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Paper 26
Date: January 7, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LEICA MICROSYSTEMS INC.,
Petitioner,

v.

THE REGENTS OF THE UNIVERSITY OF MICHIGAN,
Patent Owner.

IPR2020-01165
Patent 7,277,169 B2

Before BARBARA A. PARVIS, NATHAN A. ENGELS, and SCOTT B. HOWARD, *Administrative Patent Judges.*

ENGELS, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining No Challenged Claims Unpatentable
35 U.S.C. § 318(a)

I. INTRODUCTION

On June 26, 2020, Petitioner Leica Microsystems Inc. filed a Petition (Paper 2, "Pet.") requesting *inter partes* review of claims 1–26 of U.S. Patent No. 7,277,169 B2 (Ex. 1001, "the '169 patent"). Patent Owner, The Regents of the University of Michigan, filed a Preliminary Response. Paper 8.

After considering the arguments presented by Patent Owner's Preliminary Response, we determined that the information presented in the Petition established a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the petition. Paper 9 ("Dec."). Pursuant to 35 U.S.C. § 314, we instituted this *inter partes* review as to all of the challenged claims and all grounds raised in the Petition. Dec. 30.

Following institution, Patent Owner filed a Response. Paper 13 ("PO Resp."). Subsequently, Petitioner filed a Reply (Paper 16, "Reply") and Patent Owner filed a Sur-reply (Paper 19, "Sur-reply").

Each party presented oral arguments at a hearing on October 8, 2021. A transcript of the hearing has been entered into the record. Paper 25.

A. Related Matters

Petitioner and Patent Owner each indicates the parties and the challenged patent are involved in litigation in the United States District Court for the Northern District of California in *The Regents of the University of Michigan v. Leica Microsystems Inc.*, Case No. 5:19-cv-07470-LHK. Pet. 72; Paper 5, 1.

B. Real Parties in Interest

Petitioner states the "real party in interest is Leica Microsystems Inc." Pet. 72. Petitioner also states "Leica is wholly-owned subsidiary of Danaher

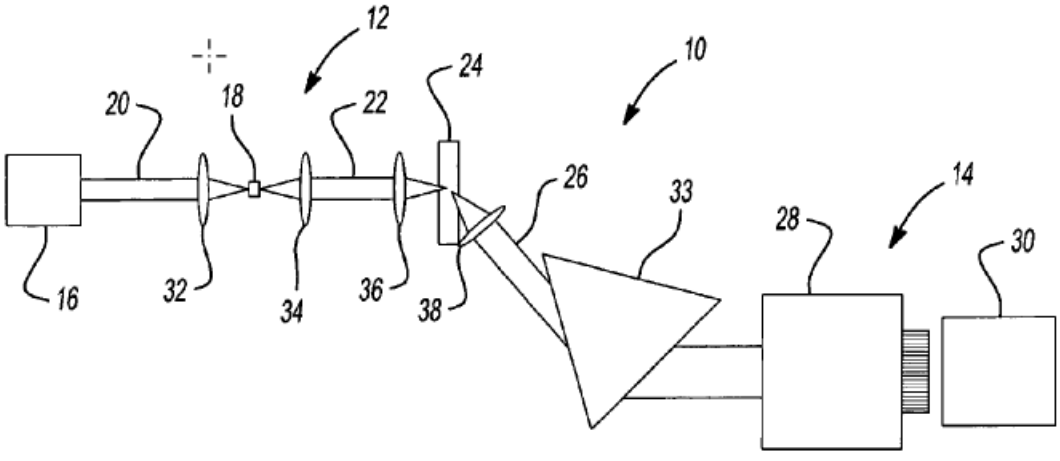
Corporation. Danaher Corporation is not a real-party-in-interest to this proceeding." *Id.*

Patent Owner "identifies the Regents of the University of Michigan" as the real party in interest. Paper 5, 1.

C. The '169 Patent

The '169 patent "relates to a method and apparatus for detecting multiple fluorophores using an ultrafast super continuum light source for excitation." Ex. 1001, 1:22–25. The patent explains that "[f]luorescence measurements are an invaluable tool for a wide variety of applications in various fields" and that "[o]ne of the most important considerations for a fluorescence detection system is to separate fluorescence signals from excitation light." Ex. 1001, 1:32–36, 2:7–9.

The '169 patent discloses a "whole spectrum fluorescence detection system" that includes "a white light generation system 12 and a detection system 14." Ex. 1001, 3:37–39. Figure 1 of the '169 patent, reproduced below, shows a schematic of the disclosed system.



Ex. 1001, Fig. 1. Figure 1 shows laser source 16, high intensity light pulse 20 directed at nonlinear material member 18 (which can modify the optical

phase of high intensity light pulse 20), ultrafast white light pulse 22, sample 24 to be tested, time-resolving detector 28, and detector 30. *Id.* at 3:40–4:54. The "ultrafast white light pulse 22 can contain a wide spectrum of light frequencies; however, its duration in time is limited and is thus not continuous unlike conventional systems." Ex. 1001, 3:55–58. The '169 patent explains:

> ultrafast white light pulse 22 can have a pulse duration on the order of picoseconds, while the fluorescence, generally indicated at 100, can have a lifetime on the order of nanoseconds. Thus, by using a time-resolving detector 28, such as a streak camera, the scattered portions of while light pulse 22 of combined signal 26 can be screened out while permitting the fluorescence to pass through.

Ex. 1001, 4:28-35. Figure 3, reproduced below, is a schematic drawing of a white light pulse and excited fluorescence in time domain.

