UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/604,252	01/23/2015	Lyndsey M. Linke	2076.35.PR2C	1976

21901 7590 01/29/2019

Smith & Hopen (private clients)
Attn: General Patent Matters
180 Pine Avenue North
Oldsmar, FL 34677

EXAMINER
SHIN, DANA H

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
01/29/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@smithhopen.com
pair@smithhopen.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte LYNDSEY M. LINKE, MO D. SALMAN, and JEFFREY WILUSZ

Appeal 2018-000788
Application 14/604,252
Technology Center 1600

Before JEFFREY N. FREDMAN, DEBORAH KATZ, and JOHN G. NEW, *Administrative Patent Judges.*

FREDMAN, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal[1,2] under 35 U.S.C. § 134(a) involving claims to methods for treating or reducing the risk of spreading avian influenza in poultry by administering siRNA compositions. The Examiner rejected the

---

[1] Appellants identify the Real Party in Interest as the Colorado State University Research Foundation (*see* App. Br. 3).

[2] We have considered and herein refer to the Specification of Jan. 23, 2015 ("Spec."); Final Office Action of Dec. 1, 2016 ("Final Act."); Appeal Brief of May 1, 2017 ("App. Br."); Examiner's Answer of Aug. 31, 2017 ("Ans."); and Reply Brief of Oct. 31, 2017 ("Reply Br.").

claims as anticipated and obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

Background

"Developing a powerful anti-influenza technology is a critical step to effectively manage and control the spread of AIV [avian influenza virus] in poultry to minimize financial losses and risks for transmission to other susceptible species, including humans" (Spec. ¶ 32). "RNA interference (RNAi) using siRNAs [small interfering RNAs] has been explored for the development [of] alternative antivirals to control diseases in humans and livestock species" (*id.* ¶ 33). "The delivery of RNAi-mediating agents has been an obstacle to its clinical [approach] . . . [s]ince siRNAs are unable to cross cell membranes independently" (*id.*).

The Claims

Claims 9–11, 15, and 22–33 are on appeal. Independent claim 9 is representative and reads as follows:

> 9. A method for treating or reducing the risk of spreading avian influenza in poultry, comprising
>
> the step of administering to said poultry a composition comprising a nonpathogenic E. coli bacterium comprising a prokaryotic vector,
>
> said vector comprising a DNA molecule encoding one or more siRNAs and one or more promoters to control transcription of the siRNAs,
>
> wherein the siRNAs interfere with one or more avian influenza viral RNA molecules and wherein the bacterium is engineered to express genes to facilitate the entry of the bacterium into a cell of the poultry and endosomal release of the siRNA upon entry into the cell of the poultry.

The Issues

A. The Examiner rejected claim 29 under 35 U.S.C. § 102(a)(1) as anticipated by Doran[3] (Final Act. 3–5).

B. The Examiner rejected claims 9–11, 15, and 22–33 under 35 U.S.C. § 103 as obvious over Doran, Xiang[4], and Perez[5] (Final Act. 5–12).

A. 35 U.S.C. § 102(a)(1) over Doran

The Examiner finds Doran discloses treating avian influenza A virus infections in poultry "by administering a cell comprising a vector encoding an anti-influenza [double stranded RNA (dsRNA)] in an aerosol, wherein the cell and the vector are each described to be a nonpathogenic *E. coli* cell and a bacterial plasmid" (Final Act. 5).

The issue with respect to this rejection is whether a preponderance of the evidence of record support the Examiner's finding that Doran anticipates claim 29?

Findings of Fact ("FF")

1. Doran teaches a method for treating avian influenza in poultry [claims 53–56], comprising the step of administering to said poultry a composition sprayed as an aerosol [claim 52] to a poultry population [claim 55], the composition comprising a nucleic acid construct and/or cell [claims 51 and 52], comprising a vector [claim 41], said vector comprising a DNA molecule encoding an siRNA

[3] Doran et al., WO 2008/138072 A1, published Nov. 20, 2008.
[4] Xiang et al., *Short Hairpin RNA-expressing bacteria elicit RNA interference in mammals*, 24 NATURE BIOTECH. 697–702 (2006).
[5] Perez, US 2011/0150912 A1, published June 23, 2011.

