

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIO-RAD LABORATORIES, INC.,
Petitioner,

v.

CALIFORNIA INSTITUTE OF TECHNOLOGY,
Patent Owner.

Case No. IPR2025-01546

U.S. PATENT NO. 12,168,797 B2

DECLARATION OF CARL A. BATT, PH.D. IN SUPPORT
OF PETITIONER FOR *INTER PARTES* REVIEW

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I. INTRODUCTION

1. I have been retained as an independent expert witness by Bio-Rad Laboratories, Inc. (“Bio-Rad” or “Petitioner”) in the above-captioned inter partes review proceeding to provide my independent evaluation and opinions regarding the validity of claims 1-2, 5-11, 13-15, and 18 of U.S. Patent No. 12,168,797 (“the ’797 patent”). I have been asked to provide my opinion regarding whether a person of ordinary skill in the art (“POSA”) of the subject matter of the above claims would have found them obvious over combinations of several references, including (1) U.S. Patent No. 9,921,154 (“Jouvenot”) (EX1003); (2) U.S. Patent Application Publication No. US 2011/0250597 A1 (“Larson”) (EX1013); (3) Joseph R. Lakowicz, *Principles of Fluorescence Spectroscopy* (3d. 2006) (“Lakowicz”) (EX1006) (4) U.S. Patent Application Publication No. US 2009/0239308 A1 (“Dube”) (EX1019); (5) U.S. Patent Application Publication No. US 2009/0258414 A1 (“Wittwer”) (EX1020); (6) U.S. Patent No. 8,614,061 “Brabetz” (EX1008); (7) U.S. Patent Application Publication No. US 2008/0003649 A1 “Maltezos” (EX1012); (8) U.S. Patent Application Publication No. US 2010/0227386 A1 (“Neuzil”) (EX1017); (9) U.S. Patent Application Publication No. US 2003/0219754 A1 (“Oleksy”) (EX1018) (10) U.S. Patent Application Publication

No. US 2012/0100600 A1 (“Slepnev”) (EX1021); and (11) European Patent Specification 0,594,763 B1 (“Lehnen”) (EX1022).

2. This declaration sets forth my analyses and opinions based on my technical background, skills, knowledge, training, education and experience in the relevant art, and the materials I have considered. As I explain below, it is my opinion that claims 1-2, 5-11, 13-15, and 18 of the '797 patent are rendered obvious by the references cited herein. I expect to testify regarding the matters set forth in this declaration if asked to do so.

II. QUALIFICATIONS AND COMPENSATIONS

A. Background and Qualifications

3. I am presently the Liberty Hyde Bailey Professor of Biology at Cornell University in the Department of Food Science and the Director of the Cornell University/Ludwig Institute for Cancer Research Partnership. I am also a founder of Main Street Science and the founder of Nanooze, an on-line science magazine for kids. I am also a co-founder and former co-director of the Nanobiotechnology Center, a National Science Foundation supported Science and Technology Center. I am also appointed as an Adjunct Senior Scientist at the MOTE Marine Laboratory in Sarasota, Florida. My current research interests are a fusion of biology and nanotechnology focusing on important biomedical problems.

4. I received my undergraduate degree in Microbiology from Kansas State University, and Master's and Ph.D. degrees from Rutgers University, Department of Food Science. From 1981 to 1985, I did postdoctoral work at the Massachusetts Institute of Technology. From 2002 to 2012, in partnership with the Ludwig Institute for Cancer Research, I established a Good Manufacturing Practices Bioproduction facility in Stocking Hall. See Appendix A (my curriculum vitae).

5. I have published over 290 peer-reviewed articles, book chapters, and reviews. In addition, from 1987-2000, I served as an editor for Food Microbiology, a peer-reviewed journal. I was also an editor for the Encyclopedia of Food Microbiology, published in 2000. In 2010, I undertook a revision of this publication that was released in 2012. I am now currently chief editor for the third revision of the Encyclopedia of Food Microbiology. In 2015-2016, I was subject editor for the Elsevier, Food Science Reference module.

B. Compensation

6. I am being compensated for my time in connection with this IPR. My compensation is not contingent on reaching any particular findings or conclusions, or on any outcome in the case. The opinions contained in this report are mine and are based on my own personal knowledge, experience, training, and study of the materials discussed below in this report.

III. SUMMARY OF OPINIONS

7. It is my opinion that claims 1-2, 5-6, 10, and 18 are obvious in view of Jouvenot. To the extent Patent Owner contends claims 1-2, 5-6, 10, and 18 are not obvious in view of Jouvenot, the claims would have been obvious in further view of Lehnert.

8. It is my opinion that claims 6-9 of the '797 patent are rendered obvious by Jouvenot in further view of Larson, Brabetz, and/or Lakowicz. To the extent Patent Owner contends claims 6-9 are not obvious in view of Jouvenot, the claims would have been obvious in further view of Lehnert.

9. It is my opinion that claim 11 of the '797 patent is rendered obvious by Jouvenot in further view of Larson, Brabetz, Maltezos, Neuzil, and/or Oleksy. To the extent Patent Owner contends claim 11 is not obvious in view of Jouvenot, the claim would have been obvious in further view of Lehnert.

10. It is my opinion that claim 13 of the '797 patent is rendered obvious by Jouvenot in further view of Larson, Maltezos, Dube, and/or Wittwer. To the extent Patent Owner contends claim 13 is not obvious in view of Jouvenot, the claim would have been obvious in further view of Lehnert.

11. It is my opinion that claim 14 of the '797 patent is rendered obvious by Jouvenot in further view of Larson and/or Maltezos. To the extent Patent Owner

contends claim 14 is not obvious in view of Jouvenot, the claim would have been obvious in further view of Lehnert.

12. It is my opinion that claim 15 of the '797 patent is rendered obvious by Jouvenot in further view of Larson, Brabetz, Lakowicz, Maltezos, Dube, and/or Wittwer. To the extent Patent Owner contends claim 15 is not obvious in view of Jouvenot, the claim would have been obvious in further view of Lehnert.

13. It is my opinion that claim 18 of the '797 patent is rendered obvious by Jouvenot in further view of Larson Maltezos, and/or Slepnev. To the extent Patent Owner contends claim 18 is not obvious in view of Jouvenot, the claim would have been obvious in further view of Lehnert.

IV. LEGAL STANDARDS

14. I am a scientist, principal investigator and instructor by trade, and the opinions I express in this declaration involve the application of my scientific knowledge and experience to the evaluation of the claims of the '797 patent and the impact of certain prior art on the '797 patent. I am not a lawyer, nor do I offer any legal opinion in this declaration. Counsel from Jones Day have advised me, however, as to various legal standards that apply to the technical issues I address in this declaration. I have applied those standards in arriving at my conclusions expressed in this declaration.

A. Claim Construction

15. I understand that when interpreting the claims of the '797 patent, I must do so from the perspective of one of ordinary skill in the art at the relevant priority date. I have not independently determined the priority date to which the '797 patent is entitled. For purposes of this proceeding, I have been asked to assume that the '797 patent has a priority date of February 3, 2012, the filing date of provisional application No. 61/594,480, the earliest-filed application to which the '797 patent claims the benefit of priority. My analysis does not change if the '797 patent is entitled to an earlier priority date falling after July 20, 2011, the filing date of provisional application No. 61/510,013 that one of the applied references relies on for the benefit of priority and incorporates by reference. Likewise, my analysis does not change if the '797 patent is entitled to a later priority date.

16. I understand that in determining whether a patent claim under *inter partes* review before the Patent Trial and Appeal Board ("PTAB") is unpatentable in view of prior art, the words of the claims of a patent are generally given their ordinary and customary meaning from the perspective of and as interpreted by a POSA at the time of the claimed invention. I also understand that patent claims are construed in light of the claim language, the patent specification (including the drawings), and the prosecution history (including the references cited during the

prosecution of the patent). Specifically, it is my understanding that in determining whether a patent claim under inter partes review before the PTAB is unpatentable in view of prior art, the PTAB uses the *Phillips*¹ standard for claim construction used in civil courts, which is to say that the claims must be given the meaning that the terms would have had to a person of ordinary skill in the art at the time of the priority date of the '797 patent consistent with the specification and file history of the '797 patent.

17. I understand that Petitioner has identified and proposed construction of certain terms in related proceedings.

18. Specifically, I understand Petitioner will contend that the claim term “F” is indefinite due to, *inter alia*, various inconsistencies within the claims such that, although one can determine that prior art is within the scope of the claims, the skilled artisan would not understand the outer bounds of “F” with reasonable certainty. As an example, consider that in claim 1, the minimum value of “F” is 3. This is because the minimum allowed value of C in the claims is 4 and there is an additional requirement that M be greater than C, such that F can only be 3 or greater. Yet, claim 4 strangely allows “F” to be 1. *See* EX1001 at claims 1, 4. Nevertheless,

¹ *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005).

in my opinion, this does not present barriers to my obviousness opinions because, as I explain herein, the prior art teaches $F=3$, which, as documented herein, is the value of F that PO contends is present in the accused products. In other words, despite some uncertainty regarding the boundary of the claims, I can confidently identify invalidating prior art.

19. Further, in view of the '797 patent's express definition of "probe," the claim term "analyte specific hybridization probes" would be understood by a skilled artisan to refer to "a reagent capable of generating a signal in the presence of a particular analyte and that hybridizes to the analyte." *See* EX1001 at 11:19-50. Likewise, given the disclosure in the specification and the mathematical formulae in the claims, a POSA would understand the term "associating, for each analyte, a first value in a first component of the cumulative signal" to contemplate associating analytes with signal values for the first component that correspond to a progression 1, 2, 4, 8, 16 and so on. *See id.* at 21:47-23:27.

20. To the extent any further construction is required, I have been asked to apply claim constructions that are consistent with Patent Owner's position in related proceedings. I reserve the right, however, to supplement my opinions if Patent Owner proposes any constructions or the Board adopts any claim constructions.

B. Obviousness

21. I understand that a claim is unpatentable under 35 U.S.C. § 103 if the claimed subject matter as a whole would have been obvious to a POSA at the time of the alleged invention, which I have been instructed to treat at present as no earlier than February 3, 2012, the filing date of provisional application No. 61/594,480, the earliest-filed application to which the '797 patent claims the benefit of priority.

22. I understand that a POSA provides a reference point from which the prior art and the alleged invention should be viewed. This reference point prevents a person of ordinary skill from using one's insight or hindsight in deciding whether a claim is obvious. I understand the use of such hindsight is impermissible.

23. I also understand that a claim can be obvious in light of a single reference or a combination of multiple prior art references. I understand that such a combination must meet certain requirements, further described below.

24. I understand that a patent claim composed of several elements is not proved obvious merely by demonstrating that each of its elements was known in the prior art. It has been explained to me that three requirements must be satisfied for a combination of prior art references to render obvious a claimed invention. First, the cited art must teach or suggest all the requirements of the invention as recited in the claims. However, I understand that a claim is obvious if a missing feature would be

a natural result of the combination of prior art elements. Second, the cited art, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the ordinary skilled artisan to modify a reference or to combine references. I understand that the reason to combine prior art references can come from a variety of sources, such as common sense, and not just from the prior art itself. Third, the proposed modification of the cited art must have had a reasonable expectation of success, determined from the vantage point of the ordinary skilled artisan at the time the invention was made. I also understand that a reasonable expectation of success does not require that success is certain.

25. I understand that only analogous art may be considered in an obviousness analysis. Art is considered analogous if it is in the same field of endeavor as the patent or if it is reasonably pertinent to the particular problem with which the patent is involved. A reference is reasonably pertinent if, though in a different field, it would have commended itself to an inventor's attention in considering the problem the inventor is addressing.

26. I understand that it is impermissible to use hindsight to arrive at the claimed invention. My understanding is that to preclude hindsight in the obviousness analysis, which I understand to be improper, there must be evidence at

the time of the invention of some reason to make the variation or combination. Furthermore, I understand that, to render a claim obvious, the prior art cannot be vague, but rather, must collectively guide a person of ordinary skill in the art towards the particular solution claimed. I understand that obviousness does not exist where the prior art discourages or teaches away from the claimed invention.

27. I understand that certain objective factors, sometimes known as objective indicia, must be taken into account in determining whether a claimed invention would have been obvious. I understand that the following is a nonexclusive list of secondary considerations to analyze for this inquiry: (i) a strong showing of commercial success of a product covered by the patent claims that can be attributed to the merits of the invention; (ii) a long felt but unmet need in the prior art that was satisfied by the invention of the patent; (iii) the willingness of industry members to license the patent at issue; (iv) evidence that those of skill in the art were skeptical as to the merits of the invention, or that prior art references taught away from the invention; (v) evidence that those of skill in the art were surprised by the capabilities of the claimed invention; (vi) praise of the invention by others skilled in the art; and (vii) deliberate copying of the invention. I further understand that contemporaneous and independent invention by others is a secondary consideration supporting an obviousness determination.

28. I understand that any assertion of the above indications must be accompanied by a nexus between the merits of the purported invention and the evidence offered. If there is no such connection between the claimed technology and the secondary evidence, then that evidence does not actually establish the purported invention was nonobvious.

V. TECHNICAL BACKGROUND AND STATE OF THE ART

29. To the extent the following discussion is similar to other declarations, the ideas contained are entirely my own and I agree with the content therein.

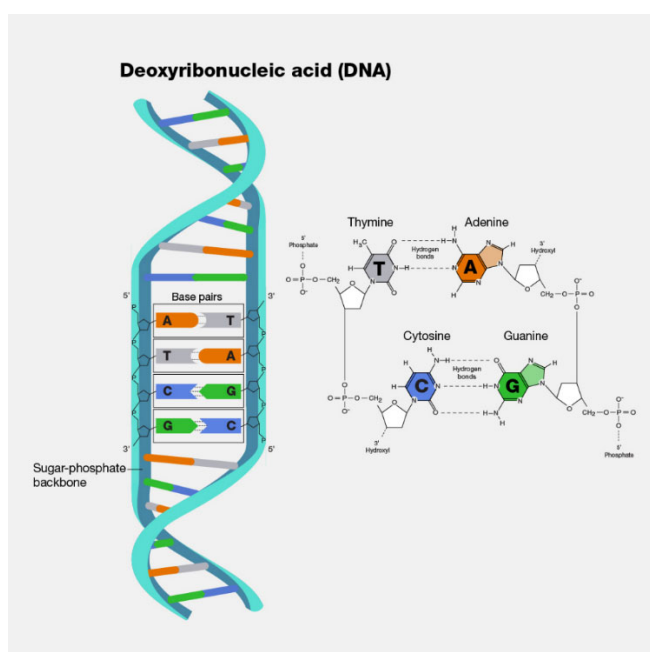
A. Polynucleotides: DNA and RNA

30. Polynucleotides are linear polymers of simpler monomeric units called nucleotides. The two most common types of polynucleotides are deoxyribonucleic acid (“DNA”) and ribonucleic acid (“RNA”). DNA and RNA carry information necessary for development, growth, and maintenance of the cells of organisms. The sequence of the monomeric units, or nucleotide sequence, in both DNA and RNA encodes or stores information needed for all cellular processes.

31. Each deoxyribonucleotide includes one of four nucleobases (cytosine (“C”), guanine (“G”), adenine (“A”), or thymine (“T”)), a sugar (deoxyribose), and a phosphate group. Each ribonucleotide similarly includes one of four nucleobases (cytosine, guanine, adenine, or uracil (“U”) (that is structurally similar to thymine, lacking a methyl group)), a sugar (ribose), and a phosphate group. Individual

nucleotides can form a polynucleotide strand, such that the sequence of the nucleotides can store genetic information.

32. The four nucleotide bases can bind to their complementary base pairs: A with T,² and C with G. As such, two strands with complementary sequences can be base-paired to form a double-stranded polynucleotide:



EX1023. Knowledge of the sequence of one strand can be used, using these base pairing rules, to determine the sequence of a complementary strand.

33. Each polynucleotide strand has two ends, on the basis of the orientation of the sugar phosphate backbone. The ends are referred to as 5' and 3', based on the orientation of the deoxyribose or ribose molecule in the backbone, with the 5' end

² In RNA, A pairs with U.

terminating in a 5'-hydroxyl group (with or without phosphate group(s)) and the 3' end terminating in a 3'-hydroxyl group. Both DNA and RNA are synthesized in the 5' to 3' direction. The complementary strands are oriented in opposite directions.

34. There are some key differences between DNA and RNA. Unlike DNA, RNA tends to be single stranded, not double stranded. Also, while both use adenine, guanine, and cytosine as bases, as noted above, RNA contains uracil instead of thymine, but T and U are functionally equivalent because they both form base pairs with adenine and denote the same genetic information.

35. Determining the sequence of polynucleotides is useful in the context of diagnosis and treatment of patients, as well as for basic scientific research. For example, determining the nucleotide sequence of an individual's genome can provide information regarding whether an individual may be susceptible to or have various disorders. Similarly, determining the polynucleotide sequences of molecules from sources such as tumors or pathogens can provide information regarding a person's current illnesses, such as various cancers or infections. Thus, determining the presence of specific sequences of polynucleotides is useful for diagnostic applications to allow for the monitoring of disease progression and allows for clinicians to tailor an appropriate treatment.

B. Multiplex PCR Amplification

36. Polymerase chain reaction (“PCR”) is a method of generating numerous copies of a polynucleotide sequence. This technique relies on the base-pairing principles of nucleotides, such that a single polynucleotide strand is a template to generate a complementary strand. Targeted sequences are amplified using an enzyme that can replicate DNA *in vitro*, specific oligonucleotide primers, and monomer nucleotides.

37. In general, the first step of PCR, “denaturation,” is separating the complementary strands of the target DNA. This separation can be accomplished through heating the DNA to its melting temperature, which separates the strands. This is followed by “annealing,” where primers, short oligonucleotides specific to a region of DNA, are allowed to anneal (or hybridize) to the complementary region in the target DNA strand. The third step is “extension.” An enzyme, DNA polymerase, adds nucleotides to extend off a primer using the target sequence and faithfully copies the sequence. The polymerase binds and extends to create a copy of the targeted DNA sequence with the borders defined by the oligonucleotide primers. These three steps together comprise one PCR cycle. Cycles are repeated to amplify DNA to any extent desired, using the replicated strands as templates for subsequent cycles. Key to the process is the use of a thermostable DNA polymerase and Taq

DNA polymerase is among the most common since it can withstand repeated denaturation.

38. In some cases, the target polynucleotide sequence for amplification is RNA. If so, the RNA can be used as a template for generating a strand of complementary DNA. This is known as reverse transcription, wherein the enzyme known as a reverse transcriptase uses a target strand of RNA as a template to generate a strand of DNA. The DNA can then be used as a template for PCR.

39. PCR can be multiplexed, that is, multiple oligonucleotide primers can be used simultaneously to amplify multiple target sequences in a single PCR at the same time. At least as of 2012, such multiplexed PCR and its use was well known in the art. Multiplex PCR provides numerous advantages, including being faster, less expensive, and more accurate than doing separate PCRs for each target.

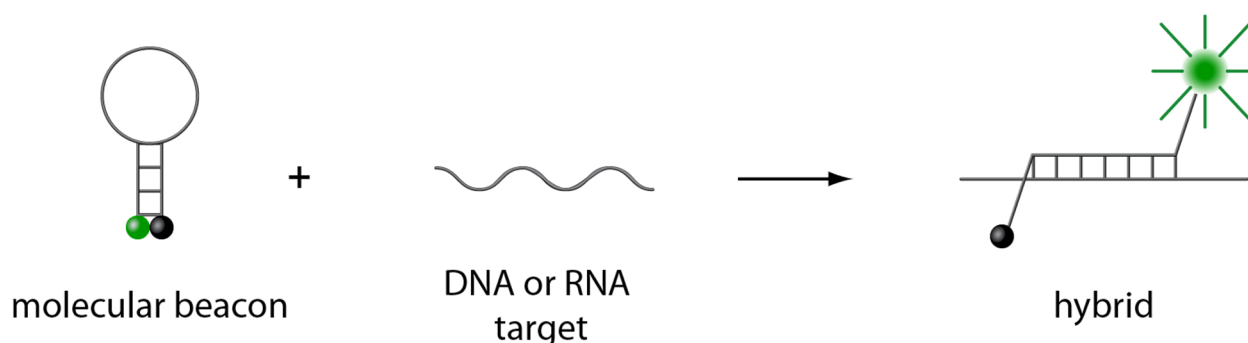
C. Fluorescence Signals and Detection of Polynucleotide Analytes

40. Prior to 2012, the use of fluorescence molecules as signals to detect polynucleotide analytes was common. Methods for doing this include, for example, hybridizing fluorescently labeled oligonucleotide probes to specific, target polynucleotide sequence(s) and detecting and/or measuring the resulting fluorescent signal from the labeled oligonucleotides that bind the target. The fluorophore portion(s) of the probes are designed to generate electromagnetic signals at particular

wavelengths when excited. In some techniques, target polynucleotide sequences with bound labeled-oligonucleotides are isolated or separated from unbound labeled-oligonucleotides and the resulting signal is measured. In other techniques, isolation or separation is not required, because a detectable signal is generated only when the labeled oligonucleotide is bound to the target polynucleotide. Generating a detectable signal without separation can be achieved by use of both a fluorophore and a “quencher” where a quencher is a molecule that can “turn off” a fluorescent signal when in close proximity to the fluorophore.

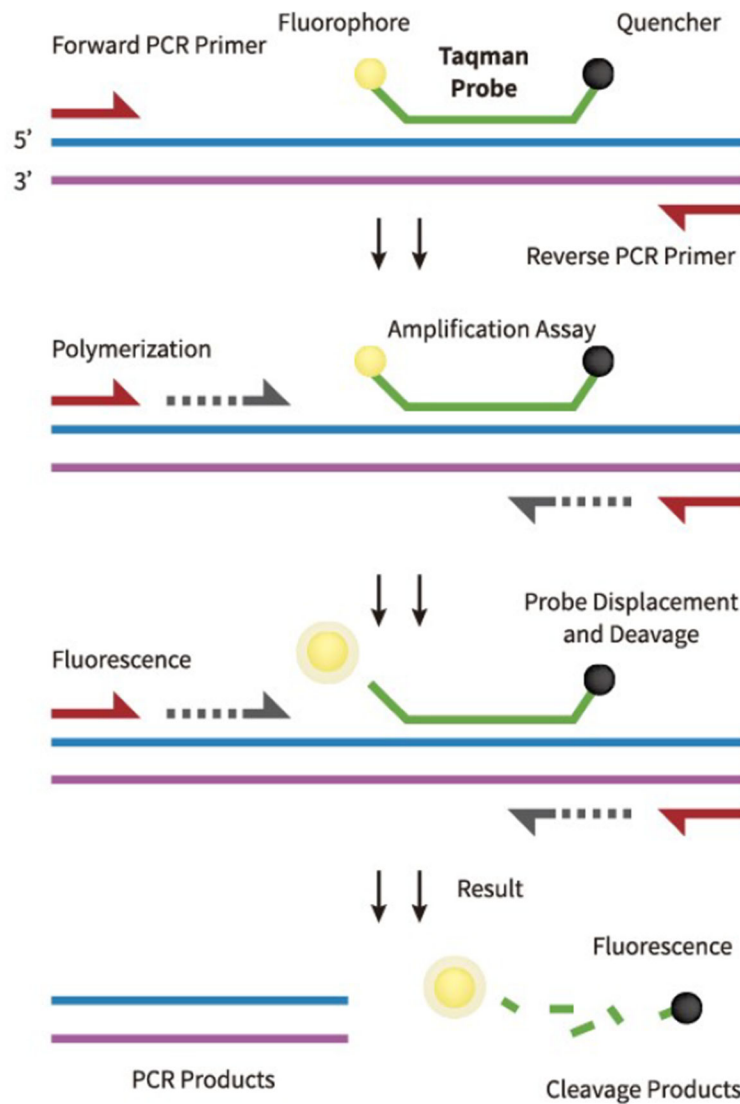
41. Two common approaches are used in conjunction with probes having both a fluorophore and a quencher. One approach is known as a “molecular beacon.” This approach uses an oligonucleotide probe with a fluorophore and a quencher on either end of the probe. The probe sequence encodes a self-complementary sequence that internally anneals, forming a hairpin, and brings the two ends (and thus the quencher and fluorophore) into close proximity with one another. When in close proximity, the quencher suppresses the fluorescent signal of the fluorophore. The probe, however, is designed to include a sequence that binds to the target sequence(s). Polynucleotide analyte(s) having target sequence(s) can be detected by contacting samples that may include the polynucleotide analyte with the probe which will hybridize to the target sequence if it is present or hybridize to itself if no

polynucleotide analyte with target sequence is present. Thus, if the probe hybridized to a polynucleotide analyte, the fluorescent label and quencher are separated from one another generating a detectable, unquenched signal. This process is depicted in the figure below:



EX1024.

