

THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GATOR BIO, INC.,

Petitioner,

v.

SARTORIUS BIOANALYTICAL INSTRUMENTS, INC.,

Patent Owner.

IPR2025-00633

U.S. Patent No. 8,647,588

PETITION FOR *INTER PARTES* REVIEW

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EXHIBIT LIST¹

Exhibit	Description
1001	U.S. Patent No. 8,647,588 (“588 patent”)
1002	Declaration of Dr. Laird Forrest
1003	Curriculum Vitae of Laird Forrest, Ph.D.
1004	Certified File History of U.S. Patent No. 8,647,588 (“588 FH”) (copies of prior art references omitted)
1005	U.S. Patent No. 4,087,248 (“Miles”)
1006	Yuxiao Yang et al., <i>Direct monitoring of antigen-antibody interactions by optical fiber bioprobe</i> , PROCEEDINGS OF SPIE, THIRD INT’L CONFERENCE ON PHOTONICS AND IMAGING IN BIOLOGY AND MEDICINE, 5254:431-436 (2003), copy obtained from British Library (“Yang”)
1007	U.S. Patent No. 4,676,377 (“Rainin”)
1008	PCT Publication No. WO 2005/047854 A2 (“WO854”)
1009	U.S. Patent No. 5,804,453 (“Chen”), which is incorporated by reference into WO854
1010	Yan Sun et al., <i>Fiber Optic Direct-Sensing Biosensor Applied in Detecting Biolayer Thickness of Nanometer Grade</i> , ACTA PHOTONICA SINICA, 31(6):657-661 (June 2002), copy obtained from British Library
1011	Certified English Translation of EX1010, Yan Sun et al., <i>Fiber Optic Direct- Sensing Biosensor Applied in Detecting Biolayer Thickness of Nanometer Grade</i> , ACTA PHOTONICA SINICA, 31(6):657-661 (June 2002) (“Sun”)

¹ Unless otherwise stated, citations in this Petition are to the original page, column, and line numbers in the exhibits. Brackets ([]) are used in citations to refer to the sequential page numbers added in the footer to exhibits.

Exhibit	Description
1012	Excerpted Transcript of May 25, 2023 Deposition of Michael Sailor, ITC Inv. No. 337-TA-1344 (“Sailor”)
1013	U.S. Patent No. 5,827,745 (“Astle”)
1014	U.S. Patent No. 5,475,610 (“Atwood”)
1015	U.S. Patent No. 3,356,462 (“Cooke”)
1016	U.S. Patent No. 5,674,047 (“Lapeus”)
1017	U.S. Patent No. 6,019,225 (“Kalmakis”)
1018	Fang Yu et al., <i>Reflectometry Interference Spectroscopy in Detection of Hepatitis B Surface Antigen</i> , CLINICAL CHEMISTRY, 46(9):1489-1490 (September 2000) (“Yu”), copy obtained from U.S. Library of Congress
1019	Weiping Qian et al., <i>Immobilization of Antibodies on Ultraflat Polystyrene Surfaces</i> , CLINICAL CHEMISTRY, 46(9):1456-1463 (2000) (“Qian”)
1020	Rudolf Lequin, <i>Enzyme Immunoassay (EIA)/Enzyme-Linked Immunosorbent Assay (ELISA)</i> , CLINICAL CHEMISTRY, 51(12):2415-2418 (2005) (“Lequin”)
1021	Corning, <i>ELISA Technical Bulletins - Nos. 1 & 2</i> (July 2001), available at https://www.labcluster.com/news4_2/Corning_elisa1_2.pdf (“Corning”)
1022	U.S. Patent No. 5,799,792 (“Abrums”)
1023	U.S. Patent No. 4,848,579 (“Barnes”)
1024	U.S. Patent Appl. Publ. No. 2006/0186014 A1 (“Ramanujam”)
1025	U.S. Patent No. 4,027,778 (“Tupper”)
1026	Joseba Zubia et al., <i>Plastic Optical Fibers: An Introduction to Their Technological Processes and Applications</i> , Optical Fiber Technology, 7:101-140 (2001) (“Zubia”)

Exhibit	Description
1027	Excerpt of Patent Owner’s Preliminary Sur-Reply (Paper 18), dated April 25, 2023, in IPR2023-00215 (“PO Surreply”)
1028	Excerpt of Patent Owner’s Prehearing Brief, in <i>Certain Bio-Layer Interferometers and Components Thereof</i> , ITC Inv. No. 337-TA-1344 (“PHB”)
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1033	Declaration of Seema Rampersad regarding Sun (EX1010)
1034	Certificate of Copyright Registration regarding Yu (EX1018)
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1036	Roy Manns, <i>History of Microplates</i> , Plastics Historical Society, available at https://plastiquarian.com/?page_id=14361 (“Manns”)
1037	U.S. Patent Appl. Publ. No. 2004/0171087 A1 (“Rech-Weichselbraun”)
1038	U.S. Patent No. 5,759,774 (“Hackett”)
1039	Gilson, Inc., <i>Manual Liquid Handling Catalog</i> (2004), available at https://web.archive.org/web/20040523093106/http://www.gilson.com:80/Products/prodPDF.asp?pID=106&pdftid=BRO (archived May23, 2005) (“Gilson”)
1040	Thomas Astle, <i>Recollections of Early Microplate Automation</i> , J. ASSOC. FOR LABORATORY AUTOMATION, 5:30-31 (2000) (“Astle-2000”)
1041	American National Standards Institute (ANSI) & Society for Laboratory Automation and Screening (SLAS), <i>for Microplates – Well Positions</i> , ANSI SLAS 4-2004 (R2012) (“ANSI/SLAS”).

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1042	Peter B. Lippa et al., <i>Immunosensors- principles and applications to clinical chemistry</i> , CLINICA CHIMICA ACTA, 314:1-26 (2001) (“Lippa”)
1043	Jay L. Bock, <i>The New Era of Automated Immunoassay</i> , AM. J. CLIN. PATHOL., 113:628-646 (2000) (“Bock”)
1044	B.H. Schneider et al., <i>Highly sensitive optical chip immunoassays in human serum</i> , BIOSENSORS & BIOELECTRONICS, 15:13-22 (2000) (“Schneider”)
1045	U.S. Patent No. 4,511,534 (“Bennett”)
1046	Andreas Brecht & Günter Gauglitz, <i>Recent developments in optical transducers for chemical or biochemical applications</i> , SENSORS AND ACTUATORS B, 38-39:1-7 (1997) (“Brecht”)
1047	Oliver Birkert & Günter Gauglitz, <i>Development of an assay for label-free high-throughput screening of thrombin inhibitors by use of reflectometric interference spectroscopy</i> , ANAL. BIOANAL. CHEM., 372:141-147 (2001) (“Birkert”)
1048	Fisher Scientific, Inc. <i>Fisher Catalog 2004/05</i> (2004) (“Fisher”)
1049	Bio-Tek Instruments, Inc., <i>Precision™ Microplate Pipetting System, Liquid Handling - Automated Microplate Pipetting Systems</i> , available at https://web.archive.org/web/20050405215350/http://www.biotek.com/products/product_print.php?pid=119 (archived April 5, 2005) (“Biotech Precision Webpage”)
1050	Excerpt of Bio-Tek Instruments, Inc., <i>Precision Microplate Pipetting System, Operator’s Manual</i> , Rev. D1 (Jan. 2005), available at https://assets.fishersci.com/TFS-Assets/CCG/EU/Biotek-Instruments/manuals/BTK011_EN%20Precision_Op_Man_Rev_D1.pdf (“Bio-Tek Precision Manual”)
1051	Seahorse Bioscience, <i>How Does XF Technology Work?</i> , available at https://web.archive.org/web/20041212090403/http://www.seahorsebioscience.com/xf_work.html (archived Dec. 12, 2004) (“Seahorse”)
1052	U.S. Patent Appl. Publ. No. 2005/0054028 A1 (“Teich”)

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1053	Thomas R. Clem et al., <i>Practical Colorimeter for Direct Measurement of Microplates in Enzyme Immunoassay Systems</i> , J. CLIN. MICROBIOL. 7(1):55-58 (1978) (“Clem”)
1054	Günther Viehhauser, <i>Simple Procedure for Large-Scale Assays for Chick Interferon</i> , APPLIED & ENVIRON. MICROBIOL., 33(3):740-743 (1977) (“Viehhauser”)
1055	Brian Law et al., <i>Chapter 7: Enzyme-Linked immunosorbent assay (ELISA) development and optimization</i> , in IMMUNOASSAY, A PRACTICAL GUIDE (1996) (“Law”)
1056	Bartels Legionella Urinary Antigen ELISA Test, 501(k) Premarket Notification (March 30, 1999), available at: https://www.accessdata.fda.gov/cdrh_docs/pdf/K991074.pdf (“Bartels”)
1057	Fiber Optics Association Reference Guide, <i>Connector Identifier</i> , available at https://www.thefoa.org/tech/connID.htm (“FOA Reference Guide”)
1058	MetroTek, <i>Bare Fiber Adapters & Kits</i> , available at https://web.archive.org/web/20010411055716/http://metrotek.com:80/mtekbfa.htm (archived April 11, 2001) (“MetroTek Website”)
1059	Metrotek, MetroTek Catalog, Issue No. 8 (2004) (“MetroTek Catalog”)

LISTING OF CHALLENGED CLAIMS

Claim 1	
[1Pre]	An apparatus for packaging an optical sensing assembly, the apparatus comprising
[1A]	at least one discrete optical sensing assembly
[1B]	comprising an optical fiber and a transparent optical element having end faces and first and second reflecting surfaces formed on the end faces, the first and second reflecting surfaces separated by at least 50 nm,
[1C]	wherein the first reflecting surface comprises a layer of analyte binding molecules;
[1D]	a substrate with a plurality of openings, each opening being configured for holding a discrete optical sensing assembly therein,
[1E]	the optical sensing assembly being positioned in the opening with a tip of the optical sensing assembly extending through the opening to be suspended from the substrate
[1F]	wherein the plurality of openings are arranged so the optical sensing assembly positioned therein avoids contacting another optical sensing assembly positioned therein, and
[1G]	wherein at least one opening holds an optical sensing assembly therein, with the tip of the optical sensing assembly extending through the opening.
Claim 2	
[2]	The apparatus of claim 1, further comprising a support member for supporting the substrate, the support member positioning the substrate so the tip of the optical sensing assembly suspended from the opening in the substrate contacts a solution in one of a plurality of wells in a container adjacent to the substrate.
Claim 3	
[3]	The apparatus of claim 2, wherein the container is a microtiter plate including 96 wells.

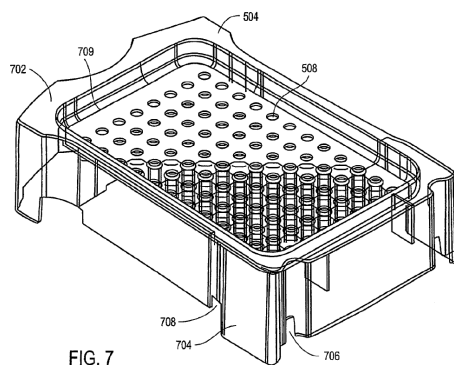
Claim 4	
[4]	The apparatus of claim 2, wherein the optical sensing assembly in the substrate is mapped to wells in a second container
Claim 5	
[5]	The apparatus of claim 2, wherein the solution is a pre-wet solution into which the optical sensing assembly is immersed.
Claim 6	
[6]	The apparatus of claim 2, wherein the solution is a protein solution into which the optical sensing assembly is immersed for immobilization of protein on the optical sensing assembly, or for measurement of interaction with another protein already immobilized on the optical sensing assembly.
Claim 7	
[7]	The apparatus of claim 2, wherein the substrate being configured for preparing the optical sensing assembly for assay further comprises the substrate being configured for pre-wet of the optical assembly before assay.
Claim 8	
[8]	The apparatus of claim 2, wherein the substrate being configured for preparing the optical sensing assembly for assay further comprises the substrate being configured protein immobilization of the optical assembly before assay.
Claim 9	
[9]	The apparatus of claim 1, wherein the optical sensing assembly further comprises a hub at an end of the assembly opposite the tip, the hub being designed for attachment to a device that moves the assembly from a first location to a second location.

Claim 10	
[10]	The apparatus of claim 1, wherein the openings include elongated barrels that allow the optical sensing assembly to be immersed in a solution in a container below the substrate without the tip of the optical sensing assembly contacting a tip of another optical sensing assembly in the substrate.
Claim 11	
[11]	The apparatus of claim 1, comprising a plurality of discrete optical sensing assemblies coated with different reagents arranged in the plurality of openings.
Claim 12	
[12]	The apparatus of claim 1, wherein the at least one optical sensing assembly comprises a hub at an end opposite the tip, and the optical sensing assembly is inserted into the opening with the hub of the assembly remaining on a first side of the substrate and the tip of the assembly being inserted through the opening to be suspended from a second side of the substrate.
Claim 13	
[13]	The apparatus of claim 1, further comprising a cover on a first side of the substrate to protect the optical sensing assembly.
Claim 14	
[14]	The apparatus of claim 13, wherein the cover comprises a recess comprising a downwardly extending center portion such that, when the cover is closed over the substrate, the cover retains the optical sensing assembly in the opening in position in the substrate.
Claim 15	
[15]	The apparatus of claim 14, further comprising a cover and a base, the cover and base being designed to lock together around the substrate forming an enclosure around the optical sensing assembly.

Claim 16	
[16]	The apparatus of claim 15, wherein the base of the apparatus is designed fit together with the cover of other apparatuses to be stackable with the other apparatuses for storage.
Claim 17	
[17]	The apparatus of claim 14, further comprising a support member for supporting the substrate, the support member positioning the substrate so the tip of the optical sensing assembly suspended from the opening in the substrate can contact a solution in one of a plurality of wells in a container adjacent to the substrate, wherein the container is a microtiter plate.
Claim 18	
[18]	The apparatus of claim 1, further comprising a base on a second side of the substrate to protect the tip of the optical sensing assembly.
Claim 19	
[19]	The apparatus of claim 18, wherein a container is positioned inside the base beneath the substrate, the container being positioned so the tip of the suspended optical sensing assembly contacts solution in one of the plurality of wells in the container.

I. Introduction

Petitioner requests *inter partes* review (“IPR”) of claims 1-19 of U.S. Patent No. 8,647,588 (“’588 patent”), currently assigned to Sartorius Bioanalytical Instruments, Inc. (“PO”). The patent and the challenged claims are generally directed to a “tip tray” apparatus for packaging sensor probes (referred to as “optical sensing assemblies”) to facilitate their use with standard microtiter plates.



EX1001, title, 1:19-22, claim 1, Fig. 7. During prosecution, the examiner repeatedly rejected the claims, reasoning that a tip tray for probes was neither novel nor nonobvious. *E.g.*, EX1004, [132]-[136]. But the examiner allowed the claims once PO amended them to recite features of probes used in “biolayer interferometry” or “reflectometric interference spectroscopy” (“BLI/RIFS”), including “an optical fiber and a transparent optical element having...first and second reflecting surfaces separated by at least 50 nm.” *Id.*, [218], [236], [239]-[240], [252].

By June 2005 and long before then, however, the de facto standard for many laboratory assays was to use microtiter plates, typically comprising 96 wells arranged in an 8x12 array. EX1002 (“Forrest”), ¶¶ 18-19; EX1013, 1:24-27;

EX1014, 3:31-48; EX1041.² To support this standard, skilled artisans designed and used complementary equipment such as 8- and 12-channel pipettes, tip trays that packaged pipette tips in an 8x12 array, and instruments for automating pipetting and assay procedures in this format. Forrest, ¶¶ 20-27; EX1039; EX1048-EX1051. They also similarly designed tip trays to package various sensor probes to facilitate their use with standard microtiter plates and instruments using such plates. Forrest, ¶¶ 28-30; EX1005, 9:49-54, 10:18-27, Figs. 5-6; EX1016, 3:14-22, Fig. 2. And contrary to the examiner's mistaken belief, BLI/RfS probes having the claimed features also were known and disclosed in the prior art, including Yang (EX1006) and WO854 (EX1008), among others, as PO's own expert admitted in a related International Trade Commission ("ITC") investigation, No. 337-TA-1344. EX1012.

As detailed in the grounds below, the challenged claims are unpatentable as obvious under 35 U.S.C. § 103(a), and trial should be instituted.³ This petition is supported by the Declaration of Laird Forrest, Ph.D., a Professor of Pharmaceutical Chemistry, Bioengineering, and Chemical and Petroleum Engineering at the University of Kansas. EX1002-EX1003.

² For purposes of this IPR only, Petitioner assumes without conceding that the challenged claims have a priority date of June 13, 2005.

³ Citations to 35 U.S.C. §§ 102 and 103 are to the pre-AIA versions applicable here.

II. Grounds for Standing (37 C.F.R. § 42.104(a))

Petitioner certifies that the '588 patent is available for IPR and that it is not barred or estopped from requesting IPR on the proposed grounds.

III. Identification of Challenge (37 C.F.R. § 42.104(b))

A. Prior Art

1. Miles

U.S. Patent No. 4,087,248 (“Miles”), entitled “Multiple Assay Machine and Method,” issued in 1978. EX1005. It is prior art under 35 U.S.C. § 102(b).

2. Yang

Yang is a printed publication entitled “Direct monitoring of antigen-antibody interactions by optical fiber bioprobe.” EX1006. It was published to participants of the Third International Conference on Photonics and Imaging in Biology on June 8-11, 2003, and republished on December 8, 2003 in Proceedings of SPIE. *Id.*, [2]. Yang is § 102(b) prior art. It was publicly accessible to conference participants in June 2003 and publicly accessible at the British Library by February 5, 2004. *Id.* (“5 February 2004” stamp); EX1031, [1], [5]-[6], [13] (explaining Yang was cataloged and publicly accessible at British Library by “5th February 2004”; attaching stamped pages); EX1032 (copyright registration noting June 8, 2003 publication date).

3. WO854

PCT Publication No. WO2005/047854A2 (“WO854”), entitled “Fiber-Optic Assay Apparatus Based on Phase-Shift Interferometry,” was published on May 26, 2005. EX1008. It is prior art under § 102(a). WO854 also incorporates by reference U.S. Patent No. 5,804,453 (“Chen”) (EX1009), which is part of WO854’s disclosure. WO854, ¶[0007]; *see Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 662-663 (Fed. Cir. 2023).⁴

Although WO854 names certain inventors in common with the ’588 patent, it is “by others” within the meaning of § 102(a) because it is by a different inventive entity. *See In re Land*, 368 F.2d 866, 876-78 (CCPA 1966); MPEP § 2136.04. Two of WO854’s named inventors (Duan Chen and Yushan Tan) are not listed on the ’588 patent, and three of the ’588 patent’s named inventors (Michael Rechnor, Sae Choo, and Scott Lockard) are not listed on WO854. Further, WO854 lists ForteBio, Inc. (a predecessor of PO) as the applicant and claims priority to two provisional applications filed on November 3, 2003 and March 31, 2004. Rechnor, Choo, and Lockard did not join ForteBio until after these priority applications were filed (EX1030) and thus could not have contributed to the disclosures in WO854.

⁴ Chen itself is § 102(b) prior art and is referenced as admitted prior art in the ’588 patent. EX1001, 1:49-52.

4. Rainin

U.S. Patent No. 4,676,377 (“Rainin”), entitled “Enclosed Pipette Tip Rack,” issued in 1987. EX1007. It is § 102(b) prior art.

B. Grounds for Challenge

Ground	Claims	Basis	References
1	1-13, 18-19	§ 103(a)	Miles (EX1005) and Yang (EX1006)
2	2-8, 13-19	§ 103(a)	Miles (EX1005), Yang (EX1006), and Rainin (EX1007)
3	1-13, 18-19	§ 103(a)	Miles (EX1005) and WO854 (EX1008) ⁵
4	2-8, 13-19	§ 103(a)	Miles (EX1005), WO854 (EX1008), and Rainin (EX1007)

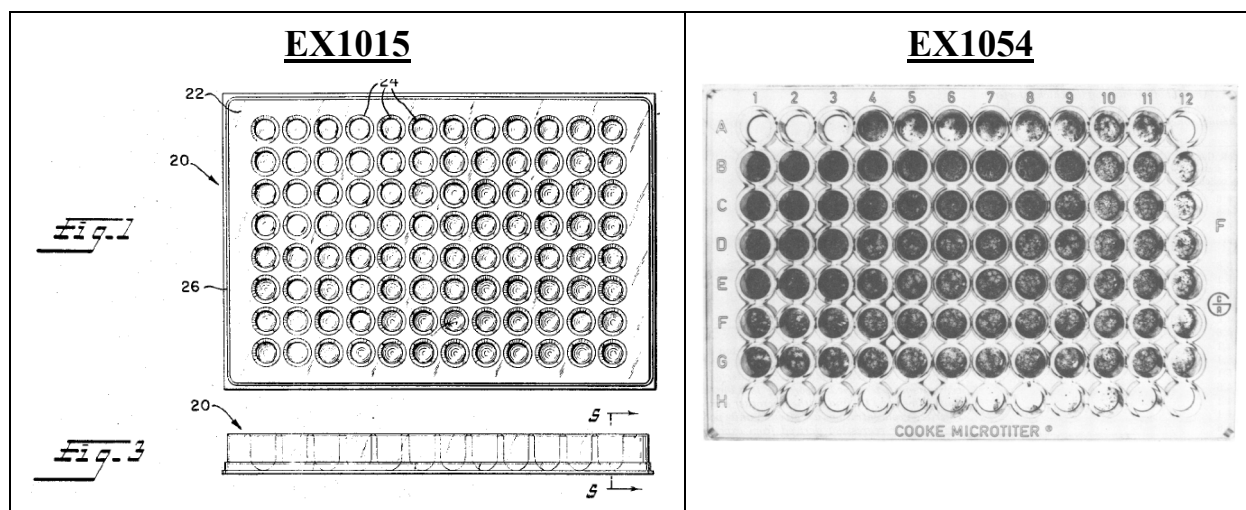
IV. Technical Background

A. Microtiter Plates

Microtiter plates (also called microplates or multi-well plates) were first introduced in the 1950s amid an influenza epidemic that prompted a need for more efficient and reliable diagnostic testing. Forrest, ¶18; EX1036, 1. Unlike the test tubes previously used in laboratory assays, microtiter plates comprise an array of wells that allow researchers to perform assays on a smaller scale (using smaller sample/reagent volumes) and also process multiple samples in parallel, thereby increasing speed and throughput. Forrest, ¶18; EX1036, 1; EX1013, 1:12-23. By the 1960s, 96-well microtiter plates were commercially available, including through

⁵ WO854 (EX1008) incorporates by reference Chen (EX1009).

Cooke Microtiter (now Dynex Technologies). Forrest, ¶18. Shown below is depiction of a 96-well microtiter plate from a 1967 patent to Cooke et al. (left) and a commercial example from Cooke Microtiter (right).



EX1015, 2:55-3:7, FIGS. 1, 3; EX1054, 741, Fig. 1; *see also* EX1053, 56, Fig. 1.

The benefits of microtiter plates led to their widespread adoption and use in laboratory assays. Forrest, ¶19. By the 1990s, the “de facto standard” for many assays was to use 96-well plates having an 8x12 array of wells, reinforced by efforts to standardize the dimensional elements of such plates across the industry.⁶ EX1013, 1:24-27; EX1040; Forrest, ¶19; *see* EX1041, 3; EX1014, 3:31-48.

