

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

DECLARATION OF LAIRD FORREST, PH.D.

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TABLE OF EXHIBITS¹

Exhibit	Description
1001	U.S. Patent No. 8,647,588 (“’588 patent”)
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”)
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”)

¹ Unless otherwise stated, citations 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
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 Bulletin - Nos. 1 & 2</i> (July 2001), available at https://www.labelcluster.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”)
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”)

Exhibit	Description
1029	Excerpt of Final Initial Determination, in <i>Certain Bio-Layer Interferometers and Components Thereof</i> , ITC Inv. No. 337-TA-1344 (“FID”)
1030	Declaration of Hong Tan
1031	Declaration of Seema Rampersad regarding Yang (EX1006)
1032	Certificate of Copyright Registration regarding Yang (EX1006)
1033	Declaration of Seema Rampersad regarding Sun (EX1010)
1034	Certificate of Copyright Registration regarding Yu (EX1018)
1035	U.S. Patent No. 6,838,051 (“Marquiss”)
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&pdfid=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”).
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”)

Exhibit	Description
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, Rev. D1</i> (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”)
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”)

Exhibit	Description
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, Laird Forrest, Ph.D., do hereby declare as follows:

I. Introduction

1. I have been retained on behalf of Gator Bio, Inc. (“Gator Bio” or “Petitioner”) in connection with the above-referenced *inter partes* review, and I submit this declaration to offer my technical opinions regarding the patentability and validity of the claims 1-19 (“challenged claims”) of U.S. Patent No. 8,647,588 (“’588 patent”). I understand that the ’588 patent is assigned to Sartorius Bioanalytical Instruments, Inc. (“Sartorius” or “Patent Owner”).

2. In forming the opinions I express in this declaration, I considered the ’588 patent, the related prosecution history, and the materials cited or referenced in this declaration, and I have further relied on my own knowledge, training, and more than 25 years of experience performing laboratory assays, including biochemical analyses using microtiter plates, tip trays, and sensor probes. Additionally, I served as a technical expert on behalf of Gator Bio in an International Trade Commission investigation brought by Sartorius: *In the Matter of Certain Bio-Layer Interferometers and Components Thereof*, No. 337-TA-1344. In that investigation, Sartorius’ expert, Dr. Michael Sailor, provided deposition testimony confirming and supporting various aspects of my opinions in this

declaration.² Thus, I refer to Dr. Sailor's testimony to the extent it relates to my opinions here.

3. I am over 18 years of age. I have personal knowledge of the facts stated in this declaration or have formed opinions based on my review of materials available to me. I could testify competently to such facts and opinions if so asked.

II. Background and Qualifications

4. I am currently a Professor in the Department of Pharmaceutical Chemistry at the University of Kansas in Lawrence, Kansas, a position I have held since 2017. I am also a Professor in Bioengineering, a position I have held since 2011, and Professor in the Department of Chemical and Petroleum Engineering, a position I have held since 2023, also at the University of Kansas. I have been a faculty member at the University of Kansas since 2007.

5. I received a Bachelor of Science in Chemical Engineering from Auburn University in 1998, a Master of Science in Chemical Engineering from the University of Illinois in 2001, and a Ph.D. in Chemical and Biomolecular Engineering from the University of Illinois in 2003. I was a Postdoctoral Fellow in the Division of Pharmaceutical Sciences at the University of Wisconsin, Madison, from 2004 to 2006. In 2006, I became Adjunct Assistant Professor in the

² EX1012, Excerpted Transcript of May 25, 2023 Deposition of Michael Sailor, ITC Inv. No. 337-TA-1344 ("Sailor").

Department of Pharmaceutical Sciences at Washington State University, a position I held concurrently with my University of Kansas position until 2011. In 2007, I accepted a position as Assistant Professor in the Department of Pharmaceutical Chemistry at the University of Kansas. I was promoted to Associate Professor at the University of Kansas in 2013. I was then promoted to the rank of Professor in 2017.

6. Since 2009, I have been a Member of the Scientific and Medical Advisory Board of Exogenesis Corporation, which develops nanoscale surface modifications for implantable medical devices. I am the co-founder of HylaPharm LLC, founded in 2011, which specializes in reformulation of anti-cancer chemotherapeutics by modification of the delivery route and drug targeting, using technologies such as targeted antibodies and peptides. Also, I am a co-founder of Hafion LLC, founded in 2016, which specializes in development of vaccines, and AeroByx LLC, founded in 2017, which specializes in the development of oral medications for treatment of neurological and metabolic diseases. In addition, I am a co-founder of Vesarex, founded in 2018, which specializes in the development of combination ultrasound/laser imaging and treatment devices, which utilize external focused energy to disrupt vascular clots. My research toward drug formulation has been competitively funded by multiple awards from the National Institutes of Health and the National Cancer Institute, the National Institute of

Allergy and Infectious Disease, the American Cancer Society, the Department of Defense, Susan G. Komen Race for the Cure, and the Pharmaceutical Research and the Pharmaceutical Research and Manufacturers of America Foundation (“PhRMA”), among others. In addition, I have been funded by the Food and Drug Administration (“FDA”) to develop methodologies for the in vitro determination of bioequivalence in follow-on complex botanical and biosimilar drug formulations.

7. I have received awards and honors in my area of research, including the Baxendale Innovation Award (2016), the University of Kansas Leading Light Award (2014), the Japan Society for Promotion of Science Visiting Scholar Fellow (2010), the American Cancer Society Research Scholar (2008 to 2012), the American Association of Colleges of Pharmacy, the New Investigators Award (2007), and the PhRMA Foundation Postdoctoral Fellow (2006), among others.

8. I am currently or have been in the past a member of various professional societies, including the American Association for Cancer Research, the American Association of Pharmaceutical Scientists, and the American Institute of Chemical Engineers. I serve or have served on numerous scientific review panels for the National Institutes of Health, the American Cancer Society, and the Association for International Cancer Research (United Kingdom). I also have been

a standing member of the American Cancer Society review panel on Cancer Drug Development (now *ad hoc*).

9. I have authored more than one hundred (100) peer-reviewed journal articles and nine (9) book chapters. I have also edited two (2) special journal issues on drug delivery and a book on drug delivery and formulation. In addition, I have filed for or received about thirty (30) United States and international patents or patent applications related to drug discovery, formulation or pharmacokinetics/pharmacology, which often involve analytical testing and assays.

10. Further, I have taught clinical chemistry and pharmaceutical analysis, including the development of assays for biological testing, to clinical pharmacy students and graduate students studying pharmaceutical sciences since 2007. I also have taught drug formulation and biopharmaceutics, including all aspects of drug excipient choice and the effects of excipient modification on drug targeting, pharmacokinetics, drug chemical stability, drug dissolution, and drug absorption, to clinical pharmacy students and graduate students studying pharmaceutical sciences since 2007.

11. I have over 25 years of experience in many aspects of analytical testing, including the use and development of enzyme and antibody-based assays, such as enzyme-linked immunosorbent assay (ELISAs), Western blotting with enzyme-based (e.g., horse radish peroxidase, alkaline phosphatase, luciferase)

detection, surface plasmon resonance (SPR) evaluation of ligand-antibody binding and enzyme activity, and biolayer interferometry (BLI) assays for antibody and peptide-ligand binding. I routinely use these analytical methods in my own research and in the course of scientific and developmental collaborations with major pharmaceutical companies. In addition, I have designed and utilized enzyme-based linkers in pharmaceutical formulation and drug design, and I have developed techniques to measure enzyme-substrate interaction (e.g., cleavage of the enzyme linker). Further, I have applied these techniques for pharmaceutical development with both small and large molecule drugs. Through both my academic research and my work with companies including Vesarex, I have extensive experience in the development of new optical-based technologies for the measurement of biochemical phenomena, such as the use of time-resolved laser-based imaging in combination secondary ultrasound imaging, further combined with novel biochemical probes, for measuring biological interactions between cells and pharmaceuticals.

12. I have provided at EX1003 a copy of my curriculum vitae and a listing of the matters in which I have testified at a deposition or trial over the last four years.

III. The Applicable Law

13. I am not a lawyer and do not have any formal legal training. I have been informed that the following legal principles are applicable with regard to the validity or patentability of a United States patent, and I have applied this law to the facts in this matter in my analysis and in rendering my opinions.

A. Claim Construction

14. I understand that the words of a patent claim are generally given their ordinary and customary meaning, which is the meaning that words would have had to a person of ordinary skill in the art (“POSA”) at the time of the invention. A POSA is deemed to read a claim term in the context of not only the particular claim in which the disputed term appears, but also the entire patent, including the other claims and the specification. Additionally, a claim term can be interpreted in light of the patent’s prosecution history. Together, the claims, specification, and prosecution history are considered the “intrinsic” record of the patent. In addition to the patent and its file history, certain “extrinsic” evidence, such as expert and inventor testimony, dictionaries, and treatises, may bear on the interpretation of the claim language, although this type of evidence may be less reliable and should not be used in contradiction of the available intrinsic evidence.

B. Obviousness

15. Obviousness Framework. I understand that a patent claim may be invalid if the differences between the subject matter claimed and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a POSA to which the subject matter pertains. To determine if a patent claim is obvious, one looks to (1) the scope and content of the prior art, (2) differences between the prior art and the claims, (3) the level of ordinary skill in the art, and (4) any secondary considerations of obviousness and nonobviousness to the extent present and further to the extent a nexus to the claimed invention is shown.

16. Reasons to Combine Teachings. I understand that the teachings of multiple references when combined may render a patent claim obvious when there is an apparent reason that would have led a POSA to combine the teachings. I have further been advised that the following rationales may support a conclusion of obviousness:

- (a) the combination involves combining prior art elements according to known methods to yield predictable results;
- (b) the combination involves a simple substitution of one known element for another to obtain predictable results;
- (c) the combination involves the use of a known technique to improve similar devices (methods, or products) in the same way;
- (d) the combination applies a known technique to a known device ready for improvement to yield predictable results;

- (e) the combination is obvious to try in that it involves choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- (f) the combination is the result of known work in one field of endeavor prompting predictable variations of such work for use in either the same field or a different one based on design incentives or other market forces; and/or
- (g) there is some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

17. Secondary Considerations of Nonobviousness. I understand that “secondary considerations” may be relevant to a determination of obviousness, and that such secondary considerations may include the following: (a) commercial success of a product using the invention if that commercial success is due to the invention, (b) a long-felt but unmet need for the claimed invention, (c) evidence of copying of the claimed invention, (d) industry acceptance after initial skepticism, and (e) praise of the invention. I am advised that the relevance of any secondary consideration of nonobviousness depends on its nexus, if any, to the merits of the claimed invention and the secondary consideration, and that it is the patent owner’s

burden to come forward with evidence of secondary considerations and the requisite nexus. I understand that a nexus exists if a secondary consideration results from one or more novel features of the claimed invention and that it does not exist where the merits of the claimed invention were readily available in the prior art.

IV. Technical Background

A. Microtiter Plates

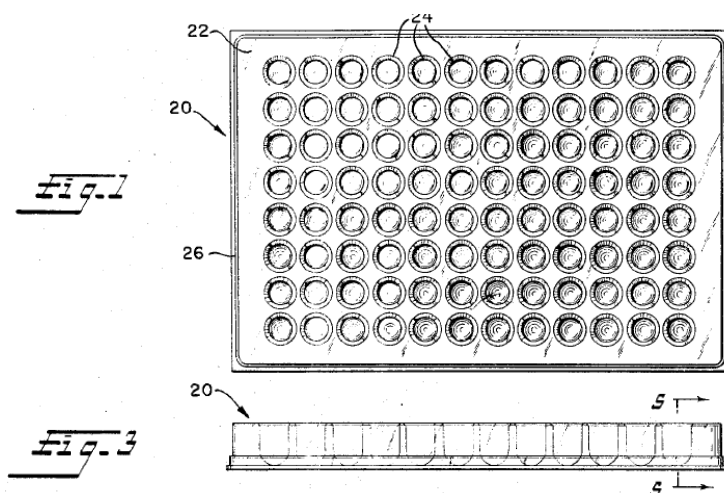
18. Microtiter plates (also known as “microplates” or “multi-well plates”) were introduced in the 1950s amid an influenza epidemic in Hungary that prompted a need for more efficient and reliable diagnostic testing.³ At the time, laboratory procedures such as assays were principally performed in test tubes, which proved to be cumbersome and slow.⁴ Microtiter plates combined multiple small test tubes (called “wells”) in an array format, which allowed assays to be performed using smaller volumes of samples and reagents and also allowed multiple samples to be processed in parallel, which increased speed and throughput.⁵ By the 1960s, 96-well microtiter plates were mass produced and widely available, including through Cooke Microtiter Ltd. (now known as Dynex

³ EX1036, Roy Manns, *History of Microplates*, The Plastics Historical Society, available at https://plastiquarian.com/?page_id=14361 (“Manns”), at [1].

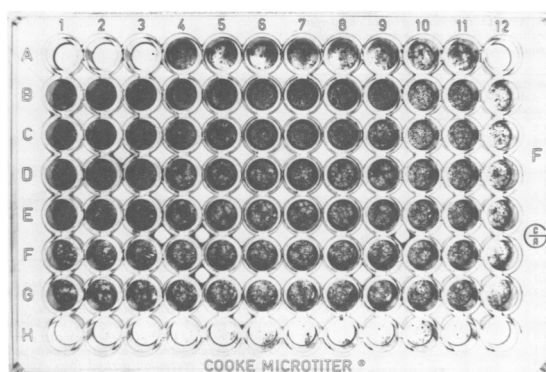
⁴ EX1036 (Manns), at [1].

⁵ EX1036 (Manns), at [1]; EX1013, U.S. Pat. No. 5,827,745 (“Astle”), at 1:12-23.

Technologies).⁶ As illustrated below, a patent issued in 1967 to Cooke et al. depicts an 8×12 array of wells arranged in the now-familiar 96-well format.⁷



Commercial examples 96-well microtiter plates from Cooke Microtiter, Ltd. can also be found throughout the literature, including the following from a 1977 paper.⁸



⁶ EX1036 (Manns), at [1]-[2]; EX1040, Thomas Astle, *Recollections of Early Microplate Automation*, J. ASSOC. FOR LABORATORY AUTOMATION, 5:30-31 (2000) (“Astle-2000”), at 2.

⁷ EX1015, U.S. Patent No. 3,356,462 (“Cooke”), at 2:55-3:7, FIGS. 1, 3.

⁸ EX1054, Günther Viehhauser, *Simple Procedure for Large-Scale Assays for Chick Interferon*, APPLIED & ENVIRON. MICROBIOL., 33(3):740-743 (1977) (“Viehhauser”), at 741, Fig. 1; see also EX1053, Thomas R. Clem et al., *Practical Colorimeter for Direct Measurement of Microplates in Enzyme Immunoassay Systems*, J. CLIN. MICROBIOL. 7(1):55-58 (1978) (“Clem”), at 56, Fig. 1.

19. By the 1990s, 96-well microtiter plates having an 8×12 array of wells had become the “de facto standard” for many laboratory assays.⁹ The use of 96-well microtiter plates was reinforced by efforts to standardize the dimensional elements of microtiter plates by the Society for Biomolecular Screening (SBS), later absorbed into the Society for Laboratory Automation and Screening (SLAS).¹⁰ Those efforts led to a standardized microtiter plate format, ANSI/SBS 4-2004, later recognized as ANSI SLAS 4-2004 (R2012), that was adopted industry wide.¹¹ This standardized format, which included 9 mm center-to-center well spacing, allowed equipment manufacturers to develop compatible instruments—such as handheld and automated multi-channel pipettes, plate readers, and robotic systems—thereby streamlining laboratory workflows and improving throughput.¹²

⁹ EX1013 (Astle), at 1:24-27; EX1014, U.S. Patent No. 5,475,610 (“Atwood”), at 3:31-48; EX1040 (Astle-2000), at 2. Standard 384- or 1536-well plates also were developed and routinely used for higher-throughput assays. See EX1021, [8].

¹⁰ EX1013 (Astle), at 1:24-27; EX1014 (Atwood), at 3:31-48; EX1040 (Astle-2000), at 2; EX1041 American National Standards Institute (ANSI) & Society for Laboratory Automation and Screening (SLAS), *for Microplates – Well Positions*, ANSI SLAS 4-2004 (R2012) (“ANSI/SLAS”), at 3.

¹¹ EX1041 (ANSI/SLAS), at 3; EX1040 (Astle-2000), at 2.

¹² EX1041 (ANSI/SLAS), at 3; EX1013 (Astle), at 1:24-45; EX1040 (Astle-2000), at 2.

B. Complementary Lab Equipment Used with Microtiter Plates

20. As the use of microtiter plates in laboratory assays became more widespread and routine, laboratory workflows also increasingly used complementary tools that matched this standard.

21. For example, handheld and automated pipettes were designed with the 8×12 format in mind.¹³ Often, these pipettes included 8 or 12 channels to transfer liquids simultaneously across an entire row or column of a microtiter plate, making the transferring process more efficient while reducing the risk of manual errors.¹⁴ Corresponding disposable pipette tips were similarly packaged in “tip trays” or “tip racks” arranged in an 8×12 array, ensuring that the pipette tips could be quickly picked up by a corresponding pipette and correctly aligned with the wells of a standard 96-well microtiter plate.¹⁵ For consistency, I use the term “tip tray” in this declaration to refer to these products.

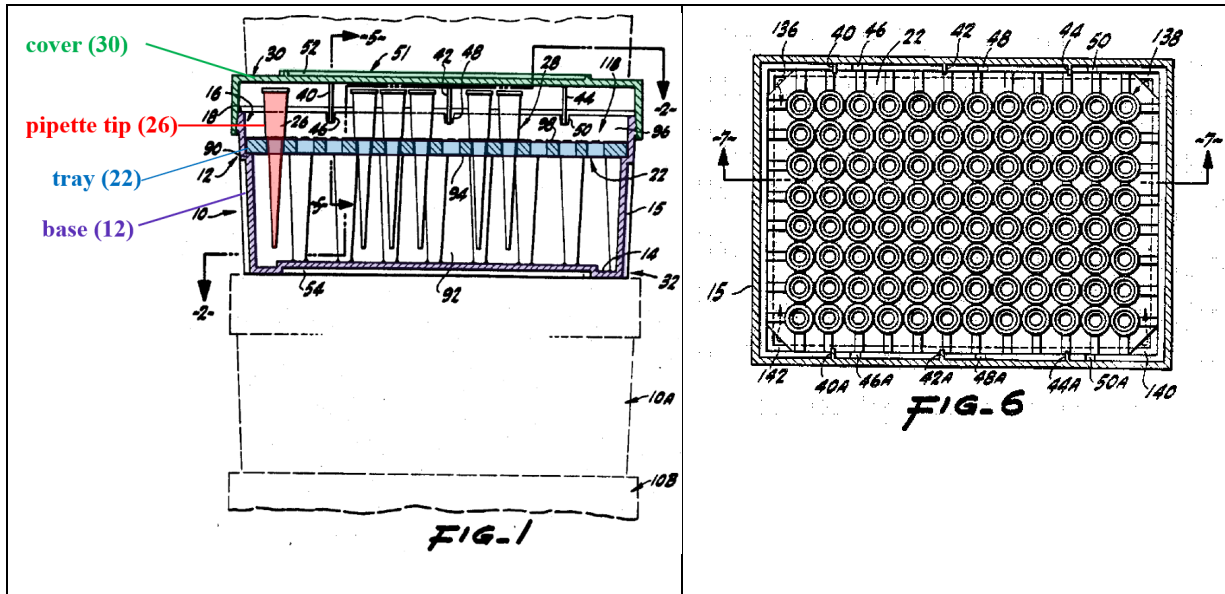
22. Rainin, a patent issued in 1987, describes a pipette tip tray having a number of features that, by June 2005, were common among commercially available pipette tip trays. As shown in the figures below, Rainin describes a tip

¹³ EX1013 (Astle), at 1:29-33.

¹⁴ EX1013 (Astle), at 1:27-29.

¹⁵ EX1007, U.S. Patent No. 4,676,377 (“Rainin”), at Fig. 6; EX1013 (Astle), at 1:24-36, Figs. 1-4.

tray holding 96 pipette tips (red) in an 8×12 array, with the tip tray (blue) housed in a stackable container having a base (purple) and cover (green).¹⁶



Each pipette tip has a proximal end or collar that has a larger diameter than the tray openings, ensuring the tip may be held in the tray until attached to the distal end of a pipette.¹⁷ Once attached, the tips can be used to dispense liquids into or withdraw liquids from microtiter plate wells.¹⁸

23. As some commercial examples, Gilson, Inc. manufactured and sold pipettes and pipette tips under the Pipetman[®] branding that were widely used in laboratories before June 2005. I myself purchased a set of Gilson Pipetman[®] pipettes in 1998 that I used for the majority of biological research assays I

¹⁶ EX1007 (Rainin), at 4:20-48, Figs. 1 (annotated), 6.

¹⁷ EX1007 (Rainin), at 5:41-45, 5:50-52, Figs. 1, 3, 4.

¹⁸ EX1007 (Rainin), at 1:10-13, Figs. 1, 4.

conducted over the next decade, including many conducted in the 96-well plate format. The images below, taken from Gilson's 2004 catalog, show a 1-channel handheld pipette (top left), 12-channel handheld pipette (top middle), the loading of pipette tips on a handheld pipette (top right), and boxed tip trays of disposable pipette tips (bottom).¹⁹



¹⁹ EX1039, Gilson, Inc., *Manual Liquid Handling Catalog* (2004), available at <https://web.archive.org/web/20040523093106/http://www.gilson.com:80/Products/prodPDF.asp?pID=106&pdfid=BRO> ("Gilson"), at [5], [7]-[9], [13]-[14].

24. Similarly, Thermo Electron sold multiple sizes of pipette tips under the Finntip[®] branding, which were available both as bulk bags and preloaded into boxed tip trays in the standard 8×12 format for easier use with standard 96-well microtiter plates.²⁰ Brinkmann Eppendorf was another manufacturer of pipette tips, who offered tips in bulk, as boxed tip trays in the standard 8×12 format, and as refill tip trays designed to rapidly reload the boxes.²¹



25. Robotic systems for carrying out pipetting procedures on standard microtiter plates also were common in laboratories by June 2005. For example, my

²⁰ EX1048, Fisher Scientific, Inc., *Fisher Catalog 2004/05* (2004) (“Fisher”), at 1185-86.

²¹ EX1048 (Fisher), at 1185, 1187.

laboratory has used a Bio-Tek Precision™ robot for many years similar to the system shown below that has been available since at least 2000.²² These robot systems could engage and release pipette tips from a standard 8×12 tip tray and transfer them between different trays, dip engaged tips in the wells of standard microtiter plates (e.g., 96-well or 384-well plates) or other vessels (e.g., troughs), wash engaged tips, and also transfer samples, reagents, or other liquids between the wells of such plates or vessels, under the control of a computer or programmable controller.²³



²² EX1049, Bio-Tek Instruments, Inc., *Precision™ Microplate Pipetting System, Liquid Handling - Automated Microplate Pipetting Systems*, 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”); EX1050, Bio-Tek Instruments, Inc., *Precision Microplate Pipetting System, Operator’s Manual*, 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”), at cover, 23.

²³ EX1050 (Bio-Tek Precision Manual), at 2-3, 16-23, 52-54.

26. Beyond pipetting instruments, by the early 2000s, a variety of analytical instruments were available for analyzing samples contained in the wells of microtiter plates.²⁴ In the late 1990s and early 2000s, I routinely used 96-well microtiter plates with optical plate readers that performed multiplexed analytical measurements of fluorescence, UV absorbance, and luminescence in this format.

27. By June 2005, there also were automated assaying instruments that analyzed samples by inserting probes into samples contained in the wells of microtiter plates. For example, Seahorse Bioscience (founded in 2001 and now owned by Agilent Technologies, Inc.) had developed an automated assaying instrument that used multiplexed probes to measure the metabolism byproducts of cells growing in the wells of microtiter plates.²⁵ As described in Seahorse's U.S. Patent Appl. Publ. No. 2005/0054028 A1 (filed in October 2003 and published in March 2005) and shown below, the instrument includes an array of pipettes 330 for transferring liquids and an array of barriers 140, 320 comprising sensors, both arranged in a complementary manner to the wells of a microtiter plate 302, such as

²⁴ EX1048 (Fisher), at 1877-81.

²⁵ EX1051, Seahorse Bioscience, *How Does XF Technology Work?*, available at https://web.archive.org/web/20041212090403/http://www.seahorsebioscience.com/xf_work.html (archived Dec. 12, 2004) ("Seahorse"); EX1052, U.S. Patent Appl. Publ. No. 2005/0054028 A1 ("Teich") (initially assigned to Thermogenic Imaging, which became Seahorse Bioscience), at ¶¶ [0082]-[0090], [0100]-[0107], Figs. 1, 3, 5a.

a standard 96-, 384- or 1536-well plate.²⁶ The barriers are carried on tubular supports/plungers 322,²⁷ and the distal ends of the barriers comprise a removable, disposable cover with “one or more optically-coupled sensors” that interface with a computerized measurement system 350, 540, for example, via optical fibers disposed within the tubular supports.²⁸ During use, the barriers are lowered into the sample wells of the microtiter plate and sensor readings are obtained by the measurement system.²⁹ I discuss other such instruments in the next section.

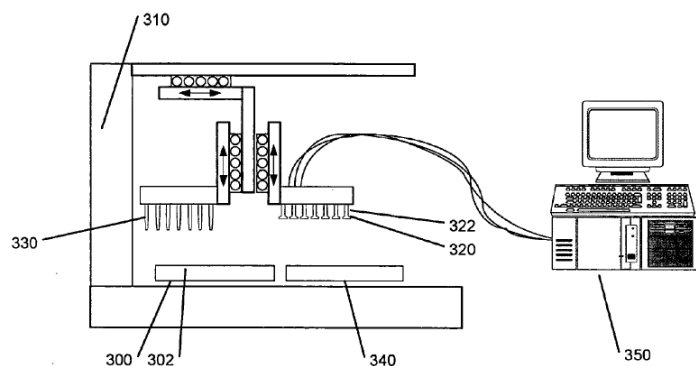


Fig. 3

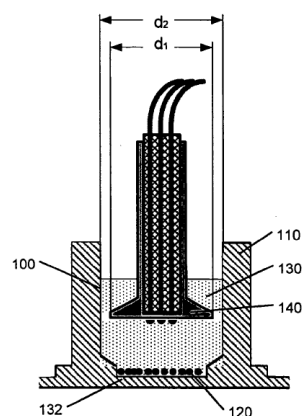


Fig. 1

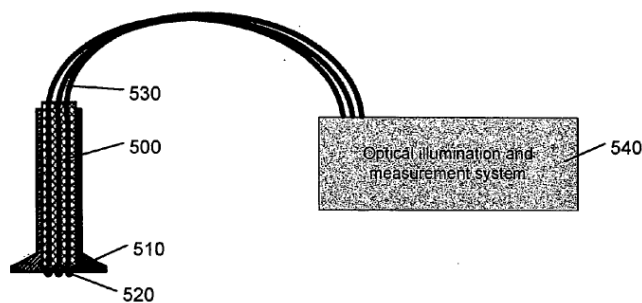


Fig. 5a

²⁶ EX1052 (Teich), at ¶¶ [0087], [0090], Figs. 1, 3.