42. A second, alternative method uses a short probe with a quencher, where the proximity allows the quencher to suppress the signal. This type of probe is generally referred to as a TaqMan probe and was described in literature as early as 1991. EX1011. The TaqMan probe is used with two PCR primers and is designed to bind to a region between the two primers. In this method, a target-bound probe is cleaved during extension by the DNA polymerase, which has an exonuclease activity. The cleavage frees the quencher and fluorophore which both diffuse away and the signal from the fluorophore is no longer quenched, thereby allowing detection of signal emitted from the fluorophore. This process is depicted in the figure below:



EX1010 at 6.

D. Quantitative PCR

43. The basic principles of PCR and fluorescent labeling can be adapted to determine the amount, or number, of target sequences within a sample. Two such adaptations include quantitative PCR (“qPCR”) and digital PCR (“dPCR”)

44. A common form of qPCR relies on the use of an oligonucleotide TaqMan probe that includes both a fluorophore (e.g., a fluorescent molecule) and a quencher, as I describe above. Prior to binding, the fluorophore and quencher are in sufficiently close proximity for the quencher to suppress (quench) the signal from the fluorophore.

45. Taq polymerase, the enzyme used in the extension step of PCR that polymerizes the extended complementary strand, also has an exonuclease function that digests the bound oligonucleotide TaqMan probe during the extension reaction. qPCR relies on this exonuclease activity to cleave the oligonucleotide probe separating the fluorophore from the quencher so as to generate the detectable signal. Specifically, in this method, both probe and primer are permitted to anneal to the polynucleotide analyte (if present) and, during the primer extension step, the Taq polymerase not only extends the primer but also cleaves any oligonucleotide probe bound to the polynucleotide, separating the fluorophore and quencher. Once the fluorophore is freed, the quencher is no longer suppressing the signal, so it generates a detectable signal that can be quantified.

46. The signal generated, i.e., the rate at which the level of fluorescence intensity increases, in qPCR, as described above, is proportional to the number of target polynucleotide analyte molecules present in the sample. Therefore, using this

technique, the relative quantity of different polynucleotides, such as the various polynucleotide analytes in a sample, can be determined by comparing the intensity of the generated signals to each other at a given point in time. Thus, by including a known amount of an analyte to serve as an internal standard, the signal from a probe for that standard can be used to compare against the signal from a probe that detects the target analyte to allow quantification of that analyte. For example, where the number of copies of a particular gene or polynucleotide sequence is known, it can be used in an assay as a measure for comparison with the signal generated for a target polynucleotide present in unknown quantities in order to determine the number of copies of the target polynucleotide analyte. EX1013 ¶¶ 94-97.

47. Digital PCR (“dPCR”) is a different form of quantitative PCR. Unlike the comparative nature of qPCR I describe above, relying on standards, dPCR relies on highly dilute samples that are divided into partitions, such as droplets, such that each partition generally has no more than a single copy of the target analyte (if any). Specifically, a sample is subjected to limiting dilution prior to qPCR. A positive result, i.e., generated signal, indicates the presence of at least one copy of the target polynucleotide analyte in the partition. The number of positive partitions, and thereby the proportion of positive partitions, can be translated into the number of copies of the target polynucleotide analyte in the sample using statistical techniques

such as the Poisson distribution. An image showing the workflow for performing dPCR using Petitioner's droplet-based products is shown below:

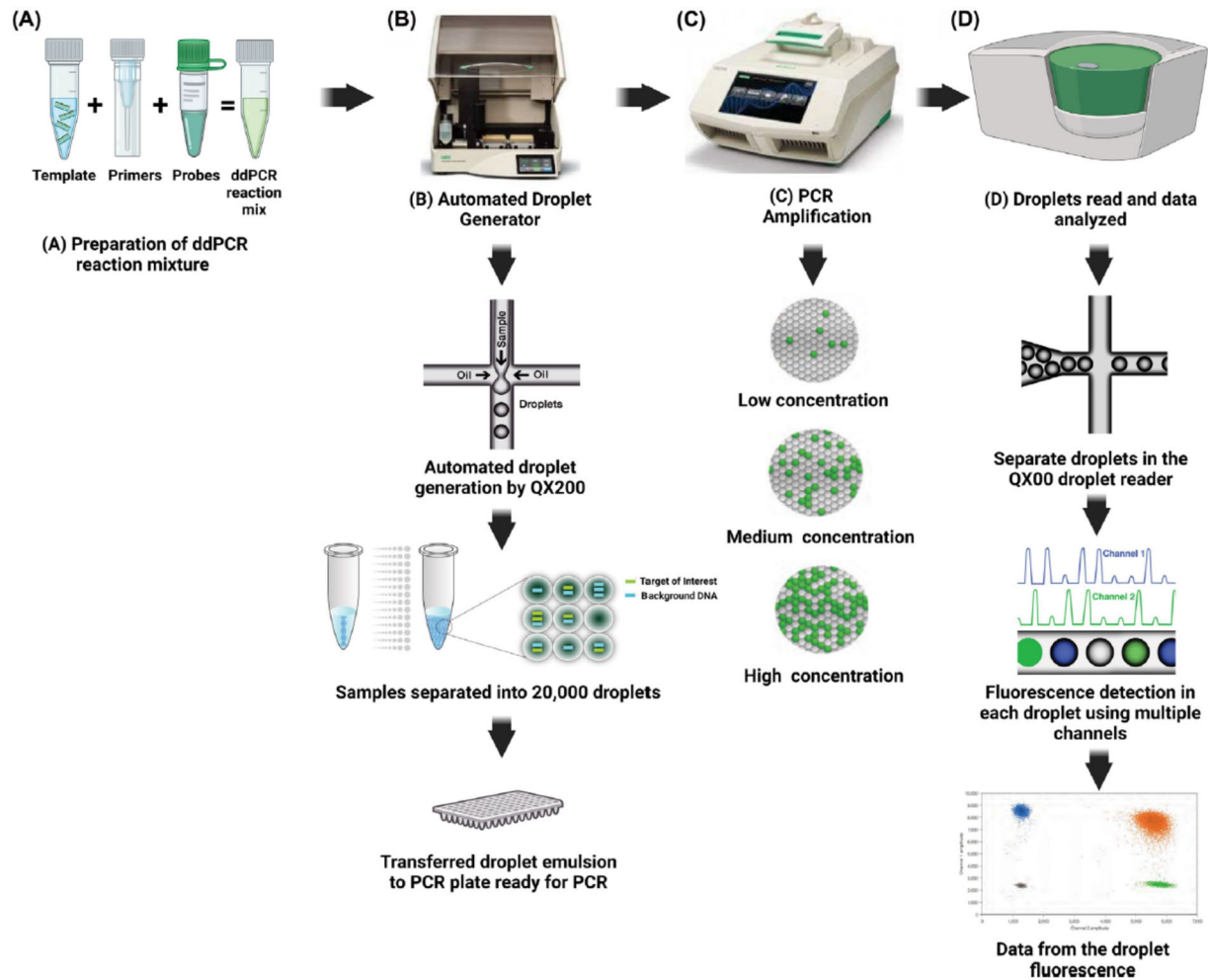


FIGURE 2.7 Overview of droplet digital polymerase chain reaction (PCR) workflow. (A) Standard ddPCR reaction mixtures are prepared in tubes. (B) The reaction mixture is separated into 20,000 droplets using an automated droplet generator, and the droplet emulsion is transferred into a 96-well PCR plate for PCR amplification. (C) PCR amplification is done, and droplets with green were designated as positive reaction and gray color as negative. (D) Using a two- or six-channel digital droplet reader, the fluorescence detection in each droplet is measured and the data is visualized using proprietary software in 1D or 2D plots. Source: Bio-Rad and images created with <http://www.BioRender.com>.

EX1015 at 12.

E. Detection and Display Apparatuses

48. Prior to 2012, the use of various equipment in the art to detect fluorescence molecules was common. Methods for detecting fluorescence included, for example, using photodetectors that detect light or other forms of electromagnetic radiation and converting it into an interpretable signal; using various types of filters, such as bandpass filters, short pass filters, and/or long pass filters to narrow the range of detectable wavelengths (e.g., colors) to an acceptable subset; using beam splitters and excitation beams to excite a given fluorescent molecule (e.g., fluorophore); and using charge coupled devices wherein an array of linked or coupled capacitors transfer electric charge to create a digital image. These methods may be used to identify both the wavelength and the intensity of emitted light.

49. Detection apparatuses also included optical waveguides, microscopes, diodes, light stimulating devices (e.g., lasers), photomultiplier tubes, and combinations thereof. To further illustrate, waveguides make use of optical elements such as lenses, prisms, mirrors, and interconnects to detect and control droplets. Waveguides can provide access to a measured channel to permit absorption or excitation of fluorescence molecules that fall within certain wavelengths. Optical channels represent a particular detection regime where a

waveband is used to detect emitted light. Accordingly, different optical channels allow detection of different wavelengths or wavelength regimes.

50. Detection modules in the art have also used cross-sectional areas to allow a certain desired molecules, cells, beads, or particles to pass through it without being slowed relative to the flow carrying the particle. Such detection modules are influenced by the nature of the sample, such as the size of droplets, beads, or molecules under study. As an example, mammalian cells can have a diameter of about 1 to 50 microns, while plant cells are generally 10 to 100 microns. Other particles, however, may have a diameter from about 20 nm to about 500 nm.

51. In conjunction with various detection apparatuses, and as disclosed *supra* § V.C., many types of fluorescent labels were regularly used in the art as labels to enable detection.

52. Apparatuses to analyze the data gathered by detectors and to display that data for further analysis were also commonly used. Generally, such apparatuses included a processor or processors, software, and a display.

VI. OVERVIEW OF THE '797 PATENT

53. The '797 patent is titled "Signal Encoding and Decoding in Multiplexed Biochemical Assays." It purports to describe "methods, systems, compositions, and kits for the multiplexed detection of a plurality of analytes in a sample." EX1001 at

Abstract. Multiplex detection is the detection or measurement of multiple different analytes in the same sample volume. *Id.* at 1:35-39. As described in the '797 patent, multiplex detection is accomplished by generating signal(s) indicating the presence of the analyte(s) and acquiring cumulative measurement(s) of signal component(s), such as fluorescence, and determining which analytes are present based on the cumulative measurement(s) of the signal(s). *Id.* at Abstract.

A. Claims

54. Claims 1-2, 5-11, 13-15, and 18 of the '797 patent are challenged in the Petition, including independent claim 1. The claims are reproduced below:

1. A system comprising:
 - a sample chamber configured to house a sample and analyte-specific reagent mixtures of analyte-specific hybridization probes and multiple fluorophores;
 - a multi-channel detector to detect:
 - a first electromagnetic signal at a first wavelength from the sample chamber, the first electromagnetic signal generated by excitement of a first fluorophore of the multiple fluorophores;
 - a second electromagnetic signal at a second wavelength from the sample chamber, the second electromagnetic signal generated by excitement of a second fluorophore of the multiple fluorophores;
 - a third electromagnetic signal at a third wavelength from the sample chamber, the third electromagnetic signal generated by excitement of a third fluorophore of the multiple fluorophores;
 - a fourth electromagnetic signal at a fourth wavelength from the sample chamber, the fourth electromagnetic

signal generated by excitement of a fourth fluorophore of the multiple fluorophores;
a processor controlled analyzer to receive, from the multi-channel detector, a cumulative signal based on the first, second, third, and fourth electromagnetic signals and apply a decoding matrix to the cumulative signal to unambiguously detect the presence or absence of at least each of M analytes by associating, for each analyte, a first value in a first component of the cumulative signal and a second value in a second component of the cumulative signal, wherein each first value is an intensity or range of intensities and each second value is a wavelength or a range of wavelengths, and wherein the second values comprise the first, second, third, and fourth wavelengths, and the determination is made without immobilization, mass spectrometry or melting curve analysis;
wherein for the positive integer M, $M = C \cdot \log_2(F+1)$, F is a positive integer and is equal to the maximum cumulative intensity of the first component of the signal, for any second value, when all of the analytes are present, and C=4, 5, or 6; and
wherein F+1 is a positive integer and wherein F+1 is a power of 2, wherein M is greater than the number of the second values used to encode the analytes (C), the multi-channel detector comprises C channels, and M and C are positive integers.

2. The system of claim 1, wherein the multi-channel detector is further configured to detect:

a fifth electromagnetic signal at a fifth wavelength from the sample chamber, the fifth electromagnetic signal generated by excitement of a fifth fluorophore of the multiple fluorophores;
a sixth electromagnetic signal at a sixth wavelength from the sample chamber, the sixth electromagnetic

signal generated by excitement of a sixth fluorophore of the multiple fluorophores; and wherein $C=6$.

5. The system of claim 1, wherein $F=3$.
6. The system of claim 5, wherein the multiple fluorophores is selected from the group consisting of a blue fluorophore, a green fluorophore, a yellow fluorophore, a red fluorophore, and any combinations thereof.
7. The system of claim 5, wherein the multiple fluorophores is selected from the group consisting of a fluorescein amidite (FAM), a cyanine 3 (Cy3), a carboxy-X-rhodamine (ROX), a cyanine 5 (Cy5), a cyanine 5.5 (Cy5.5), and any combinations thereof.
8. The system of claim 5, wherein the multiple fluorophores has a maximum excitation wavelength selected from the group consisting of about 494 nm, about 550 nm, about 567 nm, about 650 nm, about 675 nm, and any combinations thereof.
9. The system of claim 5, wherein the multiple fluorophores has a maximum emission wavelength selected from the group consisting of about 518 nm, about 565 nm, about 591 nm, about 670 nm, about 697 nm, and any combinations thereof.
10. The system of claim 5, wherein the analyte-specific hybridization probes are labeled with a fluorophore of the multiple fluorophores.
11. The system of claim 5, wherein the detector comprises four or six band pass filters.
13. The system of claim 5, wherein the multi-channel detector comprises four or six photodetectors.

14. The system of claim 5, wherein the multi-channel detector comprises photodetectors that enable the detection of blue, green, and red fluorescent signals.
15. The system of claim 5, wherein the multi-channel detector comprises photodetectors that enable the detection ranges selected from the group consisting of from about 483 nm to about 533 nm, from about 523 nm to about 568 nm, from about 558 nm to about 610 nm, from about 615 nm to about 670 nm, and any combinations thereof.
18. The system of claim 5, further comprising a display coupled to the processor controlled analyzer to visualize a plot of the first and second values.

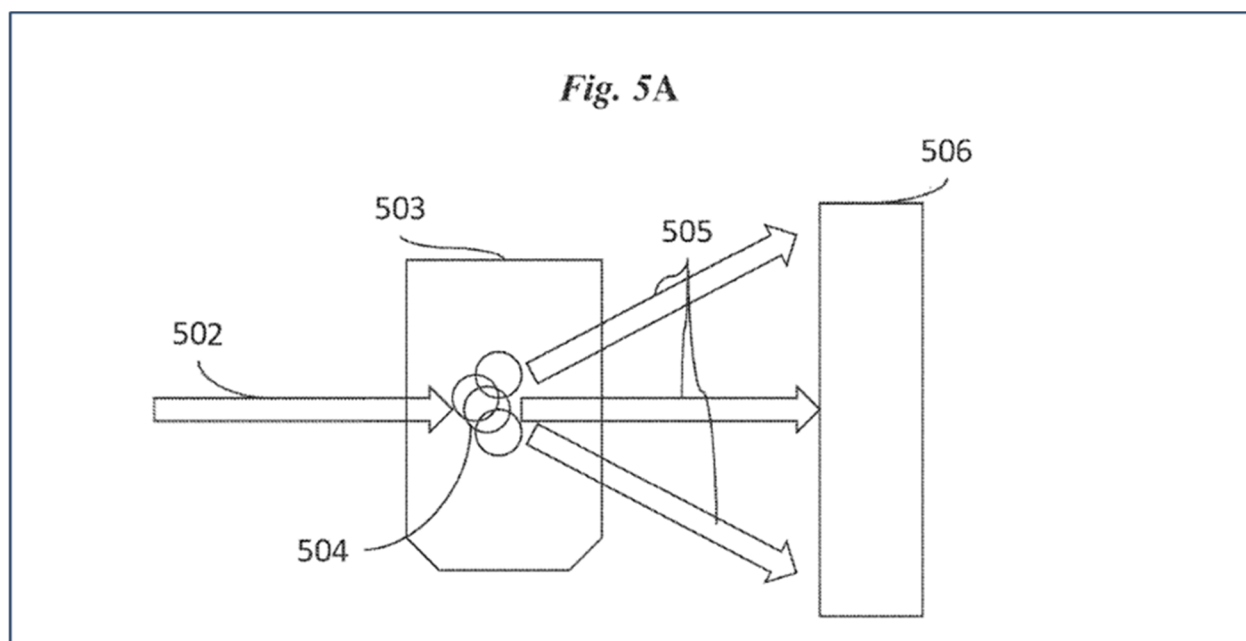
B. Specification

55. The '797 patent purports to describe multiplex detection of multiple analytes in a sample, which allows a user to perform parallel reactions on the same sample in a single solution. EX1001 at 1:35-50. This supposedly allows users to “extract rich information from a sample in a fast and efficient manner,” without “complex reporting mechanisms.” *Id.* This detection may be performed as part of a system. *Id.* at 39:8-9.

56. To achieve this multiplex detection, the specification describes analyte-specific reagent mixtures containing fluorophore-labeled hybridization probes. *Id.* at 31:39-48. The specification explains that these methods may use, “[f]or example, 1, 2, 3, . . . 50 or more probes.” *Id.* at 31:51-54. The labeled probes are used to generate electromagnetic signals, such as fluorescence, of various wavelengths or

colors. These signals are generated by excitement of the fluorophores, and are detected by a detector, such as a fluorometer. *Id.* at 35:43-58. *See also, e.g., id.* at Fig. 5. This system may utilize a computer that executes software that encodes, analyzes, and decodes the generated electromagnetic signals (as further described below), or a controller that “communicates with each of the elements and coordinates their actions. For example, a controller may initiate the encoding of a series of analytes into values of color and intensity.” *Id.* at 39:8-58.

57. An example of this system is exemplified in Figure 5A, which is reproduced below. Figure 5A shows “an instrument with a detector configured to detect both wavelength and intensity (e.g., a fluorometer).” In the figure, 502 is “at least one excitation light source” which is “directed into a chamber 503 containing analytes and reagents that generate a signal in the presence of the analytes 504. As described elsewhere, the analyte may be a nucleic acid and the reagents generating the signal may be hybridization probes comprising a fluorophore and a quencher.” *Id.* at 35:48-54. “If the analyte is present, an emission signal 505 is generated . . . the wavelength and intensity of this emission signal are measured across a spectrum by a detector capable of generating a fluorescence emission spectrum 506.” *Id.* at 35:55-58.



Id. at Fig. 5A.

58. By encoding analytes with multiple fluorophores, using a detector to detect signals produced from those multiple fluorophores, and then decoding those signals, the system purports to teach a system for the unambiguous detection of multiple analytes. Table 1 describes a simple decoding matrix for detecting four analytes with four different colored fluorophores:

TABLE 1				
Traditional encoding of four analytes with four probes, each probe having a single color, and one probe per analyte.				
	Blue	Green	Yellow	Red
A	1	0	0	0
B	0	1	0	0
C	0	0	1	0
D	0	0	0	1

Id. at 12:22-33. Using this system, one can detect analyte A by detecting blue signals. Analyte B can be detected analyte B with green signals, and so forth. In this method, each analyte is encoded as a different color, so samples with a combination of multiple analytes can be detected in samples that emit light at multiple wavelengths. For example, a sample that contains analytes C and D will be produce a composite comprised of both yellow and red light—this signal would likely appear orange. Further, a sample containing all four analytes would emit a composite signal of all four colors.

59. The '797 patent purports to teach more complicated encoding and decoding matrices. For example, Table 8 purportedly depicts the encoding of multiple analytes for each color. By changing the maximum signal intensity emitted for a given analyte in each channel, one can unambiguously detect multiple analytes in each channel:

TABLE 8					
Example of encoding method using one color and one intensity per analyte, but different intensities among analytes.					
Tier	Analyte	B	G	Y	R
1	A	1	0	0	0
	B	2	0	0	0
	C	4	0	0	0
	D	8	0	0	0
2	E	0	1	0	0
	F	0	2	0	0
	G	0	4	0	0
	H	0	8	0	0
3	I	0	0	1	0
	J	0	0	2	0
	K	0	0	4	0
	L	0	0	8	0
4	M	0	0	0	1
	N	0	0	0	2
	O	0	0	0	4
	P	0	0	0	8
		15	15	15	15

Id. at 22:10-30 (Table 8). Four colors are used in the system of Table 8. Each color is used to independently detect a distinct set of analytes. Blue is used for A-D, green is used for E-H, yellow is used for I-L, and red is used for M-P. Because each color is used independently of the others, no analyte is detected based on the use of multiple colors. Table 8 shows this because, for each analyte, there is a non-zero entry for only a single color. Analytes detected using a given color are distinguishable based on signal intensities. The spacing between signals supposedly allows differentiation between analytes during a multiplex experiment. For example, for the blue color in Table 8, intensities of 1, 2, 4, or 8 mean that analytes A, B, C, or D are present alone. An intensity of 3, however, means that analytes A and B are present (1+2=3), an intensity of 7 means analytes A, B, and C are present (1+2+4=7), and so on and so forth. This pattern allegedly prevents overlap of

intensities, as each value is “equal to the sum of all previous values plus one.” *Id.* at 22:40-43. For example, if C was assigned to 3 instead of 4, it could not be differentiated from A+B. By mapping out and encoding analytes such that every combination of present analytes emits a unique signal, the detection of analytes is supposedly unambiguous.

60. The encoding and decoding of analytes is summarized, where analytes are encoded, samples containing those analytes are made to generate signals, those signals are measured, and the presence or absence of the analytes is determined:

In some cases, this disclosure provides a method of detecting the presence or absence of each analyte of a plurality of analytes, comprising: (a) encoding each of said analytes as a first value of a signal, thereby generating a coding scheme, wherein each of said analytes is represented in said coding scheme by said first value, wherein said encoding is performed in a manner that eliminates degeneracy; (b) providing a sample comprising, or potentially comprising, at least one of said analytes; (c) contacting said sample with analyte-specific reagents that generate said first value, as represented in said coding scheme, when each of said analytes is present; (d) cumulatively measuring said first values of said signal within said sample, thereby providing a cumulative measurement; and (e) determining whether each of said analytes is present or absent based on said cumulative measurement and said coding scheme.

Id. at 3:59-4:7. The specification of the '797 patent also purports to teach a mathematical system for the encoding and decoding of analytes:

In some examples, the method described in the preceding paragraph is capable of unambiguously detecting the presence or absence of M analytes, in any combination of presence or absence, where $M = \log_2$

(F+1) and F is the maximum cumulative value of the first values when all of the analytes are present. In some cases, the first value is an intensity or range of intensities.

See id. at 4:65-5:5. The specification elaborates that the “first value” of the signal corresponds to intensity or a range of intensities, while the “second values” correspond to the wavelengths or colors used for detection.

61. The specification also states that the decoding scheme can be governed by the relationship between three variables, the number of analytes (M), the number of wavelengths or colors of fluorophores used in detection (C), and the maximum cumulative intensity of any given wavelength (F) according to the following equation:

$$M = C * \log_2(F + 1)$$

Id. at 2:11-17. In Table 8, M has a value of 16 (analytes A through P), C has a value of 4 (the number of colors), and F has a value of 15 (the maximum cumulative signal for a given color, 1+2+4+8=15). This mathematical formula is a restatement of the use of signal intensities for analytes that follows the geometric progression 1, 2, 4, 8, 16... and so on.

C. Prosecution History of the '797 Patent

62. I have reviewed the prosecution history for the '797 patent and include a brief summary of relevant actions below. I do not purport to be an expert in the

process of patent examination, but for the purposes of my opinions I wished to have a general understanding of the history of how the '797 patent came to be issued.

63. The '797 patent issued on December 17, 2024, from U.S. Patent Application No. 18/352,112 (the "'112 Application"), filed July 13, 2023, by applicant California Institute of Technology ("CalTech"). EX1001 at (21), (22), (45), and (71). The '112 Application was a continuation of U.S. Patent Application No. 16/937,464, filed on July 23, 2020 (now U.S. Patent No. 11,866,768), which was a continuation of U.S. Patent Application No. 15/914,356, filed on March 7, 2018 (now U.S. Patent No. 10,770,170), which was a continuation of U.S. Patent Application No. 14/451,876, filed on August 5, 2014 (now U.S. Patent No. 10,068,051), which was a continuation of U.S. Patent Application No. 13/756,760, filed February 1, 2013 (now U.S. Patent No. 8,838,394), which claims the priority benefit of U.S. Provisional Application Nos. 61/594,480, filed February 3, 2012, and 61/703,093, filed September 19, 2012. *Id.* at (63), (60), 1:7-19.

64. I understand that during prosecution of the '112 Application, the patent examiner identified various bases for rejecting claims, including indefiniteness, scope of enablement, obviousness, and double patenting. Eventually, the examiner allowed amended claims that were issued as the '797 patent claims. EX1025; EX1026.

VII. PERSON OF ORDINARY SKILL IN THE ART

65. I understand that whether a patent is invalid as obvious in light of the prior art is considered from the perspective of a person of ordinary skill in the art (“POSA”) at the time of the alleged invention. I am knowledgeable about what the level of ordinary skill in the art would have been at the time of the alleged invention based on my education and experience.

