UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

THERMO FISHER SCIENTIFIC INC.
Petitioner

v.

Bio-Rad Laboratories, Inc.
Patent Owner

Patent No. 8,236,504
Issued: August 7, 2012
Filed: June 30, 2010
Inventors: Kordunsky *et al*.

Title: SYSTEMS AND METHODS FOR FLUORESCENCE DETECTION WITH A MOVABLE DETECTION MODULE

Inter Partes Review No. IPR2017-00054

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,236,504 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42.1-.80, 42.100-.123

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I. Statement of the precise relief requested and the reasons therefor (37 C.F.R. § 42.22(A))

Thermo Fisher Scientific Inc. petitions for *Inter Partes* Review, seeking cancellation of claims 1-3, 6-11, 13-17 and 19-22 of U.S. Patent No 8,236,504 to Kordunsky *et al*. ("the '504 Patent") (Ex. 1001), which on its face indicates that the assignee is Bio-Rad Laboratories, Inc. (no assignment have been recorded for this patent). As set forth in detail below, claims 1-3, 6-11, 13-17 and 19-22 are unpatentable for anticipation and obviousness.

II. Overview

The claims of the '504 Patent should be canceled. They are directed to a thermal cycler with a movable detection module which contains an internal light generator and a detector (hereafter, "**optics head**"), attached to a shuttle movably mounted on a support, where the optics head views sample wells through openings in a heating element. But these claims merely recite well-known features. For example, the prior art reference "Li" (Ex. 1005, detailed below) teaches or at least suggests such a cycler. Accordingly, each claim of the '504 Patent would have been anticipated or obvious over the prior art as discussed below.

III. The '504 Patent disclosure and claims

The '504 Patent, entitled "Systems and methods for fluorescence detection with a movable detection module," issued on Aug. 7, 2012, from U.S. App. No. 12/827,521, which was filed on Jun. 30, 2010. Ex. 1001. The '504 Patent claims

priority to App. No. 11/555,642 filed Nov. 1, 2006, which is a continuation of App. No. 10/431,708, filed May 8, 2003. *Id*., Ex. 1007; Ex. 1031.

The '504 Patent claims. The '504 Patent has 22 claims. Claims 1 and 13 are the only independent claims. Each claim of the '504 Patent requires the presence of a self-contained movable "detection module" ("**optics head**") which contains both a light generator and a detector within its housing. Claim 1 is exemplary and is provided below:

> 1. A fluorescence detection apparatus for analyzing samples located in a plurality of wells in a thermal cycler, the apparatus comprising:
>
> a support structure attachable to the thermal cycler;
>
> a shuttle movably mounted on the support structure; and
>
> a detection module attached to the shuttle, the detection module including:
>
> a housing having an opening oriented toward the plurality of wells;
>
> an excitation light generator disposed within the housing; and
>
> an emission light detector disposed within the housing,
>
> wherein, when the support structure is attached to the thermal cycler, a heating element is disposed between the detection module and the sample wells and the shuttle is movable to position the detection module in optical communication with different wells of the plurality of wells through a plurality of openings extending through the heating element.

Independent claim 13 is similar to claim 1, but indicates among other things

that the cycler has an "exterior housing." Ex. 1001, claim 13.

IV. Person of ordinary skill in the art

A person of ordinary skill in the art ("**artisan**") is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. An artisan in the technical field of the '504 Patent (optical detection devices, including thermal cyclers) would have had knowledge of the scientific literature concerning the design and manufacture of analytical instruments for biological applications, which included optical detection devices and scanning assemblies, including but not limited to thermal cyclers, sequencers, microarray readers, fluorimeters, plate readers and scanners before 2003. Ex. 1002, ¶13.

With respect to the subject matter of the '504 Patent, an artisan would typically have had (i) an undergraduate degree (*e.g.*, B.Sc. or B.A.) in optics, physics, engineering (*e.g.*, mechanical, electrical or structural), analytical or physical chemistry, chemistry, biology or a related field in the engineering, biological or chemical sciences, and have had at least about one year of experience in the design or manufacture of biological analysis instruments, including optical components for fluorescence detection, for example in thermocyclers and scanners. Also, an artisan may have worked as part of a multidisciplinary team and drawn upon not only his or her own skills, but of others on the team, *e.g.*, to solve a given

problem. For example, a physicist, biologist, chemist and/or an optical engineer may have been part of a team. Ex. 1002, ¶14.

V. Claim construction

In accordance with 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable interpretations (BRI) in light of the specification and prosecution history of the '504 Patent. Claim terms not discussed below should be construed according to the BRI.

Claim 1(h) recites "**a heating element**" with a plurality of openings, and claim 13(b) recites a "**heater**" with a plurality of transparent portions, which can be holes (*see* claim 22). The '504 specification only discusses one component which has a plurality of openings or transparent portions - a "lid heater" with "holes." In particular, "[l]id heater 204 has holes 220 therethrough …and electronically controlled heating elements (not shown)." Ex. 1001, 5:1-3. For purposes of the instant petition only under the broadest reasonable interpretation, the terms "heating element" (claim 1) and "heater" (claim 13) are treated as equivalent. Under the broadest reasonable interpretation, this heating element/heater includes but should *not* be limited to the "lid heater" discussed in the '504 patent as part of an "exemplary" apparatus. Ex. 1001, 4:7-15, 4:37-66; Ex. 1002, ¶24. The '504 Patent discusses two components that have a heating function – namely, a sample unit (*i.e.*, thermal cycling block) and a "lid heater" placed on top of sample tubes.

Id. Under the broadest reasonable interpretation, either component could act as a "heating element" (claim 1) or "heater" (claim 13) if it meets all the claim requirements for this element. Claim 21 confirms that the "heater" (claim 13) or "heating element" (claim 1) is not limited to the so-called "lid heater" which is only described as placed on *top* of wells in the '504 Patent and its parent 11/555,642, as discussed further in Section VI (lack of priority). Ex. 1001, 4:37-39, 5:1-17, Figs. 2, 6; Ex. 1002, ¶24. Claim 21 requires that (1) the optics head opening must be *below* the sample wells and (2) the optics head must view sample wells "through ... the heater." Artisans would have understood that an optics head placed *below* sample wells as required by claim 21 could not view the wells "through" the lid heater, which is only described as necessarily placed on *top* of the wells. Ex. 1002, ¶24. Thus, artisans would have understood that the "heater" element of claims 13-22, and thus the equivalent "heating element" of claims 1-12, have a broader reasonable interpretation than the lid heater discussed in the '504 Patent, and are not limited to such a lid heater. Ex. 1001, 4:37-39, 5:1-17, Figs. 2, 6; Ex. 1002, ¶24.

Claims 1 and 13 also recite that the cycler has "**wells**." The '504 Patent does not define "wells" or otherwise place any constraints upon the exact format of the well. The prior-art reference "Li" applied herein discloses a cycler in which the sample wells have optical holes at the bottom (shown as element 21 in Fig. 3) to

allow Li's optics head to view samples through Li's cycling block. Ex. 1006; Ex. 1002, ¶25. Under the broadest reasonable interpretation, the term "wells" includes open-ended wells which have a "plurality of openings" that are optical holes at the bottom. Under the broadest reasonable interpretation, the "wells" can be in structural continuity or structural overlap with the openings. *Id*. Fig. 6 of the '504 Patent depicts wells (feature 210) forming a continuous channel with the openings (feature 220) of the heating element, consistent with this interpretation. Ex. 1001, Fig. 6; Ex. 1002, ¶25.

VI. Claims 1-3, 6-11, 13-17 and 19-22 are not entitled to priority before their actual filing date of June 30, 2010

The '504 Patent was filed on June 30, 2010, and claims priority to May 8, 2003, as a continuation of App. No. 11/555,642 filed Nov. 1, 2006, which is a continuation of App. No. 10/431,708, filed May 8, 2003.

But claims 1-3, 6-11, 13-17 and 19-22 are *not entitled to the priority benefit* of App. No. 11/555,642 filed Nov. 1, 2006 (hereafter, the "**Parent**"), and thus are not entitled to any priority before their actual filing date of June 30, 2010. This is because the Parent does not provide a written description of the claimed apparatus that is commensurate with the '504 claims, and only describes a particular embodiment that is narrower and differs from what is now claimed. *Lockwood v. Am. Airlines, Inc*., 107 F.3d 1565, 1571 (Fed. Cir. 1997).

A. The term "heating element" (claim 1) or "heater" (claim 13) lacks written description support in the parent

All '504 claims recite an apparatus with a "heating element" (claim 1) or "heater" (claim 13). These terms were introduced on March 12, 2012 – nearly two years after the ’504 Patent was filed. The claims require that the heating element is "disposed between the detection module and the sample [unit] wells" (claim 1) or the heater has the sample unit/wells on one side and a support structure with a detection module "on an opposite side" of the heater (claim 13). The claims further specify that the heating element contains a "plurality of openings extending through" it (claim 1) or a "plurality of transparent portions" (claim 13).

In contrast to the claims which broadly cover an apparatus with any heating element or heater, the Parent only discusses two structures with a heating function – a thermal cycling block, termed "sample unit" by the Parent, and a "lid heater." Ex. 1007, ¶¶26-32, 51, Figs. 2, 6; Ex. 1002, ¶30. As explained below, the sample unit described in the Parent does not meet the requirements of the claims, and the "lid heater" does not provide commensurate support. *Id*.; Ex. 1002, ¶30.