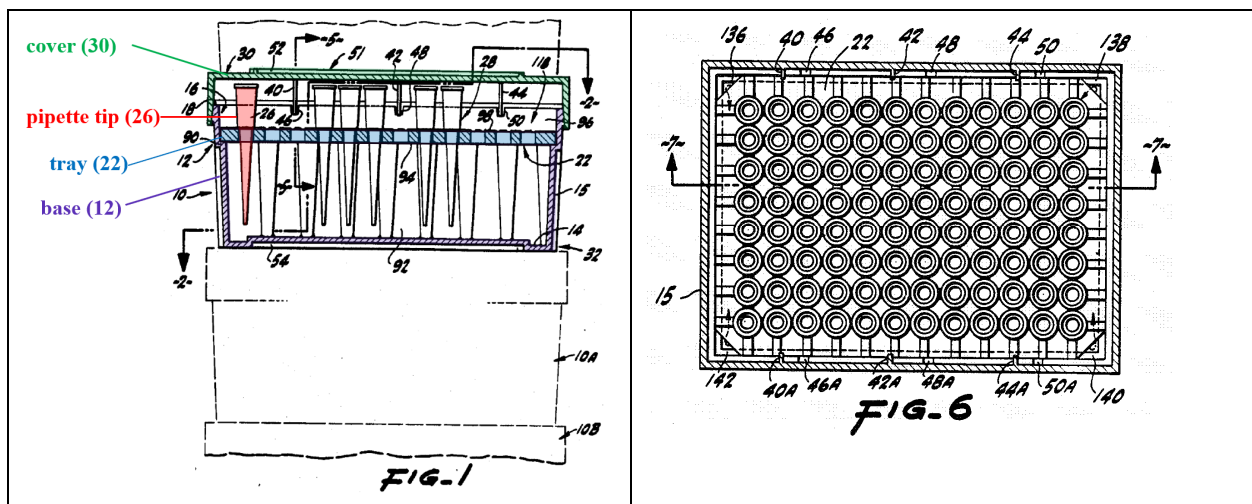
B. Complementary Lab Equipment Used with Microtiter Plates

As use of 96-well microtiter plates became routine, laboratory workflows also increasingly used tools that matched this standard. Forrest, ¶20. For example,

⁶ Standard 384- or 1536-well plates also were developed and routinely used for higher-throughput assays. EX1002, ¶19; EX1021, [8].

pipettes often comprised 8 or 12 channels to facilitate transferring liquids to and from the 8x12 array of wells in 96-well plates. EX1013, 1:27-29; Forrest, ¶ 21. These pipettes, in turn, used disposable tips that were packaged and sold in “tip trays” (also called “tip racks”). Forrest, ¶ 21. Such tip trays arranged pipette tips in an 8x12 array format that matched the layout of standard microtiter plates so that pipetting procedures could be performed efficiently while minimizing risk of error. Forrest, ¶ 21; Rainin, Fig. 6; EX1013, 1:24-36, Figs. 1-4.

As an example, Rainin (issued in 1987) describes a design for a pipette tip tray with a number of features that, by June 2005, were common in commercially-available pipette tip trays. Forrest, ¶ 22. Rainin’s tip tray holds 96 pipette tips in an 8x12 array (Fig. 6), and the tray itself is housed in a stackable container having a base and a cover (Fig. 1).



Rainin, 4:20-48, Figs. 1, 6; Forrest, ¶ 22.⁷ The tips each comprise a proximal

⁷ All annotations and emphases are added unless otherwise specified.

end/collar that is wider than the openings in the tip tray so that the tips are held in the tray. Rainin, 5:41-45, 5:50-52, Figs. 1, 3, 4; Forrest, ¶22. The proximal end/collar is also designed to attach the pipette tip to the distal end of a single- or multi-channel pipette. Forrest, ¶22; Rainin, 1:10-13, Figs. 1, 4. Thus, when needed, the tips can be loaded onto a pipette and used to transfer liquids to or from the wells of microtiter plates. Forrest, ¶22, Rainin, 1:10-13, Figs. 1, 4.

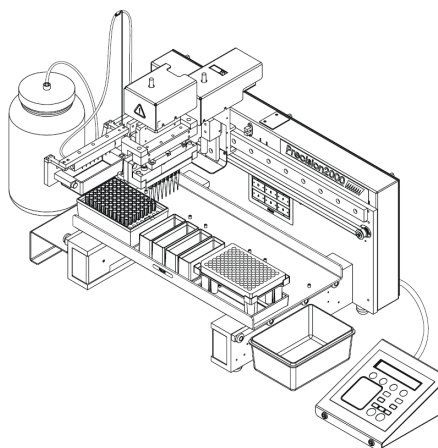
Shown below are examples of single- and multi-channel handheld pipettes and boxed tip trays that were commercially available before June 2005.





EX1039, [5], [7]-[9], [13]-[14]; EX1048, 1185-87; Forrest, ¶¶ 23-24.

Robotic systems that performed pipetting procedures on 96-well microtiter plates also were common in laboratories by June 2005. These systems, including Bio-Tek's Precision™ system (shown below), could engage and release pipette tips from a standard 8x12 tip tray, dip engaged tips in the wells of microtiter plates, and transfer liquids to and from the wells of such plates under computer control.



EX1049; EX1050, cover, 2-3, 16-23, 52-54; Forrest, ¶ 25.

Beyond pipetting instruments, various analytical instruments for use with microtiter plates were available by the early 2000s, including optical plate readers that measured fluorescence, absorbance, and luminescence, as well as assaying

instruments that analyzed samples by inserting probes into microtiter plate wells. EX1048 (Fisher), 1877-82; Forrest, ¶¶26-27. Shown below is an example of an assaying instrument from Seahorse Bioscience (now owned by Agilent Technologies) that included an array of pipettes 330 for transferring liquids to and from standard microtiter plates and an array of barriers 140, 320 comprising optical sensor probes that are inserted into the wells of such plates to perform measurements.

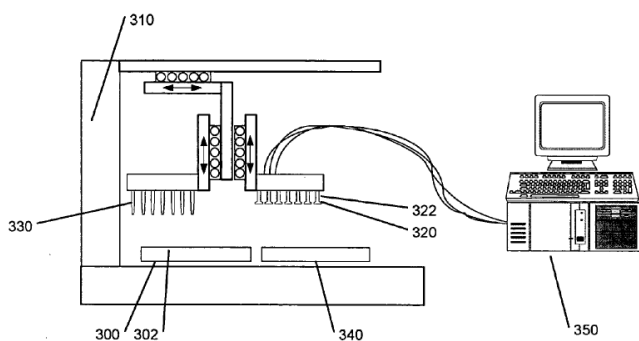


Fig. 3

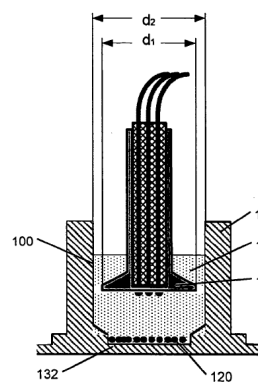


Fig. 1

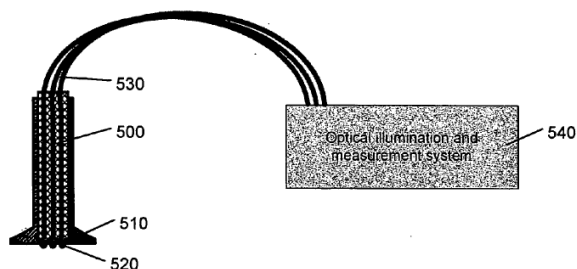


Fig. 5a

EX1052, ¶¶[0082]-[0090], [0100]-[0107], Figs. 1, 3, 5a; Forrest, ¶27.

C. Use of Tip Trays to Package Sensor Probes

By June 2005, it was recognized that sensor probes could be packaged in tip trays similar to pipette tip trays to facilitate their use with standard microtiter plates and assaying instruments. Forrest, ¶28.

For example, Miles describes sensor probes comprising pipette tips coated on their distal ends with an analyte-binding molecule such as an antibody or antigen (referred to as a “specifically bindable substance”) to bind an analyte in a sample. Miles, 2:19-34, 4:3-15, 5:53-68. Miles explains that the probes may be used in a variety of assays, including assays that provide optical readouts, for example, using “fluorescers” or “fluorogenic” reagents that provide a measurable fluorescence signal or “enzymes” that were commonly used to provide a measurable color change. *Id.*, 4:20-30, 11:63-66; Forrest, ¶ 29. As shown in Figures 5-6, Miles also describes a tip tray (blue) with an array of openings for packaging the probes (red) in a format similar to tip trays used with standard pipette tips.

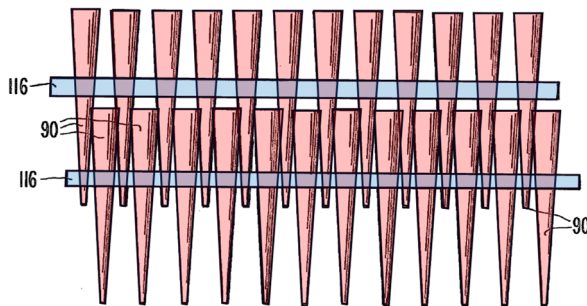


FIG. 5

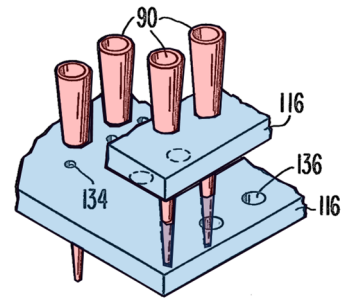
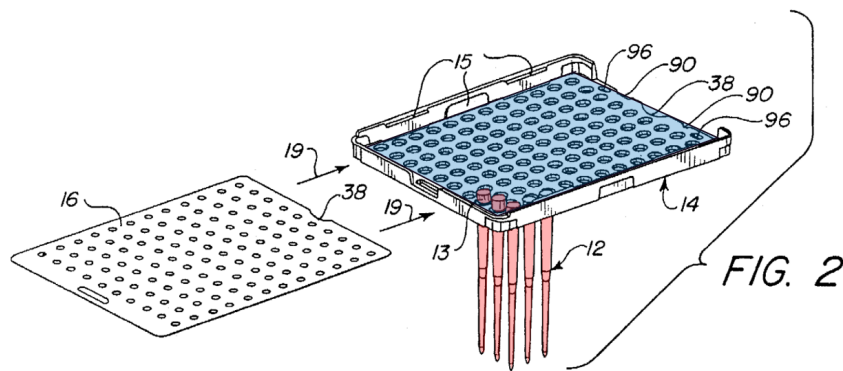


FIG. 6

Miles, 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5-6; Forrest, ¶ 29. Miles’ probes have a proximal end/collar that is designed to attach to an assay machine and that is wider than the tray openings, which allows the probes to be held in the tray. Miles, 2:45-51, 10:18-34, Figs. 2, 5-7; Forrest, ¶ 29.

As another example, U.S. Patent No. 5,674,047 (“Lapeus”) describes similar tip trays for packaging sensor probes. EX1016, abstract, 1:6-8, Fig. 2; Forrest, ¶ 30.

Lapeus explains that there was a trend among hospitals, clinics, and laboratories to use “automated analyzer systems” for assaying a variety of samples “such as blood, spinal fluid, urine, serum, plasma, and the like” and that these systems commonly used “disposable probe tips.” EX1016, 1:11-18. To facilitate using probes with such systems, Lapeus proposes to use a tip tray. *Id.*, 1:32-40, 2:60-3:9. As shown in Figure 2, Lapeus describes a tip tray (blue), similar to pipette tip trays, with an array of openings for packaging probes (red).



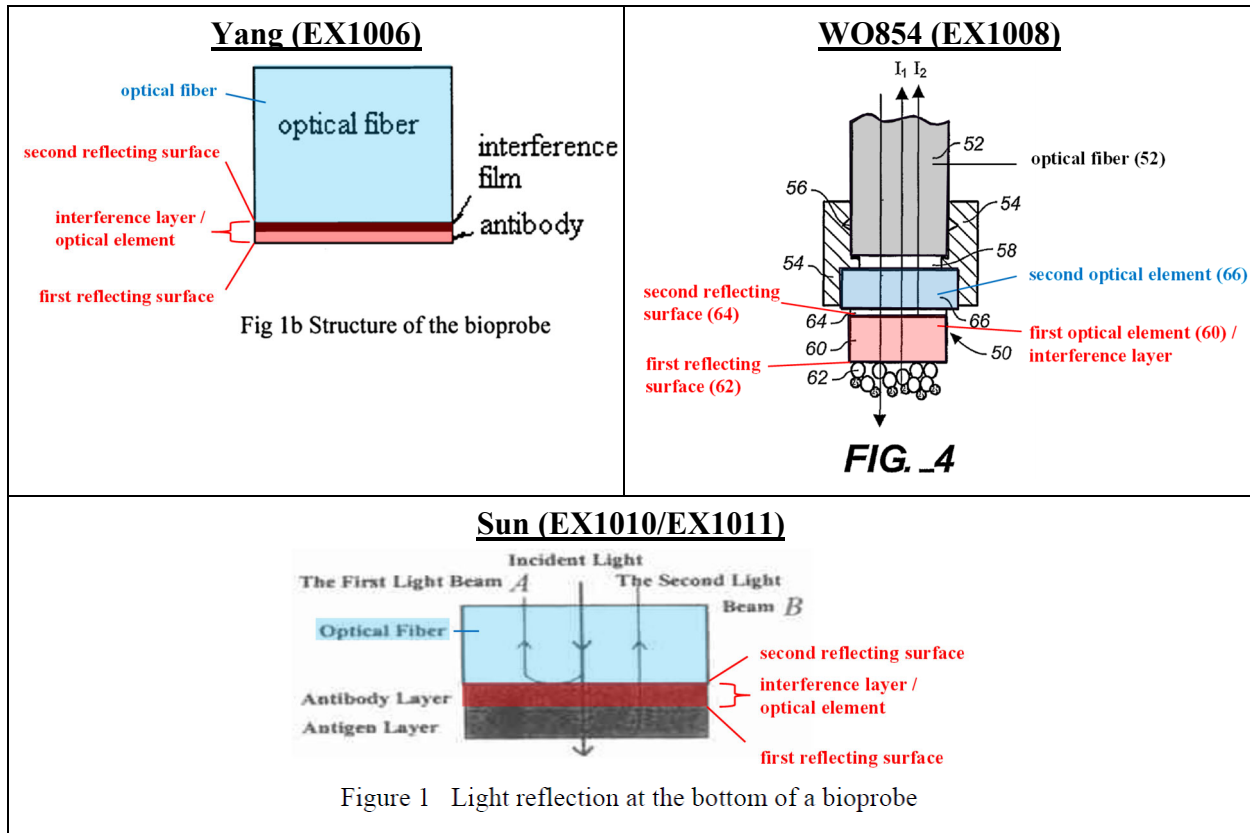
Id., 3:14-22, Fig. 2; Forrest, ¶ 30. Each probe has a proximal end/collar that attaches to an “automated analyzer system” and is wider than the openings so that the probe is held in the tray. EX1016, 2:60-3:4, 3:14-22.

D. BLI/RIfS Probes

Various sensor probes were used in laboratory assays as of June 2005, including probes for performing reflectometric interference spectroscopy or biolayer interferometry as it was later commercially known (referred to herein as “BLI/RIfS”). Forrest, ¶ 31. BLI/RIfS is a technique that uses a thin film on a substrate or on the end of an optical fiber to interact with an analyte in a sample. *Id.*,

¶32; Yang, 431-32. When a beam of white light passes through the film, it generates two partially-reflected beams of light at each interface of the film. Forrest, ¶32; Yang, 432, Fig. 1a. The reflected beams constructively and destructively interfere to create an interference pattern. Forrest, ¶32; Yang, 432, 434-35, Figs. 1b, 4. When analyte molecules bind to the film, its optical thickness increases, which results in changes in the interference pattern that can be detected using a spectrometer to infer analyte binding. Forrest, ¶32; Yang, 432, 434-45, Fig. 6.

By June 2005, probes for performing BLI/RIfS assays were known. Forrest, ¶¶32-33. As shown below, Yang, WO854, and Sun each describe a prototypical BLI/RIfS probe comprising a short segment of optical fiber coated with a transparent interference layer (optical element). Yang, 432, Fig. 1b; WO854, ¶¶[0051], [0077]-[0079], Fig. 4; EX1010/EX1011, 657, 659, Fig. 1. The interference layer has two reflecting surfaces at its proximal and distal endfaces that are separated by more than 50 nm, and the distal reflecting surface/endface is further coated with a layer of analyte-binding molecules (e.g., antibodies, antigens) for binding analyte in a sample. WO854, ¶¶[0051], [0078], Fig. 4; Yang, 432, 434, Fig. 1b; EX1010/EX1011, 657, 659 Fig. 1. During an assay, when analyte binds to the probe's distal end/tip, the resulting interference pattern varies (as registered on a spectrometer) and provides an indication of analyte binding. WO854, ¶[0079]; Yang, 434-35, Fig. 6; EX1010/EX1011, 659, Fig. 5.



Forrest, ¶ 33.

V. The '588 Patent

A. Overview

The '588 patent is directed to “[a]n apparatus for packaging an optical sensing assembly” or sensor probe. EX1001, claim 1, Although the patent discusses BLI/RIfS probes, it is not directed to BLI/RIfS probes generally and instead focuses on a “tip tray apparatus” that “package[es] and hold[s] discrete fiber optic sensors that allows for easy use of the sensor.” *Id.*, 1:18-22, 1:62-66; Forrest, ¶ 33.

The '588 patent proceeds to describe “a tip tray apparatus 500” similar to well-known pipette tip trays.

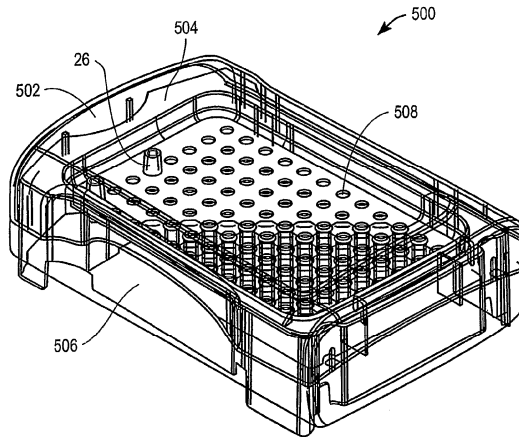


FIG. 5

EX1001, 11:22-24, Fig. 5. The tip tray apparatus 500 comprises “a substrate 504...that includes a number of openings 508 for containing one or more discrete optical assemblies 26 [probes].” *Id.*, 11:24-27. According to the patent, the openings 508 may be configured as “an array of 96 openings...in an 8x12 pattern, similar to the structure of the wells in a standard 96-well microtiter plate,” or as 384 or 1536 openings similar to a standard 384- or 1536-well microtiter plate. *Id.*, 11:57-63. The probes (optical assemblies 26) are “suspended in the openings 508 with the tip of the optical sensing assembly 26 extending away from the substrate 504,” such that “the tip of the optical sensing assembly 26 is suspended below the substrate 504 while the hub of the optical sensing assembly 26 rests above the substrate 504.” *Id.*, 11:43-50. This arrangement, the patent says, provides many of the known advantages of standard pipette tip trays, including “orienting and positioning the optical assemblies 26 (i.e., in a 96-well format) so that they can easily be picked up by a robotic instrument or a standard pipette and transferred to another location.” *Id.*, 12:63-13:1.

Moreover, similar to known storage boxes used to house pipette tip trays, the '588 patent states that the tip tray apparatus 500 may include “a base structure 506 and...cover 502” that can lock together to enclose the optical assemblies, “protect[ing] [them] during shipping, handling, and storage.” *Id.*, 12:4-15, 13:1-3. Figure 6 shows an exploded view of the tip tray apparatus 500.

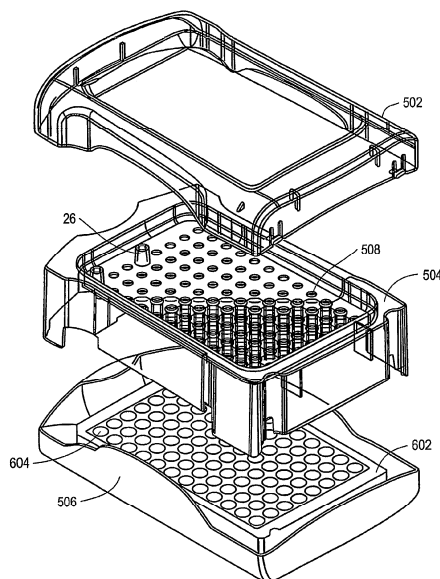


FIG. 6

Id., 12:23-24, Fig. 6.

The '588 patent further states that a container 602 may be provided below the substrate 504 for protein immobilization or pre-wetting of the optical assembly 26. *Id.*, 1:66-2:19, 7:11-16, 12:28-35, 13:6-7. The container 602 “can be a standard 96-well, 384-well, or 1536-well microtiter plate that includes an array of wells 604.” *Id.*, 12:30-32. The openings 508 in the substrate 504 “correspond generally with the wells 604 in container 602,” such that “[w]hen the tip of an optical sensing assembly 26 is placed into an opening 508 in the substrate 504, the fiber 42 portion...of the

optical sensing assembly 26...extend[s] below the substrate 504 and into the well 604 of container 602.” *Id.*, 12:38-47.

B. Prosecution History

During the ’588 patent’s prosecution, the examiner initially rejected all pending claims as anticipated or obvious based on U.S. Patent No. 6,838,051 (“Marquiss”) (EX1035). EX1004, [105]-[110], [132]-[136]. PO responded by arguing that “Marquiss fails to disclose or suggest an opening being configured for holding a discrete optical sensing assembly therein” and distinguished Marquiss as merely describing the holding of a “dispensing tip.” *Id.*, [151]-[152]. But the examiner maintained the rejections, explaining that “[a]pparatus claims must be structurally distinguishable from the prior art in terms of structure, not function.” *Id.*, [183]. According to the examiner, it was sufficient that Marquiss taught an apparatus “capable of performing the intended use as recited in the preamble, or elsewhere,” such as holding discrete optical sensing assemblies, because the claims did not “positively recite a discrete optical sensing assembly.” *Id.*

PO then amended independent claim 1 to recite “at least one discrete optical sensing assembly” comprising certain known elements of BLI/RIfS probes, including “an optical fiber and a transparent optical element having first and second reflecting surfaces” *Id.*, [218]. PO then argued that Marquiss does not teach these elements and instead “merely teaches passing fluid through dispensing elements.”

Id., [209]. Later, in response to further rejections, PO amended the claims to recite other known features of BLI/RIfS probes, including “the first and second reflecting surfaces [being] separated by at least 50 nm, wherein the first reflecting surface comprises a layer of analyte binding molecules,” and argued that these features too were not taught by the prior art. *Id.*, [236], [239]-[240].

Based on PO’s assertions, the examiner allowed the claims, under the mistaken impression that the prior art did not teach a BLI/RIfS probe having the claimed features. *Id.*, [252]. As detailed below, however, such BLI/RIfS probes were known and disclosed in Yang and WO854 (among other prior art).

VI. Level of Ordinary Skill in the Art

A person of ordinary skill in the art (“POSA”) relating to the ’588 patent would have had the equivalent of a master’s degree or doctorate in biology, chemistry, chemical engineering, bioengineering, biomedical engineering, physics, optics, or a related discipline, and 1-2 years of experience using or applying biosensors and conducting assays on standard microtiter plates. Forrest, ¶¶ 47-48.

