

Filed on behalf of: COLUMBIA

By: John P. White
jwhite@cooperdunham.com
(212) 278-0421

Anthony M. Zupcic
ColumbiaIPR@fchs.com
(212) 218-2100

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.

Petitioner,

v.

Patent of THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF
NEW YORK
Patent Owner.

Case IPR2012-00007
U.S. Patent 7,790,869

SUBSTITUTE COLUMBIA PATENT OWNER RESPONSE UNDER 37 C.F.R.
§42.120 (FILING AUTHORIZED TO REPLACE PAPER NO. 65)

TABLE OF CONTENTS

I.Introduction	5
A. Summary of Patent Owner’s Response.....	5
B. Evidence Relied Upon By Patent Owner	6
1. Declaration of George L. Trainor, Ph. D.	6
2. Deposition Testimony of George M. Weinstock, Ph. D.	6
II.The Invention Claimed in the ‘869 Patent	7
III.The Relevant Art	7
IV.The Person of Ordinary Skill in the Art	7
V.The State of the Art	8
VI.Applicable Legal Principles	10
A. Nonobviousness Under 35 U.S.C. §103	10
B. The Petitioner’s Burden of Proof.....	11
VII. The Challenges on the Basis of Which Trial Was Instituted	12
VIII. The Substitute Claims	13
IX.The Substitute Claims Are Not Anticipated by Tsien or Stemple III.....	13
A. Proposed Substitute Claims 34-54	13
X.Substitute Claims 34-54 Are Not Obvious In View of Tsien and Prober I	13
A. Illumina failed to Identify in Tsien’s Description a Starting Point for Making Novel Nucleotide Analogues.....	14
B. Tsien’s 3’-OH Labeled Nucleotide Analogues as a Starting Point...	15
1. No Reason To Make Changes to Tsien’s 3’-OH Labeled Nucleotide Analogues.....	15

2.	No Basis for Reasonably Expecting Success in Making the Claimed Invention	17
C.	Tsien's Base-Labeled Nucleotide Analogues As A Starting Point...	18
1.	No Reason to Make Changes to Tsien's Base-Labeled Nucleotides	18
2.	No Basis For Reasonably Expecting Success in Making the Invention	19
XI.	Substitute Claims 34-54 Are Not Obvious In View of Stemple and Anazawa	21
A.	Illumina Failed to Identify In Stemple's Description A Starting Point for Making Novel Nucleotide Analogues	21
B.	Stemple's 3'-OH Labeled Nucleotide Analogues As A Starting Point	22
1.	No Reason to Make Changes.....	22
2.	No Basis for Reasonable Expecting Success in Making the Invention	23
C.	Stemple's Base-Labeled Nucleotide Analogues As A Starting Point	23
1.	No Reason to Make Changes.....	24
2.	No Basis for Reasonable Expecting Success in Making the Invention	24
3.	A Person of Ordinary Skill Would Have To Proceed Contrary to Stemple III and Anazawa to Arrive at the Claimed Invention	25
4.	The Combination of Stemple III and Anazawa Would Not Teach a Person of Ordinary Skill Every Feature of the Claims	25
XII.	Illumina's Late Submitted New Evidence	26
XIII.	Objective Evidence of Nonobviousness.....	26

A.	Objective Evidence Shows that Columbia’s Inventions Have Unexpected Properties That Revolutionized the DNA Sequencing Industry	27
B.	Dr. Ju’s Invention Has Received Competitive Funding Awards and Has Been Described in Prestigious Journals	31
C.	Columbia’s Patented Sequencing Chemistry is Responsible for Illumina’s Commercial Success	33
D.	Objective Evidence Permits a Strong Inference That Illumina Copied Dr. Ju’s Nucleotide Analogues	36
E.	Others in the Field Were Skeptical that SBS Could Work	37
F.	Illumina Attempted to License the Challenged Patents	37

TABLE OF AUTHORITIES

<i>Brown & Williamson Tobacco Corp. v. Philip Morris Inc.</i> , 229 F.3d 1120 (Fed. Cir. 2000)	39
<i>Graham v. John Deere Co.</i> , 383 U.S. 1 (1966)	10
<i>In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.</i> , 676 F.3d 1063 (Fed. Cir. 2012).....	11
<i>Jazz Photo Corp. v. U.S.</i> , 439 F.3d 1344 (Fed. Cir. 2006)	12
<i>Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.</i> , 678 F.3d 1280 (Fed. Cir. 2012).....	11
<i>Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.</i> , 699 F.3d 1340 (Fed. Cir. 2012).....	11, 26, 27, 33

COLUMBIA’S PATENT OWNER RESPONSE UNDER 37 C.F.R.

§42.120

I. Introduction

This is Patent Owner’s Response to the Trial Board’s March 12, 2013 Decision Instituting an Inter Partes review of U.S. Patent No. 7,790,869 (the ‘869 Patent) in response to the Petition filed September 16, 2012 by Illumina, Inc. (“Illumina.”) The ‘869 Patent is assigned to the Trustees of Columbia University in the City of New York (“Columbia” or “Columbia University”) and Columbia Professor of Chemical Engineering Dr. Jingyue Ju (“Dr. Ju”) is the first named inventor.

A. Summary of Patent Owner’s Response

Patent Owner, Columbia’s claims of the ‘869 Patent as amended by the Motion to Amend filed concurrently herewith are not subject to any challenge on the ground of anticipation under 35 U.S.C. §102. See Exhibit 2033, ¶¶48 and 88.

In addition Columbia provides evidence which clearly establishes by a preponderance of the evidence that Illumina has failed to prove that the challenged claims of the ‘869 Patent are obvious under 35 U.S.C. §103 in view of the references cited by Illumina and relied upon by the Board in authorizing this proceeding, namely 1) Tsien and Prober I, and 2) Stemple II and Anazawa.

