practice of the invention, and because the legal standards applied by the Board were correct, we affirm.

I. Factual and Procedural Background

A. Overview of the Technology

The interferences at issue concern claims to technology for producing a hepatitis B vaccine by means of genetically altered yeast. Hepatitis B, which is transmitted by a virus ("HBV"), is a major worldwide health problem that causes, among other things, severe liver damage and death. The hepatitis B virus comprises a DNA molecule surrounded by an envelope composed of proteins including a surface antigen ("HBsAg"), a core antigen ("HBcAg"), and an "e" antigen ("HBeAg").1 Prior to the invention at issue, it was known that the surface antigen could be purified from the blood sera of certain populations of humans, particularly in Australia, who were infected with the hepatitis B virus. The HBsAg isolated from humans is called the "Australia antigen." By the mid-1970s, it was found that the HBsAg particles isolated from humans could be used in a vaccine to stimulate the production of antibodies capable of defending the body against infection by the hepatitis B virus. The 1976 Nobel Prize for Physiology or Medicine was awarded to Baruch Blumberg for his recognition of the utility of HBsAg for conferring protection to humans against hepatitis B viral infections.

As disclosed in the Rutter '238 patent, it was known by 1980 that the HBsAg

1 DNA is deoxyribonucleic acid, a generic term encompassing the many chemical materials that genetically control the structure and metabolism of living things.

antigen is comprised of a cluster of protein molecules, known as the S-protein. The structure of the particles reveals that they are formed when pairs (or "dimers") of the S-protein molecules aggregate with lipids into spherical particles having diameters ranging from about 16 to 25 nm. The patents at issue refer to these particles as "22 nm particles."

Because of the costs and difficulties associated with isolating sufficient quantities of HBsAg from humans, scientists sought to develop alternative means for producing the antigen. The approach at issue on appeal concerns the attempt to obtain HBsAg or its immunologically reactive equivalent by genetically modifying microorganisms to endow them with the capability to produce the S-protein. Prior to the invention at issue, the gene encoding for the S-protein, the HBV "s" gene, had been cloned and its nucleotide sequence determined.

As explained in the prosecution history of the Hitzeman '164 patent, prior attempts to artificially produce HBsAg in microorganisms focused on bacteria such as E. coli. Through a technique that will be described in greater detail below, E. coli were genetically modified to incorporate the HBV "s" gene. While it was found that the genetically modified, or "recombinant," bacteria expressed the S-protein, the bacteria were not able to assemble HBsAg particles, as had been isolated from human sera. Consequently, it was found that the non-particulate S-protein isolated from the recombinant bacteria did not confer immunogenicity (i.e., stimulate the production of antibodies) in humans to hepatitis B infection, as would be required for a vaccine.

Hitzeman's and Rutter's technique for producing HBsAg employs yeast, rather than bacteria. Under this method, a loop of DNA known as a "vector" (or "shuttle vector" or "plasmid") is cleaved with enzymes known as "restriction endonucleases" and mixed with

fragments of the HBV “s” gene, such that the HBV “s” gene is incorporated into the vector. Similarly, a “promoter,” the importance of which is described below, is spliced into the vector. Through a process known as “transformation,” the vector is then introduced into a population of yeast, where it is taken up into the nuclei of some of the organisms. Through the use of techniques to selectively grow the yeast that take up the vectors, colonies of yeast incorporating the vector can be obtained.

After the vector enters the nucleus of the yeast cell, an enzyme called RNA polymerase binds to the promoter region of the vector and initiates transcription of the HBV “s” gene. A messenger RNA is produced, which after exiting the nucleus and binding to a ribosome, is translated into a polypeptide chain that constitutes the S-protein. Through a process that was not fully understood by 1992 (approximately the start of the interference proceedings), the S-proteins aggregate to form particles with a diameter of roughly 22 nm, similar to the Australia antigen. The undisputed record indicates that prior to 1981 (the date of alleged conception), the ability of yeast to process the S-protein into particles was not known, and indeed there was doubt that it would occur.

The HBsAg particles expressed in the yeast strain can be extracted and isolated by centrifugation. The density of the HBsAg particles obtained from yeast is similar to that of the Australia antigen, such that the particles derived from yeast and humans have a similar “sedimentation rate” in a centrifuge. The sedimentation rate is a function of the buoyant density of the particle.