²⁷ EX1052 (Teich), at ¶ [0090], Fig. 3.

²⁸ EX1052 (Teich), at ¶ [0100], Fig. 5a

²⁹ EX1052 (Teich), at ¶ [0090], Figs. 1, 3.

C. Use of Tip Trays to Store Sensor Probes

28. By June 2005, a variety of sensor probes were used in laboratory assays. These sensor probes commonly comprised a functionalized sensing surface with a layer of immobilized analyte-binding molecules (e.g., antibodies, antigens, enzymes, receptors, oligo nucleotides, etc.) for “capturing” (binding) analyte molecules that may be present in a sample.³⁰ During an assay, when a probe is exposed to a sample, the binding of analyte molecules to the probe is transduced into a measurable signal (e.g., optical, electrochemical).³¹ It was also recognized that sensor probes could be packaged in a tip tray similar to pipette tip trays to facilitate their use with microtiter plates and assaying instruments.

29. For example, Miles, a patent issued in 1978, discloses sensor probes in the form of pipette tips coated with analyte-binding molecules such as antibodies or antigen (referred to in Miles as a “specifically bindable substance”) to bind analyte molecules that are present in samples contained in the wells of a microtiter plate.³² Miles explains that assays may be set up so that after analyte binds to the probes, the probes produce an optical signal, for example through “fluorogenic” or

³⁰ EX1042, Peter B. Luppá et al., *Immunosensors- principles and applications to clinical chemistry*, CLINICA CHIMICA ACTA, 314:1-26 (2001) (“Luppá”), at 5.

³¹ EX1042 (Luppá), at 6.

³² EX1005, U.S. Patent No. 4,087,248 (“Miles”), at 2:19-34, 4:3-15, 5:53-68, 9:55-57, 11:26-44, 12:24-26.

“fluorescent” reagents that provide a measurable, optical fluorescence signal or “enzymes” that were commonly used to provide a measurable, optical color change.³³ As shown in Figures 5 and 6 below, Miles also describes a tip tray (blue) with an array of openings for arranging and packaging multiple probes (red) in a format similar to tip trays used with pipette tips.³⁴ Each probe is conically shaped and has a proximal end or collar that is designed to attach to the receiving end of an assay machine and that also has a larger diameter than the tray openings, allowing the probes to be held in the tray.³⁵

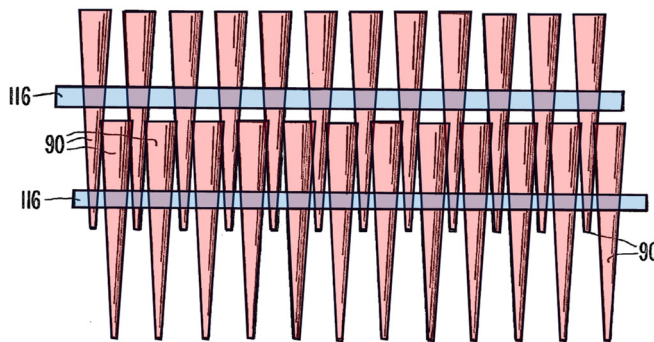


FIG. 5

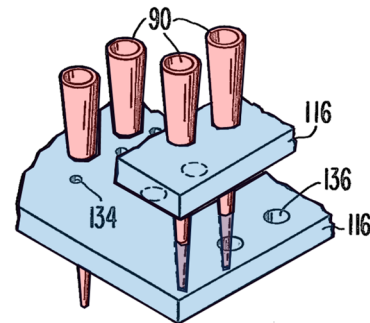


FIG. 6

30. As another example, Lapeus describes similar tip trays for storing sensor probes used in laboratory assays.³⁶ As Lapeus explains, there was a trend among hospitals, clinics, and laboratories to use “automated analyzer systems” for

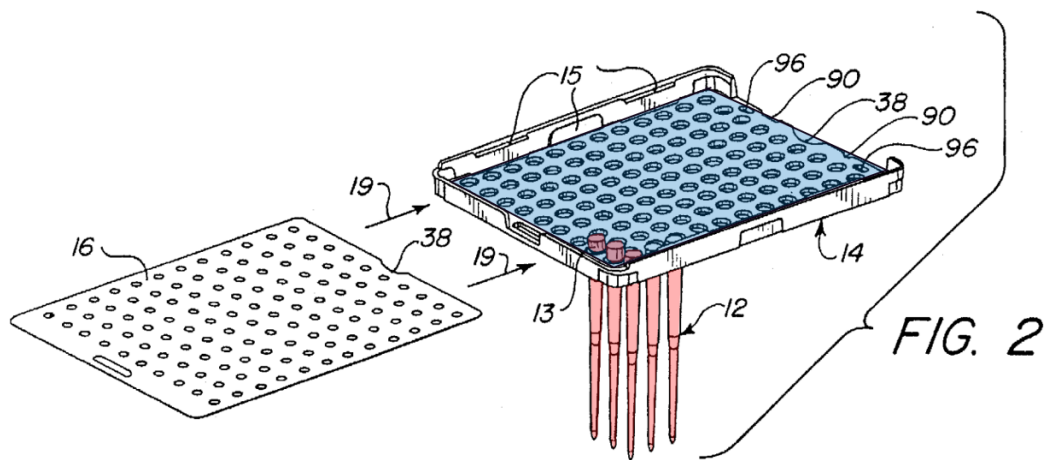
³³ EX1005 (Miles), at 4:20-30, 11:63-66; EX1012 (Sailor), 106:20-108:15.

³⁴ EX1005 (Miles), at 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5, 6 (annotated).

³⁵ EX1005 (Miles), at 2:45-51, 10:18-34, Figs. 2, 5, 6; see also Fig. 7.

³⁶ EX1016, U.S. Patent No. 5,674,047 (“Lapeus”), at abstract, 1:6-8, Fig. 2.

assaying a variety of patient samples “such as blood, spinal fluid, urine, serum, plasma, and the like,” and these systems commonly used “disposable probe tips.”³⁷ To facilitate the use of probe tips with such automated systems, Lapeus proposes using a tip tray.³⁸ For example, as shown below, Lapeus describes a tip tray (blue) with an array of openings for arranging and packaging probe tips (red) in a similar format to tip trays used with standard pipette tips.³⁹ Each probe tip has a proximal end or collar that is designed to attach to an “automated analyzer system” and has a wider diameter than the openings so that the tip is held in the tip tray.⁴⁰



³⁷ EX1016 (Lapeus), at 1:11-18.

³⁸ EX1016 (Lapeus), at 1:32-40, 2:60-3:9.

³⁹ EX1016 (Lapeus), at 3:14-22, Fig. 2 (annotated).

⁴⁰ EX1016 (Lapeus), at 2:60-3:4, 3:14-22, Fig. 2.

D. BLI/RIfS Probes

31. By June 2005, various sensor probes were used in laboratory assays. This included probes for performing “reflectometric interference spectroscopy” (RIfS) or what was later commercially known as “biolayer interferometry” (BLI).” I refer to this technique here as “BLI/RIfS” for consistency.

32. BLI/RIfS is an optical 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.⁴¹ When a beam of white light passes through the thin film, it generates two partially reflected beams of light, one at each interface of the film.⁴² The reflected beams constructively and destructively interfere with one another to create an interference pattern.⁴³ When analyte molecules bind to the film, the optical thickness of the film increases, which results in changes in the interference pattern that can be detected using a spectrometer to infer analyte binding.⁴⁴

⁴¹ EX1006, Yuxiao Yang et al., *Direct monitoring of antigen-antibody interactions by optical fiber bioprobe*, PROCEEDINGS OF SPIE, THIRD INT’L CONFERENCE ON PHOTONICS AND IMAGING IN BIOLOGY AND MEDICINE, 5254:431-436 (2003) (“Yang”), at 431-32.

⁴² EX1006 (Yang), at 432, Fig. 1a.

⁴³ EX1006 (Yang), at 432, 432, Figs. 5, 6.

⁴⁴ EX1006 (Yang), at 432, 432, Fig. 6.

33. Probes for performing BLI/RIfS assays were known as of June 2005. As annotated in the figures below, Yang, WO854,⁴⁵ and Sun⁴⁶ each describe a prototypical BLI/RIfS probe comprising a short segment of optical fiber coated with a transparent interference layer (optical element).⁴⁷ The proximal and distal endfaces of the interference layer, respectively, comprise two reflecting surfaces that are separated by more than 50 nm, and the distal reflecting surface is further coated with a layer of analyte-binding molecules (e.g., antibodies, antigens) for binding analyte molecules present in a sample.⁴⁸ During an assay, when analyte molecules bind to the distal end/tip of the probe, the resulting interference pattern varies (as registered on a spectrometer) and provides an indication of analyte binding.⁴⁹

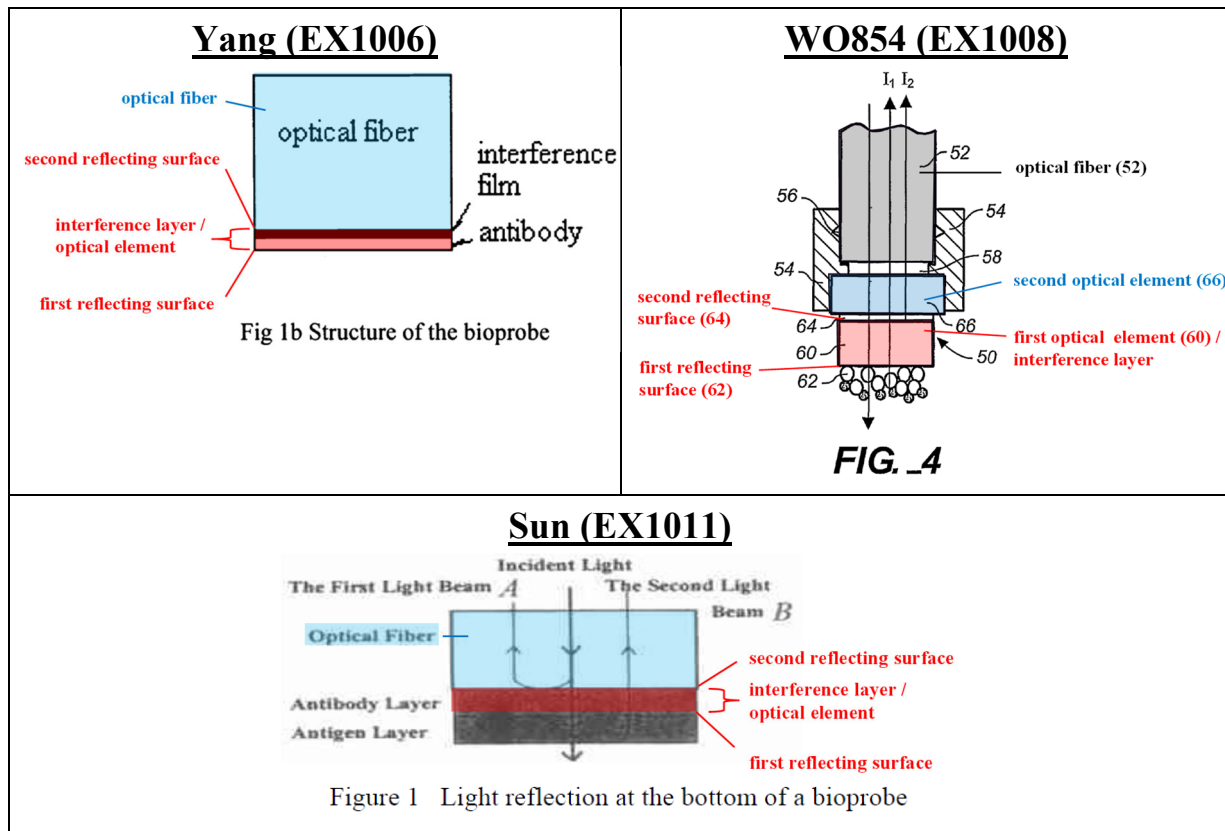
⁴⁵ EX1008, PCT Publication No. WO 2005047854 A2 (“WO854”).

⁴⁶ EX1010, Yan Sun et al., *Fiber Optic Direct-Sensing Biosensor Applied in Detecting Biolayer Thickness of Nanometer Grade*, ACTA PHOTONICA SINICA, 31(6):657-661 (June 2002). Because Sun is published in Chinese, I refer to the certified English translation at EX1011.

⁴⁷ EX1008 (WO854), at ¶¶[0051], [0077]-[0079], Fig. 4 (annotated); EX1006 (Yang), at 432, Fig. 1b (annotated); EX1010/EX1011 (Sun), at 657, 659, Fig. 1 (annotated) (Sun refers to the interference layer as a “siliconization film.”).

⁴⁸ EX1008 (WO854), at ¶¶[0051], [0078], Fig. 4; EX1006 (Yang), at 432, 434, Fig. 1b; EX1010/EX1011 (Sun), at 657, 659, Fig. 1.

⁴⁹ EX1008 (WO854), at ¶[0079], Fig. 4; EX1006 (Yang), at 434-35, Fig. 6; EX1010/EX1011 (Sun), at 659, Fig. 5.



34. Yang, for example, demonstrates operation of the BLI/RIfS principle in a study designed to measure the concentration of a biological analyte in a sample. In that study, a probe of the design above (Yang, Fig. 1b) was coated with rabbit IgG and goat anti-rabbit IgG antibodies to form a sandwich of analyte binding molecules.⁵⁰ The probe was then exposed to several concentrations of rabbit anti-goat IgG antibodies (i.e., the analyte). The binding of analyte molecules to the distal end or tip of the probe, as shown by atomic force microscopy (Fig. 5b), resulted in a detectable phase shift in the spectrum of reflected light

⁵⁰ EX1006 (Yang), at 434.

(reflectance spectrum), from which analyte binding could be inferred in real time (Fig. 6).⁵¹

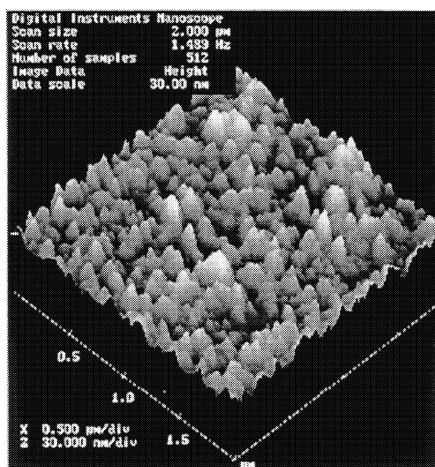


Fig 5b 3D AFM picture of protein bound onto the surface of the bioprobe

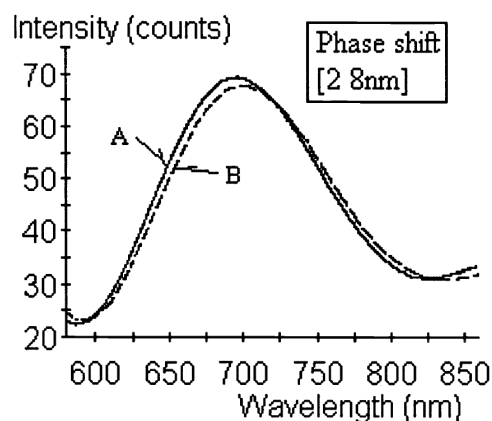


Fig 6 Caused shifting of the reflectance spectrum by the binding of protein

V. The '588 Patent

A. Overview

35. The '588 patent is entitled "Tip Tray Assembly for Optical Sensors."

It is directed to "[a]n apparatus for packaging an optical sensing assembly," which is the term the patent uses for a sensor probe.⁵² Although the '588 patent discusses BLI/RIfS probes (which the patent refers to as "optical sensing assemblies"), 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."⁵³

⁵¹ EX1006 (Yang), at 434.

⁵² EX1001 ('588 patent), at claim 1.

⁵³ EX1001 ('588 patent), at 1:18-22, 1:62-66.

36. The '588 patent proceeds to describe a “tip tray apparatus 500” similar to tip trays that were known and used in the art for packaging pipette tips.⁵⁴

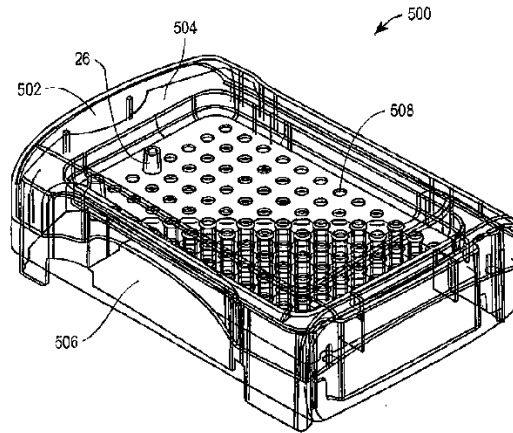


FIG. 5

37. As I discuss above, microtiter plates had become a de facto standard for many laboratory assays, and tip trays were routinely employed for arranging and packaging pipette tips in an 8×12 format. Consistent with that practice, the tip tray apparatus 500 of the '588 patent comprises “a substrate 504...that includes a number of openings 508 for containing one or more discrete optical assemblies 26.”⁵⁵ 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, configurations that were all well known.⁵⁶

⁵⁴ EX1001 ('588 patent), at 11:22-24, Fig. 5.

⁵⁵ EX1001 ('588 patent), at 11:24-27.

⁵⁶ EX1001 ('588 patent), at 11:57-63.

38. The '588 patent further explains that probes or 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.”⁵⁷ According to the patent, this arrangement 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.”⁵⁸

39. 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.”⁵⁹ Figure 6 shows “an exploded view of the tip tray apparatus 500” and “how the various pieces of the tip tray apparatus 500 fit together.”⁶⁰

⁵⁷ EX1001 ('588 patent), at 11:43-50.

⁵⁸ EX1001 ('588 patent), at 12:63-13:1.

⁵⁹ EX1001 ('588 patent), at 12:4-15, 13:1-3.

⁶⁰ EX1001 ('588 patent), at 12:23-24, Fig. 6.

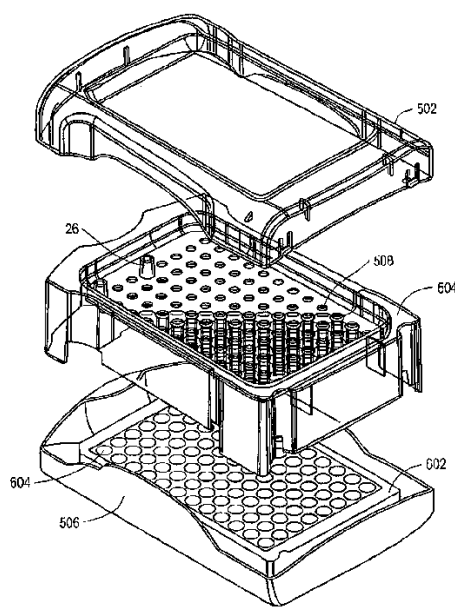


FIG. 6

40. Further, the '588 patent states that a container 602 may be provided below the substrate 504 for immobilization or pre-wetting of the optical assembly 26.⁶¹ The container 602 “can be a standard 96-well, 384-well, or 1536-well microtiter plate that includes an array of wells 604 for holding sample.”⁶² The openings 508 in the substrate 504 “correspond generally with the wells 604 in container 602,” so 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 (not shown) of the optical sensing assembly 26...extend[s] below the substrate 504 and into the well 604 of container 602.”⁶³

⁶¹ EX1001 ('588 patent), at 1:66-2:19, 7:11-16, 12:28-35, 13:6-7.

⁶² EX1001 ('588 patent), at 12:30-32.

⁶³ EX1001 ('588 patent), at 12:38-47.

B. Prosecution History

41. Based on my review of the '588 patent and its prosecution history, the '588 patent issued from Application No. 13/101,112, filed on May 4, 2011.

42. During prosecution, the Patent Office examiner initially rejected the pending claims as anticipated or obvious based on U.S. Patent No. 6,838,051 ("Marquiss").⁶⁴ The examiner reasoned that Marquiss "teach[es] an apparatus for packing an optical sensing assembly" with a "substrate (e.g., manifold 3502)" containing a "plurality of openings (e.g., aperture 3540)" through which a tip "extend[s]...to be suspended."⁶⁵

43. In response, the patentee argued that "Marquiss fails to disclose or suggest an opening being configured for holding a discrete optical sensing assembly therein" and sought to distinguish Marquiss as describing the holding of a "dispensing tip" rather than an "optical sensing assembly."⁶⁶ The examiner, however, maintained the rejections, explaining that "[a]pparatus claims must be structurally distinguishable from the prior art in terms of structure, not function."⁶⁷ According to the examiner, it was sufficient that Marquiss taught an apparatus that was "capable of performing the intended use as recited in the preamble, or

⁶⁴ EX1004 ('588 FH), at [105]-[110], [132]-[136].

⁶⁵ EX1004 ('588 FH), at [105]-[106], [132].

⁶⁶ EX1004 ('588 FH), at [151]-[152].

⁶⁷ EX1004 ('588 FH), at [183].

elsewhere,” such as holding discrete optical sensing assemblies, because the claims did not “positively recite a discrete optical sensing assembly.”⁶⁸

44. The patentee then amended independent claim 1 to recite “at least one discrete optical sensing assembly” comprising known features of BLI/RIfS probes, such as “an optical fiber and a transparent optical element having first and second reflecting surfaces.”⁶⁹ Relying on the amendment, the patentee argued that Marquiss “merely teaches passing fluid through dispensing elements” and not “an apparatus for packaging an optical sensing assembly” with the claimed optical fiber and reflecting surfaces.⁷⁰ After further rejections based on other prior art, the patentee amended the claims to add other known elements of BLI/RIfS probes, including “first and second reflecting surfaces [being] separated by at least 50 nm, wherein the first reflecting surface comprises a layer of analyte binding molecules.”⁷¹

45. Based on the patentee’s assertions, the examiner allowed the claims, under the mistaken belief that the prior art did not teach a BLI/RIfS probe having

⁶⁸ EX1004 (’588 FH), at [183].

⁶⁹ EX1004 (’588 FH), at [218].

⁷⁰ EX1004 (’588 FH), at [209].

⁷¹ EX1004 (’588 FH), at [236], [239]-[240].

the claimed features.⁷² As I discuss below, however, prior art such as Yang and WO854 (among others like Sun) had already described such BLI/RIfS probes.

C. Priority Date

46. As noted, the '588 patent issued from Application No. 13/101,112, filed on May 4, 2011, which is a divisional of Application No. 11/423,669, filed on June 12, 2006, which in turn claims priority to U.S. Provisional Application No. 60/690,325, filed on June 13, 2005. For purposes of this declaration, I have been asked to assume that the priority date of the claims of the '588 patent is June 13, 2005. I do not express any opinions regarding whether the '588 patent's claims are entitled to that priority date.

VI. Level of Ordinary Skill in the Art

47. In rendering my opinions, I have been asked to consider the level of skill possessed by a POSA in the field pertaining to the '588 patent. I have been advised that the factors relevant to determining the level of ordinary skill in the art include (1) the educational level of the named inventors, (2) the type of problems encountered in the art, (3) prior art solutions to those problems, (4) the rapidity with which innovations are made, (5) the sophistication of the technology, and (6) the educational level of active workers in the field.

⁷² EX1004 ('588 FH), at [252].

48. The '588 patent states, under the section titled "Field of the invention," that "[t]he present invention relates to an apparatus and method based on fiber optic interferometry, and in particular, to a tip tray apparatus for packaging of optical sensors used in detecting analytes."⁷³ Based on my experience and my review of the literature, a POSA in this field 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.

49. I not only qualify as a POSA but also have worked with and trained others who qualify as POSAs. I have more than 25 years of experience performing laboratory assays, including biochemical analyses using microtiter plates, tip trays, and sensor probes. Indeed, when my wife was pregnant with our second child, I was conducting 3-4 ELISAs per day, and we decided to name our daughter Eliza after the assay (although spelled with a 'z' for pronunciation reasons). I also have taught and mentored students, researchers, and industry collaborators on designing, conducting, and interpreting a variety of assays. For example, one of my recent Ph.D. trainees is a Senior Scientist in the late formulation group for mRNA/lipid nanoparticle vaccines at Pfizer, where she played a key role in the development of

⁷³ EX1001 ('588 patent), at 1:18-23.

Pfizer's pediatric COVID vaccine. Her Ph.D. work involved extensive use of bio-optical characterization methods, including ELISA and spectroscopic characterization of novel molecules and their interaction with tissue receptors. Other recent graduate and post-doctoral trainees of mine work at Amgen in early-stage small molecule formulation, Amgen in late-stage biologics formulation, Merck in biopharmaceutical analytical development and support, Merck in clinical formulation support, Azurity in pediatric formulation, Genentech in analytical development and support, and other pharmaceutical companies, including contract research organizations (CROs) that provide analytical services. I also collaborate extensively with Novartis AG to develop analytical techniques supporting their high-concentration biologics development group, which involves extensive use of optical techniques such as BLI/RIfS and surface plasmon resonance (SPR) by my trainees.

VII. Claim Construction

50. For the purposes of this declaration, I have given all the claim terms of the challenged claims their plain and ordinary meaning, as would have been understood by a POSA at the time of the alleged invention, which I have assumed is June 13, 2005 for all claims.

VIII. Opinions based on Miles and Yang

51. In my opinion, the subject matter of claims 1-13 and 18-19 of the '588 patent would have been obvious to a POSA based on the combination of Miles and Yang. As I address below, Miles discloses a tip tray for storing optical sensor probes and POSAs would have found it obvious to use such a tip tray to package BLI/RIfS probes such as those described in Yang.

A. Overview of Miles

52. Miles (EX1005), entitled “Multiple Assay Machine and Method,” is a patent that issued on May 2, 1978. I understand that Miles qualifies as prior art.

53. Miles discloses a system for conducting assays using conical pipette tips (sensor probes) that function as optical sensing assemblies, as well as the convenient packaging of these probes in tip trays.⁷⁴ It further describes using these probes with an automated assay machine to assay multiple samples simultaneously in microtiter plates.⁷⁵

54. The distal ends (tips) of Miles' probes are coated (insolubilized) with one member of a pair of “specifically bindable substances” (SBS), such as an antigen, antibody, or other analyte-binding molecule.⁷⁶ The immobilization of

⁷⁴ EX1005 (Miles), at abstract, 2:19-65.

⁷⁵ EX1005 (Miles), at 12:23-26.

