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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte KIM VAN OMMERING,
JOHANNES JOSEPH HUBERTINA BARBARA SCHLEIPEN, and
JEROEN HANS NIEUWENHUIS

Appeal 2018-008022
Application 13/498,635
Technology Center 1700

Before CATHERINE Q. TIMM, N. WHITNEY WILSON, and CHRISTOPHER L. OGDEN, *Administrative Patent Judges*.

OGDEN, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

Appellant[2] brings this appeal[3] under 35 U.S.C. § 134(a) from the Examiner's decision rejecting claims 1–10 and 12–21 in the above-identified application. We affirm.

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[1] The appeal record includes the following: Specification, Mar. 28, 2012 ("Spec."); Final Office Action, Dec. 7, 2017 ("Final Action"); Appeal Brief, May 7, 2018 ("Appeal Br."); Examiner's Answer, June 4, 2018 ("Answer"); and Reply Brief, June 8, 2018 ("Reply Br.").

[2] Appellant is the "applicant" as defined in 37 C.F.R. § 1.42. According to the Appeal Brief, the real party in interest is Koninklijke Philips, N.V. Appeal Br. 3.

[3] Appellant also appealed a previous final rejection, which we affirmed. *See Ex parte Ommering*, Appeal No. 2016-000391 (PTAB Mar. 1, 2017).

BACKGROUND

Appellant's invention "relates to the field of intensity measurements of a light scattering label bound to a surface of a support using an optical evanescent field." Spec. 1:6–7. For example, if a biomolecule is bound to a substrate in an evanescent optical field, the Specification teaches that one may measure the bond length, as well as "fluctuations in the intensity of the scattered light over time," which allows one to draw conclusions such as "the type of bond" (e.g., whether the bond is specific or non-specific). *Id.* at 2:15–21.

Independent claim 1, which we reproduce below, is representative of the invention:

> 1. A method comprising:
>
> Providing an assay comprising at least one light scattering label bound to a surface of a support by at least one bond;
>
> Directing a first light beam at a first wavelength toward the assay, and directing a second light beam at a second wavelength toward the assay; or directing a first light beam at a first angle of incidence to the assay, and directing a second light beam at a second angle of incidence to the assay; and
>
> *Measuring the fluctuations in the intensity of scattered light of the label in an optical evanescent field over time while the label is bound to the surface, wherein the intensity of the scattered light on each of the labels depends on a distance of the label to the surface of the support*.

Appeal Br. 15 (emphasis added). Claim 15 is also independent, and includes a further step of "distinguishing between specifically bound scattering labels and non-specifically bound labels." Appeal Br. 17. Claims 1–10 and 12–14 depend directly or indirectly from claim 1, and claims 16–21 depend from claim 15. *Id.* at 15–18.

The Examiner rejects all claims under 35 U.S.C. § 103(a) as being unpatentable over Stimpson[4] in view of Stock.[5] Final Action 2–9.

DISCUSSION

While the Examiner's rejection relies on both Stimpson and Stock, Appellant does not raise any arguments regarding Stock or the rationale for combining the references. *See* Appeal Br. 5–12; Reply Br. 4–8. Therefore, we focus on Stimpson in this Decision.

We reproduce Figure 1 of Stimpson below:

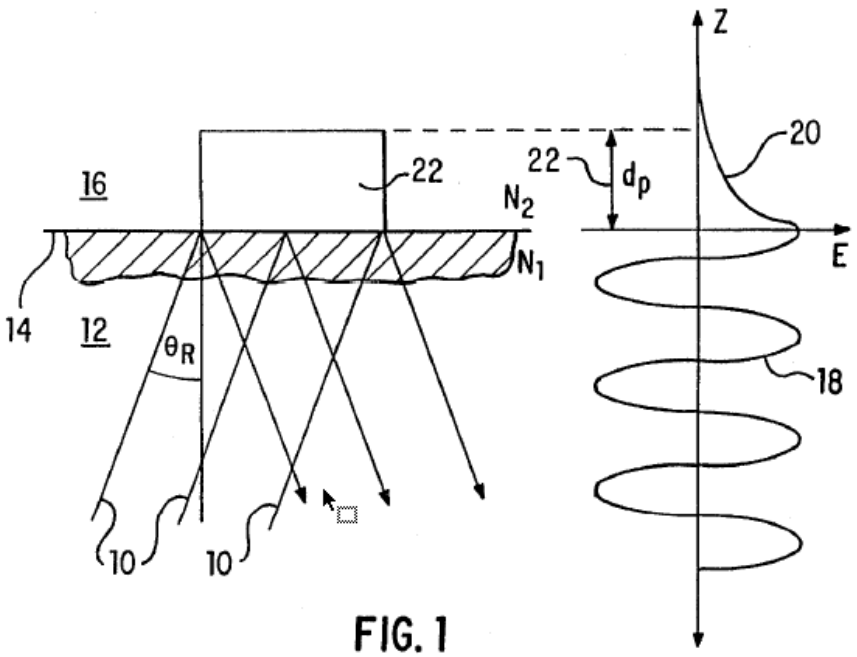

FIG. 1

On the left, Figure 1 "shows the reflection of light at an interface and, on the right, a plot of the electric field energy E as a function of the distance Z from the interface." Stimpson 7:44–47. The interface is the boundary between a

[4] Stimpson et al., US 5,599,668, issued Feb. 4, 1997 ("Stimpson").
[5] K. Stock et al., *Variable-Angle Total Internal Reflection Fluorescence Microscopy (VA-TIRFM): Realization and Application of a Compact Illumination Device*, 211 Journal of Microscopy, Vol. 211, Pt 1 July 2003, pp. 19–29 ("Stock").

denser medium (12) and a rarer medium (16). *Id.* at 1:18–22. According to Stimpson, electric field 18 is sinusoidal inside denser medium 12, but as the evanescent wave penetrates into rarer medium 16, "its energy dissipates exponentially as a function of distance Z from the interface" as shown at 20. *Id.* at 1:29–35. According to Stimpson, distance d_p is a "penetration depth," within which the evanescent wave can excite fluorescence in a sample placed there. *See id.* at 1:55–57.

As an illustration of this, we reproduce Stimpson's Figure 3 below:

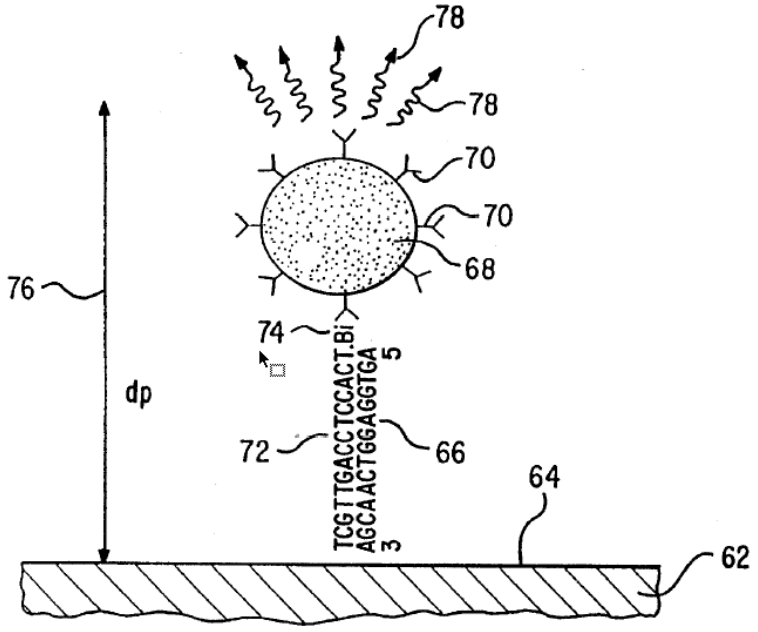

FIG. 3

Figure 3 of Stimpson depicts an oligonucleotide (66) immobilized on surface 64 of waveguide 62, within penetration depth d_p (76). *Id.* at 7:54–59, 18:62–19:3. Oligonucleotude 66 is labeled with light-scattering particle 68 and attached antibodies 70. *Id.* at 19:29–31. Stimpson teaches that one may observe the scattered light from the underside, possibly using a mirror. *See id.* at 12:60–62. According to Stimpson,

> At the sites where light-scattering specific binding complexes have formed, the scattering of light is observed as lighter areas against a darker background of the non-situs portions. The brighter the situs appears, the more LSL is bound and the more analyte is present at that situs. The method can be used to quantitate or semi-quantitate by reading the gray tones into a computer and, using calibrators, estimating the amount of analyte present at each situs.

Id. at 19:51–59 (citation omitted). Stimpson also teaches that the extent of binding "can be monitored in real time as various conditions are changed." *Id.* at 20:45–46.

Regarding claim 1, the Examiner finds that "Stimpson teaches that the intensity of the scattered light on each of the labels depends on a distance of the label to the surface of the support." Final Action 3. According to the Examiner, Stimpson also teaches comparing, at each binding site, the degree of light scattering at two different times, to obtain information that shows how much of the analyte is present at the binding site. *Id.* (quoting Stimpson 5:53–59 (reciting a step of "comparing the degree of light scattering at said situs at time t_1 with the degree of light scattering at said situs at time t_2, whereby . . . the difference over time in scattering of light provides kinetic information indicative of the amount of analyte present at said situs."); *id.* at 22:51–56 ("[T]he time-dependency (i.e. rate) of the increase or decrease in the amount of light scattering may be more accurately indicative of the levels . . . present in the fluid sample than the total amount of scatter by the reaction at any given reaction point in time.")).

Appellant acknowledges that Stimpson teaches "changes over time of the amount of light scattered." Appeal Br. 9 (citing Stimpson 21:60–23:2). This includes measuring "the **average or representative value of intensity at each situs**," which "correlates positively with **the amount of LSL [light**

scattering labels] present at the situs." *Id.* at 8 (alteration in original) (quoting Stimpson 22:36–38). As Appellant points out, Stimpson also teaches that "[m]easuring the rate of change of the **intensity of scattered light from a given region of the reactive surface versus time provides a reaction rate**." *Id*. at 9 (quoting Stimpson 22:58–60).

However, Appellant argues that Stimpson "does not describe the **measurement of the fluctuations** in the **intensity of light scattered from the labels** from a support surface." Appeal Br. 8; *see also* Reply Br. 7–8. According to Appellant, "no reference to the location of the label is presented" in the Stimpson passages that the Examiner cites in the rejection. *Id.* at 9.

In response, the Examiner points out that in Stimpson, "only [a] label confined within the penetration depth generate[s] signal." Answer 10. We agree. According to Stimpson, the evanescent wave dissipates exponentially above the surface. Stimpson 1:33–35. Thus, the label would not continue to scatter light over multiple image frames unless it remains within penetration depth d_p. Furthermore, Stimpson explicitly teaches "forming light scattering label complexes attached to" the binding site prior to taking time-dependent measurements. *See id.* at 5:38–39; *see also id.* at 11:40–42 (defining "situs" as "the delimited area in which a specific binding member for an analyte is immobilized"); 11:53–55 ("The area (size) of a situs need be large enough only to immobilize sufficient specific binding member to enable capture of the labeled analyte and light scattering particle."). Thus, a preponderance of the evidence on this record supports the Examiner's finding that Stimpson teaches taking time-dependent measurements of the intensity of light scattered from a label while it is bound to the surface.

We also agree with the Examiner that measuring light intensity at times t_1 and t_2 constitutes "[m]easuring the fluctuations in the intensity of scattered light," wherein the intensity "depends on a distance of the label to the surface of the support," as recited in claims 1 and 15. In one embodiment, Stimpson teaches obtaining the intensity images by grabbing video frames from a camera that registers changes in the scattered light. *See id.* at 22:5–19. A person of ordinary skill in the art would have understood this to suggest measuring "fluctuations in the intensity of scattered light." Moreover, according to Stimpson, the energy of the evanescent wave decreases as the distance from the interface increases. *Id.* 1:33–35. Thus, a preponderance of the evidence supports the Examiner's finding that in Stimpson's process, the light intensity depends on the distance of the label to the surface.[6]

Regarding claim 15, the Examiner finds that Stimpson discloses "distinguishing between specifically bound scattering labels and non-specifically bound labels." *See* Final Action 6. According to the Examiner, Stimpson teaches "kinetic information about the binding," so the process can distinguish between specifically bound labels and non-specifically bound labels. *Id.*