B. The Inventive Processes of Hitzeman and Rutter

1. Hitzeman’s Alleged Conception

In the years leading up to 1980, Ronald Hitzeman collaborated with John Carbon to

successfully express an “interferon” protein in yeast, using techniques analogous to those discussed above. Hitzeman and Carbon filed a patent application claiming this technique, which eventually issued on September 12, 1989 as U.S. Patent No. 4,865,989, assigned to the University of California.

In 1980, Hitzeman joined Genentech, Inc., where he continued to perform work on interferon in a collaborative effort with researchers at the University of California and the University of Washington. After successfully expressing interferon in yeast in January 1981, Hitzeman sought to apply this same technique to produce HBsAg. The goal of this work was to develop a human vaccine for hepatitis B. On February 3, 1981, Hitzeman disclosed, in a meeting with his supervisor, David Goeddel, his goals concerning the expression in yeast cells of HBsAg using the vector he had employed in his interferon experiments. Hitzeman also suggested producing HBsAg using a modified vector containing a PGK promoter, rather than the ADH promoter he had used to produce interferon. Hitzeman’s laboratory notebook contains notes from the meeting. The notes do not indicate whether Hitzeman anticipated obtaining 22 nm particles of HBsAg from yeast.

At the time of the February 3, 1981 meeting, Hitzeman allegedly possessed all the necessary DNA materials to conduct the experiments to produce HBsAg in yeast. These materials included the vector containing the ADH promoter Hitzeman had used in his prior research. Hitzeman allegedly also had access to substantial quantities of the HBV “s” gene which his co-inventor, Daniel Yansura, had manipulated to incorporate “restriction sites” to facilitate splicing the gene into the vector. Hitzeman moreover asserts that by mid-1980 he knew that Genentech had an assay for detecting HBsAg particles, and that this assay had been used successfully in prior work detecting HBsAg particles produced in

mammalian cells, and that the assay had been used in failed attempts to demonstrate production of HBsAg particles in E. coli. Hitzeman contends that by February 3, 1981, in addition to the above DNA materials and tools, he also had "a hope" that the yeast would produce HBsAg in particle form. Accordingly, he argues that by this date he had achieved complete conception of the invention of the count.

2. Rutter's Production of HBsAg Particles in Yeast

In the first week of March 1981, William Rutter of the University of California contacted Benjamin Hall of the University of Washington to discuss a possible collaboration between researchers at the two universities (including Pablo Valenzuela of the University of California and Gustav Ammerer of the University of Washington) to express HBsAg in yeast. On March 13, 1981, Rutter and Hall met in San Francisco with attorneys from Merck to describe the intended collaboration. The Rutter inventors began the study immediately. On March 27, 1981, Rutter and Hall met again with Merck, at which time Merck agreed to fund the collaboration.

During the week of April 12, 1981, the Rutter inventors discussed the details of forming a vector containing the HBV "s" gene ligated to an ADH1 promoter. On June 3, 1981, the Rutter inventors obtained positive assay results indicating that the recombinant yeast were producing HBsAg. On June 29, 1981, the Rutter inventors used a sucrose gradient to confirm that the sedimentation rate of the yeast HBsAg product was virtually identical to that of authentic (i.e., human-derived) 22 nm hepatitis surface antigen particles. The parties agree that the Rutter inventors are entitled to a date of June 30, 1981 for simultaneous conception and reduction to practice of the invention of the count.

3. Hitzeman's Production of HBsAg Particles in Yeast

By March 18, 1981, the Hitzeman inventors had designed a vector comprising an ADH promoter and the HBV "s" gene. The Hitzeman inventors were unable to test this vector, however, because researchers at the University of Washington, including Hall, would not give Genentech permission to use the vector beyond the pilot study with interferon. With the assistance of Frank Hagie, Hitzeman designed a vector containing a PGK promoter. After several months of allegedly diligent work on the project, Hitzeman and Hagie began construction of the vector with the PGK promoter on approximately June 6, 1981, and completed construction of it in early July 1981. On July 14, 1981, Hitzeman transformed yeast with the new vector, and on July 20, 1981, he confirmed through the use of a sucrose gradient and an assay to detect particles that the yeast had produced HBsAg particles having a sedimentation rate virtually identical to that of authentic 22 nm hepatitis surface antigen particles. The parties agree that Hitzeman reduced the invention of the count to practice on July 20, 1981.