Specifically, Columbia's evidence establishes by a preponderance of the evidence that a person of ordinary skill in the art would not have had a reason or motivation to make the claimed invention and would not have had a reasonable expectation of success in making the claimed invention. In addition, Columbia's evidence establishes that there are objective indicia of nonobviousness. See, Exhibit 2033, ¶¶49-87, ¶¶89-140 and ¶¶193-208.

B. Evidence Relied Upon By Patent Owner

1. Declaration of George L. Trainor, Ph. D.

In support of this response Columbia submits the Declaration of George L. Trainor, Ph. D. ("Dr. Trainor"), a synthetic chemist with extensive experience in nucleotide chemistry including particularly the design and synthesis of nucleotide analogues. Dr. Trainor is also an author on Prober I, one of the references relied upon by Illumina, and discusses this reference in his Declaration along with other prior art references. Dr. Trainor also attended the deposition of Illumina expert Dr. Weinstock and Dr. Trainor's Declaration includes references to testimony of Dr. Weinstock confirming facts presented by Dr. Trainor and supporting arguments advanced by Columbia (Exhibit 2033, ¶¶3-14.).

2. Deposition Testimony of George M. Weinstock, Ph. D.

Illumina's expert George M. Weinstock, Ph.D. ("Dr. Weinstock") was deposed on June 8, 9 and 10, 2013. His deposition testimony confirms many

important facts relied upon and positions advanced by Columbia (Exhibit 1034.)
See, Exhibit 2033, ¶18-38.

II. The Invention Claimed in the ‘869 Patent

The invention claimed in the ‘869 Patent and challenged in this trial is a novel nucleotide analogue combining all the features recited in substitute claims 34, 35, 37, 38, 41-50, 52 and 53. (Exhibit 2033 ¶¶46 and 47.)

III. The Relevant Art

The relevant art is the art concerning the design and synthesis of nucleotide analogues that can be incorporated by a polymerase for use in DNA sequencing methods. (Exhibit 2033, Trainor Decl., ¶40)

IV. The Person of Ordinary Skill in the Art

The person of ordinary skill in the art (“person of ordinary skill”) concerning the design and synthesis of nucleotide analogues for use in DNA sequencing would have a graduate degree in chemistry or chemical biology or a related discipline. In addition, the person of ordinary skill would have knowledge of synthetic nucleotide chemistry and DNA sequencing methods including the underlying biological principles and several years of experience in the design, synthesis and characterization of nucleotide analogues. The graduate students who worked with the inventore, Dr. Jingyue Ju in the Department of Chemical Engineering at Columbia University would be examples of persons of ordinary skill in the art

which Dr. Ju would have had such training but for greater experience and expertise (Exhibit 2033, Trainor Decl., ¶41 and 42)

V. The State of the Art

In 1977 two methods of DNA sequencing were described; one by Maxam and Gilbert (Exhibit 2024) and another by Sanger et. al. (Exhibit 2025). The latter became known as the Sanger dideoxy method (or the irreversible termination method) and was more widely used (Exhibit 2033, Trainor Decl., ¶19)

The Sanger dideoxy method has various drawbacks but as a result of ongoing improvements including the introduction of unique fluorescently labeled dideoxy nucleotide analogues by Prober, Trainor and others (Prober I, Exhibit 1033) the method continued to be widely used. An improved version of the Sanger dideoxy sequencing method involving irreversible chain terminators and capillary electrophoresis was the state of the art technology used for the Human Genome Project (Exhibit 2033, Trainor Decl., ¶20-33)

Beginning in the late 1980s efforts commenced to address the shortcomings in the Sanger dideoxy method, particularly the “bottleneck” created by the need to use electrophoresis. One approach focused on a sequencing by synthesis approach based on release of phosphates upon incorporation of nucleotide triphosphates into a primer extension strand (pyrosequencing) while a second method focused on including a detectable label as part of a removable 3’ capping group on the 3’OH

of the sugar (also referred to as the BASS method.) (Exhibit 2033, Trainor Decl., ¶24-29).

During the 1990s, despite some interest in base-labeled nucleotide analogues, efforts focused on including a label on the 3'OH group on the sugar in a nucleotide analogue and on the design and synthesis of new nucleotide analogues that could be incorporated by a polymerase into a primer extension strand. Results were mixed and it was recognized that new nucleotide analogues were needed for BASS sequencing. (Exhibit 2033, Trainor Decl., ¶30-35)

By October 6, 2000 Dr. Ju and his colleagues at Columbia University had conceived and filed patent applications for novel nucleotide analogues having features never before combined in a nucleotide analogue and having the desired property of being incorporated by a polymerase into a nucleic acid primer extension strand. These nucleotide analogues were detectable when incorporated and therefore the incorporated nucleotide analogue could be identified. As a result, the complementary nucleotide in a template whose sequence was desired could be determined. This represented the first stage in the development of what subsequently proved to be a technically and commercially successful method for sequencing DNA by synthesis, (Exhibit 2033, Trainor Decl., ¶36-38).