The cycling block or "sample unit" discussed in the Parent clearly does not match the claimed "heating element" (claim 1) or heater (claim 13). For example, the Parent does not mention that the sample unit has a plurality of holes (claim 1) or transparent portions (claim 13) through which the optics head can view the wells. The Parent only discusses how the sample unit is part of "[l]id assembly

112," and can contain "sample wells 210," as well as "heating elements." *Id*.; Ex. 1002, ¶31. The Parent further states that the sample unit "may be of conventional design" and that "the base and sample unit may be designed as an integrated system or separated," and that the optics head "may interrogate sample wells from any direction (*e.g*., above or below) in accordance with the design of a particular instrument." *Id*. at 31, 51, 80; Ex. 1002, ¶31. None of these teachings discloses or suggests that the sample unit has openings or transparent portions, or that wells can be viewed *through* the sample unit as the claims require. Ex. 1002, ¶31.

In addition, the sample unit as described by the Parent does not have the placement required by the claims. The claims require the heating element/heater to be placed between the detection module and wells (claim 1) or to be placed between the support and wells (claim 13). But the sample unit discussed by the Parent is under all three structures – the sample wells, detection module and support – and not between them. Ex. 1007, Figs. 2, 3; Ex. 1002, ¶32. Thus, the sample unit does not provide a written description of the claimed "heating element" (claim 1) or "heater" (claim 13).

The Parent also discusses an entirely different component within the context of an exemplary cycler apparatus – a "lid heater" – which is a single narrow example of the generic heating element/heater recited in the claims. Ex. 1007, ¶¶27-32; Ex. 1002, ¶33. In particular, the Parent does not support broad claims to

any generic heating element or heater since it only discloses a "lid heater" having one particular structure and never suggests that this can be varied in any way. *LizardTech v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1346 (Fed. Cir. 2005); *Augustine Medical, Inc. v. Gaymar Industries, Inc.*, 181 F.3d 1291, 1303 (Fed. Cir. 1999); *Ex parte Forest*, Appeal No. 2011-003338 (PTAB 2014). Ex. 1002, ¶33.

Under its plain meaning, the term "*lid* heater" indicates that the heater also serves as a lid, and this is specifically confirmed in the Parent. The Parent unequivocally states that when present, the lid heater "is in place *on* the sample unit" in order "to control the temperature of the sample *caps*" of reaction tubes and thus "prevent condensation … on the *caps*." Ex. 1007, ¶¶29, 30, Figs. 2, 6; Ex. 1002, ¶34. There is no disclosure of a lid heater that is not on top of the sample tubes and in contact with the caps. Consistent with its stated function of heating tube caps, the lid heater is invariably depicted as being directly on *top* of the sample unit, directly over and in contact with the tube caps, both in figures and words. *Id*. The Parent treats both the positioning and contact as integral features of the lid heater, not merely optional or even preferable. *Id*.

In contrast, the '504 claims omit any mention of the heater acting as a "*lid* heater" or otherwise being on top of the sample unit in contact with the caps. This broadening in the '504 claims is a material change, since the '504 claims now cover

other different heating elements, such as the thermal cycling block of the Li reference, discussed below, in a manner that was not contemplated by the Parent. The Parent only mentions in passing that the fluorometer assembly, which is described as including the support, shuttle and detection module but *not* the heating element, can be "adapted ... [to] interrogate sample wells from ... below." Ex. 1007, ¶¶ 27, 29, 32, 80; Ex. 1002, ¶35. This narrow disclosure would not have conveyed what is now more broadly claimed. *Id*.

The claims now cover cyclers such as Li's which include new and different types of heating elements, such as Li's perforated cycling block which includes the claimed "openings" to allow wells to be viewed through it. In contrast, the Parent describes the lid heater and the "sample unit"(*i.e*., cycling block) as two separate components, never suggesting that the sample unit can pass as the claimed heating element. Although the Parent mentions briefly that the fluorometer assembly (not the heater) can be modified to view wells from below, this did not suggest to artisans that the cycling block could be modified to include openings or could otherwise act as the claimed heating element. Ex. 1002, ¶36. The claims now broadly cover new and different heating elements with openings, such as Li's perforated cycling block, that are not supported by discussion of a "lid heater" of the Parent. Ex. 1002, ¶36.

The Parent moreover emphasizes the functional importance of heater's placement as a lid on the caps of sample tubes. This positioning allows the lid heater to "control the temperature of the sample *caps*," and prevent condensation" onto the sample *caps*." Ex. 1007, ¶¶29, 27; Ex. 1002, ¶37. In short, the Parent's disclosure would have deterred artisans from repositioning the lid heater under the block. *Id*.

Thus, the Parent shows a complete lack of possession of a heater with openings other than a lid heater, or a heater of a non-lid structure that is placed anywhere between the wells and a optics head, as is now claimed. The Parent only contemplates one particular configuration in which a "lid heater" acts as a heated lid for the sample tubes in order to prevent condensation onto the "caps" of sample tubes. Ex. 1007, ¶¶29, 27; Ex. 1002, ¶38. The Parent did not convey to artisans that this particular configuration could be arbitrarily dispensed with, as the '504 claims now do.

B. The terms "a plurality of openings" (claim 1) or "a plurality of transparent portions" (claim 13) lack written description support in the Parent

The '504 claims specify that the claimed apparatus comprises a heating element with "a plurality of openings extending through" it (claim 1) or a "heater having a plurality of transparent portions to permit optical communication" with each well (claim 13).

The Parent never suggests that the lid heater can have "openings" as claim 1 now specifies. The Parent instead explains that the detection module (hereafter, "**optics head**") has "openings," and that these so-called "openings" in the DM "may simply be holes ... or they may be made of any substance that has a high degree of transparency." Ex. 1007, ¶38; Ex. 1002, ¶40. Thus, the term “openings” is broader than “holes.” The Parent clearly and unambiguously indicates that (1) solid portions made of transparent material (hereafter dubbed "windows") are an alternative to "holes", and (2) the broader term "openings" includes both alternatives: holes and windows. *Id*.; Ex. 1002, ¶40. The Parent further indicates that whereas the optics head can have openings, by contrast the *lid heater only has holes*. Specifically, "[l]id heater 204 has holes 220 therethrough, matching the size and spacing of the sample wells 210" and the optics head views wells through "corresponding holes 220 in lid heater." *Id*. at ¶¶29, 32; Ex. 1002, ¶40. The Parent even refers to the optics head's "openings" and the lid heater's "holes" in the same sentence, reconfirming that the lid heater only has holes, and not openings: in particular, "[o]ptical communication ... is provided by ***opening*** 502 in opaque walls 602 [of the optics head] and a ***hole*** 220 through lid heater 204." *Id*. at ¶41; Ex. 1002, ¶40. The Parent's teachings are clear and unambiguous: the optics head has "openings" which can be windows or holes, whereas the lid heater only has holes and does not have "openings" like the optics head does.

In stark contrast to the Parent's limited disclosure, the '504 claims cover a "heating element" or "heater" that is broader than the lid heater of the Parent. For example claim 1 now states that the heating element has "openings" – a term which the Parent only uses in reference to the optics head and not the lid heater. *Id*. at ¶¶38-44, claims 1-9; Ex. 1002, ¶41. The possibility of openings on a lid heater instead of holes is a new concept missing from the Parent, since the term "openings" is defined as including windows and unspecified structures in addition to holes. Similarly, claim 13 recites a "heater having a plurality of transparent portions," and dependent claim 21 makes clear that these "transparent portions" can include holes. But the Parent never mentions "transparent portion." Ex. 1002, ¶41. Instead, the Parent only mentions openings made of a high-transparency material (*i.e*., windows) that are *not* holes. Ex. 1007, ¶38; Ex. 1002, ¶41. Thus, the term "transparent portions" as used in claim 13 (*i.e*., *including* holes per dependent claim 22) is not described in the Parent, which only discusses transparent portions that are *not* holes. Moreover, the Parent only discusses lid heaters with holes, and does not suggest lid heaters with windows as now covered by claim 13. *Id*. Thus, claim 13 is not adequately supported by the Parent.

None of the dependent claims repair the § 112 defects of the base claims. It is noted that dependent claim 22 indicates that the "plurality of transparent portions include a plurality of holes." This claim 22 also lacks § 112 support in the Parent

because its open-ended terminology ("includes") permits its "plurality of transparent portions" to include a subset of windows in addition to a subset of holes. In contrast, the Parent's disclosure is limited to lid heaters that only include holes and not windows. Even if it was obvious to use windows in a lid heater, "a description that merely renders the [claimed] invention obvious does not satisfy the [written description] requirement." *See Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010).

Because the Parent fails to adequately describe the '504 claims, the claims are not entitled to any priority before their actual filing date of June 30, 2010.

VII. Identification of the challenge (37 C.F.R. § 42.104(b))

Petitioner requests *inter partes* review of claims of the '504 Patent based on the unpatentability grounds summarized in the index below. Per 37 C.F.R. § 42.6(c), copies of the cited references accompany the Petition.