⁷⁶ EX1005 (Miles), at 2:19-34, 2:52-55, 4:3-15, 5:53-68.

analyte-binding molecules functionalizes the probe tips so that they can bind analyte molecules that may be present in a sample during an assay.⁷⁷ As Miles explains, assays may be carried out on the probe tips by introducing the tips to reagents and samples contained in the wells of microtiter plates, specifically referencing 96-well microtiter plates from Cooke Microtiter Ltd.⁷⁸ Because the probes are also pipette tips, solutions of samples and reagents may be drawn into or ejected from the tips during the course of an assay.⁷⁹

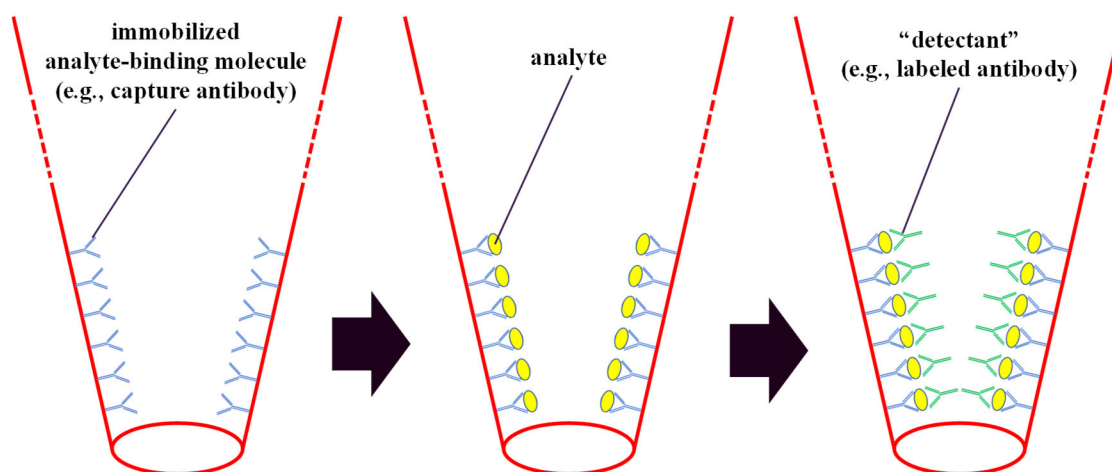
55. Miles further describes example procedures in which probe tips coated with analyte-binding molecules (e.g., capture antibodies) are used to bind analyte molecules (e.g., human growth hormone (HGH)) in solutions of samples and standards, which are then introduced to a labeled antibody or antigen (referred to in Miles as a “detectant”) to detect the presence and amount of analyte in the samples.⁸⁰ I have created the diagram below to illustrate this process of immobilizing a capture antibody to the probe tip (left), binding of analyte in a sample solution (middle), and binding of a detectant (right).

⁷⁷ EX1005 (Miles), at 2:19-34, 2:52-55, 4:3-15, 5:53-68.

⁷⁸ EX1005 (Miles), at 2:55-3:4, 12:24-26, Fig. 2; see also EX1053, 56, Fig. 1; EX1054, 741, Fig. 1 (showing commercial examples of 96-well microtiter plates from Cooke Microtiter, Ltd.).

⁷⁹ EX1005 (Miles), at 2:55-3:4.

⁸⁰ EX1005 (Miles), at 11:26-44, 12:64-13:36.



56. Miles' examples use "radioactively labelled" (radiolabeled) reagents as the "detectant."⁸¹ Recognizing the potential safety, waste-management, and health issues associated with radioactive materials, however, the industry developed and shifted to alternative labeled reagents.⁸² In my own work during the late 1990s and 2000s, I recall shifting from using radiolabeled reagents to alternative labeled reagents and detection methods that provided similar sensitivity but with little to no hazards for most biological assays. My own incentive was an accidental hand-prick with a pipette tip containing ^{32}P -radiolabeled antibody in the late 1990s. Miles, in fact, identifies and suggests using several of these known alternatives, explaining that assays may be designed to use "enzymes," "fluorescers," and "fluorogenic" substances to produce an optical readout.⁸³

⁸¹ EX1005 (Miles), at 6:49-7:31, 13:10-27.

⁸² EX1020 (Lequin), at 2145-46; EX1043, Jay L. Bock, *The New Era of Automated Immunoassay*, AM. J. CLIN. PATHOL., 113:628-646 (2000) ("Bock"), at 633.

⁸³ EX1005 (Miles), at 4:20-30, 11:63-66.

Fluorescers are molecules that when excited with an appropriate wavelength of light, emit an optical fluorescence signal that can be detected and measured to provide an indication of analyte binding.⁸⁴ Fluorogenic substances are not initially fluorescent but become fluorescent upon undergoing a chemical reaction, and the resulting optical fluorescence signal may be similarly detected and measured.⁸⁵ By June 2005, instruments for quantifying fluorescence signals in standard microtiter plates were commercially available.⁸⁶

57. Miles also refers to “enzyme immunoassays,” which by 2005 was a routinely used alternative to radiolabeled assays.⁸⁷ Enzyme immunoassays, which include ELISAs, use enzyme-labeled reagents to generate a measurable optical color change.⁸⁸ One common enzyme label is horseradish peroxidase (HRP), which may be used with the substrates hydrogen peroxide (H_2O_2) and o-phenylenediamine (OPD). The product of the reaction catalyzed by HRP is a chemical called diaminophenazine (DAP), which has a distinct color that can be

⁸⁴ See EX1043 (Bock), at 633.

⁸⁵ See EX1043 (Bock), at 633.

⁸⁶ EX1048 (Fisher), at 1879-80.

⁸⁷ EX1005 (Miles), at 4:20-30, 11:63-66; see also EX1020 (Lequin), at 2415-17; EX1012 (Sailor), at 106:20-108:15.

⁸⁸ EX1020 (Lequin), at 2416; EX1043 (Bock), at 633; EX1012 (Sailor), at 106:20-108:15.

detected and measured. Again, by June 2005, instruments for quantifying such colorimetric signals in standard microtiter plates were commercially available.⁸⁹

58. In addition to describing sensor probes and their use in assays, Miles describes a tip tray 116 (referred to in Miles as a “tip rack”) for packaging the probes.⁹⁰ As shown in Figures 5 and 6 below, the tip tray 116 (blue) includes an array of holes or openings 134, 136 (green) in which the probes 90 (red) are held and through which the distal ends/tips of the probes extend and are suspended.⁹¹ The proximal ends of the probes are designed to attach to a pipette or the mechanized syringe battery of an assay machine, and the proximal ends have a larger diameter than the openings 134, 136, allowing the probes to be held in the tip tray 116.⁹² The tip tray also holds 8 probes along one dimension (side view in Figure 4) and 12 probes along the other dimension (front view in Figures 2 and 5), which facilitates using the probes with 96-well microplates having an 8×12 array of wells and related equipment.⁹³

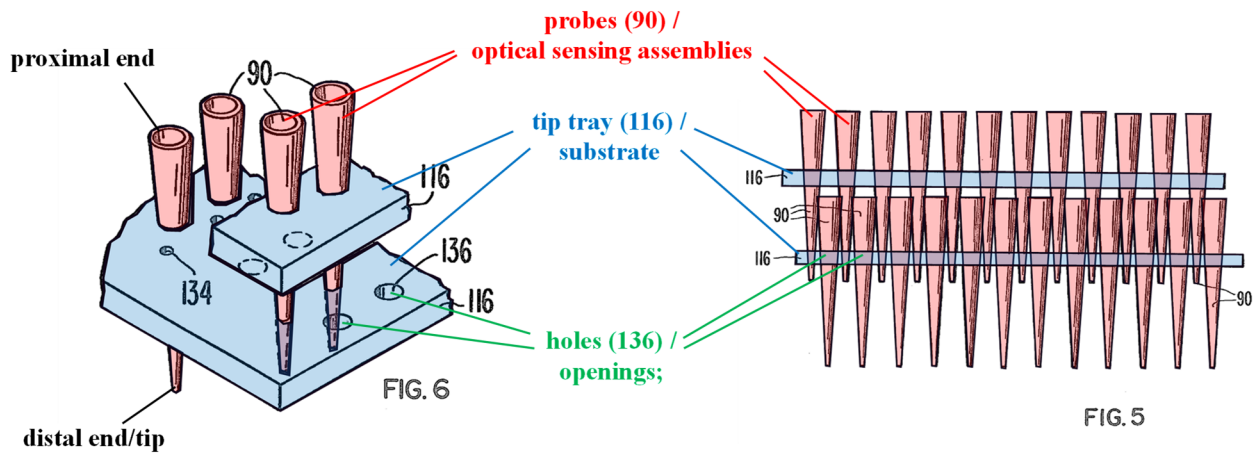
⁸⁹ EX1048 (Fisher), at 1878, 1880-81.

⁹⁰ EX1005 (Miles), at 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5, 6.

⁹¹ EX1005 (Miles), at 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5, 6 (annotated).

⁹² EX1005 (Miles), at 2:45-51, 10:28-34, Figs. 5-7.

⁹³ EX1005 (Miles), at 2:45-51, 3:41-42, 3:44-47, 12:24-26, Figs. 2, 4, 5.



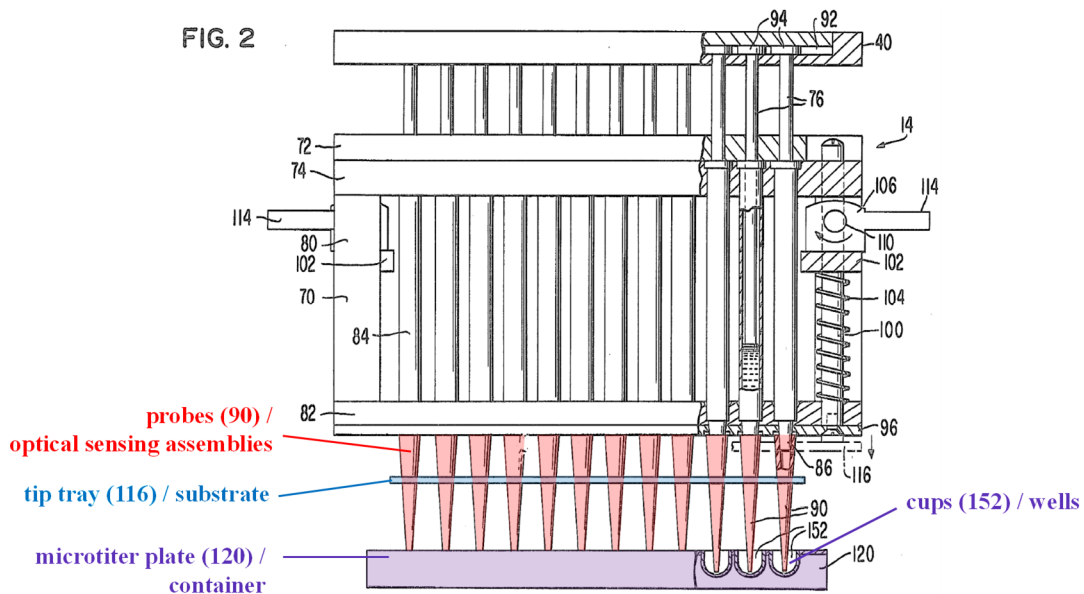
59. Miles further discloses an automated assay machine 10 containing a syringe battery 14 that uses the probes to conduct multiple assays simultaneously on a microtiter plate.⁹⁴ As shown in Figure 2 below, the syringe battery 14 may be loaded with probes 90, which are positioned in the tip tray 116 in a complimentary manner to the syringes 84 in the syringe battery.⁹⁵ A motorized lower platform 50 beneath the syringe battery 14 can be raised or lowered as needed.⁹⁶ During an assay, a microtiter plate 120 (referred to in Miles as a “sample or reagent tray”) may be placed on the platform and raised so that the tips of the probes are inserted into and “reach substantially to the bottom” of the wells 152 (“cups”), ensuring that the tips contact the samples and reagents contained in the wells.⁹⁷

⁹⁴ EX1005 (Miles), at 8:49-52, Figs. 1-2.

⁹⁵ EX1005 (Miles), at 9:49-54, 10:45-47, Fig. 2 (annotated).

⁹⁶ EX1005 (Miles), at 8:6-23, 11:26-44, Fig. 2.

⁹⁷ EX1005 (Miles), at 9:55-57, 11:26-44, Fig. 2.



B. Overview of Yang

60. Yang (EX1006), entitled “Direct monitoring of antigen-antibody interactions by optical fiber bioprobe,” was published to participants of the Third International Conference on Photonics and Imaging in Biology held on June 8-11, 2003, and was republished in Proceedings of SPIE on December 8, 2003. I refer to a version of Yang obtained from the British Library and understand that Yang has been publicly accessible at the British Library since as early as February 4, 2004, which I understand qualifies as prior art.⁹⁸ Additionally, during International Trade Commission Investigation No. 337-TA-1344, Sartorius’ expert, Dr. Michael Sailor, provided deposition testimony confirming various disclosures in Yang. I refer to Dr. Sailor’s testimony to the extent it relates to my opinions here.

⁹⁸ EX1031 (Declaration of Seema Rampersad), at [1], [5]-[6], [13]; see also EX1032 U.S. Copyright Office, Certificate of Registration (copyright registration for journal in which Yang was published, identifying June 8, 2003 publication).

61. Yang discloses a probe for “[r]eflectometric interference spectroscopy (Rifs),” which was commercially known as BLI, and explains that it is “a successful label-free method” for detecting analytes in a sample.⁹⁹ Figure 3 shows Yang’s BLI/RifS setup, in which white light from a source is transmitted through a “‘Y’ type [Y-shaped] optical fiber” to the distal end of an “optical bioprobe” and then reflected back to a detector (“a reflect spectrometer”) where an interference pattern is registered.¹⁰⁰ 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.¹⁰¹

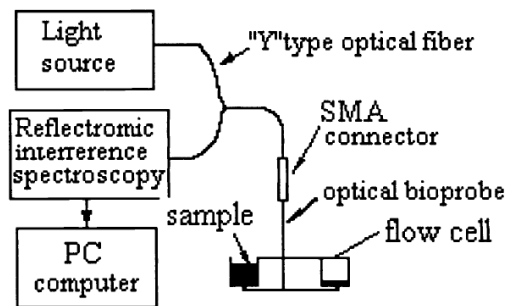


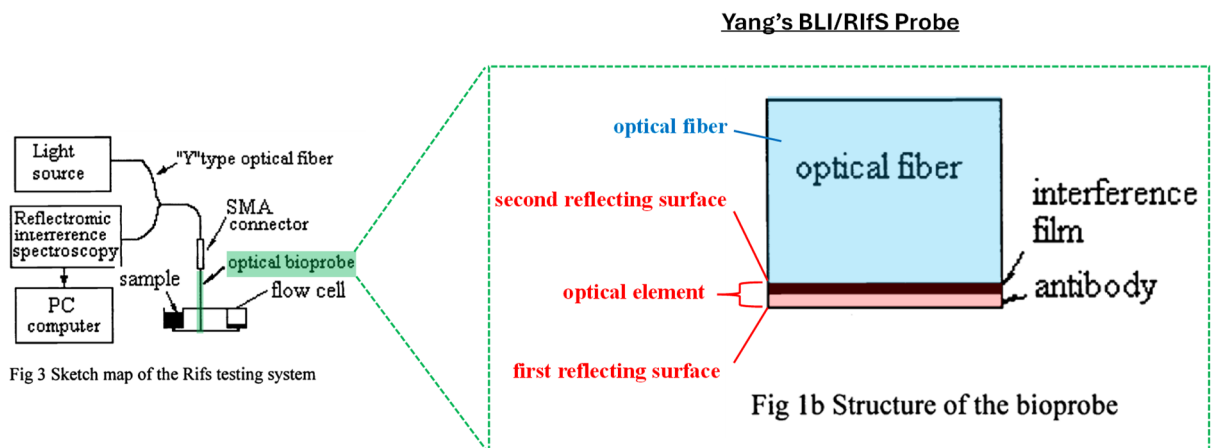
Fig 3 Sketch map of the Rifs testing system

⁹⁹ EX1006 (Yang), at 431; EX1012 (Sailor), at 282:1-5.

¹⁰⁰ EX1006 (Yang), at 433-34, Fig. 3; EX1012 (Sailor), at 283:9-284:6.

¹⁰¹ EX1006 (Yang), at 433, Fig. 3. SMA905 connectors are standardized coaxial connectors that comprise an internally threaded nut and a ferrule that holds an optical fiber. Two SMA connectors each holding an optical fiber may be removably coupled using an externally threaded mating adaptor. EX1012 (Sailor), at 285:4-12, 297:12-18; EX1057, Fiber Optics Association Reference Guide, *Connector Identifier*, available at <https://www.thefoa.org/tech/connID.htm> (“FOA Reference Guide”), at 1, 8; EX1059, Metrotek, MetroTek Catalog, Issue No. 8 (2004) (“MetroTek Catalog”), at 7 (showing SMA905 connector and adaptor). Numerous other optical fiber connectors were known. EX1057; EX1059, at 6-7.

62. As shown in Figure 1b, Yang's probe consists of a segment of optical fiber coated with a "transparent interference layer" or film (optical element).¹⁰² Yang specifies that this interference layer includes a thin tantalum pentoxide (Ta_2O_5) layer having a thickness of approximately "10~20nm" and a "transparent" layer of "special material" having a thickness of approximately "550~600nm."¹⁰³ Yang also explains that the "special material" serves as a "transducer" for "biomolecular interaction analysis" and (as shown in Fig. 1b) may be coated with antibodies (or other analyte-binding molecules) to bind analyte present in a sample.¹⁰⁴



63. Yang does not specify (and the patent claims here do not require) a particular material for the "special material." Suitable materials were known. One

¹⁰² EX1006 (Yang), at 432, Figs. 1b, 3 (annotated); EX1012 (Sailor), at 285:13-286:5.

¹⁰³ EX1006 (Yang), at 432, Fig. 1b; EX1012 (Sailor), at 288:5-289:1.

¹⁰⁴ EX1006 (Yang), at 432, 434, Fig. 1b; EX1012 (Sailor), at 285:18-286:5, 288:1-4.

example of a suitable material is polystyrene, a transparent material that was used in BLI/RIfS sensors to provide a hydrophobic surface for immobilizing antibodies.¹⁰⁵ A POSA also was well capable of implementing the interference layer of Yang's probe. As Sartorius' expert, Dr. Sailor, acknowledged, a POSA "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."¹⁰⁶ Similarly, in the context of the BLI/RIfS probe described in Sun (EX1011), Dr. Sailor explained that POSA was capable of identifying a suitable material for the interference layer and that he himself would have tried polystyrene."¹⁰⁷

64. Further, as shown in Figure 1a, the interference layer (optical element) of Yang's BLI/RIfS probe includes two reflecting surfaces, one at the proximal endface of the interference layer (between the optical-fiber portion of the probe and the interference layer) and a second at the distal endface of the interference

¹⁰⁵ EX1018, Fang Yu et al., *Reflectometry Interference Spectroscopy in Detection of Hepatitis B Surface Antigen*, CLINICAL CHEMISTRY, 46(9):1489-1490 (September 2000) ("Yu"), at 1489, Fig. 1(A) (describing BLI/RIfS sensor with polystyrene interference layer); EX1019, Weiping Qian et al., *Immobilization of Antibodies on Ultraflat Polystyrene Surfaces*, CLINICAL CHEMISTRY, 46(9):1456-1463 (2000) ("Qian"), at 1456, 1462 (describing use of polystyrene for immobilizing biomolecules); EX1012 (Sailor), at 316:20-25, 317:13-17.

¹⁰⁶ EX1012 (Sailor), at 296:18-297:9.

¹⁰⁷ EX1012 (Sailor), at 306:10-309:15, 315:25-316:17.

layer (between the interference layer and the external environment).¹⁰⁸ The two reflecting surfaces produce two interfering light beams (I_1 and I_2).¹⁰⁹ During the operation of Yang's probe, when light travels to the distal end of the probe, the incident light is partially reflected from the two reflecting surfaces back to the detector, resulting in a measurable interference pattern (reflectance spectrum).¹¹⁰

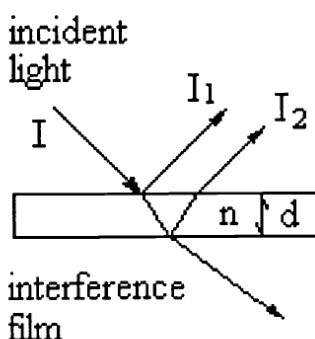


Fig 1a Schematic of the light path in the bioprobe

Given the thickness of the interference layer, the proximal and distal reflecting surfaces are separated by at least 50 nm.¹¹¹

65. During an assay, when analyte molecules in a sample bind to the layer of analyte-binding molecules on the distal end (tip) of the probe, the “optical thickness” of the interference layer increases, which is manifested as a “phase

¹⁰⁸ EX1006 (Yang), at 432, Fig. 1a; EX1012 (Sailor), at 286:6-287:9.

¹⁰⁹ EX1006 (Yang), at 432, Fig. 1a; EX1012 (Sailor), at 286:6-287:9.

¹¹⁰ EX1006 (Yang), at 432, Figs. 1a, 2, 4.

¹¹¹ EX1006 (Yang), at 432, Fig. 1a; EX1012 (Sailor), at 289:2-24.

shift” in the interference pattern, as shown for example in Figure 6 below.¹¹² Yang explains that this allows “binding events [to be] observed by detection of changes of optical thickness in real time.”¹¹³

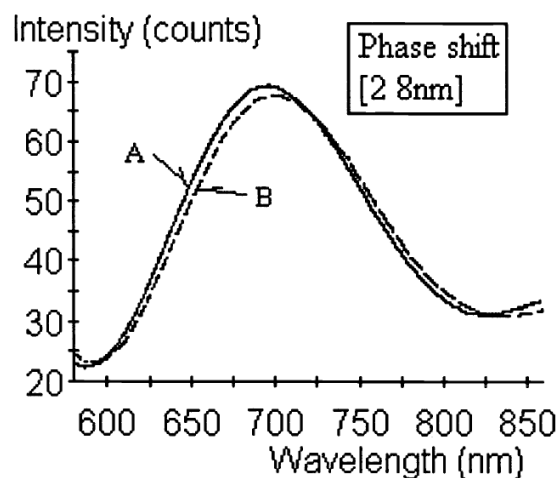


Fig 6 Caused shifting of the reflectance spectrum by the binding of protein

66. Further, for higher-throughput applications, Yang suggests combining multiple such BLI/RIfS probes to conduct multiple assays in “parallel” (i.e., simultaneously).¹¹⁴

C. Reasons for Combining Miles and Yang

67. In my opinion, a POSA would have been motivated to apply a tip tray, such as that described in Miles, to package BLI/RIfS probes, such as those disclosed in Yang (and WO854, as I address further in Section X), recognizing that

¹¹² EX1006 (Yang), at 433-434, Fig. 6; see also EX1012 (Sailor), at 287:10-25.

¹¹³ EX1006 (Yang), at 431-32, 434, Fig. 6; see also EX1012 (Sailor), at 287:10-25.

¹¹⁴ EX1006 (Yang), at 431, 436.

a tip tray would provide many of the same advantages with BLI/RIfS probes, including facilitating the use of BLI/RIfS probes with standard microtiter plates and related equipment for conducting and automating assays.

68. I understand that when a work is available in one field of endeavor, design incentives and other market forces can prompt obvious variations of it, either in the same field or a different one. I further understand that 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.

69. Here, as I discuss above (see ¶¶ 18-19), by June 2005, 96-well microtiter plates had become the “de facto standard” for performing many laboratory assays and even the dimensional elements of such plates had been standardized across the industry.¹¹⁵ POSAs were motivated to use microtiter plates (among other reasons) because they allowed assays to be run on a smaller scale, using smaller sample and reagent volumes, which further enabled the processing of multiple samples simultaneously, thus increasing speed and throughput.¹¹⁶

¹¹⁵ EX1013 (Astle), at 1:24-27; EX1014 (Atwood), at 3:31-48; EX1041 (ANSI/SLAS), at 3; EX1040 (Astle-2000), at 2.

¹¹⁶ EX1013 (Astle), at 1:24-27; EX1014 (Atwood), at 3:31-48; EX1026 (Mann), at 1.

70. The widespread and routine use of microtiter plates also motivated POSAs to design related equipment, such as pipettes, pipette tips, tip trays, plate readers, and assaying instruments, to be used with microtiter plates.¹¹⁷ For example, and as I discuss above (see ¶¶ 20-25), dispensing pipette tips were routinely packaged in tip trays that arranged the tips in an 8×12 array, which corresponds to the 8×12 array of wells in a standard 96-well microtiter plate.¹¹⁸ This arrangement allowed for efficient transfer of liquids to and from standard microtiter plates while minimizing the risk of error and facilitating the use of pipette tips with handheld and robotic pipettes, which were also designed to work in a complementary fashion with standard microtiter plates.¹¹⁹ Plate readers and assaying instruments likewise were designed to analyze samples in standard microtiter plates.¹²⁰ In my own work during the late 1990s and early 2000s, I owned single-channel pipettes made by Gilson and 8-channel pipettes made by Eppendorf, regularly purchased Fisherbrand and Eppendorf pipette tips preloaded in 8×12 tip trays, processed samples for analytical assays in 96-well microtiter plates made by Corning and Falcon, and analyzed the plates on multiplexed analytical instruments made by

¹¹⁷ EX1013 (Astle), at 1:29-33.

¹¹⁸ EX1007 (Rainin), at Fig. 6; EX1013 (Astle), at 1:34-36, Figs. 1-4; EX1039 (Gilson), at [13]-[16]; EX1048 (Fisher), at 1185-87.

¹¹⁹ EX1013 (Astle), at 1:24-36.

¹²⁰ EX1048 (Fisher), at 1877-81; EX1051 (Seahorse); EX1052 (Teich), at ¶¶ [0082]-[0090], [0100]-[0107], Figs. 1, 3, 5a.

Molecular Devices and Cary Instruments, which were preconfigured to read 96-well microtiter plate assays. Products from all of these brands interoperated together due to wide adoption and standardization of the 96-well format.

71. POSAs were familiar with these design incentives and market forces and would have recognized that similar advantages would be obtained by packaging BLI/RIfS probes in an 8×12 array format within a tip tray. Given their experience using pipettes and pipette tip trays with standard microtiter plates, POSAs were well capable of, and would have had a reasonable expectation of success, in packaging sensor probes in similar tip trays.

72. POSAs, in fact, explicitly contemplated and succeeded in using tip trays to package various sensor probes, not only to facilitate their use with microtiter plates but also to facilitate their use with robotic systems and assaying instruments that used such plates. As I discuss above (see ¶¶ 28-29, 58-59), Miles discloses a tip tray designed to package sensor probes used with an automated assay machine to conduct multiple assays simultaneously on a microtiter plate.¹²¹ Miles explains that the tip tray positions probe tips in a complementary manner to the receiving ends of the assay machine to facilitate the loading of the probes and further facilitates the use of the probes with a 96-well microtiter plate having

¹²¹ EX1005 (Miles), at 8:49-52, Figs. 1-2.

complementary wells.¹²² As a POSA would have recognized, a similar tip tray for packaging BLI/RIfS probes would facilitate their use with microtiter plates as well as robotic and automation systems.