VII. Claim Construction

Petitioner does not believe any terms need construction to resolve the issues presented here but reserves all rights to raise claim-construction arguments relevant to issues in other fora or to address the constructions of any terms PO raises here. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011).

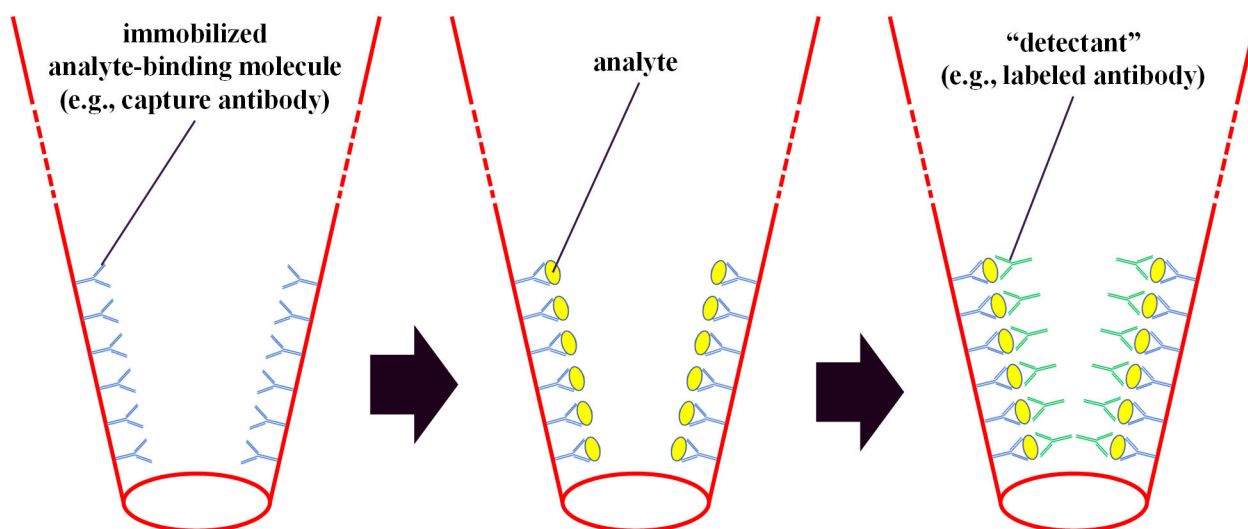
VIII. Ground 1: The Combination of Miles and Yang Renders Claims 1-13 and 18-19 Obvious Under 35 U.S.C. § 103(a)

A. Overview of the Combination

1. Miles

Miles discloses a system for conducting assays using coated pipette tips (sensor probes) that serve as optical sensing assemblies, as well as the packaging of these probes in tip trays and the use of the probes to assay multiple samples simultaneously on microtiter plates. Miles, 2:19-65; 12:23-26, Forrest, ¶¶ 52-53.

The distal ends/tips of Miles' probes are coated (insolubilized) with one member of a "specifically bindable substance[]" (SBS) pair, such as an antigen, antibody (or other analyte-binding molecule) for binding analyte in a sample. Miles, 2:19-34, 2:52-55, 4:3-15, 5:53-68. As Miles explains, assays may be carried out on the probe tips by introducing them samples and reagents in the wells of microtiter plates, specifically referencing 96-well plates from Cooke Microtiter. *Id.*, 2:55-3:4, 12:24-26, Fig. 2; *see also* EX1053, 56, Fig. 1; EX1054, 741, Fig. 1 (showing examples of Cooke Microtiter plates). Because the probes are also pipette tips, samples and reagents may be drawn into or ejected from the tips during an assay. Miles, 2:55-3:4. As illustrated in the demonstrative below, Miles further describes example assays in which coated probes are used to bind analyte (e.g., human growth hormone (HGH)) in samples and standards and then introduced to a labeled antibody or antigen (referred to as a "detectant") to detect the presence and amount of analyte.

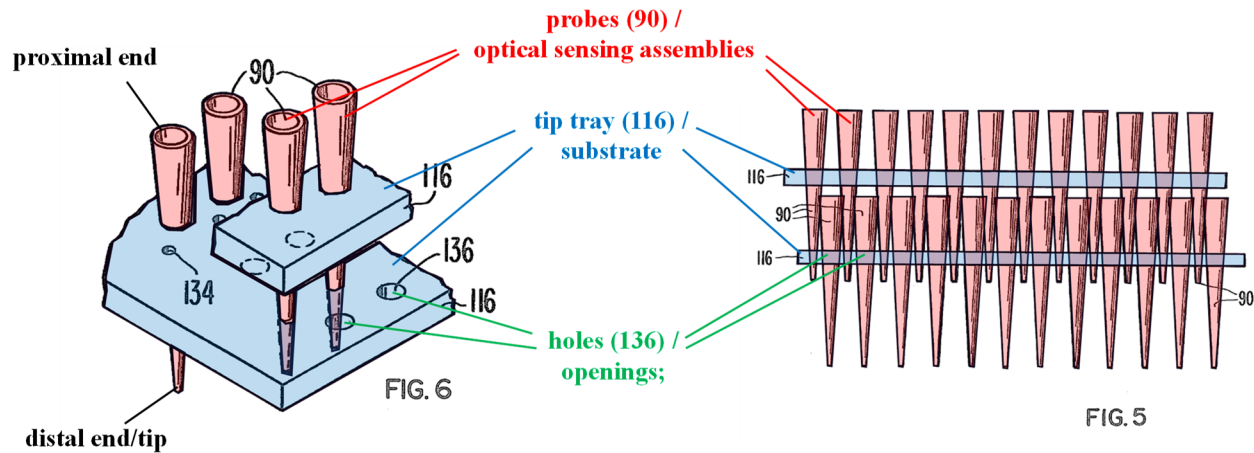


Forrest, ¶¶ 54-55; Miles, 11:26-44, 12:64-13:36.

Although Miles' examples use "radioactively labelled" (radiolabeled) antibodies or antigens as the "detectant" (e.g., *id.*, 6:49-7:31, 13:10-27), Miles explains that assays may be designed to provide optical readouts using "enzymes," "fluorescers," or "fluorogenic" reagents. *Id.*, 4:20-30, 11:63-66 (referencing "enzyme immunoassays"). Fluorescers or fluorogenic reagents are used in assays to provide a measurable optical fluorescence signal. Forrest, ¶ 56. Moreover, by 2005, enzyme-labeled reagents that generate a measurable optical color change were routinely used in assays, including enzyme-linked immunosorbent assays ("ELISAs"). *Id.*, ¶ 57; EX1020, 2415, 2417; EX1043, 633; EX1012, 106:20-108:15. Instruments for measuring such signals in standard microtiter plates also were commercially available. Forrest, ¶ 57; EX1048, 1878-81.

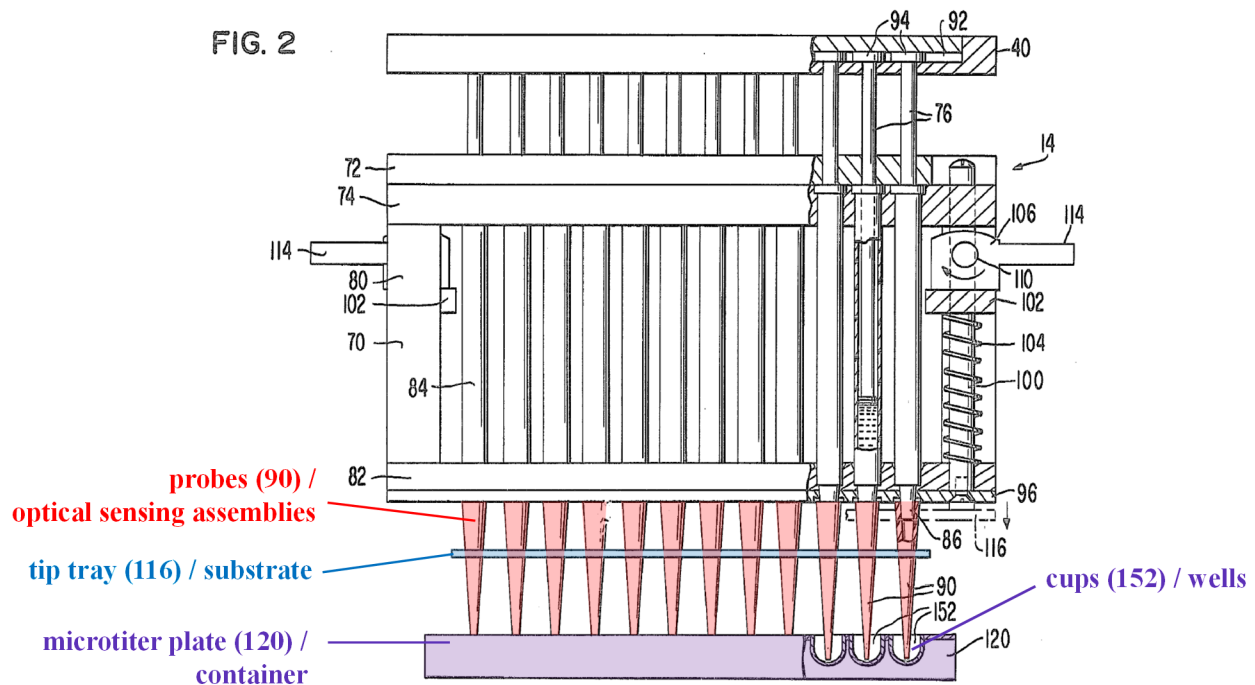
Miles additionally describes a tip tray 116 (referred to as a "tip rack") for packaging the probes. Miles, 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5-6. As

shown in Figures 5-6, the tip tray 116 (blue) comprises an array of openings 136 (green) in which the probes 90 (red) are held and through which the probes' distal ends/tips extend and are suspended.



Id.; Forrest, ¶ 58. The probes' proximal ends are designed to attach to a pipette or assay machine and are wider than the openings 134, 136, allowing the probes to be held in the tip tray 116. Miles, 2:45-51, 10:28-34, Figs. 5-7; Forrest, ¶ 58. Miles' tray also holds 8 probes along one dimension (Figure 4) and 12 probes along the other (Figures 2, 5), which facilitates using the probes with 8x12, 96-well microtiter plates and related equipment. Miles, 2:45-51, 3:41-47, 12:24-26, Figs. 2, 4-5; Forrest, ¶ 58.

Miles further discloses an assay machine 10 with a syringe battery 14 that uses the probes to perform multiple assays simultaneously on a microtiter plate. Miles, 8:49-52, Figs. 1-2. As shown in Figure 2, the syringe battery 14 may be loaded with probes 90, which are positioned in a tip tray 116 in a complimentary manner to the syringes 84 in the syringe battery.



Id., 9:49-54, 10:45-47, Fig. 2; Forrest, ¶59. The assay machine 10 includes a motorized lower platform 50 below the syringe battery 14 that may be raised or lowered as needed. Miles, 8:6-23, 11:26-44, Fig. 2. During an assay, a microtiter plate 120 (referred to as a “sample or reagent tray”) may be placed on the platform and raised into position so that the probes’ distal ends/tips are inserted into and “reach substantially to the bottom” of the wells 152 (referred to as “cups”) of the microtiter plate, ensuring that the tips contact the samples and reagents in the wells. *Id.*, 9:55-57, 11:26-44, Fig. 2.

2. Yang

Yang discloses a probe for conducting “[r]eflectometric interference spectroscopy (Rifs)” (later known as BLI), which Yang explains is “a successful label-free method” of detecting analytes in a sample. Yang, 431; Forrest, ¶61;

EX1012, 282:1-5.⁸ Figure 3 shows Yang's BLI/RIfS setup in which white light from a light source is transmitted through a Y-shaped optical fiber to the distal end of an "optical bioprobe" and then reflected back to a spectrometer where an interference pattern is registered.

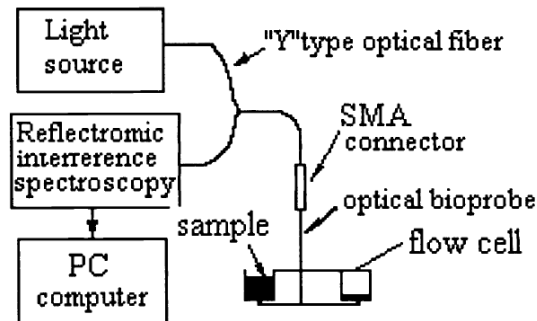
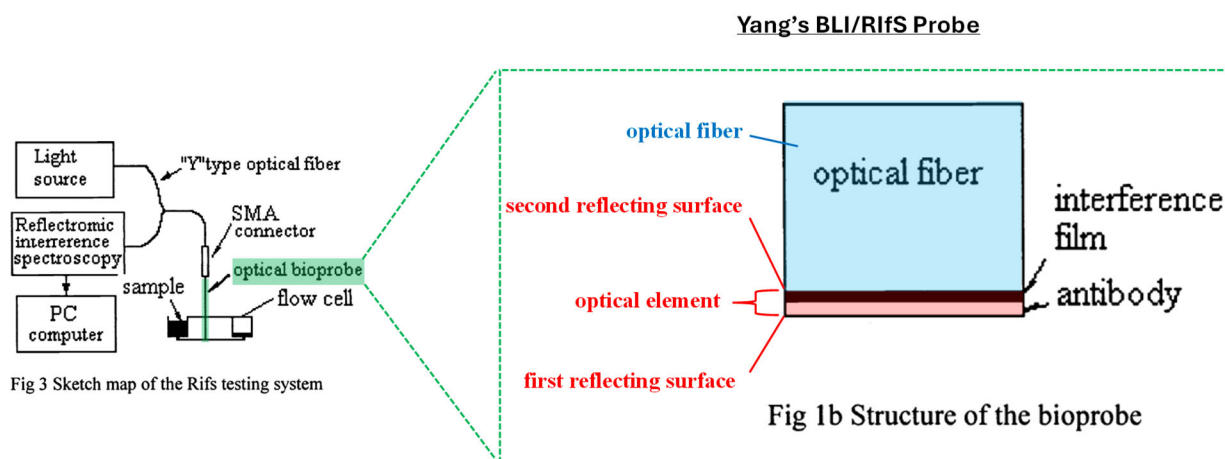


Fig 3 Sketch map of the RIfS testing system

Yang, 433, Fig. 3; Forrest, ¶61; EX1012, 283:9-284:6. The probe attaches to the Y-shaped optical fiber via "a standard SMA905 connector," a threaded coaxial connector commonly used to removably couple optical fibers. Yang, 433, Fig. 3; Forrest, ¶61 & n.101; EX1012, 285:4-12, 297:12-18. EX1057, 1, 8; EX1059, 7.

⁸ In ITC Investigation No. 337-TA-1344, where PO asserted patents directed to similar subject matter, PO's expert, Dr. Michael Sailor, provided deposition testimony confirming the disclosures of the prior art discussed here. EX1012; *see Godberson-Smith Constr. Co. v. Guntert Simmerman Const. Div., Inc.*, IPR2024-00835, Paper 9, at 29 (PTAB Nov. 14, 2024) (relying on "deposition testimony of Patent Owner's expert in related litigation").

As shown in Figure 1b, Yang's probe (green) comprises a segment of optical fiber (blue) that is coated with a "transparent interference layer" or film (red).



Yang, 432, Figs. 1b, 3; Forrest, ¶ 62; EX1012, 285:13-286:5. Yang explains that the interference layer comprises a tantalum-pentoxide (Ta_2O_5) layer having a thickness of about "10~20nm" and a "transparent" layer of "special material" having a thickness of about "550~600nm." Yang, 432, Fig. 1b; EX1012, 288:5-289:1. Yang also explains that the special material serves as a "transducer" for "biomolecular interaction analysis" and is coated with a layer of antibodies (Fig. 1b) to bind analyte present in a sample. Yang, 432, 434, Fig. 1b; EX1012, 285:18-286:5, 288:1-4.⁹

⁹ Yang does not specify (and the challenged claims do not require) a particular material for the "special material." Suitable materials were known, including polystyrene, a transparent material used in BLI/RIfS sensors to provide a hydrophobic surface for immobilizing antibodies. Forrest, ¶ 63; EX1018, 1489, Fig.

Moreover, as shown in Figure 1a, Yang's interference layer (optical element) has two reflecting surfaces on its proximal and distal endfaces, respectively, that produce two interfering reflected light beams (I_1 and I_2).

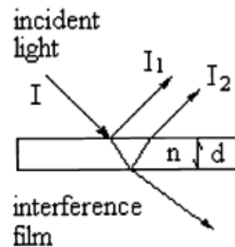


Fig 1a Schematic of the light path in the bioprobe

Yang, 432, Fig. 1a; EX1012, 286:6-287:9. Given the interference layer's thickness, the reflecting surfaces are separated by at least 50 nm. Yang, 432, Fig. 1a; Forrest, ¶64; EX1012, 289:2-24. During an assay, when analyte binds to the probe's distal end/tip, the interference layer's optical thickness increases and the resulting interference pattern varies, allowing "binding events [to be] observed...real time." Yang, 432-33, 434, Fig. 6 (shift in interference); Forrest, ¶65; EX1012, 287:10-25.

1(A); EX1019, 1456, 1462; EX1012, 316:20-25, 317:13-17. As PO's expert agreed, POSAs "would have been able to [implement] Yang's RIfS setup and identify some material that they could put in for the special material to make the RIfS setup work." EX1012, 296:18-297:9; *see also id.*, 306:10-309:15, 315:25-316:17 (discussing Sun's BLI/RIfS probe (EX1011) and explaining POSAs could identify suitable material for interference layer and would have tried polystyrene).

Further, Yang suggests combining multiple BLI/RfS probes to conduct multiple assays in “parallel” (simultaneously) for higher throughput. Yang, 431, 436; Forrest, ¶ 66.

3. Motivation to Combine Miles and Yang

POSAs would have been motivated to package BLI/RfS probes such as those described in Yang (or alternatively WO854, Grounds 3-4) in a tip tray such as that described in Miles, recognizing it would provide many of the same advantages, including facilitating using BLI/RfS probes with microtiter plates and related equipment for conducting and automating assays.

“When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one.” *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007). Similarly, “if a technique has been used to improve one device, and a [POSA] would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.” *Id.* Here, as discussed in § IV.A, by June 2005, the “de facto standard” for many assays was to use 96-well microtiter plates. Forrest, ¶¶ 18-19, 69; EX1013, 1:24-27; EX1014, 3:31-48. POSAs were motivated to perform assays on microtiter plates because that allowed assays to be run using smaller sample/reagent volumes and also allowed multiple samples to be processed simultaneously, thereby increasing speed and throughput. Forrest,

¶69; EX1013, 1:24-27; EX1014, 3:31-48; EX1026, 1.

As use of microtiter plates became widespread and routine, POSAs were motivated to design related equipment to be used with such plates. Forrest, ¶70. Pipette tips were routinely packaged in 8x12 tip trays corresponding to the 8x12 array of wells in standard 96-well microtiter plates. Forrest, ¶¶21-24, 70; Rainin, Fig. 6; EX1013, 1:34-36, Figs. 1-4; EX1039, [13]-[16]; EX1048, 1185-87. This allowed for efficient transfer of liquids to and from standard microtiter plates, while minimizing risk of error, and also facilitated using pipette tips with handheld and robotic pipettes that likewise were designed to be used with such plates. Forrest, ¶¶21, 23-25, 70; EX1013, 1:24-36; EX1014, 3:31-48; EX1049; EX1050, 16-23, 52-54. Similarly, plate readers and assaying instruments were designed to analyze samples in standard microtiter plates. Forrest, ¶¶26-27, 70; EX1048, 1877-81; EX1051; EX1052, ¶¶[0082]-[0090], [0100]-[0107], Figs. 1, 3, 5a. These design incentives and market forces would have motivated POSAs to package BLI/RIfS probes in tip trays to facilitate their use with standard microtiter plates and related equipment. Forrest, ¶71. And given their experience using pipette tip trays, POSAs would have had a reasonable expectation of success. *Id.*

Indeed, POSAs succeeded in using tip trays to package various sensor probes to facilitate their use with not only microtiter plates but also robotic systems and assaying instruments that used such plates. Forrest, ¶72. As discussed in § VIII.A.1,

Miles describes a tip tray for packaging sensor probes and provides a motivation to do so, explaining that it facilitates loading the probes onto an assay machine by positioning the probes in a complementary manner and further facilitates using the probes with a 96-well microtiter plate having complementary wells. Miles, 2:45-51, 8:26-28, 9:49-54, 10:18-20, 10:45-47, 12:23-26, Figs. 5-7; Forrest, ¶ 72.

Similarly, as discussed in § IV.C, Lapeus describes using tip trays to package sensor probes for assaying a wide range of samples “such as blood, spinal fluid, urine, serum, plasma, and the like.” EX1016, 1:11-18, 3:14-22, Fig. 2. Lapeus also shows that POSAs were motivated to use tip trays to package probes, explaining that there was a trend among hospitals, clinics, and laboratories to use “automated analyzer systems” to analyze samples and that tip trays facilitated using probes with such systems. *Id.*, 1:11-18, 1:32-40, 2:60-3:9; Forrest, ¶ 73.

Chen and WO854 provide further evidence of motivation. Forrest, ¶¶ 74-76. As discussed further in § X.A.2, Chen describes a BLI/RIfS probe that is removably coupled (via a clothespin-type connector) to an optical fiber of an assay machine. EX1009, 10:45-57, 12:24-26, Fig. 8; Forrest ¶ 74; EX1058; EX1059, 7; EX1012, 327:5-329:7, 333:15-339:7. And Chen explains that multiple, discrete probes (1-n) may be combined in a multiplexed format to perform multiple assays simultaneously and to detect different analytes in a sample.

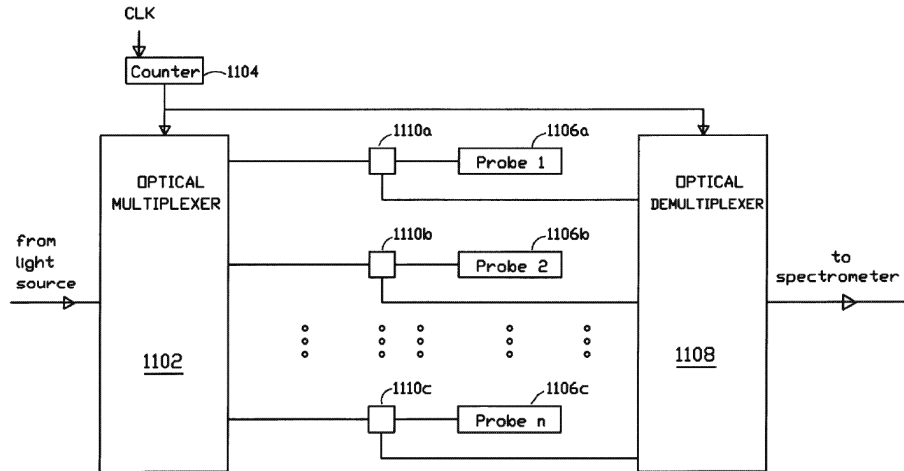


Figure 11

EX1009, 6:28, 8:17-29, 12:54-13:12, Fig. 11. PO's expert concurred that Chen describes multiplexing BLI/RfS probes and that this allows analyzing samples "for either multiple components or the same component multiple times," increasing "speed" and "throughput." EX1012, 339:17-341:2.