Ground	35 U.S.C. § (pre-3/16/2013)	Claims	Index of References
1	§102(b)	1-3, 6-11, 13-17, 19, 20, 22	Kordunsky PCT
2	§103	21	Kordunsky PCT and Li
3	§103	1-3, 6-7, 9, 13, 14, 16, 19-22	Li
4	§103	8, 10, 15	Li and Heffelfinger
5	§103	11, 17	Li and Miller

WO 2004/104547 A2 ("**Kordunsky PCT,**" Ex. 1009) published on Dec. 2, 2004, and is prior art under pre-AIA §102(b) under the correct priority date for the

'504 Patent, which is its actual filing date of Jun. 2010. Chinese Patent Publ. No. CN 1379236A ("**Li,**" Ex. 1005) published in Chinese on Nov. 13, 2002, and is prior art under pre-AIA §102(a) under the asserted priority date of May 8, 2003 and prior art under pre-AIA §102(b) under the correct priority date of Jun. 2010 for the '504 Patent. U.S. Pat. 6,043,506 ("**Heffelfinger,**" Ex. 1015) published on Mar. 28, 2000, and is prior art under pre-AIA §102(b) under the '504 Patent's asserted priority date. U.S. Pat. 5,528,050 ("**Miller,**" Ex. 1029) published on Jun. 18, 1996, and is prior art under pre-AIA §102(b) under the '504 Patent's asserted priority date.

Each claim is challenged under two non-redundant Grounds, one based on the Kordunsky PCT as primary reference, and the other on Li. The Grounds are not redundant because Li is §102(a) prior art under the asserted date that renders the claims obvious, whereas the Kordunsky PCT is not prior art under the asserted priority date but forms anticipatory art under the correct priority date. Therefore, the Grounds raise different factual and legal issues, and trial should be instituted on each. This Petition is accompanied by a supporting declaration of Petitioner's technical expert, Professor Richard Mathies.

VIII. Ground 1: Claims 1-3, 6-11, 13-17, 19, 20 and 22 are anticipated by Kordunsky PCT under pre-AIA §102(b)

As discussed in Section VI above, all '504 claims are not entitled to priority before their actual filing date of June 30, 2010. As a result, the Kordunsky PCT,

which published on Dec. 2, 2004, is prior art under the pre-AIA version of 35 U.S.C. § 102(b). Ex. 1009. The Kordunsky PCT contains substantially identical disclosure to both the Parent and the '504 Patent itself and narrowly discusses specific embodiments covered by the broader '504 claims. Although this narrow disclosure fails to provide commensurate priority support in the Parent across the scope of the '504 claims, the same narrow disclosure in the Kordunsky PCT is sufficient to anticipate since it falls within the scope of those claims. *See, e.g., Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1571 (Fed. Cir. 1997): *Chester v. Miller*, 906 F.2d 1574, 1575 (Fed. Cir. 1990); *In re Gosteli*, 872 F.2d 1008 (Fed. Cir. 1989); Appeal No. 2012-007309 (Patent Tr. & App. Bd., November 29, 2012) (finding the disclosure of priority applications sufficient to anticipate despite being insufficient for the purposes of according priority).

As shown below, claims 1-3, 6-11, 13-17, 19, 20 and 22 are anticipated by the Kordunsky PCT.

Claim 1: The Kordunsky PCT discloses all elements of claim 1, as shown in the Table below.

	Claim	**Disclosures in the Kordunsky PCT (Ex. 1009, emphasis added)**
1	A fluorescence detection apparatus for analyzing samples located in a plurality of wells in a thermal cycler, the apparatus comprising:	"A fluorescence detection apparatus for analyzing samples located in a plurality of wells in a thermal cycler and methods of use are provided. In one embodiment, the apparatus includes a support structure attachable to the thermal cycler…." **(Ex.**

		1009, Abstract, ¶11)
a	a support structure attachable to the thermal cycler;	"In one embodiment, the apparatus includes a support structure attachable to the thermal cycler." **(Ex. 1009, Abstract)**
b	a shuttle movably mounted on the support structure; and	"Movably mounted on the underside of support frame 230 is a shuttle 232..." **(Ex. 1009, ¶31)**
c	a detection module attached to the shuttle, the detection module including:	"Movably mounted on the underside of support frame 230 is a shuttle 232, which holds a detection module 234." **(Ex. 1009, ¶31)**
d	a housing having an opening oriented toward the plurality of wells	"Detection module 234 may include one or more instances of excitation/detection pair 600…. Excitation/detection pair 600 is arranged inside **opaque walls 602**…." **(Ex. 1009, FIGS. 2, 3, 5, and ¶39)** "**Optical communication** between the excitation/ detection pair 600 and reaction vessel 616 **is provided by opening** 502 in opaque walls 602" **(Ex. 1009, ¶40, see FIG. 6)** "Fig. 5A is a bottom view of one embodiment of detection module 234, showing four **openings** 502,504,506,508… arranged **inside the body** of detection module 234." **(Ex. 1009, FIG. 5A, ¶37)** "… opening 502 is placed in optical communication with one of the sample wells 210" **(Ex. 1009, ¶¶37, 38, Fig. 6)**
e	an excitation light generator disposed within the housing;	"…the excitation/detection channel including an **excitation light generator** disposed **within the detection module** and an emission light detector disposed within the detection module." **(Ex. 1009, FIG. 6, ¶13)**
f	an emission light detector disposed within the housing,	"…the excitation/detection channel including an excitation light generator disposed within the detection module and an **emission light detector** disposed **within the detection**

		module." **(Ex. 1009, FIG. 6; ¶13)**
g	wherein, when the support structure is attached to the thermal cycler,	"**Support frame 230 and supports 224** are advantageously dimensioned such that when lid 122 **is positioned in base unit 110** and closed, detection module 234 is held in close proximity to lid heater 204." **(Ex. 1009, FIG. 1; ¶31)** "When **the support structure is attached to the thermal cycler**…" **(Ex. 1009, Abstract; ¶11)** "Some examples of **base unit 110** include the DNA Engine®, Dyad™, and Tetrad™ **thermal cyclers**." **(Ex. 1009, ¶24)**
h	a heating element is disposed between the detection module and the sample wells and	"**Lid heater** 204 has holes 220 therethrough, matching the size and spacing of the sample wells 210, and electronically controlled heating elements **(Ex. 1009,** not shown)." **(Ex. 1009, FIG. 2; ¶28)**
i	the shuttle is movable to position the detection module in optical communication with different wells of the plurality of wells	"Shuttle 232 is movable in two dimensions so as to position detection module 234 in optical communication with different ones of the sample wells 210 in sample unit 202 through the corresponding **holes 220** in lid heater 204." **(Ex. 1009, ¶31)**
j	through a plurality of openings extending through the heating element.	"Shuttle 232 is movable in two dimensions so as to position detection module 234 in optical communication … through the corresponding **holes 220** in lid heater 204." **(Ex. 1009, ¶31)**

Claim 13 is substantially similar to claim 1, and is anticipated as follows.

	Claim 13	**Disclosures in the Kordunsky PCT (Ex. 1009, emphasis added)**
13 a	A thermal cycler apparatus comprising: a thermal cycler having an exterior housing and a plurality of sample wells for holding reaction	"A fluorescence detection apparatus for analyzing samples located in a plurality of wells in a thermal cycler and methods of use are provided. In one embodiment, the apparatus includes a support structure attachable to the thermal cycler…." **(Ex. 1009, Abstract, ¶11)**

	vessels;	"Lid 122 provides optical and thermal isolation for the components inside lid assembly 112." **(Ex. 1009, ¶25, see also Figs. 1, 2)**
b	a heater to prevent condensation from forming on a surface of the reaction vessels when the reaction vessels are in the sample wells,	Lid heater 204 is used to control the temperature of the sample caps **(Ex. 1009,** or other sealants) of reaction vessels sample wells 210, in order to prevent condensation from forming on the caps during thermal 30 cycling operation. **(Ex. 1009, ¶28)**
c	the heater having a plurality of transparent portions to permit optical communication with each of the plurality sample wells;	"**Lid heater** 204 has holes 220 therethrough, matching the size and spacing of the sample wells 210, and electronically controlled heating elements **(Ex. 1009,** not shown)." **(Ex. 1009, FIG. 2; ¶28)**
d	a support structure disposed inside the exterior housing on an opposite side of the heater from the sample wells;	"In one embodiment, the apparatus includes a support structure attachable to the thermal cycler." **(Ex. 1009, Abstract)** See **Figs. 2 and 6**
e	a shuttle movably mounted on the support structure; and	"Movably mounted on the underside of support frame 230 is a shuttle 232..." **(Ex. 1009, ¶31)**
f	a detection module attached to the shuttle, the detection module including: a module housing having an opening that is oriented toward the plurality of sample wells when the thermal cycler is in an operating state;	"Movably mounted on the underside of support frame 230 is a shuttle 232, which holds a detection module 234." **(Ex. 1009, ¶31)** "Detection module 234 may inc1ude one or more instances of excitation/detection pair 600…. Excitation/detection pair 600 is arranged inside **opaque walls 602**…." **(Ex. 1009, FIGS. 2, 3, 5, 6 and ¶39)** "**Optical communication** between the excitation/ detection pair 600 and reaction vessel 616 **is provided by opening** 502 in opaque walls 602" **(Ex. 1009, ¶40, see FIG. 6)** "Fig. 5A is a bottom view of one embodiment of detection module 234, showing four **openings** 502,504,506,508… arranged **inside the body** of detection module 234." **(Ex. 1009,**

		FIG. 5A, ¶37) "… opening 502 is placed in optical communication with one of the sample wells 210" **(Ex. 1009, ¶¶37, 38, Fig. 6)**
g	an excitation light generator disposed entirely within the module housing; and	"…the excitation/detection channel including an **excitation light generator** disposed **within the detection module** and an emission light detector disposed within the detection module." **(Ex. 1009, FIG. 6, ¶13)**
h	an emission light detector disposed entirely within the module housing;	"…the excitation/detection channel including an excitation light generator disposed within the detection module and an **emission light detector** disposed **within the detection module**." **(Ex. 1009, FIG. 6; ¶13)**
i	when the thermal cycler is in the operating state, the shuttle is movable to position the detection module in optical communication with different sample wells of the plurality of sample wells	"Shuttle 232 is movable in two dimensions so as to position detection module 234 in optical communication with different ones of the sample wells 210 in sample unit 202 through the corresponding **holes 220** in lid heater 204." **(Ex. 1009, ¶31)**
j	through a plurality of transparent portions extending through the heating element.	