66. In determining the definition of a POSA, I have considered the following factors: (1) the level of education and experience of those in the field; (2) the complexity of the technology at issue; (3) the rate of innovation; (4) the kinds of problems faced by those in the art; and (5) solutions to such problems known in the prior art.

67. In my opinion, a POSA would have been someone with a Ph.D. in a relevant field, such as molecular biology, genetics, biochemistry, or a related discipline, with at least a year of experience in the use and development of genetics and genomic approaches for detecting and monitoring human diseases, such as multiplex detection of target analytes in a sample via quantitative and digital PCR. Alternatively, a POSA would have been someone with greater relevant experience that has an equivalent understanding of approaches used in the field without the same amount of formal education.

68. A POSA would have a strong understanding and/or experience with the design and application of various assays to detect polynucleotide sequences. Specifically, this includes the following techniques:

- Multiplex PCR and its application in detecting and measuring polynucleotide analytes.
- The design and use of fluorescent-labeled oligonucleotide probes, including use of quenchers, and use in conjunction with multiplex PCR.
- The quantitative detection and measurement of polynucleotide analytes using fluorescent-labeled oligonucleotide probes in multiplex applications.
- Techniques for labeling probes and detecting multiple targets using fewer differently colored fluorophores than polynucleotide targets.
- Quantitative PCR and digital PCR and their application in detecting and measuring polynucleotide analytes, including in multiplex applications.

VIII. THE PARALLEL DISTRICT COURT LITIGATION

69. I have been informed that Patent Owner is asserting the '797 patent, along with related patents, in a district court litigation against Petitioner. *In re ChromaCode*, Case No. 5:23-cv-04823-EKL (N.D. Cal., filed October 5, 2023). I have been informed that Patent Owner accuses Petitioner's QX600 Droplet Digital PCR ("ddPCR") System ("QX600") and QX ONE Droplet Digital PCR System

(“QX ONE”) of infringement, along with various additional devices, software, accessories, and/or components used in connection with these systems. I have reviewed Patent Owner’s infringement allegations in its infringement contentions. *See* EX1009.

70. The QX600 and QX ONE are systems that can detect excited fluorophores to quantify target DNA concentration. For example, Patent Owner contends, consistently throughout its infringement contentions, that coding schemes fitting this description and as shown below satisfy the limitations of the ’797 patent to constitute infringement. *See* EX1009 at 57 (explaining how Petitioner’s QX600 system allegedly “applies a decoding matrix to the cumulative signal” within the meaning of claim 1 of the ’797 patent).

71. As I describe in § V.C-E, *supra*, and in detail below, (e.g., §§ IX.A.2-X.A, *infra*) the accused ddPCR systems allow detection of targeted analytes in a sample solution. This is done by generating droplets from the sample solution, where each droplet may contain one or more of the polynucleotide targets along with the necessary reagents for amplification of each of the target analytes and generating the detectable color signal. This PCR amplification is done within the droplet to generate the detectable signals and, specifically, the probes are labeled as such: probes for target 1 are labeled with color 1; probes for target 2 are labeled with color

2; and probes for target 3 and labeled with colors 1 and 2. During DNA extension, as discussed, the attached probes are cleaved and the fluorescence is detected. Target 3 will have a multi-colored burst, differentiating it from targets 1 and 2.

72. For example, the QXONE system has 4 detection channels that can detect FAM, HEX, Cy5, and Cy5.5. EX1009 at 269. Analyte-specific reagent mixtures (“e.g. primers, probes, and Bio-Rad ddPCR supermix”) are used within the QXONE. EX1009 at 256-59. Each of the channels can be used to detect a given fluorophore and then use the fluorophores detected to generate a coding scheme.

73. Based on these contentions, Patent Owner alleges that the ’797 patent is infringed by these ddPCR systems because they have a multi-channel detector capable of unambiguously detecting the presence or absence of analytes based on the number of channels available and the ability to assign an intensity to certain fluorophores. EX1009 at 3, 44, 62, 65, 73-76. The encoding system of these systems also allegedly follows the same geometric progression that the ’797 patent claims. *See id.* at 66-68.

IX. THE PRIOR ART REFERENCES OF THE GROUNDS

A. Jouvenot

1. Jouvenot is § 102(e) Prior Art

74. Jouvenot et al, U.S. Patent No. 9,921,154 entitled “Multiplexed Digital Analysis” (“Jouvenot”), is a published patent, published on March 20, 2018.

EX1003 at codes (10), (12), (45), (54). Jouvenot is the published patent, resulting from U.S. Patent Application No. 14/099,750 (“’750 Application”). The ’750 Application was filed on December 6, 2013, and claims priority benefit of four provisional applications, including Provisional Application Nos. 61/507,082 (filed July 12, 2011), 61/510,013 (filed July 20, 2011), and 61/454,373 (filed March 18, 2011). *Id.* at codes (22), (60).

75. I have been asked to opine on whether Provisional Application No. 61/507,082 (the “’082 Provisional”) (EX1004) contains adequate written description support of what Jouvenot identifies as its invention. In my opinion, the ’082 Provisional Application (EX1004) discloses, in its specification and claims, substantially the same subject matter as Jouvenot, with Jouvenot amplifying the disclosure, including adding illustrative examples and figures supported by the ’082 Provisional Application. The table below, for example, identifies written description support in the ’082 Provisional Application (EX1004) for each and every element of Jouvenot’s claim 11 (EX1003 at 26:1-20):

Jouvenot	’082 Provisional Disclosure
11. A method of performing a multiplexed digital assay, the method comprising:	“The present disclosure provides a system, including methods and apparatus, for performing a digital assay with multiplexed detection of two or more distinct targets in the same channel.” EX1004 at 3:5-7; <i>id.</i> at 3:10-14, 4:17-20, Figs. 1-2.

Jouvenot	'082 Provisional Disclosure
forming partitions that collectively contain R targets;	“The sample may be separated into partitions.” <i>Id.</i> at 7:6; <i>see also id.</i> at 6:21-23, 7:12, 8:6, 8:14, 8:22-23. “Partitions may be analyzed and signals created at any suitable time(s).” <i>Id.</i> at 9:22; <i>see also id.</i> at 10:3-11:11.
amplifying the R targets in the partitions;	“[P]reparation of the sample may render the sample (or partitions thereof) capable of amplification of each of one or more targets, if present, in the sample (or a partition thereof)” <i>Id.</i> at 6:21-23, <i>see also id.</i> at 7:12, 8:6, 8:14. “The signal may be analyzed to determine whether neither Target, Target 1 alone, Target 2 alone, or both Targets 1 and 2 are present in each droplet” <i>Id.</i> at 14:22-15:1; <i>see also id.</i> at 12:11-19:23, 15:30-31, 15:25-27, Examples 1-4.
collecting data representing amplification of each of the R targets in the partitions, all of the data being collected in fewer than R optical channels;	The “assays may involve analysis of more than two targets in the same channel.” <i>Id.</i> at 5:14-15. “[S]ome targets may be analyzed in one channel (e.g., a FAM channel), and other targets may be analyzed in other channels (e.g., a VIC channel). Three targets, two in a first channel and one in a second channel, would again generate eight clusters or populations of data.” <i>Id.</i> at 5:17-20; <i>see also id.</i> at 2:10-13, 8:6, 8:14, 8:22-9:3, 9:3-6, 9:11-13.

Jouvenot	'082 Provisional Disclosure
	From Example 1, “Fluorophores 92, 94, which <i>may be the same or different</i>, create detectable but distinguishable signals in the same channel, allowing multiplexing in that channel. The signals may be distinguishable because an aspect of the fluorescence is different for one fluorophore than for the other fluorophore(s). For example, the intensity associated with one fluorophore, following reaction, may be lower or higher than the intensity(ies) associated with the other fluorophore(s). In some embodiments, <i>one probe may be labeled with a different number of fluorophores than the other probe</i>, and/or the probes may be located in slightly different local environments, creating a different level of fluorescence for each probe following reaction. Alternatively, or in addition, both probes may be labeled <i>with the same number of fluorophores</i> (e.g., one fluorophore), but there may be <i>more or less of one probe</i> than the other in the sample, so that a greater or smaller signal is created when the reactions have occurred.” <i>Id.</i> at 13:10-15 (emphasis added); <i>see also id.</i> at 14:16-15:29, Fig. 4.
identifying from the data a plurality of partition populations each positive for a different combination of the R targets, wherein the step of identifying includes a step of resolving each partition population that is positive for	“[S]ignal is created from light detected over time in a single channel from a fluid stream containing the droplets and flowing through an examination region of the channel. The signal may be analyzed to determine whether neither

Jouvenot	'082 Provisional Disclosure
exactly two of the R targets from each partition population that is positive for only one of the R targets; and	Target, Target 1 alone, Target 2 alone, or both Targets 1 and 2 are present in each droplet.” <i>Id.</i> at 14:20-15:1. “[A]ssignment of a droplet to a particular outcome (i.e., to one of T1-/T2-, T1+/T2-, T1-/T2+, and T1+/T2+) may be performed using any suitable algorithm.” <i>Id.</i> at 15:30-31; <i>see also id.</i> at 16:4-6, 16:8-18:17, 17:23-24, 18:18-19:18, Fig. 4. “Number of positives. A number of partitions that are positive (or negative) for each target may be determined for the signal, indicated at 50. The signal detected from each partition, and the partition itself, may be classified as being positive or negative for each of the reactions/targets contributing to the signal. Classification may be based on the strength (and/or other suitable aspect) of the signal. If the signal/partition is classified as positive (+), for a given target, the reaction corresponding to that target is deemed to have occurred and at least one copy of the target is deemed to be present in the partition. In contrast, if the signal/partition is classified as negative (-), for a given target, the reaction corresponding to that target is deemed not to have occurred and no copy the target is deemed to be present in the partition (i.e., the target is deemed to be absent from the partition). The data including all permutations of positives will generally fall into 2N populations

Jouvenot	'082 Provisional Disclosure
	or clusters, assuming that each population is distinguishable.” <i>Id.</i> at 10:3-15; <i>see also id.</i> at 2:3-5, 5:4-8, 14:16-15:29, Fig. 4.
determining a respective level of each of the R targets from the data, wherein each level is specific for a single target of the R targets, and wherein the level determined for at least one of the R targets is based in part on a partition count for a partition population positive for two of the R targets.	“A concentration of each target may be estimated.... The concentration of each target may be estimated based on the respective numbers of partitions positive for the target alone and for the target in combination with any other target(s). The calculation may be based on each target having a Poisson distribution among the droplets. The concentrations may, for example, be estimated by finding solutions to a series of linear equations. The total number of partitions may be counted or, in some cases, estimated.” <i>Id.</i> at 11:2-7; <i>see also id.</i> at 14:16-15:29, Fig. 4.

76. In sum, each and every limitation of claim 11 of Jouvenot is disclosed by the '082 Provisional. Thus, the '082 Provisional provides written description support for the invention claimed in Jouvenot. Accordingly, I understand from counsel that Jouvenot is § 102(e) prior art as of the '082 Provisional Application's filing date of July 20, 2011.

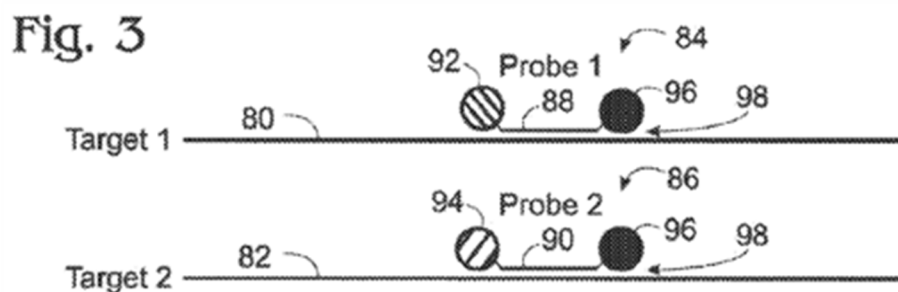
77. Further, all of the material I rely upon in Jouvenot as rendering obvious the asserted claims was present in the '082 Provisional, as I show herein through concurrent citations to the '082 Provisional application.

2. Jouvenot Overview

78. Jouvenot is directed to digital assays for the multiplexed detection of signals from labeled probes for two or more targets, where the different targets are detected by the use of hybridization probes labeled with fluorophores that emit fluorescent signals, detected by one or multiple channels. EX1003 at 5:19-31; EX1004 at 5:14-21. The fluorescent probes can emit light of different intensities, at the same or different wavelengths or colors. EX1003 at 13:46; EX1004 at 13:10. Jouvenot discloses the same system as the '797 patent, including the same experimental setup, the same use of channels and a detector, the same use of a processor to receive and analyze signals, and the same coding and decoding system to detect and identify analytes in a sample.

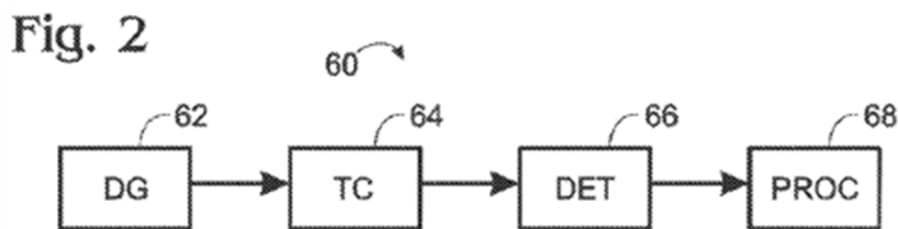
79. For example, Jouvenot teaches the multiplexed detection of signals from labeled probes for two or more targets where the labels for different targets can share the same color or colors. EX1003 at 13:10-17:12; EX1004 at 12:11-18:17. Jouvenot's Example 1 discloses assays wherein two targets are detected in any combination of presence or absence using a single unique color label. EX1003 at 13:19-15:10; EX1004 at 12:15-16:7. Jouvenot also discloses an assay wherein multiple targets are detected in any combination of presence or absence using multiple color labels. EX1003 at 15:12-17:12; EX1004 at 16:8-18:17.

80. The methods disclosed in Jouvenot are for the detection of multiple target polynucleotides in a single sample using dPCR assays. EX1003 at 4:48-50; EX1004 at 3:5-7. Fluorophore-labeled probes contact samples to report the presence of targets by generating signals during PCR. EX1003 at 4:51-5:18; EX1004 at 4:16-5:13. Signals may be based on the signal's color, intensity, or both. EX1003 at 8:32-36; EX1004 at 9:1-3. Jouvenot's Example 1 discloses droplets containing a sample mixture including "a pair of targets 80, 82 ('Target 1' and 'Target 2') and corresponding probes 84, 86 ('Probe 1' and 'Probe 2')." This is depicted in Jouvenot Figure 3:



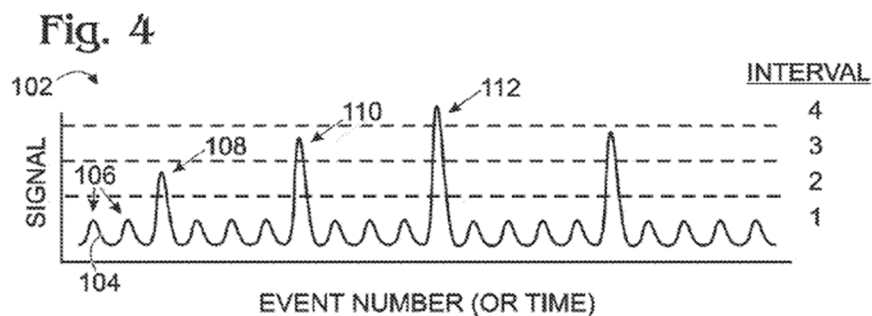
EX1003 at 13:29-32, Fig. 3; EX1004 at 12:20-13:5, Fig. 3. The probes include oligonucleotides (labeled 88 and 90) and fluorophores (labeled 92 and 94). EX1003 at 13:32-33, Fig. 3; EX1004 at 12:23-24. These samples are analyzed in "a fluid stream containing the droplets and flowing through an examination region." EX1003 at 14:26-31; EX1004 at 14:20-22. The system disclosed by Jouvenot also

incorporates a data processor “to determine the number of droplets and/or target levels.” EX1003 at 13:7-13; EX1004. The data processor is depicted as part of the system in Jouvenot Figure 2:



EX1003 at 2:36-38, EX1004 at 3:12-13, Fig. 2.

81. Jouvenot Example 1, and in particular Fig. 4, shows the depiction of signal intensity in a single channel (same color):



EX1003 at Fig. 4, 14:21-15:10; EX1004 at Fig. 4, 14:17-16:7. Figure 4 identifies analytes based on signal intensity. Specifically, assignments are made on the interval 1, 2, 3, or 4. Interval 1 represents an intensity of 0, or no targets; interval 2 represents an intensity of 1, or a first target; interval 3 represents an intensity of 2, or a second target; and interval 4 represents intensity 3 (1+2), or both targets. This

geometric progression is the same as the geometric progression disclosed in the '797 patent's specification and discussed above in § VI.B, *supra*.

B. Larson

82. Larson, U.S. Patent Application Publication No. 2011/0250597, titled "Digital Analyte Analysis," was published in October 2011. EX1013 at (43). I understand that Larson is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).

83. Larson, like the '797 patent, describes a scheme for the detection of multiple analytes in a single color channel. In particular, Larson's Figure 11a discloses a scheme virtually identical to that of Jouvenot, wherein Larson teaches an experiment using two targets. In Figure 11a, "three populations" of droplets "were readily apparent," with peaks at 0.08 V, 0.27 V, and 0.71 V visible on the graph. *Id.* Larson also discloses a fourth population containing both targets, describing a "very small peak appeared at ~0.9 V, not visible on the scale of FIG. 11a, that corresponded to droplets occupied by both genes." *Id.* ¶¶ 130-31. Larson repeatedly teaches increasing the number of color channels use to increase the number of targets consistently, on several occasions. EX1013 ¶¶ 47, 139-40, 152, 166. For example, Larson states that "[a]nother method of the invention involves performing higher-plex assays using multiple different probe colors (i.e. fluorophores).... The

maximum number of colors can be 1, or 2, or 3, or 4, or up to 10, or up to 20. The maximum number of colors can be higher than 20.” *Id.* ¶ 139.

C. Secondary References Relied Upon Herein

84. While I rely principally on Jouvenot, the following references are used herein as support for secondary challenges to the same claims and challenges to the remaining claims—claims 7-9, 11, 13-15—not subject to Ground 1.

- **Lakowicz:** published in 2006. EX1006 at 3. I understand Lakowicz is therefore prior art to the ’797 patent under pre-AIA 35 U.S.C. § 102(a).
- **Dube:** published in 2009. EX1019 at code (43). I understand Dube is therefore prior art to the ’797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).
- **Wittwer:** published in 2009. EX1020 at code (43). I understand Wittwer is therefore prior art to the ’797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).
- **Brabetz:** was filed via PCT application in 2009, published via PCT in 2010, and published in the United States in December 2011. EX1008 at codes (22), (87), (65). I understand Brabetz is therefore prior art to the ’797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).

- **Maltezos:** published in 2008. EX1012 at code (43). I understand Maltezos is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).
- **Neuzil:** published in 2010. EX1017 at code (43). I understand Neuzil is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).
- **Oleksy:** published in 2003. EX1018 at code (43). I understand Oleksy is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).
- **Slepnev:** published in April 2012, was filed in December 2011, and has a priority date of at least June 19, 2003. EX1021 at codes (22), (43), (63). I understand Slepnev is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).
- **Lehnen:** published in 1992, was internationally published (and available in the US) in 1993, and was also published via European Patent Office Bulletin in 1994. EX1022 at codes (22), (30), (86), (87). I understand Lehnen is therefore prior art to the '797 patent under pre-AIA 35 U.S.C. § 102(a) and 102(e).

X. GROUND 1: CLAIMS 1-2, 5-6, 10, AND 18 ARE OBVIOUS IN VIEW OF JOUVENOT

85. The '797 patent claims multiplex assays for detecting the presence or absence of analytes using reagent mixtures containing analyte-specific hybridization probes and multiple fluorophores. These assays can purportedly detect at least M analytes using fluorophores that emit a number of wavelengths of light, C. The '797 patent purportedly teaches that the total number of detectable analytes M can be determined by the value of F, which is the maximum intensity of light emitted when all analytes are present, when M and F are positive integers, and F+1 is a power of 2. In this system, F+1 represents the number of signal intensity populations across all wavelengths, including samples that do not contain any analyte targets.

86. The '797 patent represents this system with an equation, $M=C*\log_2(F+1)$. Using this formula, the '797 patent purportedly teaches the detection of multiple electromagnetic signals, generated by multiple fluorophores, detected by a multi-channel detector. By associating, for each analyte, a first value (intensity) and a second value (wavelength), such that the maximum cumulative intensity of any wavelength is F, and F+1 is 2, 4, 8, 16, etc., the claims propose to unambiguously detect the presence or absence M analytes.

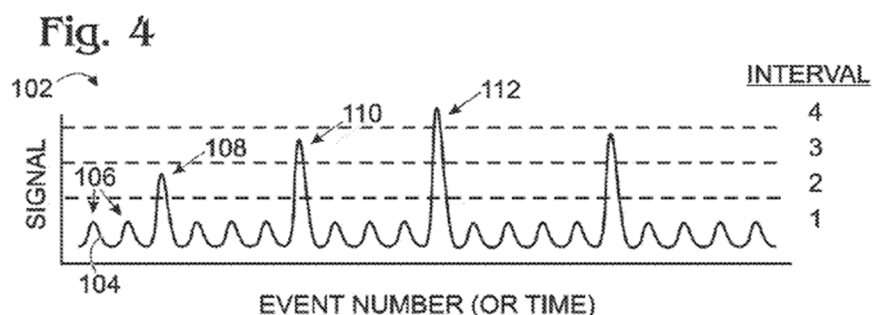
87. At its core, the '797 patent relies on nothing more than the concept of detecting a number of targets using multiple color signals, by simply assigning each

analyte a non-degenerate intensity value (using hybridization labeled with fluorophores) according to an intuitive equation. For example, examining a single wavelength of light, the system teaches that an analyte A can be assigned an intensity of 1 at a particular wavelength, and an analyte B can be assigned an intensity of 2 at the same wavelength. Thus, the value of F would be 3, the total cumulative signal when both A and B are present. Using the claimed equation, $M=(1)*\log_2(3+1)=2$, one can detect 2 analytes using the experimental setup identified in this hypothetical.³

88. This scheme is intuitive because, to unambiguously detect analytes in combination at the same wavelength, one must assign unique intensity values that, when added in any combination, are not duplicative. Thus, one could assign 3 individual analytes A, B, and C intensity values of 1, 2, and 4 (within the same color), respectively. This scheme is unambiguous and intuitive because any combination of these three analytes can be identified: a combination of A and B is 3, a combination of A and C is 5, a combination of B and C is 6, and a combination of A, B, and C is 7. No combination results in degeneracy (i.e., two combinations of analytes with the same signals). Here, $F+1=8$, which is 2 to the third power.

³ As the claims require C to be 4, 5, or 6, this example using C=1 is for illustrative purposes only.

89. Jouvenot's Figure 4, reproduced below, describes the same mathematical concepts that the '797 patent claims. This includes the use of unambiguous, progressive intensities in one channel, as well as the logarithmic pattern. Specifically, Jouvenot notes that the "data including all permutations of positives will generally fall into 2^N populations or clusters, where N is the number of targets" that can be detected using a single color signal. EX1003 at 10:23-25; EX1004 at 10:13-14.

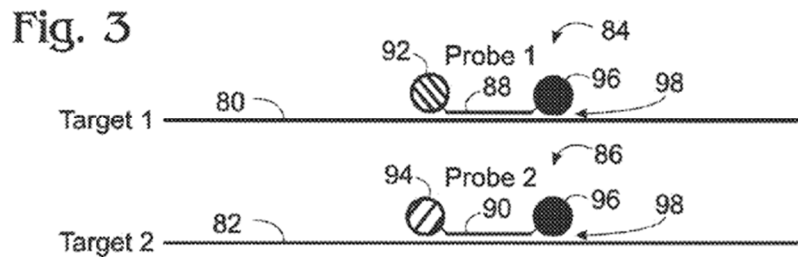


EX1003 at Fig. 4; EX1004 at Fig. 4.

90. Jouvenot's Figure 4 presents the same mathematical scheme claimed in the '797 patent. Figure 4 shows: (a) signals below a lower threshold 106, corresponding to samples with no analytes present; (b) signals of a first intensity 108, corresponding to a sample with a first target present (to which one can assign a value of 1), signals of a second intensity (higher than the first) 110, corresponding to a second analyte (to which one can assign a value of 2), and a third intensity 112, which corresponds to a sample wherein both analytes are present (to which one can

assign a value of 3). This third signal, 112, represents the maximum cumulative intensity when all analytes are present. Thus, Jouvenot's Figure 4 shows the same system disclosed by the '797 patent, where $M=2$, $C=1$, and $F=3$. As set forth below, this logic and the assignment of integer values to the different intervals in Figure 4 are supported by Patent Owner's infringement contentions, which take the same approach.