73. Likewise, as I discuss above (see ¶30), Lapeus describes the use of tip trays to package sensor probes for assaying a wide range of samples “such as blood, spinal fluid, urine, serum, plasma, and the like.”¹²³ Lapeus also explains that there was a trend among hospitals, clinics, and laboratories to use “automated analyzer systems” to analyze samples, and that tip trays facilitated the use of probes with such systems, further supporting the motivation to use tip trays for packaging BLI/RIfS probes.¹²⁴ As I discuss above (see ¶27), such automated systems were common in laboratories since at least the early 2000s and in June 2005, a POSA would have been motivated to use tip trays with sensor probes to facilitate their use with robotic and automation systems.¹²⁵

74. Chen (EX1009) and WO854 (EX1008) also support the motivation for a POSA to package BLI/RIfS probes in tip trays. Chen describes a BLI/RIfS probe that is removably coupled (via a clothespin-type connector 802) to an optical

¹²² EX1005 (Miles), at 2:45-51, 8:26-28, 9:49-54, 10:18-20, 10:45-47, 12:23-26,, Figs. 5-7.

¹²³ EX1016 (Lapeus), at 1:11-18, 3:14-22, Fig. 2.

¹²⁴ EX1016 (Lapeus), at 1:11-18, 1:32-40, 2:60-3:9.

¹²⁵ EX1051 (Seahorse); EX1052 (Teich), at ¶¶[0082]-[0090], [0100]-[0107], Figs. 1, 3, 5a.

fiber of an assay machine and explains that multiple discrete probes (1 through n, e.g., 1106a, 1106b and 1106c) may be combined in a multiplexed format (as shown in Figure 11) to perform multiple assays simultaneously and to detect different analytes in a sample.¹²⁶

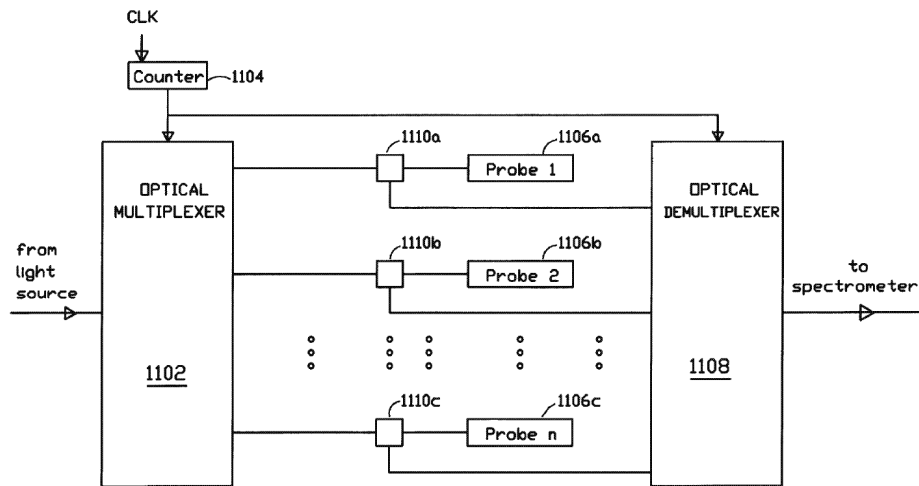


Figure 11

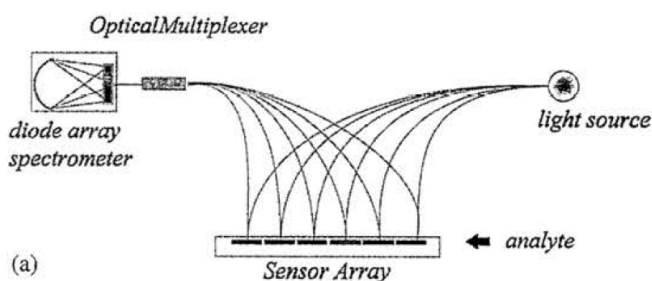
Sartorius’ expert, Dr. Sailor, concurred that Chen describes a BLI/RIfS probe and “teaches that you can use multiple [such] probes, and combine them together in multiplexed format” that allows analyzing samples “for either multiple components or the same component multiple times.”¹²⁷ He explained that such

¹²⁶ EX1009 (Chen), at 6:8, 8:17-29, 12:54-13:12, Fig. 11; (describing connector 802 as part BFA-MM from MetroTek); EX1058, MetroTek, *Bare Fiber Adapters & Kits*, available at <https://web.archive.org/web/20010411055716/http://metrotek.com:80/mtekbfa.htm> (archived April 11, 2001) (“MetroTek Website”) (showing and describing BFA-MM as removable “clothespin” type adapter for connecting optical fibers); EX1059 (MetroTek Catalog), at 7 (same); EX1012 (Sailor), at 327:5-329:7, 333:15-339:7 (Sartorius’ expert concurring).

¹²⁷ EX1012 (Sailor), at 339:17-341:2.

multiplexing “helps speed up the analysis process” and “increase the throughput.”¹²⁸ Consistent with Chen, WO854 (EX1008) also discloses a BLI/RfS probes that is removably coupled (via a gripping arms) to an optical fiber of an assay machine,¹²⁹ and WO854 proposes to combine multiple BLI/RfS probes in a “two dimensional array” format, incorporating by reference Chen’s earlier disclosure of multiplexed probes.¹³⁰ Similarly, Yang proposes combining BLI/RfS probes to perform multiple assays in “parallel” (i.e., simultaneously).¹³¹

75. Other references similarly suggested multiplexing BLI/RfS sensors. For example, Brecht and Gauglitz described BLI/RfS sensors dating back to the early 1990s and suggested in a 1995 paper to multiplex such sensors in an array format as diagramed below.¹³²



¹²⁸ EX1012 (Sailor), at 340:9-341:2.

¹²⁹ EX1008 (WO854), at ¶¶ [0077]-[0079], Fig. 4.

¹³⁰ EX1008 (WO854), at ¶ [0007], claims 22-23, 26-27; see also ¶¶ [0009], [0017], [0045], [0080]-[0081], Fig. 5.

¹³¹ EX1006 (Yang), at 431, 436,

¹³² EX1046, Andreas Brecht & Günter Gauglitz, Recent developments in optical transducers for *chemical or biochemical applications*, SENSORS & ACTUATORS B, 38-39:1-7 (1997) (“Brecht”), at 4; EX1012 (Sailor), at 341:25-344:20.

Carrying this forward, Birkert and Gauglitz described in a 2002 paper a microplate comprising a multiplexed array of BLI/RIfS sensors.¹³³ Again, addressing these references, Sartorius' expert concurred that there was a need for higher-throughput testing and this need motivated these efforts to multiplex BLI/RIfS sensors.¹³⁴

76. These express suggestions in Chen, WO854, Yang, and elsewhere to combine and multiplex multiple BLI/RIfS sensors to perform simultaneous (parallel) assays, coupled with the prevailing standard of performing laboratory assays on microtiter plates, particularly multiple simultaneous assays, further illustrate the motivation to package BLI/RIfS probes in tip trays.

77. Further, given the similarities between BLI/RIfS probes and the sensor probes described in Miles, POSAs would have had a reasonable expectation of success in packaging BLI/RIfS probes in tip trays. Both types of probes

¹³³ EX1047, Oliver Berkert & Günter Gauglitz, *Development of an assay for label-free high-throughput screening of thrombin inhibitors by use of reflectometric interference spectroscopy*, ANAL. BIOANAL. CHEM., 372:141-147 (2002) ("Birkert"), at abstract, 141, Fig. 1; EX1012 (Sailor), at 345:7-347:13.

¹³⁴ EX1012 (Sailor), at 346:14-347:4 ("Q. Doctor, Birkert and Gauglitz also teach that there was a need in pharmaceutical research at the time for screening methods that facilitate high-throughput screening; is that right? A. Yes. Q. And from your own background, do you agree that there was a need in the pharmaceutical research space for screening methods that facilitate high-throughput screening? A. Indeed, it still is. Q. And that was the motivation for Birkert and Gauglitz to combine multiple RIfS sensors in a microplate format; is that right? A. I can't speak to their motivation other than their introduction. That's how I read their motivation for this work based on their introduction, yes.").

comprise a layer of analyte-binding molecules (e.g., antibodies, antigens) coated on the distal end (tip) to bind analyte molecules present in a sample. In both, the assay is performed on the distal end (tip) of the probe, which is contacted with various samples and reagents. Therefore, POSAs seeking to perform multiple assays in parallel using BLI/RIfS probes would have naturally drawn from Miles' established use of tip trays of similar probes to conduct assays on microtiter plates.

78. I should note that POSAs would not have needed to physically combine the precise design of Miles' probe tips into a BLI/RIfS probe. Rather, POSAs would have recognized that Miles' teachings could be applied to BLI/RIfS probes by adding a structure to the proximal end of the probes that would allow them to attach to an assay apparatus, and that is appropriately sized to prevent them from falling through the corresponding openings in the tip tray.¹³⁵

D. The Combination of Miles and Yang Renders Claims 1-13 and 18-19 Obvious

1. Claim 1

79. For ease of reference, I have divided the language of claim 1 into subparts, or elements, and address each in turn.

¹³⁵ EX1005 (Miles), at 2:45-51, 10:28-34, Figs. 5-7; EX1016 (Lapeus), at 3:14-22.

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

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

80. To the extent the preamble is limiting, Miles, in combination with Yang, teaches “[a]n apparatus for packaging an optical sensing assembly.”

81. As I discuss above in the Overview of Miles (see ¶¶ 52-59), Miles discloses the use of pipette tips (sensor probes) that serve as optical sensing

assemblies.¹³⁶ The distal ends or tips of the probes are coated (insolubilized) with analyte-binding molecules, such as antigen or antibody, which provides a functionalized surface for binding analyte molecules present in a sample.¹³⁷ During an assay, the probe tips are introduced to (contacted with) solutions of samples and reagents contained in the wells of microtiter plates, such as 96-well plates.¹³⁸

82. Miles further describes example assay procedures in which probes coated with analyte-binding molecules (e.g., capture antibodies) are used to bind analyte molecules (e.g., human growth hormone (HGH)) present in sample solutions and then introduced to a labeled antibody or antigen for detecting the presence and amount of analyte.¹³⁹ Although Miles' examples employ radiolabeled antibodies or antigens, Miles also explains that the probes may be configured to produce an optical readout by using other types of labels, such as "enzymes," "fluorescers," or "fluorogenic" reagents.¹⁴⁰ Assays using fluorescers or fluorogenic substances generate a measurable optical fluorescence signal.¹⁴¹ Moreover, by June 2005, enzyme-labeled reagents that generate a measurable optical color change

¹³⁶ EX1005 (Miles), at abstract, 2:19-34, 2:45-3:18.

¹³⁷ EX1005 (Miles), at 2:19-34, 2:52-55, 4:1-19, 5:53-68.

¹³⁸ EX1005 (Miles), at 2:55-3:4, 12:24-26, Fig. 2.

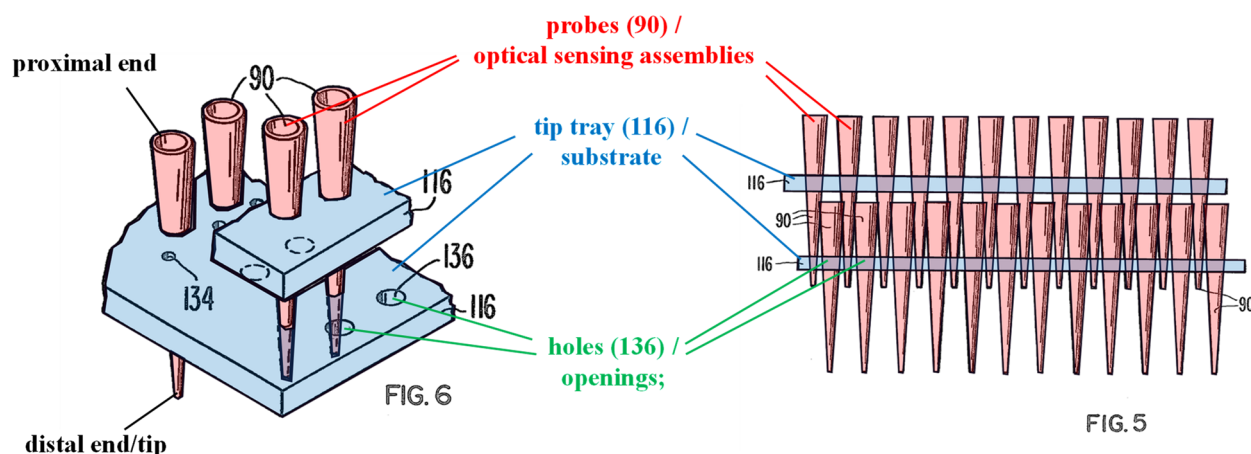
¹³⁹ EX1005 (Miles), at 12:64-13:36.

¹⁴⁰ EX1005 (Miles), at 4:20-30, 11:63-66.

¹⁴¹ EX1012 (Sailor), at 106:20-108:15.

were routinely used in assays, such as ELISAs.¹⁴² Furthermore, instruments suitable for quantifying such fluorescence and colorimetric signals in 96-well microtiter plates were commonplace by that time and were routinely used in laboratories, including my own, for conducting analytical assays.¹⁴³

83. In addition to describing the sensor probes and assays that use them, Miles discloses a tip tray apparatus for the packaging of the probes. As shown in Figures 5 and 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 distal ends/tips of the probes extend and are suspended.¹⁴⁴

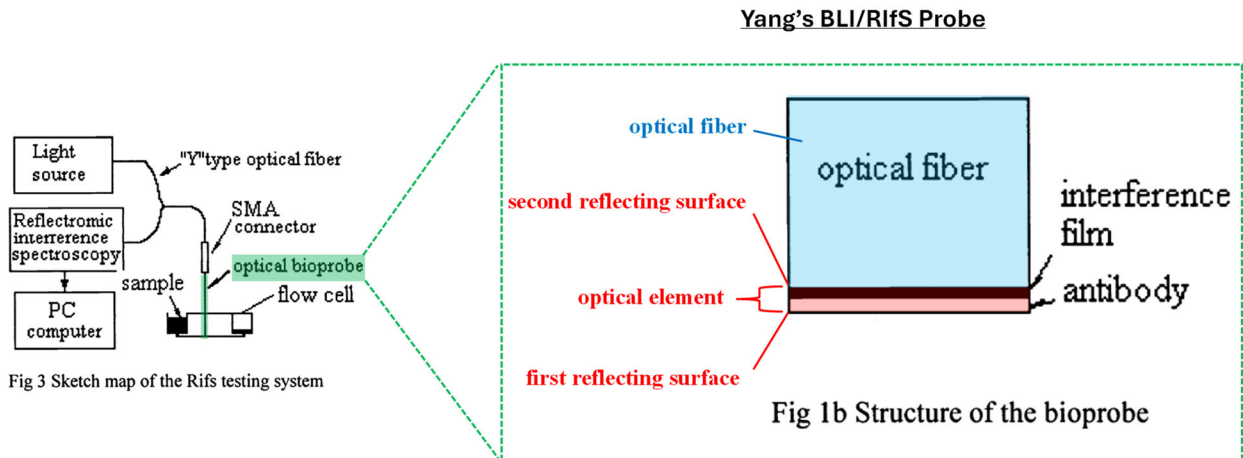


¹⁴² EX1020 (Lequin), at 2415, 2417; EX1012 (Sailor), at 106:20-108:15.

¹⁴³ EX1048 (Fisher), at 1878-81.

¹⁴⁴ EX1005 (Miles), at 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5, 6 (annotated).

84. Further, as I discuss in the Overview of Yang (see ¶¶ 60-66) and further below as to elements [1A]-[1C] (see ¶¶ 86-95), Yang describes a BLI/RIfS probe that serves as an optical sensing assembly, as shown in Figures 1b and 3.¹⁴⁵



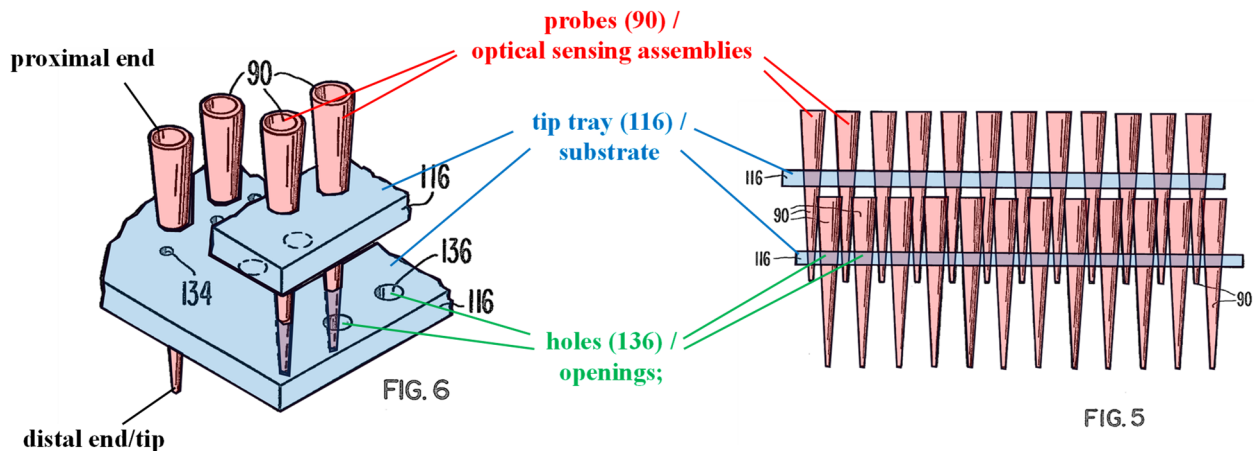
85. For the reasons I discuss above (see ¶¶ 67-78), POSAs would have been motivated to apply Miles' teachings to use a tip tray to package BLI/RIfS probes, such as those described in Yang, recognizing that this combination would facilitate the integration of BLI/RIfS probes with standard microtiter plates and related assay equipment, thereby improving the efficiency and automation of assays.

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

86. Miles, in combination with Yang, teaches a tip tray apparatus comprising “at least one discrete optical sensing assembly.”

¹⁴⁵ EX1006 (Yang), at 432, Figs. 1b, 3 (annotated); EX1012 (Sailor), at 281:12-282:5, 285:13-287:25 (Dr. Sailor concurring that Yang discloses a BLI/RIfS probe providing an optical/ interferometric readout).

87. As I address in the Overview of Miles (see ¶¶ 52-59) and as to element [1Pre] (see ¶¶ 80-85), and as shown in Figures 5 and 6, Miles discloses a tip tray 166 (blue) for packaging discrete probes 90 (red) that serve as optical sensing assemblies.¹⁴⁶ Miles also describes using such probes in assays with enzymes, fluorsceners, or fluorogenic reagents that provide an optical readout.¹⁴⁷

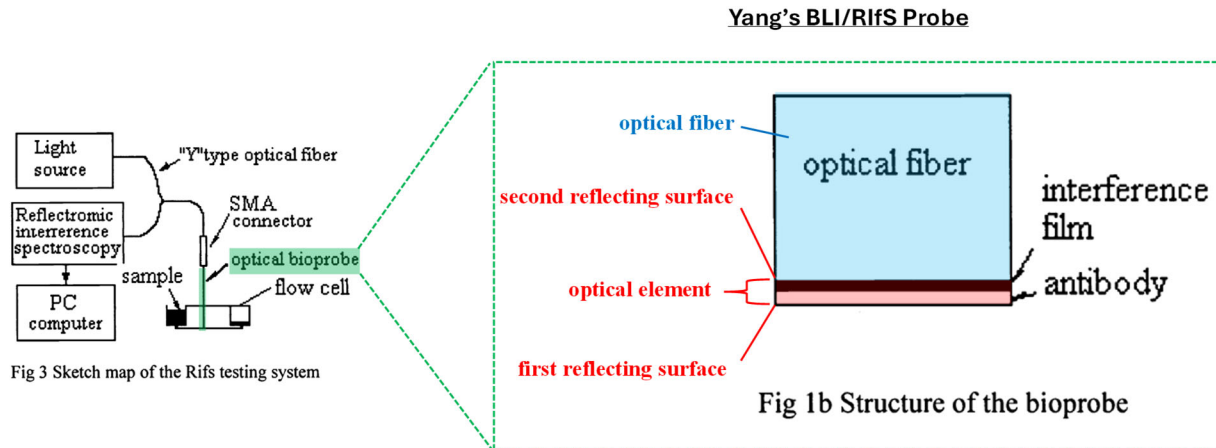


88. As I address in the Overview of Yang (see ¶¶ 60-66) and as to element [1Pre] (see ¶¶ 80-85), and as shown in Figures 1b and 3, Yang describes a BLI/RIfS probe that serves as an optical sensing assembly.¹⁴⁸

¹⁴⁶ EX1005 (Miles), at 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5, 6 (annotated); see also 4:20-30, 11:63-66 (describing the use of probes with enzyme and fluorescent/fluorogenic labels that provide optical readouts).

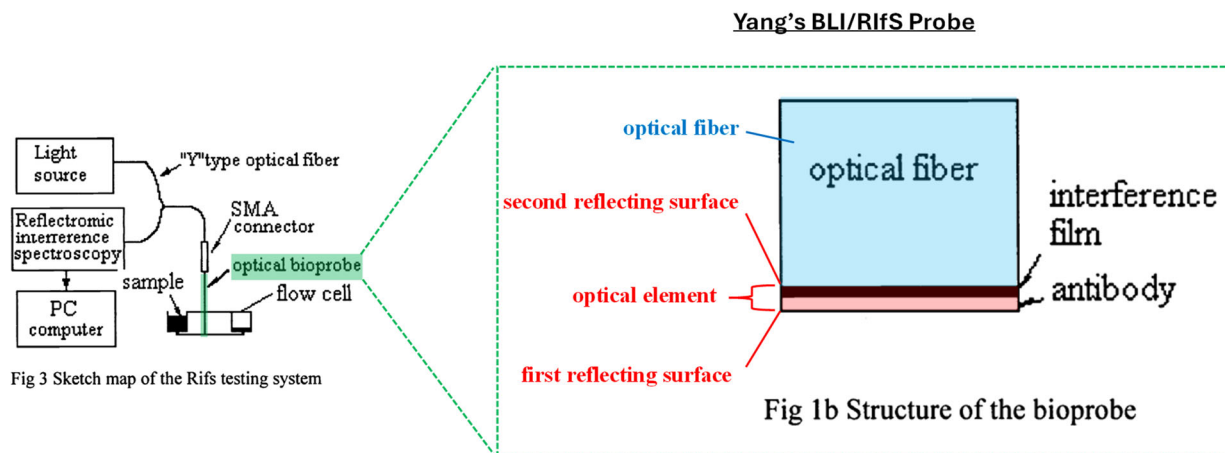
¹⁴⁷ EX1005 (Miles), at 4:20-30, 11:63-66.

¹⁴⁸ EX1006 (Yang), at 432, Figs. 1b, 3 (annotated); EX1012 (Sailor), at 281:12-282:5, 285:13-287:25 (Dr. Sailor, Sartorius' expert, concurring that Yang discloses a BLI/RIfS probe providing an optical/interferometric readout).



- c. [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”

89. As shown in Figures 1b and 3, Yang discloses a BLI/RIfS probe (optical assembly, green) comprising a segment of optical fiber (blue) coated with a “transparent interference layer” or film (optical element, red).¹⁴⁹



¹⁴⁹ EX1012 (Sailor), at 285:13-21, 291:7-10; EX1006 (Yang), at 432-33, Figs. 1b, 3 (annotated).

90. My opinion is confirmed by the testimony of Sartorius' expert, Dr. Sailor, who concurred that Yang's BLI/RIfS 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.¹⁵⁰

91. Moreover, as shown in Figure 1a below and in Figure 1b above, Yang's interference layer includes first and second reflecting surfaces on its distal and proximal endfaces, respectively.¹⁵¹ Given the thickness of the interference layer, the two reflecting surfaces are separated by at least 50 nm.¹⁵²

¹⁵⁰ EX1012 (Sailor), at 285:13-21, 291:7-10.

¹⁵¹ EX1006 (Yang), at 432, Fig. 1a.

¹⁵² EX1006 (Yang), at 432, Fig. 1a; see also 433 ("The light is partially reflected on the interfaces from the transparent interference layer in front of the bioprobe").

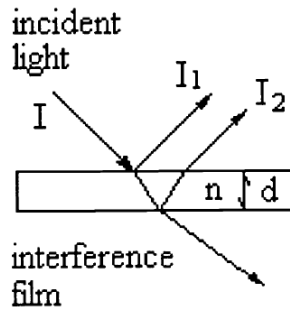


Fig 1a Schematic of the light path in the bioprobe

92. Here again, Sartorius' expert, Dr. Sailor, concurred that these features are present in Yang's BLI/RfS probe:

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.¹⁵³

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

93. As I discuss above as to element [1B] (see ¶¶ 89-92), and as shown in Figure 1a, Yang's interference layer includes first and second reflecting surfaces on its distal and proximal endfaces, respectively.¹⁵⁴

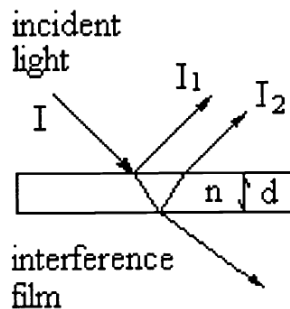


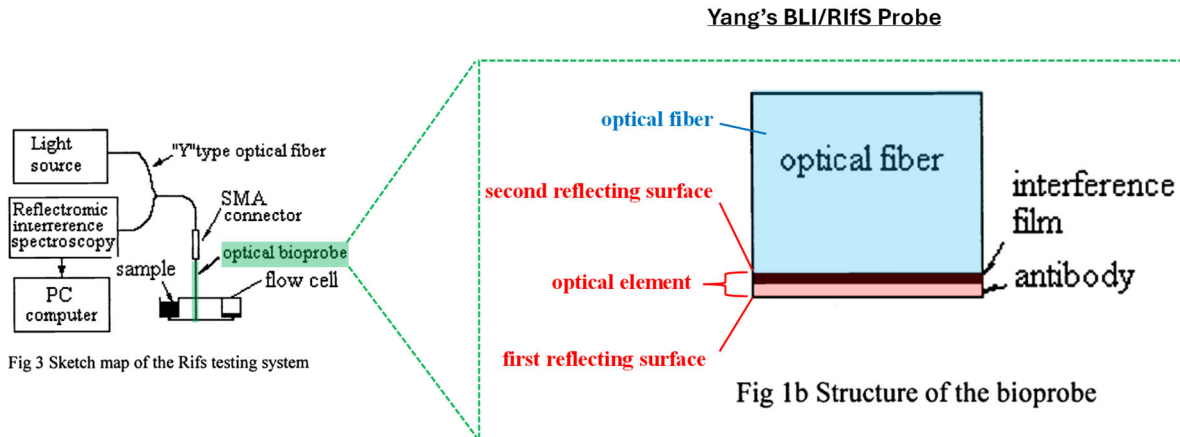
Fig 1a Schematic of the light path in the bioprobe

94. Moreover, as shown in Figure 1b, the first reflecting surface comprises a layer of antibodies (analyte-binding molecules) for binding analyte molecules present in a sample.¹⁵⁵

¹⁵³ EX1012 (Sailor), at 286:6-12, 289:2-24.