Thus, claim 13 is anticipated by the Kordunsky PCT. Dependent claims 2-3, 6-11, 14-17, 19, 20 and 22 are also anticipated as follows:

Claim	Disclosures in the Kordunsky PCT (Ex. 1009, emphasis added)
2. The fluorescence detection apparatus of claim 1 wherein an excitation optical path from the excitation light generator to the opening has a fixed length and a detection optical path from the opening to the emission light detector has a fixed length.	"Because the length of the excitation and detection optical paths do not vary from one experiment to the next, it is desirable to fixedly mount and optimize the various optical components of each excitation/ detection pair 600 inside detection module 234 during manufacture so that further adjustments during operation are not required." **(Ex. 1009, ¶34)**
3. The fluorescence detection apparatus of claim 1 further comprising: a calibration element disposed such that the detection module is movable so as to be positioned in optical communication with the calibration element, wherein the calibration element provides a known fluorescence response.	"Lid heater ... includes one or more calibration elements 222 positioned between selected ones of holes 220 or in other locations away from the holes, such as near the periphery of lid heater 204. Calibration elements 222 provide a known fluorescence response and may be used to calibrate fluorescence detectors in fluorometer assembly 206." **(Ex. 1009, ¶29)**
6. The fluorescence detection apparatus of claim 1 wherein positioning of the detection module with respect to the wells is controlled by an external computer.	"In one embodiment, the external computer is used to control the position of detection module 234 with respect to the sample wells and operations of the light source(s) and detector(s)." **(Ex. 1009, ¶51)**
7. The fluorescence detection apparatus of claim 1 wherein operation of the excitation light generator and the emission light detector is controlled by an external computer.	"In one embodiment, the external computer is used to control the position of detection module 234 with respect to the sample wells and operations of the light source(s) and detector(s)." **(Ex. 1009, ¶51)**
9. The fluorescence detection apparatus	"An excitation light path 604 includes

of claim 1 wherein the excitation light generator comprises a light-emitting diode.	a light-emitting diode (LED) or other light source 606" **(Ex. 1009, ¶39)**
10. The fluorescence detection apparatus of claim 1 further comprising at least two stepper motors mounted on the support structure, the stepper motors being operative to move the shuttle in at least two dimensions.	"... translation stages driven by stepper motors are used to move the shuttle 232 ... Stepper motor 302 operates to tum lead screw 304, thereby moving a translation stage 306 along the x direction ... Stepper motor 316 operates to tum lead screw 318, thereby moving shuttle 232 along the y direction." **(Ex. 1009, ¶32)**
11. The fluorescence detection apparatus of claim 1 wherein the detection module includes at least two emission light detectors.	"According to another aspect of the invention, the detection module may include two or more excitation light generators and two or more emission light detectors arranged to form two or more excitation/detection pairs." **(Ex. 1009, ¶12)**
14. The thermal cycler apparatus of claim 13 wherein the excitation light generator comprises a light-emitting diode.	"An excitation light path 604 includes a light-emitting diode (LED) or other light source 606" **(Ex. 1009, ¶39)**
15. The thermal cycler apparatus of claim 13 further comprising at least two stepper motors mounted on the support structure, the stepper motors being operative to move the shuttle in at least two dimensions.	"... translation stages driven by stepper motors are used to move the shuttle 232 ... Stepper motor 302 operates to tum lead screw 304, thereby moving a translation stage 306 along the x direction ... Stepper motor 316 operates to tum lead screw 318, thereby moving shuttle 232 along the y direction." **(Ex. 1009, ¶32)**
16. The thermal cycler apparatus of claim 13 further comprising a fitting on an exterior surface of the housing of the detection module, the fitting adapted to attach the detection module to the shuttle, wherein the fitting provides only	"Detection module 234 includes fittings 420 that couple to corresponding connectors" **(Ex. 1009, ¶36)** "Installation is a matter of attaching electrical connector 424 and

electrical and mechanical connections.	mechanical connectors 420 on the top of the desired detection module 234 to corresponding connectors on the underside of shuttle 234." **(Ex. 1009, ¶49)**
17. The thermal cycler apparatus of claim 13 wherein the detection module includes at least two emission light detectors.	"According to another aspect of the invention, the detection module may include two or more excitation light generators and two or more emission light detectors arranged to form two or more excitation/detection pairs." **(Ex. 1009, ¶12)**
19. The thermal cycler apparatus of claim 13 wherein movement of the shuttle and operation of the excitation light generator and the emission light detector are controlled by an external computer such that emission light is measured while the shuttle is in motion.	"This arrangement allows for a "flyover" mode of operation, in which detection module 234 is substantially continuously in motion during a scanning pass over the wells." **(Ex. 1009, ¶78)**
20. The thermal cycler apparatus of claim 13 further comprising: a plurality of optical components defining an excitation optical path for light of an excitation wavelength from the excitation light generator to the opening of the housing and a detection optical path for light of a detection wavelength from the opening of the housing to the emission light detector, wherein all of the optical components of the excitation optical path and the detection optical path are disposed within the housing of the detection module	"Because the length of the excitation and detection optical paths do not vary from one experiment to the next, it is desirable to fixedly mount and optimize the various optical components of each excitation/ detection pair 600 inside detection module 234 during manufacture so that further adjustments during operation are not required." **(Ex. 1009, ¶34)**
22. The thermal cycler apparatus of claim 13 wherein the plurality of transparent portions of the heater includes a plurality of holes extending through the heater and aligned with the sample wells.	"Lid heater 204 has holes 220 therethrough, matching the size and spacing of the 20 sample wells 210," **(Ex. 1009, ¶28)**

Accordingly, claims 1-3, 6-11, 13-17, 19, 20 and 22 are anticipated by the Kordunsky PCT under pre-AIA § 102(b). Ex. 1009, Ex. 1002, ¶56.

IX. Ground 2: Claim 21 would have been obvious over Kordunsky PCT under pre-AIA §103(a) in view of Li

Claim 21 recites the apparatus of claim 13, "*wherein the detection module is positioned such that the opening is below the plurality of sample wells*." The Kordunsky PCT discloses that its fluorescence scanning assembly can be adapted to interrogate from either above or below, depending on the design of the cycler. Ex. 1009, ¶79; Ex. 1032, 3:62-65; Ex. 1002, ¶57. Claim 21 also incorporates the requirement of base claim 13 that the cycler contains a heater with openings to prevent condensation, with the support and wells on opposite sides of the heater (*i.e.*, the heater is above the support and below the wells). The heated lid of the Kordunsky PCT does have openings, but does not have the wells and the support on opposite sides as also required by claim 21, since it is on top of both the wells and the support. Ex. 1002, ¶57.

The Kordunsky PCT also discloses a second heater in the form of a thermal cycler block. Ex. 1009; Ex. 1002, ¶57. This cycling block has the correct placement between the support and the wells, but the Kordunsky PCT does not disclose that this cycling block has a plurality of transparent portions as also required by claim 21. Ex. 1002, ¶57. It would however have been obvious in view of Li to modify the cycling block of the Kordunsky PCT to have a plurality of

holes to allow the detector to view the wells. Ex. 1009; Ex. 1002, ¶57. Li discloses a cycling block with holes for such a purpose. Ex. 1006; Ex. 1002, ¶57. The reasons for obviousness and expectation of success discussed above for base claim 13 apply equally to claim 21, which thus was obvious. Ex. 1002, ¶57.

X. Ground 3: Claims 1-3, 6-7, 9, 13-14, 16 and 19-22 would have been obvious over Li

As shown below, claims 1-3, 6-7, 9, 13-14, 16 and 19-22 would have been obvious over Li, a prior-art publication disclosing or suggesting all elements of the claims. Ex. 1005. Since Li published in Chinese; a certified English translation is provided and cited to below. Ex. 1006. Claim 1 is representative and a detailed *Graham* analysis is provided below for this claim and is also applicable to the other claims as well. *Graham v*. *John Deere Co*., 383 U.S. 1 (1966).