91. Like the '797 patent, Jouvenot is also directed to the multiplex detection of analytes using fluorophores, including both the use of multiple colored fluorophores and the detection of multiple analytes that exhibit fluorescence at the same wavelength. For example, Jouvenot discloses (with reference to Figure 3, reproduced below) that "[f]luorophores 92, 94, which may be the same or different, create detectable but distinguishable signals in the same channel, allowing multiplexing in that channel. The signals may be distinguishable because an aspect of the fluorescence is different for one fluorophore than for the other fluorophore(s). For example, the intensity associated with one fluorophore, following reaction, may be lower or higher than the intensity(ies) associated with the other fluorophore(s)." EX1003 at 13:46-53.



92. In my opinion, accordingly, Jouvenot is analogous art to the '797 patent because the two are within the same field of endeavor: multiplex detection of multiple analytes using color-labeled sequence-specific probes, including the use of probes that fluoresce across multiple wavelengths or colors, and that follows a simple, intuitive mathematical scheme.

93. It is my opinion claims 1-2, 5-6, 10, and 18 of the '797 patent are obvious in view of Jouvenot alone.

A. Claim 1

1. A system comprising:

94. It is my opinion that the preamble is non-limiting, and, if deemed limiting, a POSA would have understood Jouvenot to disclose the recited system. Jouvenot discloses systems for detecting analytes using a multiplexed assay. *See, e.g.,* EX1003 at 2:26-28; EX1004 at 3:5-7 ("The present disclosure provides a **system**, including methods and apparatuses for performing a multiplexed digital assay") (emphasis added).

95. As further described in the specification and depicted in Figures 3 and 4 (reproduced above), the system of Jouvenot contains several components:

FIG. 4 is an exemplary graph showing a signal that may be created by detecting light emitted from the probes of FIG. 3 in a digital PCR assay performed in droplets, with the signal created by detecting light from each target together in the same optical channel from a fluid stream containing the droplets.

EX1003 at 2:45-51; EX1004 at 3:18-21. *See also* EX1003 at Figs. 1-4; EX1004 at Figs. 1-4 (showing aspects of the claimed system).

96. The '797 patent teaches a similar, if not identical, system, including the detection of multiple light signals, emitted from fluorescent probes, which corresponds to a signal generated during (or as a result of) a polymerase chain reaction and detected cumulatively:

In some examples, the signal is an electromagnetic signal. . . . In some cases, the electromagnetic signal is a fluorescence emission signal. . . . In some cases, a detecting step is performed with reagents comprising hybridization probes. . . . In some examples, the signal that is measured is generated during a polymerase chain reaction. . . . In some examples, at least one cumulative measurement is performed on a solution.

EX1001 at 2:33-60.

97. Accordingly, a POSA would have understood that Jouvenot discloses a working example of the system with the same components as that described in and claimed by the '797 patent.

2. a sample chamber configured to house a sample and analyte-specific reagent mixtures of analyte-specific hybridization probes and multiple fluorophores;

98. The system of Jouvenot includes the preparation of a sample, the separation of a sample into partitions using a droplet generator, amplification with a thermocycler, and then the analysis of each droplet in a single fluid stream through an examination region. EX1004 at 14:26-31; EX1004 at 14:17-15:1. This examination region corresponds to the claimed a sample chamber. Specifically, the examination region is configured with a fluid stream, which carries droplets containing the sample, reagents, and fluorophore-labeled hybridization probes into the examination region:

The signal is created from light detected over time in a single channel from *a fluid stream containing the droplets and flowing through an examination region* of the channel. The signal may be analyzed to determine whether neither Target, Target 1 alone, Target 2 alone, or both Targets 1 and 2 are present in each droplet.

EX1004 at 14:26-31; EX1004 at 14:17-15:1. Jouvenot further explains that the droplets in the examination region contain a sample, analyte-specific hybridization probes, and multiple fluorophores. Jouvenot's Example 1 is a working practical example of the disclosed system. EX1003 at 13:19-15:10; EX1004 at 12:15-16:7. And Example 1 describes "an exemplary digital PCR assay with multiplexed detection of two targets, using two probes, analyzed in the same channel." EX1003 at 13:24-26; EX1004 at 12:16-17. The depictions in Example 1 and Figures 1-4

confirm that Jouvenot's sample chamber includes all necessary components in the sample chamber.

99. First, Jouvenot explains that a sample is partitioned, such as in a container or into droplets:

The sample may be *separated into partitions* Each partition may be and/or include a fluid volume that is isolated from the fluid volumes of other partitions. The partitions may be isolated from one another by a fluid phase, such as a continuous phase of an emulsion, by a solid phase, such as at least one wall of a container the partitions may be droplets, among others. In some embodiments, the *partitions may be droplets disposed in a continuous phase*, such that the droplets and the continuous phase collectively form an emulsion.

EX1003 at 6:58-7:2; EX1004 at 7:6-13.

100. Jouvenot then explains that the droplets contain reagent mixtures. *See* EX1003 at 7:17-21; EX1004 at 8:1-3 (explaining that these droplets or partitions, “when formed, may be competent for performance of one or more reactions in the partitions,” or “one or more reagents may be added to the partitions . . . to render them competent for reaction.”).

101. Jouvenot states that these reagents include analyte-specific reagent mixtures of hybridization probes that incorporate multiple fluorophores:

Reagents for reporting may include *a different reporter for each target of interest*. Accordingly, preparation of the sample for reporting may render the sample capable of reporting, or being analyzed for, *whether or not amplification has occurred, on a target-by-target basis*, and optionally the extent of any such amplification. The reporters each may

be a *labeled probe that includes a nucleic acid* (e.g., an oligonucleotide) labeled with a luminophore (i.e., a photoluminescent moiety), such as a *fluorophore*.

EX1003 at 6:49-57; EX1004 at 6:23-7:5. Thus, the system of Jouvenot teaches partitions or droplets containing reagent mixtures containing oligonucleotide probes with multiple fluorophores, and that these droplets are brought into the examination region for detection. The system of Jouvenot further teaches that “[s]ignals may be detected from the droplets with detector 66,” confirming that there is a chamber housing the droplets from which the signals come. EX1003 at 13:7-13; EX1004 at 12:9-10.

102. A POSA would further understand that the oligonucleotide probes of Jouvenot are analyte-specific, and function by binding to—and, with fluorescent labeling, identifying—a specific nucleic acid sequence. Jouvenot explains that the samples tested in the examination region must contain analyte-specific hybridization probes. EX1003 at 6:54-56; EX1004 at 7:4-5. (“The reporters each may be a probe that includes a nucleic acid (e.g., an oligonucleotide).”); EX1003 at 13:41-43; EX1004 at 13:6-7 (“Each oligonucleotide may provide target specificity by hybridization predominantly or at least substantially exclusively to only one of the two targets.”).

103. A POSA would further recognize that hybridization probes must be analyte-specific (or sequence-specific) to be useful for the detection of specific analytes; otherwise, they would not emit signals in the presence of specific analytes and would not be useful for detection.

104. Jouvenot is clear that the multiple analyte-specific hybridization probes are labeled with multiple fluorophores. For example, Jouvenot teaches the use of analyte-specific reagent mixtures where “[r]eagents for reporting may include *reporters for each target* of interest” and that “reporters *each* may be a probe that includes a nucleic acid (e.g., an oligonucleotide) and *a fluorophore*.” EX1003 at 6:49-57; EX1004 at 6:23-7:5. Jouvenot further explains that the disclosed assays include the use of multiple fluorophores:

- “Each probe may include an oligonucleotide 88, 90, a fluorophore 92, 94, and a quencher 96. Each of the fluorophore and the quencher may (or may not) be conjugated to the oligonucleotide by a covalent bond.” EX1003 at 13:32-36; EX1004 at 11:22-12:2.
- “Fluorophores 92, 94, which may be the same or different, create detectable but distinguishable signals in the same channel, allowing multiplexing in that channel. The signals may be distinguishable because an aspect of the

fluorescence is different for one fluorophore than for the other fluorophore(s).” EX1003 at 13:46-51; EX1004 at 13:10-13.

- “In some cases, the fluorophores themselves might be different, with one more or less intrinsically fluorescent than the other.” EX1003 at 13:63-65; EX1004 at 13:21-24.
- *See also* EX1003 at Fig. 3; EX1004 at Fig. 3:

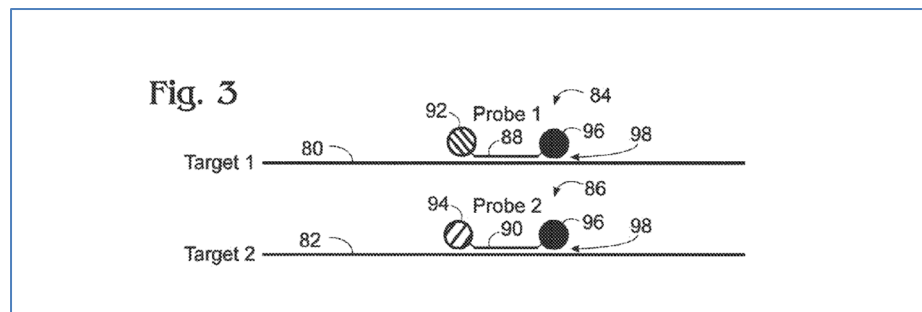


Figure 3, which depicts a sample mixture for an exemplary experiment using the Example 1 protocol, immediately above shows that the examination region of Example 1 is a sample chamber, configured to have droplets comprising analytes (targets 1 and 2), analyte-specific reagent mixtures of analyte-specific hybridization probes (labeled 88 and 90), and multiple fluorophores (labeled 92 and 94).

105. I understand that Patent Owner contends that the location in an instrument for introducing the sample, such as a chamber to hold a sample tube or a 96-well plate, is a “sample chamber” within the meaning of the EX1009, Appendix B at 15. This location in the instrument holds the sample before PCR amplification

or analyte detection. It is my opinion that this kind of sample chamber is also disclosed by Jouvenot.

106. I note, for instance, that Figure 2 of Jouvenot teaches a “partitioning assembly” integrated with a thermocycler and detector. See EX1003 at 12:53-62; EX1004 at 11:12-16. A POSA would know that the partitioning assembly includes the alleged “sample chamber” in order to hold the sample so that it may be subjected to the partitioning process. *See supra* ¶ VI.B-X. Similarly, and as further evidence that a POSA would have been motivated to use such “sample chambers” with a reasonable expectation of success, consider Larson, which teaches a digital PCR system as in Jouvenot. *Supra* ¶ IX.B. Larson discloses both a tube in a Bio-Rad thermal cycler and a location on a “readout chip” that holds the sample before and after amplification, respectively. See EX1013 ¶¶ 79, 86, 156, 193-94. Either location satisfies the claimed “sample chamber” under the interpretation of this term as set forth in PO’s infringement contentions. See, e.g., EX1009 at 6, 15, 77, 81. A POSA would have been motivated to use such sample chambers because a POSA would naturally desire a location for holding the sample subject to analysis in a biological instrument. A POSA would have had a reasonable expectation of success in using such sample chambers because they are nothing more than sample tubes or cavities for holding sample tubes of the type that had been used in the art for decades.

107. Accordingly, the examination region of Jouvenot is a “sample chamber” as claimed by the ’797 patent and, at a minimum, the claimed “sample chamber” is obvious in view of Jouvenot.

3. a multi-channel detector to detect:

a first electromagnetic signal at a first wavelength from the sample chamber, the first electromagnetic signal generated by excitement of a first fluorophore of the multiple fluorophores;

a second electromagnetic signal at a second wavelength from the sample chamber, the second electromagnetic signal generated by excitement of a second fluorophore of the multiple fluorophores;

a third electromagnetic signal at a third wavelength from the sample chamber, the third electromagnetic signal generated by excitement of a third fluorophore of the multiple fluorophores;

a fourth electromagnetic signal at a fourth wavelength from the sample chamber, the fourth electromagnetic signal generated by excitement of a fourth fluorophore of the multiple fluorophores;

108. These four claim elements correspond to nothing more than the use of four different color channels in connection with the claimed apparatus. It is my opinion that Jouvenot discloses or, at a minimum renders obvious, “a multi-channel detector to detect,” from the sample chamber, at least four distinct electromagnetic signals, at four or more wavelengths, generated from at least four fluorophores.

109. At the outset, Jouvenot discloses the use of a detector to detect signals from multiple channels (i.e., a multi-channel detector). EX1003 at 12:53-13:6; EX1004 at 11:12-15 (“FIG. 2 shows an exemplary system 60 for performing the digital assay of FIG. 1. System 60 . . . a detection assembly (a detector) 66 (‘DET’)”).

The detector of Jouvenot is used to detect light in multiple color channels:

In some embodiments, the assays may involve detection of more than two targets in the same optical channel. . . . In the same or other embodiments, *some targets may be analyzed in one channel* (e.g., a FAM channel), and one or more other *targets may be analyzed in one or more other channels* (e.g., a VIC channel). Three targets, *two in a first channel and one in a second channel*, would again generate eight clusters or populations of data, but they would be separated in a two-dimensional intensity space and so in principle more easily resolvable.

EX1003 at 5:18-31; EX1004 at 5:14-19. In disclosing that “one or more targets may be analyzed in one *or more* other channels,” Jouvenot specifically discloses the simultaneous detection of multiple different fluorophores, which a POSA would understand are used to realize the multiple color channels. EX1003 at 5:18-31; EX1004 at 5:14-19. In this regard, this passage further explains that multiple fluorophores may be used. EX1003 at 5:18-31; EX1004 at 5:14-19; *see also* EX1003 at 13:58-64; EX1004 at 13:19-21 (“Alternatively, or in addition, both probes may be labeled with the same number of fluorophores (e.g., one fluorophore) In some cases, the fluorophores themselves might be different”).

110. To understand why the use of different fluorophores reflects the use of different color channels, I note that a POSA would understand that different fluorophores could be used to generate different wavelengths of light. Typically, a fluorophore is a large molecule that absorbs energy of a particular wavelength and emits energy of a second wavelength. After a fluorophore is excited (e.g., absorbs energy from light), it generates an electromagnetic signal (e.g., fluoresces, releasing energy as light). Fluorophores emit electromagnetic signals (light) at characteristic wavelength ranges; the specific wavelengths emitted depend on the chemical structure of the fluorophore, and different fluorophores typically emit light at different wavelengths/colors. Thus, a POSA would understand that the use of multiple different wavelengths, signals, and fluorophores simply corresponds to the detection of light emitted from multiple fluorophores that fluoresce at different wavelengths/colors.

111. As to the use of four such channels, as recited in these claim elements, Jouvenot discloses the use of at least four different fluorophores that produce different colored electromagnetic signals. Specifically, Jouvenot discloses, by common name, least five different fluorophores that emit light at different wavelengths. These include FAM, VIC, ROX, TAMRA, and JOE. EX1003 at 13:46-14:2; EX1004 at 14:1-3. A POSA would understand that:

- FAM (5(6)-carboxyfluorescein) fluoresces a green color at around 520 nanometers;
- VIC (2'-chloro-7'-phenyl-1,4-dichloro-5(6)-carboxyfluorescein) fluoresces a green-yellow color at around 543 nanometers;
- ROX (5(6)-carboxy-X-rhodamine) fluoresces an orange color at around 591 nanometers;
- TAMRA (5(6)-carboxytetramethylrhodamine) fluoresces a yellow-orange color at around 563 nanometers; and
- JOE (4',5'-dichloro-2',7'-dimethoxy-5(6)-carboxyfluorescein) fluoresces a yellow-green color at around 554 nanometers.

EX1003 at 13:46-14:2; EX1004 at 14:1-3 (“FAM, VIC, ROX, TAMRA, JOE, etc., among others.”). Jouvenot’s inclusion of the phrase “etc., among others,” making the phrase an open-ended list, contemplates the inclusion of additional fluorophores even beyond those listed. EX1003 at 13:46-14:2; EX1004 at 14:1-3. Each of these fluorophores would have been suitable for generating electromagnetic signals at wavelengths for detection. In this regard, Jouvenot teaches not just four channels, but more than four channels, including six or more.

112. To the extent that Patent Owner claims that the use of four or more distinct signals, wavelengths, or fluorophores is not disclosed by Jouvenot, it is my

opinion that the use of such numbers of color channels is at least obvious in view of Jouvenot. A POSA would understand that the assay Jouvenot discloses can easily be used with four or more channels, colors, wavelengths, and fluorophores, including six or more. A POSA would also understand that the concepts Jouvenot teaches can extend to the use of four or more fluorophores in a multiplexed assay, which can be used simultaneously to detect signals from multiple analytes. Jouvenot already discloses more than four fluorophores by name—e.g., “FAM, VIC, ROX, TAMRA, JOE, and others”—which a POSA would understand as capable of generating electromagnetic signals at more than four distinct wavelengths or colors. EX1003 13:46-14:2; EX1004 at 14:1-3. A POSA would have not just known that this was possible but would have also desired to expand the assay of Jouvenot to include four or more colors and channels, including six or more.

113. Indeed, as Jouvenot expressly states, a POSA would have understood that “many applications, especially where sample is limited, could benefit greatly from higher degrees of multiplexing.” EX1003 at 2:18-20; EX1004 at 1:24-2:2. In other words, a POSA would have been motivated to increase the number of color channels so that he or she could detect more targets at the same time. Jouvenot also recognizes that multiplexing can be accomplished with many optical channels to detect many wavelengths of light. EX1003 at 2:18-20; EX1004 at 1:24-2:2. Indeed,

Jouvenot states that its assays may be “extended” to specifically detect some targets in one color channel and other targets in other color channels. *See* EX1003 at 5:18-31; EX1004 at 5:14-19. The ’797 patent also explains that “[m]any real-time PCR and quantitative PCR instruments comprise an excitation light source and band pass filters that enable the detection of fluorescent signals in four colors (e.g., blue, green, yellow, and red). Therefore, the methods of the invention can be readily applied using instruments widely used in the art.” EX1001 at 35:30-35. In other words, the ’797 patent establishes that there had been pre-existing motivation in the art to use four or more color channels and that there would have been a reasonable expectation of successfully doing this because there were “many” pre-existing instruments that already offered precisely this functionality.

114. As further evidence of motivation in the art to use four or more color channels and reasonable expectation of successfully doing so, consider the Larson reference, which, as explained below, expressly describes an assay little different from Jouvenot’s assay. Larson teaches the use of the detection of multiple analytes in multiple optical channels throughout for the purpose of increasing the number of targets one can detect:

- “In another aspect of the invention, *adding multiple colors increases the number of possible reactions geometrically*, rather than linearly as with

qPCR, because individual reactions can be labeled with multiple fluorophores.” EX1013 ¶ 47 (emphasis added).

- “Another method of the invention involves performing higher-plex assays using *multiple different probe colors (i.e. fluorophores)*.” *Id.* ¶ 139 (emphasis added).
- “Another method of the invention involves performing higher-plex assays using *multiple different probe colors (i.e. fluorophores)*, however unlike the strategy above where each target is identified by single type of probe with a unique color and intensity, instead in this method *a single target may be identified by multiple probes that constitute a unique signature of both colors and intensities.*” *Id.* ¶ 140 (emphasis added).
- “A method of the invention involves optimizing the pattern of colors and intensities of the different probes for maximum multiplexing while still achieving adequate specificity for each individual reaction. Although rectangular arrays of droplet populations were demonstrated for the 5- and 9-plex reactions, another desirable pattern is the tight-packed hexagonal array. However the invention is not constrained to any particular array strategy.” *Id.* ¶ 152.

- “As described above, it is anticipated that greater numbers of colors will be used for both multiplexing and for optical labels. Hence, embodiments of the invention include histograms of dimensionality greater than two, such as 3, or 4, or up to 10, or up to 20. Histograms of dimensionality greater than 20 are also incorporated into the invention.” *Id.* ¶ 166.

To help understand why such disclosure in Larson is so directly relevant to the question of motivation to use more than four channels in a system like that of Jouvenot’s and expectation of success, consider that Larson’s Fig. 11a shows a scheme for the multiplexed detection of analytes that is just like the scheme in Jouvenot for detecting all possible combinations of two targets in a single color channel:

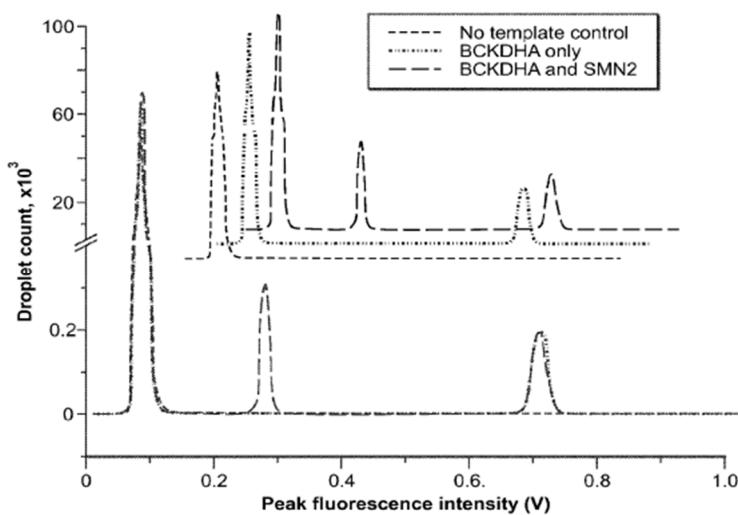


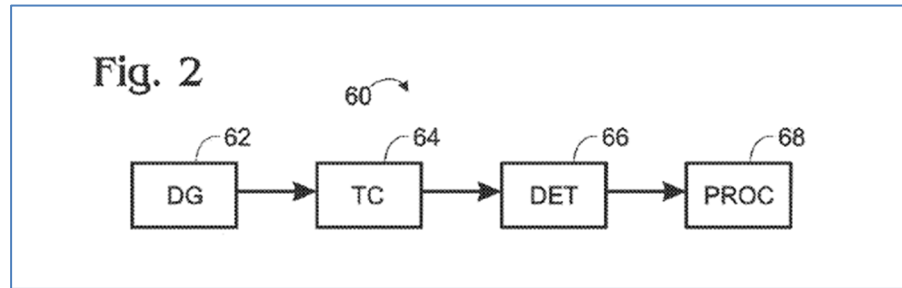
FIG. 11a

Id. at Fig. 11a. As described in § IX.B.1, *supra*, Larson teaches an experiment using two targets, wherein “three populations” of droplets “were readily apparent,” with peaks at 0.08 V, 0.27 V, and 0.71 V, and a “very small peak appeared at ~0.9 V, not visible on the scale of FIG. 11a, that corresponded to droplets occupied by both genes.” EX1013 ¶¶ 130-31. Thus, Larson’s disclosure of multiple color channels provides confirmation that a POSA would have been motivated to use four or more color channels in a system like that of Jouvenot Example 1 and would have expected success in doing so.

115. Accordingly, a POSA would have understood that Jouvenot discloses the use of a multi-channel detector, configured to detect multiple electromagnetic signals, at multiple wavelengths, emitted from multiple fluorophores.

4. a processor controlled analyzer to

116. It is my opinion that Jouvenot discloses “a processor controlled analyzer.” In Figure 2, reproduced below, Jouvenot discloses a processor: “FIG. 2 shows an exemplary system 60 for performing the digital assay of FIG. 1. System 60 may include . . . *a data processing assembly (a data processor) 68 (“PROC”)*, or any combination thereof, among others.” EX1003 at 12:53-59; EX1004 at 11:13-16.



EX1003 at Fig. 2; EX1004 at Fig. 2. Jouvenot elaborates that the processor “may be, or may be included in, a controller that communicates with and controls operation of any suitable combination of the assemblies.” EX1003 at 12:60-62; EX1004 at 11:16-18. The processor may also determine the number of droplets and/or target levels. EX1003 at 13:7-13; EX1004 at 12:6-10. Jouvenot also states that the assignment of droplets to particular outcomes may be performed using any suitable algorithm, further showing that the processor acts as an analyzer. EX1003 at 14:63-65; EX1004 at 15:30-31. In fact, to use an algorithm suitable for decoding data from a digital PCR assay, a POSA would almost certainly have used a processor-controlled analyzer (e.g., computer).

117. Jouvenot further discloses that this processor functions as an analyzer because the disclosed processor also can identify and analyze data. EX1003 at 13:4-12; EX1004 at 11:6-10 (“The signals may be processed by processor 68.”); *see also* EX1003 at 14:26-28; EX1004 at 14:23-15:2 (“The signal may be *analyzed* to determine whether neither Target, Target 1 alone, Target 2 alone, or both Targets 1

and 2 are present in each droplet”). Thus, the processor of Jouvenot is a “processor controlled analyzer.”

118. Accordingly, a POSA would have understood that Jouvenot discloses the use of a “processor controlled analyzer.”

- a. **receive, from the multi-channel detector, a cumulative signal based on the first, second, third, and fourth electromagnetic signals and**

119. It is my opinion that the processor disclosed in Jouvenot is configured to receive a cumulative signal from the multi-channel detector, wherein the cumulative signal is “based on” the combination of the four or more electromagnetic signals described above.

