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.
13/124,411	04/15/2011	Ingo Roehl	0159-AX01US1	6223

56719 7590 12/20/2019

MEDLER FERRO WOODHOUSE & MILLS PLLC
8201 Greensboro Drive, Suite 1060
McLean, VA 22102

EXAMINER
SISSON, BRADLEY L

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
12/20/2019	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):

aferro@medlerferro.com
docketing@medlerferro.com
tmedler@medlerferro.com

UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE PATENT TRIAL AND APPEAL BOARD

_____

Ex parte INGO ROEHL, MARKUS SCHUSTER, and STEPHAN SEIFFERT

_____

Appeal 2019-001375
Application 13/124,411[1]
Technology Center 1600

_____

Before DONALD E. ADAMS, ERIC B. GRIMES, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for detecting a target therapeutic RNA oligonucleotide having a predefined sequence and RNA oligonucleotide metabolites of said target therapeutic RNA oligonucleotide, which have been rejected as obvious. Oral argument was heard on December 9, 2019. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

---

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as LGC Group, which is the owner of Axolabs GmbH. (Appeal Br. 3.)

STATEMENT OF THE CASE

Appellant's Specification states that "[o]ligonucleotides of known sequences are commonly used in a wide variety of chemical and biological applications." (Spec. 1.) Methods are known for the detection of oligonucleotides, including the use of peptide nucleic acids (PNAs) and anion-exchange high performance liquid chromatography (HPLC). (*Id.*) Appellant's invention is directed to a method of detecting an oligonucleotide in a sample along with its metabolites in a single assay that employs fluorescence spectroscopy for quantitative detection of the oligonucleotide and its metabolites. (Spec. 3–4.)

Claims 1–3, 6–8, 13–15, 17, 19, and 20 are on appeal. Claim 1 is representative and reads as follows:

> 1. A method for detecting a target therapeutic RNA oligonucleotide having a pre-defined sequence and RNA oligonucleotide metabolites of said target therapeutic RNA oligonucleotide, comprising the steps of:
>
> (a) preparing a sample containing or suspected of containing said target therapeutic RNA oligonucleotide having said pre-defined sequence and said RNA oligonucleotide metabolites of said target therapeutic RNA oligonucleotide, wherein said target therapeutic RNA oligonucleotide has a length of 10 nucleotides up to 29 nucleotides, and wherein said RNA oligonucleotide metabolites are said target therapeutic RNA oligonucleotide from which 1 or more nucleotides have been deleted from the 3'- and/or the 5'- end, and/or said RNA oligonucleotide metabolites are said target therapeutic RNA oligonucleotide comprising phosphorylated 3'- or 5'- ends, and wherein said sample is an extracellular or intracellular sample,
>
> (b) forming a hybridization mixture by contacting the sample with a fluorescently labeled peptide nucleic acid (PNA) probe,

(c) hybridizing the PNA probe to said target therapeutic RNA oligonucleotide having said pre-defined sequence and hybridizing the PNA probe to said RNA oligonucleotide metabolites of said target therapeutic RNA oligonucleotide, wherein said PNA probe and said target therapeutic RNA oligonucleotide having said pre-defined sequence are fully complementary over at least 10 nucleotides of said target therapeutic RNA oligonucleotide having the pre-defined sequence,

(d) separating hybridized moieties formed between said PNA probe and said target therapeutic RNA oligonucleotide having said pre-defined sequence, and hybridized moieties formed between said PNA probe and said RNA oligonucleotide metabolites of said target therapeutic RNA oligonucleotide, from unhybridized moieties by anion exchange high performance liquid chromatography (HPLC), wherein signals associated with said hybridized moieties formed between said PNA probe and said RNA oligonucleotide metabolites of said target therapeutic RNA oligonucleotide are separated from a signal associated with hybridized moieties formed between said PNA probe and said target therapeutic RNA oligonucleotide, and

(e) detecting quantitatively in a single fluorescence spectroscopy measurement said hybridized moieties formed between said PNA probe and said target therapeutic RNA oligonucleotide having said pre-defined sequence and hybridized moieties formed between said PNA probe and said RNA oligonucleotide metabolites of said target therapeutic RNA oligonucleotide.

(Appeal Br. 31–32.)

The prior art relied upon by the Examiner is:

Name	Reference	Date
Fougerolles	US 2006/0094032 A1	May 4, 2006
Verdin	US 2008/0200566 A1	Aug. 21, 2008
Tcherepanova	US 2007/0248578 A1	Oct. 25, 2007
Lao	US 2006/0014191 A1	Jan. 19, 2006
Goix	US 2008/0064113 A1	Mar. 13, 2008

The following ground of rejection by the Examiner is before us on review[2]:

Claims 1–3, 6–8, 13–15, 17, 19, and 20 under 35 U.S.C. § 103 as unpatentable over Fougerolles, Verdin, Tcherepanova, Lao, and Goix.

DISCUSSION

The Examiner finds that Fougerolles teaches "using HPLC to study siRNA fragments including the degrees of degradation due to exo-and endonucleases." (Final Action 28.) The Examiner finds that Fougerolles defines siRNA to mean "a double stranded RNA molecule that is capable of blocking gene expression in a highly conserved regulatory mechanism known as RNA interference (RNAi)" and thus meets the claim requirement of detecting a target therapeutic RNA oligonucleotide. (*Id.* at 28–29.) The Examiner explains that Fougerolles "teaches performing HPLC analysis whereby different sequences are separated by different retention times, and that the end result can be 'graphically represented.'" (Ans. 11–12 (citing Fougerolles ¶ 274 and Fig. 11).) Regarding Figure 11 of Fougerolles, the Examiner notes that the vertical axis values are milli Absorbance Units

[2] The Examiner withdrew the rejection of claims under 35 U.S.C. § 112, first, second, and fourth paragraph in the Answer. (Ans. 10.)

"mAU," "which speaks directly to the quantity of material present in the sample," and coupled "with the variety of peaks seen in the graphs, which represent the size of the nucleic acids molecule(s), and, if present, any fragments of same, clearly provides both quantitative and qualitative analysis." (*Id.* at 13.)

The Examiner notes that while Fougerolles does not teach the siRNA oligonucleotide has a length of 10 nucleotides up to 29 nucleotides, Verdin teaches that siRNA can range in that size. (Final Action 29.) The Examiner relies on Tcherepanova for its teaching that subtractive hybridization was known to be used to separate a unique RNA from other RNA. (*Id.* at 29–30.) The Examiner relies on Lao for teaching that it was known to use peptide nucleic acid ("PNA") probes to detect siRNA among other target molecules. (*Id.* at 30.) The Examiner relies on Goix for teaching "a method whereby target molecules of interest can be detected and quantified at extremely low concentrations." (*Id.*) In particular, the Examiner notes that Goix teaches that nucleic acids can be detected using ATTO-Tec dyes that are capable of emitting at least about 200 photons when stimulated by laser emitting light at the excitation wavelength of the moiety. (*Id.* at 30–32.) According to the Examiner, it would have been obvious to one of ordinary skill in the art to have modified the method of Fougerolles

> by removing full-length siRNA from the population of RNA fragments in the sample so as to enhance the accurate detection and quantification of siRNA fragments whereby such is achieved by performing subtractive hybridization (Tcherepanova) wherein PNA probes are used (Lao et al.) and are labeled with a fluorescent dye such as one of the Atto dyes disclosed by Goix et al., for to do so would have allowed the ordinary artisan to take advantage of the sensitive Atto

> fluorescent dyes/labels and the highly sensitive and accurate quantification system disclosed by Goix.

(*Id.* at 32.)

We determine that the Examiner has not set forth a factual basis sufficient to support a conclusion of obviousness of Appellant's claimed invention. While we agree with the Examiner that step (d) requires separating target RNA oligonucleotide-PNA, RNA oligonucleotide metabolites of target-PNA, and nonhybridized PNA, and that step (e) embraces fluorescence spectroscopy of fractions eluting from the column (Final Action 34), we disagree with the Examiner's apparent conclusion that removal of target RNA from the sample being assayed prior to quantitative fluorescence spectroscopy measurement in step (e) "is deemed to be fairly encompassed by claim 1, step (d)" (Ans. 14).

Appellant's claim 1 requires that after hybridization of the target therapeutic RNA oligonucleotide and the RNA oligonucleotide metabolite with PNA in step (c) and separation of the unhybridized moieties therefrom by anion exchange HPLC in step (d), the signal from the hybridized target therapeutic RNA is separated from the signal from the hybridized metabolite (also in step (d)) and, in (step (e)), a fluorescence spectroscopy measurement is used to quantitatively detect both the target and the metabolite separated via the HPLC carried out in step (d). In other words, the elution through the column during HPLC serves to separate the signals of the metabolite from the target (as well as from unhybridized PNA) and a quantitation by fluorescence spectroscopy is effected, such that the metabolites and target quantity are assessed in a single HPLC assay. (*See* Appeal Br. 24.)

We agree with Appellant that Fougerolles does not teach that the target siRNA and its metabolites are detected in a single HPLC run. (Appeal

Br. 26.) As the Examiner notes (Final Action 28), Fougerolles teaches using HPLC to study siRNA fragments when the siRNA is incubated in serum containing exo- and endonucleases. (Fougerolles ¶ 274, Fig. 11.) There is no indication in the specification of Fougerolles that in a single assay both the target and the fragments are identified. And we agree with the Appellant that "[a] person of ordinary skill in the art would in no way be able to determine whether such fragments [in Fig. 11] represent the signals associated with a target therapeutic RNA and metabolites of the target therapeutic RNA." (Reply Br. 5; Appeal Br. 26.) The Examiner does not rely on any other prior art to meet this requirement of the claim. (*See* Final Action 29 (describing the teachings of Verdin and Tcherepanova relative to the claimed invention); Final Action 30–31 (describing the teachings of Lao and Goix relative to the claimed invention).) Because the Examiner's prior art combination fails to teach or suggest a method of detecting a target oligonucleotide and a metabolite thereof in a single assay in which a single sample is passed over an anion exchange HPLC column, we reverse the Examiner's obviousness rejection.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–3, 6–8, 13–15, 17, 19, 20	103(a)	Fougerolles, Verdin, Tcherepanova, Lao, Goix		1–3, 6–8, 13–15, 17, 19, 20

REVERSED