[claim 39] and a promoter to control transcription of the siRNA [claims 18–23], wherein the siRNA interferes with an avian influenza viral molecule [claims 1 and 24] (Doran claims 1, 18–24, 39, 41, 51–55, cf. 7:24–36).

2. Doran teaches, "nucleic acid molecules comprising and/or encoding double stranded regions for RNA interference" which "refers generally to a process in which a double-stranded RNA molecule reduces the expression of a nucleic acid sequence with which the double-stranded RNA molecule shares substantial or total homology" (Doran 15:16–23).

3. Doran teaches, "it may be desirable to insert the . . . nucleic acid molecule . . . into a vector." The vector may be "derived from [a] bacterial plasmid[]" (Doran 24:23–32).

4. Doran teaches, "the nucleic acid will typically comprise a suitable promoter operably linked to the open reading frame encoding the double-stranded RNA" (Doran 19:15–17).

5. Doran teaches, "preferably the . . . nucleic acid molecule is a short interfering RNA (siRNA) or a short hairpin RNA (shRNA)" (Doran 6:3–4, 16:1–3, 16:26–32).

6. Doran teaches a "host cell into which the nucleic acid construct . . . has been introduced. The host cell of this invention can be used as, for example, a production system for producing or expressing the dsRNA molecule. For *in vitro* production, eukaryotic cells or prokaryotic cells can be used" (Doran 25:4–8).

7. Doran teaches, "[u]seful prokaryotic cells include bacterial cells, such as *E. coli*, for example JM109, DH5a, and HB101, or *Bacillus subtilis*" (Doran 25:17–18).

8. Doran teaches an embodiment where "the nucleic acid construct . . . is administered via pulmonary delivery, such as by inhalation of an aerosol. . . . [T]he aerosol may be administered by an inhalation device . . . providing rapid local uptake of the nucleic acid molecules into relevant pulmonary tissues" (Doran 29:11–16).

9. Doran teaches: "host cells of the invention may be used to treat and/or prevent influenza A virus infection in a subject . . . In one embodiment, the method comprises administering the nucleic acid construct, the isolated and/or exogenous nucleic acid, the vector, and/or the cell in drinking water or in an aerosol . . . " (Doran 7:17–31).

Principles of Law

The Examiner bears the initial burden of establishing a *prima facie* case of anticipation. *In re King,* 801 F.2d 1324, 1326–1327 (Fed. Cir. 1986). For a prior art reference to anticipate a claim, it must disclose all of the limitations of the claim, "arranged or combined in the same way as in the claim." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012).

Analysis

We adopt the Examiner's findings of fact and conclusion of law (see Final Act. 3–5; FF 1–9) and agree that Doran anticipates claim 29. We address Appellants' arguments below.

Appellants contend Doran "does not show 'the identical invention . . . in as complete detail as contained in the . . . claim' nor are the elements pointed to in Doran 'arranged as required by the claim'" (App. Br. 12). Appellants contend that the Examiner is "picking, choosing, and combining

various disclosures not related to each other" (Reply Br. 14; App. Br. 16, *citing In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972) and *Net MoneyIn, Inc. v. Verisign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008)). Appellants contend the Examiner pieced together "many claims with numerous options . . . while making diversions into the specification when the specifics could not be found in the claims of Doran" (App. Br. 15).

We do not find this argument persuasive because the Examiner does not pick and choose from distinct chemical precursors to provide the specific substitutions of a generic compound per *In re Arkley*, nor combine two separate protocols each containing only a subset of components per *Net MoneyIn*. (*See In re Arkley*, 455 F.2d 588; *see also Net MoneyIn*, 545 F.3d at 1371). Rather, the Examiner identifies Doran as teaching a dsRNA encoding a siRNA and a promoter to control transcription of siRNA (FF 1). Administering the dsRNA treats or prevents avian influenza in poultry by causing RNAi (FF 1). Although Doran teaches a number of different ways of delivering the dsRNA, one way is an aerosol composition for "providing rapid local uptake of the nucleic acid molecules into relevant pulmonary tissues" (FF 8). This is an embodiment contemplated by the avian influenza virus treatment methods of chickens listed in Doran's claims 51, 52, and 56 as it depends from the siRNA of claim 39 in a vector of claim 41 that is in a cell of claim 42 (FF 1). *See Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1377 (Fed.Cir.2005) (distinguishing cases in which a prior art reference discloses a genus from those in which it discloses a number of species as part of a list). Doran's claims and specification of Doran also list the remaining limitations of the dsRNA, e.g. being introduced into a nonpathogenic *E. coli* host cell in the form of a prokaryotic (e.g., bacterial)