¹⁵⁴ EX1006 (Yang), at 432, Fig. 1a; EX1012 (Sailor), at 286:6-287:4.

¹⁵⁵ EX1006 (Yang), at 432, Figs. 1b, 3 (annotated).



Yang also describes an example assay in which the distal end of the probe (first reflecting surface) is coated with sandwiched layers of rabbit IgG antibodies and goat anti-rabbit-IgG antibodies (i.e., analyte-binding molecules) that bind goat anti-rabbit IgG antibodies (i.e., analyte) present in a sample.¹⁵⁶

95. Again, my opinion is confirmed by the testimony of Sartorius' expert, Dr. Sailor, who concurred that Yang's BLI/RIfS probe includes these features:

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?

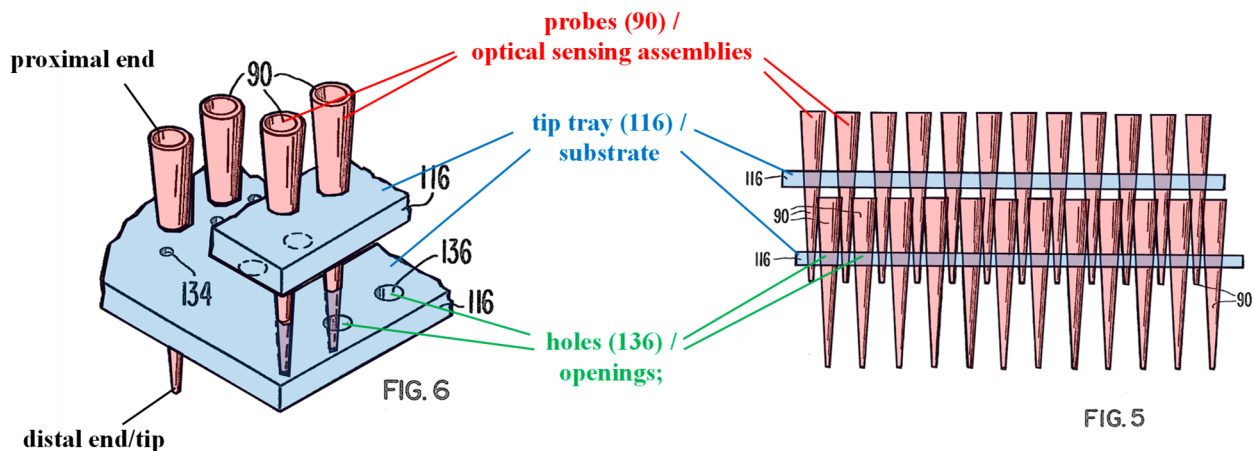
A. Yes, that's correct.¹⁵⁷

¹⁵⁶ EX1006 (Yang), at 434.

¹⁵⁷ EX1012 (Sailor), at 285:18-286:5.

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

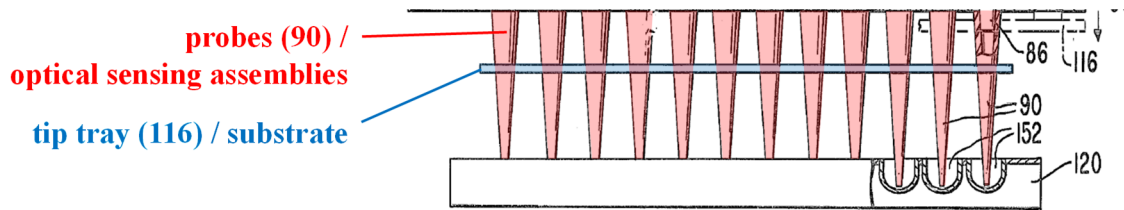
96. As I discuss in the Overview of Miles (see ¶¶ 52-59) and as to element [1Pre] (see ¶¶ 80-85), and as shown in Figures 5 and 6, Miles describes a substrate in the form of a tip tray 116 (blue) having a plurality of holes or openings 136 (green) that are configured to hold a plurality discrete probes 90 (red) that serve as optical sensing assemblies.¹⁵⁸



97. For purposes of element [1D], one can consider the “substrate” as a stacked arrangement of tip trays (as shown in Figures 5 and 6 above), or alternatively as a single, standalone tip tray. For example, Figure 2 shows a single tip tray 116 (blue) of probes 90 (red) loaded onto an assay machine where each of

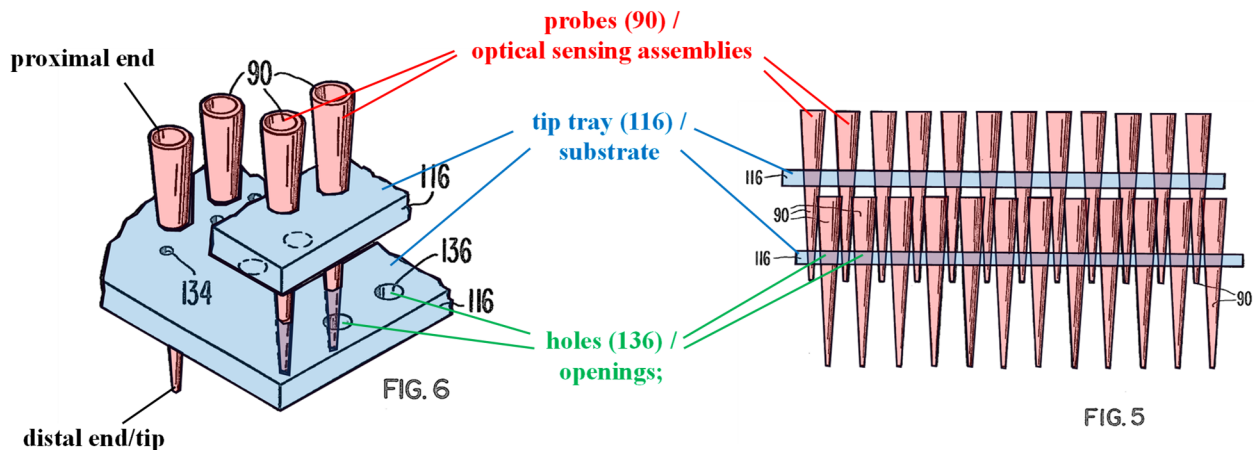
¹⁵⁸ EX1005 (Miles), at 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5, 6 (annotated); see also 4:20-30, 11:63-66 (describing the use of probes with enzyme and fluorescent/fluorogenic labels that provide optical readouts).

the plurality of openings is configured to hold a discrete probe.¹⁵⁹



- f. [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”

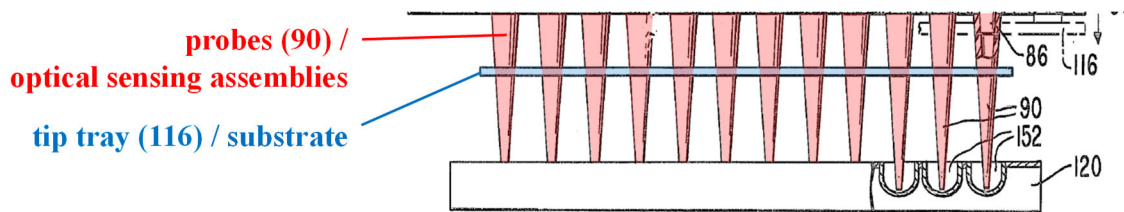
98. As I discuss in the Overview of Miles (see ¶¶ 52-59) and as to element [1Pre] (see ¶¶ 80-85), and as shown in Figures 5 and 6, Miles describes probes 90 (optical sensing assemblies, red) positioned in the openings 136 (green) of tip tray 116 (substrate, blue) with the distal ends/tips of the probes extending through the openings and suspended from the tip tray.¹⁶⁰



¹⁵⁹ EX1005 (Miles), at 9:49-57, 10:45-47, 11:26-30, Fig. 2 (cropped, annotated); see also 10:28-34, Fig. 7 (showing single tip tray in an injection block for loading onto the receiving ends of an assay machine).

¹⁶⁰ EX1005 (Miles), at 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5, 6 (annotated).

99. Again, the “substrate” may refer to a stacked arrangement of multiple tip trays (as shown in Figures 5 and 6), or alternatively, a single, standalone tip tray. For example, Figure 2 shows probes 90 (red) positioned in the openings of single tip tray 116 (blue) with the distal ends/tips of the probes extending through the opening and suspended from the tip tray.¹⁶¹

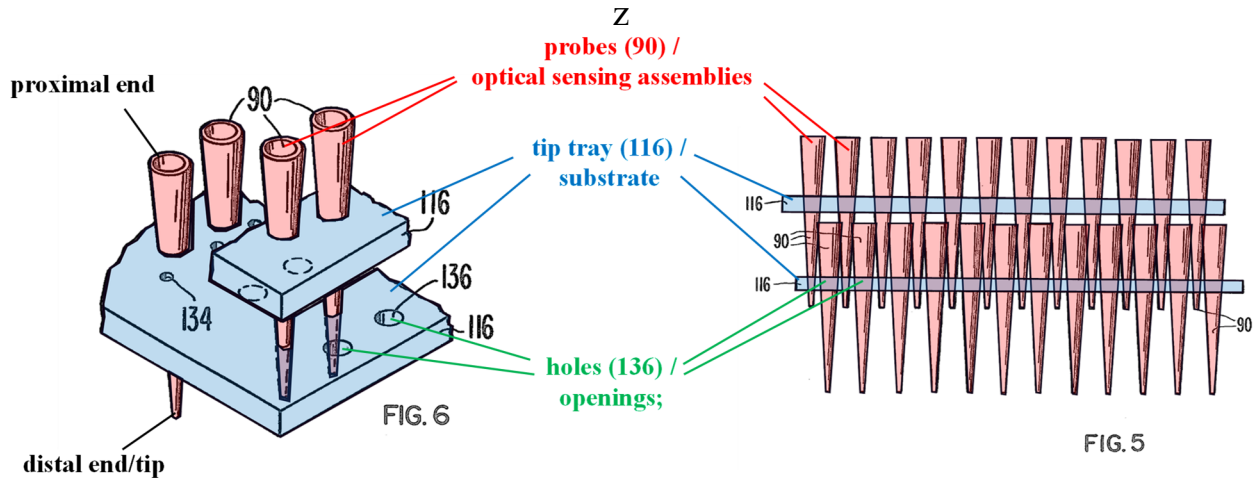


- g. **[1F]: “wherein the plurality of openings are arranged so the optical sensing assembly positioned therein avoids contacting another optical sensing assembly positioned therein”**

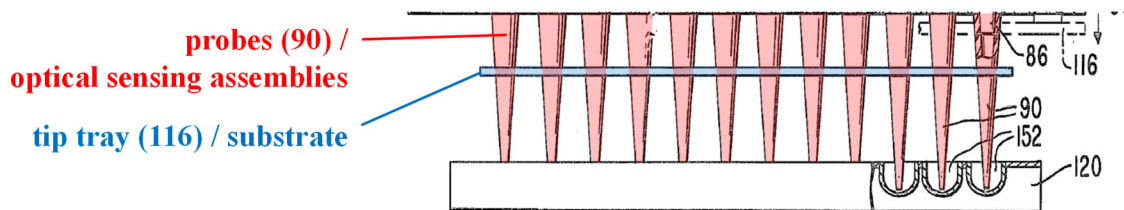
100. As I discuss in the Overview of Miles (see ¶¶ 52-59) and as to element [1Pre] (see ¶¶ 80-85), and as shown in Figures 5 and 6, Miles describes probes 90 (optical sensing assemblies, red) positioned in a plurality of openings 136 (green) in a tip tray 116 (substrate, blue).¹⁶²

¹⁶¹ EX1005 (Miles), at 9:49-57, 10:45-47, 11:26-30, Fig. 2 (annotated, cropped); see also 10:28-34, Fig. 7 (showing single tip tray in an injection block for loading onto an assay machine).

¹⁶² EX1005 (Miles), at 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5, 6 (annotated).



101. Figure 5 and 6 show that the plurality of openings are arranged in a manner that spaces apart the probes and avoids the probe tips from contacting one another.¹⁶³ 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.¹⁶⁴

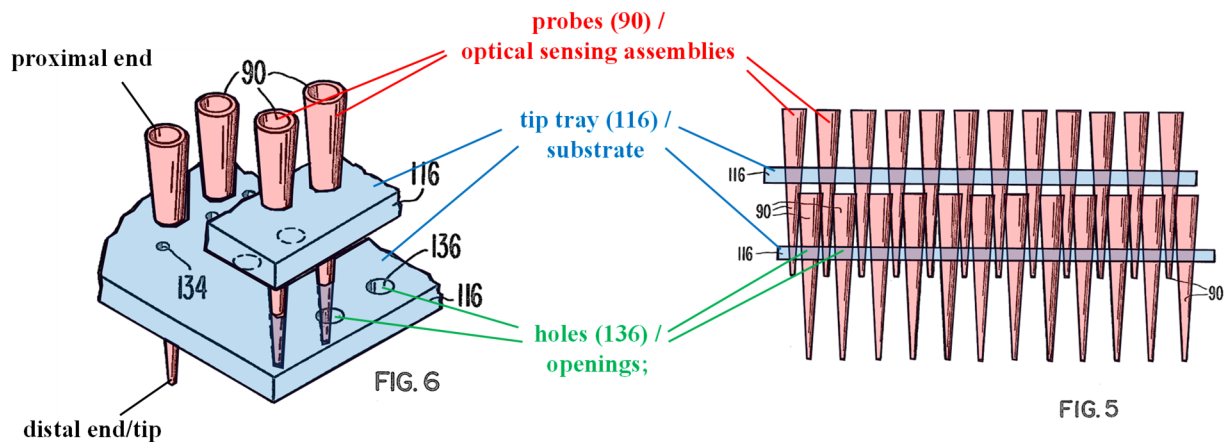


¹⁶³ EX1005 (Miles), at Figs. 5, 6.

¹⁶⁴ EX1005 (Miles), at Fig. 2 (annotated, cropped); see also 10:28-34, Fig. 7 (showing single tip tray in an injection block for loading onto an assay machine).

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

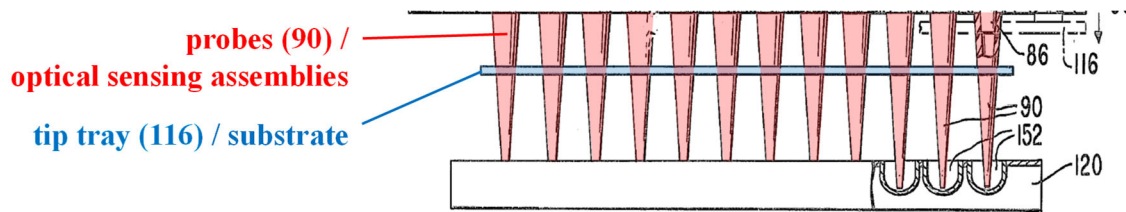
102. As I discuss in the Overview of Miles (see ¶¶ 52-59) and as to element [1E] (see ¶¶ 98-99), and as shown in Figures 5 and 6, Miles describes a tip tray (blue) with a plurality of openings (green) that hold multiple, discrete probes (optical sensing assemblies, red) and through which the distal ends/tips of the probes extend.¹⁶⁵



103. This can also be seen in Figure 2, which shows a single tip tray 116 (blue) holding multiple probes 90 (red) with the distal ends or tips of the probes extending through the openings.¹⁶⁶

¹⁶⁵ EX1005 (Miles), at 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5, 6 (annotated).

¹⁶⁶ EX1005 (Miles), at 9:49-57, 10:45-47, 11:26-30, Fig. 2 (annotated, cropped); see also 10:28-34, Fig. 7 (showing single tip tray in an injection block for loading onto an assay machine).



2. Claims 2-4

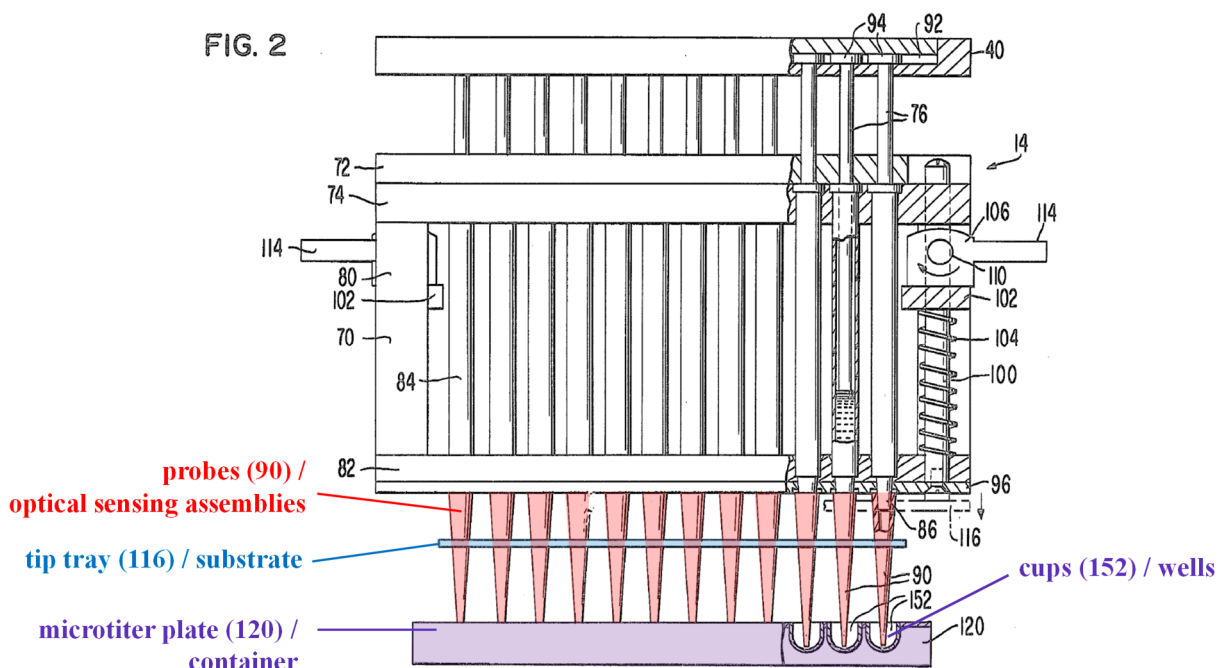
104. Claims 2-4 depend from claim 1 and purport to combine and use the tip tray apparatus of claim 1 with containers, such as a 96-well microtiter plate. I have included the language of claims 2-4 in the following table and address them below.

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.

105. As I discuss in the Overview of Miles (see ¶¶ 52-59) and as to element [1E] (see ¶¶ 98-99), 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 distal ends/tips of the probes extend and are suspended.

106. With respect to claim 2, Miles describes the use of such a tip tray of probes in conjunction with an assay machine for assaying samples in a multi-well microtiter plate. For example, Figure 2 shows a tip tray 116 (substrate, blue) of probes 90 (optical sensing assemblies, red) loaded onto the tip-receiving ends 86 of a syringe battery 14 in the assay machine.¹⁶⁷



107. As Miles explains, a microtiter plate 120 (container, purple) containing a plurality of wells 152 may be placed on a motorized lower platform 50 below the syringe battery 14.¹⁶⁸ During an assay, the platform holding the

¹⁶⁷ EX1005 (Miles), at 9:49-57, 10:45-47, 11:26-30, Fig. 2 (annotated).

¹⁶⁸ EX1005 (Miles), at 8:6-23, 11:26-44.

microtiter plate 120 may be raised, or alternatively the syringe battery may be lowered, using an electronically controlled and programmable driving means¹⁶⁹ so that the distal ends (tips) of probe 90 are inserted into and “reach substantially to the bottom” of the wells 152, which may contain sample, reagent, or wash solutions.¹⁷⁰ In this configuration, the receiving ends 86 of the syringe battery 14 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 of the tip tray, contact a solution in one of the wells 152 of the microtiter plate 120 (container). This is 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.”¹⁷¹

108. With respect to claim 3, Miles discloses that the microtiter plate 120 may be a 96-well plate, such as one sourced from Cooke Microtiter Ltd.¹⁷² Miles also describes its tip tray as holding 8 probes along one dimension (side view in Figure 4) and 12 probes along the other dimension (front view in Figures 2 and 5),

¹⁶⁹ EX1005 (Miles), at 8:6-23.

¹⁷⁰ EX1005 (Miles), at 2:55-3:4, 9:55-57, 11:26-44, 17:56-58, Fig. 2.

¹⁷¹ EX1001 (’588 patent), at 13:9-15.

¹⁷² EX1005 (Miles), at 12:24-26, Fig. 2; see also 2:55-65, 9:55-57; EX1053, 56, Fig. 1; EX1054, 741, Fig. 1 (showing commercial examples of 96-well microtiter plates from Cooke Microtiter, Ltd.).

which facilitates using the probes with a 96-well microtiter plate.¹⁷³ Moreover, as I explain above (see ¶¶ 18-19), POSAs would have found it obvious to use a 96-well microtiter plate, given that such plates had become the “de facto standard” for performing many laboratory assays as of June 2005, reinforced by efforts to standardize the dimensional elements of microtiter plates across the industry.¹⁷⁴

109. With respect to claim 4, Miles describes using the assay machine to successively introduce the probes 90 to different solutions contained in multiple microtiter plates. For example, Miles describes a procedure in which a tip tray 116 containing probes 90 is first introduced to a first microtiter plate containing solutions of capture antibodies, followed by washing of the probes and their introduction to a second microtiter plate containing samples and standards.¹⁷⁵ The probes are then washed and introduced to a third microtiter plate containing labeled detection antibodies.¹⁷⁶ Miles further explains that the order of the probes is

¹⁷³ EX1005 (Miles), at 2:45-51, 3:41-42, 3:44-47, 10:45-64, Figs. 2, 4, 5.

¹⁷⁴ EX1013 (Astle), at 1:24-27; EX1014 (Atwood), at 3:31-48; EX1041 (ANSI/SLAS), at 3; EX1040 (Astle-2000), at 2.

¹⁷⁵ EX1005 (Miles), at 10:65-11:15 (discussing introducing probes to first microtiter plate with capture antibodies and washing), 11:26-35 (discussing introducing probes to second microtiter plate with samples and standards and then washing).

¹⁷⁶ EX1006 (Miles), at 11:36-62 (discussing introducing probes to third microtiter plate containing labeled detection antibodies, washing the probes again, and taking a reading).

maintained and likewise that “the original organization of the samples and standards, if any, is maintained throughout the assay, so that each sample retains a particular position for ease of recording results, particularly by automated means.”¹⁷⁷ This enables the probes in the tip tray to be mapped from the wells of one microtiter plate to the next, ensuring that results can be tracked and recorded.

3. Claims 6 and 8

110. Claims 6 and 8 depend from claim 2 and additionally recite immobilizing proteins on the probe or optical sensing assembly. I have included the language of claims 6 and 8 in the following table and address them below.

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.

111. As I discuss with respect to Claim 2 (see ¶¶ 105-107), Miles discloses an assay machine that immerses a tip tray 116 (substrate) of probes 90 (optical

¹⁷⁷ EX1005 (Miles), at 18:38-42; see also 9:49-54 (discussing the maintenance of the order of the probe tips).

sensing assemblies) in successive microtiter plates containing different solutions (e.g., sample, reagent, and wash solutions).¹⁷⁸

112. With respect to claim 6, Miles describes a procedure in which, before running an “immunoassay,” a tip tray of probes 90 (optical sensing assemblies) is immersed in a microtiter plate containing solutions of antibodies (which are proteins) to immobilize them on the probe tips.¹⁷⁹ This initial, pre-assay step functionalizes the probe tips so that they can bind the target analyte. Miles then describes performing the immunoassay by immersing the coated, functionalized probes in a microtiter plate containing solutions of samples and standards, followed by immersing the probes in microtiter plate containing a solution of labeled detection antibodies to detect analyte binding.¹⁸⁰ These latter steps allow for measuring the interaction between the immobilized antibodies and other proteins, such as analyte molecules in the samples or the detection antibodies.¹⁸¹

113. POSAs similarly performed protein immobilization steps to functionalize BLI/RIfS probes, such as those described in Yang (or WO854, as I

¹⁷⁸ EX1005 (Miles), at 2:55-3:4, 9:55-57, 11:26-44, 17:56-58, Fig. 2.

¹⁷⁹ EX1005 (Miles), at 10:65-11:15.

¹⁸⁰ EX1005 (Miles), at 11:26-35 (discussing introducing probes to sample and reagent solutions), 11:36-44 (discussing introducing probes to labeled detection antibodies).

¹⁸¹ EX1005 (Miles), at 11:53-62.

address in Section X), before conducting an assay. For example, Yang explains that a BLI/RIfS probe may be immersed in solutions of antibodies (e.g., rabbit IgG and goat anti-rabbit IgG antibodies, both proteins) to immobilize those antibodies on the probe tip.¹⁸² As with Miles' probe, this functionalizes the BLI/RIfS probe tip to bind the target analyte. Then, during the assay itself, the coated probe is immersed in a sample solution to bind analyte molecules present in a sample.¹⁸³ Again, as with Miles' probes, the later introduction of the coated, functionalized BLI/RIfS probes to samples during an assay permits measurement of the interaction of the immobilized antibodies with analyte molecules present in the sample. This was not unique to the probes in Miles and Yang. WO854 likewise describes functionalizing BLI/RIfS probes by immersing them in a solution of analyte-binding molecules for immobilization and then immersing the coated probes in samples to measure interaction of immobilized analyte-binding molecules with analyte molecules.¹⁸⁴

114. With respect to claim 8, Miles describes a tip tray 116 (substrate) configured for protein immobilization because it is configured to function with an assay machine so that the suspended tips of probes 90 (optical sensing assemblies)

¹⁸² EX1006 (Yang), at 434.

¹⁸³ EX1006 (Yang), at 434.

¹⁸⁴ EX1008 (WO854), at ¶¶[0054]-[0056], [0079], [0103]-[0107], [00110]-[00113], [00118]-[00120].

contact solutions in a microtiter plate positioned below, such as solutions of proteins (e.g., capture antibodies or other analyte-binding molecules) for immobilization on the probe tip.¹⁸⁵ This design allows the probe tips to be efficiently coated with the desired protein before an assay, highlighting the versatility and utility of such a tip tray for immunoassays and similar applications.

4. Claims 5 and 7

115. 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.” I have included the language of claims 5 and 7 in the following table and address them below.

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.

116. 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.”¹⁸⁶ It further defines “pre-wet” as “a procedure in which a sensor coated

¹⁸⁵ EX1005 (Miles), at 10:65-11:15

¹⁸⁶ EX1001 ('588 patent), at 2:3-7.

with immobilized binding proteins is hydrated to restore their biological activity.”¹⁸⁷

117. As I discuss above with respect to claim 2 (see ¶¶ 105-107) and claims 6 and 8 (see ¶¶ 110-114), Miles describes an assay machine that immerses a tip tray 116 (substrate) of probes 90 (optical sensing assemblies) in successive microtiter plates containing sample, reagent, or wash solutions.¹⁸⁸ Miles also outlines a procedure in which, before running an “immunoassay,” the probes are immersed in a microtiter plate containing solutions of capture antibodies to immobilize the antibodies on the probe tips.¹⁸⁹ This pre-assay immobilization step functionalizes the probe tips so they can bind the target analyte during an assay. POSAs used the same approach to functionalize BLI/RIfS probes, such as those described in Yang (or WO854, as I address in Section X), to bind the target analyte in an assay.¹⁹⁰

118. With respect to claim 5, Miles does not explicitly describe a pre-wetting step. Nonetheless, a POSA would have found such a step obvious. By 2005, immunoassays routinely employed functionalized surfaces that were pre-coated with proteins (e.g., antibodies, antigens, or other analyte-binding

¹⁸⁷ EX1001 (’588 patent), at 2:3-7.

¹⁸⁸ EX1005 (Miles), at 2:55-3:4, 9:55-57, 11:26-44, 17:56-58, Fig. 2.

¹⁸⁹ EX1005 (Miles), at 10:65-11:15.

¹⁹⁰ EX1006 (Yang), at 434; EX1008 (WO854), at ¶¶ [0054]-[0056].

molecules) and stored in a dry state for later use.¹⁹¹ Before running an assay, these dried surfaces would be rehydrated (pre-wetted) to restore the biological activity of the immobilized proteins.¹⁹² Dry storage of pre-prepared, functionalized surfaces simplified assays and was particularly useful during transport, such as during shipment of commercial kits. This concept was also extended to optical biosensors that were prepared and stored dry and then pre-wetted before running an assay.¹⁹³ POSAs thus would have found it obvious to pre-prepare Miles' probes or BLI/RfS probes with functionalized surfaces, store them dry, and then (when needed) immerse the probes in a pre-wet solution before carrying out an assay.

119. With respect to claim 7, Miles' tip tray 116 (substrate) is "configured for pre-wet" of probes 90 (optical sensing assemblies) before performing an assay, because it is configured to function with an assay machine in a manner that allows the suspended probe tips to contact solutions in a microtiter plate, such as a pre-

¹⁹¹ EX1021, Corning, *ELISA Technical Bulletin - Nos. 1 & 2* (July 2001), available at https://www.labcluster.com/news4_2/Corning_elisa1_2.pdf ("Corning"), at [2]; EX1037, U.S. Patent Appl. Publ. No. 2004/0171087 A1 ("Rech-Weichselbraun"), at abstract, ¶¶ [0001], [0031]-[0033], claim 1; EX1038, U.S. Patent No. 5,759,774 ("Hackett"), at 1:66-2:10; EX1045, U.S. Patent No. 4,511,534 ("Bennett"), at 1:11-19.

¹⁹² EX1021 (Corning), at [2]; EX1037 (Rech-Weichselbraun), at abstract, ¶¶ [1001], [0033], claim 1; EX1038 (Hackett), at 1:66-2:10.

¹⁹³ EX1044 (Schneider), at abstract ("This interferometer configuration employs a reference sensing region that can be functionalized separately from the specific sensing region. Optical chips were stored dry after surface functionalization, and rehydrated in serum.").

wet solution. This design aligns with the recognized practice of rehydrating dried, functionalized surfaces to restore the biological activity of immobilized proteins before conducting an assay.

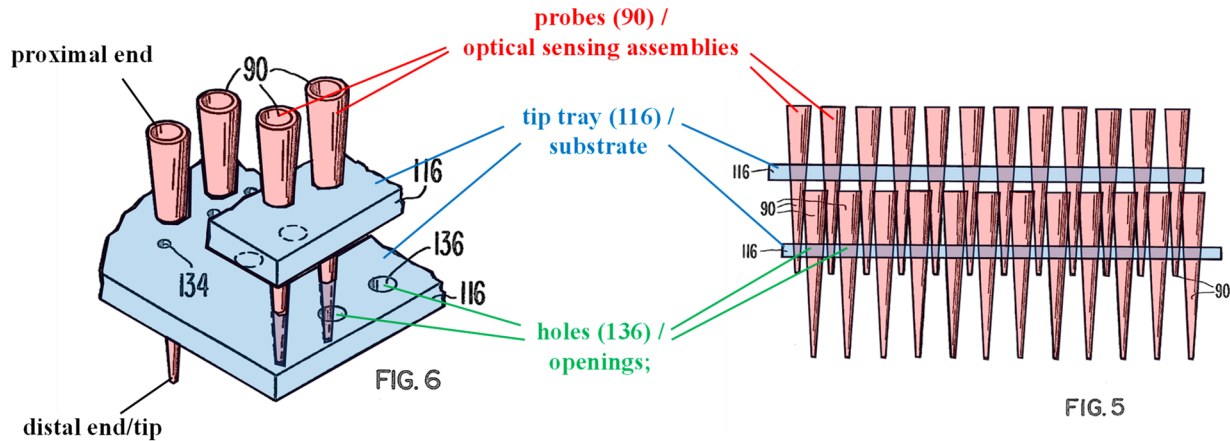
5. Claims 9 and 12

120. Claims 9 and 12 depend from claim 1 and additionally recite a “hub” on the optical sensing assembly. I have included the language of claims 9 and 12 in the table below and address each in turn.

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.

121. As I discuss in the Overview of Miles (see ¶¶ 52-59) and as to element [1Pre] (see ¶¶ 80-85), and as shown in Figures 5 and 6, Miles describes probes 90 (optical sensing assemblies, red) positioned in a plurality of openings 136 (green)

in a tip tray 116 (substrate, blue).¹⁹⁴ Each probe 90 has a proximal end/collar that is opposite to the distal end/tip and that serves as a “hub.”



122. With respect to claim 9, Miles explains that the proximal end/collar (hub) is designed to attach the probes 90 to the tip-receiving ends 86 of the syringes in the assay machine.¹⁹⁵

123. With respect to claim 12, as shown above in Figures 5 and 6, the proximal end/collar (hub) of each probe 90 has a larger diameter than the openings 136 in the tip tray 116 (substrate). The larger diameter of the hub prevents the probes from slipping through the openings and ensures that they are held in the tip tray. Thus, when a probe is positioned in one of the openings in the tip tray, the hub remains on the top (first) side of the tip tray while the distal end/tip of the

¹⁹⁴ EX1005 (Miles), at 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5, 6 (annotated).

¹⁹⁵ EX1005 (Miles), at 2:45-51, 10:28-34, Figs. 2, 7.

probe is inserted through the opening and is suspended from the bottom (second) side of the tip tray 116.¹⁹⁶

124. Again, I should note that a POSA would not have needed to physically combine the precise hub structure of Miles' probe into a BLI/RIfS probe. Rather, a POSA would have recognized that Miles' teachings may be applied to package BLI/RIfS probes in a tip tray by providing some structure on the proximal end of the probes that attaches the probes to a corresponding assay apparatus and that also is appropriately sized to retain the probes in the openings in the tip tray.¹⁹⁷

6. Claim 10

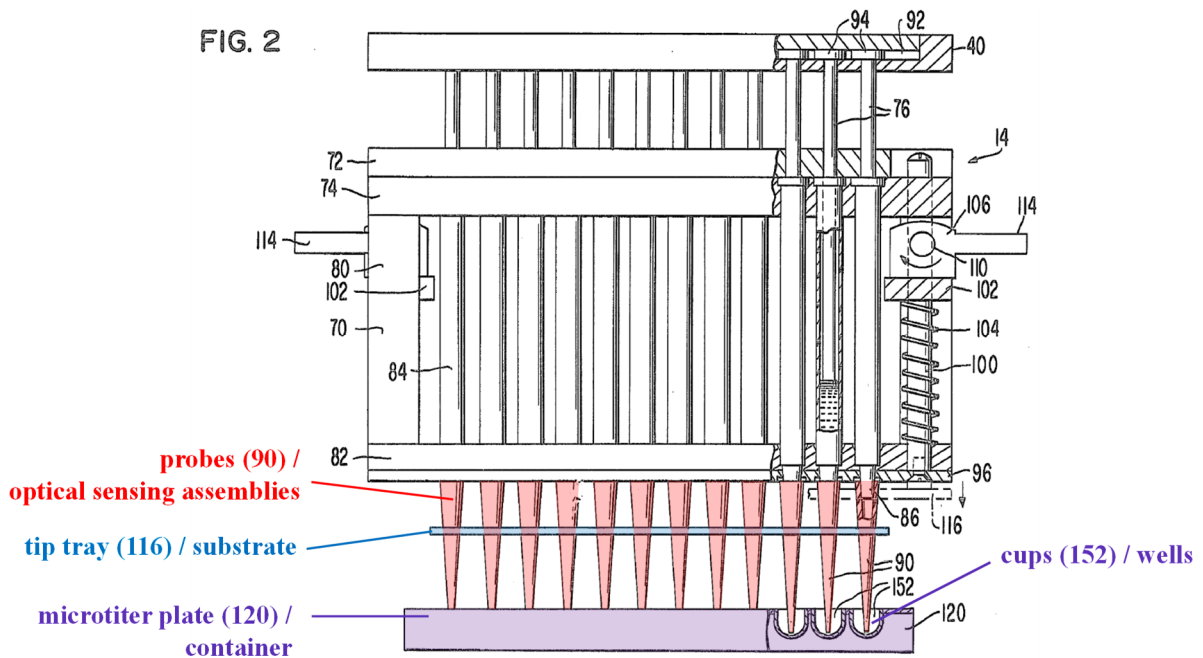
125. Claim 10 depends from claim 1 and recites that "the openings include elongated barrels that allow the optical sensing assembly to be immersed in a solution in a container below the substrate without the tip of the optical sensing assembly contacting a tip of another optical sensing assembly in the substrate."

126. As I discuss with respect to claim 2 (see ¶¶ 105-107), and as shown below in Figure 2, Miles describes loading a tip tray 116 (substrate, blue) of probes 90 (optical sensing assemblies, red) onto the tip receiving ends 86 of an assay machine and immersing the probe tips in solutions contained in a multi-well

¹⁹⁶ EX1005 (Miles), at 2:45-51, 10:28-34, Figs. 2, 7.

¹⁹⁷ EX1016 (Lapeus), at 3:14-21 (teaching similar features in probes used with a tip tray).

microtiter plate 120 (container, purple) positioned below the tip tray.¹⁹⁸ Figure 2 also shows that the tip tray 116 has a sufficient thickness such that the openings 136 each form an elongated barrel. This configuration spaces apart the probe tips 90 so that they do not contact one another while they are immersed in the solutions contained in the microtiter plate.



127. Notably, claim 10 does not specify dimensions for the “elongated barrel.” To the extent that the claim requires a barrel of longer length (whatever that may be) than what Miles describes, a POSA would have found it obvious to vary the dimensions of the barrel to achieve the desired separation between the probe tips and would have had a reasonable expectation of success given that elongated barrels were a known feature of tip trays. For example, reflecting that

¹⁹⁸ EX1005 (Miles), at 9:49-57, 10:45-47, 11:26-30, Fig. 2 (annotated).

POSAs were motivated to use elongated barrels, Kalmakis describes a similar tip tray comprising elongated barrels (referred to as “sleeves”) to position and separate tips.¹⁹⁹

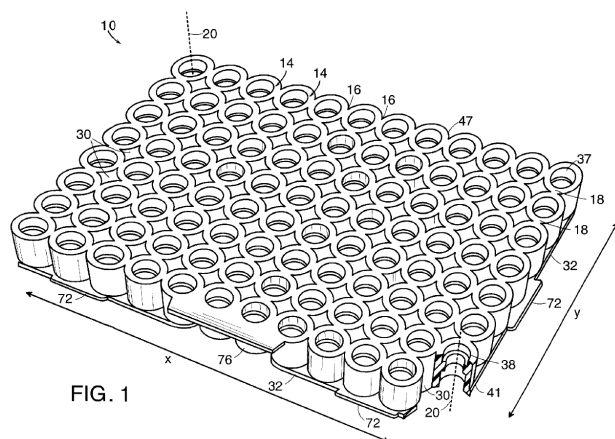


FIG. 1

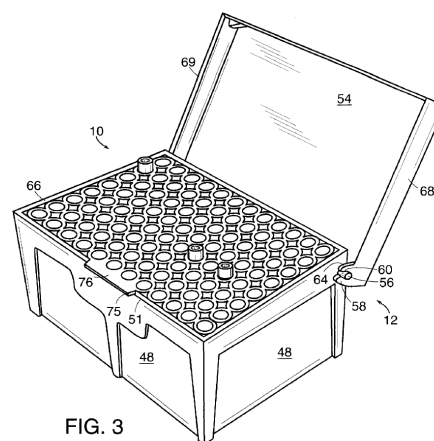


FIG. 3

7. Claim 11

128. 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 language can be understood in one of two ways: (1) there are at least two probes that are each coated with two different reagents, or (2) there are at least two probes and the reagents coated on one probe differ from those on the other. Under either interpretation, Miles renders the subject matter obvious.

129. As I discuss with respect to element [1D] (see ¶¶ 96-97), and as shown in Figures 5 and 6, Miles discloses a tip tray 116 (substrate) with a plurality of

¹⁹⁹ EX1017, U.S. Patent No. 6,019,225 (“Kalmakis”), at abstract, 3:19-23, Figs. 1, 3.

openings 136 for arranging a plurality of discrete probes 90 (optical sensing assemblies).²⁰⁰ Miles also explains that the probes may be coated with different analyte-binding molecules (reagents) to functionalize the probe tips to bind and detect a wide variety of analytes,²⁰¹ and further that each probe may be coated with multiple, different reagents, such as “multiple layers of IgG” antibody reagents.²⁰² As I also discuss with respect to claims 6 and 8 (see ¶¶ 110-114), POSAs similarly functionalized the sensing tips of BLI/RfS probes, often with multiple, different reagents. For example, Yang describes coating a BLI/RfS probe with multiple layers of antibodies (e.g., rabbit IgG and goat anti-rabbit IgG) that serve as analyte-binding molecules.²⁰³ WO854 likewise describes coating a BLI/RfS probe with multiple reagents, including “bifunctional reagents” that, in turn, help immobilize “biological molecules” (e.g., antigen, antibodies), and further describes probes coated with a “multi-layer matrix” of analyte binding molecules or multiple different analyte-binding molecules for binding different analytes.²⁰⁴

130. To the extent claim 11 requires at least two probes that are each coated with different reagents, that also would have been obvious based on Miles. Miles

²⁰⁰ EX1005 (Miles), at 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5, 6.

²⁰¹ EX1005 (Miles), at 2:19-34, 17:29-32.

²⁰² EX1005 (Miles), at 15:36-16:7.

²⁰³ EX1006 (Yang), at 434.

²⁰⁴ EX1008 (WO854), at ¶¶ [0054]-[0055], [0080].

specifically notes that combining probes in a tip tray permits using the probes with an assay machine to perform “multiple assays” “simultaneously” on a microtiter plate.²⁰⁵ Yang similarly suggests combining BLI/RIfS probes to perform multiple assays in “parallel.”²⁰⁶ A POSA would have recognized that combining different probes (each coated and functionalized with different reagents) would permit detecting different analytes in the same sample or different samples, thereby streamlining parallel testing.

131. Chen reflects that POSAs were in fact motivated to do so with BLI/RIfS probes, explaining that multiple, different BLI/RIfS probes may be combined and used together in a multiplexed format to perform multiple assays simultaneously and to detect different analytes.²⁰⁷ As Sartorius’ expert acknowledged, this provided known benefits, such as helping “speed up the analysis process” and “increase the throughput.”²⁰⁸ Likewise, WO854 (which I discuss further in Section X) incorporates by reference Chen and proposes combining multiple BLI/RIfS probes in a “two dimensional array.”²⁰⁹ These

²⁰⁵ EX1005 (Miles), at abstract, 17:64-68.

²⁰⁶ EX1006 (Yang), at 431, 436.

²⁰⁷ EX1009 (Chen), at 6:28, 8:17-29, 12:54-13:12, Fig. 11.

²⁰⁸ EX1012 (Sailor), at 340:9-341:2.

²⁰⁹ EX1008 (WO854), at ¶[0007], claims 22-23, 26-27; see also ¶¶[0009], [0017], [0045], [0080]-[0081], Fig. 5.

disclosures in Chen and WO854 (among others)²¹⁰ underscore the recognized benefits of using multiple probes coated with different reagents to perform multiple assays in parallel.

8. Claims 13 and 18-19

132. 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. I have included the language of claims 13 and 18-19 in the following table and address them below.

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 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	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.

133. As an initial matter, I note that claim 17 recites a base on “a second side” of the substrate, but neither claim 1 nor claim 18 recite “a first side,” and thus the meaning of “a second side” is not reasonably certain. For purposes of this

²¹⁰ EX1046 (Brecht), at 4; EX1047 (Birkert), at abstract, 141, Fig. 1; EX1012 (Sailor), 341:25-347:6.

declaration, I have been asked to interpret claim 18 as requiring a base on at least one side of the substrate.

134. As I discuss in the Overview of Miles (see ¶¶ 52-59) and with respect to Claim 2 (see ¶¶ 105-107), 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.²¹¹

135. With respect to claims 13 and 18, Miles explains that during an assay, probes 90 may be treated with sample or reagent solutions, which may require incubating the probes for a period of time (e.g., 0.5–12 hours).²¹² Miles also explains that this incubation may be carried out in a storage support box 144.²¹³ As shown in Figure 4 below, the storage support box 144 consists of an open-topped box 146 (green) that serves as a base (claim 18).²¹⁴ The bottom portion (purple) of the syringe battery provides a cover (claim 13) that “serv[es] to enclose” the tip tray 116 (blue) and the probes 90 (red).²¹⁵ Together, the base and cover protect the

²¹¹ EX1005 (Miles), at 9:49-57, 10:45-47, 11:26-30, Figs. 2.

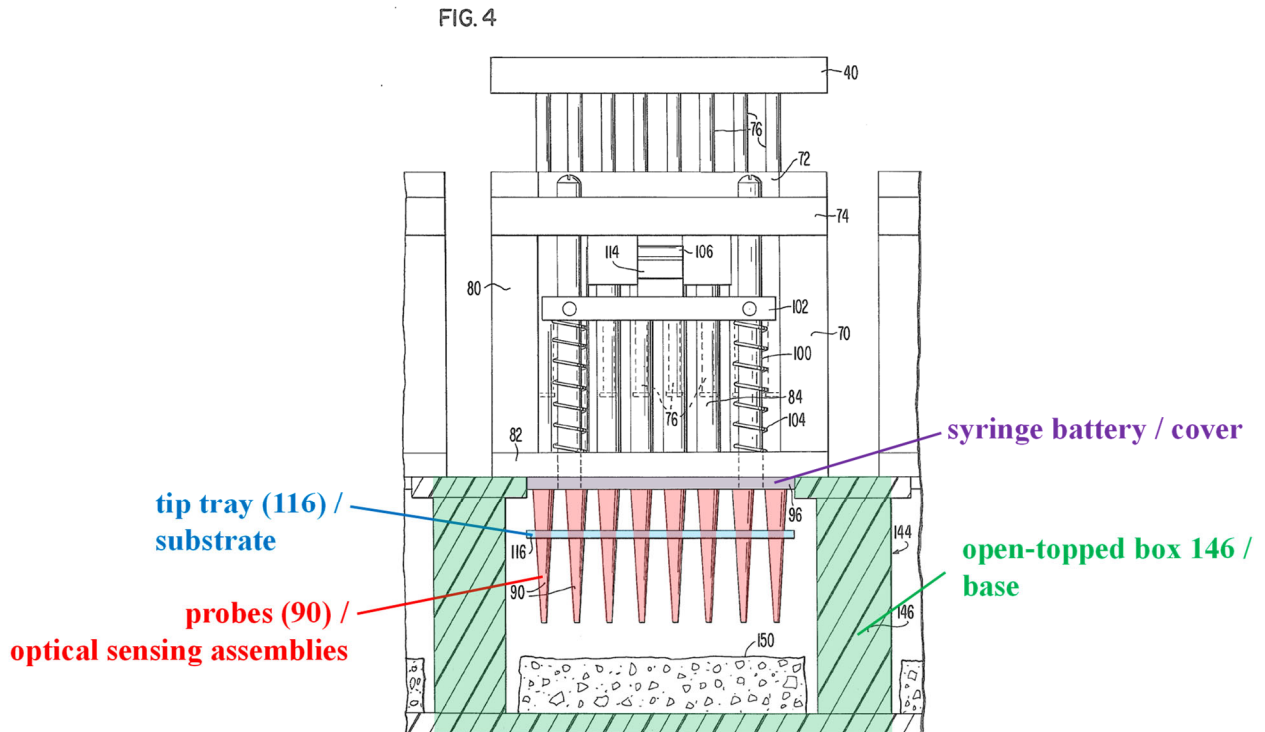
²¹² EX1005 (Miles), at 6:29-38, 11:16-44, Fig. 4.

²¹³ EX1005 (Miles), at 8:45-48, 13:2-6, 16:9-13, Fig. 4.

²¹⁴ EX1005 (Miles), at 11:20-25, Fig. 4 (annotated).

²¹⁵ EX1005 (Miles), at 11:20-25, Fig. 4.

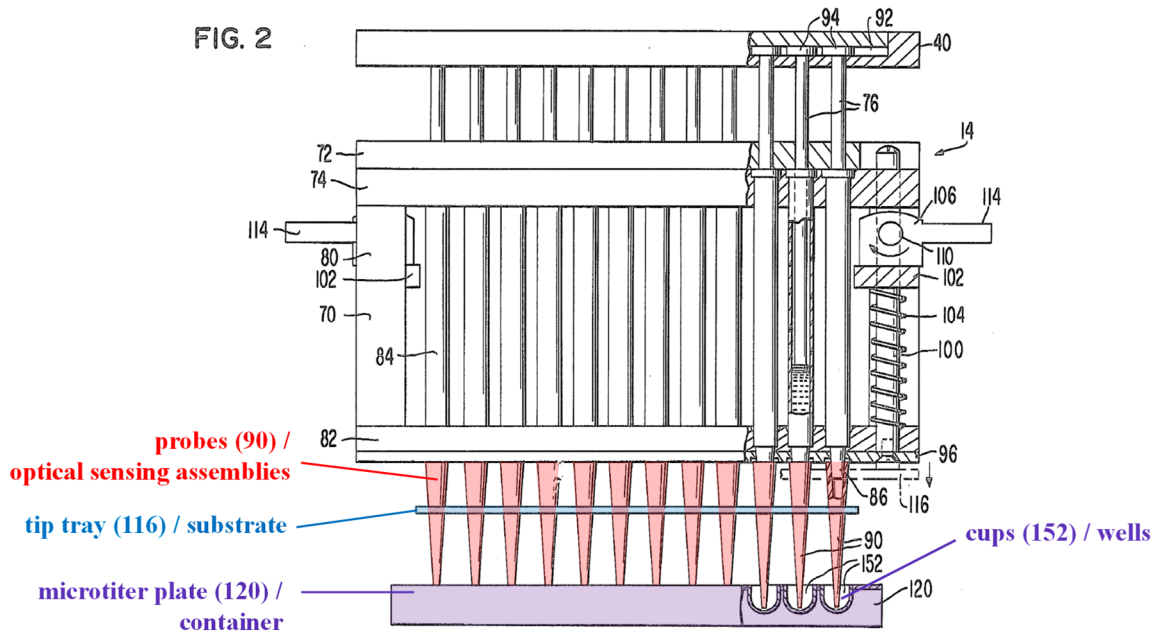
probes 90 (claims 13 and 18) by providing “controlled temperature and humidity conditions.”²¹⁶



136. With respect to claim 19, Miles does not explicitly describe the storage support box 144 as including a container such as a microtiter plate. Nevertheless, as I explain with respect to claim 2 (see ¶¶ 105-107), and as shown in Figure 2 below, Miles describes loading a tip tray 116 (blue) of probes 90 (red) onto the syringe battery of the assay machine and bringing a microtiter plate 120 (green) into position so that the suspended probe tips are inserted into and contact solutions in the wells 130 of the microtiter plate.²¹⁷

²¹⁶ EX1005 (Miles), at 11:16-35; see also 8:45-48, 13:2-6, 16:9-13, Fig. 4.

²¹⁷ EX1005 (Miles), at 9:55-57, 11:26-44, Fig. 2 (annotated).



137. A POSA would have found it obvious, and would have been motivated, to place the microtiter plate 120 (purple) within the storage support box 144. Doing so would allow the probes to be introduced to sample and reagent solutions and also incubated all in one step and all at the same location. Miles reinforces this motivation by explaining that the storage support box 144 advantageously provides humidity- and temperature-controlled conditions.²¹⁸

IX. Opinions Based on Miles, Yang, and Rainin

138. In my opinion, the subject matter of claims 2-8 and 13-19 of the '588 patent would have been further obvious to a POSA based on the combination of Miles, Yang, and Rainin. As I explain above, POSAs would have been motivated to package BLI/RfS probes (such as those described in Yang) in a tip tray (such

²¹⁸ EX1005 (Miles), at 8:45-48, 11:16-35, 13:2-6, 16:9-13.

as that described in Miles). Rainin discloses a protective storage box comprising a base and a cover for conveniently storing such tip trays.

A. Overview of Miles

139. I provide above an overview of Miles at ¶¶ 52-59.

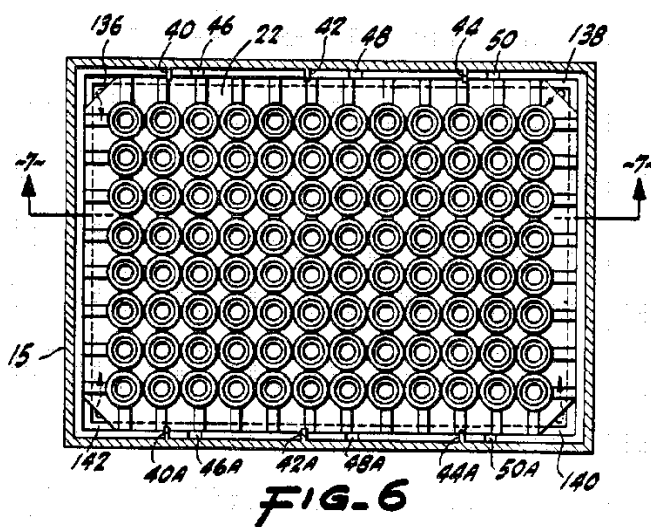
B. Overview of Yang

140. I provide above an overview of Yang at ¶¶ 60-66.

C. Overview of Rainin

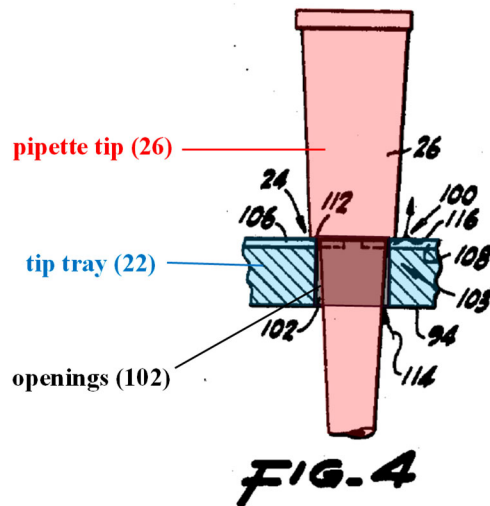
141. Rainin (EX1007), entitled “Enclosed Pipette Tip Rack,” is a patent that issued on June 30, 1987. I understand that Rainin qualifies as prior art.

142. Rainin discloses pipette tip trays housed in stackable boxes for convenient storage. As shown in Figure 6, each tip tray 22 includes 96 openings 102 (also referenced as 118) arranged in an 8×12 array, corresponding to the layout of standard 96-well microtiter plates.²¹⁹



²¹⁹ EX1007 (Rainin), at 5:41-56, 6:8-13, Fig. 6.

143. Moreover, as shown in Figure 4, the openings 102 hold and suspend pipette tips 26 (red), which extend through tip tray 22 (blue) from one side to the other.²²⁰ Each pipette tip 26 has a proximal end/collar that is designed to attach to a pipette and that has a wider diameter than the openings 102 to prevent the tip from falling through the openings 102.²²¹



144. Figure 1 (below) further shows tip tray 22 (blue) housed in a storage box/enclosure 32 comprising a container/base 12 (green) and a cover 30 (purple).²²² A shoulder 90 “extends around the interior” of base 12 to support the tip tray 22 at an appropriate height, keeping the suspended pipette tips elevated and preventing contact with the bottom of the container.²²³ Together, base 12 and cover 30 enclose

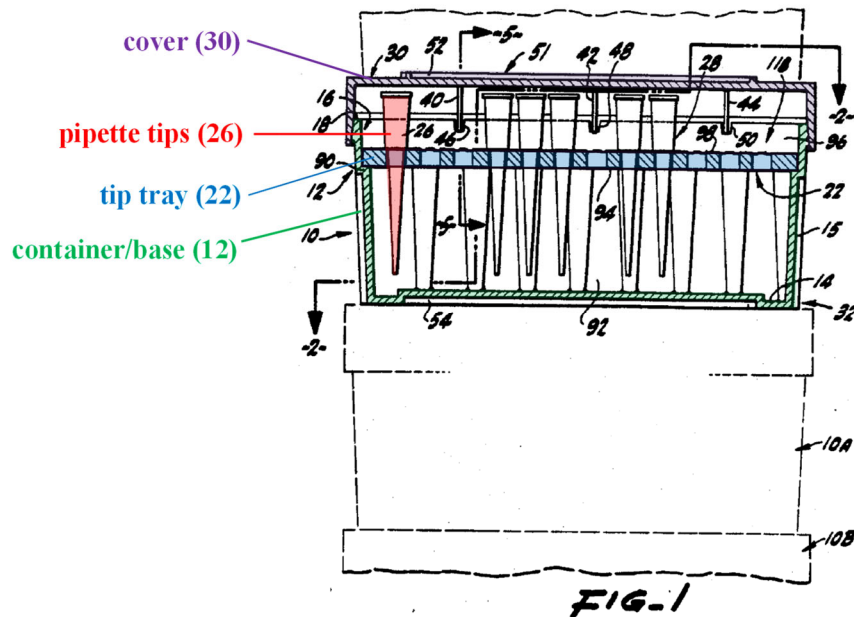
²²⁰ EX1007 (Rainin), at 5:41-56, Fig. 4 (annotated).

²²¹ EX1007 (Rainin), at 5:41-56, Fig. 4, see also Figs. 1, 3.

²²² EX1007 (Rainin), at 4:20-48, Fig. 1 (annotated).

²²³ EX1007 (Rainin), at 5:31-36.

tip tray 22 to create a “dust-free” configuration that “resist[s] intrusion of dust and other contaminants.”²²⁴



145. Rainin also explains that the storage box may be designed for stacking.²²⁵ As shown in Figure 1 above, the cover 30 may include a protrusion 52 that fits into a recess 54 in container/base 12, allowing multiple boxes to be securely stacked.²²⁶ This feature makes it easier to store and transport multiple trays while maintaining sterility and protecting the pipette tips.

²²⁴ EX1007 (Rainin), at 4:41-46, 5:1-7.

²²⁵ EX1007 (Rainin), at 5:7-10.

²²⁶ EX1007 (Rainin), at 5:7-10.

D. Reasons for Combining Miles, Yang, and Rainin

146. As I address above (see ¶¶ 67-78), a POSA would have been motivated to use a tip tray, similar to that disclosed in Miles, to package BLI/RIfS probes, such as those disclosed in Yang (and WO854), recognizing that a tip tray would provide similar advantages when used with BLI/RIfS probes, such as enabling the efficient use of BLI/RIfS probes with standard microtiter plates and related assay equipment. Building on this, and as I discuss in the Overview of Rainin (see ¶¶ 141-145), Rainin describes a stackable storage box comprising a base and a cover for conveniently storing and protecting such tip trays.²²⁷ A POSA would have been motivated to use a storage box with a tip tray housing BLI/RIfS probes because, as Rainin explains, the box encloses the tip tray and creates a “dust-free” environment that “resist[s] intrusion of dust and other contaminants.”²²⁸

147. In fact, by June 2005, pipette tip trays were routinely packaged and sold in stackable storage boxes (comprising a base and cover) to safeguard the tips from contamination during transport and storage, ensuring that the tips remained sterile until they were used.²²⁹ These storage boxes typically included a guarantee

²²⁷ EX1007 (Rainin), at 4:20-48, 5:7-10, Fig. 1.

²²⁸ EX1007 (Rainin), at 4:41-46, 5:1-7.

²²⁹ EX1039 (Gilson), at [13]-[16] (depicting commercially available tip trays housed in storage boxes).

of sterilization and would identify the date on which the tips were sterilized.²³⁰ Laboratories also expected pipette tip trays to be packaged in a storage box both because sterility is important for most assays and because most commercially available tip trays came housed in storage boxes for that reason.

148. Apart from sterility, a POSA would have recognized that Rainin's storage box houses a tip tray holding 96 tips arranged in an 8×12 array in a manner that facilitates using the tips with a 96-well microtiter plate (and related equipment), as disclosed in Miles.²³¹ As I explain above (see ¶¶ 18-27, 58-59), by June 2005, the 96-well (8×12) microtiter plate format was the “de facto standard” for conducting many laboratory assays because it facilitated automating and performing multiple assays simultaneously, and POSAs thus designed related equipment with this standard in mind.²³² These considerations also would have motivated POSAs to use a tip tray and storage box such as that described in Rainin to package BLI/RfS probes.

²³⁰ EX1039 (Gilson), at [16] (advertising that storage box “includes the date of sterilization and [a] red sticker [that] guarantees sterilization”).

²³¹ EX1005 (Miles), at 2:55-65, 12:24-26, Fig. 2.

²³² EX1005 (Miles), at 2:55-65, 12:24-26, Fig. 2; EX1013 (Astle), at 1:24-27; EX1014 (Atwood), at 3:31-48; EX1039 (Gilson), at [13]-[16] (showing commercially available boxed tip trays having standard 8×12 array), 4-6, 18-21 (showing related equipment used with standard 96-well microtiter plates); EX1048 (Fisher), at 1185-87 (showing commercially available boxed tip trays having standard 8×12 array), 1877-82 (showing related equipment used with standard 96-well microtiter plates).

E. The Combination of Miles, Yang, and Rainin Renders Claims 2-8 and 13-19 Obvious

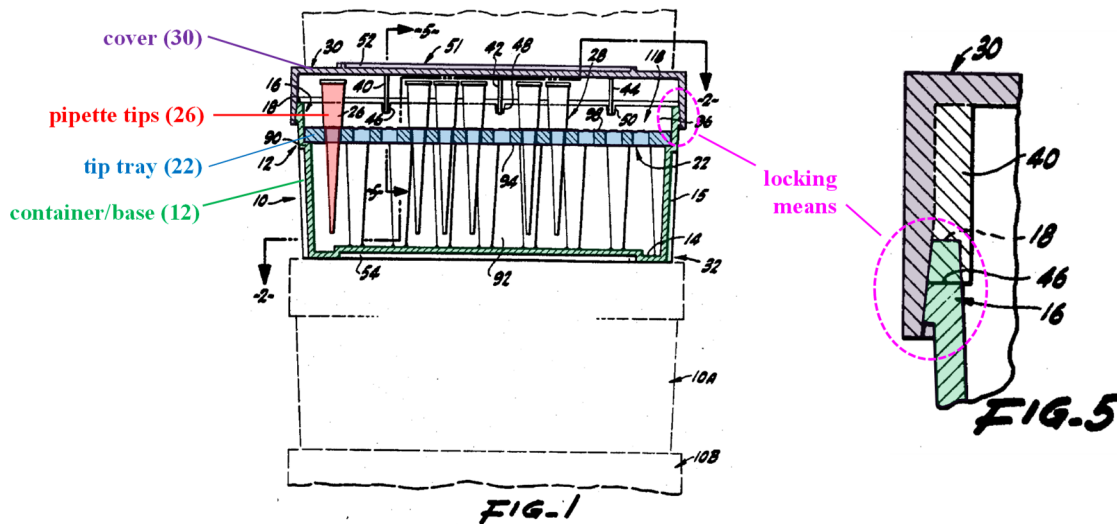
1. Claims 13-16 and 18

149. Claims 13 and 18 depend from claim 1, and claims 14-16 depend from claim 13. These claims recite additional features of a box that houses the tip tray apparatus of claim 1. I have included the language of claims 13-16 and 18 in the following table and address them below.

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.

150. With respect to claims 13, 15, and 18, as shown in Figures 1 and 5, Rainin discloses 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).²³³ The cover 30 and base 12 lock together to form an “enclosure” around the tip tray 22 (substrate).²³⁴ As Rainin explains, this enclosure protects the tips 90 and provides a “dust-free” configuration that “resist[s] intrusion of dust and other contaminants.”²³⁵



151. With respect to claim 16, Rainin explains that the storage box 32 is designed to be stackable.²³⁶ For example, as shown in Figure 1, the cover 30 may incorporate a protrusion 52 that fits into a recess 54 in the base 12.²³⁷ This allows multiple boxes to be securely stacked, thus simplifying transport and storage.

²³³ EX1007 (Rainin), at 4:20-48, Figs. 1, 5 (annotated).

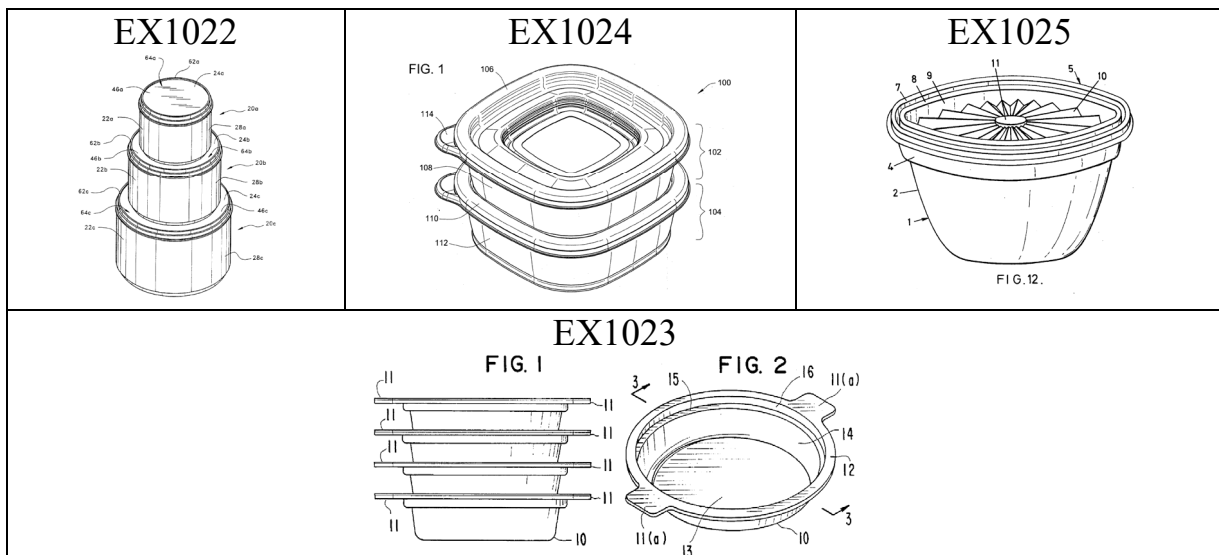
²³⁴ EX1007 (Rainin), at 4:41-46, 5:1-7; see also 2:3-30, 6:8-13, Figs. 1, 5 (showing the cover in the second position with locking means engaged), 7 (showing the cover in the first position with locking means disengaged).

²³⁵ EX1007 (Rainin), at 4:41-46, 5:1-7.

²³⁶ EX1007 (Rainin), at 5:7-10, Fig. 1.

²³⁷ EX1007 (Rainin), at 5:7-10, Fig. 1.

152. With respect to claim 14, Rainin does not explicitly disclose that the storage box 32 may be designed so that the recess 54 is instead provided in the cover 30 and the protrusion 52 is instead provided in the base 12. A POSA, however, would have found it obvious to switch the locations of the recess 54 and protrusion 52 and would have had a reasonable expectation of success because this was a common and familiar alternative design for stackable containers. Indeed, one can find numerous examples of stackable containers with a downwardly extending recess in the cover and a corresponding protrusion in the base.²³⁸



It was also well known that providing a recess in the cover would reduce the space in a container to help secure its contents during storage and transport.²³⁹ A POSA

²³⁸ EX1022, U.S. Patent No. 5,799,792 (“Abrums”), at 5:4-13, 5:29-49, Figs. 1, 4, 6; EX1023, U.S. Patent No. 4,848,579 (“Barnes”), at 2:9-12, Figs. 1-2; EX1024, U.S. Publ. 2006/0186014A1 (“Ramanujam”), at ¶¶ [0031], [0033], [0041], Figs. 1-5; EX1025, U.S. Patent No. 4,027,778 (“Tupper”), at 1:23-30, 3:52-65, Fig. 12.

²³⁹ EX1023 (Barnes), at 2:55-3:2.

thus would have been motivated to use a recessed cover with Rainin's storage box 32 to reduce the space between the cover and the tip tray and help retain and minimize the movement of the tips during storage and transport.

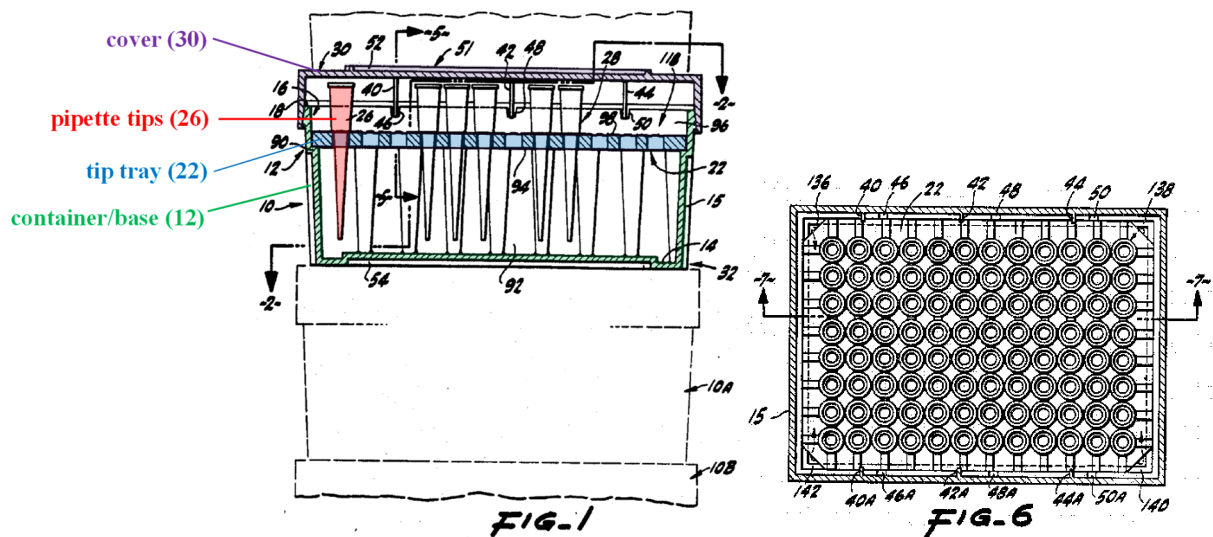
2. Claims 2, 3, 17, and 19

153. Claims 2, 3, 17, and 19 directly or indirectly depend from claim 1. These claims recite additional elements that support the tip tray apparatus of claim 1 so that the tips of the optical assemblies contact a solution in a multi-well container or microtiter plate. I have included the language of claims 2, 3, 17, and 19 in the following table and address them below.

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.
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154. As shown below in Figure 1, Rainin describes a storage box 32 comprising a cover 30 (purple) and base 12 (green), and the base includes a shoulder 90 that supports a tip tray 20 (substrate, red).²⁴⁰ 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 (claims 2, 17, and 19) in the tip tray 22.²⁴¹



155. Rainin does not explicitly disclose that the base 12 may include a multi-well container or microtiter plate. A POSA, however, would have found it

²⁴⁰ EX1007 (Rainin), at 4:20-48, 5:31-36, Figs. 1 (annotated), 6.

²⁴¹ EX1007 (Rainin), at 4:20-48, 5:31-36, Figs. 1, 6.

obvious to integrate a 96-well microtiter plate (claim 3) into 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). For example, as I discuss above with respect to claims 2 and 5-8 in the Miles and Yang combination (see ¶¶ 105-107, 110-119), Miles describes an assay machine that immerses a tip tray 116 of probes 90 in successive microtiter plates containing samples, reagents, or wash solutions.²⁴² Miles also explains that, before an assay is run, the probes need to be immersed in a solution of antibodies or other analyte-binding molecules and subsequently washed so that these molecules become coated or immobilized (insolubilized) on the distal ends/tips of the probes.²⁴³ Only after the probes are coated and functionalized in this manner are they introduced to samples and reagents to carry out the assay.²⁴⁴ As I discuss above (see ¶¶ 113, 118), POSAs similarly coated and functionalized the sensing tips of BLI/RfS probes.²⁴⁵

156. POSAs, thus, would have understood that it can be advantageous to conduct these preparatory (pre-assay) steps “offline”—that is, before loading the probes on the assay machine—especially in a busy laboratory environment where the machine is in high demand. Common steps in biochemical assays such as

²⁴² EX1005 (Miles), at 2:55-3:4, 9:55-57, 11:26-44, 17:56-58, Fig. 2.

²⁴³ EX1005 (Miles), at 10:65-11:15.

²⁴⁴ EX1005 (Miles), at 11:26-44, 11:53-62.

²⁴⁵ EX1006 (Yang), at 434; WO854, [0054]-[0055], [0080].

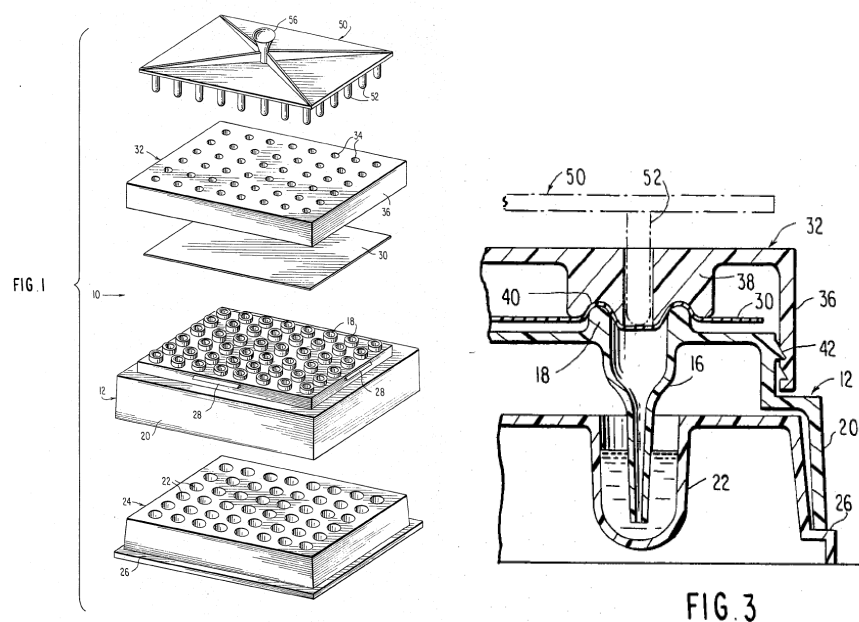
antibody immobilization to solid surfaces can take 1 to 24 hours or longer to reach equilibrium.²⁴⁶ By performing steps like antibody immobilization, washing, and possibly other reagent applications offline, labs can streamline the overall assay workflow, reduce the active time needed on the assay machine, and free up the machine to perform other assays. In addition, to obtain consistent results in a standardized assay, i.e. be robust, steps must be performed in a consistent manner with known validated materials, supplies, and reagents. To control for potential externalities, kits for standardized assays, such as FDA-approved clinical assays, typically include all required reagents and materials (e.g. microtiter plates) given that third-party materials, even if readily available, may not perform in a known manner and provide consistent results in the assay.²⁴⁷ Thus, a POSA would be strongly motivated to include a microtiter plate into the base of a tip tray apparatus, since inclusion of crucial components as part of a testing set was common.

157. POSAs also would have had a reasonable expectation of success of including a microtiter plate in the base of a tip tray apparatus because similar structures were known. For example, U.S. Patent No. 4,511,534 to Bennett (issued

²⁴⁶ EX1055, Brian Law et al., *Chapter 7: Enzyme-Linked immunosorbent assay (ELISA) development and optimization*, in IMMUNOASSAY, A PRACTICAL GUIDE (1996) (“Law”), at 144; see also EX1005 (Miles), at 6:35-37 (explaining incubation periods may take up to 12 hours).

²⁴⁷ EX1056, 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”), at 9.

in 1985) describes an apparatus that positions pipette tips (in a plate assembly 12) over a microtiter plate 24 so that the tips are immersed in solutions contained in the wells of the plate.²⁴⁸ Bennett further describes the need for such a device to pre-wet dried functionalized surfaces before conducting an assay.²⁴⁹



3. Claims 4-8

158. I incorporate my discussion of claims 3-8 with respect to the Miles and Yang combination (¶¶ 109-119).

X. Opinions based on Miles and WO854

159. In my opinion, the subject matter of claims 1-13 and 18-19 of the '588 patent would have been obvious to a POSA based on the combination of Miles and WO854. My opinions regarding the combination of Miles and WO854 are

²⁴⁸ EX1045 (Bennett), at 3:33-47, 4:52-64, Figs. 1, 3.

²⁴⁹ EX1045 (Bennett), at 1:11-19.

substantially the same as my opinions regarding the combination of Miles and Yang (which I address above in Section VIII), except that I rely on WO854 for disclosure of a BLI/RIfS probe instead of Yang.

A. Overview of Miles

160. I provide above an overview of Miles at ¶¶ 52-59.

B. Overview of WO854

161. WO854 (EX1008), entitled “Fiber-Optic Assay Apparatus Based on Phase-Shift Interferometry,” was published on May 26, 2005. I understand that WO854 qualifies as prior art.

162. WO854 describes a fiber-optic sensor probe (optical sensing assembly) for detecting analyte in a sample using BLI/RIfS. As shown in Figure 4 below, the probe is removably coupled to an optical fiber 52 via gripping arms 54.²⁵⁰ The probe itself comprises a first optical element 60 (red) that has a thickness greater than 50 nm and a second optical element 66 (blue), which may be a glass or polymeric material.²⁵¹ The first optical element comprises two reflecting surfaces (62, 64), the first of which comprises a layer of analyte-binding molecules for binding analyte in a sample.²⁵² During an assay, when analyte molecules bind to the analyte-binding molecules on the distal end/tip of the probe, the resulting

²⁵⁰ EX1008 (WO854), at ¶¶ [0077]-[0079], Fig. 4 (annotated).

²⁵¹ EX1008 (WO854), at ¶¶ [0051], [0078].

²⁵² EX1008 (WO854), at ¶¶ [0078]-[0079].

interference pattern (as registered on a spectrometer) varies and provides an indication of analyte binding.²⁵³

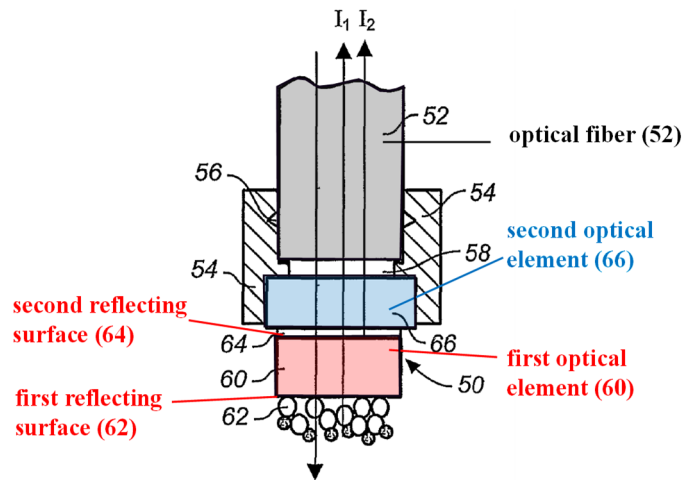


FIG. 4

163. WO854 explains that multiple analyte-binding regions may be combined on the distal end of a probe, allowing the probe to assay multiple, different analytes in a single sample.²⁵⁴ WO854 also includes claims covering arrangements in which multiple discrete probes (optical assemblies) are combined into a “two dimensional array” format.²⁵⁵ Further, WO854 incorporates by reference the earlier Chen patent, which discloses a similar BLI/RIfS probe 700 that is removably coupled to an optical fiber of an assay instrument via a clothespin-type connector 802.²⁵⁶ As shown below in Figure 11, Chen explains that

²⁵³ EX1008 (WO854), at ¶¶ [0010], [0056], [0079].