C. Patent Prosecution and Subsequent Publications

1. Prosecution History of the Hitzeman '387 Application

Rutter and Hitzeman filed multiple patent applications directed toward the above invention. Of particular relevance to this appeal are statements made by Hitzeman during the prosecution of Application Serial No. 06/599,387 ("the Hitzeman '387 application"), filed on April 12, 1984, which is a parent application of the Hitzeman '164 patent. The relevant claims of the Hitzeman '387 application recited that the HBsAg obtained from yeast is "in particle form." On January 24, 1986, the examiner rejected Hitzeman's claims under 35 U.S.C. § 103 for obviousness in light of prior art disclosing the production of HBsAg by bacteria. On June 23, 1986, Hitzeman filed an amendment with the PTO, and

attempted to traverse the rejection by explaining that the results obtained were "new and surprising" in light of his discovery that the yeast not only produced HBsAg, but did so in particle form. The argument in support of amendment points out that the prior art references cited by the examiner "do not teach that the bacteria are able to assemble and secrete HBsAg particles." The argument continues, stating:

> One skilled in the art at the time this application was filed would not have been able to reasonably predict that HBsAg could be expressed by yeast and, even if this was reasonably predictable, would not have expected yeast to process and assemble HBsAg particles having substantially the same buoyant density as HBsAg particles from virally-infected sources.

In the argument supporting amendment, Hitzeman emphasized the importance of his discovery that the HBsAg derived from the recombinant yeast was in particle form, noting that particulate HBsAg was much more effective in vaccines than unassembled S-protein. The argument states:

> Particulate HBsAg is particularly useful in vaccines because it is able to elicit high titer antibodies that cross-react with infectious virus. Poor immunoreactivity is a significant problem with HBsAg expressed in other microorganisms than yeast.

Hitzeman asserted, moreover, that it was especially surprising to obtain particulate HBsAg from yeast, recognizing that yeast are simple cells that are far removed from the mammalian cells that have been found to perform post-translational processing of the S-protein into particles. The argument in support of amendment states:

> Yeast are eukaryotic cells, but are more akin to bacteria than mammalian cells in many ways. The citations already of record in this case would have suggested to the ordinary artisan that yeast are incapable of functioning like higher eukaryotes when complex processing requirements are imposed. For example, Beggs et al. point out that yeast are incapable of splicing rabbit B-globin from genomic DNA, even though recombinant mammalian cells (murine L cells or monkey cells) are capable of doing so (p. 840). This would suggest that yeast also would

be unable to conduct complex post-translational processing.

Hitzeman subsequently abandoned the '387 application, after filing a continuation application which issued as the Hitzeman '164 patent. All claims of the Hitzeman '164 patent recite an HBsAg particle "having a sedimentation rate which is virtually identical to that of authentic 22 nm hepatitis surface antigen particles."

2. Hitzeman's 1983 Publication

In 1983, Hitzeman published a paper in which he describes his success at obtaining HBsAg particles from recombinant yeast. See Hitzeman et al., Expression of Hepatitis B Virus Surface Antigen in Yeast, 11 Nucleic Acids Research 2745 (1983). In the article, he reports that his experiments indicated that the particles do not actually form in the yeast, but rather that the particles may be formed extracellularly, or formed during the purification process after non-aggregated protein has been extracted from the yeast. The article states:

> Previous observations show that viral particles bud off the membranes of infected animal cells. In the yeast expression system we have not observed any HBsAg particles in the media of producing cells, even though yeast cells secrete a number of their own proteins (40) and even foreign proteins (36, 41). If the natural mechanism of secretion for 22 nm particles is a budding process, then one might not expect secretion of HBsAg from yeast cells in which the cell membrane is surrounded by a cell wall. Furthermore, our experiments suggest that the particle may result from the glass bead extraction procedure and yeast may thus be defective in initiating a budding process.

Id. (emphasis added). Whether the particles are formed in the yeast prior to extracting the HBsAg, or whether the particles are formed when the yeast cells are disrupted and the HBsAg is purified, remained an open question at least until 1992 (when the interference commenced), according to a declaration submitted by Dr. Darrell Peterson on behalf of

Hitzeman.

D. The Interferences

As noted above, on July 30, 1990, the PTO declared the '416 interference between the '504 Rutter application and the '164 Hitzeman patent. The count of the '416 interference, which has two alternate forms, recites a DNA expression vector capable of replication in yeast such that it is expressed to produce hepatitis B surface antigen "in particle form having a sedimentation rate which is virtually identical to that of authentic 22 nm hepatitis surface antigen particles," or, alternatively, a method for producing such particles.2

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2 Count 1, the sole count at issue in the '416 interference, has two alternate forms. In full, these read as follows:

> A DNA expression vector capable of replication and phenotypic selection in [a] yeast host strain comprising a promoter compatible with a yeast host strain and a DNA sequence encoding hepatitis B surface antigen, said sequence being positioned together with translational start and stop signals in said vector under control of said promoter such that in a transformant yeast strain it is expressed to produce hepatitis B surface antigen <u>in particle form having a sedimentation rate which is virtually identical to that of authentic 22 nm hepatitis surface antigen particles</u>;
>
> or
>
> a method of producing hepatitis B surface antigen in particle form suitable for use in conferring immunogenicity to hepatitis B virus in a susceptible human which comprises:
>
> (a) providing a DNA transfer vector capable of replication and phenotypic selection in yeast host strains,
>
> (b) providing a DNA fragment comprising a promoter compatible with a yeast host strain,
>
> (c) providing a DNA fragment encoding hepatitis B surface antigen,

On October 22, 1992, the PTO declared the '989 interference between the '238 Rutter patent and the '863 Hitzeman application. The count in the '989 interference is directed to a product-by-process, reciting an "HBsAg particle which . . . has a sedimentation rate which is virtually identical to that of authentic 22 nm HBsAg particles."3

On June 30, 1999, the Board issued Final Decisions for each interference. Except as noted, the Board's conclusions apply equally to both interferences. The Board held that the particle size and sedimentation rate limitations of the counts are material limitations, and thus that Hitzeman was required to demonstrate that he envisioned that expression of

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(d) assembling the fragments of steps (a), (b), and (c) together with translational start and stop signals for the fragment of step (c) to form a replicable expression vector so that said sequence of step (c) is under control of said promoter,

(e) transforming a yeast strain with the vector of step (d),

(f) allowing the yeast transformant to grow under fermentation conditions until said hepatitis B surface antigen is produced therein, and

(g) recovering said hepatitis B surface antigen <u>in particle form having a sedimentation rate which is virtually identical to that of authentic 22 nm hepatitis surface antigen particles</u>.

(emphasis added).

3 The sole count of the '989 interference reads, in full:

an <u>HBsAg particle</u> which

(i) <u>has a sedimentation rate which is virtually identical to that of authentic 22 nm HBsAg particles</u> or which is in unglycosylated form, and

(ii) is produced in yeast cells transformed with a DNA segment encoding mature HBsAg.

(emphasis added).

the HBV "s" gene in yeast would result in the production of HBsAg particles having a sedimentation rate virtually identical to that of authentic 22 nm HBsAg particles. Moreover, the Board found that Hitzeman's alleged "hope" of obtaining particles was uncorroborated, and that the evidence, at best, suggested that Hitzeman had a general goal, or research plan, to express HBsAg in yeast. Accordingly, the Board concluded that Hitzeman failed to establish conception of the particle size and sedimentation rate limitations prior to reducing the invention to practice.

II. Discussion

A. Standard of Review

When a patent application is filed that would interfere with any pending application or with any unexpired patent, the Director of the PTO is authorized to declare an interference to determine which party was the first to invent the claimed subject matter. See 35 U.S.C. § 135(a). In determining priority of invention, the Board must consider "not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other." 35 U.S.C. § 102(g). Accordingly, priority of invention is awarded to the first party to reduce an invention to practice unless the other party can show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing that invention to practice. Cooper v. Goldfarb, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1900-01 (Fed. Cir. 1998). Priority therefore depends upon conception and reduction to practice. Priority, conception, and reduction to practice are questions of law that are based on subsidiary factual findings. Id.

Before the Board, Hitzeman, as the junior party, bore the burden to prove by a preponderance of the evidence that he conceived of the invention of the count before Rutter. See Environ Prods., Inc. v. Furon Co., 215 F.3d 1261, 1265, 55 USPQ2d 1038, 1041-42 (Fed. Cir. 2000); 37 C.F.R. § 1.657(b). On appeal, this court's review of the Board's decision is confined to the factual record compiled by the Board, and we must affirm the Board's factual determinations if they are supported by substantial evidence. In re Gartside, 203 F.3d 1305, 1315, 53 USPQ2d 1769, 1774 (Fed. Cir. 2000). The "substantial evidence" standard requires us to inquire whether the Board's decision is based upon "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." Id. at 1312, 53 USPQ2d at 1773 (quoting Consolidated Edison Co. v. NLRB, 305 U.S. 197, 229-30 (1938)). We review questions of law, such as the Board's legal conclusions concerning priority, conception, and reduction to practice, de novo. Id. at 1315, 53 USPQ2d at 1774.