plasmid vector, so that a person of ordinary skill in the art reading the reference would at once envisage the claimed arrangement (FF 2–7). *See id.*

Appellants contend "Doran is talking about aerosolizing nucleic acids, not 'a composition sprayed as an aerosol to a poultry population the composition comprising a nonpathogenic *E. coli* bacterium . . .' as required by the claim 29" (App. Br. 22).

We find this argument unpersuasive because Doran expressly teaches that: "host cells of the invention may be used to treat and/or prevent influenza A virus infection in a subject . . . In one embodiment, the method comprises administering the nucleic acid construct, the isolated and/or exogenous nucleic acid, the vector, and/or the cell in drinking water or in an aerosol . . . " (FF 9). Doran further lists *E. coli* as a host cell (FF 7). Thus, Doran does teach treatment of influenza with aerosolized host cells containing the siRNA nucleic acids and lists *E. coli* as one of the host cells that may be used (FF 1–9).

Appellants contend that Doran is non-enabling for the invention as claimed (*see* Reply Br. 21). To support this argument, Appellants cite to the U.S. counterpart application of Doran (US 12/451,540) in which the Examiner rejected the claims as non-enabled for making a transgenic chicken resistant to Influenza A virus infection (*see* App. Br. 18).

We find this argument to be unpersuasive for several reasons. First, the claims of the related application were drawn to an entirely different invention of a transgenic chicken rather than the treatment method disclosed in claim 56 as it depends from claims 39, 41, 42, 51, and 52 of Doran. Thus, whether the transgenic chicken is enabled is irrelevant to the enablement of the treatment claims.

Second, "[a] prior art printed publication cited by an examiner is presumptively enabling barring any showing to the contrary by a patent applicant." *In re Morsa*, 713 F.3d 104, 109 (Fed. Cir. 2013). The prior art is enabling if "a person of ordinary skill in the art could make or use the claimed invention without undue experimentation based on the disclosure *of that particular document*." *Id.* at 110. Doran teaches working examples of nucleic acid molecules comprising prokaryotic vectors, each comprising a dsRNA encoding a siRNA and a promoter, which effectively inhibit the production of avian influenza (FF 1–8). Appellants' reference to a non-enabled related application claiming a transgenic chicken does not address whether Doran enables treating avian influenza A virus infections in poultry by administering a cell comprising a vector encoding an anti-influenza dsRNA in an aerosol, wherein the cell and the vector are each described to be a nonpathogenic *E. coli* cell and a bacterial plasmid.

Third, Appellants do not provide any persuasive evidence that Doran is non-enabling for the teachings that the Examiner relies on, and therefore have not demonstrated that the Examiner errs.

In their Reply Brief, Appellants submit three new arguments that Doran is non-enabling, specifically: (1) Doran does not enable "administering primordial germ cells in drinking water or in an aerosol," (2) Doran's bacteria possess neither *Inv* nor *HlyA* and are thus non-invasive, and (3) "[b]oth Appellant's and Xiang's plasmid used the prokaryotic T7 promoter" (Reply Br. 22–28). Here Appellants raise new arguments in the Reply Brief and without good cause. *Ex parte Borden*, 93 U.S.P.Q.2d 1473–1474 (B.P.A.I. 2010) (informative) ("The reply brief is not an opportunity to make arguments that could have been made during prosecution, but were not. Nor is the reply brief an opportunity to make arguments that could have

been made in the principal brief on appeal to rebut the Examiner's rejections, but were not"). Because of the timing of the filing after the Examiner's Answer, we lack the benefit of the Examiner's expert opinion. Also, because "[a]ny bases for asserting error, whether factual or legal, that are not raised in the principal brief are waived," we do not consider these belated arguments. *Id.*

Conclusion of Law

A preponderance of the evidence of record support the Examiner's conclusion that Doran anticipates the method of claim 29.