WO854 similarly discloses a BLI/RfS probe (optical assembly) that is removably coupled to an optical fiber of an assay machine and proposes to combine multiple such probes in a "two dimensional array" format, incorporating by reference Chen's earlier disclosure of multiplexed probes. WO854, ¶¶ [0007], [0077]-[0079], Fig. 4, claims 22-23, 26-27; *see also id.*, ¶¶ [0009], [0017], [0045], [0080]-[0081], Fig. 5.¹⁰ Consistent with Chen and WO854, Yang also proposes

¹⁰ Other prior art similarly described multiplexing BLI/RfS sensors. Forrest, ¶ 75; EX1012, 341:25-344:20, 345:7-347:13 (PO's expert discussing EX1046-EX1047 and agreeing that need for higher-throughput testing motivated multiplexing).

combining BLI/RIfS probes to perform multiple assays in “parallel” (simultaneously). Yang, 431, 436. These suggestions to combine multiple BLI/RIfS probes to perform simultaneous assays, coupled with the prevailing standard of performing simultaneous assays on microtiter plates, would have motivated POSAs to use a tip tray to package BLI/RIfS probes to facilitate their use with standard microtiter plates. Forrest, ¶ 76.

Further, POSAs would have had a reasonable expectation of success in packaging BLI/RIfS probes in tip trays given the similarities between such probes and those described in Miles that had already been used with tip trays. *Id.*, ¶ 77. Both types of probes comprise a layer of analyte-binding molecules (e.g., antibodies, antigen) coated on the probe’s distal end/tip to bind analyte present in a sample. *Id.* And in both, the assay is performed on the probe’s distal end/tip, which is contacted with samples and reagents. *Id.* Thus, POSAs seeking to conduct assays in parallel using BLI/RIfS probes would have drawn from Mile’s use of a tip tray of similar probes for conducting parallel assays on microtiter plates. *Id.*

To be sure, POSAs need not have “physically combined” or “bodily incorporated” the precise design of Miles’ probes into a BLI/RIfS probe. *Allied Erecting & Dismantling Co. v. Genesis Attachments, LLC*, 825 F.3d 1373, 1381 (Fed. Cir. 2016) (collecting cases). Rather, POSAs would have recognized that Miles’ teachings may be applied to BLI/RIfS probes by providing some structure on

the proximal ends of the probes that allows them to attach to a corresponding assaying apparatus and that is further appropriately sized to prevent the probes from falling through the tray openings. Forrest, ¶ 78; Miles, 2:45-51, 10:28-34, Figs. 5-7; EX1016, 3:14-22 (teaching similar features in probes used with tip tray).

B. Claim 1

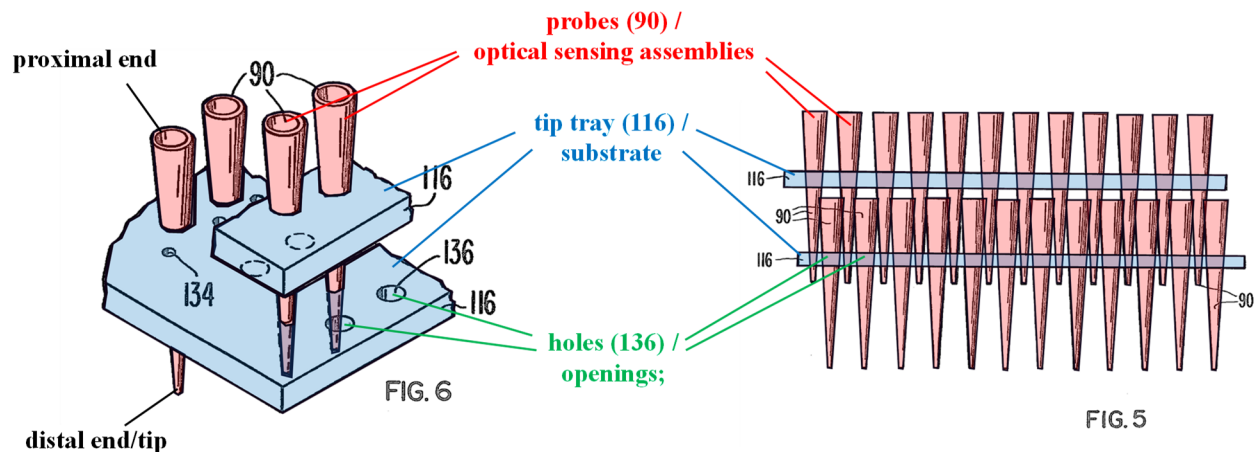
1. [1Pre]: “An apparatus for packaging an optical sensing assembly the apparatus comprising”

To the extent the preamble [1P] is limiting, Miles, in combination with Yang, teaches “[a]n apparatus for packaging an optical sensing assembly.” Forrest, ¶¶ 80-85. As discussed in § VIII.A.1 (Miles Overview), Miles discloses pipette tips (sensor probes) that serve as optical sensing assemblies. Miles, abstract, 2:19-34, 2:45-3:18. The probes’ distal ends/tips are coated (insolubilized) with an analyte-binding molecule such as an antigen or antibody. *Id.*, 2:19-34, 2:52-55, 4:1-19, 5:53-68. During an assay, the probes are contacted with samples and reagents contained in the wells of microtiter plates, such as 96-well plates. *Id.*, 2:55-3:4, 12:24-26, Fig. 2.

Miles describes example assays in which coated probes are used to bind analyte (e.g., human growth hormone (HGH)) in sample solutions and then introduced to labeled antibody or antigen reagents for detecting the presence and amount of analyte. *Id.*, 12:64-13:36. Although the examples use radiolabeled reagents, Miles explains that the probes may be configured to provide an optical readout using “enzymes,” “fluorescers,” or “fluorogenic” reagents. *Id.*, 4:20-30,

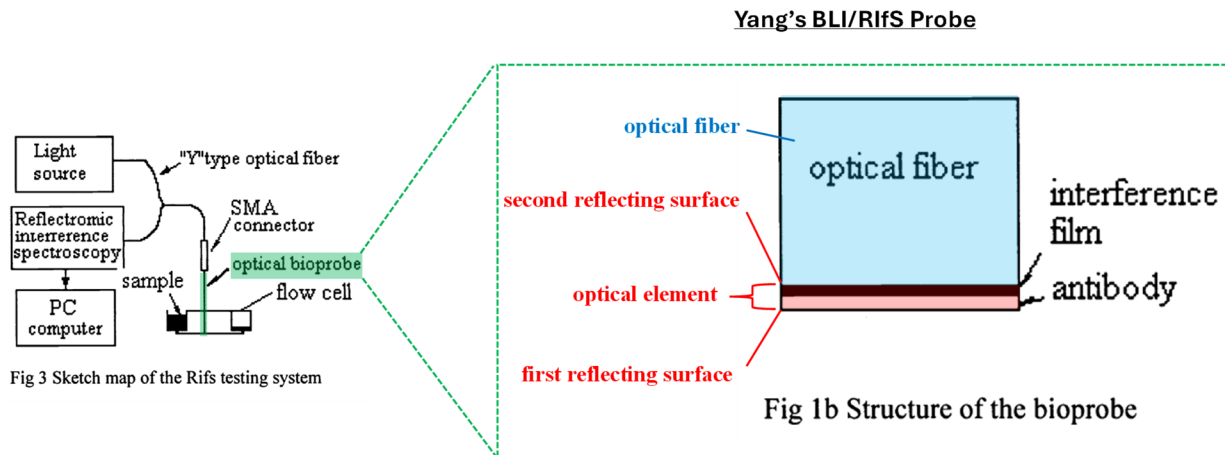
11:63-66. Assays using fluorescers or fluorogenic reagents provide a measurable optical fluorescence signal. Forrest, ¶82. Moreover, by 2005, enzyme-labeled reagents that generate a measurable optical color change were a known alternative to radiolabeled reagents and were routinely used in assays such as ELISAs. *Id.*; EX1020, 2415, 2417; EX1012, 106:20-108:15.

Miles also discloses a tip tray apparatus for packaging the probes. For example, as shown in Figures 5-6, Miles describes a tip tray 116 (blue) comprising an array of openings 136 (green) in which the probes 90 (red) are held and through which the probes' distal ends/tips extend and are suspended.



Miles, 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5-6; Forrest, ¶83.

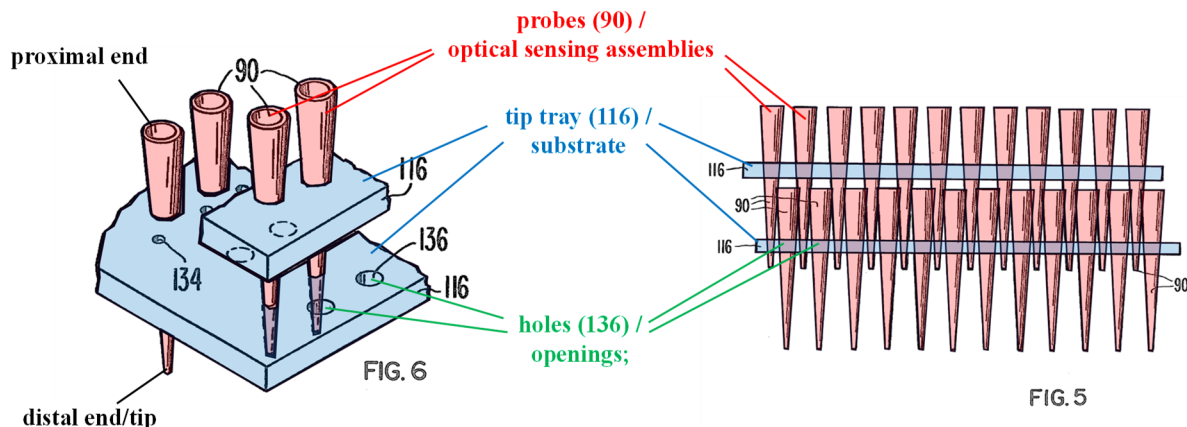
Further, as discussed in § VIII.A.2 (Yang Overview) and below in §§ VIII.B.2-VIII.B.4 ([1A]-[1C]), Yang describes a BLI/RfS probe that serves as an optical sensing assembly, as shown in Figures 1b and 3.



Yang, 432-33, Figs. 1b, 3; Forrest, ¶84; EX1012, 281:12-282:5, 285:13-287:25 (PO's expert concurring that Yang discloses BLI/RIfS probe). As discussed in § VIII.A.3, POSAs would have been motivated to use a tip tray such as that in Miles to package BLI/RIfS probes such as those in Yang.

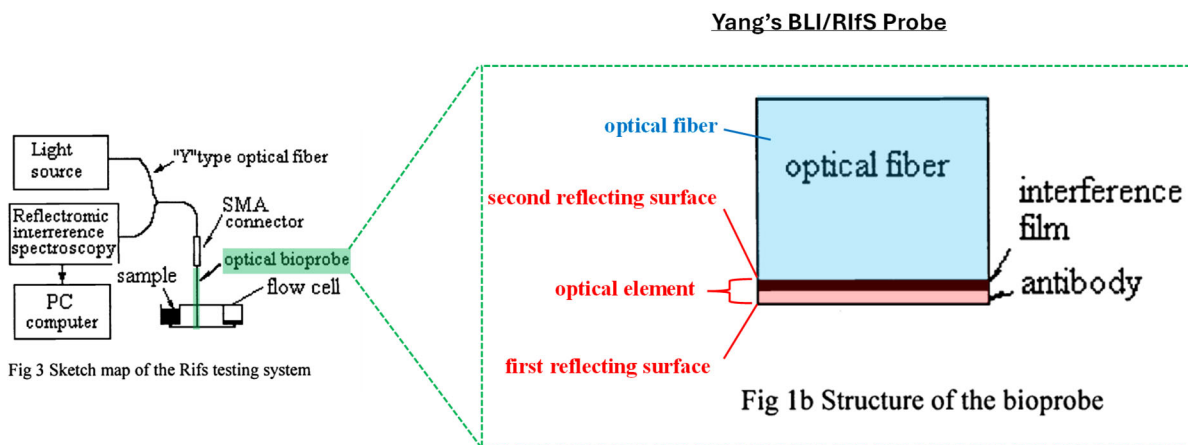
2. [1A]: “at least one discrete optical sensing assembly”

Miles, in combination with Yang, teaches a tip tray apparatus comprising “at least one discrete optical sensing assembly.” Forrest, ¶¶86-88. For example, as discussed in §§ VIII.A.1 (Miles Overview) and VIII.B.1 ([1Pre]), and as shown in Figure 5-6, Miles discloses a tip tray 166 (blue) for packaging discrete probes 90 (red) that serve as optical sensing assemblies.



Forrest, ¶87; Miles, 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5-6; *see also id.*, 4:20-30, 11:63-66 (describing using probes with enzymes or fluorescent/fluorogenic reagents that provide optical readouts).

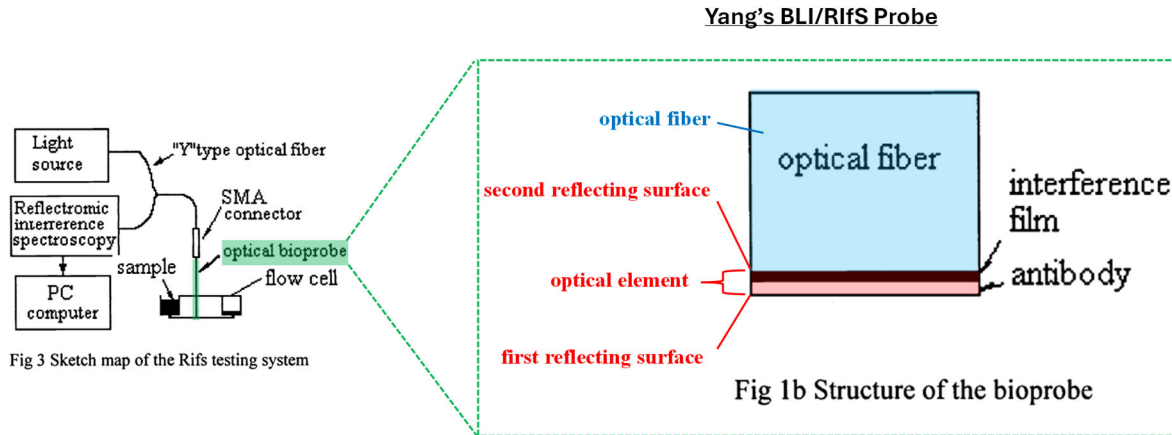
Further, as discussed in §§ VIII.A.2 (Yang Overview) and VIII.B.1 ([1Pre]), and as shown in Figures 1b and 3, Yang describes a BLI/RIfS probe that serves as an optical sensing assembly.



Yang, 432-33, Figs. 1b, 3; Forrest, ¶88; EX1012, 281:12-282:5, 285:13-287:25 (PO's expert concurring that Yang discloses BLI/RIfS probe).

3. [1B]: “comprising an optical fiber and a transparent optical element having end faces and first and second reflecting surfaces formed on the end faces, the first and second reflecting surfaces separated by at least 50 nm”

Yang discloses a BLI/RIfS probe (optical sensing assembly, green) comprising a segment of optical fiber (blue) coated with a “transparent interference layer” or film (optical element, red).



Yang, 432-33, Figs. 1b, 3; Forrest, ¶¶ 89-90. PO's expert concurred that Yang's probe includes these features:

Q. Now, if you look at figure 1B of Yang..., Yang's bioprobe includes an optical fiber portion to it, correct?

A. That's correct.

Q. The optical fiber portion of the probe is co[ated] on its distal end with an interference layer or film and an antibody layer, correct?

A. Yeah, that's what's depicted in figure 1B, yes.

Q. For Yang's RIfS setup to work, Doctor, the interference layer would have to be able to transmit light to and from the distal end of the probe, correct?

A. It has to transmit some of the light, yes.

EX1012, 285:13-21, 291:7-10.

Moreover, as shown in Figure 1a (below) and in Figure 1b (annotated above), Yang's interference layer comprises first and second reflecting surfaces on its distal

and proximal endfaces, respectively, and given the interference layer's thickness, the reflecting surfaces are separated by at least 50 nm.

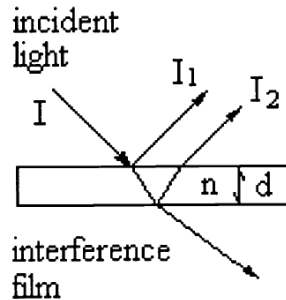


Fig 1a Schematic of the light path in the bioprobe

Yang, 432, Fig. 1a; *see also id.*, 433 (incident “light is partially reflected on the interfaces [of] the transparent interference layer”); Forrest, ¶¶91-92. Again, PO’s expert concurred:

Q. Now, if you look over to figure 1A, Yang’s interference layer, you would agree has two reflecting surfaces?

A. Yeah, what’s depicted in figure 1A [which] is meant to indicate the schematic of the light path. And as you see, as I described earlier, the things depicted I_1 and I_2 are the reflections from those two interfaces.

Q. And as the two reflecting surfaces that we talked about in Yang, the two sides of the interference layer, you’d agree that those are separated by at least 50 nanometers; is that correct?

A. Yes, the two reflecting surfaces are separated by at least 50 nanometers based on the dimensions that are given.

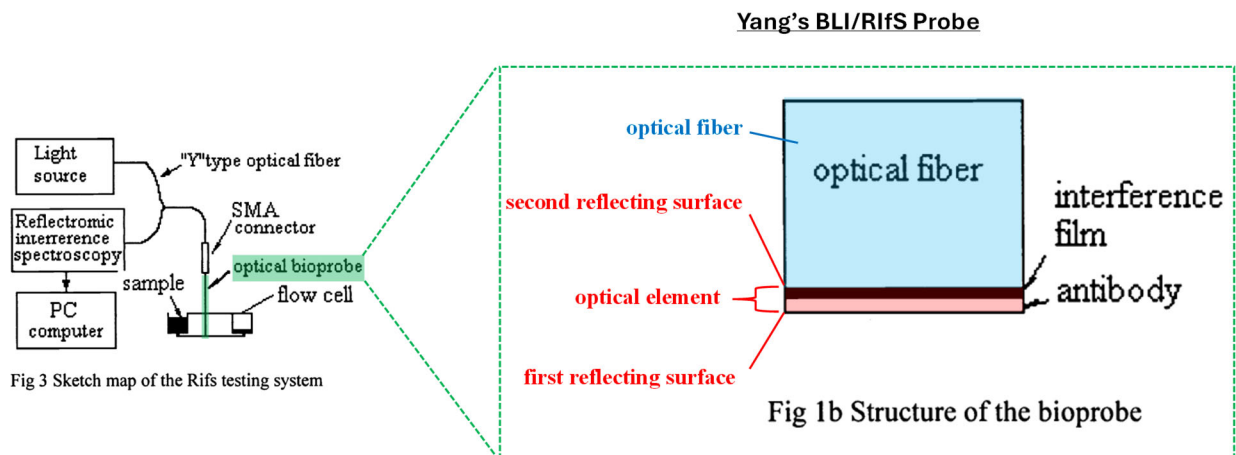
Q. ... [T]he two reflecting surfaces in Yang's bioprobe are separated by about 560 to 620 nanometers; is that right?

A. Yeah.

EX1012, 286:6-12, 289:2-24.

4. [1C]: "wherein the first reflecting surface comprises a layer of analyte binding molecules"

As discussed in § VIII.B.3 ([1B]), Yang's interference layer (optical element) comprises first and second reflecting surfaces on its distal and proximal endfaces, respectively. Yang, 432, Fig. 1a; EX1012, 286:6-287:4. Moreover, as shown in Figure 1b, the first reflecting surface comprises a layer of antibodies (analyte-binding molecules) for binding analyte in a sample.



Yang, 432, 434 (describing coating of multiple antibody layers), Figs. 1b, 3; Forrest, ¶¶ 94-95. PO's expert concurred:

Q. The optical fiber portion of the probe is co[ated] on its distal end with an interference layer or film and an antibody layer, correct?

A. Yeah, that's what's depicted in figure 1B, yes.

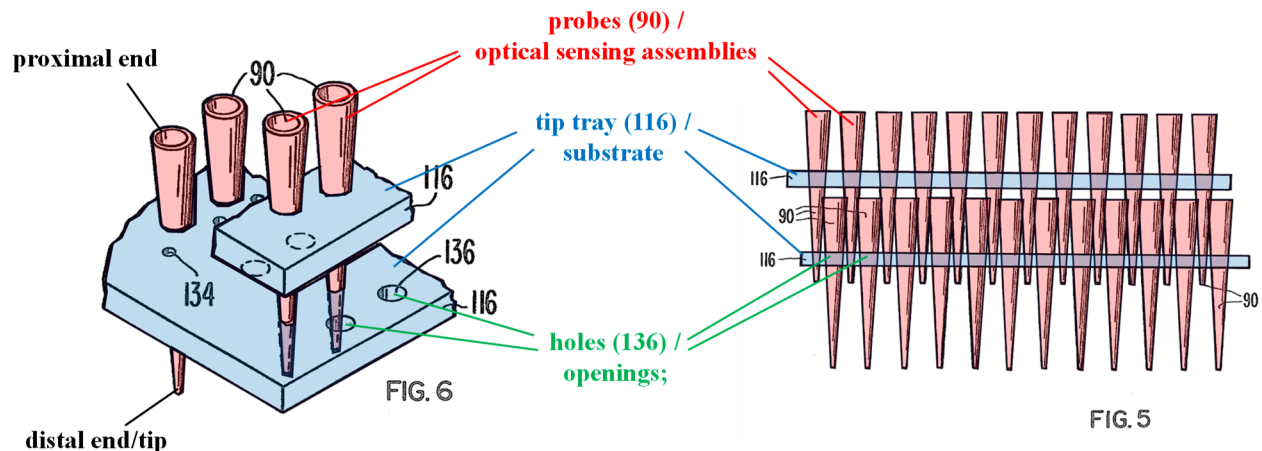
Q. And to your understanding, the purpose of the antibody layer in Yang's RIfS setup is to bind an analyte in a sample; is that correct?

A. Yes, that's correct.

EX1012, 285:18-286:5.

5. [1D]: “a substrate with a plurality of openings, each opening being configured for holding a discrete optical sensing assembly therein”

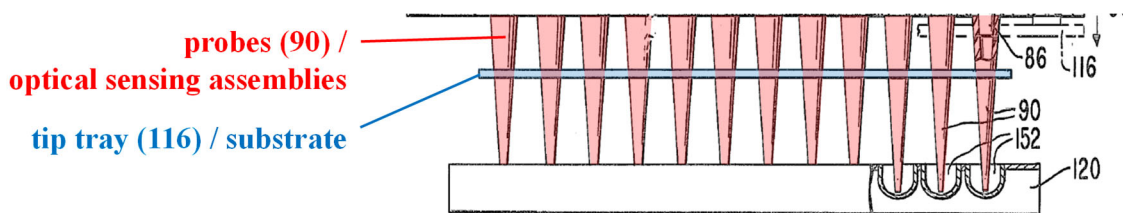
As discussed in §§ VIII.A.1 (Miles Overview) and VIII.B.1 ([1Pre]), and as shown in Figure 5-6, Miles describes a substrate in the form of a tip tray 116 (blue) having a plurality of openings 136 (green) that are configured to hold a plurality discrete probes 90 (red) that serve as optical sensing assemblies.



Miles, 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5-6; *see also id.*, 4:20-30, 11:63-

66 (describing using probe with enzymes or fluorescent/fluorogenic reagents that provide optical readouts); Forrest, ¶¶96.