B. Are the Particle Size and Sedimentation Rate Limitations Material Limitations of the Count?

Hitzeman contends that the Board erred in requiring him to demonstrate that he had conceived of the particle size and sedimentation rate limitations of the counts prior to June 30, 1981, the date of Rutter's simultaneous conception and reduction to practice. Hitzeman argues that it is sufficient to demonstrate that he had conceived of all the DNA materials recited in the counts. According to Hitzeman, the formation of HBsAg particles in yeast is an inherent result of introducing the vector they designed into yeast. He argues that "[s]pecific conception of this result is not necessary." We disagree.

This court and its predecessor have long recognized that "nothing is better settled in patent law than that in interference cases express limitations in counts may not be ignored." McBride v. Teeple, 109 F.2d 789, 799, 44 USPQ 523, 533 (CCPA 1940) (citing cases). Accordingly, all limitations in interference counts "will be regarded as material to the invention covered by the counts." Meitzner v. Corte, 537 F.2d 524, 530, 190 USPQ 407, 412 (CCPA 1976). In establishing conception, "a party must show possession of every feature recited in the count, and that every limitation of the count must have been known to the inventor at the time of the alleged conception." Coleman v. Dines, 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed. Cir. 1985).

On rare and special occasions, we have stated that commonplace properties of a claimed invention may be deemed "inherent" to the invention, and that specific conception of these properties is not required. For example, in a count directed to a new crystalline form of ampicillin that recited the compound's molecular weight, we held that it was sufficient to possess the claimed compound and to characterize it by water content and infrared spectrograph, without demonstrating knowledge of the compound's molecular weight. See Silvestri v. Grant, 496 F.2d 593, 599, 181 USPQ 706, 709 (CCPA 1974). In Silvestri we held that it was not necessary to show that the inventors had actually determined the molecular weight of the ampicillin because this property "add[s] nothing to the count beyond that determined by the water content and infrared spectrograph." Id. This reasoning follows from the recognition that "attorneys often write compound claims including a statement of some inherent property, general or specific," and that "[w]here the balance of the claim fully identifies the compound . . . and the property is inherent, we fail to see that such statements add anything to the claim definition of the named compound." In

re Ruschig, 343 F.2d 965, 973 n.8, 145 USPQ 274, 286 n.8 (CCPA 1965); see also Mycogen Plant Science, Inc. v. Monsanto Co., 2001 WL 238215, at *20 (Fed. Cir. Mar. 12, 2001) (stating that prior conception of a sequence of "nucleotides" was sufficient to support conception of "codons," because skilled artisans recognize that a series of three nucleotides constitutes a codon, by definition); Riney v. Thomas, 77 F.2d 525, 528, 25 USPQ 418, 421 (CCPA 1935) ("The mere fact that Thomas may have so framed certain of the claims of his patent to include an inherent quality of Riney's invention which, perhaps, was not specifically mentioned by Riney in his disclosure, does not, in our opinion, entitle Thomas to the benefit of an invention which was, in fact, first conceived by Riney."). "Inherent" properties, such as those discussed in Silvestri, are the rare exceptions to the rule that a party must show possession of "every feature" recited in the count and that "every limitation" of the count must have been known to the inventor at the time of the alleged conception. Coleman, 754 F.2d at 359, 224 USPQ at 862. To invoke the "inherent conception" rule of Silvestri, the inventor needs to show that the allegedly inherent property adds nothing to the count beyond the other recited limitations, and is redundant to the count. Silvestri, 496 F.2d at 599, 181 USPQ at 709. In the context of priority determinations, the allegedly inherent limitation cannot be material to the patentability of the invention. Moreover, consistent with the law of inherent anticipation, an inherent property must necessarily be present in the invention described by the count, and it must be so recognized by persons of ordinary skill in the art. See Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991); Riney, 77 F.2d at 528, 25 USPQ at 421 (noting that the inherent property "would be at once apparent to any one skilled in the art").