120. As I explain in Section X.A.3, *supra*, Jouvenot discloses, or at least renders obvious, a multi-channel detector for four or more channels, and a processor that receives signals from that detector. EX1003 at 12:53-59; EX1004 at 11:12-16. Jouvenot also explains that this multi-channel detector is configured to detect multiple electromagnetic signals at multiple wavelengths emitted from multiple fluorophores. EX1003 at 5:18-31; EX1004 at 5:14-21. Jouvenot further teaches that these signals may be cumulative or composite signals:

The light detected from each reporter may be light emitted from a luminophore (e.g., a fluorophore). The light detected in a given channel may be detected such that light from different reporters is ***summed or accumulated*** without attribution to a particular reporter. Thus, the

signal for a given channel may be a *composite signal* that represents two, three, *four, or more assays* and thus two, three, *four, or more targets.*”).

EX1003 at 8:40-47; EX1004 at 9:5-10; *see also* EX1003 at 4:56-60; EX1004 at 4:19-23 (“The reporters may include the same fluorophore, such as FAM or VIC, or different fluorophores with similar spectral characteristics, so that light from *two or more fluorophores can be collected simultaneously* in the same optical channel.”).

121. The specification further contemplates that the processor may receive these signals from the multi-channel detector. As shown in Figure 2, those signals are detected by a detector, then transmitted to a processor. EX1003 at Fig. 2, 12:62-66; EX1004 at Fig. 2, 11:23-12:2 (“The arrows between the assemblies indicate movement or transfer of . . . signals/data, between the assemblies.”). Further, Jouvenot explains that the disclosed processor can analyze data from multiple channels:

In the same or other embodiments, some targets may be analyzed in one channel (e.g., a FAM channel), and other targets may be analyzed in other channels (e.g., a VIC channel). Three targets, two in a first *channel and one in a second channel*, would again generate eight clusters or populations of data, but they would be separated in a two-dimensional intensity space and so in principle more easily resolvable.

EX1003 at 5:23-31; EX1004 at 5:14-21. In other words, Jouvenot teaches the use of a processor that receives and analyzes composite signals from a multi-channel detector. The system of Jouvenot therefore discloses a “processor controlled

analyzer to receive, from the multi-channel detector, a cumulative signal based on the first, second, third, and fourth electromagnetic signals.”

122. To the extent that Patent Owner contends that Jouvenot does not disclose a cumulative signal based on the first, second, third, and fourth electromagnetic signals (e.g., should Patent Owner argue that Jouvenot discloses no cumulative signals, or only a cumulative signal from fewer than four channels) it is my opinion that a POSA would find this limitation obvious in view of Jouvenot. As explained above, Jouvenot discloses a detector for the detection of signals in multiple channels, EX1003 at 12:53-59; EX1004 at 11:12-16, and explains that those signals may be summed or accumulated. EX1003 at 8:40-47; EX1004 at 9:5-10. Jouvenot also discloses a processor to receive and analyze those signals, as explained in Section X.A.4, *supra*, and the use of four or more fluorophores, as explained in Section X.A.3, *supra*. At a minimum, as I explain above, it would have been obvious to a POSA to combine these elements and extend the use of the system disclosed in Jouvenot to include a processor to receive and analyze a composite signal of four or more wavelengths, detected in four or more channels, from four or more fluorophores. *See* EX1003 at 13:46-14:2; EX1004 at 13:10-14:3 (describing aspects of multiplexing and use of multiple fluorophores); EX1003 at 5:27-31; EX1004 at 5:19-21 (describing the detection of multiple fluorophores in multiple channels).

Using the cumulative signal based on the first, second, third, and fourth electromagnetic signals would also allow for the unambiguous detection of the specific combination of at least eight different target analytes present in a droplet (i.e., two targets for each channel).

123. Accordingly, a POSA would have understood that Jouvenot discloses or at least renders obvious the use of a processor controlled analyzer that receives, “from the multi-channel detector, a cumulative signal based on the first, second, third, and fourth electromagnetic signals.”

b. apply a decoding matrix to the cumulative signal to unambiguously detect the presence or absence of at least each of M analytes

124. It is my opinion that the processor disclosed in Jouvenot is configured to “apply a decoding matrix to the cumulative signal to unambiguously detect the presence or absence of at least each of M analytes.”

125. The '797 patent explains how a decoding matrix can supposedly be used, according to the claims, to unambiguously detect the presence or absence of analytes. The word “decoding,” in the '797 patent, “generally refers to a method of determining which analytes are present based on the cumulative signal and a coding scheme or *decoding matrix that enables the conversion of a cumulative signal to information* concerning the presence or absence of one or more analytes.” EX1001

at 10:20-25. Thus, using a processor controlled analyzer to apply a decoding matrix, one can supposedly identify, from the cumulative signal, the presence or absence of analytes in solution.

126. Table 8 shows one example of a decoding matrix:

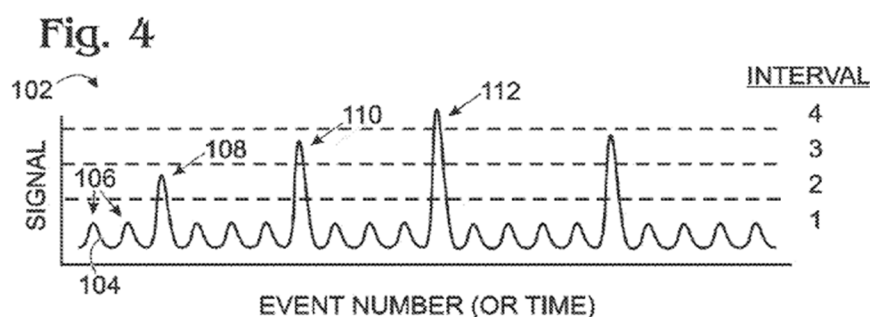
TABLE 8					
Example of encoding method using one color and one intensity per analyte, but different intensities among analytes.					
Tier	Analyte	B	G	Y	R
1	A	1	0	0	0
	B	2	0	0	0
	C	4	0	0	0
	D	8	0	0	0
2	E	0	1	0	0
	F	0	2	0	0
	G	0	4	0	0
	H	0	8	0	0
3	I	0	0	1	0
	J	0	0	2	0
	K	0	0	4	0
	L	0	0	8	0
4	M	0	0	0	1
	N	0	0	0	2
	O	0	0	0	4
	P	0	0	0	8
		15	15	15	15

Id. at 22:10-30 (Table 8). This matrix purports to show how one can identify samples by assigning intensity values that can be unambiguously detected in any combination. *Id.* For example, in the blue channel, a signal of intensity 1 can be unambiguously assigned to analyte A, a signal of intensity 2 can be unambiguously assigned to analyte B, and a signal of intensity 3 is an unambiguous combination of analytes A and B. *Id.* One can similarly detect analytes E, F, G, and H with the same system in the green channel, and so on. *Id.* By assigning unambiguous

intensity values that are capable of detection in any combination, one can supposedly determine whether analytes are present or absence in any combination.

127. As in Table 8, the idea is that one can unambiguously detect multiple targets in the same channel by assigning analytes intensity values that are powers of 2: 1 (2^0), 2 (2^1), 4 (2^2), 8 (2^3), 16 (2^4), 32 (2^5), and so forth. This exponential pattern also appears when considering the number of unique intensity combinations as a function of the number of analytes in the system. For example, a system for testing two analytes will necessarily need four groups of data corresponding to 2^2 (4) groups: one group with no analytes; a second group with only the first analyte present; a third group with only the second analyte present; and a fourth group with both analytes present. Similarly, a system with three analytes will produce 2^3 (8) groups, and a system with four analytes will produce 2^4 (16) groups. Thus, this intuitive mathematical scheme forms the basis for the decoding system of the '797 patent. The same pattern is disclosed by Jouvenot, which explains that a system will produce a number of clusters of similar intensity that corresponds to 2^N , where N is the number of analytes. EX1003 at 10:23-26; EX1004 at 10:13-14 ("The data including all permutations of positives will generally fall into 2^N populations or clusters, where N is the number of targets, assuming that each population is distinguishable.").

128. Jouvenot's Example 1 teaches the same system and pattern in the '797 patent's Table 8, especially Jouvenot's Figure 4, reproduced below, which shows a system utilizing a decoding matrix analogous to that of Table 8 the '797 patent, wherein analytes are assigned an unambiguous signal (i.e., a unique value of wavelength and intensity) that can be detected in any combination:



EX1003 at Fig. 4; EX1004 at Fig. 4. Jouvenot explains how the intensities in Figure 4 can be used to identify different combinations of two different targets in one channel:

Peaks 106 with maxima in Interval 1 correspond to droplets containing no Target (T1-/T2-). The measured signal corresponds to background (e.g., background fluorescence, scattering, etc.) and does not reflect the presence or amplification of either Target.

Peaks 108 with maxima in Interval 2 correspond to droplets containing Target 1 but not containing Target 2 (T1+/T2-). The measured signal corresponds to signal from Target 1 plus background and reflects amplification of Target 1 implying the presence of Target 1.

Peaks 110 with maxima in Interval 3 correspond to droplets containing Target 2 but not containing Target 1 (T1-/T2+). The measured signal corresponds to signal from Target 2 plus background and reflects amplification of Target 2 implying the presence of Target 2.

Peaks 112 with maxima in Interval 4 correspond to droplets containing both Targets 1 and 2 (T1 +/T2+). The measured signal corresponds to signal from both Targets 1 and 2 plus background and reflects amplification of Targets 1 and 2 implying the presence of Targets 1 and 2.

EX1003 at 14:36-56; EX1004 at 15:5-24. Background signals (labeled 106) in a first interval below a lower threshold correspond to samples with no analytes present. Signals (labeled 108) in a second interval above a lower threshold and below a middle threshold correspond to a sample with only the first analyte present. Signals (labeled 110) in a third interval above a middle threshold and below an upper threshold correspond to a sample with only the second analyte present. Finally, signals (labeled 112) above an upper threshold correspond to a sample wherein both analytes are present. Based on the intervals and thresholds, one can unambiguously determine whether the first or second analyte, both, or neither are present. This system, which examines two analytes, will produce $2^2=4$ intervals or clusters of data.

129. The Figure 4 intensities can be assigned integer values—1, 2, 3, and 4—as depicted in matrix form below:

Target	Intensity
No Targets	0
Target 1	1
Target 2	2

Target	Intensity
Target 1 + Target 2	3

This is analogous to the encoding matrix disclosed in Table 8 of the '797 patent, where the first and second analytes are given intensities of 1 and 2, respectively. EX1001 at 21:65-67 (“Table 8 . . . illustrat[es] four tiers of encoding based on four colors and intensities 1, 2, 4, and 8.”). Adding a third and fourth analyte in the channel of this matrix would require assigning intensity 4 for the first, and intensity 8 for the second, so as not to overlap with the intensities in the matrix. The resulting decoding matrix would be:

Target	Intensity
No Targets	0
<i>Target 1</i>	<i>1</i>
<i>Target 2</i>	<i>2</i>
Target 1 + Target 2	3
<i>Target 3</i>	<i>4</i>
Target 1 + Target 3	5
Target 2 + Target 3	6
Target 1 + Target 2 + Target 3	7

Target	Intensity
<i>Target 4</i>	8
Target 1 + Target 4	9
Target 2 + Target 4	10
Target 1 + Target 2 + Target 4	11
Target 3 + Target 4	12
Target 1 + Target 3 + Target 4	13
Target 2 + Target 3 + Target 4	14
Target 1 + Target 2 + Target 3 + Target 4	15

The emphasized single target entries in the encoding matrix reflect the same scheme as Figure 8 within a single channel. Each analyte is detected by an intensity that is a power of 2. Were the spaces between analytes smaller, there would be ambiguity or degeneracy in the detection scheme.

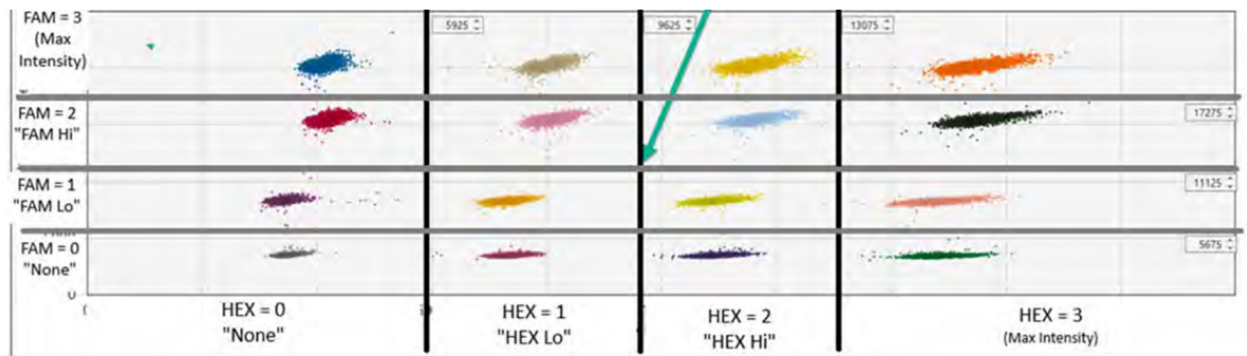
130. Patent Owner's own infringement contentions in the District Court litigation reflect this interpretation. In the parallel District Court proceedings, Patent Owner contends that Petitioner infringes claim 1 of the '797 patent. Specifically,

Patent Owner accuses Petitioner's QX600 and QX ONE products of infringement based on the same threshold approach as seen in Jouvenot's Figure 4:

- “The thresholds above thus are understood to discretize the signal intensity values measured on each of the two channels on each plot into four levels 0, 1, 2, and 3.” EX1009 at 49.
- The “processor controlled analyzer (e.g., a computer connected to the QX600 Droplet Reader running the QX Manager Software) *uses the thresholds to set the boundaries of discrete signal intensity levels* discrete channel intensity levels (e.g., None, Hi, Lo).” *Id.* at 47, 51, 190 (emphasis added).
- “The boundaries of these discrete channel intensity levels are set by thresholds.” *Id.* at 48-49.
- “Overlaying the discretized signal intensity levels described above in relation to the threshold lines shows how the specific regions relate to the detected signal intensity levels.” *Id.* at 54.
- “The processor controlled analyzer (e.g., a computer connected to the QX600 Droplet Reader running the QX Manager Software) *utilizes thresholds.*” *Id.* at 45-46 (emphasis added).

Patent Owner thus accuses Petitioner of using the same system of assigning threshold values as seen in Figure 4 and described above.

131. In its infringement contentions, Patent Owner assigns integer values to large intensity ranges based only on threshold lines. In the below figure, where patent owner assigns integer values of 0, 1, 2, and 3 to intensities in FAM and HEX channels:



Id. at 50 (notation of discretized channel signal intensity levels and threshold line emphasis added by Patent Owner). Patent Owner alleges that these thresholds reflect the claimed integer values. To the extent this is so, the system in Jouvenot's Example 1 and Figure 4—wherein all four combinations of two different targets are detected by four distinct intensity levels in a single color channel—discloses the same thing. Patent Owner also expressly describes this threshold approach:

On information and belief, the processor controlled analyzer (e.g., a computer connected to the QX600 Droplet Reader running the QX Manager Software) ***applies a decoding matrix*** to assign the above target analyte combinations to the available regions formed by the discretized signal channel levels, and then droplet data with signal channel levels falling within a given discretized signal channel region is associated with the target analyte combination assigned to that region.

Id. at 55. Jouvenot’s Example 1 uses the same threshold approach as Petitioner’s QX600 and QX ONE products. This is further illustrated by the matrix Patent Owner attached to the infringement contentions:

Analyte	FAM	HEX	Cy5	Cy5.5	ROX	ATTO 590
a	1	0	0	0	0	0
b	2	0	0	0	0	0
c	0	1	0	0	0	0
d	0	2	0	0	0	0
e	0	0	1	0	0	0
f	0	0	2	0	0	0
g	0	0	0	1	0	0
h	0	0	0	2	0	0
i	0	0	0	0	1	0
j	0	0	0	0	2	0
k	0	0	0	0	0	1
l	0	0	0	0	0	2

Id. at 56-57. This matrix shows the same type of decoding system as in Table 8; a signal of 0 corresponds to the presence of no analytes in that channel, while a first analyte is encoded as intensity 1, and a second is encoded as intensity 2. The presence of both analytes can be detected at intensity 3. Both systems use the same progression in each channel.

132. Thus, Patent Owner’s own infringement contentions support a finding that the ’797 patent is obvious in view of Jouvenot because the same overall scheme they now accuse of infringing based on detecting the four different combinations of two targets using four different intensity levels of a single color had long since been disclosed in Jouvenot.

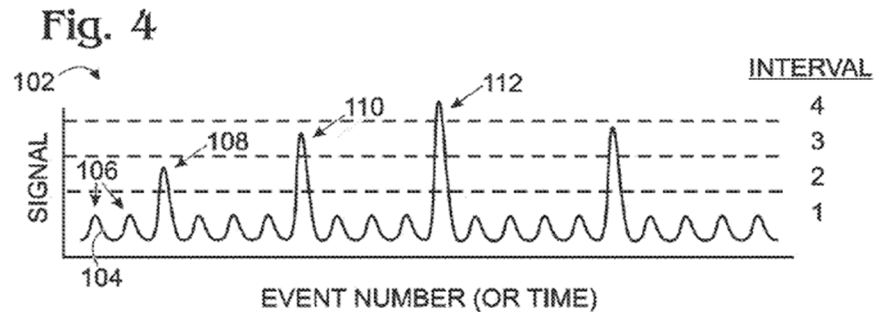
133. What's more, as I explain above, Jouvenot (and Larson) contemplate, or at least render obvious, performing detection in four or more channels for the express purpose of increasing the number of targets that one can detect. *See* Section IX, *supra*. The '797 patent, in fact, makes clear that four color instrumentation had previously existed in "many" incarnations. EX1001 at 35:30-35. In view of this, it would have been a no-brainer for a skilled artisan to simply take the scheme disclosed in Figure 4 of Jouvenot and, rather than use it in one color channel, duplicate it in four or more independent color channels to detect more targets. This would have been nothing more than the straightforward idea of, for instance, digging a hole faster and deeper by using multiple workers each with their own shovel rather than having a single worker do the task with just one shovel. Because the detection scheme in Figure 4 of Jouvenot works in one channel, it will work equally well in multiple independent channels and a POSA interested in detecting larger number of targets would have been motivated to do precisely this with a reasonable expectation of success. A POSA would have understood that doing this would be nothing more than scheme depicted in Figure 8 of the '797 patent, which is not novel or inventive but rather obvious. This pattern forms the basis of encoding and decoding the systems of both Jouvenot and the '797 patent for the unambiguous detection of the presence or absence of any number of analytes.

134. In my opinion, the remaining elements of this limitation are also disclosed by Jouvenot. Jouvenot explains that this decoding may be done by a processor: EX1003 at 13:10-11; EX1004 at 12:9-10 (“Signals may be processed by processor 68”). Jouvenot also explains that this decoding matrix-based detection method, including that shown in Figure 4, can be used for the unambiguous detection of analytes. EX1003 at 14:65-15:1; EX1004 at 15:31-33 (“In the example above, peak heights (i.e., intensity values) associated with each outcome are sufficiently different that each can be unambiguously identified and assigned.”). And, as explained below, this detection would have been limited to M analytes. *See Section X.A.4, infra.*

135. Accordingly, a POSA would have understood that Jouvenot discloses or at least renders obvious the use of a processor controlled analyzer to “apply a decoding matrix to the cumulative signal to unambiguously detect the presence or absence of at least each of M analytes.”

- c. **by associating, for each analyte, a first value in a first component of the cumulative signal and a second value in a second component of the cumulative signal, wherein each first value is an intensity or range of intensities and each second value is a wavelength or a range of wavelengths, and wherein the second values comprise the first, second, third, and fourth wavelengths,**

136. It is my opinion that this limitation is disclosed by Jouvenot's Figure 4, which is part of Example 1:



EX1003 at Fig. 4; EX1004 at Fig. 4. In this figure, the “signal is created from light detected over time in a single channel.” EX1003 at 14:26-28; EX1004 at 14:20-21. The intensity of each signal is assigned a particular threshold or interval corresponding to the presence or absence of each target. EX1003 at 14:31-56; EX1004 at 15:1-24. The intervals on the right side of Figure 4 show how whole-number values can be assigned for each intensity. The peaks of Figure 4 (106, 108, 110, and 112) show signals of four different intensities in different intervals. Thus, Figure 4 teaches “associating, for each analyte, a first value in a first component,” which is the intensity of the signal.

137. As set forth in Section X.4b, *supra*, the decoding matrix of Jouvenot also illustrates the process of assigning a second value (wavelength):

The signal may represent an aspect of light, *such as the intensity of the light, detected in the same optical channel* from reporters for two or more distinct targets. The signals optionally may include *data collected*

in two or more different optical channels (e.g., in different wavelength ranges (wavebands) and/or color regimes) from reporters for the same and/or different targets). The light detected from each reporter may be light emitted from a luminophore (e.g., a fluorophore). The light detected in a given channel may be detected such that light from different reporters is summed or accumulated without attribution to a particular reporter.

EX1003 at 8:32-47; EX1004 at 8:24-9:5. This passage clarifies that the signals may be associated with **both** intensity and wavelength/color. Thus, Jouvenot teaches “associating, for each analyte, a first value in a first component of the cumulative signal and a second value in a second component of the cumulative signal, wherein each first value is an intensity or range of intensities, and each second value is a wavelength or a range of wavelengths.”

138. Further, it is my opinion that a POSA would find it obvious to extend the system of Jouvenot to include an assay “wherein the second values comprise the first, second, third, and fourth wavelengths”—or, in other words, to identify analytes using multiple wavelengths of light. As explained in Section X.A.3, *supra*, Jouvenot discloses the use of multiple fluorophores, wavelengths, and colors. EX1003 at 13:46-14:2; EX1004 at 14:10-15:3. As further explained in Section X.A.4.a, *supra*, Jouvenot also teaches the use of composite signals. See EX1003 at 8:40-47; EX1004 at 9:910 (“Thus, the signal may be a composite signal that represents two, three, four, or more reactions and thus two, three, four, or more targets of the reactions.);

EX1003 at 4:56-60; EX1004 at 4:20-23 (“The reporters may include the same fluorophore, such as FAM or VIC, or different fluorophores with similar spectral characteristics, so that light from each reporter can be collected simultaneously in the same channel.”). And, as further described in Section X.A.3, *supra*, a POSA would understand that, in some applications, a higher degree of multiplexing is beneficial. Duplicating the system of Figure 4 of Jouvenot across multiple color channels would have been a no-brainer for a skilled artisan and, as I note above, would have been nothing more than the straightforward idea of, for instance, digging a hole faster and deeper by using multiple workers each with their own shovel rather than having a single worker do the task with just one shovel.

139. Thus, it would be obvious to a POSA to extend the assays of Jouvenot by duplicating it across different channels and fluorophores such that “the second values comprise the first, second, third, and fourth wavelengths,” or the use of four colors or wavelengths. Accordingly, a POSA would have understood that Jouvenot, discloses or renders obvious the use of a processor controlled analyzer “by associating, for each analyte, a first value in a first component of the cumulative signal and a second value in a second component of the cumulative signal, wherein each first value is an intensity or range of intensities and each second value is a

wavelength or a range of wavelengths, and wherein the second values comprise the first, second, third, and fourth wavelengths.”

5. and the determination is made without immobilization, mass spectrometry or melting curve analysis;

140. Jouvenot also does not discuss—because the disclosed system does not include—immobilization, mass spectrometry, or melting curve analysis. A POSA would understand that the assay system disclosed in Jouvenot, like the one described in the '797 patent, does not involve the use of any of these techniques. As described above, Jouvenot teaches the analysis of samples by moving a fluid stream through a single channel, which is brought into an examination area where the light emitted from fluorophores is analyzed. A POSA would understand that this method does not require, and is inconsistent with, immobilization, mass spectrometry, and melting curve analysis. Instead, the Jouvenot method relies purely on the spectroscopic analysis of molecules in solution, which can be done simply by analyzing the light emitted from a droplet after excitation.

141. Accordingly, a POSA would have understood that Jouvenot discloses a system for the detection of analytes without immobilization, mass spectrometry, or melting curve analysis.

6. wherein for the positive integer M , $M=C*\log_2(F+1)$, F is a positive integer and is equal to the maximum cumulative

intensity of the first component of the signal, for any second value, when all of the analytes are present, and $C=4, 5$, or 6 ;

142. It is my opinion that this limitation, “wherein for the positive integer M , $M=C*\log_2(F+1)$, F is a positive integer and is equal to the maximum cumulative intensity of the first component of the signal, for any second value, when all of the analytes are present, and $C=4, 5$, or 6 ,” which merely describes the use of an intuitive mathematical formula, is disclosed or at a minimum obvious in view of Jouvenot.