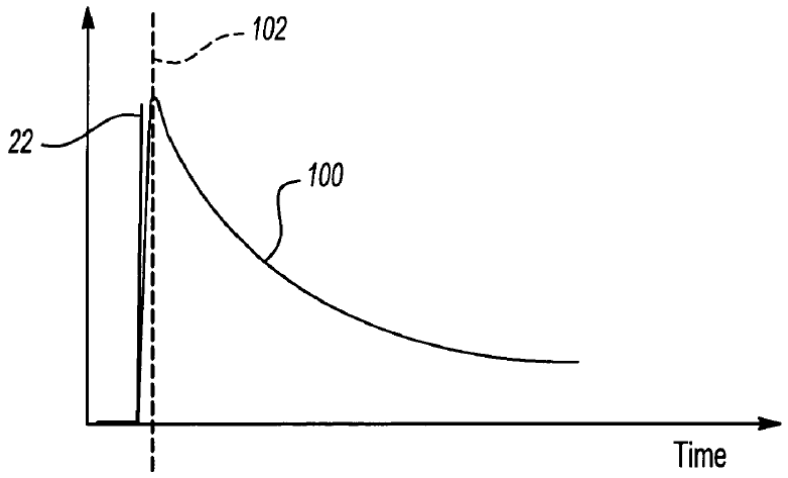


Figure 3 illustrates white light pulse 22, fluorescence 100, and delay line 102. Ex. 1001, 4:28–31, 5:30–33.

According to the '169 patent, the disclosed technique "not only allows one to excite a large variety of fluorophores in a wide wavelength range, but also significantly simplifies the system configuration by using a single laser source and eliminating the requirements of using many sets of filters and

dichroic mirrors as used in conventional fluorescence detection systems." Ex. 1001, 4:54–60. The '169 patent also discloses "time-resolving detector 28 can be a streak camera." Ex. 1001, 5:10–13.

D. Illustrative Claim

The Petitioner challenges claims 1–26 of the '169 patent. Pet. 15–16. Claims 1, 10, and 19 are independent claims, and claim 1 is illustrative of the claimed subject matter:

> 1. A fluorescence detection system for testing a sample, said sample having a plurality of fluorophores, said fluorescence detection system comprising:
>
> a single-source white light generation system outputting a supercontinuum white light pulse comprising an entire spectrum of white light, said supercontinuum white light pulse exciting the plurality of fluorophores of the sample to emit fluorescence; and
>
> a time-resolving detector receiving said fluorescence and at least a portion of said supercontinuum white light pulse, said time-resolving detector separating said fluorescence from said portion of said supercontinuum white light pulse.

Ex. 1001, 7:43–55.

E. Alleged Grounds of Unpatentability

Petitioner asserts that claims 1–26 would have been unpatentable on the following grounds:

Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1–3, 6–10, 12, 15–21, 24–26	103(a)[1]	Folestad,[2] Laporte[3]
1–3, 6–10, 12, 15–21, 24–26	103(a)	Folestad, Marriott[4]
1–3, 6–10, 12, 15–21, 24–26	103(a)	Folestad, Wittmershaus[5]
1–3, 5, 6–8, 10, 12, 14–17, 19–21, 23, 24, 26	103(a)	Marriott, Birk[6]
4, 5, 13, 14, 22, 23	103(a)	Folestad, Laporte, Zeylokovich[7]
4, 5, 13, 14, 22, 23	103(a)	Folestad, Marriott, Zeylokovich
4, 5, 13, 14, 22, 23	103(a)	Folestad, Wittmershaus, Zeylokovich
4, 5, 13, 14, 22, 23	103(a)	Marriott, Birk, Zeylokovich

[1] Based on the February 16, 2006 filing date of the '169 patent, the pre-AIA version of § 103(a) applies.
[2] WO 01/22063 Al, published Mar. 29, 2001 (Exhibit 1011) ("Folestad").
[3] Pierre Laporte, et al., OPTICAL SYSTEMS IN ULTRAFAST BIOPHOTONICS, Proceedings of the International Society of Optical Engineering, Volume 5249, 2004, pp. 490–500. (Exhibit 1014) ("Laporte").
[4] Gerard Marriott, et al., "Time resolved imaging microscopy," Biophysical Journal, Vol. 60, Dec. 1991, pp. 1374–87. (Exhibit 1016) ("Marriott").
[5] Bruce Wittmershaus, et al., "Picosecond studies at 77 K of energy transfer in chloroplasts at low and high excitation intensities," Biochimica et Biophysica Acta, Vol. 806, 1985, pp. 93–106. (Exhibit 1021) ("Wittmershaus").
[6] US 6,611,643 B2, iss. Aug. 26, 2003. (Exhibit 1009) ("Birk").
[7] I. Zeylikovich, et al., "Coherence properties of the supercontinuum source," Applied Physics B, Vol. 77, 2003, pp. 265–68. (Exhibit 1018) ("Zeylikovich").

Claims Challenged	35 U.S.C. §	Reference(s)/Basis
11	103(a)	Folestad, Laporte, Alfano[8]
11	103(a)	Marriott, Birk, Alfano
11	103(a)	Folestad, Wittmershaus, Alfano
11	103(a)	Marriott, Birk, Alfano
7, 9, 16, 18, 25	103(a)	Marriott, Birk, Laporte

II. ANALYSIS

A. Legal Standards

In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), the Supreme Court set out a framework for assessing obviousness under § 103 that requires consideration of four factors: (1) the "level of ordinary skill in the pertinent art," (2) the "scope and content of the prior art," (3) the "differences between the prior art and the claims at issue," and (4) "secondary considerations" of non-obviousness such as "commercial success, long-felt but unsolved needs, failure of others, etc." 383 U.S. at 17–18. Patent Owner did not present evidence of secondary considerations in this proceeding.