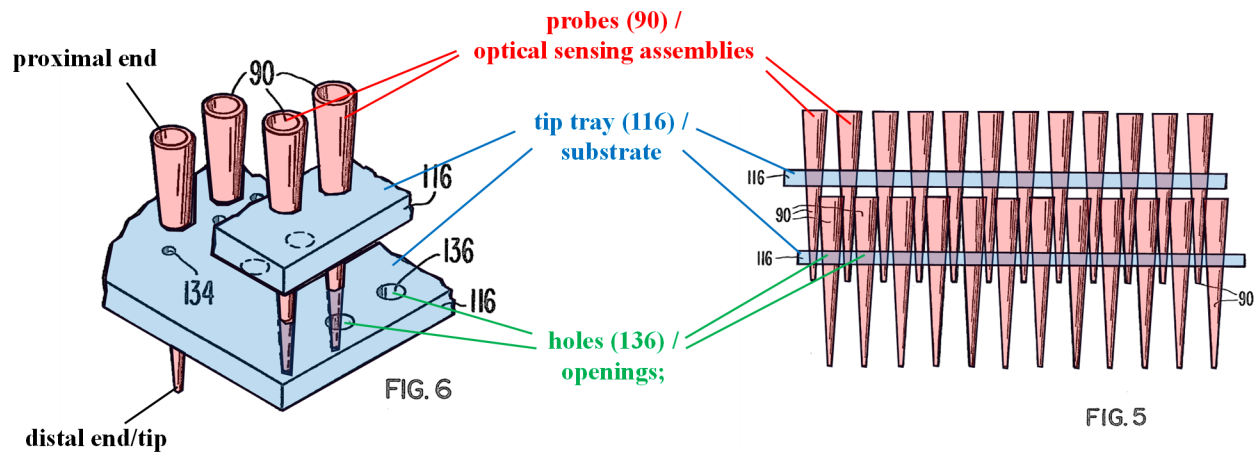
For purposes of element [1D], the “substate” may be a stacked arrangement of tip trays (Figures 5-6) or a standalone tray. For example, Figure 2 shows a single tip tray 116 (blue) of probes 90 (red) loaded onto an assay machine where each of the plurality of openings is configured to hold a discrete probe.



Miles, 9:49-57, 10:45-47, 11:26-30, Fig. 2 (cropped); *see also id.*, 10:28-34, Fig. 7 (showing single tip tray before loading onto assay machine); Forrest, ¶¶97.

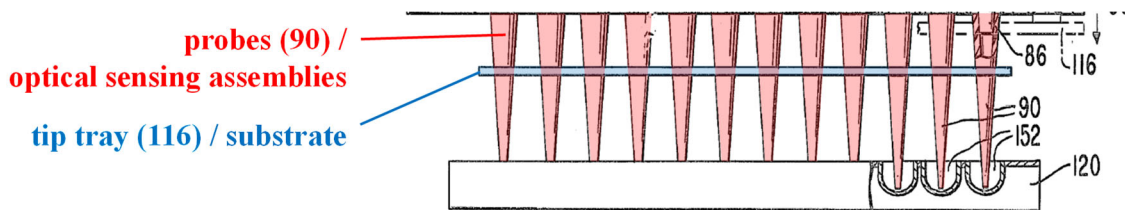
6. [1E]: “the optical sensing assembly being positioned in the opening with a tip of the optical sensing assembly extending through the opening to be suspended from the substrate”

As discussed in §§ VIII.A.1 (Miles Overview) and VIII.B.1 ([1Pre]), and as shown in Figures 5-6, Miles describes probes 90 (optical sensing assemblies, red) positioned in the openings 136 (green) of tip tray 116 (substrate, red) with the probes’ distal ends/tips extending through the openings and suspended from the tray.



Miles, 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5-6; Forrest, ¶ 98.

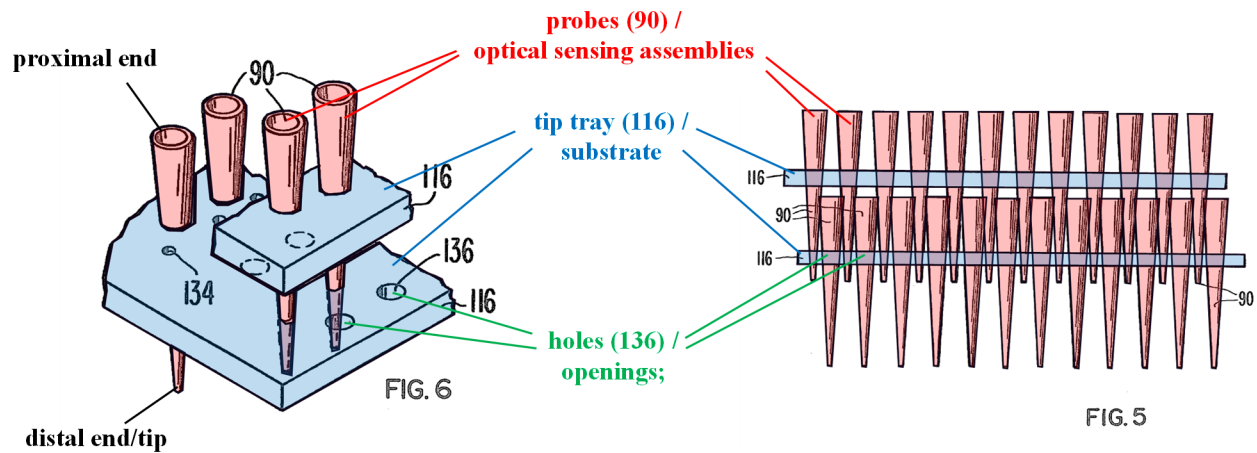
Again, the “substate” may be a stacked arrangement of tip trays or a single tray. For example, Figure 2 shows probes 90 (red) positioned in the openings of single tip tray 116 (blue) with the probes’ distal ends/tips extending through the openings and suspended from the tray.



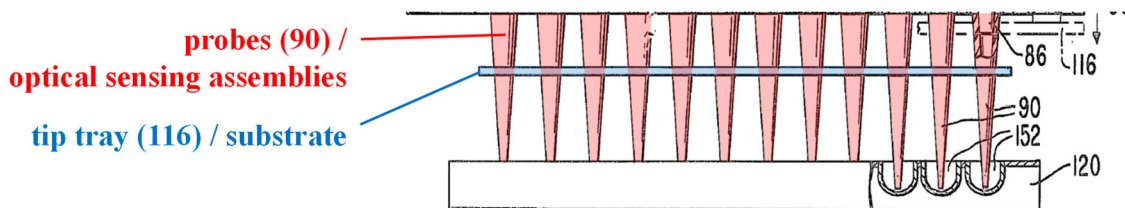
Miles, Fig. 2 (cropped); *see also id.*, 10:28-34, Fig. 7 (single tip tray); Forrest, ¶ 99.

7. [1F]: “wherein the plurality of openings are arranged so the optical sensing assembly positioned therein avoids contacting another optical sensing assembly positioned therein”

As discussed in §§ VIII.A.1 (Miles Overview) and VIII.B.1 ([1Pre]), and as shown in Figures 5-6, Miles describes probes 90 (optical sensing assemblies, red) positioned in a plurality of openings 136 (green) in a tip tray 116 (substrate, blue).



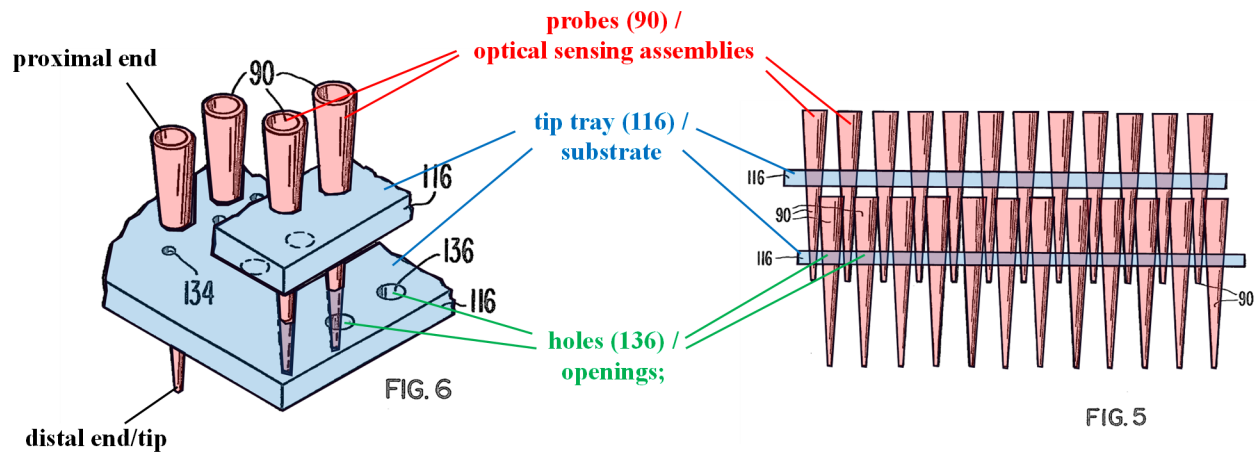
Miles, 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5-6; Forrest, ¶ 100. Figure 5-6 show that the plurality of openings are arranged in a manner that spaces apart the probes so they do not contact one another. *Id.*, Figs. 5-6; Forrest, ¶ 101. This can also be seen in Figure 2, which shows a single tip 116 tray (blue) with the openings arranged so that probes 90 (red) positioned in them do not contact one another.



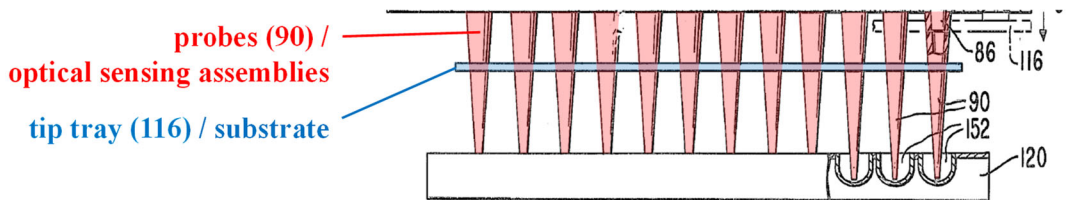
Miles, Fig. 2 (cropped); *see also id.*, 10:28-34, Fig. 7 (single tip tray); Forrest, ¶ 101.

8. [1G]: “wherein at least one opening holds an optical sensing assembly therein, with the tip of the optical sensing assembly extending through the opening”

As discussed in §§ VIII.A.1 (Miles Overview) and VIII.B.6 ([1E]), and as shown in Figures 5-6, Miles describes a tip tray with a plurality of openings 136 (green) that hold multiple, discrete probes (optical sensing assemblies, red) and through which the probes’ distal ends/tips extend.



Miles, 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5-6; Forrest, ¶ 102. This can also be seen in Figure 2, which shows a single tip tray 116 (blue) holding multiple probes 90 (red) with the probe's distal ends/tips extending through the openings in the tray.



Miles, Figs. 2 (cropped); *see also id.*, 10:28-34, Fig. 7 (single tip tray); Forrest, ¶ 103.

C. Claims 2-4

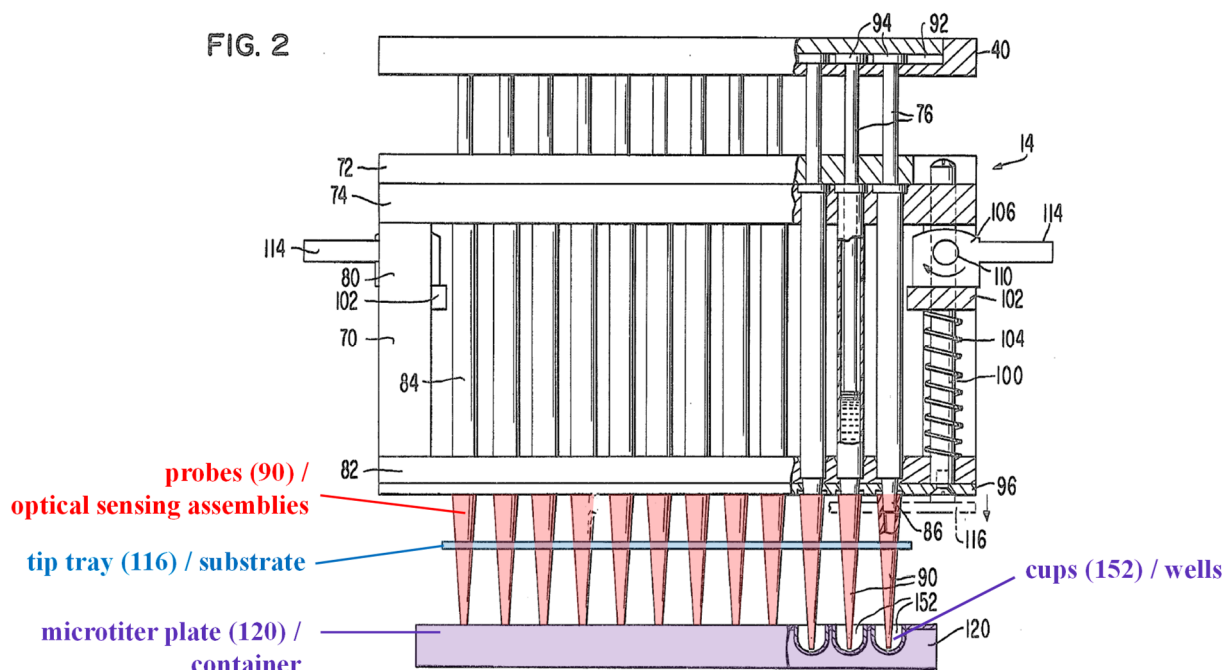
Claim 2-6 purport to combine and use the tip tray apparatus of claim 1 with a container such as a 96-well microtiter plate.

Claim 2	The apparatus of claim 1, further comprising a support member for supporting the substrate, the support member positioning the substrate so the tip of the optical sensing assembly suspended from the opening in the substrate contacts a solution in one of a plurality of wells in a container adjacent to the substrate.
----------------	--

Claim 3	The apparatus of claim 2, wherein the container is a microtiter plate including 96 wells.
Claim 4	The apparatus of claim 2, wherein the optical sensing assembly in the substrate is mapped to wells in a second container containing different samples.

As discussed in §§ VIII.A.1 (Miles Overview) and VIII.B.6 ([1E]), Miles discloses an apparatus comprising a tip tray 116 (substrate) with a plurality of openings 136 that hold probes 90 (optical sensing assemblies) and through which the probes' distal ends/tips extend and are suspended.

As to claim 2, Miles describes the use of such a tip tray of probes with an assay machine to assay samples in a multi-well microtiter plate. Forrest, ¶¶ 105-106. For example, Figure 2 shows a tip tray 116 (blue) of probes 90 (red) loaded onto the tip receiving ends 86 of a syringe battery 14 in the assay machine.



Miles, 9:49-57, 10:45-47, 11:26-30, Figs. 2; Forrest, ¶ 106.

As Miles explains, a microtiter plate 120 (purple) having a plurality of cups/wells 152 may be placed on a motorized platform 50 below the syringe battery 14. Miles, 8:6-23, 11:26-44. During an assay, the microtiter plate 120 may be raised into position so that the probes' distal ends/tips are inserted into and "reach substantially to the bottom" of the wells 152 of the plate, which may contain sample, reagent, or wash solutions. *Id.*, 2:55-3:4, 9:55-57, 11:26-44, 17:56-58, Fig. 2. In this configuration, the syringe battery's receiving ends 86 serve as support members that support and position the tip tray 116 (substrate) so that the distal ends/tips of the probes 90 (optical sensing assemblies), which are suspended from the openings 136 in the tip tray, contact solutions in the wells 152 of the adjacent microtiter plate 120 (container). Forrest, ¶ 107. This is also consistent with the '588 patent's explanation that certain procedures can be performed with "the substrate 504 plus container 602...placed onto the robotic instrument." EX1001, 13:9-15.

As to claim 3, Miles discloses that the microtiter plate 120 may be a 96-well plate such as that from Cooke Microtiter. Miles, 12:24-26, Fig. 2; *see also id.*, 2:55-65, 9:55-57; *see also* EX1053, 56, Fig. 1; EX1054, 741, Fig. 1 (showing Cooke Microtiter plates). Moreover, POSAs would have found it obvious to use a 96-well microtiter plate as that was the "de facto standard" for performing many laboratory

assays as of 2005. Forrest, ¶¶ 18-19, 108; EX1013, 1:24-27; EX1014, 3:31-48; EX1040, 2; EX1041, 3.

As to claim 4, Miles describes using the assay machine to introduce the tips of probes 90 (optical sensing assemblies) to solutions in successive microtiter plates (containers). Forrest, ¶ 109. For example, Miles outlines a procedure where a tip tray of probes 90 are introduced to a first microtiter plate containing solutions of capture antibodies and then washed (Miles, 10:65-11:15), before being introduced to a second microtiter plate containing different samples and standards (*id.*, 11:26-35).¹¹ Miles also explains that the order of the probes in the tip tray and “the original organization of the samples and standards...is maintained throughout the assay, so that each sample retains a particular position for ease of recording results, particularly by automated means.” *Id.*, 9:49-54, 18:38-42. Thus, the probes in the tip tray are mapped from the wells of one microtiter plate to the next. Forrest, ¶ 109.

D. Claims 6 and 8

Claims 6 and 8 depend from claim 2 and additionally recite immobilizing proteins on the probe/optical sensing assembly.

¹¹ The probes are then washed, introduced to a third microtiter plate with detection antibodies, and washed again before a reading is taken. EX1006, 11:36-62.

Claim 6	The apparatus of claim 2, wherein the solution is a protein solution into which the optical sensing assembly is immersed for immobilization of protein on the optical sensing assembly, or for measurement of interaction with another protein already immobilized on the optical sensing assembly.
Claim 8	The apparatus of claim 2, wherein the substrate being configured for preparing the optical sensing assembly for assay further comprises the substrate being configured protein immobilization of the optical assembly before assay.

As discussed in § VIII.C (claim 2), Miles describes an assay machine that immerses a tip tray 116 of probes 90 in successive microtiter plates containing different solutions (e.g., sample, reagent, and wash solutions). Miles, 2:55-3:4, 9:55-57, 11:26-44, 17:56-58, Fig. 2.

As to claim 6, Miles outlines a procedure where before running an “immunoassay,” a tip tray of probes (optical sensing assemblies) are immersed in a microtiter plate containing solutions of antibodies (proteins) to immobilize the antibodies on the probes’ distal ends/tips. Miles, 10:65-11:15. This pre-assay step functionalizes the probe tips to bind analyte. Forrest, ¶ 112. The immunoassay is then performed by immersing the coated probes in a microtiter plate containing samples/standards (Miles, 11:26-35), followed by immersing the probes in a solution of labeled detection antibodies to detect analyte binding (*id.*, 11:36-44). These latter

steps permit measuring the immobilized antibodies' interaction with other proteins such as the analyte or the detection antibodies. Miles, 11:53-62; Forrest, ¶ 112.

POSAs similarly immobilized analyte-binding molecules on the distal ends/tips of BLI/RIfS probes, such as those described in Yang (or WO854, Grounds 3-4), to functionalize the probes before conducting an assay. Forrest, ¶ 113. For example, Yang describes immersing a BLI/RIfS probe in solutions of antibodies (e.g., rabbit-IgG and goat-anti-rabbit-IgG antibodies, both proteins) to immobilize those antibodies on the probe tip. Yang, 434. Then, during an assay, the coated probe is immersed in a sample solution to bind analyte (e.g., rabbit-anti-goat-IgG antibodies). *Id.*; *see also* WO854, ¶¶ [0054]-[0056], [0079] (also describing immersing BLI/RIfS probes in solution of analyte-binding molecules for immobilization and then immersing coated probes in samples). Again, the immobilization step functionalizes the probe tips before an assay, while the later introduction of samples during an assay permits measuring the immobilized antibodies' interaction with analyte. Forrest, ¶ 113.

As to claim 8, Miles describes a tip tray configured for protein immobilization because the tray is configured to function with an assay machine and have the suspended probe tips contact solutions in a microtiter plate, such as solutions of proteins (e.g., antibodies) for immobilization. Miles, 10:65-11:15; Forrest, ¶ 114.

E. Claims 5 and 7

Claims 5 and 7 depend from claim 2 and additionally recite a “pre-wet solution” or a substrate “configured for pre-wet of the optical assembly.”

Claim 5	The apparatus of claim 2, wherein the solution is a pre-wet solution into which the optical sensing assembly is immersed.
Claim 7	The apparatus of claim 2, wherein the substrate being configured for preparing the optical sensing assembly for assay further comprises the substrate being configured for pre-wet of the optical assembly before assay.

The '588 patent states that “[s]ensors coated with proteins can be stored dry in order to preserve the activity of the proteins until they are to be used in an assay.” EX1001, 2:3-7. And it defines “pre-wet” as “a procedure in which a sensor coated with immobilized binding proteins is hydrated to restore their biological activity.” *Id.*

As discussed in §§ VIII.C (claim 2) and VIII.D (claim 6, 8), Miles describes an assay machine that immerses a tip tray 116 of probes 90 in successive microtiter plates containing sample, reagent, or wash solutions. Miles, 2:55-3:4, 9:55-57, 11:26-44, 17:56-58, Fig. 2. Miles also outlines a procedure where before running an “immunoassay,” the probes are first immersed in a microtiter plate containing solutions of antibodies to immobilize the antibodies on the probe tips. *Id.*, 10:65-11:15. This pre-assay immobilization functionalizes the probes to bind analyte, as

was similarly done with BLI/RIfS probes such as those described in Yang (or WO854, Grounds 3-4). Forrest, ¶¶ 113, 117; Yang, 434; WO854, ¶¶ [0054]-[0056].

As to claim 5, Miles does not explicitly describe a pre-wetting step, but such a step would have been obvious to POSAs. In the 2005 timeframe, immunoassays routinely used functionalized surfaces that were pre-coated with a protein (e.g., antibodies, antigens) and stored dry for later use, and then before performing an assay, the dried surfaces would be pre-wetted (rehydrated) to restore the biological activity of the immobilized proteins. Forrest, ¶ 118; EX1021, [2]; EX1037, abstract, ¶¶ [0001], [0032]-[0033], claim 1; EX1038, 1:66-2:10; EX1045, 1:11-19. Dry storage of prepared surfaces simplified assays and was particularly useful during shipping and handling. Forrest, ¶ 118. This basic concept was also used with optical biosensors that were prepared and stored dry, and then pre-wetted before running an assay. *Id.*; EX1044, abstract (“[o]ptical chips were stored dry after surface functionalization, and rehydrated”). POSAs thus would have found it obvious to prepare both Miles’ probes and BLI/RIfS probes with functionalized surfaces, store them dry, and then (when needed) immerse the probes in a pre-wet solution before carrying out an assay. Forrest, ¶ 118.