143. This limitation merely describes the use of an intuitive mathematical scheme that is part of the schemes disclosed in Jouvenot. Table 8 of the '797 patent shows a decoding matrix that satisfies these mathematical requirements. In particular, the scheme in table at satisfies the equation $M=C*\log_2(F+1)$, where:

- $C=4$ (four channels/colors);
- $F=15$ (maximum cumulative intensity when all analytes are present);
- $F+1=16$, a positive integer, and a power of 2 ($2^4=16$);
- $M=C*\log_2(F+1)=4*\log_2(15+1)=16$ (number of analytes detectable, A through P);
- $M > C$ ($16 > 4$); and
- M and C are positive integers.

TABLE 8					
Example of encoding method using one color and one intensity per analyte, but different intensities among analytes.					
Tier	Analyte	B	G	Y	R
1	A	1	0	0	0
	B	2	0	0	0
	C	4	0	0	0
	D	8	0	0	0
2	E	0	1	0	0
	F	0	2	0	0
	G	0	4	0	0
	H	0	8	0	0
3	I	0	0	1	0
	J	0	0	2	0
	K	0	0	4	0
	L	0	0	8	0
4	M	0	0	0	1
	N	0	0	0	2
	O	0	0	0	4
	P	0	0	0	8
		15	15	15	15

EX1001 at 22:10-30 (Table 8). Thus, the decoding matrix of Table 8 reflects the intuitive mathematical equation that is the basis for claim 1; the same mathematical basis is disclosed in Jouvenot's Figure 4 and Example 1.

144. As described in § X.A.3, *supra*, it would be obvious to expand the system of Jouvenot for the use of four or more channels. This obvious four channel version of the system disclosed in Jouvenot's Example 1 satisfies all these requirements:

- C=4 (four channels);
- F=3 (maximum cumulative intensity at any wavelength when all analytes are present);
- F+1=4, a positive integer, and a power of 2 ($2^2=4$);

- $M = C * \log_2(F+1) = 4 * \log_2(3+1) = 8$ (the number of analytes detectable, two targets per channel across four channels);
- $M > C$ ($8 > 4$); and
- M and C are positive integers (8 and 4).

145. To the extent that Patent Owner claims that Jouvenot does not disclose every aspect of this equation (i.e., that Jouvenot does not disclose the use of a variable C to account for the use of this system with multiple channels or colors, or does not teach a system that includes the use of multiple channels or colors, such as a four-channel system), it is my opinion that this limitation is obvious in view of Jouvenot, as this equation simply takes the formula for detecting a single channel, multiplied by an integer number of channels C . The simplicity of this formula can be illustrated with an 8-analyte system where $C=4$. According to the language of claim 1 of the '797 patent (and as seen in Section X.A.7, *infra*), the variable C corresponds to “the second values used to encode the analytes (C),” and “the multi-channel detector comprises C channels”; in other words, C corresponds to the number of colors or wavelengths used to detect analytes, which equals the number of channels used for detection. EX1001 at 78:48-50. It follows that the expression (M/C) , or M divided by C , corresponds to the number of analytes detected in each channel. Thus, in an 8-analyte system using four different colors, $M=8$ (targets) and

$C=4$ (channels), such that $8=4*\log_2(F+1)$. Simplifying the equation (i.e., dividing each side of the equation by 4) provides the number of targets per channel, $(M/C)=2=\log_2(F+1)$. Solving for the remaining variable F provides $F=3$. This corresponds to a system where two analytes are detected per channel, where a first analyte is assigned a value of 1, a second analyte is assigned a value of 2, and a combination of the two is detected at a value of 3. Thus, $F=3$ corresponds to the “maximum cumulative intensity of the first component of the signal,” detected at any given wavelength (“for any second value”), “when all of the analytes are present.”

146. Each aspect of this limitation in the '797 patent is obvious in view of Jouvenot, including that “ F is a positive integer and is equal to the maximum cumulative intensity.” The use of the variable F is apparent because, when analytes are assigned intensity values that are integers, the total number of analytes that can be examined in a single channel is equal to $\log_2(F+1)$ when $F+1$ is a power of 2. The specification further explains that intensities (or a range of intensities) are to be *encoded*. See EX1001 at 2:1-5 By encoding an intensity (or a “range of intensities,”) as a positive integer value, the sum (or “maximum cumulative intensity”) is necessarily a positive integer. This is consistent with the scheme depicted in

Jouvenot's Figure 4, where signals are encoded as positive integer levels on the right side of the figure.

147. Accordingly, a POSA would have understood that Jouvenot discloses a system for the detection of analytes "wherein for the positive integer M , $M=C*\log_2(F+1)$, F is a positive integer and is equal to the maximum cumulative intensity of the first component of the signal, for any second value, when all of the analytes are present, and $C=4, 5$, or 6 ."

- 7. wherein $F+1$ is a positive integer and wherein $F+1$ is a power of 2, wherein M is greater than the number of the second values used to encode the analytes (C), the multi-channel detector comprises C channels, and M and C are positive integers.**

148. It is my opinion that Jouvenot discloses a system "wherein $F+1$ is a positive integer and wherein $F+1$ is a power of 2, wherein M is greater than the number of the second values used to encode the analytes (C), the multi-channel detector comprises C channels, and M and C are positive integers." As discussed above, it is my opinion that this limitation merely describes the use of an intuitive mathematical scheme that is fully disclosed by Jouvenot.

149. As discussed in Section X.A.6, *supra*, it would be obvious to a POSA that $F+1$ must be a positive integer. Jouvenot's specification explicitly describes this mathematically, noting that the "data including all permutations of positives will

generally fall into 2^N populations or clusters, where N is the number of targets” that can be detected using a single color signal. EX1003 at 10:23-25; EX1004 at 10:13-14. The inverse properties of logarithms and exponents show that these two expressions are equal—when examining data for M analytes, where each analyte and combination of analytes exhibits a nondegenerate intensity value, one can expect F+1 populations. Including one population when no analytes are present, the number of populations will be equal to F+1. The $\log_2$ of F+1 will provide the number of analytes that can be tested on that channel. Inversely, if one knows the number of analytes, M, the inverse expression 2^M will equal F+1, or the number of clusters. Thus, it would be obvious in view of Jouvenot that F+1 must be a positive integer and a power of 2.

150. Further, it would have been obvious to use the system disclosed in Jouvenot for the detection of M analytes “wherein M is greater than the number of the second values used to encode the analytes (C).” As explained in Jouvenot, it is useful to detect several analytes in fewer channels, because “instruments with more optical channels, to detect emission from an equivalent number of dyes, are more expensive than those with fewer channels.” EX1003 at 2:15-18. The claims of Jouvenot further describe detection of R analytes with fewer than R channels—equivalently disclosing a system where there are more analytes than channels or

colors used. EX1003 at 25:33-39. Thus, it would be obvious in view of Jouvenot to detect M analytes, wherein M is greater than the number of the second values (e.g., wavelengths or colors) used to encode the analytes.

151. Further, it would have been obvious in view of Jouvenot that “the multi-channel detector comprises C channels.” Jouvenot explicitly discloses this, noting that “[d]etector 66 may provide a plurality of optical channels in which data can be collected. The detector may have a distinct sensor or detection unit for each optical channel.” EX1003 at 13:4-6. In other words, Jouvenot describes a system wherein a multi-channel detector can detect channels equal to the number of colors or wavelengths (C) used to encode the analytes.

152. It would also have been obvious to a POSA that M and C are positive integers. A POSA would understand that, when counting real objects—such as analytes to be tested (M), or the number of wavelengths used to detect them (C)—one will traditionally use positive integers to count 1, 2, 3, 4, or more analytes or wavelengths.

153. Accordingly, a POSA would have understood that the mathematical equation and definitions, as described in this limitation, are merely an intuitive illustration of the system described in Jouvenot. Thus, this limitation is obvious in view of the systems and methods disclosed by Jouvenot.

B. Claim 2: The system of claim 1, wherein the multi-channel detector is further configured to detect:

a fifth electromagnetic signal at a fifth wavelength from the sample chamber, the fifth electromagnetic signal generated by excitement of a fifth fluorophore of the multiple fluorophores;

a sixth electromagnetic signal at a sixth wavelength from the sample chamber, the sixth electromagnetic signal generated by excitement of a sixth fluorophore of the multiple fluorophores;

and wherein C=6.

154. It is my opinion that a POSA would find claim 2 of the '797 patent obvious in view of Jouvenot. As explained in Section X.A.3, *supra*, it would have been obvious to expand the system of Jouvenot, particular Jouvenot's example 1 and Figure 4. It is my opinion that, for the same reasons described Section X.A.3, it is further obvious to extend the use of these assays to include a fifth and sixth electromagnetic signal from the sample chamber, generated from a fifth and sixth fluorophore.

155. Jouvenot contemplates extending the disclosed assays in "in various ways," including detecting different targets in different color channels. EX1003 at 5:19-31 ("assays may be extended in various ways."); EX1004 at 5:14-21; EX1003 at 5:18-31; EX1004 at 5:14-19. As I explain above, the Larson reference further would motivate a skilled artisan to use an increasing number of channels, including even up to 10 or 20. *See supra* ¶ IX.B.

156. For the foregoing reasons, it is my opinion that claim 2 of the '797 patent is obvious in view of Jouvenot.

C. Claim 5: The system of claim 1, wherein F=3.

157. It is my opinion that a POSA would find claim 5 of the '797 patent obvious in view of Jouvenot. As explained in § X.A.6, *supra*, the system wherein F=3 is disclosed in Jouvenot's Figure 4 and Example 1. Thus, claim 5 of the '797 patent is obvious in view of Jouvenot.

D. Claim 6: The system of claim 5, wherein the multiple fluorophores is selected from the group consisting of a blue fluorophore, a green fluorophore, a yellow fluorophore, a red fluorophore, and any combinations thereof.

158. It is my opinion that a POSA would find claim 6 of the '797 patent obvious in view of Jouvenot. Jouvenot already discloses the use of multiple fluorophores, including "FAM, VIC, ROX, TAMRA, JOE, etc., among others." EX1003 at 14:1-2; EX1004 at 14:2-3. As explained in § X.A.3, *supra*, A POSA would understand that:

- FAM (5(6)-carboxyfluorescein) fluoresces a green color at around 520 nanometers;
- VIC (2'-chloro-7'-phenyl-1,4-dichloro-5(6)-carboxyfluorescein) fluoresces a green-yellow color at around 543 nanometers;

- ROX (5(6)-carboxy-X-rhodamine) fluoresces an orange color at around 591 nanometers;
- TAMRA (5(6)-carboxytetramethylrhodamine) fluoresces a yellow-orange color at around 563 nanometers; and
- JOE (4',5'-dichloro-2',7'-dimethoxy-5(6)-carboxyfluorescein) fluoresces a yellow-green color at around 554 nanometers.

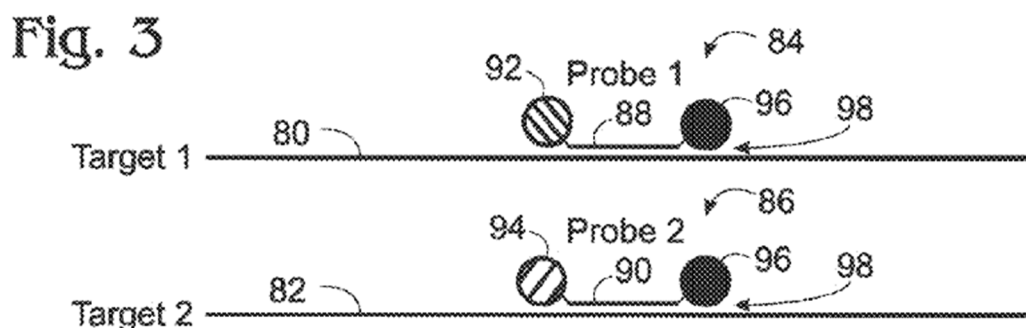
EX1003 at 13:46-14:2; EX1004 at 14:1-3. A POSA would have had a reasonable expectation of success in using these fluorophores because they were well-known off-the-shelf components in the art that were known to work well for PCR analysis. Moreover, because Jouvenot discloses only green and yellow fluorophores (FAM, VIC, ROX, TAMRA, and JOE), any combination of four Jouvenot-disclosed fluorophores would all be either green and/or yellow. Therefore, a POSA using any combination of the five fluorophores disclosed by Jouvenot with the obvious four-channel version of Example 1 would meet this claim.

159. This is supported by Patent Owner's infringement contentions, wherein Patent Owner does not allege that Petitioner uses a blue fluorophore. EX1009 at 78-84. For the same reason, I understand that the specific use of a red fluorophore is also not required.

160. For the foregoing reasons, it is my opinion that claim 6 of the '797 patent is obvious in view of Jouvenot.

E. Claim 10: The system of claim 5, wherein the analyte-specific hybridization probes are labeled with a fluorophore of the multiple fluorophores.

161. It is my opinion that claim 10 of the '797 patent is disclosed by Jouvenot. In particular, § X.A.2, *supra*, describes the hybridization probes used in Jouvenot to include the multiple fluorophores. Further, Example 1 of Jouvenot, including Figure 3 (reproduced below) clearly describes analyte-specific hybridization probes that are labeled with fluorophores:



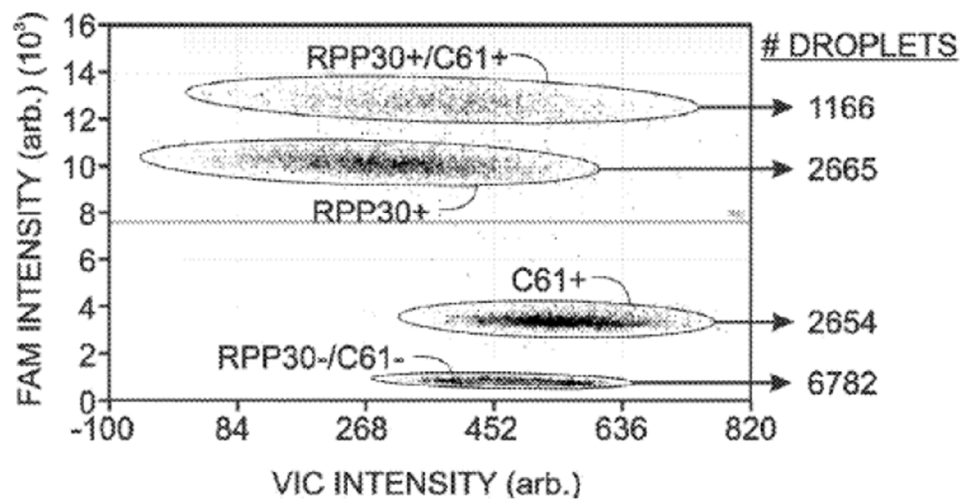
EX1003 at Fig. 3, 13:29-32; EX1004 at Fig. 3, 12:20-13:5 (“Each *probe* may include . . . a *fluorophore* 92, 94”).

162. For the foregoing reasons, it is my opinion that claim 10 of the '797 patent is obvious in view of Jouvenot.

F. Claim 18: The system of claim 5, further comprising a display coupled to the processor controlled analyzer to visualize a plot of the first and second values.

163. It is my opinion that a POSA would find it obvious to use “a display coupled to the processor controlled analyzer to visualize a plot of the first and second values,” as in claim 18 of the '797 patent, in view of Jouvenot. First, Jouvenot includes in its disclosure plots of the values obtained from the system of Jouvenot, such as in Figure 5:

Fig. 5



EX1003 at Fig. 5; EX1004 at Fig. 5. This figure shows, on each axis, the intensity of signals collected at a particular wavelength. *See also* EX1003 at Fig. 7; EX1004 at Fig. 7 (showing a similar visual depiction of data). Thus, for each second value (wavelength), data is plotted according to the intensity at that wavelength. By using

the origin on the left and bottom of the plot, one can identify, the intensity of a particular signal in both the FAM and VIC channels.

164. It would have been obvious to a POSA to visualize data using a display in this way, especially because wavelength and intensity are very commonly used to construct graphical depictions of fluorescence, and because the use of a display coupled to a processor was common in the art. Accordingly, it is my opinion that claim 18 of the '797 patent is obvious in view of Jouvenot.

XI. GROUND 1(a): CLAIMS 6-9 ARE OBVIOUS IN VIEW OF JOUVENOT, LARSON, BRABETZ, AND/OR LAKOWICZ

165. It is my opinion that claims 6-9 of the '797 patent are obvious in view of the combination of Jouvenot, Larson, Brabetz, and/or Lakowicz.

A. claim 6: The system of claim 5, wherein the multiple fluorophores is selected from the group consisting of a blue fluorophore, a green fluorophore, a yellow fluorophore, a red fluorophore, and any combinations thereof.

166. It is my opinion that, to the extent claim 6 of the '797 patent is not obvious in view of Jouvenot, it is obvious in view of Jouvenot in combination with Larson, Brabetz, and/or Lakowicz.

167. First, as described in § X.A.3, *supra*, Jouvenot discloses the use of, by common name, at least five different fluorophores that emit light at different wavelengths. These include FAM, VIC, ROX, TAMRA, and JOE, which include at

least green and yellow fluorophores. EX1003 at 13:46-14:2; EX1004 at 14:1-3. A

POSA would understand that:

- FAM (5(6)-carboxyfluorescein) fluoresces a green color at around 520 nanometers;
- VIC (2'-chloro-7'-phenyl-1,4-dichloro-5(6)-carboxyfluorescein) fluoresces a green-yellow color at around 543 nanometers;
- ROX (5(6)-carboxy-X-rhodamine) fluoresces an orange color at around 591 nanometers;
- TAMRA (5(6)-carboxytetramethylrhodamine) fluoresces a yellow-orange color at around 563 nanometers; and
- JOE (4',5'-dichloro-2',7'-dimethoxy-5(6)-carboxyfluorescein) fluoresces a yellow-green color at around 554 nanometers.

168. Second, Larson provides additional disclosure of the use of multiple fluorophores, including at least additional blue and red fluorophores. A POSA would understand that:

- DAPI, or 4',6-diaminidino-2-phenylindole, fluoresces a blue color at approximately 461 nanometers; and
- Cy5 and Cy5.5, which are both cyanine derivatives, fluoresce red colors at approximately 670 and 695 nanometers, respectively.

EX1013 ¶ 90. Larson further discloses a wide variety of additional fluorophores which a POSA would have understood to be compatible with the system described in both Jouvenot and the '797 patent.

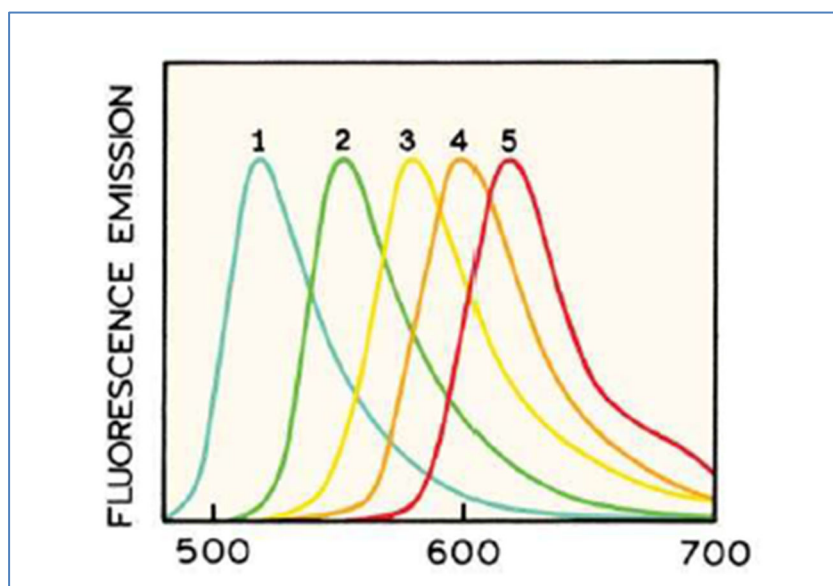
169. Third, Brabetz discloses a variety of blue, green, yellow, and red fluorophores in Table 1, which is reproduced below:

TABLE 1					
Known fluorescent dye combinations and virtual filtersets for ABI Prism ® Genetic Analyzers.					
Fluorescence dye combinations and colour canals					
Blue	Green	Yellow	Red	Orange (far red)	Recommended virtual filterset
6-FAM	JOE	TAMRA	ROX	—	F or A
6-FAM	TET	HEX	TAMRA	—	C
5, 6-FAM	JOE	TAMRA	ROX	—	F or A
6-FAM	JOE	NED	ROX	—	F
6-FAM	HEX	NED	ROX	—	F or D
6-FAM	VIC	NED	PET	LIZ	G5

5, 6-FAM: 5- and 6-carboxyfluorescein;
6-FAM: 6-carboxyfluorescein;
JOE: 6-carboxy-4', 5'-dichloro-2', 7'-dimethoxy-fluorescein;
HEX: 4,7,2',4',5',7'-hexachloro-6-carboxy-fluorescein;
TET: 4,7,2',7'-tetrachloro-6-carboxy-fluorescein;
TAMRA: 6-carboxytetramethyl-rhodamine;
VIC: 2'-chloro-7-phenyl-1,4-dichloro-6-carboxy-fluorescein;
NED: 2'-chloro-5'-fluoro-7',8'-benzo-1,4-dichloro-6-carboxyfluorescein;
ROX: 5- and 6-carboxy-X-rhodamin;
PET and LIZ are unpublished proprietary dyes of Applied Biosystems (Foster City, CA, USA).

EX1008 at 2:40-60. A POSA would have understood the fluorophores disclosed in Brabetz to be compatible with the system described in both Jouvenot and the '797 patent.

170. Fourth, Lakowicz discloses multiple additional fluorophores in a variety of colors, including blue, green, yellow, and red fluorophores, as seen in Lakowicz's Figure 3.11:



EX1008 at 70. As the caption of Figure 3.11 explains, Figure 3.11 shows “emission spectra of goat anti-mouse IgG conjugates of (1) fluorescein, (2) rhodamine 6G, (3) tetramethylrhodamine, (4) Lissamine rhodamine B, and (5) Texas Red dyes.” *Id.* As seen in the Figure, (1) fluorescein emits blue light, (2) rhodamine 6G emits green light, (3) tetramethylrhodamine emits yellow light, and (5) Texas Red dyes emit red light.

171. The fluorophores described in Jouvenot, Larson, Brabetz, and Lakowicz were all well-known in the art as of the priority date of the '797 patent. Further, these fluorophores had all been successfully used with PCR assays and were known in the art to work well for applications similar to the claims of the '797 patent. This is supported by the '797 patent itself, which treats the disclosed fluorophores as only a subset of those that were known in the art and recognized that the

development of additional fluorophores was a continuous and ongoing topic of research in the relevant field as of the priority date. *See* EX1001 at 34:57-61 (“The fluorophores that may be used with the invention are not limited to any of the fluorophores described herein. For example, fluorophores with improved properties are continually developed, and these fluorophores could readily be used with the methods provided in this disclosure.”).

172. It is further my opinion that a POSA would be motivated to combine Jouvenot with these additional references, which are all directed to the same field (namely, the detection of multiple analytes with dPCR assays). As these references show, a wide variety of fluorophores (including blue, green, yellow, and red fluorophores) were known in the art. As “higher degrees of multiplexing” is desirable, a POSA would be motivated to use multiple different fluorophores that emit different colors of light. EX1003 at 2:20, EX1004 at 3:1-2. A POSA would also understand that the use of additional fluorophores would provide one with greater flexibility of choice when performing the methods described in the ’797 patent, allowing a user to optimize the resolution and precision of the methods therein. It is thus my opinion that a POSA would have been motivated to combine Larson, Brabetz, and/or Lakowicz with the system of Jouvenot, particularly the obvious four-channel version of Jouvenot’s Example 1, with a reasonable

expectation of success and would arrive at the purported invention of the '797 patent. Additionally, spectral overlap increases as fluorescence bleeds across channels, so a POSA would have been motivated to look at varied fluorophore literature to increase the number of fluorophores available to reduce noise.

173. Thus, it is my opinion that claim 6 of the '797 patent is obvious in view of the combination of Jouvenot and Larson, Brabetz, and/or Lakowicz.

B. Claim 7: The system of claim 5, wherein the multiple fluorophores is selected from the group consisting of a fluorescein amidite (FAM), a cyanine 3 (Cy3), a carboxy-X-rhodamine (ROX), a cyanine 5 (Cy5), a cyanine 5.5 (Cy5.5), and any combinations thereof.

174. It is my opinion that claim 7 of the '797 patent is obvious in view of the combination of Jouvenot, Larson, Brabetz, and/or Lakowicz.

175. As described in § X.A.3, *supra*, Jouvenot discloses the use of FAM and ROX, EX1003 at 13:46-14:2; EX1004 at 14:1-3. Further, Larson discloses the use of Cy3, Cy5, and Cy5.5. EX1013 ¶ 90. Brabetz and Lakowicz, as described in § XI.A, disclose a variety of additional fluorophores known to one in the art.

176. These fluorophores would have been known to a POSA as of the priority date of the '797 patent. In fact, the mere fact that the '797 patent recites these fluorophores by common name itself suggests that these fluorophores were readily known and available for use in the art. *See* EX1001 at 33:67, 34:8, 45:29-

30, 48:50, 49:10, 49:14, 49:33 (describing the FAM, ROX, Cy3, Cy5, and Cy5.5 with reference to only their common names).

