

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SPECTRUM SOLUTIONS L.L.C.,

Petitioner

v.

DNA GENOTEK INC.,

Patent Owner

Case IPR2022-01347

Patent 11,002,646

**DECLARATION OF VINCENT A. FISCHETTI, PH.D., IN SUPPORT OF
PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT 11,002,646**

Spectrum Ex. 1011
IPR Petition - USP 11,002,646

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I, Vincent A. Fischetti, Ph.D., declare and state as follows:

1. I have been retained by Knobbe, Martens, Olson & Bear, LLP, counsel for Spectrum Solutions L.L.C. (“Spectrum”). I understand that Spectrum is petitioning for *inter partes* review of U.S. Patent No. 11,002,646 (“the ’646 patent,” Ex. 1001) and requests that the United States Patent and Trademark Office (“USPTO”) cancel claims 1, 3-8, and 11-12 of the ’646 patent as unpatentable. The following discussion and analysis provide my opinion as to why I believe the challenged claims would have been obvious to a person of ordinary skill in the art (“POSA”) as of its earliest priority date of 2011. This declaration is provided after my review and analysis of the ’646 patent, the prior art discussed herein, relevant background technology, and is also based on my education and experience, as well as additional materials identified herein.

I. BACKGROUND AND QUALIFICATIONS

2. My experience and qualifications are summarized in my *curriculum vitae*, a copy of which is provided as Ex. 1018.

3. I am a professor at the Rockefeller University, where I am head of the Laboratory of Bacterial Pathogenesis and Immunology. I received my B.S. in bacteriology from Wagner College in 1962 and my M.S. in microbiology from Long Island University in 1967. I received my Ph.D. in microbiology from New York University in 1970. I served as a post-doctoral fellow at the Rockefeller University

from 1970 to 1972 and at the Albert Einstein College of Medicine from 1972 to 1973.

4. I became an assistant professor at the Rockefeller University in 1973, an associate professor in 1978, and a professor in 1990. I am a faculty member in the David Rockefeller Graduate Program and the Tri-Institutional M.D.-Ph.D. Program. My major field of expertise is in bacterial pathogenesis, particularly *Streptococcus*, *Staphylococcus*, *Bacillus*, *Pseudomonas*, and *Acinetobacter* to name a few. Most of my studies deal with human diseases caused by bacterial infections. I study the mechanism by which these infections occur and devise ways to prevent or treat these infections.

5. I am a member of the American Society for Microbiology, the American Academy for Microbiology, and the National Academy of Inventors. I currently serve as an Advisory Editor for *Trends in Microbiology* and the *Journal of Experimental Medicine*. I previously served on the editorial board of numerous publications, including the *Journal of Immunology* and *Infection and Immunity*. Also, from 1989-1999, I served as the Editor-in-Chief of the journal *Infection and Immunity*.

6. I have given more than 150 invited lectures at national and international conferences, major research institutes, and universities in numerous countries in the

areas of biochemistry, immunology, bacterial pathogenesis, molecular diagnostics and vaccine development.

7. I have authored over 250 original scientific articles and over 90 book chapters, as well as having co-authored two hard copy textbooks and one electronic textbook on bacterial pathogenesis. These publications have been in the general areas of microbiology, immunology, bacterial pathogenesis, molecular diagnostics, and vaccine development. My work related to a novel anthrax anti-infective was featured as the cover story on the journal *Nature* in 2002. I am also an inventor on numerous U.S. and foreign patents in the areas of streptococcal vaccine development, bacteriophage lysins and lytic enzymes, and methods and compositions for isolation of cellular components.

8. I am also the named inventor on a patent (U.S. Patent No. 5,643,767), which describes a container and method of use for isolating cellular components, and particularly RNA, from a biological sample. The container included a cap having a compartment for storing a material that was then mixed with the contents of the container after the cap was placed on the container.

9. Over the course of my career, and long prior to the earliest filing date of the '646 patent (2011), I frequently used reagents for preserving biological samples, including bacterial cells, human pharyngeal cells and saliva. For example, in my work related to human infection by bacteria, I regularly used freezing,

lyophilization, paraformaldehyde, and alcohol, to preserve human and bacterial cells so that we could analyze DNA, RNA and protein molecules from the samples using a variety of analytical techniques including electron microscopy, florescent microscopy, DNA and RNA sequencing, and flow cytometry (FACS), to name a few.

II. LEGAL STANDARDS

10. I am not an attorney. I have not independently researched the law on patentability. I have been provided guidance as to the applicable patent law in this matter. The paragraphs below express my understanding of the relevant legal principles related to the patent validity analysis as provided herein.

11. It is my understanding that a patent claim is “obvious,” and therefore unpatentable, if the claimed subject matter as a whole would have been obvious to a person of ordinary skill in the art at the time of the alleged invention. I also understand that an obviousness analysis takes into account the scope and content of the prior art, the differences between the claimed subject matter and the prior art, and the level of ordinary skill in the art at the time of the invention.

12. In determining the scope and content of the prior art, it is my understanding that a reference is considered appropriate prior art if it falls within the field of the inventor’s endeavor. In addition, a reference is prior art if it is reasonably pertinent to the particular problem with which the inventor was involved. A

reference is reasonably pertinent if it logically would have commended itself to an inventor's attention in considering his problem. If a reference relates to the same problem as the claimed invention, that supports use of the reference as prior art in an obviousness analysis.

13. To assess the differences between prior art and the claimed subject matter, it is my understanding that the law requires the claimed invention to be considered as a whole. This “as a whole” assessment requires showing that one of ordinary skill in the art at the time of invention, confronted by the same problems as the inventor and with no knowledge of the claimed invention, would have selected the elements from the prior art and combined them in the claimed manner.

14. It is my further understanding that the law recognizes several rationales for combining references or modifying a reference to show obviousness of claimed subject matter. Some of these rationales include: combining prior art elements according to known methods to yield predictable results; simple substitution of one known element for another to obtain predictable results; a predictable use of prior art elements according to their established functions; applying a known technique to a known method or product ready for improvement to yield predictable results; choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; 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; and choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.

15. I also understand that an obviousness analysis must consider whether there are additional factors that would indicate that the invention would not have been obvious. These factors include whether there was: (i) a long-felt need in the industry; (ii) any unexpected results; (iii) skepticism of the invention; (iv) a teaching away from the invention; (v) commercial success; (vi) praise by others for the invention; and (vii) copying by other companies. I also understand that there must be a nexus between any such factor and the claimed invention. I am not aware of any evidence that would suggest that the claims of the '646 patent would have been non-obvious.

III. THE PERSON OF ORDINARY SKILL IN THE ART

16. I understand that obviousness is analyzed from the perspective of a hypothetical person of ordinary skill in the art ("POSA"). I have conducted my analysis herein from the perspective of a POSA using the earliest priority date of the '646 patent (2011) as the relevant time frame.

17. In considering the level of skill in the art for the '646 patent at the relevant time period, I have taken into account the levels of education and experience of those working in the field at the time, the types of problems encountered in the

field, the sophistication of the technology. I understand that a person of ordinary skill in the art is a hypothetical person that is deemed to be aware of the content of the analogous technical literature in the relevant field.

18. The invention described in the '646 patent relates to devices for collecting samples of bodily fluids, and particularly naturally expressed bodily fluids, e.g. saliva, urine. Ex. 1001, 1:21-24. It also “relates generally to functional genomics and the isolation and preservation of cells from such bodily fluids” *Id.*, 1:25-29. The patent therefore includes both mechanical aspects and chemical/biological aspects. During my career I have worked with persons with mechanical engineering education and experience. These co-workers were mostly engineers and fabricators working in the Instrument Shop at Rockefeller University. The University provided this shop to help scientists develop instruments and devices for their various experiments. I have reviewed the background of the named inventors of the '646 patent (via LinkedIn®) and I learned, not surprisingly, that one of the two named inventors of the '646 patent had training and experience in mechanical engineering and medical devices and the other had training and experience in microbiology or pharmacology. *See* Exs. 1006 and 1007. A hypothetical person of ordinary skill in the art would have a combination of these two skill sets. With respect to the mechanical aspects, I understand from Karl Leinsing (Ex. 1002) that a person of ordinary skill (“POSA”) would have had at least

a Bachelor's degree in mechanical engineering, biomedical engineering, or similar technical degree and at least three years of experience in the medical device industry, including experience with containers and valves used in disposable medical devices. Such a person would have worked as part of a team and collaborated with a person having training and experience in the relevant chemical/biological aspects of the invention described in the '646 patent, namely the preservation of biological samples. As to the chemical/biological aspects of the invention, in my opinion a POSA would have had a Ph.D. in microbiology, molecular biology, biochemistry, or a related discipline and at least two years of post-graduate experience in the area of biological sample preservation and nucleic acid extraction, preservation, and analysis.

IV. THE '646 PATENT

19. Claim 1 is the sole independent claim of the '646 patent. The claim is set forth below (bracketed labels have been added for convenient reference).

Claim 1	
Preamble	1. A kit for collecting and preserving a biological sample, the kit comprising:
1[a]	a sample collection vessel, the sample collection vessel comprising:
1[a][i]	a sample collection reservoir having an opening configured to receive the biological sample from a user into the sample collection reservoir;

Claim 1	
1[a][ii]	a connection member disposed on an exterior portion of the sample collection vessel and adjacent to the opening;
1[b]	a cap, the cap comprising;
1[b][i]	a reagent chamber configured to store a reagent; and
1[b][ii]	a complementary connection member configured to engage the connection member of the sample collection vessel; and
1[c]	a movable annular valve configured to associate with the cap and with the opening of the sample collection reservoir, the movable annular valve comprising:
1[c][i]	an inner cylinder in fluid-tight association with the cap and comprising a sidewall,
1[c][ii]	the sidewall comprising a fluid vent;
1[c][iii]	and an outer cylinder in fluid-tight association with the inner cylinder and associated with the opening of the sample collection reservoir,
1[c][iv]	the outer cylinder comprising an aperture defined by an interior sidewall of the outer cylinder,
1[c][v]	wherein the aperture accommodates at least a portion of the inner cylinder,
1[c][vi]	wherein the interior sidewall obstructs the fluid vent when the movable annular valve is closed, and
1[c][vii]	wherein the interior sidewall does not obstruct the fluid vent when the movable annular valve is open.

20. According to the introductory clause or preamble of claim 1, the claimed invention is directed to a “kit for collecting and *preserving a biological sample.*” The claimed kit includes, *inter alia*, “a sample collection reservoir having

an opening configured to receive *the biological sample*” Ex. 1001, 22:16-21 (emphases added). I understand in a district court case the parties have disputed the construction of these terms.

21. I understand Spectrum has asserted in the district court action that “biological sample” should be construed as “cells” and “preserving a biological sample” should be construed as “preventing the cells from having their antigens degraded, such that they can be purified or enriched based on their antigens, and preventing alterations in the cellular epigenome.” Ex., 1013, 29-32; *see also* Ex. 1001, 16:23-27.

22. I understand Patent Owner has asserted that the terms “biological sample” and “preserving a biological sample” should be given their plain and ordinary meaning. Patent Owner also asserts that if construction of “preserving a biological sample” is required, it should be construed as “slowing degradation of a biological sample.” Ex. 1014, 24-28. Finally, Patent Owner contends that the term “preserving a biological sample” is not limiting at all. *Id.*, 26. I have been informed Patent Owner is asserting the ’646 patent in the district court lawsuit and has alleged infringement based on a product that includes reagents that lyse cells, thereby releasing the intracellular contents for nucleic acid testing.

23. I have not been asked to nor am I offering an opinion regarding the legal issue of claim construction or on the legal issue of whether the “preserving” terms

of the claim are limitations of the claimed invention. Rather, I am addressing whether the claimed invention would have been obvious to a POSA in view of the prior art in the event either proffered construction were adopted. In my opinion, the construction of “biological sample” and “preserving a biological sample” does not affect the question of whether the invention recited in the ’646 patent claims would have been obvious. In my opinion, the claimed invention would have been obvious regardless of whether the “preserving” terms are limiting and how the terms are construed if they are limiting. In reaching that conclusion, I have focused on the “preserving” aspect of the claimed invention. For the device-specific limitations of the claims, I rely upon Mr. Leinsing’s opinion that the claimed device would have been obvious in view of Plant in combination with Cho or Patterson. *See* Ex. 1002.

V. THE CHALLENGED CLAIMS WOULD HAVE BEEN OBVIOUS

A. The Challenged Claims Would Have Been Obvious in View of Plante and Cho or Patterson Based on Plante’s Teaching of a Device Used for Preserving DNA in a Biological Sample

24. If the claims are interpreted to encompass a device configured to preserve some portion of a biological sample, such as preserving DNA from a saliva sample, the challenged claims would have been obvious in view of Plante in combination with Cho or Patterson. Plante explicitly discloses a device for such use.

25. Plante discloses a sample collection system “configured for ease-of-use by unskilled users and further configured for safe conveyance via standard shipping

services.” Ex. 1003, [0017]. The system includes a receiving vessel and a sealing cap. *Id.*, [0018]. The sealing cap includes a pierceable liquid reservoir. *Id.*, [0021]. The reservoir holds a preserving fluid to preserve the saliva sample. *Id.*, [0041].

26. The reservoir is sealed to protect the fluid until it is mixed with the sample. *Id.* Plante states that once mixed with the preserving fluid the biological sample can be preserved in the sample collection vessel for extended periods of time. *Id.*, [0018] (“suitable for long-term and durable storage of a DNA in a saliva sample”). Plante does not describe a specific example of the preserving fluid. I understand a patent is written for persons skilled in the art to which the patent is directed, i.e., a POSA. A POSA would have known of preserving fluids to use for whatever his/her desired objective might be. So, for example, to preserve DNA in a saliva sample such as described in Plante, a POSA would have known to use any number of preserving fluids. I had been using such compositions for years prior to the ’646 patent’s 2011 priority date. For example, one would add the biological sample to a conventional buffer such as TRIS, containing SDS or other cationic detergents, and EDTA or other chelating agents. This would lyse the cells and denature any nucleases released in the process. When the sample was later analyzed these denatured proteins would be centrifuged to remove them and alcohol would be added to the supernatant to precipitate the DNA, which had been preserved for the analysis of interest. Additionally, U.S. Patent Publication 2009/0312285 A1 (Ex.

1016), describes various compositions that would have been known to a POSA for use in collecting and storing biological specimens prior to the '646 patent. *Id.*, [0004]. As described in Ex. 1016, the specimens could include a variety of biological samples, including saliva. *Id.*, [0110]. The compositions allow for analysis of the DNA from the sample after extended periods of time.

B. The Also Claims Would Have Been Obvious In View Maples In Combination With Plante And Cho Or Patterson

27. I have also considered the obviousness of the claimed invention of the '646 patent under the following circumstances: (1) “preserving a biological sample” in the preamble of claim 1 is construed as a limitation and (2) the term is construed, per the definition in the '646 patent specification, as “preventing the cells from having their antigens degraded, such that they can be purified or enriched based on their antigens and preventing alterations in the cellular epigenome.” Ex. 1001, 16:23-27. In my opinion, under these circumstances, the claims would have been obvious at least in view Maples in combination with Plante and Cho or Patterson.

1. Disclosure of W0 2004/017895 to Maples (“Maples,” Ex. 1009)

28. Maples is entitled “Formaldehyde-Ammonium Salt Complexes for the Stabilization of Blood Cells.” Ex. 1009. Maples initially provides the following background for its described invention:

Cells and biological tissue generally maintain their structure, function, antigen makeup, and chemical constituents within the body. However,

once removed from the natural environment of the body, cells and tissue begin to experience immediate changes in these aspects. Thus the preservation and retention of the integrity of cells and biological tissues removed from the body is a continuing challenge in the medical fields, particularly in the fields of blood preservation and organ transplantation.

Id., 1:5-9.

29. Maples further explains, “For accurate research and diagnosis, it is necessary to store and preserve blood and other tissues in a fashion that best represents the *in vivo* state of that tissue and not the changes caused by removal from the body's environment, such as withdrawal into a container or test tube.” *Id.*, 2:13-16.

30. Maples describes a number of different preservatives used for preserving cells that predated its disclosure. *Id.*, 2-4. Maples then states, “There remains a need in the art for methods and compositions for stabilizing blood and tissue upon removal from the body, to prevent and/or reduce[] cellular activation and response to environmental change without changing the antigenic makeup of the cells.” *Id.*, 4:28-31.

31. Maples also states the following regarding the usefulness of its described preservative: “Thus, this reagent is useful as a *general cell preservative*, as a reagent in DNA and RNA studies, in platelet enumeration methods, in the

assessment of platelet reactivity, e.g., for platelet/leukocyte aggregate studies, in the study of anti- cellular (auto) antibodies and plasma (soluble) analytes, among other uses.” *Id.*, 19:16-19 (emphasis added).

32. Maples describes exemplary compositions of the preserving reagent, which include formaldehyde (or paraformaldehyde), ammonium salt(s), a phosphatase inhibitor, a protease inhibitor, and a buffer. *Id.*, 30, 42 (claim 1). The ’646 patent specification describes similar components used to preserve cells of a sample. *See, e.g.*, Ex. 1001, 16:47 – 17:14 (composition includes fixing agent, such as formaldehyde or paraformaldehyde, and a protease inhibitor).

2. Preserving the Cells of a Biological Sample in a Sample Collection System According to the Combination of Plante With Cho or Patterson Would Have Been Obvious in View of Maples

33. Based on the Declaration of Karl Leinsing (Ex. 1002), I understand Plante, in combination with Cho or Patterson, renders obvious a device having the features recited in claims 1, 3-8, and 11-12 of the ’646 patent. Plante discloses the use of the device for preserving DNA in a saliva sample. Plante explicitly describes the use of a “preserving fluid” for mixing with the biological sample, which can then preserve the sample, and specifically the DNA of the sample, for extended periods of time. Ex. 1003, [0018] (“suitable for long-term and durable storage of a DNA in a saliva sample”). Plante is silent as to whether the DNA is preserved while the cells of the sample remain intact or whether the DNA is preserved after being released

from the cells. To the extent the claims of the '646 patent are interpreted to be directed to a device that preserves the cells such as described in the specification of the '646 patent, it would have been obvious to a POSA to use a prior art device according to Plante/Cho or Plante/Patterson to preserve the cells of the collected biological sample.

34. Plante specifically describes its device is adapted to be used for the purpose of preserving DNA in a biological sample, but does not describe a particular preserving fluid, undoubtedly because such preserving fluids were known to a POSA. A POSA would select a preserving fluid suitable for whatever particular diagnostic or analysis was to be performed on the sample. And Maples describes a general purpose preservative for the types of use to which Plante pertains: “Thus, this reagent is useful as a general cell preservative, as a reagent in DNA and RNA studies . . . , among other uses.” Ex. 1009, 19:16-19. And Maples specifically teaches that its preservative reagent is combined with a sample after the sample has been removed from the *in vivo* state and deposited into “a container or test tube.” *Id.*, 2:13-16. Plante describes such a container.

35. A POSA would have had reason to use a preservative for preserving cells, such as taught in Maples, because it would have been no more than a predictable use of a prior art preservative fluid for its established function. One of

skill in the art would have had a reasonable expectation of success in doing so, as is clearly evident from the results described in Maples. Ex. 1009, 33-41.

36. Additionally, Plante’s teaching of a “preserving fluid” without specifying a particular preserving fluid constitutes a teaching, suggestion, or motivation to a POSA to select a known preserving fluid suiting the needs of the analysis to be performed on the sample. A POSA would have known at the time that saliva contains cells, including blood cells, and that preserving such cells for diagnostic purposes would be desirable.

37. In sum, the challenged claims would have been obvious if the preamble of claim 1 is limiting and construed in accordance with the definition in the ’646 patent specification, i.e., preserving cells such that cells’ antigens are not degraded.

VI. CONCLUSION

38. For the reasons explained above, it is my opinion that the challenged claims of the ’646 patent would have been obvious.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed on July 27, 2022 at New York City.

A handwritten signature in black ink, appearing to read 'Vincent A. Fischetti', written in a cursive style.

Vincent A. Fischetti, Ph.D.

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