As to claim 7, Miles’s tip tray 116 (substrate) is “configured for pre-wet” of probes 90 (optical sensing assemblies) before performing an assay because the tray

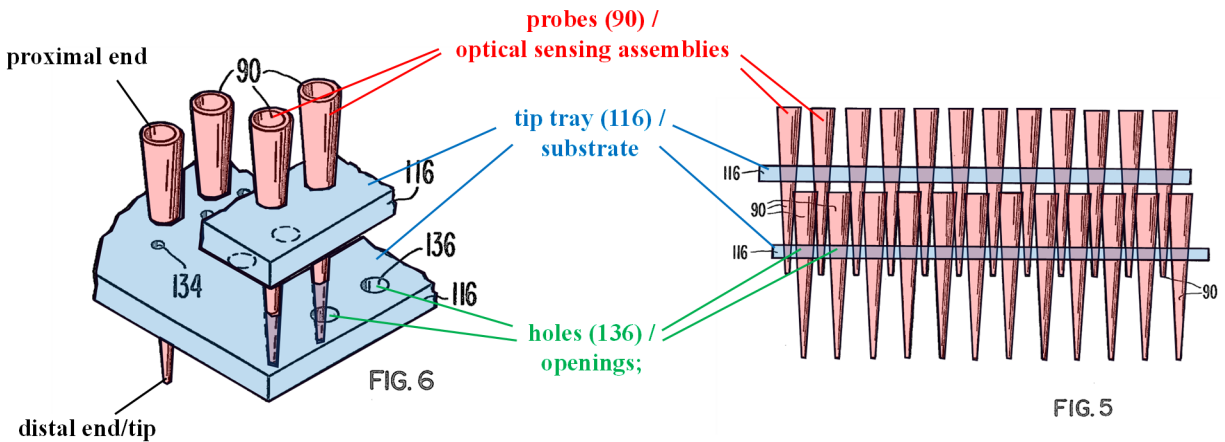
is configured to function with an assay machine and have the suspended probe tips contact solutions in a microtiter plate, such as a pre-wet solution. Forrest, ¶ 119.

F. Claims 9 and 12

Claims 9 and 12 depend from claim 1 and additionally recite a “hub” on the probe/optical sensing assembly.

Claim 9	The apparatus of claim 1, wherein the optical sensing assembly further comprises a hub at an end of the assembly opposite the tip, the hub being designed for attachment to a device that moves the assembly from a first location to a second location.
Claim 12	The apparatus of claim 1, wherein the at least one optical sensing assembly comprises a hub at an end opposite the tip, and the optical sensing assembly is inserted into the opening with the hub of the assembly remaining on a first side of the substrate and the tip of the assembly being inserted through the opening to be suspended from a second side of the substrate.

As discussed in §§ VIII.A.1 (Miles Overview) and VIII.B.1 ([1Pre]), Miles describes probes 90 (optical sensing assemblies, red) positioned in a plurality of openings 136 in a tip tray 116 (substrate, blue).



Miles, 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5-6; Forrest, ¶ 121. Each of the probes 90 has a proximal end/collar that is opposite to the distal end/tip and that serves as a “hub.” Forrest, ¶ 121.

As to claim 9, Miles explains that the proximal end/collar (hub) is designed to attach the probes 90 (optical sensing assemblies) to the tip receiving ends 86 of the syringes in the assay machine. Miles, 2:45-51, 10:28-34, Figs. 2, 7; Forrest, ¶ 122.

As to claim 12, Miles depicts in Figure 5-6 that the proximal end/collar (hub) is wider than the openings 136 in the tip tray 12, which allows the probes to be held in the tray 116. Miles, Figs. 5-6. Thus, when a probe (optical sensing assembly) is inserted into an opening in the tray (substrate), the hub remains on the top (first) side of the tray while the distal end/tip is inserted through the opening and is suspended from the bottom (second) side of the tray. *Id.*; Forrest, ¶ 123.

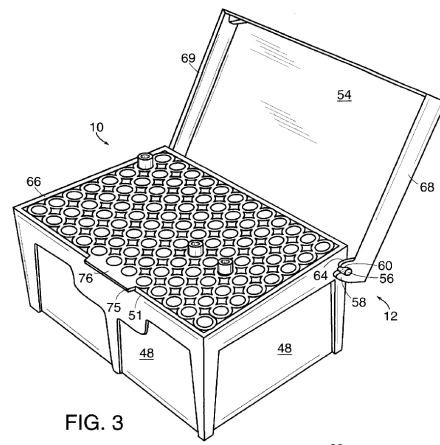
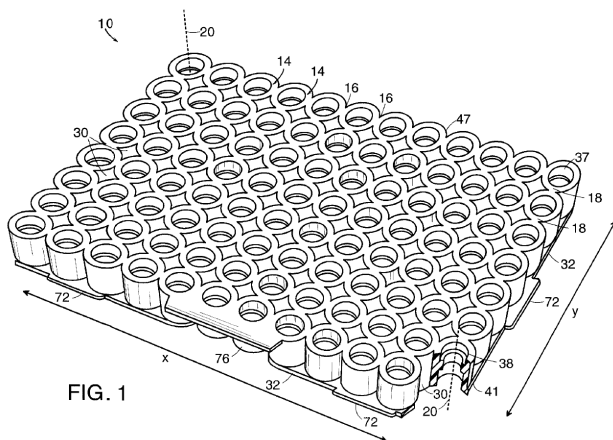
To be sure, POSAs need not have “physically combin[ed]” or “bodily incorporated” the precise hub structure of Miles’ probe into a BLI/RIfS probe. *Allied Erecting*, 825 F.3d at 1381. Rather, POSAs would have recognized that Miles’

Claim 10 depends from claim 1 and recites that “the openings include elongated barrels that allow the optical sensing assembly to be immersed in a solution in a container below the substrate without the tip of the optical sensing assembly contacting a tip of another optical sensing assembly in the substrate.” As discussed in § VIII.C (claim 2), Miles describes loading a tip tray 16 (blue, substrate) of probes 90 (red, optical sensing assemblies) onto the tip receiving ends 86 of an assay machine and immersing the probe tips in solutions contained in a microtiter plate (purple, container) positioned below the tip tray.



Miles, 9:49-57, 10:45-47, 11:26-30, Figs. 2; Forrest, ¶ 126. As shown in Figure 2, the tip tray 116 has a thickness such that the openings 136 in the tip tray form an elongated barrel, and this arrangement suffices to separate the probe tips so that they do not contact one another while they are immersed in the solutions contained in the microtiter plate's wells. Forrest, ¶ 126.

Claim 10 does not specify any dimensions for the “elongated barrel.” But to the extent it requires a longer barrel than what Miles discloses, POSAs would have found it obvious to vary the barrel's dimensions to achieve the desired separation between the probe tips, with a reasonable expectation of success, as this was a known feature of tip trays. Forrest, ¶ 127; *see In re Magna Elecs., Inc.*, 611 F. App'x 969, 974 (Fed. Cir. 2015) (citing *In re Kuhle*, 526 F.2d 553, 555 (CCPA 1975)). For example, reflecting that POSAs were motivated to use elongated barrels, U.S. Patent No. 6,019,225 describes a similar tip tray comprising elongated barrels (referred to as “sleeves”) to position and separate tips.



EX1017, abstract, 3:19-23, Figs. 1, 3

H. Claim 11

Claim 11 depends from claim 1 and recites “a plurality of discrete optical sensing assemblies coated with different reagents arranged in the plurality of openings.” This could be interpreted as either (1) that there are at least two probes that are each coated with two different reagents, or (2) that the reagents coated on one probe differ from those on another. Forrest, ¶ 128. Miles renders both obvious.

As discussed in § VIII.B.5 ([1D]), Miles discloses a tip tray 116 (substrate) with a plurality of openings 136 for arranging a plurality of discrete probes 90 (optical sensing assemblies). Miles, 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5-6. Miles also explains that the probes may be coated with different analyte-binding reagents to functionalize the probe tips to bind and detect a wide variety of analytes, *id.*, 2:19-34, 17:29-32, and that each probe may be coated with multiple, different reagents, *id.*, 15:36-16:7 (describing coating probes with “multiple layers of IgG” antibody reagents). Forrest, ¶ 129. As discussed in § VIII.D, POSAs similarly functionalized the sensing tips of BLI/RIfS probes, often with multiple different reagents. Forrest, ¶¶ 113, 129; Yang, 434 (functionalizing BLI/RIfS probe by coating with multiple, different reagents); WO854, ¶¶ [0054]-[0055], [0080] (same).

To the extent claim 11 requires the reagents coated on one probe to differ from those on another, that too would have been obvious based on Miles. Miles provides a motivation by explaining that combining probes in a tip tray permits using the

probes with an assay machine to perform “multiple assays” “simultaneously” on a microtiter plate. Miles, abstract, 17:64-68. Yang similarly suggests combining BLI/RfS probes to perform multiple assays in “parallel.” Yang, 431, 436. As POSAs would have recognized, combining different probes (each coated and functionalized with different reagents) in a tip tray would permit detecting different analytes in the same sample or different samples. Forrest, ¶¶ 130-31.

As addressed in § VIII.A.3, Chen reflects that POSAs were motivated to do so, explaining that multiple, different BLI/RfS probes may be combined and used together in a multiplexed format to perform multiple assays simultaneously and to detect different analytes, increasing speed and throughput. EX1009, 6:28, 8:17-29, 12:54-13:12, Fig. 11; EX1012, 339:17-341:2 (PO’s expert concurring). Similarly, WO854 (discussed further in § X.A.2) incorporates Chen and proposes to combine multiple BLI/RfS probes in a “two dimensional array.” WO854, ¶ [0007], claims 22-23, 26-27; *see also id.*, ¶¶ [0009], [0017], [0045], [0080]-[0081], Fig. 5.

I. Claims 13 and 18-19

Claims 13 and 18-19 depend from claim 1 and recite additional features such as a cover, a base, and a container within the base.

Claim 13	The apparatus of claim 1, further comprising a cover on a first side of the substrate to protect the optical sensing assembly.
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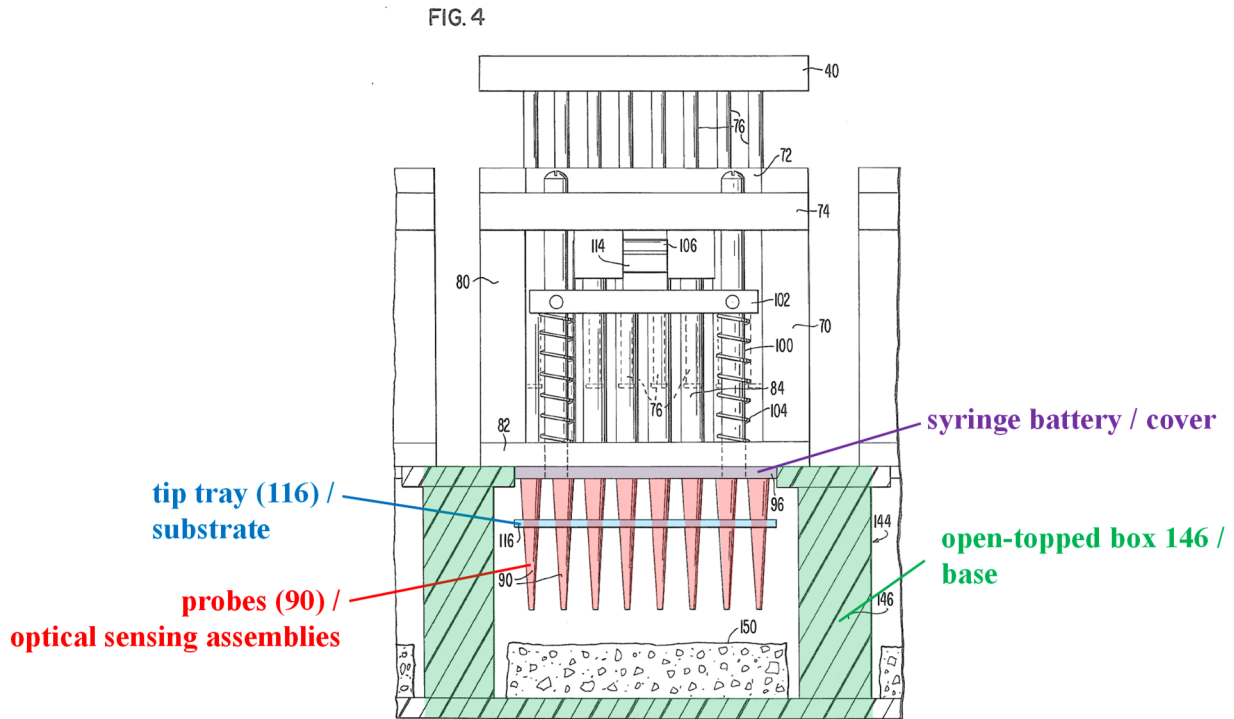
Claim 18	The apparatus of claim 1, further comprising a base on a second side of the substrate to protect the tip of the optical sensing assembly. ¹²
Claim 19	The apparatus of claim 18, wherein a container is positioned inside the base beneath the substrate, the container being positioned so the tip of the suspended optical sensing assembly contacts solution in one of the plurality of wells in the container.

As discussed above in §§ VIII.A.1 (Miles Overview) and VIII.C (claim 2), Miles discloses the use of a tip tray 116 (substrate) of probes 90 (optical sensing assemblies) with an assay machine to assay samples on a microtiter plate (container). Miles, 9:49-57, 10:45-47, 11:26-30, Figs. 2; Forrest, ¶ 134.

As to claims 13 and 18, Miles explains that during an assay, the probes 90 may be treated with sample or reagent solutions, which may require incubating the probes for some time (e.g., 0.5-12 hours). Miles, 6:29-38, 11:16-44, Fig. 4. And Miles explains that this incubation may be carried out in a storage support box 144. *Id.*, 8:45-48, 13:2-6, 16:9-13, Fig. 4. As shown in Figure 4, the storage support box 144 comprises an open-topped box 146 (green) that serves as a base (claim 18), and

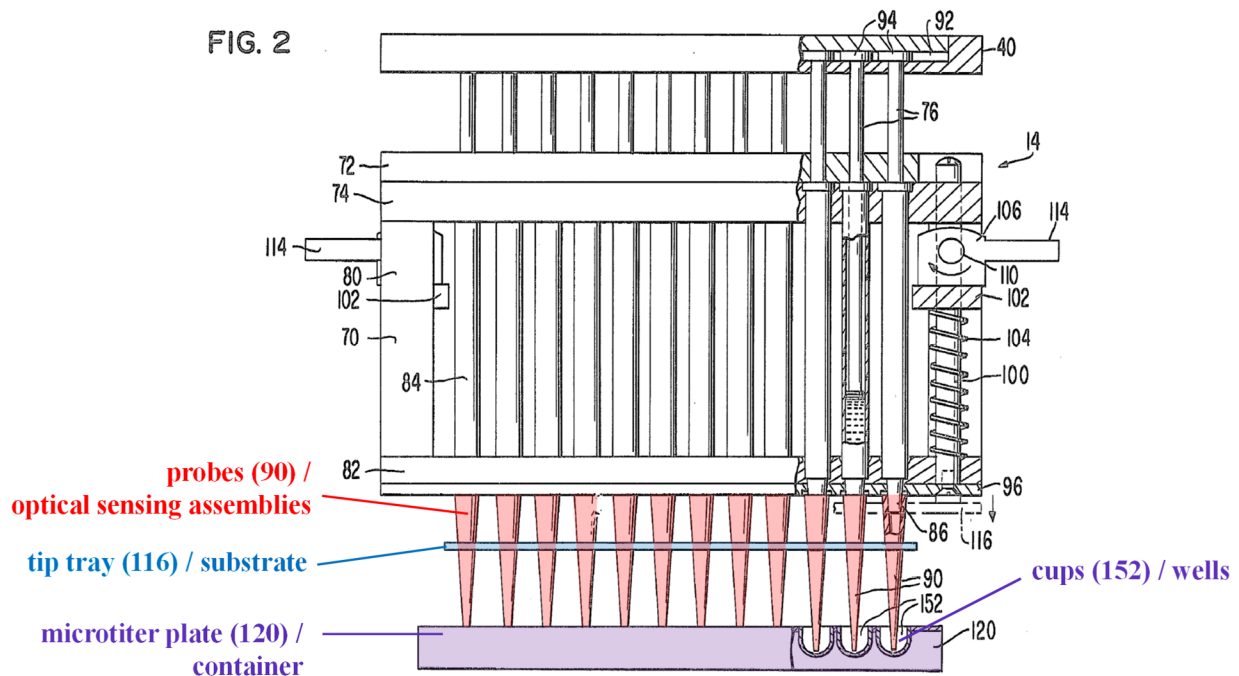
¹² Claim 18 recites a base on “a second side” of the substrate, but neither claim 1 nor claim 18 recites “a first side,” so “a second side” does not have a reasonably-certain meaning. Forrest, ¶ 133. For purposes of this IPR, Petitioner interprets claim 18 as requiring a base on at least one side of the substrate.

the bottom part (purple) of the syringe battery provides a cover (claim 19) that “serv[es] to enclose” the tip tray 116 (blue) and probes 90 (red).



Id., 11:20-25, Fig. 4; Forrest, ¶ 135. Together, the base and cover protect the probes 90 (claims 13 and 18) by providing “controlled temperature and humidity conditions.” Miles, 11:16-35; *see also id.*, 8:45-48, 13:2-6, 16:9-13; Forrest, ¶ 135.

As to claim 19, Miles does not explicitly describe the storage support box 144 as including a container. But as discussed in § VIII.C (claim 2), Miles describes loading a tip tray 116 of probes 90 onto the syringe battery of the assay machine and bringing a microtiter plate 120 into position so that the suspended probe tips are inserted into and contact solutions in the wells 130 of the microtiter plate.



Miles, 9:55-57, 11:26-53, Fig. 2; Forrest, ¶ 136. POSAs would have found it obvious and been motivated to carry out this procedure with the microtiter plate 120 positioned in the storage support box 144 so that probes can be introduced to sample/reagent solutions and incubated all in one step and at the same location. Forrest, ¶ 137. Miles provides further motivation by explaining that the storage support box advantageously provides humidity- and temperature-controlled conditions. Miles, 8:45-48, 11:16-35, 13:2-6, 16:9-13; Forrest, ¶ 137.

IX. Ground 2: The Combination of Miles, Yang, and Rainin Renders Claims 2-8 and 13-19 Obvious Under 35 U.S.C. § 103(a)

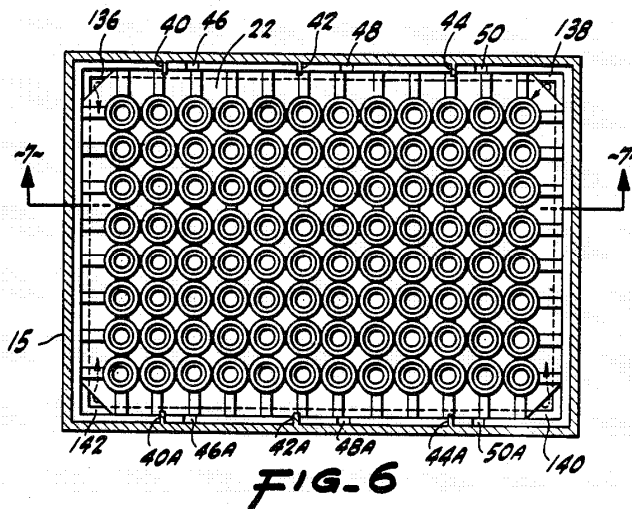
A. Overview of the Combination

1. Miles and Yang

An overview of Miles and Yang is provided in §§ VIII.A.1-VIII.A.2.

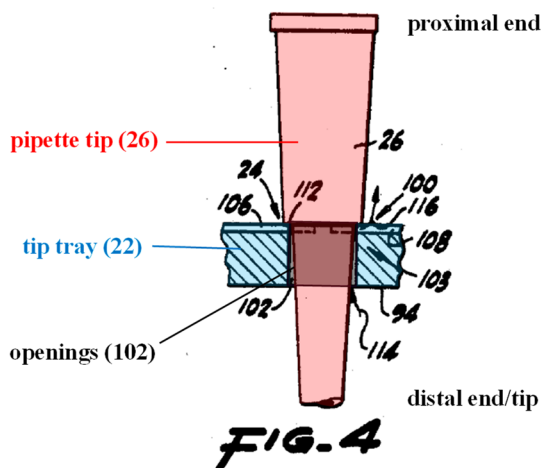
2. Rainin

Rainin discloses pipette tip trays housed in stackable storage boxes. As shown in Figure 6, each tip tray 22 includes 96 openings 102 (also referenced as 118) that are arranged in an 8x12 array, matching the layout of 96-well microtiter plates.



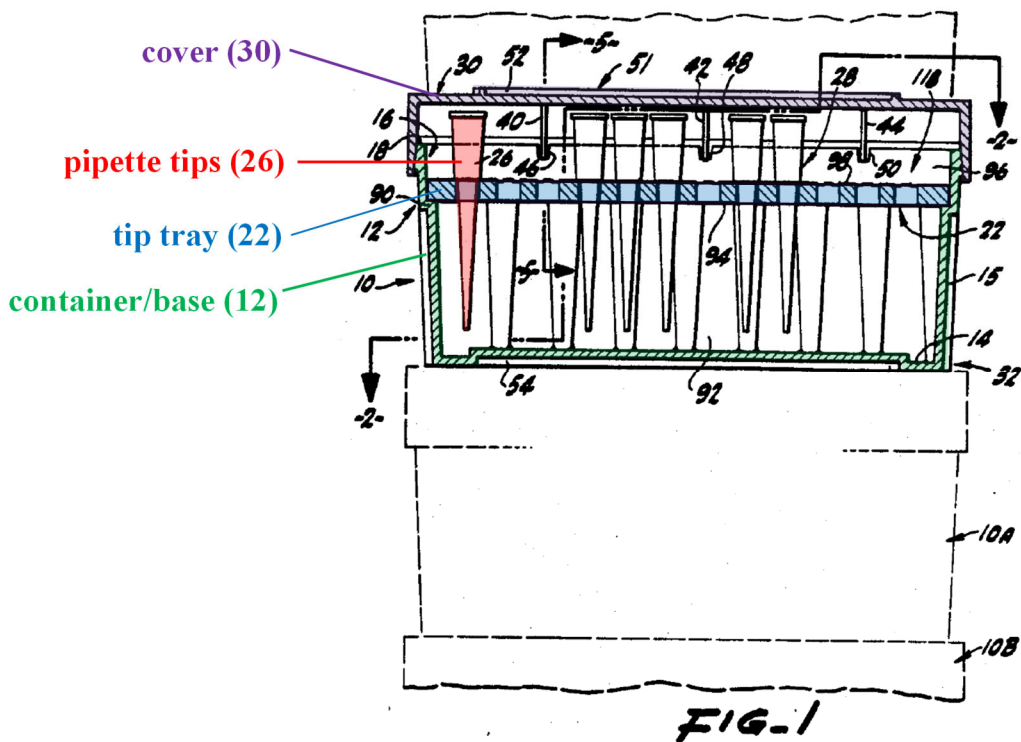
Rainin, 5:41-56, 6:8-13, Fig. 6; Forrest, ¶ 142.

Moreover, as shown in Figure 4, the openings 102 hold the pipette tips 26 (red), which extend through the tip tray 22 (blue) from one side to the other, with the distal end/tip suspended below from the tray.



Rainin, 5:41-56, Fig. 4; Forrest, ¶ 143. The pipette tips 26 each have a proximal end/collar that is designed to attach to a pipette and is wider than the openings 102, preventing the tips from falling through the openings. Rainin, 5:41-56, Fig. 4; *see also id.*, Figs. 1, 3; Forrest, ¶ 143.

Further, as shown in Figure 1, the tip tray 22 (blue) is housed in a storage box/enclosure 32 comprising a container/base 12 (green) and a cover 30 (purple).