Later developments followed but the design and synthesis of these novel nucleotide analogues that were incorporated into a primer extension strand was the critical development and is the invention described in the claims (Exhibit 2033, Trainor Decl, ¶38.) More than five years later, even Petitioner Illumina was filing patent applications describing the formidable obstacles associated with the design and synthesis of nucleotide analogues that could be used in sequencing by synthesis. (Exhibit 2033, Trainor Decl., ¶ 38)

VI. Applicable Legal Principles

A. Nonobviousness Under 35 U.S.C. §103

A claimed invention is obvious under 35 U.S.C. §103 “if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.” Obviousness is a legal question based on underlying factual findings including: (1) the scope and content of the prior art, including what the prior art teaches explicitly and inherently; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 14 (1966). Objective indicia of nonobviousness when present must be considered in order to determine obviousness. *Transocean Offshore Deepwater Drilling, Inc. v.*

Maersk Drilling USA, Inc., 699 F.3d 1340, 1349 (Fed. Cir. 2012). A party seeking to invalidate a patent as obvious must demonstrate “that a skilled artisan would have had reason to combine the teachings of the prior art reference to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.” *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012).

A determination of whether a new chemical compound would have been *prima facie* obvious over particular prior art compounds follows a two part inquiry. *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). First, “the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or start points, for further development efforts,” and second “whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify the lead compound to make the claimed compound with a reasonable expectation of success.” *Id.* at 1291-92.

B. The Petitioner’s Burden of Proof

35 U.S.C. § 316(e) states “[i]n an inter partes review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.” The Federal Circuit has

defined a preponderance of the evidence as meaning “the greater weight of the evidence, evidence which is more convincing than evidence which is offered in opposition to it.” *Jazz Photo Corp. v. U.S.*, 439 F.3d 1344, 1350 (Fed. Cir. 2006).

VII. The Challenges on the Basis of Which Trial Was Instituted

Inter Partes Review of the ‘869 Patent has been authorized based on the following challenges:

- I. Claims 12, 13, 17, 20-26, 28, 29, 31 and 33 under 35 U.S.C. § 102(b) as anticipated by Tsien et al., PCT Publication WO 91/06678 (Exhibit 1002) (“Tsien”);
- II. Claims 15 and 16 under 35 U.S.C. §103(a) as obvious in view Tsien and Prober et al., *Science* 238, 336-341 (1987) (Exhibit 1003) (“Prober I”);
- III. Claims 12, 13, 17, 20-23, 25, 26, 28, 29 and 31 under 35 U.S.C. § 102(a) as anticipated by Stemple et al., U.S. Patent No. 7,270,951 (Exhibit 1008) (“Stemple III”)
- IV. Claims 15 and 16 under 35 U.S.C. §103(a) as obvious in view of Stemple III and Anazawa et al., PCT Publication WO 98/33939 (Exhibit 1011) (“Rabani”);

(Paper 38 at 33; Paper 54 at 18; Exhibit 2033, Trainor Decl., ¶1)

VIII. The Substitute Claims

Columbia has today filed a motion to amend replacing the challenged claims with substitute claims 34, 35, 37, 38, 41-50, 52 and 53. Substitute claim 34 corresponds to challenged claim 15, which depended from challenged claim 12, simply rewritten as an independent claim. All other substitute claims depend from substitute claim 34.

As explained in the motion to amend there is no basis to deny the motion and Columbia responds to the grounds of challenge on the basis of the substitute claims.

IX. The Substitute Claims Are Not Anticipated by Tsien or Stemple III

A. Proposed Substitute Claims 34-54

Substitute claim 34 is claim 15 rewritten as an independent claim. Each of claims 35-54 depend directly or indirectly from claim 34. A trial on the ground of anticipation under 35 U.S.C. §102 by Tsien or by Stemple III was not instituted with respect to claim 15. Therefore, substitute claim 34 obviates the challenges under 35 U.S.C. §102 on the basis of Tsien and on the basis of Stemple III.

X. Substitute Claims 34-54 Are Not Obvious In View of Tsien and Prober I

A key aspect of substitute claims 34-54 is the use of a novel nucleotide analogue in which the following features are combined;

- a) includes a deaza-substituted base to which a label is attached;
- b) includes a removable chemical moiety capping the 3'OH group of the sugar; and
- c) is incorporated into a nucleic acid primer extension strand

(Exhibit 2033, Trainor Decl., ¶33-59)

A. Illumina failed to Identify in Tsien's Description a Starting Point for Making Novel Nucleotide Analogues

In order to assess the obviousness of the nucleotide analogue and methods recited in substitute claims 34-54 there must be a starting point as part of a rationale. However, in its Petition and in the supporting Declaration of Dr. Weinstock no starting point is identified and no rationale for the obviousness of the novel nucleotide analogue is provided (Exhibit 2033, Trainor Decl., ¶49-52, 55.) For this reason alone, Illumina's Petition is fatally defective.

Nevertheless, Columbia has attempted to identify a starting point for an obviousness analysis in Tsien. Specifically, Columbia has, with Dr. Trainor's input, determined that the logical starting point to a person of ordinary skill would be the 3'-OH labeled nucleotide described as preferred in Tsien. Columbia has then applied an obviousness analysis based on the 3'-OH labeled nucleotides being the starting point. The only other starting point Columbia can envision is the base-

labeled nucleotide analogues described in Tsien. (Described below, see Exhibit 2033, Trainor Decl., ¶¶49-87 for a detailed discussion.)

Applying either analysis leads to the same result: substitute claims 34-54 are not obvious in view of Tsien and Prober I.

B. Tsien's 3'-OH Labeled Nucleotide Analogues as a Starting Point

Since Tsien's stated preference is to use a 3'-OH labeled nucleotide analogue which incorporates a label as part of a removable 3'-OH blocking group and since the only examples in Tsien, examples 1-6, concern a 3'-OH labeled nucleotide analogue a person of ordinary skill in the art would have understood this to be the starting point for making new nucleotide analogues given Tsien's focus and the focus in the art on such an approach. (Exhibit 2033, Trainor Decl., ¶¶49-52, 53-58.)