²⁵⁴ EX1008 (WO854), at ¶¶ [0009], [0017], [0045], [0080]-[0081], Fig. 5.

²⁵⁵ EX1008 (WO854), at claims 22-23, 26-27.

²⁵⁶ EX1008 (WO854), at ¶ [0007]; EX1009 (Chen), at 10:45-57, Fig. 8, 12:24-26

multiple such discrete probes (1 through n, e.g., 1106a, 1106b and 1106c) may be combined and used together in a multiplexed format to perform multiple assays simultaneously and to detect different analytes in a sample.²⁵⁷ Sartorius' expert, Dr. Sailor, concurred that Chen describes a BLI/RfS probe and "teaches that you can use multiple [such] probes, and combine them together in multiplexed format" that allows samples to be analyzed "for either multiple components or the same component multiple times."²⁵⁸ He further explained that such multiplexing "helps speed up the analysis process" and "increase the throughput."²⁵⁹

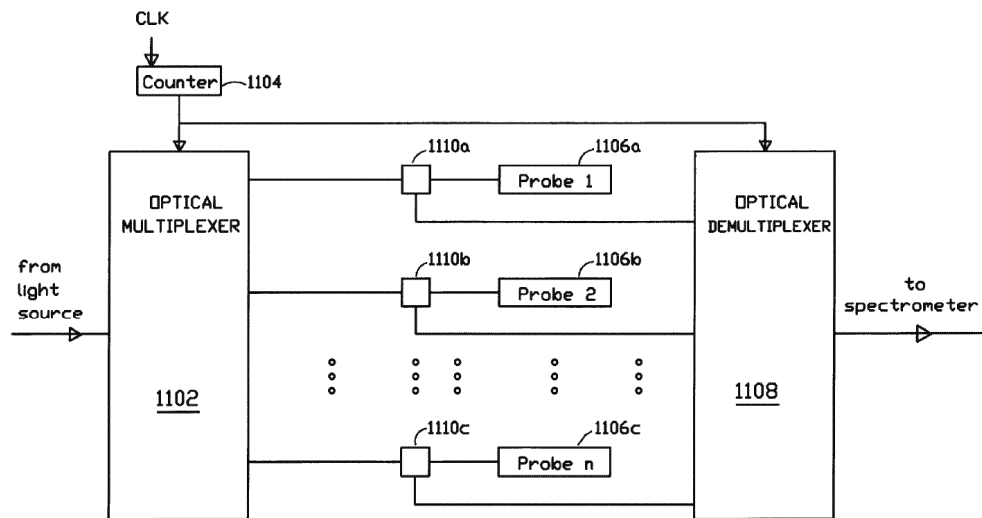


Figure 11

(describing connector 802 as part BFA-MM from MetroTek); EX1058 (MetroTek Website) (showing and describing BFA-MM as removable "clothespin" type adapter for connecting optical fibers); EX1059 (MetroTek Catalog), at 7 (same); EX1012 (Sailor), at 327:5-329:7, 333:15-339:7 (Sartorius' expert concurring).

²⁵⁷ EX1009 (Chen), at 6:28, 8:17-29, 12:54-13:12, Fig. 11.

²⁵⁸ EX1012 (Sailor), at 339:17-341:2.

²⁵⁹ EX1012 (Sailor), at 340:9-341:2.

C. Reasons for Combining Miles and WO854

164. As I address above with respect to combining Miles and Yang (see ¶¶ 67-78), a POSA would have been motivated to package BLI/RIfS probes such as those described in WO854 (or alternatively Yang) in a tip tray such as that described in Miles. I address below the claim elements for which I rely on WO854 and incorporate my analysis as to the remaining elements from my discussion of the Miles and Yang combination.

D. The Combination of Miles and WO854 Renders Claims 1-13 and 18-19 Obvious

1. Claim 1

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

165. To the extent the preamble is limiting, Miles in combination with WO854 teaches “[a]n apparatus for packaging an optical sensing assembly.”

166. As I discuss above in the Overview of Miles (see ¶¶ 52-59), Miles discloses the use of pipette tips (sensor probes) that serve as optical sensing assemblies.²⁶⁰ The distal ends or tips of the probes are coated (insolubilized) with analyte-binding molecules, such as antigen or antibody, which provides a functionalized surface for binding analyte molecules present in a sample.²⁶¹ During

²⁶⁰ EX1005 (Miles), at abstract, 2:19-34; 4:20-25; 12:23-26.

²⁶¹ EX1005 (Miles), at 2:19-34, 2:52-55, 4:3-19, 5:53-68.

an assay, the probe tips are introduced to (contacted with) solutions of samples and reagents contained in the wells of microtiter plates, such as 96-well plates.²⁶²

167. Miles further describes example assay procedures in which probes coated with analyte-binding molecules (e.g., capture antibodies) are used to bind analyte molecules (e.g., human growth hormone (HGH)) present in sample solutions and then introduced to a labeled antibody or antigen for detecting the presence and amount of analyte.²⁶³ Although Miles' examples employ radiolabeled antibodies or antigens, Miles also explains that the probes may be configured to produce an optical readout by using other types of labels, such as "enzymes," "fluorescers," or "fluorogenic" reagents.²⁶⁴ Assays using fluorescers or fluorogenic substances generate a measurable optical fluorescence signal.²⁶⁵ Moreover, by June 2005, enzyme-labeled reagents that generate a measurable optical color change were routinely used in assays, such as ELISAs.²⁶⁶ Furthermore, instruments suitable for quantifying such fluorescence and colorimetric signals in 96-well

²⁶² EX1005 (Miles), at 2:55-3:4, 12:24-26, Fig. 2.

²⁶³ EX1005 (Miles), at 12:64-13:36.

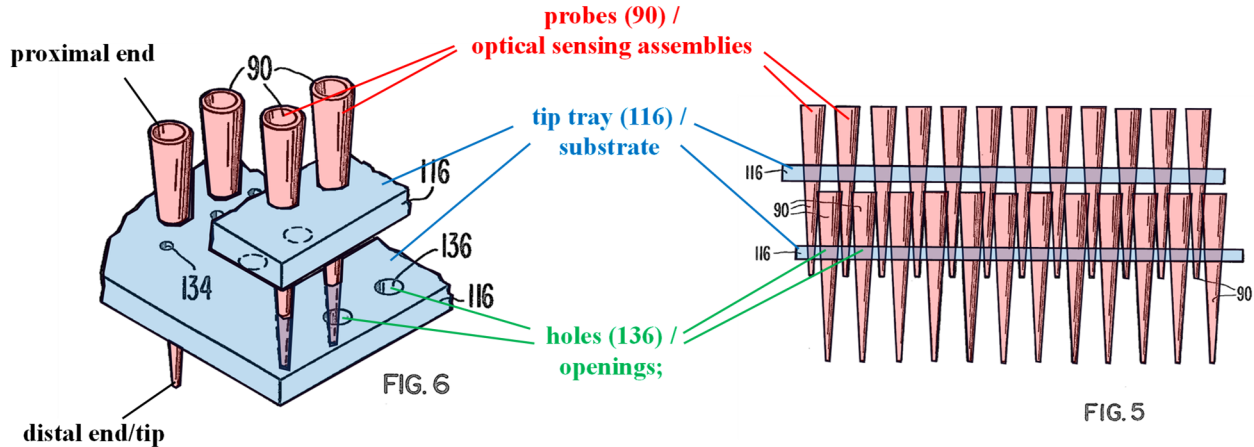
²⁶⁴ EX1005 (Miles), at 4:20-30, 11:63-66.

²⁶⁵ EX1012 (Sailor), at 106:20-108:15.

²⁶⁶ EX1020 (Lequin), at 2415, 2417; EX1012 (Sailor), at 106:20-108:15.

microtiter plates were commonplace by that time and were routinely used in laboratories for conducting analytical assays, including my own.²⁶⁷

168. In addition to describing the sensor probes and assays that use them, Miles discloses a tip tray apparatus for packaging the probes. As shown in Figures 5 and 6 below, 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 distal ends/tips of the probes extend and are suspended.²⁶⁸

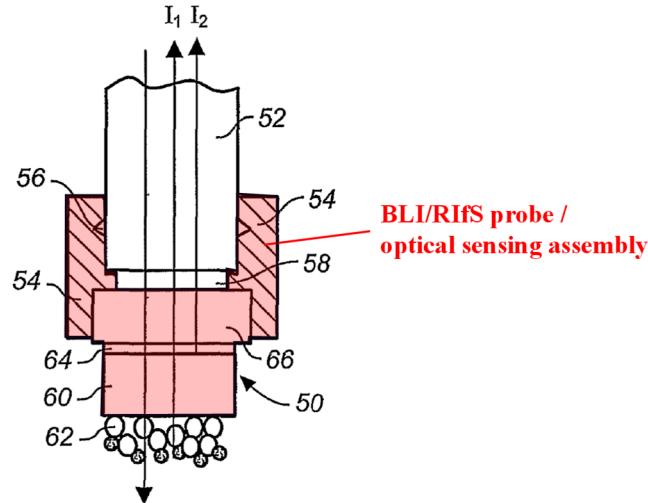


169. Further, as I discuss in the Overview of WO854 (see ¶¶ 161-163) and discuss further below as to elements [1A]-[1C] (see ¶¶ 171-179), WO854 describes a BLI/RIfS probe that serves as an optical sensing assembly, as shown in Figure 4.²⁶⁹

²⁶⁷ EX1048 (Fisher), at 1878-81.

²⁶⁸ EX1005 (Miles), at 2:45-51, 8:26-36, 9:49-54, 10:18-27, Figs. 5, 6 (annotated).

²⁶⁹ EX1008 (WO854), at ¶¶ [0077]-[0079], Fig. 4 (annotated); see also ¶ [0051], Fig. 2.

**FIG. 4**

170. Notably, Figures 2 and 4 of WO854 show probes that are substantially identical to the optical sensing assembly 26 in Figure 2 of the '588 patent.²⁷⁰ For the reasons I discuss above regarding motivation (see ¶¶ 67-78), POSAs would have been motivated to apply Miles' teachings to use a tip tray to package BLI/RIfS probes, such as those described in WO854. This combination would facilitate the integration of BLI/RIfS probes with standard microtiter plates and related assay equipment, thereby improving the efficiency and automation of assays.

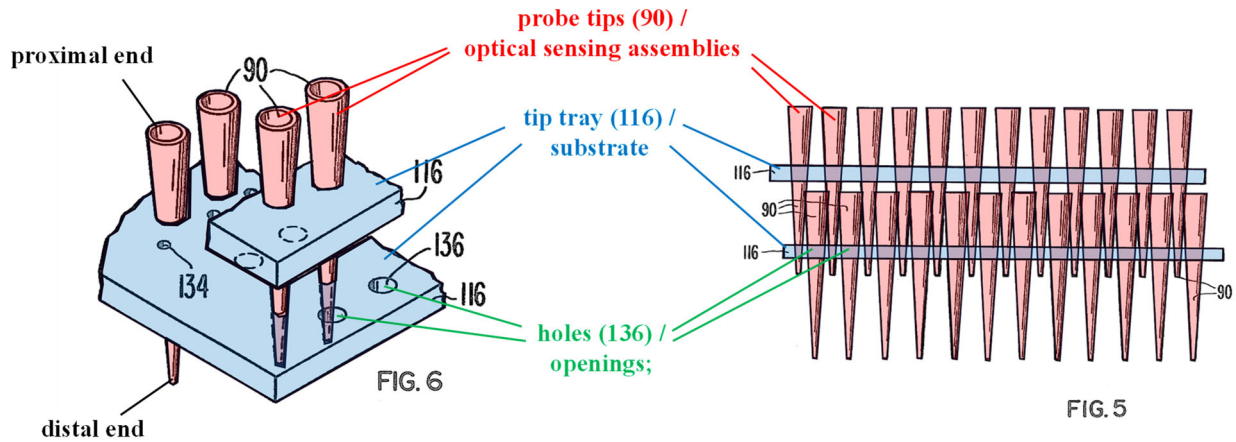
b. [1A]: “at least one discrete optical sensing assembly”

171. Miles, in combination with WO854, teaches a tip tray apparatus comprising “at least one discrete optical sensing assembly.”

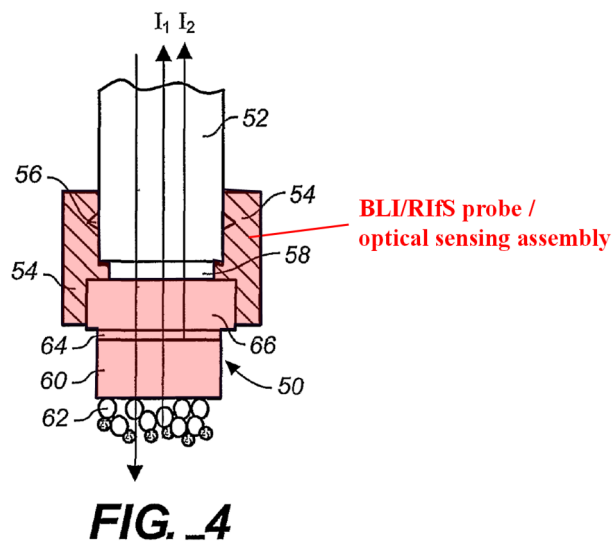
172. As I address in the Overview of Miles (see ¶¶ 52-59) and as to element [1Pre] (see ¶¶ 165-170), and as shown in Figures 5 and 6, Miles discloses a tip tray

²⁷⁰ EX1001 ('588 patent), at 8:17-39, Fig. 2.

166 (blue) for packaging discrete probes 90 (red) that serve as optical sensing assemblies.²⁷¹



173. As I address in the Overview of WO854 (see ¶¶ 161-163) and as to element [1Pre] (see ¶¶ 165-170), and as shown in Figure 4 below, WO854 describes a BLI/RfS probe that serves as an optical sensing assembly.²⁷²



²⁷¹ EX1005 (Miles), at 2:45-51, 8:26-36, 9:49-50, 10:18-27, Figs. 5, 6 (annotated); see also 4:20-30, 11:63-66 (describing the use of probes with enzyme and fluorescent/fluorogenic labels that provide optical readouts).

²⁷² EX1008 (WO854), at ¶¶[0077]-[0079], Fig. 4 (annotated).

- c. [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”

174. As shown in Figure 4 below, WO854 discloses a BLI/RIfS probe comprising a first optical element 60 and a second optical element 66.²⁷³

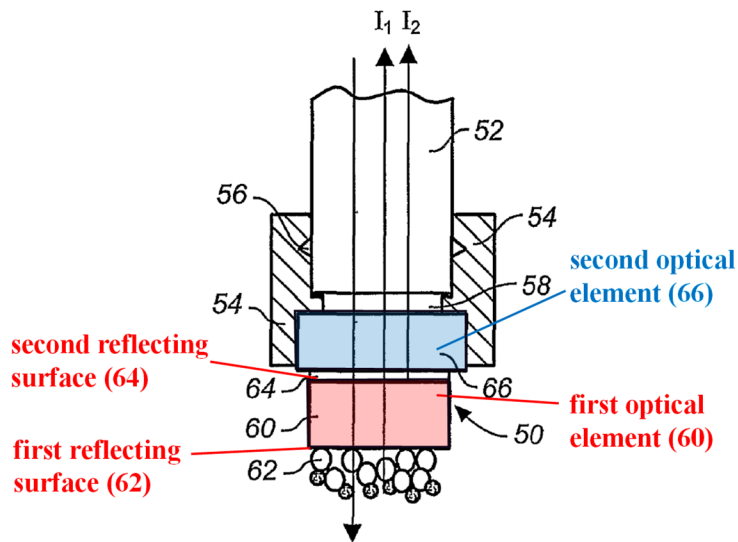


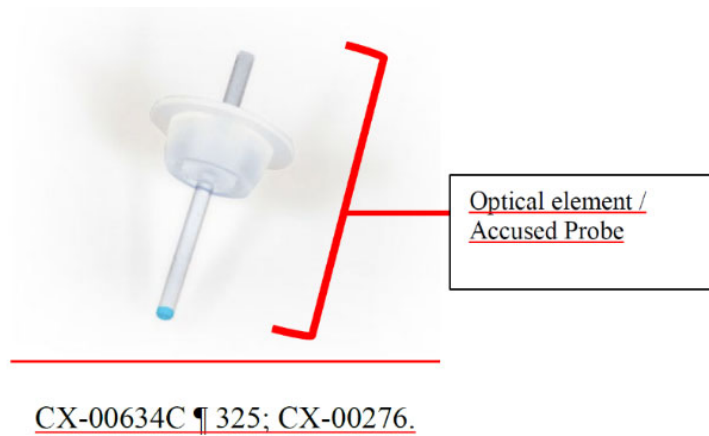
FIG. 4

175. As to an “optical fiber,” WO854 discloses that the second optical element 66 is preferably comprised of “glass or a polymeric material having an index of refraction of between about 1.4 and 1.6,” which is consistent with typical glass and plastic optical fibers.²⁷⁴ Notably, in ITC Investigation No. 337-TA-1344, where I served as a technical expert, Sartorius acknowledged that an “optical element” in this context may include an optical fiber. In particular, Sartorius

²⁷³ EX1008 (WO854), at ¶[0078], Fig. 4 (annotated).

²⁷⁴ EX1008 (WO854), at ¶[0078]; EX1026 (Zubia), at abstract, 107 (Table 2).

asserted related patents (three originating from the same family as WO854) and identified the optical fiber portion of the accused probes as an “optical element.”²⁷⁵



Relying on Sartorius’ assertion, the presiding Administrative Law Judge (ALJ) concluded that the accused “probes are an optical element comprised of optical fiber with an optical layer with two reflective surfaces.”²⁷⁶

176. I have also reviewed the record from IPR2023-00215 of U.S. Patent 8,305,585 (also from the same family as WO854), where Sartorius argued that it “does not take the position that an optical fiber cannot be a component of an optical element.”²⁷⁷

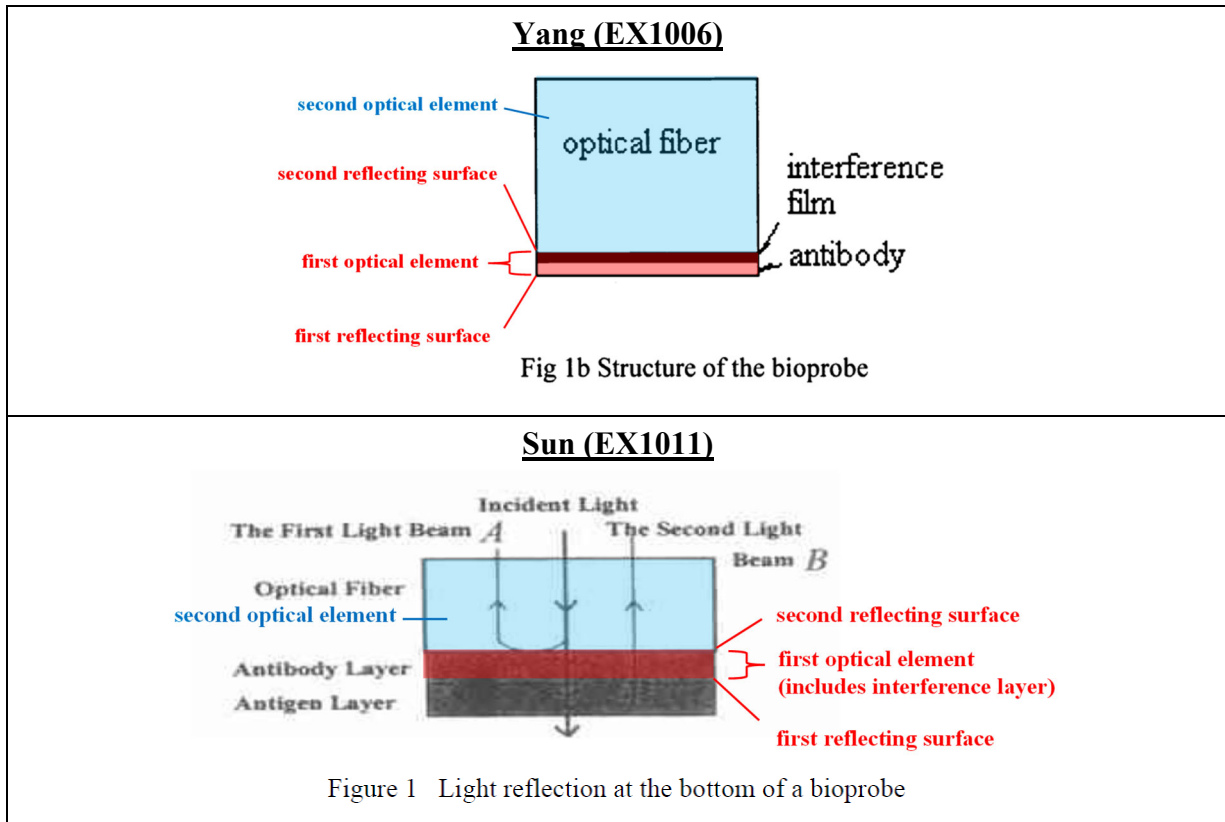
177. To the extent that WO854 does not explicitly describe using an optical fiber as the second optical element 66, a POSA would have found it obvious to use

²⁷⁵ EX1028 (Sartorius’ Prehearing Brief), at 92-94, 112-13, 326, 335-36.

²⁷⁶ EX1029 (Final Initial Determination), at 11, 60.

²⁷⁷ EX1027 (Excerpt of Patent Owner’s Preliminary Sur-Reply), at 6.

an optical fiber and would have had a reasonable expectation of success. This is because, as I describe above in the Technical Background (see ¶¶ 31-34), similar BLI/RIfS probes comprising an optical fiber were already known, as disclosed in references such as Yang and Sun.²⁷⁸



178. 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.” For example, WO854 explains that the first optical element 60 comprises end faces that form the first and

²⁷⁸ EX1006 (Yang), at 434-35, Fig. 6 (annotated); EX1010/EX1011 (Sun), at 659, Fig. 5 (annotated).

second reflective surfaces 62, 64, respectively.²⁷⁹ It also explains that this first optical element 60 (similar to optical element 38 of the assembly in Figure 2) comprises a “transparent” material (e.g., a transparent glass or polymeric material) and provides at least a 50 nm separation between the first and second reflecting surfaces 62, 64.²⁸⁰ Further, as shown in Figure 4 above, the first optical element 60 is necessarily transparent, given that both the incident light beam (downward arrow) and the reflected beam I₁ (upward arrow) are able to pass through it.²⁸¹

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

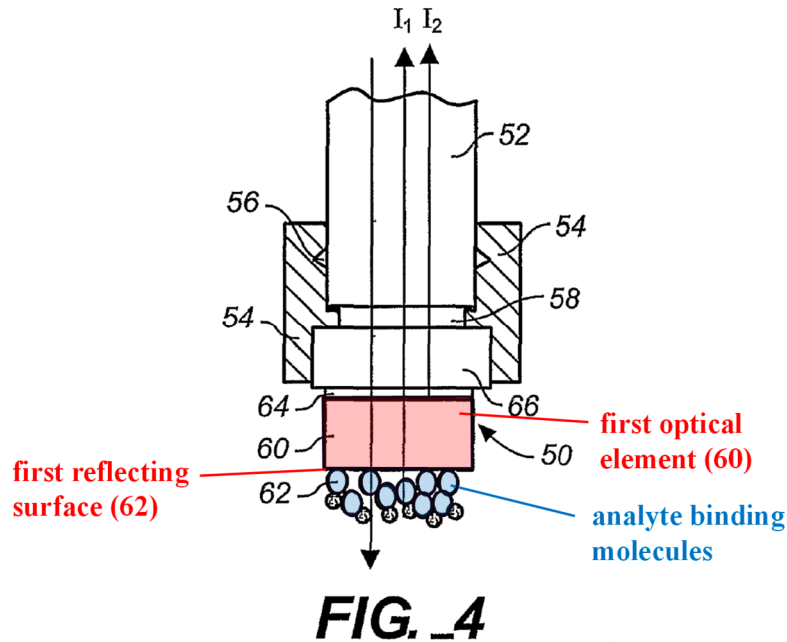
179. As I discuss above as to element [1B] (see ¶¶ 174-178), and as shown in Figure 4 below, WO854 discloses a first optical element 60 (red) comprising a first reflecting surface 62, where the first reflecting surface 62 comprises a layer of “analyte-binding molecules” (blue) for binding analyte.²⁸²

²⁷⁹ EX1008 (WO854), at ¶ [0078], Fig. 4.

²⁸⁰ EX1008 (WO854), at ¶¶ [0051]-[0052], [0078], Figs. 2, 4; see also ¶¶ [0010], [0013], [0020].

²⁸¹ EX1008 (WO854), at Fig. 4.

²⁸² EX1008 (WO854), at ¶ [0079], Fig. 4 (annotated); see also ¶¶ [0051]-[0052], Fig. 2.



e. [1D]-[1G]

180. I incorporate my discussion of elements [1D]-[1G] with respect to the Miles and Yang combination (see ¶¶ 96-103).

2. Claims 2-13 and 18-19

181. I incorporate my discussion of claims 2-13 and 18-19 with respect to the Miles and Yang combination (see ¶¶ 104-137).

XI. Opinions based on Miles, WO854, and Rainin

182. In my opinion, the subject matter of claims 2-8 and 13-19 of the '588 patent would have been further obvious to a POSA based on the combination of Miles, WO854, and Rainin. My opinions regarding the combination of Miles, WO854, and Rainin are substantially the same as my opinions regarding the

combination of Miles, Yang, and Rainin (which I address above in Section IX), except that I rely on WO854 for disclosure of a BLI/RIfS probe instead of Yang.

A. Overview of Miles

183. I provide above an overview of Miles at ¶¶ 52-59.

B. Overview of WO854

184. I provide above an overview of WO854 at ¶¶ 161-163.

C. Overview of Rainin

185. I provide above an overview of Rainin at ¶¶ 141-145.

D. Reasons for Combining Miles, WO854, and Rainin

186. As I address above with respect to combining Miles and Yang (see ¶¶ 67-78), a POSA would have been motivated to package BLI/RIfS probes such as those described in WO854 (or alternatively Yang) in a tip tray such as that described in Miles. Further, as I address above with respect to combining Miles, Yang, and Rainin (see ¶¶ 146-148), a POSA would have been motivated to use a protective storage box comprising a base and a cover for conveniently storing such tip trays.

E. The Combination of Miles, WO854, and Rainin Renders Claims 2-8 and 13-19 Obvious

187. I incorporate my discussion of claims 2-8 and 13-19 with respect to the Miles, Yang, and Rainin combination (see ¶¶ 108-119, 149-158).

* * *

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, that all statements made of my own knowledge are true, and that all statements made on information and belief are believed to be true. I understand that willful false statements are punishable by fine or imprisonment or both.

Date: February 24, 2025

A handwritten signature in cursive script that reads "Laird Forrest".

Laird Forrest, Ph.D.