B. Claim Construction

We apply the claim construction standard articulated in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*), and its progeny. 37 C.F.R. § 42.100(b) (as amended Oct. 11, 2018).

[8] Robert F. Alfano, Ed., The Supercontinuum Laser Source, Springer Science+Business Media, New York, 1989. (Exhibit 1017) ("Alfano").

Petitioner indicates that the claims do not need an express construction to resolve the issues presented in this proceeding, but Petitioner provides as a potential clarification a proposed construction of the phrase "a member having a non-linear refractive index" in claims 2, 10, and 20. Pet. 14. Petitioner contends that, "in the context of the '169 patent, the claimed 'member' is a broad term used to describe materials exhibiting a non-linear refractive index in the presence of an ultrafast laser pulse." Pet. 14.

Patent Owner does not directly address claim construction in its Response. *But see* PO Resp. at 35, n. 5 (arguing Petitioner interprets claim 1 to require "excit[ing] a sample using an entire continuous spectrum").

We determine that no express claim constructions are necessary. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (explaining that only those claim terms that are in controversy need to be construed and only to the extent necessary to resolve the controversy).

C. Level of Ordinary Skill in the Art

In determining the level of ordinary skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

Petitioner contends:

> A person of ordinary skill in the art at the time of the present case would have had an undergraduate degree in optics, physics or electrical engineering, and either a MS degree in those fields or five years of experience in an industrial, academic or

> government laboratory with the relevant technologies such as femtosecond lasers, supercontinuum light sources, fluorescence microscopy, photonic crystal fibers, nonlinear optics, and time-resolved detection of light.

Pet. 13–14 (citing Ex. 1002 ¶ 11 (Declaration of Wayne H. Knox)). Patent Owner does not address the level of ordinary skill in the art, and Patent Owner's declarant, David W. Piston, Ph.D., states that he applies Petitioner's definition of ordinary skill for his Declaration. *See* Ex. 2017 ¶¶ 23–24.

Based on the evidence of record, including the testimony of the parties' declarants, we apply the level of ordinary skill articulated by Petitioner.

D. Summary of Prior Art References

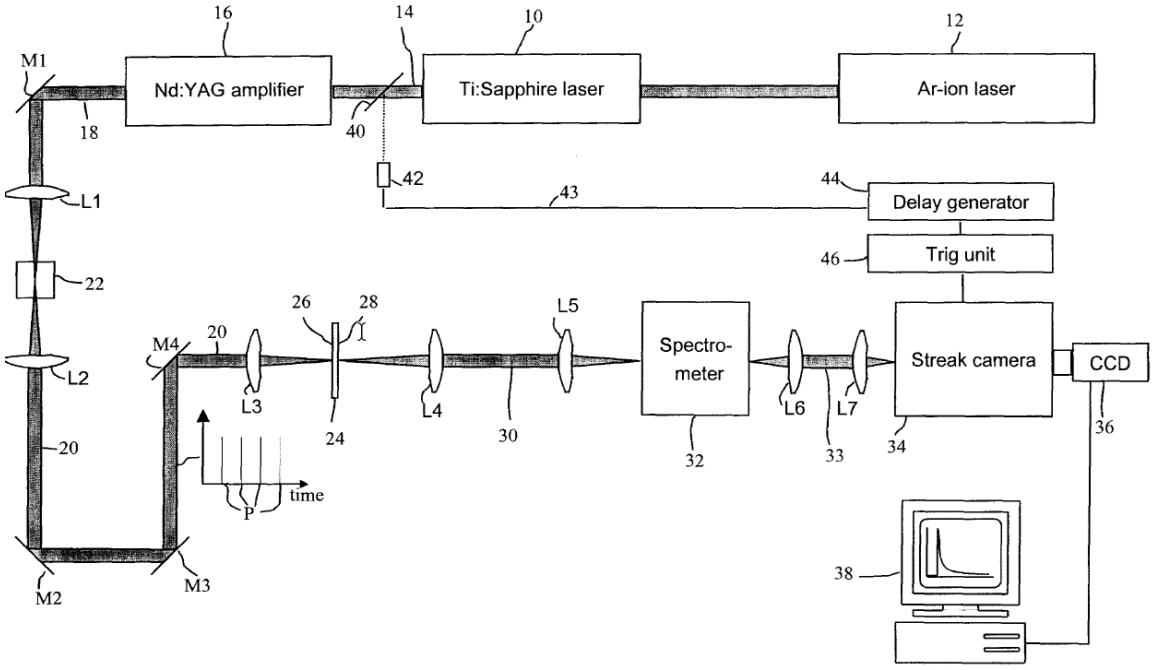
1. Folestad (Ex. 1011)

Titled "Method and Apparatus for Spectrometric Analysis of Turbid, Pharmaceutical Samples," Folestad is a PCT application that "relates to a method of analysing a turbid pharmaceutical sample, e.g. a tablet, a capsule . . . or a similar sample forming a pharmaceutical dose." Ex. 1011, codes (54), (57). Folestad states that "[n]on-invasive, non-destructible analysis of whole tablets can be carried out by means of near-infrared (NIR) or Raman spectrometry." Ex. 1011, 1:18–19.

In Folestad, "the intensity of the emitted radiation from the sample is measured both as a function of the wavelength and as a function of the photon propagation time through [the] sample." Ex. 1011, 3:10–13. Thus, by "time resolving the information from the excitation of the sample in combination with wavelength resolving the information, [Folestad's] invention makes it possible to establish quantitative analytical parameters of the sample, such as content, concentration, structure, homogeneity, etc." Ex.

1011, 3:25–29. The "excitation beam of radiation used in the present invention may include infrared radiation, especially near infrared (NIR) radiation of in the range corresponding to wavelengths of from about 700 to about 1700 nm, particularly from 700 to 1300 nm," but "may also include visible light (400 to 700 nm) and UV radiation." Ex. 1011, 4:1–5.