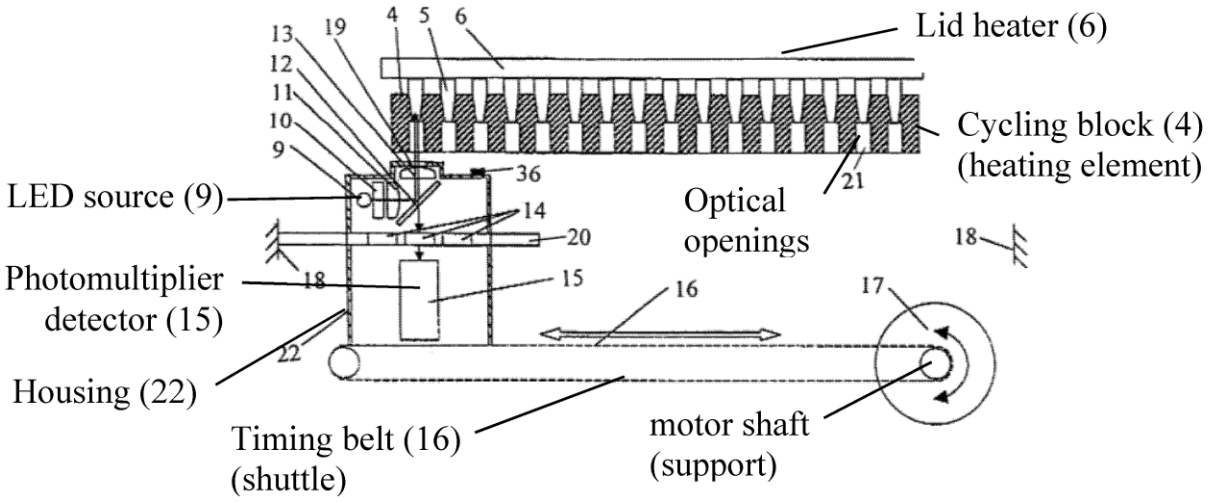
A) The first two Graham inquiries: Determining the scope and content of the prior art and ascertaining the differences from the claims: There are no real differences between the challenged claims and the art; Li discloses or suggests all elements of the claims. Representative claim 1 is directed to a fluorescence detection apparatus in a thermal cycler ("**cycler**") having a detection module ("**optics head**") with its light generator and detector placed "**in-head**" within the housing of the optics head itself, instead of being placed outside it. The optics head is attached to a movable **shuttle** on a support structure ("**support**") attachable to the cycler; the shuttle can move to position the optics head in view of different

wells. The cycler further contains a **heating element** between the sample wells and the optics head, which has optical **openings** to allow light to pass through. Ex. 1002, ¶59.

Li discloses or suggests a cycler with all these limitations, as discussed below. Li was published in Chinese, and was cited by the Patent Owner during prosecution many years after the '504 Patent's effective filing date, although Patent Owner did not provide an English translation. Ex. 1006; Ex. 1002, ¶60. Although Li does not literally mention that its support (a stepper motor shaft shown in the center of stepper motor element 17 in Fig. 1) is attached to the rest of the cycler, artisans understood that this attachment was obvious. Ex. 1002, ¶60. Artisans understood that the stepper motor shaft (shown in the center of stepper motor element 17 in Fig. 1) should obviously be attached to the cycler in order to work effectively as a support for a moving head. Ex. 1002, ¶60. This is reinforced by Fig. 1 which shows that the optics head and belt have a specific placement relative to the other components of the cycler, such that the "fluorescence detection unit is located below the thermal cycling unit." Ex. 1006, 8:1, Fig 1; Ex. 1002, ¶60. Li's shuttle (a belt) is of different structure from the "exemplary" shuttle described by the '504 Patent (a moving platform), but the claims are not limited to any particular shuttle, and even if Li's belt did not qualify as a shuttle, it would have been obvious

to incorporate a shuttle such as a platform or holder onto Li's belt on which Li's optics head could be placed, as a routine design choice. Ex. 1006; Ex. 1002, ¶60.

Independent claim 1: Li discloses or suggests all elements of claim 1, as shown in Fig. 3 of Li, reproduced below.



Claim 1 (preamble). As Prof. Mathies explains, artisans would have understood that Li disclosed a "*fluorescence detection apparatus for analyzing samples ... in ... wells in a thermal cycler*" as recited in claim 1 (preamble). Ex. 1001, 15:2-4; Ex. 1002, ¶62. For example, Li discloses a real-time "fluorescence quantitative PCR analyzing system" that is a thermal cycler, which includes "a thermal cycling unit, [and] a fluorescence detection unit" wherein "the thermal cycling unit [I]" has "a row of wells." Ex. 1006, Abstract, claim 1; Ex. 1002, ¶62. Li's sample wells have optical openings [21] at the bottom to allow Li's optics head to view samples through Li's cycling block, consistent with the claims and

disclosure of the '504 Patent, which place no constraints upon the exact format of the sample well. Ex. 1006; Ex. 1002, ¶62.

Claim 1(b) and (c). Artisans would have understood that Li taught or at least suggested "*a support structure attachable to the thermal cycler; [and] a shuttle movably mounted on the support*" as required by claim 1(b) and (c). Ex. 1001, 15:5-6; Ex. 1002, ¶63. Li's thermal cycling unit includes a shuttle in the form of a "belt capable of moving back and forth," movably mounted on a support in the form of a shaft bearing a "a stepper motor [17]" (this shaft is shown in the reproduction of Fig. 3 above). Ex. 1006, claim 1, 3:10, 6:15-27, 8:16-17; Ex. 1002, ¶63. Although Li does not literally mention that its support is attached to the rest of the cycler, artisans understood that this attachment was obvious. Ex. 1002, ¶63. It was obvious that the shaft should be attached to the cycler to work effectively as a support for a moving head. Ex. 1002, ¶63. This is reinforced by Fig. 1 which shows that the optics head and belt have a specific placement relative to the other components inside the cycler, such that the "fluorescence detection unit is located below the thermal cycling unit." Ex. 1006, 8:1, Fig 1; Ex. 1002, ¶63.

Claim 1(c). Artisans would have understood that Li disclosed a "*detection module*" ("**optics head**") which is "*attached to the shuttle*." As discussed for claim 1(b), Li's cycler has an optics head in the form of a "fluorescence detection unit [II]," with the head's "housing [22] fixed on ... [a] belt" (*i.e.*, shuttle) that is

"capable of moving back and forth" in order to place Li's optics head in view of different sample wells. *Id*. at claim 1, 3:10, 6:15-27, 8:16-17; Ex. 1002, ¶64.

Claim 1(d). Artisans would have understood that Li's detection module ("**optics head**") had a "*housing having an opening oriented toward the plurality of wells*." Ex. 1002, ¶65. Li's optics head has a "housing [22]." Ex. 1006, 3:17, 8:19; Ex. 1002, ¶65. This housing had an opening in the form of "a hole [19]." *Id*. at 3:18, 8:20; Ex. 1002, ¶65. Since Li's optics head is "located below" the cycling block and the hole is "provided on top of the housing," the hole is thus oriented towards the sample wells above it, so that light from Li's optics head is "focused ... onto the bottom of the tube" in the sample well, as shown in Fig. 3. *Id*. at 8:16-20, 8:28-9:1; Ex. 1002, ¶65.

Claim 1(e) and (f). Artisans would have understood that Li's optics head included an "*excitation light generator*" and an "*emission light detector*." Ex. 1002, ¶66. Li's optics head includes an "excitation light source [9]" as a generator and "a photomultiplier tube [15]" as detector, so that "excitation light emitted from the excitation light source" is focused "onto the bottom of the tube 5 which enables the reactants ... to emit a fluorescence ... received by the photomultiplier tube 15 ... [and] converted to an electronic signal." Ex. 1006, 8:16-9:7; Ex. 1002, ¶66. Li's "excitation light source [9]" (generator) and "photomultiplier tube [15]" (detector)

are shown to be "*within the housing*" (specifically, "housing 22") of Li's optics head in Fig. 3. *Id*. at 8:16-27, Fig. 3; Ex. 1002, ¶66.

Claim 1(g). As already discussed for claim 1(a), artisans would have understood that Li disclosed or at least suggested that its support structure is "*attached to the thermal cycler*." Although Li does not literally mention that its support (*i.e*., the shaft of stepper motor 17 in Fig. 3) is attached to the rest of the cycler, artisans understood that this attachment was obvious. Ex. 1002, ¶67. It was obvious that the shaft should be attached to the cycler in order to work more effectively as a support for a moving head. Ex. 1002, ¶67. This is reinforced by Fig. 1 which shows that the optics head and belt have a specific placement relative to the other components of the cycler, such that the "fluorescence detection unit is located below the thermal cycling unit." Ex. 1006, 8:1, Fig 1; Ex. 1002, ¶67.

Claim 1(h). Artisans would have understood that the cycling block in Li's cycler is "*a heating element ... disposed between the detection module and the sample wells*." Ex. 1001, 15:14-20; Ex. 1002, ¶68. As discussed in the claim construction section, the claimed "heating element" is not limited to the exemplary 'heated lid' discussed in the '504 Patent, and can include other heating elements such as the cycling block. *Id*.; Ex. 1002, ¶68. The cycling block of Li's cycler is a "*heating element*" because it can "heat ... [the samples] ... so as to meet the temperature requirements for PCR amplification." Ex. 1006, 10:2-3; Ex. 1002, ¶68.