With Tsien's 3'-OH labeled nucleotide analogues as a starting point there would have been at least five differences between the 3'-OH labeled nucleotides of Tsien and the nucleotide analogues recited in the claims. (Exhibit 2033, Trainor Decl., ¶59.)

1. No Reason To Make Changes to Tsien's 3'-OH Labeled Nucleotide Analogues

With the 3'-OH labeled nucleotide analogues of Tsien as a starting point the person of ordinary skill would have had no reason to make any changes and certainly no reason to make the multiple changes needed to address the differences

between Tsien's 3'-OH labeled nucleotides and the nucleotide analogues recited in the substitute claims. (Exhibit 2033, Trainor Decl., ¶¶60-65 and ¶¶68-77.)

Specifically, there would have been no reason to change the preferred reversibly terminating 3'OH labeled nucleotide analogues of Tsien to move the label from the 3'OH group to the base since introducing modifications at two positions in a nucleotide analogue would have been understood by a person of ordinary skill to be more likely to result in a nucleotide analogue that a polymerase would not incorporate into a primer extension strand (Exhibit 2033, Trainor Decl., ¶¶50).

Further, there would have been no reason for a person of ordinary skill to change the purine bases in the nucleotide analogues of Tsien to deaza-purine analogues since no problem was described with the purine bases which are the natural bases normally incorporated by polymerases and since Tsien provided non-deaza examples. Illumina has suggested a reason to change the purines to deazapurines were possible problems associated with sequencing G:C rich DNA sequences. However, in the context of the claimed invention which concerns the identification of a single nucleotide analogue incorporated into a primer extension strand, a person of ordinary skill would have understood that there would be no

problems associated with sequencing G:C rich regions (Exhibit 2033, ¶¶74-77). Therefore, this argument is nothing more than a red herring.

Still further, one of ordinary skill seeking to make new reversibly terminating 3'-OH labeled nucleotide analogues would not have looked to the irreversibly terminating ddNTPs of Prober I which were not, and could not be modified to be reversible chain terminators (Exhibit 2033, Trainor Decl., ¶¶90)

2. No Basis for Reasonably Expecting Success in Making the Claimed Invention

Even if one of ordinary skill would have been motivated to make new nucleotide analogues based on Tsien's 3'-OH labeled nucleotide analogues as a starting point, a person of ordinary skill confronting the many differences between Tsien's 3'-OH labeled nucleotides and the nucleotide analogues recited in the claims would have had no basis for reasonably expecting he or she would be successful. Since neither Tsien nor Prober I disclose any chemistry relevant to making such a nucleotide analogue, a person of ordinary skill would have had to design new chemical procedures to attempt to address the differences between the nucleotide analogues described by Tsien and the nucleotide analogue recited in the claim. Designing new synthetic procedures involves many uncertainties inherent in chemistry and chemical synthesis as well as the additional uncertainty whether any nucleotide analogue once made, would be incorporated into a primer extension

strand. Therefore, a person of ordinary skill would not have had any reasonable expectation of success (Exhibit 2033, Trainor Decl., ¶¶66, 78-87.)

Given both the lack of reason to make the nucleotide analogues recited in the claims and the lack of any basis for reasonably predicting success in making substitute claims 34-54 would not have been obvious to a person of ordinary skill in view of Tsien and Prober I.

C. Tsien's Base-Labeled Nucleotide Analogues As A Starting Point

If contrary to the understanding of a person of ordinary skill and the lack of any suggestion to do so, a person of ordinary skill assumed that the starting point for making new nucleotide analogues would be Tsien's base-labeled nucleotide analogues, at least 7 differences exist between Tsien's base-labeled nucleotide analogues and the nucleotide analogues and these differences would have had to be addressed (Exhibit 2033, Trainor Decl., ¶¶67.)

1. No Reason to Make Changes to Tsien's Base-Labeled Nucleotides

Once again a person of ordinary skill would have had no reason to make any, let alone all, of the 7 changes needed or to look to Prober I to address any of these 7 differences, let alone all of them (Exhibit 2033, Trainor Decl., ¶¶68-77.)

Thus, there was no reason to use a deaza-purine labeled at the 7-position given Tsien's specific guidance to the contrary that a label on the 8-position of a non-deaza purine was "ideal." (Exhibit 2033, Trainor Decl., ¶¶70-73.)

Further, there would have been reason to change the uncleavable linkers on the 8-position of the purine labeled nucleotide analogues of Tsien to a cleavable linker, particularly since the linker in Prober I is uncleavable (Exhibit 2033, Trainor Decl., ¶73.)

Still further, as noted above, Illumina's red herring reason to solve a problem with sequencing G:C rich regions is not applicable to the claimed invention which only recites incorporation of a single nucleotide analogue and detection of this incorporated nucleotide. In this context no such problem existed and a person of ordinary skill would have known no such problem existed. (Exhibit 2033, Trainor Decl. ¶¶74-77.)

2. No Basis For Reasonably Expecting Success in Making the Invention

Once again, if despite all the reasons not to do so a person of ordinary skill in the art were motivated to make a nucleotide analogue having all the features combined in the nucleotide analogue recited in the claims, he or she could not have done so by combining the description in Tsien's and Prober I (Exhibit 2033, Trainor Decl., ¶78.) The linkers in Prober are uncleavable (Exhibit 2033, ¶79.) The

ddNTPs of Prober I cannot be modified to convert them into dNTPs (Exhibit 2033, Trainor Decl., ¶80.) New chemical procedures would have been needed, the development of which were fraught with difficulties and uncertainties (Exhibit 2033, ¶81-82.)

Dr. Weinstock repeatedly disclaimed any knowledge of the chemistry needed to synthesize novel nucleotide analogues merely predicting nucleotide analogues having the features recited in the claims could be made.