Folestad discloses the use of a TI:sapphire laser pumped by an argon ion laser as an excitation source. Ex. 1011, 6:26–28. Then, "[i]n order to create an excitation beam 20 of 'white' light, the laser beam 18 is passed through a water filled cuvette 22 via a mirror M1 and a first lens system L1." Ex. 1011, 7:1–3. Figure 1a of Folestad, reproduced below, shows a schematic layout of the disclosed system.

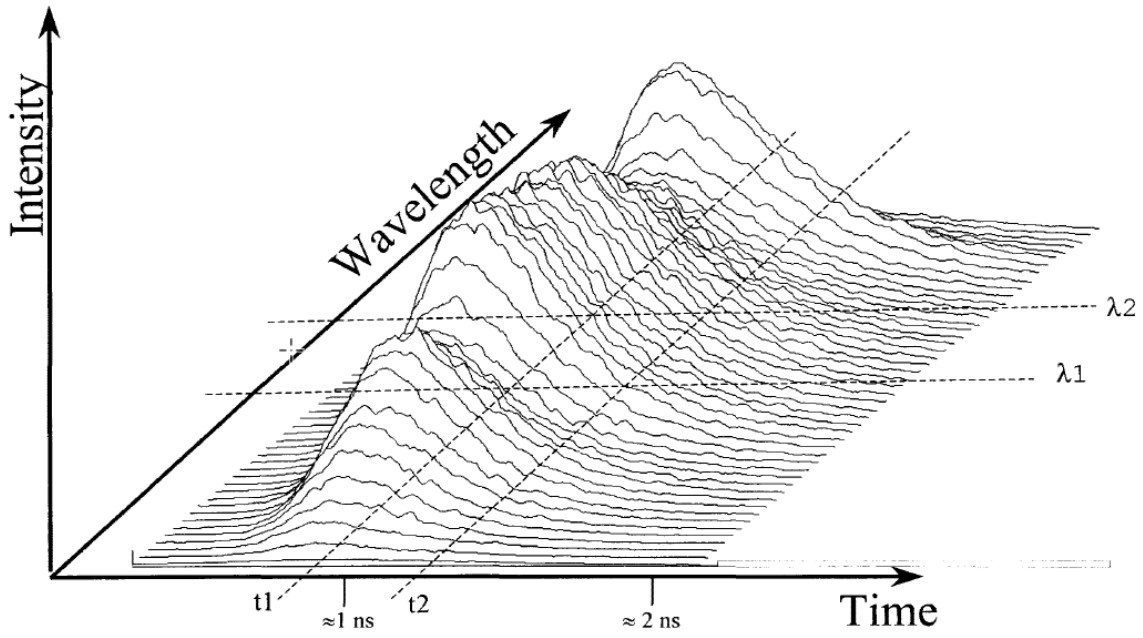


Ex. 1011, Fig. 1a. Figure 1a shows an Argon ion laser 12, "pumping" a Ti:Sapphire laser 10, where the beam passes through amplifier 16, lenses L1, L2, and L3, to sample 24, before the beam is captured in streak camera 34. Ex. 1011, 6:26–7:23.

> The pulse length of each excitation pulse P is short enough and the time spacing between two consecutive excitation pulses P is long enough in relation to the transit time of the beam (i.e. in relation to the time taken for each pulse to be completely measured in time), such that any interference is avoided between the detected light from one given excitation pulse P_n and the detected light from the next excitation pulse P_{n+1}.

Ex. 1011, 7:14–19. The "detected light beam 33 is passed via lens system L6/L7 to a time-resolved detection unit, which in this embodiment is implemented as a streak camera." Ex. 1011, 7:21–23. The "intensity of the emitted light is measured as a function of time in time-synchronism with each excitation of the sample." Ex. 1011, 8:7–8.

Figure 3b, reproduced below, shows a 3D plot of results from the instrument.



Ex. 1011, Fig. 3b. Figure 3b "illustrates how the time-resolved spectroscopy according to the invention results in an intensity 20 measurement as a

function of both wavelength and photon propagation time." Ex. 1011, 9:18–20.

2. Laporte (Ex. 1014)

Titled "Optical Systems in Ultrafast Biophotonics," Laporte is an article that proposes new methods in the field of "biophotonics," the main goals of which "are the control and processing of *in vivo* biological tissues and the monitoring of biomolecule dynamics." Ex. 1014, 490. In particular, Laporte states that it is "focused on the monitoring of the activity of the grey nucleus or the cerebral cortex in freely moving or anaesthetised rodents and birds by optical methods." Ex. 1014, 490.

Laporte describes using "a one kilohertz chirp pulse amplification laser system" source and a single-shot streak camera for detection using either time-resolved propagation (TRP) or time-resolved emission (TRE). Ex. 1014, 490. In particular, Laporte describes one experiment that uses TRP to study brain tissue of an anaesthetized rat and another experiment that uses TRE to study brain tissue of a freely moving, unanaesthetized mouse. Ex. 1014, 491–92.

Laporte's Figures 2 and 3, reproduced below, are annotated photographs of Laporte's experiments.

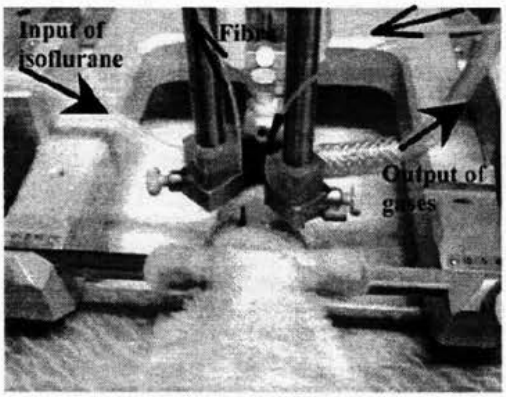


Fig 2: TRP with anaesthetized rat preparation. Under stereotaxic conditions. An interhemispheric measurement is illustrated.