This cycling block is also "*disposed between the detection module* [*i.e.*, optics head] *and the sample wells*" since Li's "row of wells" is on the top of the cycling block whereas Li's optics head is "located below" the cycling block. Ex. 1001, 15:14-20; Ex. 1006, 6:15-27; Ex. 1002, ¶68. . Thus, Li discloses "*a heating element ... disposed between the detection module and the sample wells*" as required by claim 1(h).

Claim 1(i). Artisans would have understood that Li's shuttle "*is movable to position the detection module in optical communication with different wells of the plurality of wells*" during scanning. Ex. 1001, 15:14-20; Ex. 1002, ¶69. As mentioned, Li's shuttle is a "belt capable of moving back and forth," which movement causes the optics heads mounted on it to "make a back and forth movement to detect the fluorescence from each tube one by one." Ex. 1006, 6:15, 9:8-10; Ex. 1002, ¶69.

Claim 1(j). Artisans would have also understood that Li's optics head viewed the sample wells "*through a plurality of openings extending through the heating element*." As discussed for claim 1(h), Li's cycling block acts as the claimed "*heating element,*" and has optical openings at the bottom of the wells to allow the optics head underneath to view the samples through the block (*see* Fig. 3). Ex. 1006, 14; Ex. 1002, ¶70. These optical openings "*extend[] through the heating element*" because they are in continuity with the sample wells which are on

the top surface of the cycling block, and thus extend from the top to the bottom of the cycling block. Ex. 1002, ¶70.

B) The third Graham inquiry: the level of ordinary skill in the art in the pertinent art and the state of the art. The skill level and knowledge of an artisan was exceptionally deep and rich with respect to the use of optics heads and scanning assemblies in real-time cyclers. Thermal cyclers were not merely a matter of academic interest, but part of everyday life to artisans since advent of "end point" PCR in the mid-1980s, and of real-time PCR in the 1990s (*i.e.*, quantitative PCR involving optical detection during the course of the reaction). Ex. 1034, 31; Ex. 1035, 247; Ex. 1036, 17; Ex. 1030, 32; Ex. 1002, ¶71. Thermal cyclers were found in every lab and clinic, and typically were one of the most-used instruments there. *Id*.

Claim 1 merely recites a scanning assembly (*i.e.*, a support and shuttle) in the broadest terms possible, such that practically any scanning assembly falls within the scope of the claims, including Li's. Artisans familiar with real-time cyclers would have found it obvious that the support should be attached to the cycler in order to work effectively as a support for a moving head. Ex. 1002, ¶72. More than a dozen prior-art references disclosed scanning assemblies for moving an optical detector. Ex. 1010, Figs. 30-36, cols. 35-36; Ex. 1011, 9:23-32; Ex. 1012, 17:13-24, Fig. 5-6; Ex. 1013, 11:24-34, Fig. 10; Ex. 1014, 2:1-3:65, Fig. 1B;

Ex. 1015, 9:27-60, Figs. 1, 4; Ex. 1016, Fig. 6; Ex. 1017, ¶¶72-75, Fig. 6; Ex. 1018, Abstract, 4:39-41, Fig. 1; Ex. 1019, 3:1-4:65, Figs. 1-2; Ex. 1020, 11:6-12:65, Figs. 11-15; Ex. 1021, 3:1-65, Fig. 1; Ex. 1022, 4:13-26, Fig. 1; Ex. 1023, 4518; Ex. 1024, p. 3-10, Fig. 3-6; Ex. 1002, ¶72. Five of these prior-art scanning assemblies were used to move an optical module to scan samples in a thermal cycler. Ex. 1010, Figs. 30-36, cols. 35-36; Ex. 1011, 9:23-32; Ex. 1012, 17:13-24, Fig. 5-6; Ex. 1013, 11:24-34, Fig. 10; Ex. 1023, 4518; Ex. 1024, p. 3-10, Fig. 3-6; Ex. 1002, ¶72. Scanning assemblies were readily available on the market for routine combination with a detector of choice. Ex. 1018, Fig. 1, Abstract, 4:39-41; Ex. 1022, 4:13-26, Fig. 1; Ex. 1002, ¶¶72. Thus, it was a well-known and even typical practice to mount a movable shuttle on a support to provide a convenient attachment site for an optics head for scanning sample wells in a thermal cycler. Ex. 1002, ¶72.

C) Rationales for obviousness. Li discloses or at least suggests a device meeting all limitations of claim 1.

Li did not literally mention attachment of the support (a stepper motor shaft) to the cycler, but artisans would have found it obvious that Li's shaft should have such attachment to work more effectively as a support. Ex. 1002, ¶74. In any event, the mere disclosure of a movable optics head, without more, would have made a scanning assembly obvious to an artisan. As the Patent Office has recognized, a

scanning assembly was clearly essential to make Li's modular optics head movable. Ex. 1025, p. 46; Ex. 1002, ¶74. The intrinsic record confirms that the scanning assembly is not an inventive feature of the claim. The '504 Patent consistently treats the "movable detection module" (*i.e.*, optics head) as the "invention," and only discusses the scanning assembly as a means for making the optics head movable. Ex. 1001, 1:20-24, 2:60-65; Ex. 1002, ¶74. The Patent Office dismissed the scanning assembly as claimed as a "well known concept" disclosed in the prior art, a finding that the applicant did not dispute. Ex. 1004, p. 27; Ex. 1002, ¶74. The applicants invariably relied on the optics head rather than the scanning assembly in prosecution. The scanning assembly was included in the claims to ensure operability rather than patentability, since it was deemed essential to make the head movable. Ex. 1025, p. 46, p. 25; Ex. 1002, ¶74. Artisans did not need the teachings of the '504 Patent to find such an assembly obvious.

Li also discloses a shuttle in the form of a belt. Li's belt is a "shuttle" since the '504 Patent does not mandate that the shuttle is a moving platform, although its "exemplary" apparatus includes a shuttle that is a moving platform, which can be moved by "movable mountings" such as "belt drives" (which typically includes belts movably mounted on pulleys). Ex. 1006, 3:14-18, 6:15-27, 8:16-28; Ex. 1002, ¶75.

And even if Li's belt were not considered to be a shuttle, it was obvious as a routine design choice to use a shuttle having the particular structure discussed in the '504 Patent (a moving platform). The "shuttle" element is not only a trivial and well-worn concept but makes no working difference. Ex. 1002, ¶76. The design or presence of the shuttle does not change the working of the optics head in any real way. The intrinsic record confirms that the inclusion of a shuttle is merely an optional design choice. The '504 Patent affirms that the optics head can be movably mounted in any manner to the support (with or without a shuttle), and only discusses the shuttle as part of an "exemplary apparatus." Ex. 1001, Abstract, 4:7-14, 5:44-6:48; Ex. 1002, ¶76. Although the specification discusses easy detachability of the head as a useful option, it also makes clear that the head can be mounted directly on – and easily detachable from – the support itself, without a shuttle in between. *Id*. The shuttle is never treated as a distinguishing feature during prosecution, and in fact omitted from the earliest-issued claims of related patents. Ex. 1026, claims 1-18; Ex. 1002, ¶76. Moreover, a shuttle in the shape of a moving platform was well known as a design choice to artisans. Eight prior-art publications used a shuttle of such shape to move an optical module in a scanning device. Ex. 1010, Figs. 30-36, cols. 35-36; Ex. 1012, 17:13-24, Fig. 5-6; Ex. 1011, 9:23-32; Ex. 1014, 2:1-3:65, Fig. 1B; Ex. 1015, 9:27-60, Figs. 1, 4; Ex. 1021, 3:1-65, Fig. 1; Ex. 1022, 4:13-26, Fig. 1; Ex. 1023, 4518; Ex. 1024, p. 3-10, Fig. 3-6;

Ex. 1002, ¶76. Three of these references used such a shuttle in a thermal cycler. Ex. 1010, Figs. 30-36, cols. 35-36; Ex. 1012, 17:13-24, Fig. 5-6; Ex. 1011, 9:23-32; Ex. 1002, ¶76.

Li's cycler thus renders every element of the claims obvious.

Reasonable Expectation of Success. An artisan had a reasonable expectation of success in arriving at the apparatus of claim 1 from Li's disclosure. Ex. 1002, ¶78. Although Li does not literally indicate that its support is attached to the (rest of the) cycler, such attachment was obvious to artisans. Ex. 1002, ¶78. Li disclosed a shuttle in the form of a belt, and moreover it would have been routine to substitute another type of shuttle instead of a belt if so desired. Ex. 1002, ¶78. Thus, claim 1 is obvious over Li's scanning cycler (notwithstanding objective indicia of nonobviousness which are discussed for all claims in Section XIV, below).

Independent Claim 13 (preamble) and (a). As discussed already for claim 1(preamble) and (a), artisans would have understood that Li disclosed a "*thermal cycler apparatus comprising a thermal cycler having ... a plurality of sample wells*" as required by claim 13(preamble) and (a). Ex. 1001, 15:61-63; Ex. 1002, ¶79. Li discloses that its sample wells are "*for holding reaction vessels*." In particular, each sample well has a "tube [5] disposed in the well." Ex. 1006, claim 1, 3:10; Ex. 1002, ¶79.