Rainin, 4:20-48, Fig. 1; Forrest, ¶ 144. A shoulder 90 “extends around the interior” of the base 12 to support the tip tray 22, keeping the suspended pipette tips elevated and preventing contact with the base 12. Rainin, 5:31-36. Together, the base 12 and cover 30 enclose tip tray 22 to provide a “dust-free” configuration that “resist[s] intrusion of dust and other contaminants” *Id.*, 4:41-46, 5:1-7.

Rainin additionally explains that the storage box may be stackable. *Id.*, 5:7-10. For example, as shown in Figure 1, the cover 30 may include a protrusion 52 that fits into a recess 54 in the container/base 12, allowing multiple boxes to be stacked securely. *Id.*; Forrest, ¶ 145.

3. Motivation to Combine Miles, Yang, and Rainin

As discussed in § VIII (Ground 1), POSAs would have been motivated to package BLI/RIfS probes such as those in Yang (or alternatively WO854, Grounds 3-4) in a tip tray such as that in Miles. In turn, as discussed in § IX.A.2 (Rainin Overview), Rainin describes a stackable storage box comprising a base and a cover for conveniently storing and protecting such tip trays. Rainin, 4:20-48, 5:7-10, Fig. 1. Rainin further provides a motivation for using such a storage box with a trip tray, explaining that it encloses the tip tray and provides a protective “dust-free” configuration that “resist[s] intrusion of dust and other contaminants.” Rainin, 4:41-46, 5:1-7; Forrest, ¶ 146. Indeed, by June 2005, pipette tip trays were routinely packaged and sold in stackable storage boxes comprising a base and a cover to protect the tips and ensure sterility during transport and storage. Forrest, ¶ 147; EX1039, [13]-[16]; EX1048, 1185-87.

POSAs also would have been motivated to use a storage box such as that described in Rainin, recognizing that it houses a tip tray of 96 tips arranged in an 8x12 array in a manner that facilitates using the tips with a 96-well microtiter plate

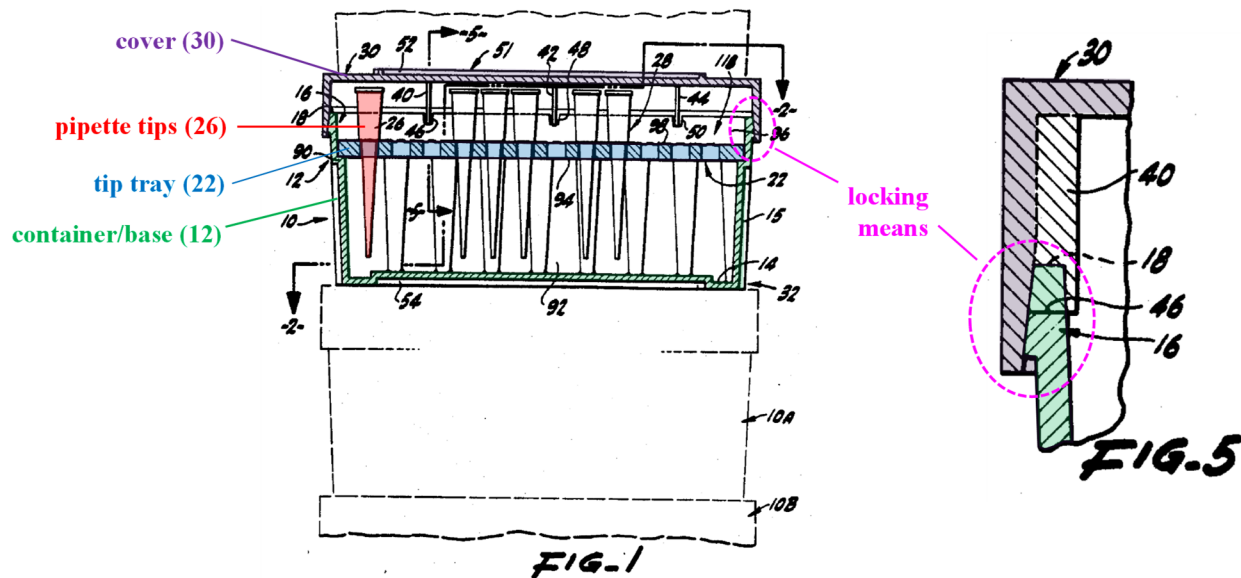
(and related equipment), as disclosed in Miles and which by 2005 was the “de facto standard” for conducting many laboratory assays. Forrest, ¶ 148; Miles, 2:55-65, 12:24-26, Fig. 2; EX1013, 1:24-27; EX1014, 3:31-48.

B. Claims 13-16 and 18

Claims 13 and 18-19 recite additional features of a box that houses the tip tray apparatus of claim 1.

Claim 13	The apparatus of claim 1, further comprising a cover on a first side of the substrate to protect the optical sensing assembly.
Claim 14	The apparatus of claim 13, wherein the cover comprises a recess comprising a downwardly extending center portion such that, when the cover is closed over the substrate, the cover retains the optical sensing assembly in the opening in position in the substrate.
Claim 15	The apparatus of claim 14, further comprising a cover and a base, the cover and base being designed to lock together around the substrate forming an enclosure around the optical sensing assembly.
Claim 16	The apparatus of claim 15, wherein the base of the apparatus is designed fit together with the cover of other apparatuses to be stackable with the other apparatuses for storage.
Claim 18	The apparatus of claim 1, further comprising a base on a second side of the substrate to protect the tip of the optical sensing assembly.

As to claims 13, 15, and 18, Rainin discloses and depicts in Figures 1 and 5 a storage box 32 that supports a tip tray 26 (red) of pipette tips 26 and that comprises a cover 30 (purple) and a container/base 12 (green).

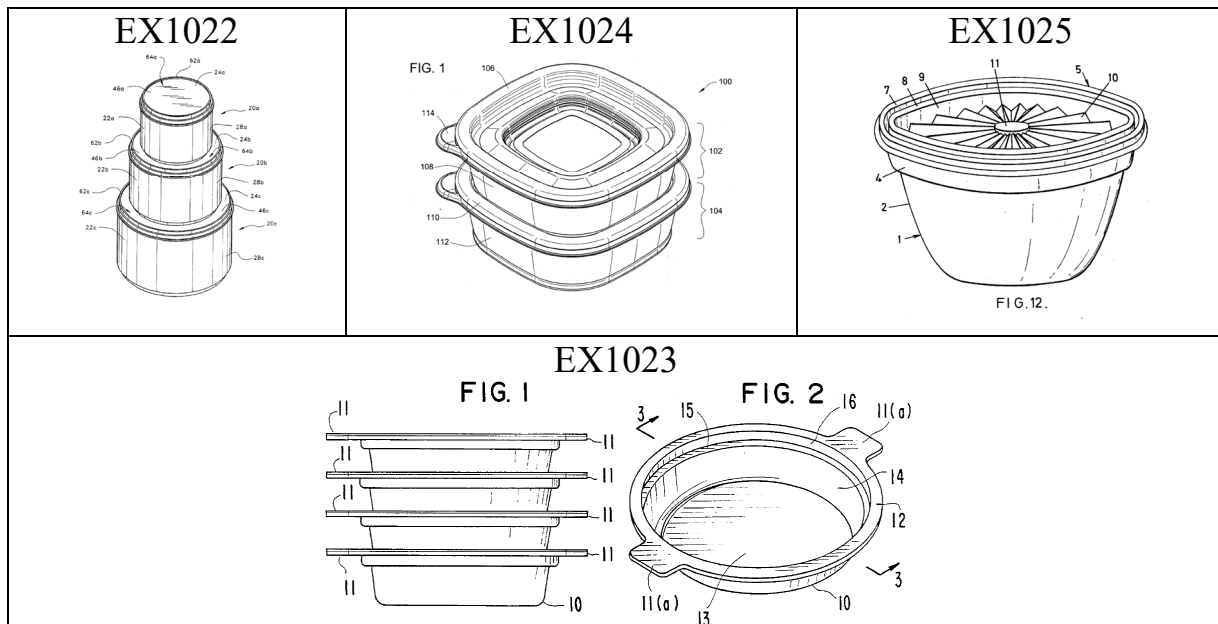


Rainin, 4:20-48, Figs. 1, 5; Forrest, ¶ 150. Moreover, the cover 20 and base 12 lock together to provide an “enclosure” around the tip tray 22 (substrate). Rainin, 4:41-46, 5:1-7 *see also id.*, 2:3-30, 6:8-13, Figs. 1, 5 (cover with locking means engaged), 7 (cover with locking means disengaged). As Rainin explains, this enclosure protects the tips 90 and provides a “dust-free” configuration that “resist[s] intrusion of dust and other contaminants” *Id.*, 4:41-46, 5:1-7.

As to claim 16, Rainin explains that the storage box 32 is designed to be stackable, for example as shown in Figure 1 by providing a protrusion 52 in the cover 30 that fits into a recess 54 in the base 12. *Id.*, 5:7-10, Fig. 1; Forrest, ¶ 151.

As to claim 14, Rainin does not explicitly disclose that the storage box 32 may be designed with the recess 54 is in the cover 30 and the protrusion 52 in the base 12. POSAs, however, would have found it obvious to switch the locations of the recess 54 and protrusion 52, with a reasonable expectation of success, as this was a

common alternative design for stackable containers. Forrest, ¶ 152; *see In re Yufa*, 452 F. App'x 998, 1001 (Fed. Cir. 2012) (mere change in location is obvious); *In re Gazda*, 219 F.2d 449, 452 (CCPA 1955) (mere reversal of parts is obvious). Indeed, examples of stackable containers with a downwardly extending recess in the cover and a mating protrusion in the base are legion.



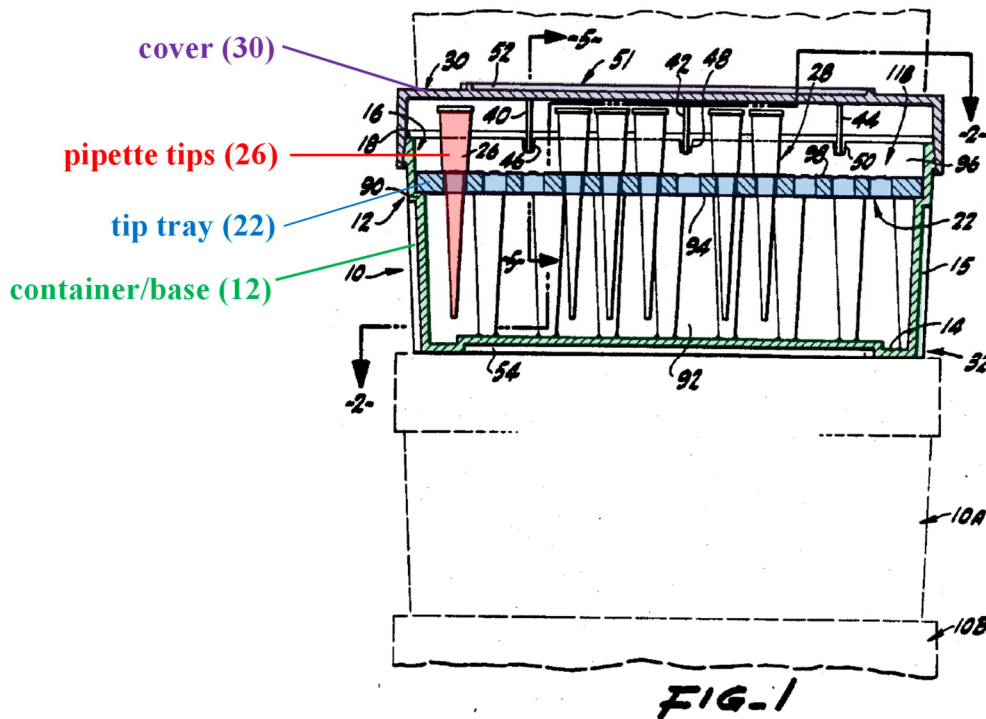
EX1022, 5:4-13, 5:29-49, Figs. 1, 4, 6; EX1023, 2:9-12, Figs. 1-2; EX1024, ¶¶ [0031], [0033], [0041], Figs. 1-5; EX1025, 1:23-30, 3:52-65, Fig. 12. Moreover, it was well-understood that providing a recess in the cover would reduce the space in a container to help secure its contents during storage and transport. Forrest, ¶ 152; EX1023, 2:55-3:2. POSAs thus would have been motivated to use a recessed cover with Rainin's storage box to reduce the space between the cover and the tip tray, thereby helping to retain and minimize the movement of the tips during storage and transport. Forrest, ¶ 152.

C. Claims 2, 3, 17, and 19

Claims 2, 3, 17, and 19 recite additional features that support the apparatus of claim 1 so that the tips of the probes/optical sensing assemblies contact a solution in a multi-well container or microtiter plate.

Claim 2	The apparatus of claim 1, further comprising a support member for supporting the substrate, the support member positioning the substrate so the tip of the optical sensing assembly suspended from the opening in the substrate contacts a solution in one of a plurality of wells in a container adjacent to the substrate.
Claim 3	The apparatus of claim 2, wherein the container is a microtiter plate including 96 wells.
Claim 17	The apparatus of claim 14, further comprising a support member for supporting the substrate, the support member positioning the substrate so the tip of the optical sensing assembly suspended from the opening in the substrate can contact a solution in one of a plurality of wells in a container adjacent to the substrate, wherein the container is a microtiter plate.
Claim 19	The apparatus of claim 18, wherein a container is positioned inside the base beneath the substrate, the container being positioned so the tip of the suspended optical sensing assembly contacts solution in one of the plurality of wells in the container.

Rainin describes a storage box 32 comprising a cover 30 and base 12, wherein the base includes a shoulder 90 that supports a tip tray 20 (substrate) of 96 tips 26.



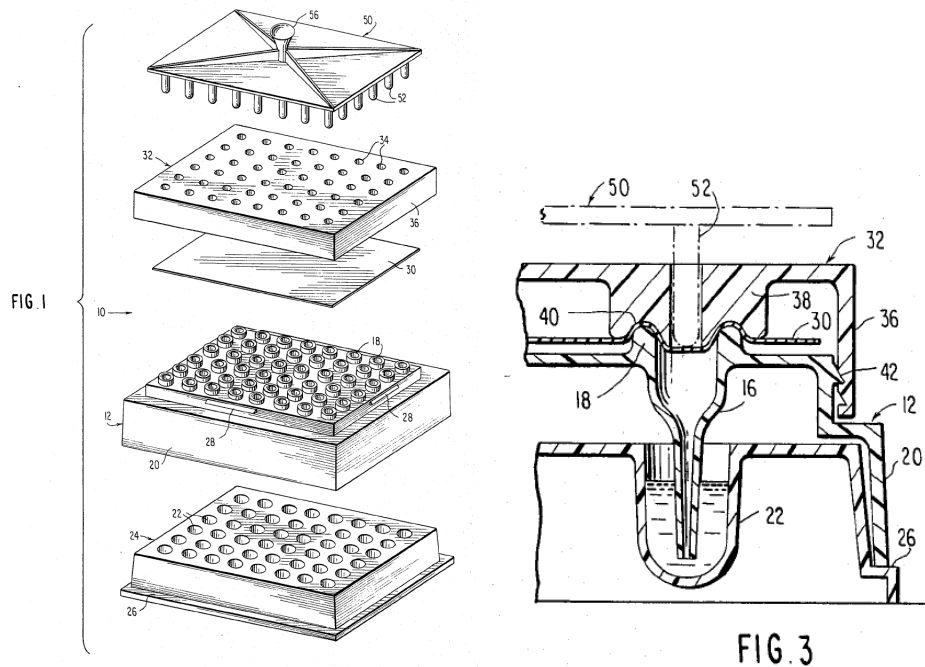
Rainin, 4:20-48, 5:31-36, Fig. 1, 6 (showing 96 tips); Forrest, ¶ 154. The shoulder 90 serves as a support member for supporting the tip tray 22 (claims 2 and 17) and positioning it in the base 12 so that the tips 26 are suspended from the openings 102, 118 in the tip tray (claims 2, 17, and 19). Forrest, ¶ 154.

Rainin does not explicitly disclose that the base 12 may include a multi-well container or microtiter plate. POSAs, however, would have found it obvious to incorporate a 96-well microtiter plate (claim 3) in the base 12 so that each of the 96 suspended tips may be immersed in solutions contained in the wells of such a plate (claims 2, 17, and 19). *Id.*, ¶ 155. For example, as discussed in §§ VIII.C-VIII.E (Ground 1, claims 2 and 5-8), Miles describes an assay machine that immerses a tip tray 116 of probes 90 in successive microtiter plates containing sample, reagent, or wash solutions. Miles, 2:55-3:4, 9:55-57, 11:26-44, 17:56-58, Fig. 2. Miles further

explains that before an assay is conducted on a sample, the probes need to be functionalized by contacting them with a solution of antibodies or other analyte-binding molecules and then washed so that the analyte-binding molecules are coated or immobilized on the probes' distal ends/tips. Miles, 10:65-11:15; Forrest, ¶ 155. Only after the probes are functionalized as such are they introduced to samples to perform an assay. Miles, 11:26-44, 11:53-62; Forrest, ¶ 155. As discussed in § VIII.D, POSAs similarly functionalized the sensing tips of BLI/RIfS probes. Forrest, ¶¶ 118, 129, 155; Yang, 434; WO854, ¶¶ [0054]-[0055], [0080].

As POSAs would have understood, it can be advantageous to include a microtiter plate in a tip tray's base so that preparatory steps, some of which can take 1 to 24 hours or longer, may be done in an "offline" configuration before loading the probes onto the assay machine, particularly in a busy lab where the machine is in high demand. Forrest, ¶ 156 (citing EX1055, 144; Miles, 6:35-37). Performing such steps offline helps streamline an assay and minimize machine time. *Id.* Moreover, to ensure consistent, robust results, standardized assays (e.g., FDA-approved clinical assays) must be performed with known, validated materials, supplies, and reagents, which is why kits for standardized assays typically include all required components, such as microtiter plates, to control for potential externalities. *Id.* (citing EX1056, 9). Given the standard practice of including essential components in testing kits, POSAs would have been strongly motivated to include a microtiter plate in the base

of a tip tray apparatus. *Id.* POSAs also would have had a reasonable expectation of success as similar apparatuses for immersing pipette tips in a microtiter plate were known and disclosed in prior art such as U.S. Patent No. 4,511,534.



EX1045, 3:33-47, 4:52-64, Figs. 1, 3; *see also, id.*, 1:10-19 (describing need for such a device to pre-wet dried, functionalized surfaces); Forrest, ¶ 157.

D. Claims 4-8

See discussion of claims 4-8 in Ground 1 (§§ VIII.C-VIII.E).

X. Ground 3: The Combination of Miles and WO854 Renders Claims 1-13 and 18-19 Obvious Under 35 U.S.C. § 103(a)

Petitioner's proposed combination and arguments in Ground 3 are substantially the same as in Ground 1 (addressed in § VIII) except that Petitioner relies on WO854 (EX1008) for disclosure of a BLI/RfS probe instead of Yang (EX1006). Petitioner thus addresses only those elements of the challenged claims

for which it relies on WO854 and incorporates the discussion and analysis of the remaining elements as set forth in Ground 1.

A. Overview of the Combination

1. Miles

An overview of Miles is provided in § VIII.A.1.

2. WO854

WO854 describes a fiber-optic sensor probe (optical sensing assembly) for detecting analyte in a sample using BLI/RIfS. Forrest, ¶ 162. As shown in Figure 4, the probe is removably coupled to an optical fiber 52 via gripping arms 54.

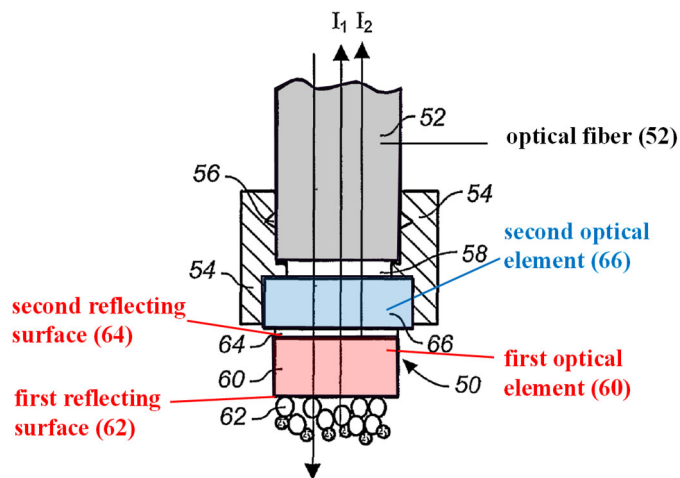


FIG. 4

WO854, ¶¶ [0077]-[0079], Fig. 4; Forrest, ¶ 162. The probe comprises a first optical element 60 (red) having a thickness greater than 50 nm and a second optical element 66 (blue), which may be a glass or polymeric material. WO854, ¶¶ [0051], [0078]. The first optical element comprises two reflecting surfaces (62, 64), the first of which comprises a layer of analyte-binding molecules for binding analyte. *Id.*, ¶¶ [0078]-

[0079]. During an assay, when analyte binds to the probe's distal end/tip, the resulting interference pattern (as registered on a spectrometer) varies and provides an indication of analyte binding. *Id.*, ¶¶ [0010], [0056], [0079].

According to WO854, multiple analyte-binding regions may be combined on the distal end of a probe to assay multiple analytes in a sample. *Id.*, ¶¶ [0009], [0017], [0045], [0080]-[0081], Fig. 5. WO854 also claims arrangements in which multiple discrete probes are combined together in a “two dimensional array” format. *Id.*, claims 22-23, 26-27. Further, WO854 incorporates Chen (*id.*, ¶ [0007]), which describes a similar BLI/RIfS probe 700 that is removably coupled to an optical fiber of an assay machine via a clothespin-type connector 802. EX1009, 10:45-57, 12:24-26, Fig. 8; Forrest ¶ 163; EX1058; EX1012, 327:5-329:7, 333:15-339:7. As depicted in Figure 11, Chen explains that multiple, discrete probes (1-n) may be combined in a multiplexed format to perform multiple assays simultaneously and to detect different analytes in a sample.

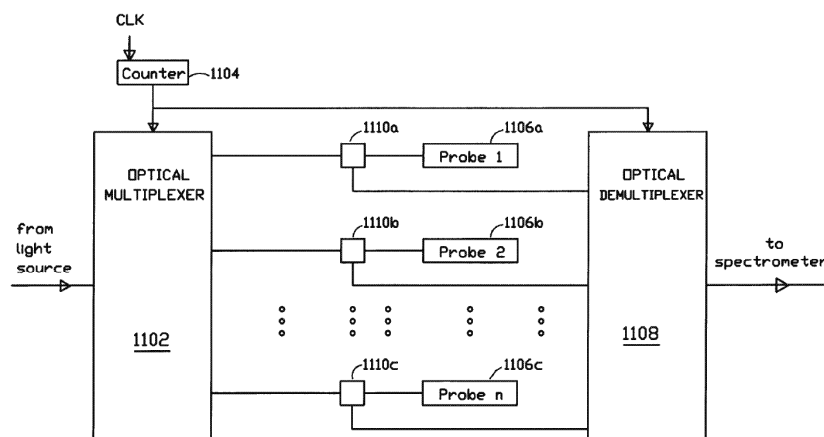


Figure 11

EX1009, 6:28, 8:17-29, 12:54-13:12, Fig. 11; Forrest, ¶ 163; EX1058; EX1059, 7; EX1012, 339:17-341:2 (PO's expert concurring).