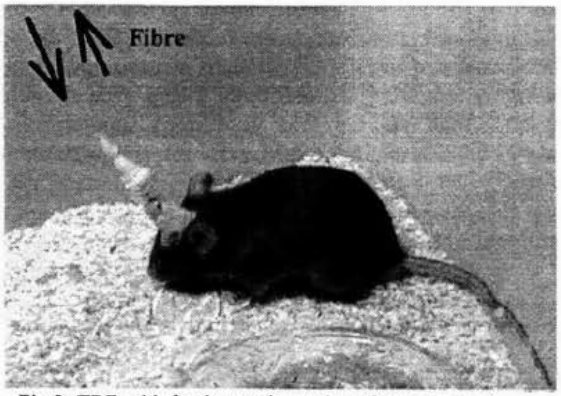


Fig 3: TRE with freely moving rodent (here a mouse). In the case of rat, two cannula on the head could be used.

Figure 2 of Laporte shows an anaesthetized rat having a source fiber focused on the rat's brain with a detection fiber set at a 5mm spacing for an experiment using TRP. Ex. 1014, 493. Figure 3 of Laporte shows a freely moving mouse with a fiber optic extending through a cannula into the mouse's skull for an experiment using TRE. Ex. 1014, 493.

Laporte states that for the TRP setup, the laser's beam is focused into pure water to generate a white light continuum. Ex. 1014, 490, 493. "After propagation through tissue, a single-shot streak camera with single photo-electron counting capability performs the picosecond time-resolved spectroscopy of the collected photons." Ex. 1014, 493. Laporte states that its streak camera is a Hamamatsu Streakscope C4334 with single photo-electron counting capability triggered with a fast photodiode that performs picosecond time-resolved spectroscopy of collected photons with two picosecond time resolution per pixel. Ex. 1014, 493.

3. Marriott (Ex. 1016)

Titled "Time Resolved Imaging Microscopy," Marriott is a journal article that discloses "[a]n optical microscope capable of measuring time resolved luminescence (phosphorescence and delayed fluorescence) images." Ex. 1016, 1374. Among other things, Marriott's "technique employs two phase-locked mechanical choppers and a slow-scan scientific CCF camera attached to a normal fluorescence microscope" (Ex. 1016, 1374) to create "a simple time resolved delayed luminescence microscope capable of recording images of very weak long lived luminescence from organic chromophores used as stains for biological material" (Ex. 1016, 1375).

In its discussion of "materials and methods," Marriott describes sample preparation that includes staining with noncovalent dyes, stating

"[s]ubconfluent 3T3 cells were grown on cover slips and labeled with AO [acridine orange], phosphine, and proflavine." Ex. 1016, 1375. Marriott states that although its samples were "depleted of oxygen, the living cells remain viable for several hours at temperatures between 4-37ºC, presumably by using anaerobic pathways for survival." Ex. 1016, 1375.

4. Wittmershaus (Ex. 1021)

Co-authored by Petitioner's declarant, Wayne H. Knox, Ph.D., Wittmershaus is a journal article titled "Picosecond studies at 77 K of energy transfer in chloroplasts at low and high excitation intensities." Ex. 1021, 93. Wittmershaus states that "[s]pinach chloroplast chlorophyll fluorescence at 685 and 735 nm (F_{685} and F_{735}) has been time-resolved with a low-jitter streak camera system." Ex. 1021, 93. Wittmershaus describes experimental results "in the form of 685 and 735 nm fluorescence intensities as a function of time after pulse excitation." Ex. 1021, 94.

E. Grounds 1–3, 5–7, 9–11: Obviousness Grounds Based on Folestad

Petitioner argues "Folestad teaches a detection system that is not meaningfully distinguishable from the one disclosed and claimed by the '169 patent." Pet. 19. With Folestad as the primary reference, each of Petitioner's Grounds 1–3, 5–7, and 9–11 includes a claim-by-claim, element-by-element comparison of each of claims 1–26 to Folestad in combination with one or more secondary references, along with reasons for combining the references, citing the Declaration of Wayne H. Knox (Ex. 1002) as additional support. Pet. 19–49.

In our Decision Granting Institution of *Inter Partes* Review, we explained that, at that stage, Petitioner had not shown a reasonable likelihood of prevailing on the Folestad-based grounds. In particular, we

determined that at the institution stage, Petitioner had not shown an adequate rationale for combining Folestad with the secondary references. Dec. 17.

1. Reasons to Combine Folestad and Secondary References

Petitioner argues Folestad teaches a system in which a "supercontinuum white light pulse is incident directly upon [a] sample" (Pet. 27), but Petitioner acknowledges that Folestad describes samples that do not include fluorophores (Pet. 28). Advancing a number of different reasons, Petitioner contends that "[p]lacing the samples of Laporte, Marriott, or Wittmershaus at the location of the sample in the system disclosed by Folestad would have been obvious to the [person of ordinary skill in the art]." Pet. 21 (citing Ex. 1002 ¶¶ 108–120); *accord* Reply 5–7.

Petitioner contends samples could be switched in place of Folestad's sample "without needing to modify Folestad's components . . . to yield predictable results (i.e., a system that is able to perform time-resolved scattering and fluorescence measurements)." Pet. 22 (citing Ex. 1002 ¶¶ 114–116); *accord* Reply 9–11. Petitioner also argues the desire to "examine fluorescence from multiple fluorophores" and "engage in time-resolved detection of such fluorescence, . . . as well as the availability and cost of laboratory equipment, would have led the POSA to use the Folestad system for experimentation on a variety of samples, including those with multiple fluorophores." Pet. 23 (citing Ex. 1002 ¶ 118); *accord* Reply 6–7. According to Petitioner, "[a]t the very least a POSA would have been led to try to use a sample including multiple fluorophores in Folestad's system and when the POSA did so, it would have resulted in the claimed subject matter when Folestad's supercontinuum excited the fluorophores and caused them to emit fluorescence." Pet. 23 (citing Ex. 1002 ¶ 118). Further, Petitioner contends such use of Folestad's system with different samples "represents

merely a new use for an old and obvious system." Pet. 24; *accord* Reply 6–7.

Based on the complete record, we determine the weight of the evidence does not sufficiently support Petitioner's arguments that the challenged claims would have been obvious based on the combination of Folestad and the secondary references. As Petitioner acknowledges, Folestad does not address fluorescence. Pet. 25. In fact, Folestad does not teach or even suggest studying a sample having fluorophores, much less a sample having multiple fluorophores. Pet. 25 ("Folestad does not mention that [its] sample has a plurality of fluorophores, or that [its] system is specifically intended for fluorescence detection."); Ex. 2017 ¶ 35.

Folestad teaches using its system to analyze "turbid pharmaceutical samples, e.g. a tablet, a capsule or a similar sample forming a pharmaceutical dose." Ex. 1011, code (57). Folestad's stated purpose is to "establish quantitative analytical parameters of the sample, such as content, concentration, structure, homogeneity, etc." Ex. 1011, 3:27–29.

The difference in Folestad's intended purpose and the challenged claims is significant. As noted by Patent Owner's declarant Dr. Piston, Folestad measures excitation light transmitted through and scattered from a sample. Ex. 2017 ¶¶ 38–40. As stated in Folestad, "[b]oth the transmitted radiation and the reflected radiation from the irradiated sample comprise photons with different time delay. Accordingly, the time-resolved and wavelength resolved detection may be performed on transmitted radiation only, reflected radiation only, as well as a combination of transmitted and reflected radiation." Ex. 1011, 3:30–33. Petitioner's proposed combination of Folestad and the secondary references requires not only replacing the

samples, but also replacing Folestad's teachings of detection of transmitted or reflected radiation with detection of fluorescence.

Weighing against Petitioner's arguments, Folestad teaches activating and deactivating a streak camera at "exact predetermined points of time" to study turbidity. Ex. 1011, 8:13–15. And the "exact predetermined points of time" are very short. Folestad teaches using a repeating laser pulse with the length of each pulse on the order of femtoseconds (Ex. 1002 ¶¶ 46, 140) and with a streak camera taking measurements two picoseconds apart (Reply 9) for a matter of one or two nanoseconds (Ex. 1011, 9:13 ("The time axis in Figs. 3a and 3b is in nano second scale."), Fig. 3b (depicting measurements of less than 2 nanoseconds)).

In contrast to Folestad's apparent focus on one or two nanoseconds between excitation pulses, Dr. Knox's testimony indicates that fluorescence has relatively longer lifetimes in relatively larger ranges. Dr. Knox states that (i) "the 1/e decay time of [Laporte's] rat brain fluorescence signal is about 280 picoseconds under 450 nm excitation light" (Ex. 1002 ¶ 147) (ii) Laporte's "lipoamide dehydrogenase has a decay time on the order of tens of nanoseconds" (Ex. 1002 ¶ 148), (iii) "Wittmershaus's fluorophores all had decay times that were longer than 100 picoseconds" (Ex. 1002 ¶ 149), and (iv) Marriott's "Acridine Orange dye exhibits prompt fluorescence lifetimes of 1.7–1.9 nanoseconds in certain configurations and a red prompt fluorescence lifetime in the range of 16–18 nanoseconds," while "[t]he AO fluorescence lifetimes can 'vary between 5 and 20 ns'" (Ex. 1002 ¶ 150 (quoting Ex. 1016 p. 1378)). *See also* Ex. 1001, 4:28–35 (describing use of an ultrafast white light pulse with a duration on the order of picoseconds while fluorescence can have a lifetime on the order of nanoseconds). Thus, the evidence of record reflects very specialized, precise

measurements for the detection of fluorescence, but the record lacks evidence regarding whether and how a person of ordinary skill would have configured Folestad's system (e.g., what "exact predetermined points of time" would have been required to activate and deactivate Folestad's camera) to measure fluorescence, particularly given the evidence that different fluorophores exhibit fluorescence with different lifetimes and the fact that those lifetimes differ from the reflected and transmitted radiation emissions measured in Folestad.

Moreover, Petitioner's suggestion that combining the prior art amounts to "simply swapping samples" is not consistent with the references' disclosures. Folestad's samples were pharmaceuticals such as tablets or capsules (Ex. 1011, code (57)), while Laporte studied the brain tissue of living animals—a freely moving mouse and an anaesthetized rat (Ex. 1014, Figs. 2, 3). Marriott's samples were living 3T3 cells grown on cover slips and incubated and processed under specific conditions such that the cells remain viable despite being depleted of oxygen "presumably by using anaerobic pathways for survival." Ex. 1016, 1375. And Wittershaus's samples were spinach leaves prepared into "[c]hloroplast suspensions placed in a glass cuvette of path-length 1 or 0.5 mm," methodically cooled to 80 K (-315ºF), and "mounted on a copper sample holder attached to the cold finger of a closed cycle helium refrigerator system." Ex. 1021, 94.

The details provided regarding sample preparation and testing are not consistent with Petitioner's arguments that the proposed combinations of the prior art amount to simple substitutions, that the combinations would have been obvious to try, or that replacing Folestad's pharmaceuticals with a live mouse would have been merely a new use for an old system. *See* Pet. 22–24. We find no evidentiary support from Dr. Knox's conclusory suggestion

that substituting such samples would have been "something so basic and known to those skilled in the art that it is not even described by the patent references" (Ex. 1002 ¶ 116). *See TQ Delta, LLC v. CISCO Sys., Inc.*, 942 F.3d 1352, 1358 (Fed. Cir. 2019) ("Conclusory expert testimony does not qualify as substantial evidence.").[9] To the contrary, each of the secondary references describes sample preparation and testing procedures in detail, reflecting expert-level knowledge and expert-level considerations that guided the experiments. Petitioner's proposed use of Folestad's system to analyze the samples of Laporte, Marriott, or Wittmershaus—each of which describes a complete system for detecting and measuring the fluorescence relevant to the samples at issue—essentially discounts the references' teachings in favor of Folestad's teachings, which does not even mention fluorescence. Excessive hindsight guides that proposal, not the generalized "desire to examine fluorescence from multiple fluorophores and engage in time-resolved detection of such fluorescence" (Pet. 22–23).

Nor does the "availability and cost of laboratory equipment" support Petitioner's arguments that a person of ordinary skill would have selected Folestad's system (instead of Laporte's, Marriott's, or Wittmershaus's) to "repurpose" Folestad's system for the study of fluorescence. Pet. 22; Reply 6. First, the record lacks adequate evidence of the equipment available to a person of ordinary skill, and second, our analysis turns on the references' teachings, not on a hypothetical situation in which a person of ordinary skill wants to study fluorescence and happens to have the "$300,000-$500,000" of equipment on hand to "repurpose" Folestad's

[9] Dr. Knox's testimony does not disclose the underlying facts or data on which his opinion is based and, therefore, is entitled to little or no weight. *See* 37 C.F.R. § 42.65(a).

system. *See* Pet. 22; Reply 6 (citing Ex. 1002 ¶ 119). Again, we determine Petitioner's arguments reflect excessive hindsight in the suggestion that a person of ordinary skill would have selected Folestad's supercontinuum white light laser and streak camera to perform the experiments taught by the secondary references, with essentially no evidence that Folestad's system would have provided any improvement or benefit.

2. Conclusion Regarding Folestad-Based Grounds

Based on the Petition and the evidence of record, we find insufficient evidence to establish that a person of ordinary skill would have had reason to combine the teachings of Folestad with Laporte, Marriott, or Wittmershaus to arrive at the inventions of independent claims 1, 10, and 19. Accordingly, Petitioner has not shown by a preponderance of the evidence that claims 1, 10, and 19, nor dependent claims 2–9, 11–18, and 20–26, are unpatentable.

F. Grounds 4, 8, 12, 13: Obviousness Grounds Based on Marriott

For the Marriott-based grounds, Petitioner provides claim-by-claim, element-by-element comparisons of claims 1–26 to Marriott in various combinations with Birk, Zeylokovich, Alfano, and Laporte, citing the Knox Declaration as additional support. Pet. 53–69. Patent Owner disputes Petitioner's showing regarding the claim's requirements of a sample having a plurality of fluorophores and a supercontinuum white light pulse exciting the plurality of fluorophores to emit fluorescence. PO Resp. 5–28.

1. Sample Having a Plurality of Fluorophores

Each of independent claims 1, 10, and 19 recites a sample having a plurality of fluorophores and a supercontinuum white light pulse exciting the

plurality of fluorophores to emit fluorescence.[10] According to Petitioner, "Marriott describes a system used to perform time-resolved fluorescence detection experiments on a sample dyed with at least three fluorophores: AO, phosphine, [and] proflavine." Pet. 50.

Petitioner reads the following statement from Marriott to teach or suggest samples having at least those three fluorophores:

> Subconfluent 3T3 cells were grown on cover slips and labeled with AO, phosphine, and proflavine . . . .

Ex. 1016, 1375 (*see* Pet. 53–54 (citing Ex. 1016, 1375); Reply 11 (quoting Ex. 1016, 1375)). According to Petitioner, Marriott's use of "and" instead of "or" indicates that Marriott's samples contained all three fluorophores. Reply 11.

We disagree with Petitioner. First, Marriott primarily reports results of the detection and measurement of fluorescence in samples dyed with different concentrations of AO. Ex. 1016, 1375 ("For some experiments with high concentrations of AO (>5 μM) . . . ."), 1378 (discussing different concentrations of AO), Fig. 2 ("Prompt fluorescence and delayed emission images of living 3T3 cells which have been bathed in a solution with [AO] = 0.5 μM (*top*) and 1.0 μM (*bottom*)."), Fig. 3 ("Prompt fluorescence and phosphorescence of 3T3 cells which have been . . . bathed in buffer with 50 μM AO."); *see* Sur-reply 12 (citing Ex. 1016, 1377–83, Figs. 2–6). With

[10] Although the parties do not specifically address whether the claims' preambles are limiting, the parties agree that the claims require a sample having a plurality of fluorophores and excitation of a sample having multiple fluorophores. Pet. 53, 55–56 (addressing claim 1), 59 (addressing claim 10), 61 (addressing claim 19); Reply 12 (arguing the challenged claims are satisfied "so long as the [sample's] cells are stained with at least two fluorophores"); PO Resp. 5–6.

the description of those experiments, Marriott describes using a single wavelength for excitation that is matched to the peak excitation wavelength of AO. *See* Sur-reply 12 (citing Ex. 1016, 1379, 1383); Reply 19. Although Marriott refers to experiments involving other fluorophores (Ex. 1016, 1375, 1381), Marriott does not specifically mention experiments on samples having more than one fluorophore nor does Marriott report results from experiments on a sample having more than one fluorophore. *Cf.* Reply 12 (arguing that results from experiments on samples with proflavine and phosphine "were not particularly interesting to Marriott; it does not mean they were not there").

We credit Dr. Piston's testimony that a person of ordinary skill would have understood Marriott to describe different samples stained with AO, phosphine, or proflavine, and not a mixture of those fluorophores. Ex. 2017 ¶¶ 45, 50, 56–58. Consistent with Patent Owner's arguments, Dr. Piston testifies that the three fluorophores would not be excited with the same wavelength and that Marriott's teachings of an excitation with a 488 nm laser would not have provided significant excitation of either phosphine or proflavine. Ex. 2017 ¶ 54. Petitioner does not present sufficient evidence to the contrary.

Petitioner's emphasis on Marriott's use of "and" in "AO, phosphine, ***and*** proflavine" (Reply 11) is not convincing. At best, Petitioner's argument relies on a grammatical ambiguity, with no clear indication that Marriott intended to emphasize "and" in its listing of sample labels. To the contrary, if samples were labeled "AO, phosphine, and proflavine," such a label would not distinguish one sample from another and would be inconsistent with Marriott's discussion of samples dyed with AO. In the context of Marriott's disclosures, including its description of preparations of multiple

samples and multiple experiments with excitation sources of different wavelengths, we agree with Patent Owner that a better reading of Marriott's statement is that it is a list of individual labels applied to different samples.

In its Reply, Petitioner argues Marriott also discloses a sample having two distinct species of AO, each of which is a "fluorophore" having distinct optical properties. Reply 14–15. Petitioner contends it raised that argument in the Petition, citing pages 41 and 42 of the Petition. Reply 14 n.4. The relevant portions of pages 41 and 42 of the Petition, however, are part of Petitioner's challenge to claim 19 as part of Petitioner's Ground 2, obviousness of claim 19 based on Folestad in view of Marriott. The Petition does not rely on two distinct species of AO for Grounds 4, 8, 12, and 13, which use Marriott as the primary reference. *See* Pet. 50–62. Because the Petition controls our review, the allegations in Petitioner's Reply cannot satisfy Petitioner's burden. *See Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1330–31 (Fed. Cir. 2019) (holding that "an IPR petitioner may not raise in reply 'an entirely new rationale' for why a claim would have been obvious"); *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) ("It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify 'with particularity' the 'evidence that supports the grounds for the challenge to each claim.'" (quoting 35 U.S.C. § 312(a)(3))).

2. Conclusion Regarding Marriott-Based Grounds

Based on the Petition and the evidence of record, we determine Petitioner has not established by a preponderance of the evidence that Marriott teaches or reasonably suggests the multiple-fluorophores limitations of independent claims 1, 10, and 19. Accordingly, Petitioner has not shown

by a preponderance of the evidence that claims 1, 10, and 19, nor dependent claims 2–9, 11–18, and 20–26, are unpatentable.

III. CONSTITUTIONAL CHALLENGES

Patent Owner presents arguments that the Board and its procedures violate due process and the right to an impartial, disinterested tribunal under the Administrative Procedure Act. PO Resp. 65–66. Subsequently, that argument has been rejected by the United States Court of Appeals for the Federal Circuit. *Mobility Workx, LLC v. Unified Patents*, 15 F.4th 1146, 1153–56 (Fed. Cir. 2021) (finding "no merit" to Mobility's argument of structural bias).

Patent Owner also presents arguments that the Board is unconstitutionally appointed. PO Resp. 66–67. We do not reach Patent Owner's arguments because the Supreme Court resolved the issue in *United States v. Arthrex*, 141 S.Ct. 1970, 1986–87, 1997 (2021).

IV. CONCLUSION

Petitioner has *not* established by a preponderance of the evidence that claims 1–26 of the '169 patent are unpatentable.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–26 have not been proven by a preponderance of the evidence to be unpatentable; and

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

In summary:

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1–3, 6–10, 12, 15–21, 24–26	103(a)	Folestad, Laporte		1–3, 6–10, 12, 15–21, 24–26
1–3, 6–10, 12, 15–21, 24–26	103(a)	Folestad, Marriott		1–3, 6–10, 12, 15–21, 24–26
1–3, 6–10, 12, 15–21, 24–26	103(a)	Folestad, Wittmershaus		1–3, 6–10, 12, 15–21, 24–26
1–3, 5, 6–8, 10, 12, 14–17, 19–21, 23, 24, 26	103(a)	Marriott, Birk		1–3, 5, 6–8, 10, 12, 14–17, 19–21, 23, 24, 26
4, 5, 13, 14, 22, 23	103(a)	Folestad, Laporte, Zeylokovich		4, 5, 13, 14, 22, 23
4, 5, 13, 14, 22, 23	103(a)	Folestad, Marriott, Zeylokovich		4, 5, 13, 14, 22, 23
4, 5, 13, 14, 22, 23	103(a)	Folestad, Wittmershaus, Zeylokovich		4, 5, 13, 14, 22, 23

4, 5, 13, 14, 22, 23	103(a)	Marriott, Birk, Zeylokovich		4, 5, 13, 14, 22, 23
11	103(a)	Folestad, Laporte, Alfano		11
11	103(a)	Marriott, Birk, Alfano		11
11	103(a)	Folestad, Wittmershaus, Alfano		11
11	103(a)	Marriott, Birk, Alfano		11
7, 9, 16, 18, 25	103(a)	Marriott, Birk, Laporte		7, 9, 16, 18, 25
Overall Outcome				1–26

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