Hitzeman asserts that the particle size and sedimentation rate limitations of the counts are "inherent," in the sense that the yeast, once transformed by the claimed vector, necessarily produce particles having the claimed size and sedimentation rate. Although it may be true in a scientific sense that the yeast "inherently" produce the claimed particles, that does not mean that the particle size and sedimentation rate limitations are "inherent" in a legal sense, such that the inventors need not establish specific conception of these features. Hardly redundant of the other limitations, this feature is central to the patentability and utility of the claimed invention, and it provided the basis for Hitzeman to distinguish his claims from the prior art. As noted above, Hitzeman attempted to traverse a prior art rejection in light of prior bacterial production of non-particulate HBsAg by asserting that "[o]ne skilled in the art at the time this application was filed would not have been able to reasonably predict that HBsAg could be expressed by yeast and, even if this was reasonably predictable, would not have expected yeast to process and assemble HBsAg particles from virally-infected sources." In light of this statement to the PTO, and the others quoted above, it can hardly be said that the particle size limitation "adds nothing" to the counts, see Silvestri, 496 F.2d at 599, 181 USPQ at 709, or that persons of ordinary skill would have recognized that yeast would yield particulate HBsAg, see Continental Can, 948 F.2d at 1268, 20 USPQ2d at 1749. Rather, the undisputed evidence indicates that the particle size and sedimentation rate limitations are central to the patentability of the invention. Accordingly, we agree with the Board that the particle size and sedimentation rate limitations are material limitations of the counts, for which Hitzeman had the burden of establishing conception.

C. Is Hitzeman's Alleged "Hope" of Obtaining Particles Sufficient to Establish

Conception of the Particle Size and Sedimentation Rate Limitations of the Counts?

Hitzeman asserts that the Board erred by failing to rule that he had conceived of the particle size and sedimentation rate limitations prior to Rutter. Hitzeman alleges that by February 3, 1981, he had a "hope" that the yeast, once transformed with the claimed vector, would yield HBsAg in particle form having a sedimentation rate which is virtually identical to that of authentic 22 nm HBsAg particles. Before the Board, Hitzeman attempted to corroborate this alleged hope by pointing out that the whole point of the experiments was to devise a human vaccine against hepatitis B. According to Hitzeman, because it was well known in the art that particulate HBsAg having a roughly 22 nm diameter was effective in vaccines, and because it was known that attempts to create vaccines from bacteria failed for lack of formation of HBsAg particles, Hitzeman asserts that his conception of HBsAg in particle form "is the only thing that makes sense." Hitzeman also notes that once he had determined that the yeast had expressed HBsAg, he immediately performed an assay to determine if particles had formed. As corroborated by this and other circumstantial evidence, Hitzeman asserts that his hope of obtaining particles is sufficient to establish conception of the particle size and sedimentation rate limitations.

In arguing whether Hitzeman adequately conceived of the particle size and sedimentation rate limitations, both parties rely heavily on the legal standard for conception we articulated in Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d 1223, 1228, 32 USPQ2d 1915, 1919 (Fed. Cir. 1994). In Burroughs, we stated:

> [T]he test for conception is whether the inventor had an idea that was definite and permanent enough that one skilled in the art could understand

> the invention; the inventor must prove his conception by corroborating evidence, preferably by showing a contemporaneous disclosure. An idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue. The conception analysis necessarily turns on the inventor's ability to describe his invention with particularity. Until he can do so, he cannot prove possession of the complete mental picture of the invention. These rules ensure that patent rights attach only when an idea is so far developed that the inventor can point to a definite, particular invention.

Id. (emphasis added, citations omitted). The parties, of course, diverge as to whether Hitzeman's alleged hope of obtaining particles is sufficient to constitute a "definite and permanent idea" of the invention.

There appears to be no dispute that Hitzeman had identified a research plan to produce a hepatitis B vaccine for humans. Moreover, the parties appear to agree that it was known in the art that HBsAg particles having a diameter of roughly 22 nm were useful for such vaccines, whereas non-particulate S-protein, as had been produced by bacteria, was ineffective as a vaccine. Although the Board made no specific finding on this point, and we of course cannot engage in appellate fact-finding, it appears probable that the goal of Hitzeman's research was to obtain particulate HBsAg, with such particles having a sedimentation rate which is virtually identical to that of authentic 22 nm HBsAg particles. For the purposes of this opinion, we will assume that Hitzeman did hope to obtain this result.

We note that Hitzeman chose to claim the invention by reciting the particular result of an intracellular process, i.e., the production of 22 nm HBsAg particles in yeast that had been transformed with a vector containing the HBV "s" gene. By reciting this result as a limitation of the counts, Hitzeman was required to have a "definite and permanent idea of

the complete and operative invention," including that yeast would express the HBV "s" gene, and that the expressed S-protein would be assembled into 22 nm particles. Gunter v. Stream, 573 F.2d 77, 80, 197 USPQ 482, 484 (CCPA 1978) (quoting Mergenthaler v. Scudder, 11 App.D.C. 264, 276, 1897 C.D. 724, 741 (1897)). Only by demonstrating that he had a definite and permanent understanding as to whether and how the yeast would produce the 22 nm particles could Hitzeman establish conception of the particle size and sedimentation rate limitations prior to reducing the invention to practice.

The defect in Hitzeman's case is not that his "hope" was uncorroborated. Written documentation of Hitzeman's hope on February 3, 1981 would not have changed the outcome of this appeal. Rather, the critical deficiency is that Hitzeman specifically claimed the result of a biological process (i.e., the expression by yeast of the S-protein, followed by the assembly of the S-protein into particles) with no more than a hope, or wish, that yeast would perform this assembly process that had never before been achieved in yeast. Such a bare hope is insufficient to establish conception. Cf. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) ("It is not sufficient to define [a gene] solely by its principal biological property, e.g., encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property."). Alternatively stated, Hitzeman's hope was the basis of his research plan to determine whether yeast might both express the S-protein and assemble it into particles. This research plan was set forth with the knowledge that bacteria did not assemble the S-protein monomers into particles. Nothing in the record suggests that Hitzeman had a reasonable expectation that using yeast as a host cell, rather than bacteria, would yield

successful assembly of particles, which he specifically claimed. When a research plan requires extensive research before the inventor can have a reasonable expectation that the limitations of the count will actually be met, complete conception has not occurred. See Meitzner v. Corte, 410 F.2d 433, 437, 161 USPQ 599, 603 (CCPA 1969) (quoting Alpert v. Slatin, 305 F.2d 891, 894, 134 USPQ 296, 299 (CCPA 1962) ("If after the claimed conception date extensive research was found necessary before achieving minimum satisfactory performance obviously the mental embodiment of that date was a mere hope or expectation, a statement of a problem, but not an inventive conception.")). The policy behind the patent laws, of course, is to "promote disclosure of inventions, not of research plans." Fiers v. Revel, 984 F.2d 1164, 1169, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993).

To establish conception of the particle size and sedimentation rate limitations, Hitzeman would have had to demonstrate that he had, at the time of alleged conception, a definite and permanent understanding that yeast, once transformed with the HBV "s" gene, would not only express the S-protein, but would also assemble it into particles. Hitzeman's statement during prosecution history that "[o]ne skilled in the art at the time this application was filed would not have been able to reasonably predict that HBsAg could be expressed by yeast [and done so in particle form]" demonstrates that he lacked a complete conception, i.e., one that included the particle size and sedimentation rate limitations. Moreover, as shown by Hitzeman's 1983 article published in Nucleic Acid Research, quoted above, it appears that Hitzeman remained unclear for at least two years after reducing his invention to practice as to how the particles are formed in yeast.

It is not necessary that all biotechnology inventions such as Hitzeman's be characterized by simultaneous conception and reduction to practice. See Amgen, 927

F.2d at 1206-07, 18 USPQ2d at 1021 ("In some instances, an inventor is unable to establish a conception until he has reduced the invention to practice through a successful experiment."). There may be situations where an organism's performance of certain intracellular processes might be reasonably predictable, and evidence of such predictability might be sufficient to support a finding of conception prior to reduction to practice. In this case, however, substantial evidence supports the Board's finding that Hitzeman lacked reasonable certainty that the yeast would produce the particles recited in the counts. Accordingly, the Board was correct in its conclusion that Hitzeman's conception of the invention was simultaneous with his July 20, 1981 reduction to practice.

Hitzeman urges that our holding in Burroughs compels a contrary result, and reads this case to say that an inventor need not have a "reasonable expectation" that he possessed each limitation of the count. Burroughs, 40 F.3d at 1228, 32 USPQ2d at 1920. Hitzeman relies particularly on the following statement:

> Barr and Novopharm suggest that the inventor's definite and permanent idea must include a reasonable expectation that the invention will work for its intended purpose. They argue that this expectation is of paramount importance when the invention deals with uncertain or experimental disciplines, where the inventor cannot reasonably believe an idea will be operable until some result supports that conclusion. Without some experimental confirmation, they suggest, the inventor has only a hope or an expectation, and has not yet conceived the invention in sufficiently definite and permanent form. But this is not the law. An inventor's belief that his invention will work or his reasons for choosing a particular approach are irrelevant to conception.

Id. (citation omitted). The above statement in Burroughs, however, was not dealing with whether an inventor had a reasonable expectation of producing the claimed device or composition, but instead whether the inventor had a reasonable expectation that the device or composition, once completed, would work for its intended purpose. Here, in contrast,

we are focusing on whether the inventors had a reasonable expectation that they would produce the claimed invention. Burroughs concerned six patents directed toward administering a drug, AZT, to AIDS patients. It was undisputed that the inventors had already synthesized the AZT. The claims of the first five patents recited various permutations of administering the AZT to patients, without reciting details of how the human body would react to the drug. See id. at 1225 n.3, 32 USPQ2d at 1917 n.3. As to the claims of these five patents, we held, as quoted above, that the developers of AZT had sufficiently established conception of the limitations of the claims (i.e., the drug itself and the intention to administer it to humans), and that it was immaterial that the inventors lacked a "reasonable expectation" as to how non-claimed aspects of the drug would work (i.e., the particular effect of the drug on the body). Id. at 1228, 32 USPQ2d at 1920. However, as to the claims of the sixth patent, which recited details of an anticipated immune response to the drug (i.e., "a method of increasing the number of T-lymphocytes in a human infected with the [HIV] virus . . . ."), we held that this claim was not conceived in advance of further studies because of uncertainty as to whether administering AZT actually would promote T-lymphoctye production, i.e., the claimed intended use. Id. at 1231-32, 32 USPQ2d at 1923. Thus, the inventors in Burroughs lacked a "definite and permanent idea" as to whether this recited claim limitation of the sixth patent would be met by administering the drug. Id. at 1230, 32 USPQ2d at 1923. In the present case, like the claims of the sixth patent discussed in Burroughs, Hitzeman claimed the specific result of a biological process. Because Hitzeman failed to show that he had a reasonable expectation that the claimed result of the biological process would occur, his conception argument cannot prevail.

We note that both parties and the Board addressed Hitzeman's putative conception by relying on cases concerning nunc pro tunc conception. See, e.g., Knorr v. Pearson, 671 F.2d 1368, 1374-75, 213 USPQ 196, 201-02 (CCPA 1982); Breen v. Henshaw, 472 F.2d 1398, 1401, 176 USPQ 519, 521 (CCPA 1973); see also Heard v. Burton, 333 F.2d 239, 242-44, 142 USPQ 97, 98 (CCPA 1964). For doctrinal clarity, we point out that these cases are largely inapposite to the present dispute. This court has long refused to recognize attempted nunc pro tunc reductions to practice. See Cooper v. Goldfarb, 2001 WL 202474 (Fed. Cir. Mar. 2, 2001); Knorr, 671 F.2d at 1375, 213 USPQ at 201; Breen, 472 F.2d at 1401, 176 USPQ at 521. Nunc pro tunc conception involves the situation where an inventor actually possessed a claimed device at the time of his alleged conception, but failed to recognize the device's inventive features at that time. As articulated in cases such as Heard, an inventor who failed to appreciate the claimed inventive features of a device at the time of alleged conception cannot use his later recognition of those features to retroactively cure his imperfect conception. See Heard, 333 F.2d at 243, 142 USPQ at 100 ("We point out . . . that the count calls for a particular form of alumina and we think that appellant's failure to recognize that he had produced a new form, regardless of what he called it, is indicative that he never conceived the invention prior to appellees' filing date."). Here, there was no suggestion that Hitzeman had already obtained the expressed protein without recognition of its particulate form; rather, the question is whether his prospective hope of obtaining particles was sufficient to establish conception.

D. Miscellaneous Motions

Regarding the '416 interference, Hitzeman argues that the Board erred in granting

Rutter's motion to strike testimony by Drs. Dreesman and Peterson concerning the alleged inherency of the 22 nm HBsAg particles. Because, as described above, Hitzeman's inherency argument is misplaced, and because it appears that the Board acted well within its discretionary authority in limiting Hitzeman's rebuttal testimony to the matters presented during Hitzeman's case-in-chief, we discern no reversible error in the Board's decision to strike the testimony at issue.

In the '989 interference, Hitzeman also argues that the Board erred in granting Rutter's motion to substitute Count A. Hitzeman contends that because the particle size and sedimentation rate limitations are inherent features, it was error to add these limitations to the count. As discussed above, the evidence shows that the particle size and sedimentation rate limitations are central to the patentability of the invention. Accordingly, we find no error in the Board's decision to substitute the count. At the very least the decision to substitute was not an abuse of discretion.

III. Conclusion

Because we conclude that under well settled case law the particle size and sedimentation rate limitations of the counts are material limitations, and because we agree that Hitzeman's alleged hope of obtaining HBsAg in particle form is insufficient to establish complete conception of these limitations, we affirm the conclusion of the Board that Hitzeman did not conceive of the invention of the counts in February 1981, but only did so when he had reduced it to practice on July 20, 1981. Accordingly, the Board's decision awarding priority of the counts to Rutter is

AFFIRMED.