B. 35 U.S.C. § 103 over Doran, Xiang, and Perez

The Examiner determines that one of ordinary skill in the art would have been motivated to use Xiang's bacteria-mediated trans-kingdom RNAi when administering the cell comprising a vector encoding dsRNA as claimed by Doran, to induce RNAi-based therapeutics by avoiding art-recognized shortcomings and provide several advantages (Final Act. 7).

Issue

The issue with respect to this rejection is whether a preponderance of the evidence of record supports the Examiners' conclusion that claims 9–11, 15, and 22–33 would have been obvious over Doran, Xiang, and Perez?

Findings of Fact

10. Doran teaches a nucleic acid construct that encodes two or more RNA molecules, wherein each RNA molecule comprises a nucleotide sequence corresponding to a different influenza A virus gene (Doran claims 16, 17).

11. Doran teaches:

> it is of significant benefit to express multiple shRNAs from the one transgene to further reduce the risk of viral target sequence variability to an RNAi strategy. These 'Multi-Warhead' (MWH) transgenes are comprised of multiple transcription units, each with a different chicken pol III promoter . . . expressing individual shRNA molecules targeting the conserved sequences of different influenza A genes . . .

(Doran 36:13–18).

12. Xiang teaches, "[n]onpathogenic [*E. coli*] were engineered to transcribe shRNAs from a plasmid containing the invasin gene *Inv* and the listeriolysin O gene *HlyA*, which encode two bacterial factors needed for successful transfer of the shRNAs into mammalian cells" (Xiang Abstract).

13. Xiang teaches, "*E. coli* encoding shRNA . . . induce significant gene silencing . . . These results provide an example of trans-kingdom RNAi in higher organisms and suggest the potential of bacteria-mediated RNAi for functional genomics, therapeutic target validation and development of clinical compatible RNAi-based therapeutics" (Xiang Abstract).

14. Xiang teaches, "[e]ngineered bacteria may help to achieve potent RNAi for desired therapeutic effects with versatility and less costs. . . . Because the shRNA is released inside target cells by the engineered bacteria, this RNAi approach may have the advantage of mitigating the Toll-like receptor-mediated immunostimulatory effect of siRNA" (Xiang 700).

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

Analysis

We adopt the Examiner's findings of fact and conclusion of law (*see* Final Act. 5–12; FF 1–14) and agree that claims 9–11, 15, and 22–33 are obvious over Doran, Xiang, and Perez. We address Appellants' arguments below.

Claims 9–11, 22–26, and 29–31

Appellants repeat their arguments set forth against anticipation, contending "Doran was intending to make transgenic chickens that are less susceptible to avian influenza infection," and "Doran does not teach a 'composition administered to a poultry population where the composition comprises a **nonpathogenic *E. coli* bacterium** . . . ' Nor does that composition comprise a prokaryotic vector" (App. Br. 27–28). As discussed above, we are not persuaded by these arguments. We further note that the "picking and choosing" argued by Appellants against anticipation "may be entirely proper in the making of a 103, obviousness rejection." *Arkley*, 455 F.2d at 587. Because the Examiner properly identifies where Doran discloses a method for treating avian influenza in poultry by administering an aerosol composition comprising a nonpathogenic *E. coli* bacterium comprising a prokaryotic vector comprising a dsRNA encoding a siRNA and a promoter (FF 1–9), we are not persuaded that the Examiner errs in describing the teachings of Doran.

Appellants contend that Doran, Xiang, and Perez do not teach "administering an aerosolized nonpathogenic *E. coli* bacterium" (App. Br.

28; underlining omitted). In particular, Appellants contend that "Doran is talking about aerosolizing nucleic acids, not a 'composition sprayed as an aerosol'" and "Xiang was using oral or intravenous administration of their composition to induce gene silencing in the intestinal epithelium and in human colon cancer xenografts in mice" (App. Br. 30). Appellants further contend that Doran "does not teach administering *E. coli* to poultry" and "[t]he Examiner **never** argues that Xiang or Perez teach this element/aspect" (Reply Br. 29).