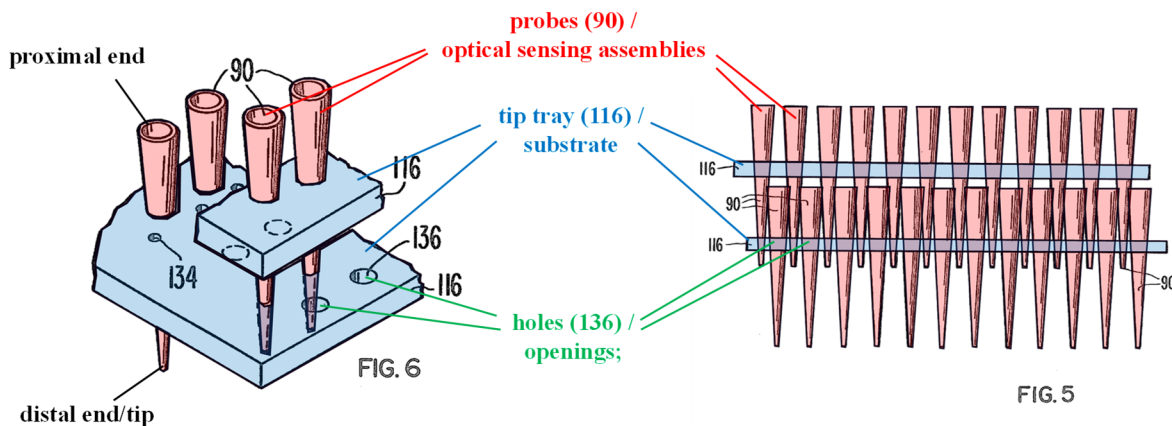
3. Motivation to Combine Miles and WO854

As discussed in § VIII.A.3 (Ground 1), POSAs would have been motivated to package BLI/RfS probes such as those in WO854 (or alternatively Yang) in a tip tray such as that in Miles.

B. Claim 1

1. [1Pre]: “An apparatus for packaging an optical sensing assembly the apparatus comprising”

To the extent the preamble [1P] is limiting, Miles in combination with WO854 teaches “[a]n apparatus for packaging an optical sensing assembly.” Forrest, ¶¶ 165-70. As discussed in § VIII.A.1 (Miles Overview) and § VIII.B.1 ([1Pre], Ground 1), and summarized briefly here, Miles discloses a tip tray 116 for packaging pipette tips 90 (probes or optical sensing assemblies) that are coated and functionalized on their distal ends/tips with analyte-binding molecules (e.g., antigen, antibodies).



Miles, 2:19-34, 2:45-55, 4:3-19, 5:53-68, 8:26-36, 9:49-54, 10:18-27, Figs. 5-6; Forrest, ¶¶ 53-54, 166, 168. During an assay, the probes are engaged by an assay machine and introduced to samples and reagents in microtiter plates, such as 96-well plates. Miles, 2:55-3:4, 12:24-26, Fig. 2; Forrest, ¶¶ 55, 166-67. The probes also may be configured to provide an optical readout using “enzymes,” “fluorescers,” or “fluorogenic” reagents. Miles, 4:20-30, 11:63-66; Forrest, ¶¶ 56-57, 167.

Further, as discussed in § X.A.2 (WO854 Overview) and below in §§ X.B.2-X.B.4 ([1A]-[1C]), WO854 describes a BLI/RIfS probe that serves as an optical sensing assembly, as shown for example in Figure 4.

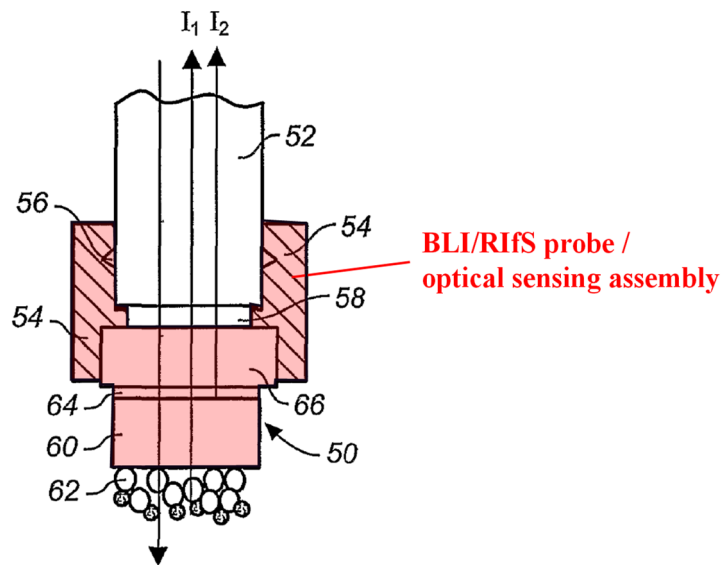


FIG. 4

WO854, ¶¶ [0077]-[0079], Fig. 4; *see also id.*, ¶ [0051], Fig. 2; Forrest, ¶ 169. Notably, WO854 describes probes that are substantially identical to the '588 patent's optical sensing assembly. *Compare* WO854, Figs. 2, 4, *with* EX1001, Fig. 2. As

discussed in § VIII.A.3, POSAs would have been motivated to use a tip tray such as that in Miles to package BLI/RIfS probes such as those in WO854.

2. [1A]: “at least one discrete optical sensing assembly”

Miles, in combination with WO854, teaches a tip tray apparatus comprising “at least one discrete optical sensing assembly.” Forrest, ¶¶ 171-173. As discussed in §§ VIII.A.1 (Miles Overview) and VIII.B.1([1Pre], Ground 1), Miles discloses a tip tray 166 (blue) of discrete probes 90 (red) that serve as optical sensing assemblies. Forrest, ¶¶ 81-83, 172.

Further, as discussed in §§ X.A.2 (WO854 Overview) and X.B.1 ([1Pre]), and shown in Figure 4, WO854 describes a BLI/RIfS probe (optical sensing assembly).

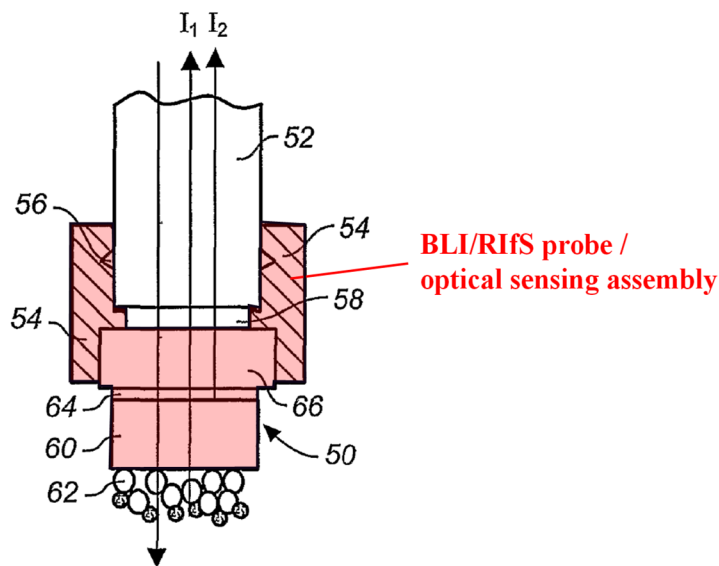


FIG. 4

WO854, ¶¶ [0077]-[0079], Fig. 4; Forrest, ¶ 173.

3. [1B]: “comprising an optical fiber and a transparent optical element having end faces and first and second reflecting surfaces formed on the end faces, the first and second reflecting surfaces separated by at least 50 nm”

WO854 discloses a BLI/RIfS probe having the features of element [1B]. Forrest, ¶¶ 174-78. As shown in Figure 4, the probe comprises a first optical element 60 and a second optical element 66.

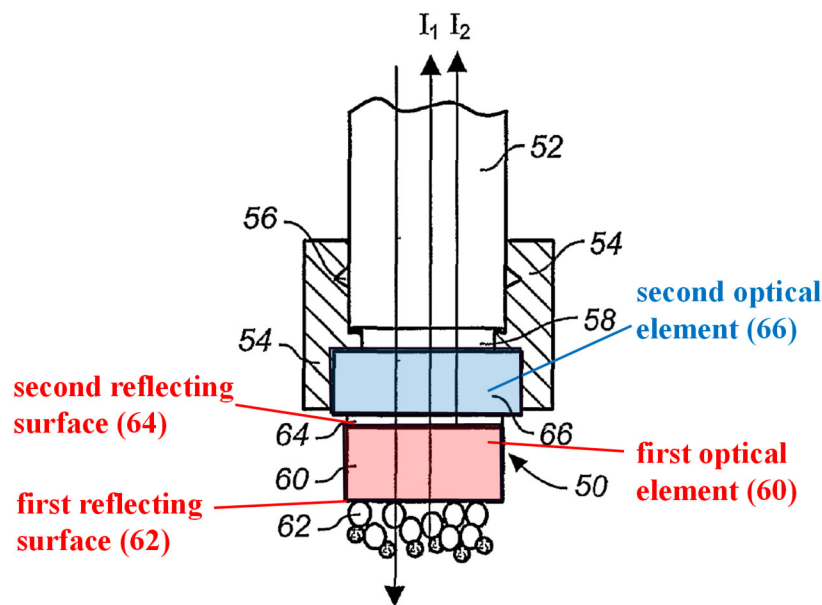
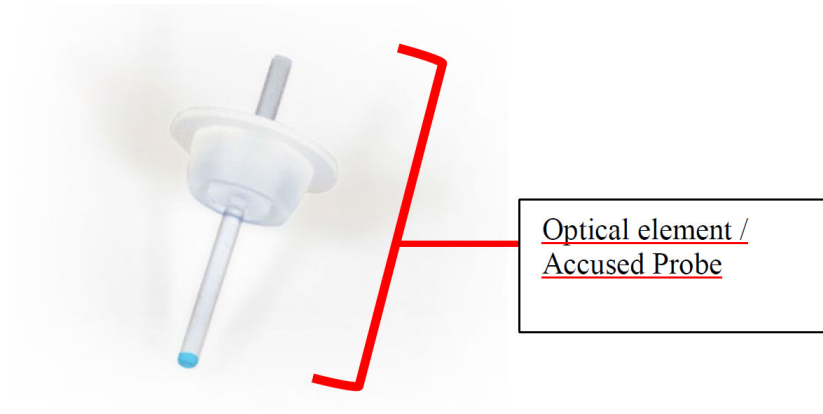


FIG. 4

WO854, ¶[0078], Fig. 4; Forrest, ¶174.

As to the requirement of an “optical fiber,” WO854 discloses that the second optical element 66 is preferably comprised of a “glass or a polymeric material having an index of refraction of between about 1.4 and 1.6,” which is consistent with known glass and plastic optical fibers. WO854, ¶[0078]; EX1026, abstract, 107 (Table 2); Forrest, ¶175. Notably, PO has represented that an “optical element” in this context

may comprise an optical fiber. For example, in ITC Investigation No. 337-TA-1344, PO asserted several related patents (including three from the same family as WO854) and identified the optical-fiber portion of the accused probes as an optical element.

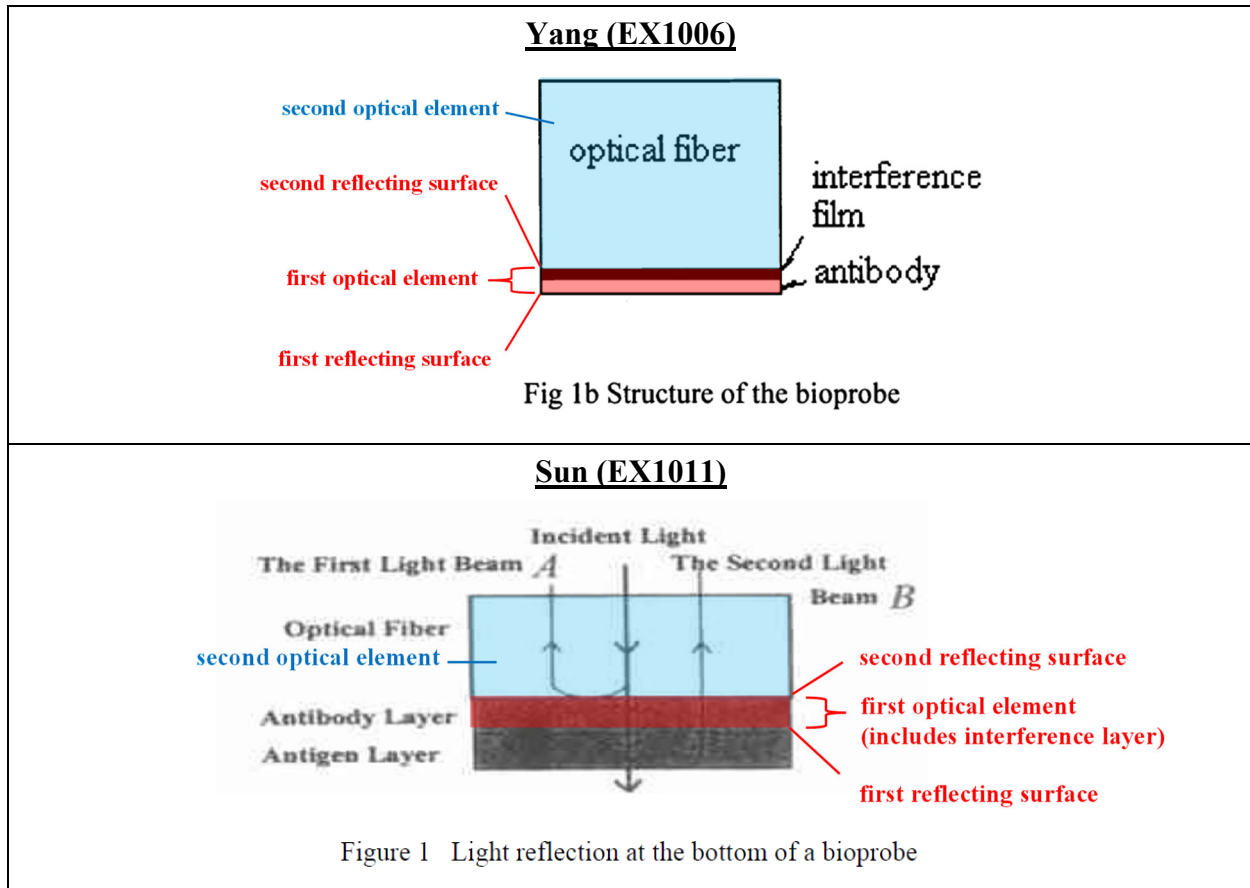


CX-00634C ¶ 325; CX-00276.

EX1028, 92-94, 112-13, 326, 335-36.¹³ Relying on PO’s assertion, the presiding ALJ concluded that the accused “probes are an optical element comprised of optical fiber with an optical layer with two reflective surfaces.” EX1029, 11, 60.

To the extent WO854 does not explicitly describe using an optical fiber as the second optical element 66, POSAs also would have found it obvious to use an optical fiber, with a reasonable expectation of success, given that similar BLI/RIfS probes comprising an optical fiber were already known and disclosed in references such as Yang and Sun (*see* §§ IV.D and VIII.A.2).

¹³ *See also* EX1026, 6 (PO protesting in IPR2023-00215 that it “does not take the position that an optical fiber cannot be a component of an optical element”).



Forrest, ¶¶ 33-34, 77.

WO854 additionally discloses “a transparent optical element having end faces and first and second reflecting surfaces formed on the end faces, the first and second reflecting surfaces separated by at least 50 nm.” *Id.*, ¶ 178. For example, WO854 explains that the first optical element 60 comprises endfaces that form first and second reflective surfaces 62, 64, respectively. WO854, ¶ [0078], Fig. 4. WO854 also explains that the first optical element 60 (similar to the optical element 38 of the assembly in Figure 2) comprises a “transparent” material (e.g., a glass or polymeric material) that provides a separation of at least 50 nm between the first and second reflecting surfaces 62, 64. *Id.*, ¶¶ [0051]-[0052], [0078]; *see also id.*,

¶¶ [0010], [0013], [0020]. Further, as shown in Figure 4 (above), the first optical element 60 is necessarily transparent because the incident light beam (down arrow) and reflected light beam I_1 (up arrow) are able to pass through it. *Id.*, Fig. 4.

4. [1C]: “wherein the first reflecting surface comprises a layer of analyte binding molecules”

As discussed in § X.B.3 ([1B]), WO854 discloses a first optical element 60 comprising a first reflecting surface 62. WO854, ¶ [0078], Fig. 4. WO854 explains and depicts in Figure 4 that the first reflecting surface 62 comprises a layer of “analyte-binding molecules” (blue) for binding analyte.

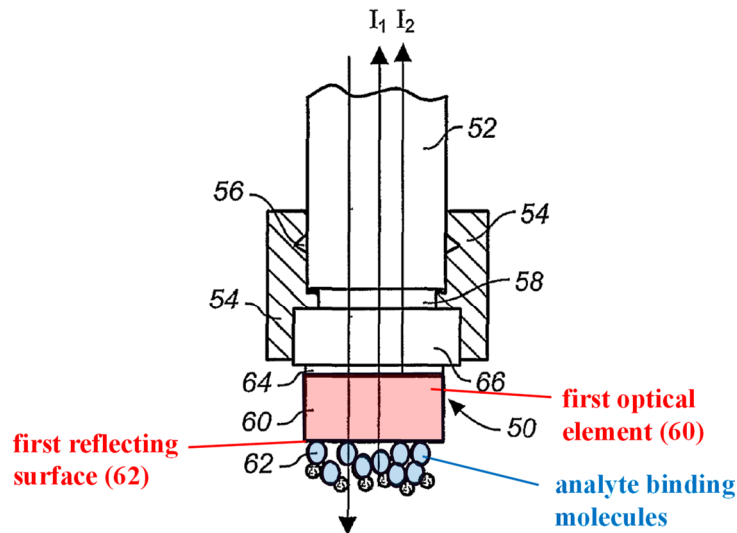


FIG. 4

Id., ¶ [0079], Fig. 4; Forrest, ¶ 179.

5. [1D]-[1G]

See discussion of elements [1D]-[1G] in Ground 1 (§§ VIII.B.5-VIII.B.8).

C. Claims 2-13 and 18-19

See discussion of claims 2-13 and 18-19 in Ground 1 (§§ VIII.C-VIII.I).

XI. Ground 4: The Combination of Miles, WO854, and Rainin Renders Claims 2-8 and 13-19 Obvious Under 35 U.S.C. § 103(a)

Petition's proposed combination and arguments in Ground 4 are substantially the same as in Ground 2 (addressed in § IX) except that Petitioner relies on WO854 (EX1008) for disclosure of a BLI/RIfS probe instead of Yang (EX1006). As discussed in § VIII.A.3, POSAs would have been motivated to package BLI/RIfS probes such as those in WO854 (or alternatively Yang, Grounds 1-2) in a tip tray such as that in Miles. And as discussed in § IX.A.3, POSAs would have been motivated to use a storage box comprising a base and a cover for storing and protecting such tip trays. Miles, WO854, and Rainin disclose or render obvious the elements of claims 2-8 and 13-19 as set forth in §§ IX.B-IX.D (Ground 2).

XII. The Discretionary Factors Favor Institution

The factors considered under 35 U.S.C. § 325(d) all weigh in favor of institution. *See Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017) (precedential); *Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH*, IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020) (precedential).

Under the first part of the *Advanced Bionics* framework, *Becton* factors (a), (b), and (d) strongly favor institution because each of the petition grounds relies on Miles, which was not before the examiner during prosecution. Notably, PO repeatedly argued during prosecution that the prior art failed to disclose a tip-tray

apparatus for packaging sensor probes, as opposed to dispensing tips. *See* § V.B; EX1004, [151]-[152], [208]-[209]. Miles, however, describes precisely such a tip tray for sensor probes. *See* § VIII.A.1. Similarly, Rainin (Grounds 2 and 4) describes a storage box for enclosing a tip tray and was not before the examiner. *See* § IX.A.2.

To the extent the Board reaches the second part of the *Advanced Bionics* framework, it too, along with *Becton* factors (c), (e), and (f), strongly favors institution. During prosecution, the examiner allowed the claims after PO amended them to recite features of BLI/RIfS probes, under the mistaken view that the prior art did not disclose such probes. But as addressed in the petition grounds, such BLI/RIfS probes were known and disclosed in Yang and WO854. *See* §§ IV.D, VIII.A.2, X.A.2. Yang and WO854 were included among *117 references* that PO identified in an IDS during prosecution (EX1004, [157]-[162]), but the examiner did not issue any rejections based on them or give any indication that the relevant disclosures were substantively considered. Moreover, Petitioner presents additional evidence here, including testimony by PO's own expert confirming that Yang (among other references) discloses a BLI/RIfS probe having the claimed features as well as a declaration by Petitioner's expert and accompanying exhibits showing how the combinations in each ground teach the challenged claims.

XIII. Mandatory Notices Under 37 C.F.R. § 42.8

A. Real Parties-in-Interest (§ 42.8(b)(1))

The Petitioner and real party-in-interest is Gator Bio Inc. Out of an abundance of caution, Petitioner also identifies Hong Tan (Gator Bio Inc.'s CEO) and Access Medical Systems, Ltd. (Gator Bio, Inc.'s holding company) as real parties-in-interest.

B. Related Matters (§ 42.8(b)(2))

On February 18, 2025, PO filed and served an amended complaint in the following civil action that asserts the '588 patent against Petitioner: *Sartorius Bioanalytical Instruments, Inc. v. Gator Bio Inc. and Hong Tan*, No. 5:22-CV-01417 (N.D. Cal.). This litigation, which had been stayed until February 12, 2025, is still in its early stages. Petitioner has not yet responded to the amended complaint and discovery has yet to begin.

Additionally, PO asserted that Petitioner infringed certain patents directed to similar subject matter in the following ITC investigation: *In the Matter of Certain Bio-Layer Interferometers and Components Thereof*, Inv. No. 337-TA-1344. The ITC investigation concluded with a final determination no violation in favor of Petitioner that was affirmed by the Commission. EX1029, 178. As discussed in this petition, the deposition testimony (EX1012) of PO's expert from that investigation confirms the disclosures of the prior art and supports the grounds presented here.

C. Lead and Back-Up Counsel (§ 42.8(b)(3))

Petitioner designates the following lead and back-up counsel, and submits herewith a Power of Attorney pursuant to 37 C.F.R. § 42.10(b).

Lead Counsel	Back-up Counsel
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D. Service Information (§ 42.8(b)(4))

Please address all correspondence to lead and back-up counsel at the addresses shown above. Petitioner consents to electronic service by e-mail.

Date: February 24, 2025

Respectfully submitted,

/Hari Santhanam/

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned hereby certifies that the foregoing Petition includes 13,896 words, excluding the parts exempted by § 42.24(a)(1), and is in compliance with § 42.24(a)(1)(i).

This word count was calculated by using the built-in word-count tool in Microsoft Word 2016, the software used to prepare the document.

/Hari Santhanam/
Hari Santhanam

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true copy of the foregoing Petition for Inter Partes Review of U.S. Patent No. 8,647,588 along with all exhibits and powers of attorney were served on February 24, 2025 as indicated below.

Via FedEx Overnight delivery to the assignee of the patent at the correspondence address of record:

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And via electronic mail on the counsel of record in the concurrent litigation:

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