Claim 13(b). Artisans would have understood that Li's cycler had a "*heater to prevent condensation from forming on ... the reaction vessels when ... in the sample wells*." Cyclers in general were designed to heat the sides of the sample tubes right up to the tube caps in order to prevent condensation onto the sides of the tubes during such heating. Ex. 1001, 16:1-5; Ex. 1002, ¶80. As shown in Fig. 3, the sample volume is so small that the "reactants [are] at the bottom of the tube" in Li's cycler, but Li's cycling block contacts and heats the sides of the tube almost to the very top, thereby preventing condensation onto the sides of the tubes during heating. Ex. 1006, 8:28-9:1, 8:5-12; Ex. 1027, ¶¶7, 50, 63; Ex. 1002, ¶80.

Claim 13(c). As discussed already for claim 1(j), artisans would have understood that the heater had "*transparent portions to permit optical communication with each of the ...wells*." Ex. 1001, 16:1-5; Ex. 1002, ¶81. Dependent claim 22 makes clear that the "*transparent portions*" recited in claim 13 can be holes. As discussed for claim 1(h) and (j), Li's cycling block is a heater with a plurality of optical openings at the bottom of each well, which are holes aligned with the sample wells. Ex. 1002, ¶81.

Claim 13(d). Artisans would have understood that Li's cycler had "*a support structure disposed inside the exterior housing*" of the cycler. As discussed already for claim 1(b) Li's cycler had a support structure (a stepper motor shaft), which further was disposed within an exterior "housing V" as shown in Fig. 1. Ex. 1006,

Fig. 1, 7:29-31; Ex. 1002, ¶82. Artisans would have recognized the necessity for an exterior housing to prevent ambient light from interfering with detection. Ex. 1002, ¶82.

Claim 13(d) further specifies that the support is "*on an opposite side of the heater from the ...wells*" Ex. 1001, 16:6-7; Ex. 1002, ¶83. As shown in Fig. 3, Li's support (a stepper motor shaft) is on the underside of the heater (cycling block), opposite from the sample wells on the topside of the cycling block. Ex. 1006, claim 1, 6:15-27, Fig. 3; Ex. 1002, ¶83.

Claim 13(e). As discussed already for claim 1(b), artisans would have understood that Li's cycler had a "*shuttle movably mounted on the support structure*" Ex. 1001, 15:6; Ex. 1002, ¶84.

Claim 13(f). As discussed already for claim 1(c) and (d), artisans would have understood that Li's cycler had a "*detection module attached to the shuttle ... including a module housing having an opening ... oriented toward the ...wells when the thermal cycler is ... operating*." Ex. 1001, 16:9-13; Ex. 1002, ¶85.

Claim 13(g) and (h). As discussed above for claim 1(e) and (f), artisans would have understood that Li's cycler had an "*excitation light generator*" and an "*emission light detector*" that were "*disposed entirely within the module housing*." Ex. 1001, 16:13-16; Ex. 1002, ¶86. As shown in Fig. 3, Li's generator and detector

are within the optics head housing. Ex. 1001, 16:13-16; Ex. 1006, Fig. 3; Ex. 1002, ¶86.

Claim 13(i). As discussed already for claim 1(i) and (j), artisans would have understood that the "*shuttle is movable to position the detection module in optical communication with different sample wells ... through the transparent portions of the heater*." Ex. 1001, 16:18-22; Ex. 1002, ¶87.

The rationales for obviousness discussed above for claim 1 at the beginning of this Ground apply equally to claim 13. Ex. 1002, ¶88. There was further incentive to ensure that Li's cycler had "*an exterior housing*" and that the support was "*disposed inside the exterior housing*." Ex. 1001, 15:61-63, 16:6-7; Ex. 1002, ¶88. Artisans knew that a cycler needed an opaque exterior housing in order to ensure that its contents and in particular the sample wells were "light-sealed to prevent external light sources from influencing fluorescence detection." Ex. 1028, ¶59; Ex. 1002, ¶88. In addition, there was strong reason to prevent sample condensation in real-time cyclers, since condensation changed the sample volume and thus its fluorescence properties. Ex. 1033, 2:57-65; Ex. 1002, ¶88. There also was a reasonable expectation of success, for at least the reasons discussed for claim 1. Thus, claim 13 was obvious for at least the same reasons as claim 1. Ex. 1002, ¶88.

Claims 2 and 20. Claims 2 and 20 recite the apparatus of claims 1 and 13 respectively, wherein an "*excitation optical path from the ... generator to the opening*" of the optics head and a "*detection optical path from the opening to the ... detector*" both have "*a fixed length*" (claim 2) or are both defined by "*a plurality of optical components*" for light of an excitation or detection wavelength, wherein "*all of the optical components ... are disposed within the housing*" of the optics head (claim 20). Ex. 1001, 15:21-25, 16:53-55. Base claims 1 and 13 were obvious as discussed above. Further, Li's optics head is self-contained such that all optical components are enclosed within its housing: in particular, Li's optics head includes "a lens 13, a dichroic mirror 12 ... a photomultiplier tube 15 ... a plurality of filters 14 ... an excitation light source 9, a filter 10, and a lens 11 disposed ... in the housing" of the optics head. Ex. 1006, 8:16-27; Ex. 1002, ¶89. Since these optical components are in fixed positions, they define an optical path of fixed length as required by claim 2. Ex. 1002, ¶89. Fig. 3 shows that all optical components are contained within the housing of Li's optics head as also required by claim 20. Ex. 1006, Fig. 3; Ex. 1002, ¶89. Thus, Li's optics head meets the added requirements of claims 2 and 20. The rationales for obviousness and expectation of success already discussed in this Ground for base claims 1 and 13 apply equally to claims 2 and 20, which thus were obvious. Ex. 1002, ¶89.

Claim 3. Claim 3 recites the apparatus of claim 1, further comprising "*a calibration element disposed such that the detection module is movable so as to be positioned in optical communication with the calibration element, wherein the calibration element provides a known fluorescence response*." Base claim 1 was obvious as discussed above. Moreover, Li uses such a calibration element. Ex. 1001, 15:28-32; Ex. 1002, ¶90. Li uses a calibration element in the form of an "a plurality of tubes ... used to hold standard reactants with known concentrations," where Li's computer "compares the fluorescence intensity of the reactant to be detected with the fluorescence intensity of standard reactant." Ex. 1006, 8:12-13, 10:14-16; Ex. 1002, ¶90. The reasons for obviousness and expectation of success discussed above for base claim 1 apply equally to claim 3. Thus, claim 3 was obvious. *Id*.

Claims 6, 7 and 19. Claims 6, 7 and 19 recite the apparatus of claims 1 and 13 respectively, wherein an "*external computer*" controls the "*positioning of the detection module with respect to the wells*" (claim 6), or the "*operation of the ... generator and ... detector*" (claim 7), or both the "*movement of the shuttle and operation of the ... generator and the ... detector ... such that emission light is measured while the shuttle is in motion*" (claim 19). Ex. 1001, 15:40-45, 16:40-44. Base claims 1 and 13 were obvious as discussed above. And in Li's cycler, the "excitation light source 9" (generator), the "photomultiplier tube 15" (detector) and

the "belt 16" (shuttle), are all controlled by a control circuit which in turn is controlled by a computer. Ex. 1006, 8:16-28; Ex. 1002, ¶91. Specifically, "the instruction signal sent by the computer IV [wa]s converted to a control signal by the microprocessor 25" of the control circuit. Ex. 1006, 9:30-31; Ex. 1002, ¶91. The reasons for obviousness and expectation of success discussed above for base claims 1 and 13 apply equally to claims 6, 7 and 19, which thus were obvious. Ex. 1002, ¶91.

Claims 9 and 14. Claims 9 and 14 recite the apparatus of claims 1 and 13, wherein the "*generator comprises a light-emitting diode*." Base claims 1 and 13 were obvious as discussed above. Further, Li's optics head contains exactly such a "light-emitting diode" (LED) as generator. Ex. 1006, 8:27-28; Ex. 1002, ¶92. The reasons for obviousness and expectation of success discussed above for base claims 1 and 13 apply equally to claims 9 and 14. It is also known that LED sources are an "inexpensive alternative ... particularly useful for certain specified wavelengths," providing further incentive to use LEDs in Li's optics head. Ex. 1029, 5:46-48; Ex. 1002, ¶92. Claims 9 and 14 thus were obvious. Ex. 1002, ¶92.

Claim 16. Claim 16 recites the apparatus of claim 13 further comprising "*a fitting on an exterior surface of the housing of the detection module, the fitting adapted to attach the detection module to the shuttle, wherein the fitting provides only electrical and mechanical connections*." This claim merely recites a routine

design choice, and the Patent Office has correctly recognized that this limitation does not serve to distinguish the claims from the art. Ex. 1004, p. 45-46 (rejecting original claim 19 reciting such a fitting for the same reasons as base claim 16); Ex. 1002, ¶93. Artisans were already familiar with appropriate fittings which provided mechanical or electrical connections between a detachable optics head and a shuttle. For example, Ackley disclosed a scanner with an "optical sensor module 20" (optics head) which "comprises a generally rectangular housing [i.e., fitting] that fits snugly within a corresponding receptacle" of a scan head (shuttle), with a "bore provided in a portion of the housing to secure the sensor module 20 to the scan head 14" (i.e., mechanical connection), and "connector 22 of the sensor module 20 to provide an electrical connection between the sensor module 20 and the other elements of the scanner." Ex. 1037, 4:45-67; Figs. 2-4, 2:63-3:21; *see also* Ex. 1038, 6:47-67; Ex. 1022, cols. 6-7; Ex. 1002, ¶93. The reasons for obviousness and expectation of success discussed for base claim 13 apply equally to claim 16. Moreover, Li's optics head needed electrical connections to power and control its internal light generator and detector, and also needed mechanical connections for stable attachment to a movement means, giving artisans ample reason to provide the optics head with the fitting of claim 16.