We do not find these arguments persuasive because they fail to address the combined teachings of the references. "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). Even, *arguendo*, if we were persuaded by Appellants' argument that Doran, at best, teaches aerosolizing nucleic acids (not *E. coli* cells), Xiang expressly provides the motivation to combine those nucleic acids with a nonpathogenic *E. coli* delivery vehicle to achieve potent RNAi for improved therapeutic effect with versatility and less costs (FF 14). Thus, when the references are considered together, Xiang complements Doran's method of treating avian influenza in poultry with an aerosolized nucleic acid for RNAi by improving shRNA delivery inside target cells with engineered bacteria (FF 12–14).

Appellants argue against the Examiner's cited motivation to combine the references. First, Appellants contend "the proposed modification would render the prior art invention . . . being modified unsatisfactory for its intended purpose" because "the introduction of the bacterium [of Xiang]

would not result in a transgenic chicken, thus negating the intended purpose of the Doran reference" (App. Br. 27, 28). Appellants further contend:

> one would not be motived to modify Doran's bacteria-mediated trans-kingdom RNAi system . . . with the teaching of Xiang, because Xiang teaches that bacteria mediated trans-kingdom RNAi overcome so many problems. This is because Doran already supposedly taught a bacteria-mediated trans-kingdom RNAi system so it would already be free of those problems.

(App. Br. 36).

We do not find these arguments persuasive because the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference . . . Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. *In re Keller*, 642, F.2d 413, 424 (C.C.P.A. 1977). As discussed above, Doran's teachings are not limited to creating a transgenic chicken and include a method of treating avian influenza in poultry by administering a dsRNA as an aerosol composition (FF 1). Xiang suggests an improvement to Doran's method using an engineered bacteria containing *Inv* and *HlyA* to mediate trans-kingdom RNAi with Doran's dsRNA and siRNA for treating avian influenza (FF 13). Because the person of ordinary skill in the art is also a person of ordinary creativity, they would have employed the steps needed to improve the method of Doran to achieve the desired therapeutic effect with versatility at less cost as taught by Xiang (FF 14).

Claims 15, 27, 28, 32, and 33

Appellants contend Doran teaches away from administering two separate nonpathogenic *E. coli* bacteria, as recited by independent claims 15 and 32 (App. Br. 31–32). Appellants contend Doran teaches away by stating

"'it is of significant benefit to express multiple shRNAs from the one transgene to further reduce the risk of viral target sequence variability to an RNAi strategy'" (App. Br. 32). Referring to page 36 of Doran (FF 11), Appellants argue, "[r]educing the risk of viral target sequence variability refers to having multiple genes targeted in that fixed transgene. We are advocating the opposite; have a single gene targeted by each bacteria . . . but mix the bacteria together to create a mixed population that targets multiple viral genes" (Reply Br. 35).

We do not find this argument persuasive. "The prior art's mere disclosure of more than one alternative does not constitute a teaching away from . . . because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed." *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Here Doran teaches the desirability of administering dsRNAs having a nucleotide sequence corresponding to different influenza A virus genes to reduce the risk of viral target sequence variability (FF 11, 12). By listing the benefits of MWH transgenes, Doran does not criticize, discredit, or otherwise discourage expressing individual shRNA molecules in separate *E. coli* cells. Rather, a person of ordinary skill in the art, having ordinary creativity, would have been able to combine the benefits of Doran's targeting multiple RNA sequences with Xiang's trans-kingdom *E. coli* mediated RNAi to reduce the risk of viral target sequence variability.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that the prior art renders claims 9–11, 22–26, and 29–31 obvious. The evidence of record supports the Examiner's conclusion that the prior art renders claims 15, 27, 28, 32, and 33 obvious.

SUMMARY

In summary, we affirm the rejection of claim 29 under 35 U.S.C. § 102(a)(1) as anticipated by Doran.

We affirm the rejection of claims 9–11, 15, and 22–33 under 35 U.S.C. § 103 as obvious over Doran, Xiang, and Perez.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED