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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte TODD M. KINSELLA[1]

Appeal 2014-001115
Application 12/965,714
Technology Center 1600

Before ULRIKE W. JENKS, TINA E. HULSE, and TAWEN CHANG, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims directed to a method of making a cyclic polymer. The Examiner rejects the claims as obvious and on the ground of nonstatutory obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

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[1] According to Appellant, the real party in interest is Rigel Pharmaceuticals, Inc. (App. Br. 3.)

STATEMENT OF THE CASE

According to the Specification, the "methods find particular use in production of cyclic polymers. In particular, the subject methods find particular use in producing cyclic polymers (e.g., cyclic peptides) that are not genetically encodable, using a cell-free system." (Spec. ¶ 117). The Specification describes a

> "semi-synthetic" composition in which a first part of the composition (i.e., the C and N-terminal intein domains) are made in a cell, and a second part of the composition (i.e., the polymer) is made synthetically. As discussed above, the polymer region of an intein composition may contain one or many non-naturally occurring amino acids and in certain embodiments, may contain only non-naturally occurring amino acids.

(Spec. ¶ 104.)

Claims 19–22 and 24–26 are on appeal, and can be found in the Claims Appendix of the Appeal Brief. Claim 19 is representative of the claims on appeal, and reads as follows (emphasis added):

> 19. A method for making a cyclic polymer, comprising:
> incubating a compound of the structure:
> $$D_1\text{-}X_{(n)}\text{-}D_2$$
> wherein D_1 is a first catalytic domain of an intein;
> wherein $X_{(n)}$ is a polymer comprising n residues of a monomer X, n is at least 2, the polymer is *not genetically encodable and is not made by a cell*, and the polymer has a first reactive site for said intein at its N-terminus; and
> wherein D_2 is a second catalytic domain of an intein, having at its N-terminus
> a second reactive site for said intein;
> under intein reaction conditions to produce said cyclic polymer.
>
> (App. Br. 12, Claims Appendix)

Appellant seeks review of the following rejections:

I. claims 19–22 and 24–26 under 35 U.S.C. § 103(a) as unpatentable over Benkovic[2] in view of Wyrick;[3] and

II. claims 19–22 and 24–26 on the grounds of nonstatutory obviousness-type double patenting over claims 1, 2, and 6 of the '571 patent[4] in view of Benkovic and further in view of Wyrick.

Obviousness over Benkovic and Wyrick

The Examiner finds that Benkovic teaches compounds having the following structure D_1-$X_{(n)}$-D_2 but acknowledges that the reference "does not teach X-monomers that are not made by a cell" as required by the claim limitation "wherein the polymer that is made up of monomer X is not genetically encodable" (Ans. 4). The Examiner looks to Wyrick for teaching methods of modifying proteins by crosslinking them with DNA (*see* Ans. 4). The combination of references, according to the Examiner, results in the modification of the genetically encodable cyclic proteins as disclosed in Benkovic with the art-recognized crosslinking modification as disclosed in Wyrick to arrive at a polymer containing monomers that are not genetically encodable (*see* Ans. 5). According to the Examiner, Figs. 16–19 of Benkovic "explicitly suggest cyclic DNA binding proteins, which constitutes the precise type of protein of interest to Wyrick" (Advisory Action.[5] 4). The

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[2] Benkovic et al., US 2007/0207502 A1, published Sept. 6, 2007 ("Benkovic").
[3] Wyrick et al., US 7,575,869 B2, issued Aug. 18, 2009 ("Wyrick").
[4] Kinsella, US 7,208,571 B2, issued Apr. 24, 2007 ("the '571 patent").
[5] Advisory Action mailed Feb. 6, 2013

Examiner reasons that you would make this modification in order to produce a cyclic compound that is crosslinked with DNA to study regulatory networks of DNA binding (Final Action[6] 5). "One of ordinary skill in the art would have had a reasonable expectation of success in applying formaldehyde per Wyrick et al[.] toward modifying the cyclic proteins prepared in the manner of Benkovic et al[.] because formaldehyde crosslinking constitutes an art-recognized robust technique exploited in the art for decades" (*id.*).

Appellant contends that the Examiner's rationale is flawed because "DNA binding proteins are linear molecules. They are not cyclic, and there is no reason to expect that a cyclic version of a linear DNA binding protein (especially one that has been cross-linked using formaldehyde) would retain the ability to bind to DNA" (App. Br. 5). Appellant contends that based on the combination of references "one of skill would [not] have a reason to study transcription factors that have been treated with formaldehyde and then cyclized" (Reply Br. 2). Appellant contends that the Examiner has not sufficiently articulated why one of ordinary skill would look to first cyclize a DNA binding protein and then treat it with formaldehyde in order to create a cyclic polymer D_1-$X_{(n)}$-D_2 that is not genetically encoded and made by a cell as claimed (*see* App. Br. 9).

The issue is: Does the evidence of record support the Examiner's conclusion that the combination of references renders obvious the claimed method of making a cyclic polymer with monomers that are not genetically encodable and not made by a cell?

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[6] Final Action mailed Nov. 16, 2012 ("Final Act.").

Findings of Fact

FF1. Fig. 16 of Benkovic is reproduced below:

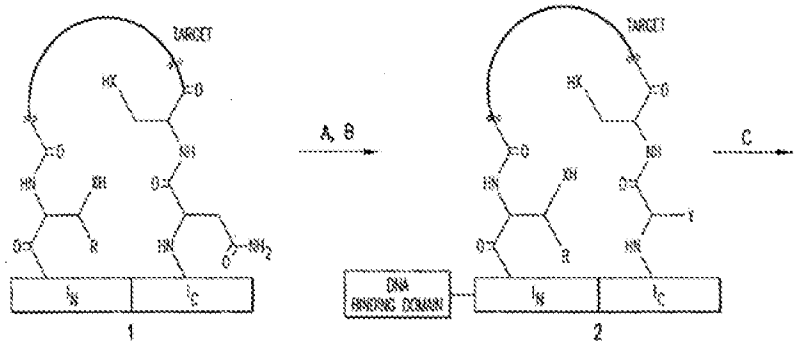

FIG.16A

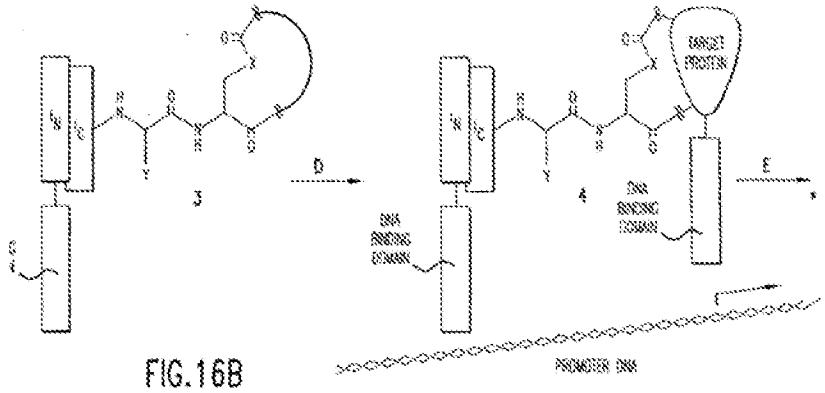

FIG.16B

In this method, an active intein intermediate (specie 1) is mutagenized . . . to introduce a DNA-binding domain downstream of I_N (step B) to yield specie 2. The intein-mediated cyclization reaction will proceed until the lariat intermediate (specie 3) is formed (step C). I_N and I_c form a strong non-covalent complex. The resulting lariat intermediate is then co-expressed with a target protein attached to a DNA-binding domain (step D). Interaction of the lariat intermediate with the target protein (specie 4) causes activation of a promoter region (step E) leading to expression of the reporter gene (*). This method can be modified such that a known molecule (in place of an unknown target protein) is attached to a DNA-binding domain, so that lariat intermediates displaying a looped peptide that binds the known molecule can be identified.

(Benkovic ¶ 134).

FF2. Wyrick teaches that "DNA binding protein of a cell is linked (e.g., covalently crosslinked) to genomic DNA of a cell" (Wyrick, Abstract). Specifically, the "cells are fixed with formaldehyde, harvested by sonication, and DNA fragments that are crosslinked to a protein of interest are enriched by immunopercipitaion with a specific antibody" (Wyrick 10:67–11:1).

Principle of Law

"An examiner bears the initial burden of presenting a prima facie case of obviousness." *In re Huai-Hung Kao*, 639 F.3d 1057, 1066 (Fed. Cir. 2011). In satisfying this initial burden, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992). Stated differently, to establish obviousness, there must be "an apparent reason to combine the known elements in the fashion" recited in the claims. *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 418 (2007).

Analysis

Appellant acknowledges that "Benkovic teaches that a cyclic peptide can be appended to a transcription factor . . . . Benkovic does not teach a cyclic transcription factor" (Reply Br. 7). Similarly, Appellant argues that Wyrick also does not mention cyclic transcription factors but is rather "cited to provide [a] method in which proteins are cross-linked using formaldehyde" (App. Br. 4). According to Appellant, "[i]t is unclear how either of the cited references alone or in combination could teach or suggest

a cyclic transcription factor when nether [sic] of the references even so much as mentions such a thing" (Reply Br. 7). In other words, Appellant contends that the Examiner has not sufficiently articulated why one of ordinary skill would look to cyclize a DNA binding protein and then cross link this protein with formaldehyde (*see* App. Br. 9 ("none of the references provide any motivation to cyclize a DNA binding protein")).

We find that Appellant has the better position. The Examiner acknowledges that Benkovic teaches compounds having the structure D_1-$X_{(n)}$-D_2 but does not teach that X should be a polymer that is "not genetically encodable and is not made by a cell" (Ans. 4). The Examiner reasons that if Benkovic's molecule D_1-$X_{(n)}$-D_2 is modified after production then the polymer X is no longer genetically encodable or made by the cell. The Examiner looks to the teachings of Wyrick to suggest using formaldehyde modification to arrive at a polymer that is not genetically encodable (*see* Ans. 4 ("crosslink with DNA via formaldehyde treatment in the manner of Wyrick")). In particular, the Examiner notes that "[f]ormaldehyde reacts with proteins for instance at lysine residues to form a side chain bearing a reactive immonium cation functional group, constituting an amino acid monomer not made by cells" (Final Act. 5). The Examiner reasons that a skilled artisan would be motivated to perform these modifications because Benkovic "explicitly indicate[s] DNA binding proteins are of particular interest and (ii) characterization of regulatory networks of DNA binding proteins is useful toward mapping the cell cycle as well as identifying gene function, each important according to Wyrick" (Ans. 5). We are not persuaded by the Examiner's rationale. Just because protein modifications are known in the art does not explain why one of

ordinary skill in the art would want to make such modifications especially to polymer X that is to be cyclized.

The Examiner's reason for combining the references is that both Benkovic and Wyrick suggest studying DNA binding protein interactions with genomic DNA (*see* Ans. 5). It is true that both references disclose using DNA binding protein domains; however, an interest in studying DNA binding does not explain why a person of ordinary skill in the art would want to move the DNA binding domain from the position shown in Benkovic's Fig. 16 (FF1, *see also* Benkovic Fig. 17-19) to the position where it becomes cyclized. Wyrick discloses crosslinking DNA binding protein with genomic DNA to precipitate and obtain DNA fragments in order to determine what genomic sequences the DNA protein binds (FF2). Benkovic's molecules without any modification would be expected to work in Wyrick's methods (FF1 & FF2). In other words, the DNA binding domains that are not cyclized as shown in Benkovic (*see* FF1) would function similarly to the DNA binding proteins in Wyrick. Wyrick's formaldehyde crosslinking methods "facilitate the dissection of the cells['] regulatory network of gene expression across the entire genome and aid in the identification of gene function. . . . [The work] forms the foundation for a complete map of the transcriptional regulatory network that controls the yeast cell cycle" (Wyrick 3:50–57; Ans. 5). This however does not explain why the ordinary artisan would look to place the DNA binding domain protein in between the split inteins as disclosed in structure D_1-$X_{(n)}$-D_2. We agree with Appellant's position that the Examiner has not adequately explained why the ordinary artisan would move the DNA binding domain from the current position disclosed in Benkovic's molecules (*see* FF1) into

the target protein position that is cyclized by the split inteins. *See KSR Int'l Co. v. Teleflex Inc., 550 U.S* at 418 (obviousness rejections require "some articulated reasoning with some rational underpinning").

As the Examiner has failed to adequately articulate any other rationale explaining how the combination of references discloses a cyclic polymer that is not genetically encodable and is not made by a cell, we are constrained to reverse each rejection that relies on Benkovic and Wyrick.

Nonstatutory Obviousness-Type Double Patenting of the '571 Patent in View of Benkovic and Wyrick

With respect to the nonstatutory obviousness-type double patenting rejection of the '571 patent in view of Benkovic and Wyrick, the Examiner applies the same rationale as disclosed for the obviousness rejections above, which we found unpersuasive. We agree with Appellant's position that the Examiner has not adequately explained why the ordinary artisan would move the DNA binding domain from the current position disclosed in Benkovic's molecules (*see* FF1) into the target protein position that is cyclized by the split inteins.

SUMMARY

We reverse the rejection of claims 19–22 and 24–26 under 35 U.S.C. § 103(a) as unpatentable over Benkovic in view of Wyrick.

We reverse the rejection of claims 19–22 and 24–26 on the grounds of nonatatutory obviousness-type double patenting over claims 1, 2, and 6 of the ’571 patent in view of Benkovic and further in view of Wyrick.

REVERSED