His musings are totally speculative and unsupported by any scientific reason or literature. The persons with whom he testified he consulted concerning synthetic chemistry recognized there were formidable problems (Exhibit 2033, Trainor Decl., ¶83-84.)

A person of ordinary skill would not have had any basis for reasonable expectation that such nucleotide analogues could be successfully made or if made would be successfully incorporated by a polymerase given the prior art history of mixed results (Exhibit 2033, ¶86-87.)

Therefore, in view of the preceding, a person of ordinary skill looking at Tsien and Prober I would have had neither a reason to make the nucleotide analogues recited in the claims nor a reasonable expectation of success of doing so nor a reasonable expectation success of using them in the claimed method which

requires incorporation. Therefore, substitute claims 34-54 would not have been obvious to one of ordinary skill in view of Tsien and Prober I.

XI. Substitute Claims 34-54 Are Not Obvious In View of Stemple and Anazawa

A. Illumina Failed to Identify In Stemple's Description A Starting Point for Making Novel Nucleotide Analogues

In order to assess the obviousness of a compound as recited in substitute claims 34, 35, 37, 38, 41-50, 52 and 53, the person of ordinary skill must start at a starting point as part of a rationale. However, Illumina's Petition and in the supporting declaration of Dr. Weinstock no starting point is identified and no rationale for the obviousness of the novel nucleotide analogue is provided (Exhibit 2033, Trainor Decl., ¶¶89-94, 96.) For this reason alone Illumina's Petition is fatally defective.

Nevertheless, Columbia has attempted to identify a starting point for an obviousness analysis in Stemple III. Specifically, Columbia has determined that the logical starting point to a person of ordinary skill would be the 3'-OH labeled nucleotide described as preferred in Stemple III. Columbia has then applied an obviousness analysis based on this starting point. The only other starting point Columbia can envision is the base-labeled nucleotide analogues described in

Stemple III. (See Exhibit 2033, Trainor Decl., ¶¶95-140 and 193-220 for a detailed discussion by Dr. Trainor.)

Applying either analysis leads to the same result: substitute claims 34, 35, 37, 38, 41-50, 52 and 53 are not obvious in view of Stemple III and Anazawa.

B. Stemple's 3'-OH Labeled Nucleotide Analogues As A Starting Point

Since Stemple III stated preference is to use a 3'OH labeled nucleotide analogue which incorporates a label as part of a removable 3'-OH blocking group and since the only examples in Stemple III concern a 3'-OH labeled nucleotide analogue a person of ordinary skill in the art would have understood this to be the starting point for making new nucleotide analogues given the focus in Stemple III and in the art on such an approach. (Exhibit 2033, Trainor Decl., ¶100-108.)

With the 3'-OH labeled nucleotide analogues of Stemple III as a starting point there would have been at least six (6) differences between the 3'-OH labeled nucleotides of Stemple III and the nucleotide analogues recited in the claims. (Exhibit 2033, Trainor Decl., ¶100.)

1. No Reason to Make Changes

With the 3'-OH labeled nucleotide analogues of Stemple III as a starting point the person of ordinary skill would have no reason to make any changes and certainly no reason to make the multiple changes needed to address the differences

between Stemple III 3'-OH labeled nucleotides and the nucleotide analogues recited in the claims. (Exhibit 2033, Trainor Decl., ¶101-106.)

Specifically, there would have been no reason to change the preferred reversibly terminating 3'-OH labeled nucleotide analogues of Stemple III to move the label from the preferred position of being on the 3'-OH group to the base because introducing modifications at two positions in a nucleotide analogue would have been thought to more likely to result in a nucleotide analogue that did not incorporate into a primer extension strand. (Exhibit 2033, Trainor Decl., ¶107.)

2. No Basis for Reasonable Expecting Success in Making the Invention

There also would have been no expectation that any modification of the 3'-OH labeled nucleotide analogues of Stemple III would be incorporated by a polymerase. (Exhibit 2033, Trainor Decl., ¶107.)

C. Stemple's Base-Labeled Nucleotide Analogues As A Starting Point

If, contrary to the understanding of a person of ordinary skill and the lack of any suggestion to do so, a person of ordinary skill assumed that the starting point for making new nucleotide analogues would be Stemple III's base-labeled

nucleotide analogues at least 4 differences between Stemple III's base-labeled nucleotide analogues and the nucleotide analogues would have had to be addressed (Exhibit 2033, Trainor Decl., ¶108.)

1. No Reason to Make Changes

Once again a person of ordinary skill would have had no reason to make many of the changes needed or to look to Arazawa to address any of the 4 differences let alone all of them (Exhibit 2033, Trainor Decl., ¶109-122.)

2. No Basis for Reasonable Expecting Success in Making the Invention

Once again if despite all the reasons not to do so a person of ordinary skill in the art were motivated to make a nucleotide analogue having all the combined features as recited in the claims he or she could not have done so by combining the description in Stemple III and Arazawa. The (Exhibit 2033, Trainor Decl., ¶¶128-135.)

3. A Person of Ordinary Skill Would Have To Proceed Contrary to Stemple III and Anazawa to Arrive at the Claimed Invention

To arrive at the invention of proposed claim 34, a person having ordinary skill would have had to proceed contrary to Anazawa's express teaching to not cap the 3'-OH position when labeling the base, and instead synthesize a nucleotide that has both "a base that is attached to a detectable label through a cleavable linker," as well as "a cleavable chemical group capping the 3'OH group," where each had to have been cleavable by means other than light. Additionally, one would have had to also use a deazapurine base, a further deviation from the three types of nucleotide analogs taught by Stemple III and Anazawa. (Exhibit 2033, Trainor Decl., ¶¶123-127.)