In particular, the Examiner finds that Stimpson teaches that labels are specifically bound to the surface at each situs, and that the light at each situs correlates with the amount of these specifically bound labels. *See id.* at 11 (citing Stimpson 4:35–38 ("[L]ight scattering at each situs correlates to the presence or amount of the analyte for which the immobilized specific

[6] We note that neither claim 1 nor claim 15 requires one to actually measure the distance between the labels and the support. *See* Appeal Br. 15, 17.

binding member at that situs is specific.")). The Examiner also points to Stimpson's teaching "that the reagents and sample, e.g. conjugate sample solution, need not be washed off the capture site to allow detection. . . . [T]he unbound LSLs in the present invention generally diffuse away from the penetration depth and cease to give a signal even without physical removal." *Id.* at 11–12 (quoting Stimpson 21:15–25). Thus, the Examiner finds that in Stimpson's process, light scattering at each situs corresponds to specifically bound labels, whereas light scattering at each non-situs correlates with labels that are not specifically bound (or not bound at all) to the surface. *See id.* at 12.

Appellant argues, based on Stimpson's definitions of *situs* and *non-situs*, that "it is not clear . . . that a scattering label is the same thing as a 'situs' as defined [in Stimpson]." Appeal Br. 10. In particular, Appellant argues that "it is not clear that a 'situs' is the same thing as a **specifically bound label**, or that a 'non-situs' is the same thing as a **non-specifically bound label**." Appeal Br. 10 (citing Stimpson 7:31–33, 11:40–44). According to Appellant, Stimpson teaches measuring "the **average or representative value** of **intensity at each situs**," and this intensity correlates with "**the amount of LSL [light scattering labels] present at the situs**." *Id.* (quoting Stimpson 22:36–38). Thus, Appellant argues that "a situs is not an LSL, but perhaps the location of a plurality of labels." *Id.*

This argument is unpersuasive of reversible error. The Examiner's rejection does not depend on each "situs" being the same thing as a light scattering label. Stimpson defines a "situs" as an area on the reactive surface at which specific binding occurs. Stimpson 11:40–44. Logically, then, when scattering occurs at a situs, this indicates specific binding, whereas if

scattering occurs at a non-situs area, this indicates that specifically bound labels are not present. This is sufficient for "distinguishing between specifically bound scattering labels and non-specifically bound labels," as recited in claim 15.[7]

Appellant also argues that the Examiner's determinations "do not follow immediately" from the cited portions of Stimpson, and the Examiner has not provided any supporting evidence, such as an affidavit. Appeal Br. 11; Reply Br. 7.

This argument is not persuasive of reversible error. An obviousness rejection must take into account "the background knowledge possessed by a person having ordinary skill in the art," which may include "the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). The Examiner properly reads Stimpson in the context of what a person of ordinary skill in the art would have understood at the time of invention. Moreover, the Examiner does not make any inferential leap that does not follow as a logical consequence of Stimpson's disclosure.

For the above reasons, and based on the Examiner's findings and conclusions as a whole, which we find persuasive, the preponderance of the evidence supports the Examiner's rejection. Appellant has not shown

[7] We note that claim 15 does not place any limitation on the number of labels at each measurement site, and does not require distinguishing between non-specifically bound labels and non-bound labels. Although Stimpson teaches coating the surface to minimize non-specific binding, Stimpson only describes this as a *preference*. *See* Stimpson 15:18–22; *see also* 45:8–12, 46:20–24, 47:38–42, 48:61–65, 50:32–36 (dependent claims reciting a surface coating).

reversible in the rejection of independent claims 1 or 15, and Appellant does not specifically address the patentability of the dependent claims. Therefore, we sustain the Examiner's decision as to all claims.

CONCLUSION

The following table summarizes the decision:

Claims Rejected	**Basis**	**Affirmed**	**Reversed**
1–10, 12–21	§ 103 Stimpson, Stock	1–10, 12–21	

DECISION

The Examiner's decision is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended. *See* 37 C.F.R. §§ 1.136(a)(1)(iv), 41.50(f) (2018).

AFFIRMED