United States Court of Appeals for the Federal Circuit

02-1120,-1160

(Serial no. 08/630,654, 08/278,774)

IN RE RICHARD A. BERG,
PAUL D. TOMAN, and DONALD G. WALLACE

Richard Aron Osman, Science & Technology Law Group, of Hillsborough, California, argued for appellant.

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Appealed from: United States Patent and Trademark Office
Board of Patent Appeals and Interferences

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DECIDED: February 20, 2003

Before BRYSON, Circuit Judge, PLAGER, Senior Circuit Judge, and PROST, Circuit Judge.
BRYSON, Circuit Judge.

Appellants Richard A. Berg, Paul D. Toman, and Donald G. Wallace seek review of two decisions of the United States Patent and Trademark Office Board of Patent Appeals and Interferences, one sustaining a rejection of the appellants' application as obvious under 35 U.S.C. § 103(a) and the other upholding the rejection of a related divisional application for the same reason. We affirm.

I

In 1994, the appellants filed a patent application, Serial No. 08/278,774 ("the '774 application"), claiming "Mutated Recombinant Collagens." Independent claim 1 is representative of the claimed subject matter:

> 1. A recombinant procollagen polypeptide chain comprising a natural collagen polypeptide chain, a first natural procollagen C-terminal propeptide and a first non-natural site-specific proteolytic agent recognition site, wherein said first non-natural site-specific proteolytic agent recognition site is located between said collagen chain and said first propeptide.

The appellants subsequently filed a divisional application, Serial No. 08/630,654 ("the '654 application"), claiming nucleic acids that encode the proteins claimed in the '774 application. Independent claim 21 is illustrative of the subject matter of the divisional application:

> 21. A nucleic acid encoding a recombinant procollagen polypeptide chain comprising a natural collagen polypeptide chain, a first natural procollagen C-terminal propeptide and a first non-natural site-specific proteolytic agent recognition site, wherein said first non-natural site-specific proteolytic agent recognition site is located between said collagen polypeptide chain and said first propeptide, and said propeptide is located at the C-terminus of said procollagen polypeptide chain.

The patent examiner who reviewed the two applications rejected certain claims in each application for obviousness. For the '774 application, the examiner concluded that independent claim 1 and dependent claims 2-3, 6-9, 14-16, and 18 were unpatentable over four prior art references—Chu, Prockop, and Olsen in view of Carter. For the '654 application, the examiner rejected independent claim 21 and dependent claims 22-30 as unpatentable over three prior art references—Ryan in view of Carter and Prockop II, a different reference by Prockop. The appellants appealed the rejections to the Board.

The Board agreed with the examiner that Chu, Prockop, and Olsen in view of Carter established an unrebutted prima facie case of obviousness for all but two of the appealed claims of the '774 application, and that Ryan in view of Carter and Prockop II established an unrebutted prima facie case of obviousness for all of the appealed claims of the '654 application. Accordingly, the Board affirmed the examiner's rejection of the claims that are at issue in this appeal. The Board subsequently denied the appellants' requests for reconsideration, and this appeal followed.

II

Collagen is a natural protein found in humans and, in somewhat different form, in other animals. It has been used in a wide range of applications, including as a substrate for cell cultureware and in human reconstructive therapy. As the major macromolecule in most human connective tissue, collagen has many potential therapeutic applications. Because of difficulties encountered in obtaining and using non-human collagen or human collagen from cadavers and placentas, it has been considered desirable to produce human collagen as a recombinant protein expressed in E. coli bacteria.

When collagen is synthesized, it is typically expressed as a precursor, procollagen, which consists of collagen with additional peptide extensions at either end of the molecular chain, i.e., at the amino and carboxyl ends (also known as the N-terminus and the C-terminus). The peptide extensions are then removed by specific proteolytic enzymes, known as proteases, to produce collagen.

The claimed invention is a polypeptide chain in which a natural procollagen C-terminal propeptide is fused to a collagen peptide via a non-natural site-specific proteolytic agent recognition site, i.e., a site at which a particular protease can cleave the peptide chain into two pieces. The natural procollagen C-terminal propeptide is useful in folding the peptide into its proper shape, but after the folding process is complete, the C-terminal propeptide can be cleaved off by an appropriate enzyme and purified out of the composition, leaving only the mature collagen.

III

Obviousness is a question of law supported by underlying facts. In re Gartside, 203 F.3d 1305, 1316, 53 USPQ2d 1769, 1776 (Fed. Cir. 2000). What the prior art teaches and whether it teaches away from the claimed invention are questions of fact. In re Bell, 991 F.2d 781, 784, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). On appeal, the Board's factual findings are reviewed for substantial evidence. Gartside, 203 F.3d at 1316, 53 USPQ2d at 1776. Because the appellants' arguments focus on the teachings of the prior art, our obviousness inquiry focuses on whether the Board's factual conclusions as to those teachings are supported by substantial evidence.

Because the appellants treat the two related applications together, we do the same. With respect to the '774 application, the appellants did not argue dependent claims 2-3, 8-9, 14-16, or 18 separately to the Board, nor do they in this appeal. The rejected claims therefore stand or fall with representative independent claim 1. With respect to the '654 application, the appellants did not argue dependent claims 22-30 of that application separately to the Board or to us, so the rejected claims stand or fall with representative independent claim 21. See In re Dance, 160 F.3d 1339, 1340 n.2, 48 USPQ2d 1635, 1636 n.2 (Fed. Cir. 1998).

In the prosecution of the '774 application, the examiner found that Chu and Prockop teach human procollagen and its N- and C-terminal propeptides, and that Olsen teaches the C-terminal propeptide of type 1 procollagen. In addition, the examiner relied on Carter as teaching that genes can be engineered so as to produce fusion proteins, and that those fusion proteins can be specifically cleaved using various chemical and enzymatic means. In the prosecution of the '654 application, the examiner found that Ryan teaches a nucleic acid sequence encoding a recombinant procollagen chain comprising a natural collagen polypeptide chain. In addition, the examiner concluded that Prockop II contains the following disclosures: (1) a vector comprising a recombinant human procollagen gene; (2) a promoter not naturally linked to the recombinant gene, and (3) the C-propeptide and N-propeptide of procollagen. The examiner further explained that the C-terminal propeptide is necessary for proper chain assembly of collagen molecules, a teaching found in the Prockop reference. The Board affirmed the examiner's interpretation of each of the prior art references, and the appellants do not challenge those interpretations.

Based on the prior art references of record, the examiner concluded that it would have been obvious to a person of ordinary skill in the art to create a recombinant DNA system for the production of procollagen in which the recombinant procollagen chain consisted of a natural collagen polypeptide and a first natural propeptide, with a first non-natural site-specific proteolytic agent recognition site located between them. It is that conclusion to which the appellants object.

The appellants do not dispute that procollagens (including their natural N- and C- terminal propeptides) and the genes that encode them are well known in the art. Instead, they challenge the conclusion of the examiner and the Board that Carter provided the motivation for the inventions claimed in the two applications. The examiner and the Board viewed Carter broadly, as disclosing that two proteins can be fused together for a variety for reasons, and that once those proteins are expressed they can be chemically or enzymatically separated at specific sites on the protein chain. Based on that teaching, the examiner and the Board concluded that the prior art made it obvious that one could engineer a gene to code for a natural collagen polypeptide chain fused with a natural procollagen C-terminal propeptide via a non-natural site-specific proteolytic agent recognition site, and that, once expressed, the two proteins could be separated enzymatically or chemically by particular known agents at that site. As the examiner explained: "One could make a cleavage site that could be readily and easily cleaved using a site-specific cleavage means instead of using the cleavage means used in the processing of natural collagen." Thus, both the examiner and the Board concluded that because it was well known from the prior art that two proteins could be fused at a particular cleavage site, and because the sequences and properties of procollagen and collagen were well known, it would have been obvious to fuse the natural collagen peptide with the natural procollagen C-terminal propeptide at a cleavage site that would respond to an enzyme other than one found naturally within the human body. The examiner explained this point in some detail:

> The propeptides of procollagen are normally cleaved during processing of the gene product to mature collagen. The C-terminal propeptide of procollagen is required for proper chain assembly of collagen molecules. Since collagen is a triple helical molecule, proper chain assembly is critical for the production of biologically active collagen. A person having ordinary skill in the art would recognize that by keeping the C-terminal propeptide at the C-terminus of the procollagen chain, as it is found in nature, a properly folded recombinantly produced procollagen molecule could be produced. However, the ordinary artisan would be aware of the fact that production of mature collagen would require removal of this C-terminal propeptide. By including a non-natural site-specific proteolytic agent recognition site in the genetic construct for expressing procollagen between the regions encoding collagen and the C-terminal propeptide, the resultant hybrid protein could be cleaved using a number of enzymatic or chemical means at the disposal of the skilled artisan and which would be prechosen by designing the appropriate sequence into the hybrid protein.

The examiner further stated that by designing an artificial proteolytic agent recognition site into the procollagen chain between the C-terminal propeptide and the collagen chain, the skilled artisan would not have to rely on using the naturally occurring protease that cleaves the C-terminal propeptide from the collagen chain. Thus, the examiner explained, the host cells that would be relied on to manufacture the hybrid protein, which do not naturally produce the requisite mammalian protease, could be used to produce mature collagen by being engineered to produce the protease specific for the site designed into the procollagen chain.

The appellants argue that Carter does not provide the necessary motivation to create a protein consisting of a natural collagen chain separated from a natural procollagen C-terminal propeptide by a non-native cleavage site. They read Carter narrowly, treating it primarily as a discussion of the use of "affinity handles," which Carter teaches are polypeptides with a high affinity for a particular ligand that can be used for purification of fusion proteins. They further argue that to the extent the examiner reasoned that Carter suggests the use of the procollagen C-terminal propeptide as an affinity handle to purify the collagen, no person of ordinary skill in the art would read Carter in that manner. That is because, the appellants explain, collagen-specific antibodies are widely known and commercially available, and a skilled artisan would therefore not use an affinity handle to purify collagen.

The appellants further argue that even if there were no available collagen-specific antibodies, Carter would, at most, suggest genetically engineering an affinity handle onto the collagen. The appellants explain that because there are many well-known affinity handles with high affinity ligands that can be used for purification, Carter would not suggest using a natural procollagen C-terminal propeptide in the place of one of those known affinity handles.

Although the appellants' criticism of the Board's discussion of Carter focuses on Carter's specific teachings with respect to affinity handles, that was not the exclusive basis on which the Board found Carter to be relevant to the obviousness inquiry. Thus, while the appellants argue that procollagens are not affinity handles as Carter describes them, that contention does not undermine the Board's conclusion that the more general teachings of Carter as to fusion proteins, combined with the prior art teachings as to the structure, function, and synthesis of procollagen and collagen, render the appellants' claimed

inventions obvious. The examiner and the Board found that the prior art references, including Carter, provided the motivation to fuse the natural collagen chain and the C-terminal propeptide at a non-native cleavage site. As noted above, the examiner and the Board found that the C-terminal propeptide provides benefits in post-translational processing of the procollagen peptide, which a person of ordinary skill in the art would have been motivated to preserve. The examiner summarized that motivation as follows:

> A person having ordinary skill in the art would recognize that by keeping the C-terminal propeptide at the C-terminus of the procollagen chain, as found in nature, a properly folded recombinantly produced procollagen molecule could be produced. This is because the C-terminal propeptide is necessary for proper chain assembly of collagen molecules. By including a non-natural site-specific proteolytic agent recognition site in the genetic construct for expressing procollagen, the resultant hybrid protein could be cleaved using a number of enzymatic or chemical means at the disposal of the skilled artisan and which would be prechosen by designing the appropriate sequence into the hybrid protein.

The examiner found that the prior art gave rise to a second motivation for making the claimed fusion protein with a non-natural site-specific cleavage site located between the C-terminal propeptide and the collagen chain—to simplify purification of the synthesized product. The examiner explained:

> Including a non-natural cleavage site in a procollagen construct would give the skilled artisan the ability to choose by what means cleavage of the collagen chain from the C-terminal propeptide was to be achieved and would give such an artisan the flexibility to weigh parameters such as the expense of the chemical or enzymatic agent to be used, the harshness of the conditions, the specificity of the cleavage agent and the efficiency of the agent.

The Board upheld these findings as to the motivation to make the fused protein of the asserted claims. The appellants insist that the examiner and the Board erred in finding a prima facie case of obviousness because, the appellants contend, the prior art references would not provide a person of ordinary skill in the art with the motivation to make the claimed inventions. The appellants, however, have not pointed to any clear flaw in the reasoning of the examiner and the Board on this issue, nor have they pointed to any evidence of record indicating that the findings of the examiner and the Board on this issue are unsupportable.

As persons of scientific competence in the fields in which they work, examiners and administrative patent judges on the Board are responsible for making findings, informed by their scientific knowledge, as to the meaning of prior art references to persons of ordinary skill in the art and the motivation those references would provide to such persons. Absent legal error or contrary factual evidence, those findings can establish a prima facie case of obviousness. In this case, the appellants have not pointed to any legal error affecting the Board's obviousness analysis. Nor have they pointed to sufficient factual grounds, either in the record or in any judicially noticeable sources, to question the findings made by the examiner and the Board as to the teachings of the prior art and the motivation that the prior art references would give to a skilled artisan to make the claimed invention. We therefore sustain the Board's conclusion that the recited prior art references established a prima facie case of obviousness with respect to the appealed claims of the '774 and '654 applications.

IV

The appellants attempt to rebut the prima facie case of obviousness by arguing that the prior art teaches away from their claimed inventions. See In re Haruna, 249 F.3d 1327, 1335, 58 USPQ2d 1517, 1522 (Fed. Cir. 2001). They contend that prior art references such as Prockop II disclose that expression of recombinant collagen in systems that do not naturally express the requisite procollagen-modifying enzymes requires the artisan to engineer the cells to express the necessary processing enzymes rather than engineering the collagen genes themselves to facilitate processing. The appellants fail to demonstrate, however, how re-engineering the cells to facilitate processing instead of engineering the collagen genes teaches away from their approach. Specifically, they do not explain how the disclosures of the prior art show that their claimed invention is unlikely to be productive of the desired result. See In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). The mere fact that there is an alternative means of expressing recombinant collagen in the prior art does not preclude the development of a new model that is obvious over the prior art. See In re Beattie, 974 F.2d 1309, 1312-13, 24 USPQ2d 1040, 1042 (Fed. Cir. 1992) (holding that an alternative to a well-entrenched theory does not preclude a finding of obviousness because the recommendation of a new system "does not require obliteration of another"). The appellants' arguments that the prior art teaches away from their claimed invention are thus without merit.

V

Because the appellants have not shown why the Board's conclusions regarding the disclosures in the prior art are not supported by substantial evidence, we agree that Chu, Prockop, and Olsen in view of Carter create a prima facie case of obviousness of claims 1-3, 8-9, 14-16, and 18 of the '774 application and that Ryan in view of Carter and Prockop II constitutes a prima facie case of obviousness for claims 21-30 of the '654 application. Because the appellants did not present persuasive evidence or argument in rebuttal, see In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984), we affirm the decisions of the Board rejecting these claims.

AFFIRMED.