4. The Combination of Stemple III and Anazawa Would Not Teach a Person of Ordinary Skill Every Feature of the Claims

The only two reasonable starting points in Stemple III, i.e. the nucleotide analogues of Fig. 1A or of Fig. 1B, if combined with Anazawa cannot result in the nucleotide analogue as claimed. (Exhibit 2033, Trainor Decl., ¶¶136-140.)

XII. Illumina's Late Submitted New Evidence

During re-direct examination during Dr. Weinstock's recent deposition Illumina, despite the objections of Columbia's counsel improperly marked five documents as exhibits (Exhibits 1029-1033) and adduced testimony concerning them. Columbia reserves the right to seek that these exhibits be stricken from the record since any such exhibits should have been filed previously and at a minimum Columbia's counsel should have been notified in advance of Illumina's intent to adduce testimony concerning these exhibits so that Columbia could have brought this matter to the Board's attention. Nevertheless, with prejudice to its other rights, Columbia's declarant Dr. Trainor has commented on Exhibits 1029-1033 in paragraph 141 to 192 of his declaration (Exhibit 2033.)

XIII. Objective Evidence of Nonobviousness

If the Trial Board finds Illumina's challenges establish a *prima facie* case of obviousness based on the first three *Graham* factors, evidence of objective indicia of nonobviousness (the fourth *Graham* factor) **must** be considered as part of the nonobviousness inquiry. *Transocean*, 699 F.3d at 1348-49. Objective evidence may be the most important nonobviousness evidence presented:

evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been

obvious in light of the prior art was not. ***This objective evidence must be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.***

Id. at 1349 (citations omitted; emphasis added).

Here, Illumina's obviousness challenges fail because objective evidence shows *inter alia*: (1) Dr. Ju's inventions have yielded unexpectedly improved properties and results not present in the prior art; (2) Dr. Ju's invention has received praise and awards; (3) Illumina's sequencing products are commercially successful because they use Dr. Ju's claimed products and methods; (4) Illumina copied the design of its nucleotide analogues from Dr. Ju; (5) there was skepticism in the field that nucleotide analogues and methods like those claimed in the Ju patents could ever be made to work for practical purposes; and (6) Illumina repeatedly attempted to license the challenged patents and to acquire Illumina's exclusive licensee IBS, including as recently as 2012.

**A. Objective Evidence Shows that Columbia's
Inventions Have Unexpected Properties
That Revolutionized the DNA Sequencing Industry**

Despite the lack of any reasonable expectation that a nucleotide analogue having all the features combined as recited in the claims – *i.e.*, with a removable chemical moiety capping the 3'-position of the nucleotide sugar, and a cleavably-linked label attached to the nucleotide base – would be incorporated into a primer

extension strand, such nucleotide analogues are in fact successfully and efficiently incorporated. (Exhibit 2033, Trainor Decl., ¶202.)

Importantly, Columbia's claimed nucleotide analogues and methods have unexpectedly yielded advantages that go far beyond incorporation of a single nucleotide analogue into a primer extension strand by a polymerase and detection of the incorporated nucleotide analogue – they have revolutionized the DNA sequencing industry. (Exhibit 2033, Trainor Decl., ¶¶203-214.)

Using the claimed nucleotide analogues and methods, Columbia reported successfully sequencing a 20-nucleotide DNA template, an important threshold in the development of sequencing technology. (Exhibit 2033, Trainor Decl., ¶¶204-208.) They did so using four nucleotide analogues, each having both a cleavably-linked label attached to the base (two pyrimidines and two deazapurines), and a removable chemical moiety capping the 3'-OH group of the sugar. (Exhibit 2033, Trainor Decl., ¶¶204-208.) It was unexpected that a 20-nucleotide DNA template could be successfully sequenced using such nucleotide analogues. (Exhibit 2033, Trainor Decl., ¶209.)

The nucleotide analogues and methods claimed in the patents also allowed sequencing of a 20-nucleotide DNA template *better* than another SBS sequencing method – pyrosequencing – a result that was unexpected. (Exhibit 2033, Trainor

Decl., ¶¶205-209.) In contrast to pyrosequencing, the nucleotide analogues and methods invented by Dr. Ju “clearly identified” all 20 nucleotides in the DNA template, including hard to sequence “repeat” regions containing runs of consecutive adenosine residues. (Exhibit 2033, Trainor Decl., ¶206.)

That clear identification was possible because Dr. Ju’s nucleotide analogues separated the removable chemical moiety capping the 3’-OH of the nucleotide sugar position from the cleavably-linked label attached to the nucleotide base. That separation resulted in nucleotide analogues that could be repeatedly incorporated into a primer extension strand and then detected. (Exhibit 2033, Trainor Decl., ¶209.)

Thus, not only was it unexpected that Dr. Ju’s claimed nucleotide analogues recited in the claims would be incorporated *at all* by a polymerase, it was very unexpected that they would yield significantly improved results compared to pyrosequencing.

Nucleotide analogues having all the features combined as in the claims have also been reported to provide “perfectly matched” readouts when used in SBS. For example, Batista et al. 2008 reported: “[w]e used Solexa sequencing technology (Seo et al., 2004) to generate 29,112,356 small-RNA cDNA reads that perfectly matched the *C. elegans* genome.” (Exhibit 2033, Trainor Decl., ¶210.) It would

have been difficult if not impossible to obtain such a large number of “perfectly matched” reads using pyrosequencing.¹ (Exhibit 2033, Trainor Decl., ¶¶210.)

The Batista paper is only one of hundreds that use nucleotide analogues that have the features recited in the claims to successfully sequence very long stretches of nucleotides. (Exhibit 2033, Trainor Decl., ¶¶211-212.) In fact, nucleotide analogues having the features in the claims have been used in “massively parallel” sequencing systems to quickly sequence entire genomes, a result that would have been entirely unexpected given the state of the art in October 2000.

Yet another unexpected property of and result associated with the methods of using the nucleotide analogue and methods recited in the claims is the ability to sequence DNA having G:C rich regions. (Exhibit 2033, Trainor Decl., ¶¶213-214.)

The foregoing provides evidence that properties of Columbia’s nucleotide analogs and the results achieved by the associated methods as claimed were unexpected relative to the state of the art in October 2000.

¹ Solexa was acquired by Illumina and is now Illumina Cambridge Ltd.

B. Dr. Ju's Invention Has Received Competitive Funding Awards and Has Been Described in Prestigious Journals

Dr. Ju's inventive work has received multiple competitive funding awards. (Exhibit 2033, Trainor Decl., ¶¶ 215-224.) Specifically, the work presented in the patents was supported by National Science Foundation ("NSF") award no. BES0097793. (Exhibit 2033, Trainor Decl., ¶¶217-218.) In connection with that award, the NSF ranked Dr. Ju's grant proposal as number two of 38 proposals considered, and all reviewers rated the proposal "Excellent to Very Good." (Exhibit 2033, Trainor Decl., ¶218.)

The nucleotide analogues and methods claimed in the patent-at-issue here are also described in several publications by Dr. Ju in the prestigious Proceedings of the National Academy of Sciences ("PNAS"). Among those publications is Ju, J. *et al.*, *Four-color DNA sequencing by synthesis using cleavable fluorescent nucleotide reversible terminators*, 103 PROC. NAT'L ACAD. SCI. 19635 (Oct. 2006) ("Ju 2006") (Ex. 2037). (Exhibit 2033, Trainor Decl., ¶219.) Reviewer comments for Ju 2006 indicated that the paper was in the top 10% in its field. (Exhibit 2033, Trainor Decl., ¶220.)

Reviewer comments also stated that "[Dr. Ju's] manuscript presents a novel approach involving DNA sequencing by synthesis using four fluorescent reversible terminators;" that it "clearly establishes a unique and robust strategy for DNA

sequencing by synthesis on a chip;” and that “the general principle shown in the manuscript can be extended to develop a very high throughput DNA sequencing chip system that can be used routinely for a wide range of applications.” (Exhibit 2033, Trainor Decl., ¶221.)

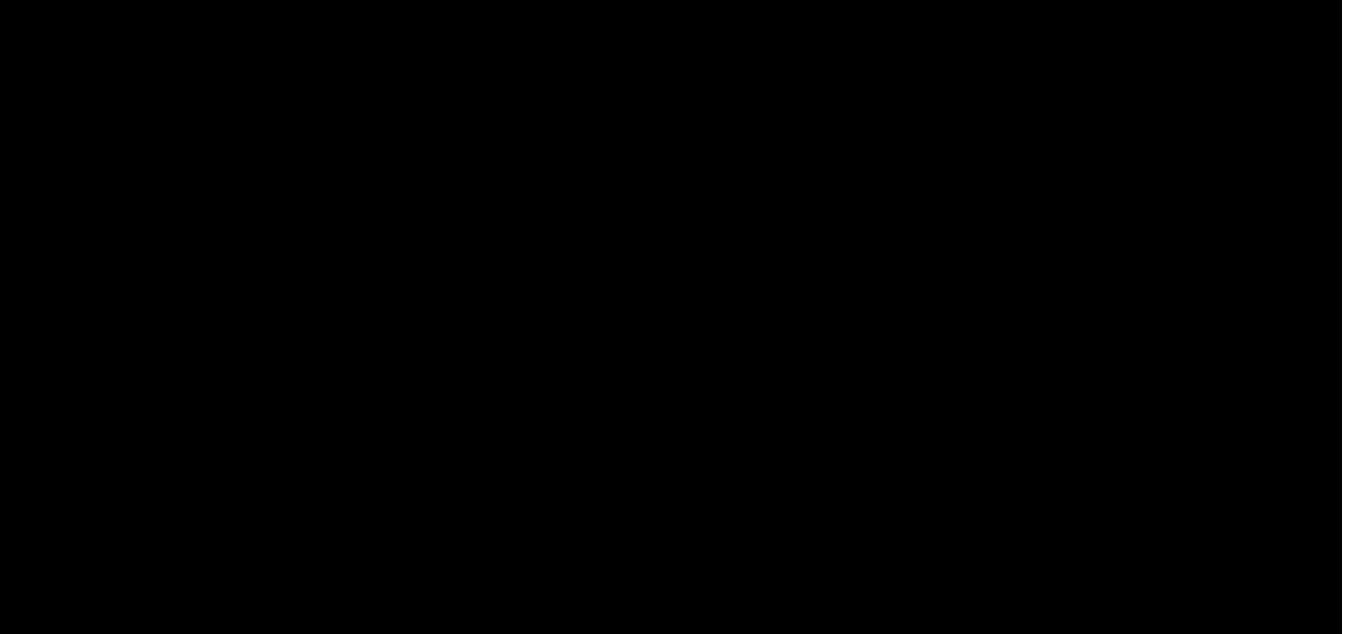
In addition, in 2001 Dr. Ju received a Packard Fellowship from the David & Lucile Packard Foundation, a private foundation that provides grants to non-profit organizations. (Exhibit 2033, Trainor Decl., ¶222.) The Packard Fellowship related to Dr. Ju’s SBS work and provided Dr. Ju with \$625,000 of funding for his SBS work. (Exhibit 2033, Trainor Decl., ¶222.)