177. As explained in § XI.A, *supra*, a POSA would have been motivated to combine the methods of Jouvenot (particularly, the obvious four-channel version of Jouvenot's Example 1) with Larson, Brabetz, and/or Lakowicz with a reasonable expectation of success to arrive at the claimed invention of the '797 patent. Thus, it is my opinion that claim 7 of the '797 patent is obvious in view of the combination of Jouvenot and Larson, Brabetz, and/or Lakowicz.

C. Claim 8: The system of claim 5, wherein the multiple fluorophores has a maximum excitation wavelength selected from the group consisting of about 494 nm, about 550 nm, about 567 nm, about 650 nm, about 675 nm, and any combinations thereof.

178. It is my opinion that claim 8 of the '797 patent is obvious in view of the combination of Jouvenot, Larson, Brabetz, and/or Lakowicz.

179. As explained in § XI.A-B, *supra*, Jouvenot discloses the use of both FAM and ROX. A POSA would understand that FAM has a maximum excitation of approximately 494 nanometers, which is supported by Lakowicz. *See* EX1006 at 638 (explaining that the use of fluorescein derivatives allows for "measurements with [an] excitation wavelength[] near . . . 495 nm."). Similarly, a POSA would understand that ROX, a rhodamine derivative, fluoresces around 567 nm. *See id.* at

661 (explaining that rhodamine fluoresces at a wavelength around 570 nm). Thus, Jouvenot discloses the 494 nm and 567 nm portions of claim 8.

180. Larson further discloses the use of Cy3, Cy5, and Cy5.5 fluorophores, among many others. EX1013 ¶ 90. A POSA would understand that Cy3 fluoresces at approximately 550 nm, Cy5 fluoresces at approximately 650 nm, and Cy5.5 fluoresces at approximately 675 nm. The approximate excitation wavelengths of at least Cy3 and Cy5 are also confirmed by Lakowicz. EX1006 at 677 (showing emission spectra of Cy3 with a peak at approximately 550 nm, and Cy5 with a peak at approximately 650 nm).

181. This is further supported by Patent Owner's infringement contentions, wherein Patent Owner alleges that Petitioner infringes this claim through its use of:

- FAM for the limitation "about 494 nm,"
- Cy5 for "about 650 nm,"
- Cy5.5 for "about 675 nm," and
- ROX for "about 567 nm."

EX1009 at 97-103.

182. As explained in § XI.A-B, *supra*, a POSA would have found it obvious to use FAM, Cy3, ROX, Cy5, and Cy5.5 with the obvious four-channel version of Example 1. In doing so, a POSA would also be using fluorophores having maximum

excitation wavelengths selected from the claimed set of wavelengths described in claim 8 of the '797 patent. In short, to the extent claim 7 is obvious, claim 8 is necessarily obvious as well because it is merely describing properties of the fluorophores already recited in claim 7. It is thus my opinion that claim 8 of the '797 patent are obvious in view of Jouvenot in combination with Larson, Brabetz, and/or Lakowicz.

D. Claim 9: The system of claim 5, wherein the multiple fluorophores has a maximum emission wavelength selected from the group consisting of about 518 nm, about 565 nm, about 591 nm, about 670 nm, about 697 nm, and any combinations thereof.

183. It is my opinion that claim 9 of the '797 patent is obvious in view of the combination of Jouvenot, Larson, Brabetz, and/or Lakowicz, for largely the same reasons explained in § XII.C.

184. Similar to the allegations of infringement of claim 8, Patent Owner alleges that Petitioner's products infringe claim 9 of the '797 patent through Petitioner's use of several fluorophores that a POSA would have been aware of as of the priority date of the '797 patent. Specifically, Patent Owner alleges that Petitioner is infringing claim 9 of the '797 patent through its use of:

- FAM for "about 518 nm,"
- Cy5 for "about 670 nm,"
- Cy5.5 for "about 697 nm,"

- and ROX for “about 591 nm.”

EX1009 at 103-109. As explained in § XI.C, a POSA would further understand that Cy3 would fluoresce at approximately 565 nm. Importantly a POSA would also understand that the wavelength of light emitted by a fluorophore can vary greatly depending on the solvent and local environment it is in. *See generally* EX1006 at 205-232.

185. As explained in § XI.A-C, *supra*, a POSA would have found it obvious to use FAM, Cy3, ROX, Cy5, and Cy5.5 with the obvious four-channel version of Example 1. In doing so, a POSA would also be using fluorophores having maximum excitation wavelengths selected from the claimed set of wavelengths described in claim 9 of the '797 patent. In short, to the extent claim 7 is obvious, claim 9 is necessarily obvious as well because it is merely describing properties of the fluorophores already recited in claim 7. It is thus my opinion that claim 9 of the '797 patent is obvious in view of Jouvenot in combination with Larson, Brabetz, and/or Lakowics.

XII. GROUND 1(b): CLAIM 11 IS OBVIOUS IN VIEW OF JOUVENOT, LARSON, BRABETZ, MALTEZOS, NEUZIL, AND/OR OLEKSY

186. Claim 11 of the '797 patent recites: “Claim 11: The system of claim 5, wherein the detector comprises four or six band pass filters.” EX1001 at 79:23-24.

It is my opinion that claim 11 is obvious in view of the combination of Jouvenot, Larson, Brabetz, Maltezos, Neuzil, and/or Oleksy.

187. A POSA would understand band-pass filters to be a standard piece of equipment in fluorescence spectroscopy. Band-pass filters are devices that allow specific wavelengths of light (or narrow ranges thereof) to pass through the filter, while other wavelengths are filtered out. For example, Maltezos explains that “the excitation light may be limited by a band pass filter,” and that “it may desirable to suppress [unwanted] luminescence even further by using optical band-pass filters.” EX1012 ¶¶ 140, 163. Oleksy also discloses that band-pass filters can be “emission filters that allow transmittance of light centered on the wavelength of the light *emitted by the fluorophore*.” EX1018 ¶ 101 (emphasis added). Band-pass filters were thus well known as of the priority date of the ’797 patent.

188. Neuzil even discloses the use of band-pass filters in multiple different aspects of the same invention:

- “Excitation filter 116 may be a band pass filter, and such filters are known.” EX1017 ¶ 44.
- “Emission filter 124 may, for example, be a band pass filter.” *Id.* ¶ 44.

That band-pass filters were used in multiple ways shows that a POSA would have been motivated to use band-pass filters for spectroscopic measurement, including

for multiplexed PCR assays. The use of band-pass filters would be known by a POSA to eliminate interference and noise and allow for better resolution and more consistent signal detection at the desired wavelength.

189. A POSA viewing Jouvenot and Larson would have been motivated to combine their teachings with those of Brabetz, Maltezos, Neuzil, and Oleksy with a reasonable expectation of success because they all pertain to PCR experiments (like Jouvenot Example 1 and Larson Figure 11) involving optical detection of light signals from fluorophores. EX1008 at 2:12-60; EX1012 ¶¶ 60, 101, 142, 144, 163, 194; EX1017 ¶¶ 11-35, 36, 44, 49; EX1018 ¶¶ 86, 103, 157, 169-82. A POSA would have understood that the optical components, such as band pass filters, disclosed by Brabetz, Maltezos, Neuzil, and Oleksy would have worked with the obvious four-channel version of Example 1, and would have been motivated to use them because they were standard components in the art useful for creating multi-channel detection systems. A POSA would have likewise had a reasonable expectation of success because these are standard optical components well-known in the art to work with a variety of PCR experiments. EX1008 at 1:45-2:35; EX1012 ¶¶ 60, 101, 144; EX1017 ¶¶ 11-35, 36, 44, 49; EX1018 ¶¶ 5-51, 86.

190. Consistent with the foregoing, I understand the '797 patent acknowledges that "band pass filters are commonly employed in a variety of

laboratory instrumentation, including quantitative PCR machines.” EX1001 at 28:11-13. It likewise acknowledges that “[m]any real-time PCR and quantitative PCR instruments comprise an excitation light source and band pass filters that enable the detection of fluorescent signals in four colors (e.g., blue, green, yellow, and red).” *Id.* at 35:30-33. Because such band pass filters were commonly used in existing systems for the detection of four colors and were known to work well, and because a POSA would have been motivated to implement a four-channel version of Example 1, a POSA would have been motivated to utilize four or six band pass filters for this purpose with a reasonable expectation of success. *See supra* § X.

191. As to the use of four or six band-pass filters specifically, this would similarly be obvious. First, as explained in §§ X.A.3 and X.B, *supra*, it would have been obvious to expand the assays of Jouvenot’s Example 1 to include four or six optical channels; it would have similarly been obvious to include four or six band-pass filters to improve detection and resolution in those channels. Similarly, Brabetz discloses that the “current configuration” of devices known in the art used “up to 5 wavelength bands” that “can be defined ... by digital band pass filters” that were known in art and used in multiplexed PCR assays. EX1008 at 2:22-24.

192. Thus, it is my opinion that claim 11 of the '797 patent is obvious in view of the combination of Jouvenot, Larson, Brabetz, Maltezos, Neuzil, and/or Oleksy.

XIII. GROUND 1(c): CLAIM 13 IS OBVIOUS IN VIEW OF JOUVENOT, LARSON, MALTEZOS, DUBE, AND/OR WITTWER

193. Claim 13 of the '797 patent recites: “The system of claim 5, wherein the multi-channel detector comprises four or six photodetectors.” EX1001 at 79:33-34. It is my opinion that claim 13 of the '797 patent is obvious in view of the combination of Jouvenot, Larson, Maltezos, Dube, and/or Wittwer.

194. For many of the same reasons as explained in §§ X.A.3, XI.B, and XII. it would be obvious to include four or six photodetectors in view of the disclosure of Jouvenot’s Example 1. Jouvenot discloses the detection of multiple signals with a multi-channel detector. As explained in § X.A.3, *supra*, the use of multiple optical channels—including four or six optical channels—with the obvious multi-channel version of Jouvenot’s Example 1. Jouvenot already discloses a plurality of optical channels, and it would be obvious to include photodetectors for use with those channels. *See* EX1003 at 13:4-13; EX1004 at 12:6-10. A POSA would further find it obvious to use four or six photodetectors within the system of Jouvenot. Similarly, Larson contemplates the use of many optical channels—and discloses PCR assays with a “maximum number of colors” that “can be 1, or 2, or 3, or 4, or up to 10, or

up to 20,” and even “higher than 20.” EX1013 ¶ 1039. Larson also discloses the use of “detection apparatuses” that “can be optical or electrical detectors or combinations thereof.” *Id.* ¶ 89. Thus, Larson thus discloses the use of many different colors and fluorophores—including four, six, , and multiple different optical detectors.

195. Maltezos, Dube, and Wittwer provide additional support for this opinion. Maltezos discloses a “photodetector array” that includes “a plurality of photodetectors.” EX1012 ¶ 149; *see also id.* ¶¶ 60, 101, 144 (further disclosing the use of photodetectors). Likewise, Dube discloses “an array of photodetectors wherein each pixel or group of pixels corresponds to a reaction chamber.” EX1019 ¶¶ 147, 152. Finally, Wittwer discloses a system where “emitted fluorescence signals are acquired by photodetectors.” EX1020 ¶ 375, Figure 53. Each of these sources teaches the use of multiple photodetectors.

196. In my opinion, a POSA viewing Jouvenot and Larson would have been motivated to combine their teachings with those of Maltezos, Dube, and Wittwer because they all pertain to PCR experiments (like Jouvenot Example 1 and Larson Figure 11) involving optical detection of lights signals from fluorophores. EX1012 ¶¶ 60, 101, 142, 144, 163, 194; EX1019 ¶¶ 133-47, 155-57; EX1020 ¶¶ 34-120, 375-83. A POSA would have understood that the optical components, such as

photodetectors, disclosed by Maltezos, Dube, and Wittwer would have worked with the obvious four-channel version of Example 1, and would have been motivated to use them because they were standard components in the art useful for creating multi-channel detection systems allowing for detection of a specific range of wavelength. *See supra* § XII (discussing creating multi-channel systems from band-pass filters and photodetectors). A POSA would have likewise had a reasonable expectation of success because these are standard optical components well-known in the art to work with various PCR experiments. EX1012 ¶¶ 60, 101, 134, 144, 149; EX1019 ¶¶ 147-152; EX1020 ¶¶ 375, 379. I note that the '797 patent even admits that the “wavelength and intensity may also be determined using a combination of a photodetector and band pass filters. This configuration is used in several thermal cyclers known in the art.” EX1001 at 35:59-62.

197. Thus, it is my opinion that claim 13 of the '797 patent is obvious in view of the combination of Jouvenot, Larson, Maltezos, Dube and/or Wittwer.

XIV. GROUND 1(d): CLAIM 14 IS OBVIOUS IN VIEW OF JOUVENOT, LARSON, AND MALTEZOS

198. Claim 14 of the '797 patent recites: “The system of claim 5, wherein the multi-channel detector comprises photodetectors that enable the detection of blue, green, and red fluorescent signals.” EX1001 at 79:35-37. It is my opinion that

claim 14 of the '797 patent is obvious in view of the combination of Jouvenot, Larson, and Maltezos.

199. For many of the same reasons as explained in §§ X.A.3, X.B, and, in particular, XI.A, it would be obvious to include photodetectors for the detection of blue, green, and red fluorescent signals in view of the disclosure of Jouvenot's Example 1.

200. Jouvenot already includes the use of multiple fluorophores, including "FAM, VIC, ROX, TAMRA, JOE, etc., among others." EX1003 at 13:46-14:2; EX1004 at 14:1-3. A POSA would understand at least FAM to fluoresce a green color, and that the use of "etc., among others," is intended to encompass the use of additional fluorophores not disclosed. Similarly, Larson discloses the use of blue and red photodetectors, as explained in § XI.A, *supra*, including DAPI, which fluoresces a blue color, and both Cy5 and Cy5.5, which fluoresce red colors.

Maltezos also discloses the use of multiple photodetectors to detect a variety of wavelengths of light in the visible spectrum, including "optical assemblies" that are configured for excitation/detection at multiple wavelengths, "such as: 365/460, 470/510, 530/555, 585/610, 625/660, 680/712 nm." EX1012 ¶ 135. This is further demonstrated by Table 1 of Maltezos:

TABLE 1

Color	Dominant wavelength (nm) or CCT (K)		Typical Luminous or Radiant flux @ 700 mA
	Min.	Max.	
White	4500 K	8000 K	76 lm
Royal Blue	455 nm	465 nm	385 mW
Blue	465 nm	475 nm	28 lm
Cyan	500 nm	510 nm	75 lm
Green	520 nm	535 nm	80 lm
Amber	585 nm	595 nm	57 lm
Red-Orange	610 nm	620 nm	86 lm
Red	620 nm	635 nm	61 lm

EX1012 ¶ 136 (Table 1).

201. It is my opinion that A POSA would also understand that the use of these fluorophores necessitates the use of photodetectors to detect emitted light of different colors. It is further my opinion that a POSA would be motivated to combine the systems described in Jouvenot, particularly a four-channel version of the system of Jouvenot's Example 1, with multiple photodetectors configured to detect blue, green, and red light.

202. Specifically, as I explain above for claim 13, a POSA would have been motivated to combine Jouvenot and Larson with Maltezos and would have reasonably expected success. *See supra* § XIII. A POSA would have been motivated to use the Maltezos photodetectors that detect blue, green, and red

fluorescent signals because POSAs understood that these photodetectors are useful to create a multi-channel detector for use with the obvious four-channel version of Example 1 set forth in claims 6-9, which involve the detection of particular colors. *See supra* §§ XI (discussing creating multi-channel systems from band-pass filters and photodetectors), XII.

203. Indeed, it seems clear to me that the '797 patent itself admits motivation and reasonable expectation of success with respect to this claim, stating the alleged invention can be “accomplished by measuring the intensity of a signal across a spectrum of wavelengths, or by using band pass filters that restrict the passage of certain wavelengths of light, thereby allowing only light of certain wavelengths to reach a photodetector. Many real-time PCR and quantitative PCR instruments comprise an excitation light source and band pass filters that enable the detection of fluorescent signals in four colors (e.g., blue, green, yellow, and red).” EX1001 at 35:26-33. The '797 patent concludes in view of this that “the methods of the invention can be readily applied using instruments widely used in the art.” *Id.* at 35:34-35. Given this disclosure in the '797 patent, it is clear to me that this claim is obvious.

204. Thus, it is my opinion that claim 14 of the '797 patent is obvious in view of the combination of Jouvenot, Larson, and Maltezos.

XV. GROUND 1(e): CLAIM 15 IS OBVIOUS IN VIEW OF LARSON, BRABETZ, LAKOWICZ, MALTEZOS, DUBE, AND/OR WITTWER

205. Claim 15 of the '797 patent recites: "The system of claim 5. wherein the multi-channel detector comprises photodetectors that enable the detection ranges selected from the group consisting of from about 483 nm to about 533 nm, from about 523 nm to about 568 nm, from about 558 nm to about 610 nm, from about 615 nm to about 670 nm, and any combinations thereof." EX1001 at 79:38-43. It is my opinion that claim 15 of the '797 patent is obvious in view of the combination of Jouvenot, Larson, Brabetz, Lakowicz, Maltezos, Dube, and/or Wittwer.

206. As explained in § XIII, a POSA would have been motivated to use multiple photodetectors with the system of Jouvenot's Example 1. As further explained in § XI.C-D, a POSA would have found it obvious to use multiple fluorophores, including, e.g., FAM, Cy3, ROX, Cy5, and Cy5.5, with the same system. In doing so, a POSA would also be using fluorophores having maximum excitation wavelengths selected from the claimed set of wavelengths described in claim 8 of the '797 patent. A POSA would further find it obvious to include multiple photodetectors to detect those multiple fluorophores, at the disclosed wavelength ranges; as explained below, this is also supported by Lakowicz. It would be obvious to a POSA to include photodetectors configured to detect:

- a FAM fluorophore, which a POSA would understand to fluoresce within the range of about 483 nm to about 533 nm;
- a Cy3 fluorophore, which a POSA would understand to fluoresce within the range of about 523 nm to about 568 nm;
- a ROX fluorophore, which a POSA would understand to fluoresce within the range of about 558 nm to about 610 nm;
- a HEX fluorophore, which a POSA would understand to fluoresce from about 523 nm to about 568 nm;
- a Cy5 fluorophore, which a POSA would understand to fluoresce from about 615 nm to about 670 nm;
- an ATTO 590 fluorophore, which a POSA would understand to fluoresce from about 615 nm to about 670 nm;

The disclosure of these wavelength ranges is also supported by Maltezos' Table 1, which also discloses the use of fluorophores that emit wavelengths within the ranges claimed by claim 15:

TABLE 1

Color	Dominant wavelength (nm) or CCT (K)		Typical Luminous or Radiant flux @ 700 mA
	Min.	Max.	
White	4500 K	8000 K	76 lm
Royal Blue	455 nm	465 nm	385 mW
Blue	465 nm	475 nm	28 lm
Cyan	500 nm	510 nm	75 lm
Green	520 nm	535 nm	80 lm
Amber	585 nm	595 nm	57 lm
Red-Orange	610 nm	620 nm	86 lm
Red	620 nm	635 nm	61 lm

EX1012 ¶ 139 (Table 1). A POSA would also understand that the wavelength of light emitted by a fluorophore can vary greatly depending on the solvent and local environment it is in. *See generally* EX1006 at 205-232. Because of this phenomenon, fluorophores can emit a range of wavelengths of light—like the ranges disclosed in claim 15 of the '797 patent. Therefore, to the extent a fluorophore emits a particular peak wavelength of light, a POSA would be motivated to capture a range of wavelengths around this particular wavelength to be sure and capture the full quantity of light from the fluorophore.

207. As also explained in § XI.C-D, the obviousness of this claim is supported by Patent Owner's own infringement contentions, wherein Patent Owner accuses Petitioner of the use of FAM (about 483 nm to about 533 nm), HEX (about

523 nm to about 568 nm), Cy5 (about 610 nm to about 670 nm), ROX (about 558 nm to 610 nm), and ATTO 590 (about 615 nm to about 670 nm). *See, e.g.*, EX1009, Appendix B at 117-121; *id.*, Appendix A at 132-140. As disclosed above, Jouvenot teaches the use of FAM. EX1003 at 13:46-14:2; EX1004 at 14:1-3. Larson discloses the use of Cy5, Cy5.5, Atto dyes, FAM, and ROX, among others. EX1013 ¶ 90. The use of HEX was also well known in the art. *See* EX1018 ¶ 30. As I explain above, it would be obvious to use these fluorophores, which emit light in the same wavelengths as claimed in the '797 patent's claim 15, with the system of Jouvenot's Example 1. To the extent these fluorophores are obvious, so too is this claim.

208. Thus, it is my opinion that claim 15 of the '797 patent is obvious in view of the combination of Jouvenot, Larson, Brabetz, Lakowicz, Maltezos, Dube and/or Wittwer.

XVI. GROUND 1(f): CLAIM 18 IS OBVIOUS IN VIEW OF JOUVENOT, LARSON, MALTEZOS, AND/OR SLEPNEV

209. Claim 18 of the '797 patent recites: "The system of claim 5, further comprising a display coupled to the processor controlled analyzer to visualize a plot of the first and second values." EX1001 at 79:48-50. It is my opinion that claim 18 of the '797 patent is obvious in view of the combination of Jouvenot, Larson, Maltezos, and/or Slepnev.

210. First, a POSA would have known that using a display to visualize data, including a “display coupled to [a] processor,” was well-known in the art. Maltezos and Slepnev, for example, include displays:

- “Generally, a computer comprises a *central processing unit* . . . an output device such as *a display terminal*, and an input device such as a keyboard.”

EX1012 ¶ 167.

- “In one embodiment, the data generation device comprises a signal detector, a display monitor and a computer processor coupled to the control circuit and the display monitor.” EX1021 ¶ 141.

211. It is my opinion that a POSA would have been motivated to combine the teachings of Jouvenot, Larson, Maltezos and Slepnev with a reasonable expectation of success, because, for instance, they all pertain to PCR assays and polynucleotide quantification experiments. In particular, a POSA would be motivated to include a display coupled to a processor with the system of Jouvenot’s Example 1 and/or Larson Figure 11. Jouvenot already discloses graphical methods of displaying data (*see, e.g.*, EX1003 at Figs. 5-7; EX1004 at Figs. 5-7), and a POSA would have found it obvious to add a display to more easily visualize that data. EX1012 ¶¶ 173-98; EX1021 ¶ 12, 54, 102-04. A POSA would have understood that the displays disclosed by Maltezos and Slepnev would have worked with the obvious

four-channel version of Example 1 with such a display because, at the priority date, displays had long been a standard component well-known in the art to work with PCR experiments and were used for displaying scientific data for visualization. EX1012 ¶¶ 12, 116, 132, 147, 165-72, 212; EX1021 ¶ 141-43.

212. Thus, it is my opinion that claim 13 of the '797 patent is obvious in view of the combination of Jouvenot, Larson, Maltezos, and/or Slepnev.

XVII. GROUNDS 2-2(F): CLAIMS 1-2, 5-11, 13-15, AND 18 ARE OBVIOUS IN FURTHER VIEW OF LEHNEN

213. While it is my opinion that claims 1-2, 5-11, 13-15, and 18 are obvious in view of the combinations of references described in Grounds 1-1(f), which is incorporated herein, the same claims are further obvious in view of Lehn. Grounds 2-2(f) are based on the same rationale as for Grounds 1-1(f), with the added inclusion of Lehn, which, as I explain above,

214. It is my opinion that, to the extent Jouvenot and Larson are deemed to not disclose encoding analytes by the geometric progression described in claim 1 of the '797 patent (e.g., a pattern of analytes encoded with intensities that correspond to successive powers of 2, e.g., 1, 2, 4, 8, 16, 32, etc.), for example, should Patent Owner argue that signals in Jouvenot Example 1 (especially Figure 4) and Larson (especially Figure 11) do not exactly match this progression, a POSA would find the use of this geometric progression obvious in view of Lehn.

215. Lehnert discloses the use of the same encoding system and explains the utility of encoding analytes based on the use of powers of 2. Lehnert teaches assigning analytes a unique signal intensity, and that each combination of the presence or absence of these analytes can be detected unambiguously. *See* EX1022 at 13:15-53. (“if the reagent had been designed with proportions 1:2:4 . . . the resulting histogram would be uniquely interpretable. . . . thus correctly identifying the respective analytes unambiguously.”). Throughout, Lehnert discloses “reagent of proportions 1:2:4” and “reagent of proportions 1:2:4:8.” Lehnert explains that this algorithm “can be utilized to determine the proportions of unequivocal analytical utility to be used in the preparation of a reagent containing m subpopulations,” much like the equation $M=C*\log_2(F+1)$ can be used to calculate the number of analytes tested in the system of the ’797 patent. EX1022 at 13:15-53.

216. Lehnert uses a geometric progression that follows the same progression as the formula in the ’797 patent. Each analyte is encoded using a unique proportion of bead subpopulations to ensure each combination is unique. The approach is described as “uniquely interpretable.” EX1022 at 13:31-35.