Claim 21. Claim 21 recites the apparatus of claim 13, "wherein the detection module is positioned such that the opening is below the plurality of sample wells."

As the '504 Patent acknowledges, it was obvious and routine to adapt the fluorescence scanning assembly to interrogate from either above or below, depending on the design of the cycler. Ex. 1001, 14:53-60; Ex. 1032, 3:62-65; Ex. 1002, ¶94. The reasons for obviousness and expectation of success discussed above for base claim 13 apply equally to claim 21, which thus was obvious. Ex. 1002, ¶94.

Claim 22. Claim 22 recites the apparatus of claim 13, "*wherein the plurality of transparent portions of the heater includes a plurality of holes extending through the heater and aligned with the sample wells*." As discussed for claim 1(h) and (j), Li's cycling block acted as a heater with a plurality of holes aligned with the sample wells. Ex. 1006, Fig. 3; Ex. 1002, ¶95. The reasons for obviousness and expectation of success discussed above for base claim 13 apply equally to claim 22, which thus was obvious. Ex. 1002, ¶95.

Accordingly, the challenged claims would have been obvious in view of the above, notwithstanding objective indicia of non-obviousness discussed in Section XIV, below. Ex. 1002, ¶96.

XI. Ground 4: Claims 8, 10 and 15 would have been obvious over Li and Heffelfinger

Claim 8. Claim 8 recites the apparatus of claim 1, wherein "*the detection module is detachably attached to the shuttle*." Base claim 1 was obvious over Li as discussed above. Further, Heffelfinger taught that its scan head is "coupled to a

scan head mount" (shuttle), optionally through a translation stage, and it is clear from Fig. 4 that the scan head mount is designed for easy detachment of the scan head. Ex. 1015, 9:30-31, 10:32-34; Ex. 1002, ¶97. Heffelfinger elsewhere taught that one advantage of a modular design for a detection system is that a module could "be easily and quickly replaced" as needed. Ex. 1015, 8:24-29; Ex. 1002, ¶97. From these combined teachings, artisans would have found it obvious to mount Li's optics head in a detachable manner onto Heffelfinger's shuttle. The reasons for obviousness and expectation of success discussed above for base claim 1 apply equally to claim 8. There was further reason to make the sensor module removable for easier repair and replacement, and customization to the optical profile of a particular PCR assay by choice of sensor module with appropriate optics components. Claim 8 thus was obvious. Ex. 1002, ¶97.

Claim 10 and 15. Claims 10 and 15 recite the apparatus of claims 1 and 13, further comprising "*at least two stepper motors mounted on the support structure, the stepper motors being operative to move the shuttle in at least two dimensions*." Base claims 1 and 13 were obvious over Li as discussed above. Further, Heffelfinger discloses a "[s]can head" (optics head) that is "coupled to a scan head mount" (shuttle), where two stepper motors move the shuttle in two dimensions. Ex. 1015, 9:27-40; Ex. 1002, ¶98. More specifically, Heffelfinger's shuttle is moved "along translation arm 405 under the power of scanning motor 407" and a

"second scanning motor 413 controls movement of arm assembly 409 along [second] arm 411," where "motors 407 and 413" can be "stepping motors." Ex. 1015, 9:32-39, 9:54-56; Ex. 1002, ¶98. The reasons for obviousness and expectation of success discussed above for base claims 1 and 13 apply equally to claims 10 and 15, which thus were obvious. Ex. 1002, ¶98.

XII. Ground 5: Claims 11 and 17 would have been obvious over Li and Miller

Claims 11 and 17 recite the apparatus of claims 1 and 13, wherein "*the detection module includes at least two ... detectors*." Base claims 1 and 13 were obvious over Li as discussed above. And artisans knew, as evidenced by Miller, the benefits of a 'dual-head' configuration, in which two individual optics heads, each with a separate generator and detector, are enclosed together within the same housing side by side to form a single (composite) detection module. Ex. 1029, Figs. 1-4; Ex. 1002, ¶99. Miller's two-headed module could advantageously monitor two different wavelengths simultaneously, allowing multiplexed analysis – a highly desired feature in cyclers, as the '504 Patent acknowledges. Ex. 1029, 1:64-2:1; Ex. 1030, 33; Ex. 1001, 11:31-39; Ex. 1002, ¶99. The reasons for obviousness and expectation of success discussed above for base claims 1 and 13 apply equally to claims 11 and 17. Claims 11 and 17 thus were obvious. Ex. 1002, ¶99.

XIII. Objective indicia do not support patentability

To Petitioner's knowledge, the patent owner did not proffer any evidence of objective indicia of nonobviousness during prosecution of the '504 patent, and Petitioner is not aware of any such evidence. Ex. 1002, ¶100-102. If the patent owner relies on objective indicia, Petitioner requests an opportunity to rebut such evidence. *See* IPR2013-00368, Paper No. 8 at 13 (2013).

XIV. Certification that the patent may be contested via inter partes review by the Petitioner and Standing (37 C.F.R. § 42.104(a))

Petitioner certifies that (1) the '504 Patent is available for IPR and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '504 Patent. This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed herewith are a Power of Attorney and Exhibit List under 37 C.F.R. § 42.10(b) and § 42.63(e), respectively.

XV. Mandatory notices (37 C.F.R. § 42.8(a)(1))

Real Party-In-Interest (§ 42.8(b)(1)) is: Thermo Fisher Scientific Inc.

Related Matters (§ 42.8(b)(2)): The '504 Patent is asserted against Petitioner in *Bio-Rad Labs*, *Inc*. *v*. *Thermo Fisher Scientific Inc*., C.A. No. 16-358 (D. Del.) (RGA). Petitioner is concurrently filing another IPR petition No. 2017-00055 of the same claims 1-3, 6-11, 13-17 and 19-22 of the '504 Patent, based on different grounds. A related App. No. 14/480,512 is currently pending.

Designation of Lead and Back-Up Counsel (§ 42.8(b)(3)):

Lead Counsel	Back-Up Counsel
Ashita Doshi (Reg. No. 57327) Thermo Fisher Scientific Inc. 5823 Newton Dr. Carlsbad, CA 92008 760-603-7200 (tel) 760-476-6048 (fax) ashita.doshi@thermofisher.com	Phil Makrogiannis (Reg. No. 47766) Thermo Fisher Scientific Inc. 5823 Newton Drive, Carlsbad, CA 92008 760-603-7200 (tel) 760-476-6048 (fax) TFS_PTAB@thermofisher.com LifeTechDocket@system.foundationip.com

Notice of service information and fees (37 C.F.R. § 42.8(b)(4)):

Please direct all correspondence regarding this Petition to counsel at the above addresses. Petitioner consents to service by email at the addresses above. The required fee is paid through Deposit Acct. No. 50-3994 (Customer ID No. 52059). The Office is authorized to charge any fee deficiency, or credit any overpayment, to Deposit Acct. No. 50-3994 (Customer ID No. 52059).

XVI. Conclusion

Each of claims 1-3, 6-11, 13-17 and 19-22 would have been obvious over the art discussed above, notwithstanding any assertions of objective indicia of nonobviousness. The Board should institute *inter partes* review for each challenged claim.

Respectfully submitted,

/Ashita Doshi/

Date: October 14, 2016

Ashita Doshi
Registration No. 57327
Attorney for Petitioner
Thermo Fisher Scientific Inc.
5823 Newton Dr. Carlsbad, CA 92008
760-603-7200 (tel)
ashita.doshi@thermofisher.com

37 C.F.R. § 42.24(d) CERTIFICATION

The undersigned hereby certifies that this submission, excluding the tables of contents, certificate of word count, exhibit list, and certificate of service, contains 12,339 words, as determined using the standard word counting feature of the Microsoft Word program.

/Ashita Doshi/

Date: October 14, 2016

Ashita Doshi
Registration No. 57327
Attorney for Petitioner
Thermo Fisher Scientific Inc.
5823 Newton Dr. Carlsbad, CA 92008
760-603-7200 (tel)
ashita.doshi@thermofisher.com

CERTIFICATION OF SERVICE (37 C.F.R. §§ 42.6(e), 42.105(a))

The undersigned hereby certifies that the above-captioned "Petition for *Inter Partes* Review of U.S. Patent No. 8,236,504 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123" was served in its entirety on this date, upon Patent Owner's correspondence address of record for U.S. Patent No. 8,236,504 via FEDEX®:

KILPATRICK TOWNSEND & STOCKTON LLP

Two Embarcadero Center

Eighth Floor

San Francisco, CA 94111-3834

/Ashita Doshi/

Date: October 14, 2016

Ashita Doshi
Registration No. 57327
Attorney for Petitioner
Thermo Fisher Scientific Inc.
5823 Newton Dr. Carlsbad, CA 92008
760-603-7200 (tel)
ashita.doshi@thermofisher.com