217. It is my opinion that A POSA would be motivated to use this signal progression because the proportions allow for the unambiguous identification of analytes, as Lehnert expressly teaches. *See* EX1022 at 13:31-35. I believe that a

POSA would have a reasonable expectation of success in using this approach because a POSA would have known to adjust the intensity of analytes for detection, as disclosed in Jouvenot. For example, Jouvenot teaches that:

[T]he intensity associated with one fluorophore, following reaction, may be lower or higher than the intensity(ies) associated with the other fluorophore(s). In some embodiments, one probe may be *labeled with a different number of fluorophores* than the other probe, and/or the probes may be *located in slightly different local environments*, creating a different level of fluorescence for each probe following reaction. Alternatively, or in addition, both probes may be labeled with the same number of fluorophores (e.g., one fluorophore), but there may be *more or less of one probe than the other in the sample*, so that a greater or smaller signal is created when the reactions have occurred.

EX1003 at 13:51-63; EX1004 at 13:13-21. In view of Jouvenot's disclosure of varying intensities, and Lehnert's disclosure of this system for unambiguous detection, based on using powers of 2, a POSA would be motivated to combine the system of Jouvenot and Lehnert (and the other references disclosed in Ground 1), with the mathematical system disclosed in Lehnert.

218. Thus, it is my opinion that claims 1-2, 5-11, 13-15, and 18 are obvious in view of the combinations of references described in Ground 1 and are further obvious in view of Lehnert.

DECLARATION

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.

Dated: September 15, 2025

By: *Carl Batt*

APPENDIX A

Carl A. Batt

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EDUCATION:

October 1981 - Ph.D. Rutgers University, Department of Food Science

October 1979 - M.S. Rutgers University, Department of Food Science

December 1975 - B.S. Kansas State University, Microbiology

ACADEMIC EXPERIENCE:

1998-present **Professor, Department of Food Science**
Cornell University

1991-1998 **Associate Professor, Department of Food Science**
Cornell University

1985-1991 **Assistant Professor, Department of Food Science**
Cornell University

1984-1985 **Research Scientist, Department of Applied Biological Sciences**
Massachusetts Institute of Technology

1982-1984 **Postdoctoral Research Associate, Department of Nutrition and Food Science**
Massachusetts Institute of Technology

OTHER EXPERIENCE:

2021-present **Managing Partner, Empire Syrups**

Empire Syrups is restarting cultivation of sweet sorghum in New York State and establishing an eco-friendly process to produce a unique and versatile sweetener.

that have their roots in traditional fermentations but take advantage of modern science.

2020-2021 **Food Safety Expert, Ample Hills Creamery**

Food safety expert for the largest ice cream plant in New York City. Served as interim food safety manager and hired permanent food safety manager. Member of the food safety team

2018-2024 **Managing Partner, Salvatore BKLYN, Brooklyn, NY**

Created business plan and product pipeline for line extensions of the fresh cheese business.

Interfaced with all customers on sales, quality and safety of products. Acquired production and distribution rights to Tin Foods LLC. Established a vinegar production process and product line to expand Tin Foods LLC

2018-2024 **Food Safety and Quality Assurance Manager, Salvatore BKLYN, Brooklyn, NY**

Established HACCP and GMP program for fresh cheese operation. Developed a new cream cheese product that has no stabilizers.

2010-present **Adjunct Senior Scientist, MOTE Marine Laboratory, Sarasota, FL**

The appointment was for a sabbatical year and continued on as a consultant to the current President of the MOTE.

2000-present **Principal consultant, Stone Fence Collaborative. Groton, NY**

An organization that is focused on strategic advising and presubmission grant development advice for colleges and universities.

1999-2011 **Director, Cornell University/Ludwig Institute for Cancer Research Partnership Cornell University.**

The Partnership was a multiyear \$20M+ enterprise funded by the LICR that included the design, construction and operation of Good Manufacturing Practice facility on the Cornell Ithaca campus. The CU/LICR Partnership produced Phase I recombinant proteins that were used in clinical trials in the US and throughout the world.

2005-2009 **Founder and President, Illuminaria LLC, Ithaca, NY.**

Illuminaria was an early stage start-up company that sought to commercialize microfluidic technology developed in the Batt Laboratory. Early-stage funding was obtained via the SBIR program.

2004-2010 **Co-Founder, Main Street Science Inc. (not for profit) Ithaca, NY**

Main Street Science was a not-for-profit established to help develop and distribute learning materials for K-12 with an emphasis on STEM.

2001-2004 **Founder, Project Leader, Alliance for Nanomedical Technologies Cornell University**

The Alliance for Nanomedical Technology was a NYS Center for Advanced Technology. The \$3M in funding represented the highest level of support given by the NYS CAT at the time. Its membership included 26 NYS companies and supported collaborative research efforts between the Cornell faculty and these member companies.

1999-2004 **Co-Director, Co-Founder Nanobiotechnology Center Cornell University**

The NBTC was a National Science Foundation supported Science and Technology Center which is one of the largest center-funding mechanisms of the NSF with annual funding of \$4M. The NBTC was also supported by a grant from NYS on the order of approximately \$7M for the 10 years the center held its STC status.

1999-2016 **Co-Founder and Science Advisor, Agave BioSystems, Ithaca NY**

Agave BioSystems is a research and development organization that has conducted research for a number of federal agencies including DOD, NASA, and DOE. Its core activities are in the area of nanofabrication and molecular biology.

1996-2001 **Founder and Director, Laboratory for Molecular Typing, Cornell University**

The Laboratory for Molecular Typing was established as a fee-for-service operation offering customers molecular typing based upon the Dupont Riboprinter. The LMT has as its clients a number of large food, pharmaceutical and specialty chemical companies.

PROFESSIONAL ACTIVITIES:

Graduate Fields: Food Science, Microbiology, Biomedical and Biological Sciences, Biomedical Engineering, Materials Science, Electrical Engineering

2023- **Chief-Editor**, Encyclopedia of Food Microbiology (3rd Edition)

2005- **Editor**, Nanooze (www.nanooze.org)

2015-2016 **Subject-Editor**, Food Microbiology, Food Science Reference Module

2009-2015 **Chief-Editor**, Encyclopedia of Food Microbiology (2nd Edition)

2007-2009 **Editorial Advisory Board**, Wiley Encyclopedia of Chemical Biology

2003-2008 **Advisory Board**, Sciencenter (Ithaca, NY)

2001-2004 **Editorial Board**, Protein Expression and Purification

2001-2005 **Editorial Board**, Journal of Food Science

1987-2000 **Chief-Editor**, Food Microbiology

1996-1999 **Editor**, Encyclopedia of Food Microbiology

1987-1992 **Editorial Board**, Food Biotechnology

1987-1991 **Consultant** USAID -NIAB, Faisalabad, Pakistan

1988-1989 **Chairman**, Central New York IFT

AWARDS:

1988	Yoplait Institute Research Award
1990	Samuel Cate Prescott Award (Institute of Food Technologists)
1997	Teaching Excellence Award (Department of Food Science)
2000	Liberty Hyde Bailey Professor (College of Agriculture and Life Sciences)
2001	Faculty Fellows in Service (Cornell University)
2003	Kaplan Family Distinguished Faculty Fellowship in Service-Learning (Cornell University)
2005	Rutgers Alumni Research Award
2007	NSF Discovery Corps Fellow
2008	CALS Promoting Diversity Award (College of Agriculture and Life Sciences)

ACTIVITIES:

Public engagement media

It's a Nanoworld. Traveling museum exhibition (2003) co-developer. Served as co-PI, developer on tour in the US, 1M+ visitors, supported by the National Science Foundation. On permanent tour in the US.

Too Small to See. Traveling museum exhibition (2008) co-developer. Served as PI, developer, on tour in the US, 1M+ visitors, supported by the National Science Foundation. On permanent tour in the US.

Nanooze. Web-site, print magazine (2005-present). Founder and editor. Each edition is distributed to more than 100,000 students in the U.S., supported by the National Science Foundation.

Nanooze radio series. (2009) Co-developer. Produced in collaboration with Earth Sky, a series of six radio episodes aired 2009 with a total listener audience in excess of 12M. Supported by the USDA.

Science Chronicles. (2009) Co-developer. A series of six pod-casts that tracked the activities of a postdoctoral associate over the course of a year. Produced as a podcast series in collaboration with Earth Sky.

Take a Nanooze Break. (2010-2020). Permanent exhibition at Walt Disney World, Lake Buena Vista, FL. Developer, 3M+ visitors each year, supported by the National Science Foundation.

Nanooze Labs. (2011-2014) A long-term exhibition at Disneyland, Anaheim CA. Developer, 5M+ visitors each year, supported by the National Science Foundation

Technical advisor "Mysteries of the Unseen World" an IMAX film produced by Day's End Pictures Inc. and National Geographic. 2012

University committees

Undergraduate Honors Program, CALS-1990-1991

NIH Biotechnology Training Program Grant Executive Committee 1990-1995

Life Safety, Food Science Department, 1992-present

Planning, A Food Science Department committee that serves to advise the department chairperson, 1993-present

Scientific Administrative Board Cornell Biotechnology Program, Center for Advanced Technology, 1993-1996.

Graduate Admissions-Graduate Field of Food Science and Technology, 1993-1995.

The Future of the Geneva Food Science and Technology Department CALS committee initiated at the request of Dean David Call to help chart the future of the Food Science and Technology Department at the Agricultural Experiment Station in Geneva. 1995

Graduate Admissions-Graduate Field of Microbiology, 1996-2005.

Laboratory for Molecular Typing. Founder and managing director. A facility associated with Biotechnology Institute BioResource Center dedicated to providing genetic typing of bacteria. 1995-2000

Nanotechnology: Frontiers in Biology, Chairman. A workshop sponsored by NSF, National Nanofabrication Users Network and the Cornell Nanofabrication Facility November 20-21, 1996.

Nanofabrication Committee. A committee initiated at the Dean's request on future directions for the College of Engineering in nanotechnology. December 1, 1996-1997

Office of Economic Development. A university committee whose mission is to foster economic development in the community. 1997-1999

Stocking Hall Renovation Committee, 1997-1999

Cornell University Genomics Taskforce. A university committee to explore our future directions in genomics. 1998-2003

Executive Committee Nanobiotechnology Center -Advisory committee to Nanobiotechnology Center. 2000-2004

Life Sciences Building Committee. A university committee to design a new building which will be the cornerstone for genomics at Cornell University. 2000-2002

Life Sciences Advisory Council. A Provost-appointed committee to provide guidance to the Provost in the area of Cornell's investment in the Life Sciences. 2000-2002

Johnson Graduate School of Management Nanotech Club. Faculty advisor 2004-2009

Cornell Nanofabrication Facility User Committee. 2008-2013

IGEM Cornell University Chapter. Faculty advisor 2008-2010

Outside committees

Board of Directors- Ithaca Montessori School. 1998-2002; President 1999-2002, Interim Director, summer 1999

Business Innovation Center. A Tompkins County-Cornell joint venture in business assistance. 1998-2001

Advisory Board. Department of the Army, Research and Technology Directorate. 2000-2002

Bacteriology Advisory Board. American Type Culture Collection 2000-2002

Advisory Board. Sciencenter, Ithaca NY 2003-2007

User Proposal Review Committee Center for Integrative Nanotechnologies, 2008- present (Chair 2012-2019)

External Advisory Board. Center for Catalytic Bioscavenger Medical Defense Research Center of Excellence (U-54), NIH 2009- present (Chair 2012-2019)

Advisory Committee. Active Polymer Center for Pattern Integration. ERC, MEST, Korea 2009-present

WV EPSCoR RII External Technical Advisory Board 2009-2015

Monitoring and Assessment Panel-University of Hawaii IMUAIII NSF EPSCoR 2010-2013

External Advisory Board United Tribes Technical College, NSF TCUP 2017-Present

External Advisory Board Intertribal Research & Resource Center NSF 2019-Present

(<https://uttc.edu/irrc/>)

Assignments

Scientific Advisory Committee-University of Minnesota-Symposium on Application of Biotechnology in the Food Processing Industry. October 8, 1984. St. Paul, MN.

Biotechnology: Microbial principles and processes for fuels, chemicals and biologicals Lecturer-Summer course Massachusetts Institute of Technology, Cambridge, MA. 1984-1994.

Zone supervisor-Environmental Health, Radioisotopes, Stocking Hall 1987-1999

Safety Issues of Transgenic Plants Invited-Rapporteur, Boyce Thompson Institute, Cornell University, Ithaca, NY, May 1-2, 1989

Second Symposium on the Genetic Engineering of Animals Organizing committee-, Cornell University, July 25-28, 1989
Safety of foods of animal origin: Charting the course Invited Participant. College of Veterinary Medicine, Texas A&M University, College Station, TX June 25-28, 1991 (see Acuff, G.R., Albanese, R.A., Batt, C.A. et al. [1991]).
NSF panel member-NSF ERC review team September 29, 1999.
Committee on Science witness-US House of Representatives H.R. 766 Nanotechnology Research and Development Act of 2003. March 19, 2003
NIH-NIAID panel member-SBIR Infectious Diseases and Microbiology 2000-2008.
NIH panel member-SBIR Biodefense Bacterial Agents 2004-2009
NCI Centers of Cancer Nanotechnology Excellence (CCNEs) Review Panel 2005, 2014
Earth and Sky Nanotechnology Advisor 2005-present
DEPSCoR review panel 2007- present
NIH-nano review panel 2007- 2009
Air Force Research Laboratory-Wright Patterson, Advisory Panel- Nano-Bio Institute for Aerospace. 2008
NSF-CREST review panel 2009-present
NSF-SBIR review panel 2008-present
Canadian grant review panel 2007- present
Austrian Science Fund grant review panel 2007- present
Israel Science Foundation grant review panel 2007- present
Republic of Georgia Shota Rustaveli National Science Foundation review panel 2009-present
Singapore National Research Foundation 2009-present
NIH F31 Fellowship review panel 2009-2019
NIH RC review panel 2009
Research Corporation for Science Advancement review panel 2009-present
American Chemical Society-Petroleum Research Fund reviewer 2009-present
Department of Energy reviewer 2010-present
NIH SEPA review panel 2010
USDA-Nanotechnology for Agricultural and Food Systems- Panel manager 2011-2012
International Review Committee for the Biotechnology and Food Engineering Faculty, Technion, Haifa Israel 2011
Reviewer, North Dakota EPSCoR 2011-present
DOE- Center for Integrated Nanotechnology-review panel chair 2011-
NSF ERC review panel 2011
Reviewer, Rhode Island EPSCoR 2011-present
Sitting Bull College, advisor/evaluator Research Experience for Undergraduates Summer program, 2011
Science Foundation Ireland review panel 2011-present
Reviewer, South Dakota EPSCoR 2011-present
Israeli Council for Higher Education International Assessment Committee for Biotechnology and Biotechnology Engineering. Chair, 2012.
Reviewer, North Dakota EPSCoR 2011-present
Strategic advisor, Rochester Institute of Technology 2012-present
Science Foundation Ireland site visit review panel-Trinity College, Dublin. Chair, 2012
Strategic advisor, George Mason University, 2012-2018
MITACS Canada reviewer 2013-present
Reviewer, Guam EPSCoR 2011-2015

Reviewer, West Virginia EPSCoR 2011-present
Technical advisor "Unseen Worlds" an IMAX film produced by Day's End Pictures Inc. 2012-2014.
NSF NanoBio Hub site visit review team, 2013-2016
Technical reviewer, National Geographic, 2013-2018
NSF I/UCRC review panel 2014
Strategic advisor, George Washington University, 2014-present
Reviewer, Alaska EPSCoR 2011-present
NSF SEES CBET review panel 2014
NCI Small Grants Program for Cancer Research (R03/R21) 2014
United Tribes Technical College, advisor/program evaluator Research Experience for Undergraduates Summer program, 2014-
Reviewer, New Hampshire EPSCoR 2011-present
Reviewer, Nevada EPSCoR 2013-present
Advisor, cGMP facility planning, National Institutes of Health 2015-
Strategic Advisor, Missouri EPSCoR program 2016-2019
NSF CBET Career review panel 2016
Reviewer, New Zealand MBIE fund 2018-present
NIH NCI panel 2018
NSF Engineering Research Center review panel 2019
NSF Research Training program review panel 2021
NSF SBIR review panel 2022
NSF Engines review panel 2023
International Review Committee for the Biotechnology and Food Engineering Faculty, Technion, Haifa Israel 2023

Extension

(I have just begun to account for extension activities that I have not captured since 1985, some activities are reflected in 'Public engagement media')

Advisor, Crown Finish Caves, 2017-present. Helped to navigate challenges in supply chain and preventative controls for *Listeria* contamination.

Advisor, Ample Hill Creamery, 2018-present. Assisted production manager in evaluating safety concerns and mitigating risk. Helped students network to gain internships.

Advisor, Shaker and Spoon. 2020-present. Assisted in food science and food safety challenges in the subscription-box business.

Advisor, Brooklyn Larder. Provided advice on food safety plans and expansion of current product lines.

PUBLICATIONS

Peer reviewed publications:

Batt, C. and Solberg, M. (1982) Asexual developmental markers in an aflatoxigenic strain of *Aspergillus parasiticus*. *Can. J. Microbiol.* 28:1206-1209.

Batt, C. and Solberg, M. (1983) Effect of volatile components of carrot seed oil in growth and aflatoxin production by *Aspergillus parasiticus*. *J. Food Sci.* 48:762-764.

Batt, C. and Solberg, M. (1985) Association of lactase activity with conidiation in an aflatoxigenic strain of *Aspergillus parasiticus*. *FEMS Letters* 27:277-280.

Batt, C.A., Claps, M.C., Bodis, M.S., Jamas, S. and Sinskey, A.J. (1985) Analysis of xylose operon regulation by Mud-lac fusion: Trans effect of plasmid coded xylose operon. *Can. J. Microbiol.* 31:930-933.

Batt, C.A., Carvallo, S., Easson, D.D., Akedo, M. and Sinskey, A.J. (1985) Evidence for a xylose metabolic pathway in *Saccharomyces cerevisiae*. *Biotechnol. Bioeng.* 28:549-543.

- Batt, C.A., Shanabruch, W. and Sinskey, A.J. (1985) Expression of pAM β I tetracycline resistance in *Corynebacterium glutamicum*: Segregation of antibiotic resistance due to intramolecular recombination. *Biotech. Lett.* 7:717-722.
- Batt, C.A., Novak, S.R., O'Neill, E.O., Ko, J. and Sinskey, A.J. (1986) Hyperexpression of *Escherichia coli* xylose isomerase. *Biotechnol. Prog.* 2:140-144.
- Jamieson, A.C., Vandeyar, M.A., Kang, Y.C., Kinsella, J.E. and Batt, C.A. (1987) Cloning and nucleotide sequence of the bovine β -lactoglobulin gene. *Gene* 61: 85-88.
- Chow, J.J., Batt, C.A. and Sinskey, A.J. (1988) Characterization of *Lactobacillus bulgaricus* bacteriophage χ 2. *Appl. Environ. Microbiol.* 54: 1138-42.
- Hahm, Y.T. and Batt, C.A. (1988) Genetic transformation of an *argB*⁻ strain of *Aspergillus oryzae*. *Appl. Environ. Microbiol.* 54, 1610-1611.
- Vandeyar, M.A., Weiner, M.P., Hutton, C.J. and Batt, C.A. (1988) A simple and rapid method for the selection of oligonucleotide-directed mutants. *Gene* 65, 129-133.
- Kim, S.G. and Batt, C.A. (1988) Heterologous expression of the *Escherichia coli* β -galactosidase gene in *Streptococcus lactis* by translational fusion. *Food Microbiol.* 5, 59-73
- Wong, D.W.S., Yee, L.N.H. and Batt, C.A. (1989) Thermal inducible expression of xylose isomerase and its performance in a hollow fiber bioreactor. *J. Ind. Microbiol.* 4, 1-5.
- Wong, D.W.S., Batt, C.A. and Kinsella, J.E. (1990) Purification and characterization of rat liver transglutaminase. *Inter. J. Biochem.* 22, 53-59.
- Batt, C.A., Jamieson, A.J. and Vandeyar, M.A. (1990) Identification of essential histidine residues in the active site of the *Escherichia coli* xylose (glucose) isomerase. *Proc. Natl. Acad. Sci. USA* 87, 618-622
- Batt, C.A. (1990) A simple procedure for the *in vitro* selection of oligonucleotide primed site-directed mutations. *DNA Prot. Eng. Tech.* 2, 48-50.
- Batt, C.A., Rabson, L.D., Wong, D.W.S. and Kinsella, J.E. (1990) Expression of recombinant bovine β -lactoglobulin in *Escherichia coli*. *Agr. Biol. Chem.* 54, 949-955.
- Silva, M., Wong, D.W.S. and Batt, C.A. (1990) Cloning and sequencing of the genomic bovine β -lactoglobulin gene. *Nucl. Acid. Res.* 18, 3051.
- Hahm, Y.T. and Batt, C.A. (1990) Expression and secretion of thaumatin from *Aspergillus oryzae*. *Agr. Biol. Chem.* 54, 2513-2520.
- Batt, C.A., Webb, J., Oren, P. and Flick, P. (1990) An improved method for oligonucleotide mediated site-directed mutagenesis. *Biotechniques* 9, 555-556.
- Kim, J.H. and Batt, C.A. (1991) Molecular characterization of a *Lactococcus lactis* bacteriophage F4-1. *Food Microbiol.* 8, 15-26.
- Kim, J.H. and Batt, C.A. (1991) Nucleotide sequence and deletion analysis of a gene coding for a structural protein of *Lactococcus lactis* bacteriophage F4-1. *Food Microbiol.* 8, 27-32.
- Kim, S.G. and Batt, C.A. (1991) Identification of a nucleotide sequence conserved in *Lactococcus lactis* bacteriophages. *Gene* 98, 95-100.
- Kim, S.G. and Batt, C.A. (1991) Antisense mRNA mediated bacteriophage resistance in *Lactococcus lactis*. *Appl. Environ. Micro.* 57, 1109-1113.
- Wong, D.W.S., Batt, C.A. and Kinsella, J.E. (1991) Expression of the transglutaminase gene in *Escherichia coli*. *Inter. J. Biochem.* 23, 947-953.
- Chung, D.K., Kim, J.H. and Batt, C.A. (1991) Molecular cloning and nucleotide sequence of the major capsid protein of *Lactococcus lactis* ssp. *cremoris* bacteriophage F4-1. *Gene* 101, 121-125.
- Tortorello, M.L., Billota, S., Woolf, H.D., Bender, J. and Batt, C.A. (1991) Extending the shelf-life of cottage cheese: Identification of spoilage flora and their control using food grade preservatives. *Amer. Cult. Dairy Prod. J.* 26:8-12.

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- Winters, D.A. and Batt, C.A. (1991) Irreversible denaturation of *Lactobacillus bulgaricus* β -galactosidase. Milchwissenschaft **46**, 753-757.
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- Kim, J.K., Kim, S.G., Chung, D.K., Bor Y.C. and Batt, C.A. (1992) Use of antisense mRNA to engineer a bacteriophage resistant lactic acid starter culture. J. Ind. Microbiol **10**, 71-78.
- Chung, D.C. Chung, S.K. and Batt, C.A. (1992) Antisense RNA directed against the major capsid protein of *Lactococcus lactis* subsp. *cremoris* confers resistance to the host strain. Appl. Microbiol. Biotechnol. **37**, 235-240.
- Jamieson, A.C. and Batt, C.A. (1992) Fluorescent properties of the *Escherichia coli* D-xylose isomerase active site. Prot. Eng. **5**, 235-240.
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Batt, C.A. Food, Nanooze **20**: 1-18 (2024)

Batt, C.A. Jobs, Nanooze **21**: 1-18 (2024)

Clinical trials:

The following clinical trials have been carried out using material produced by the Cornell University/Ludwig Institute for Cancer Research Partnership.

NCT01154049- Study to Evaluate the Safety of the Vaccine Prepared SM14 Against Schistosomiasis

NCT00112957 Vaccine Therapy in Treating Patients With Stage II, Stage III, or Stage IV Ovarian Epithelial, Fallopian Tube, or Peritoneal Cancer

NCT00299728 NY-ESO-1 Protein with Montanide and CpG 7909 as Cancer Vaccine in Several Tumors

Patents:

Monoclonal antibody-based assay for *Listeria monocytogenes* U.S. Pat. #5,294,537 issued March 15, 1994.

Methods of detecting bovine Herpesvirus 1 (BHV-1) in semen by nucleic acid amplification. U.S. Pat. #5,545,523 issued August 15, 1996.

Enhanced on-chip SERS based biomolecular detection using electrokinetically active microwells. U.S. Pat. # 9,057,099 issued June 16, 2015.

Expert witness work (served as a consultant for party that is underlined, only cases that involved deposition or other hearings are included):

Applera Corp. v. Bio-Rad Lab. Inc., et al., No. 3:04-cv-01881-RNC (D. Conn.)

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Esoterix v. Life Technologies No. 1:12-cv-00411-CCE-JEP (United States District Court for the Middle District of North Carolina, Greensboro Division).

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