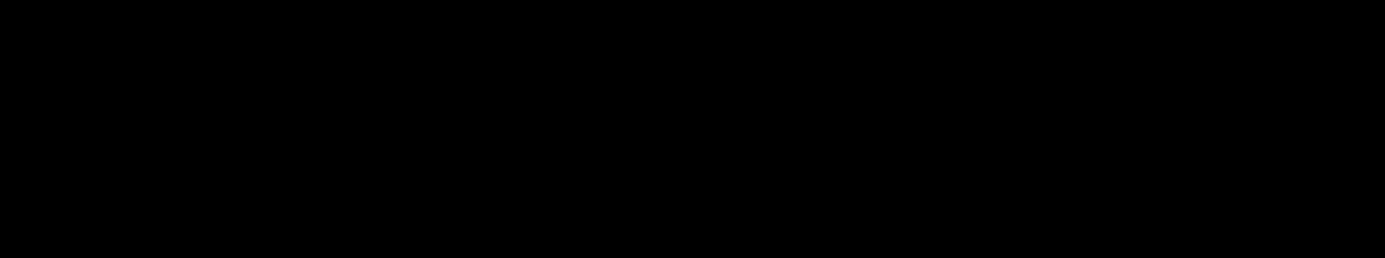
According to the Packard Foundation website, the Packard Foundation “established the Fellowships for Science and Engineering to allow the nation’s most promising professors to pursue science and engineering research early in their careers with few funding restrictions and limited reporting requirements.” (Exhibit 2033, Trainor Decl., ¶223.)

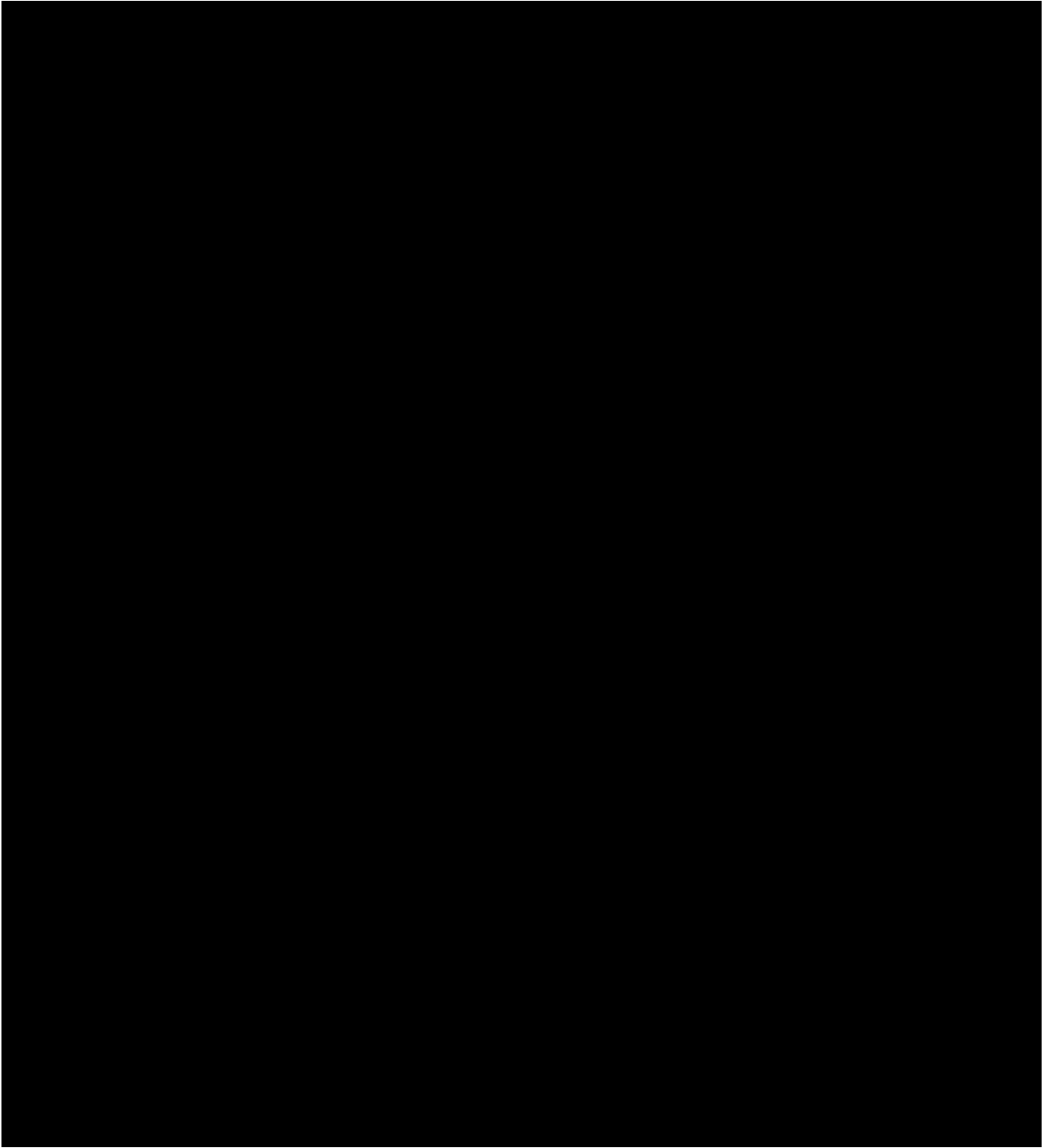
Thus, Dr. Ju’s inventions have been the subject of multiple competitive funding awards and journal publications, which is objective evidence that weighs against a finding of obviousness.

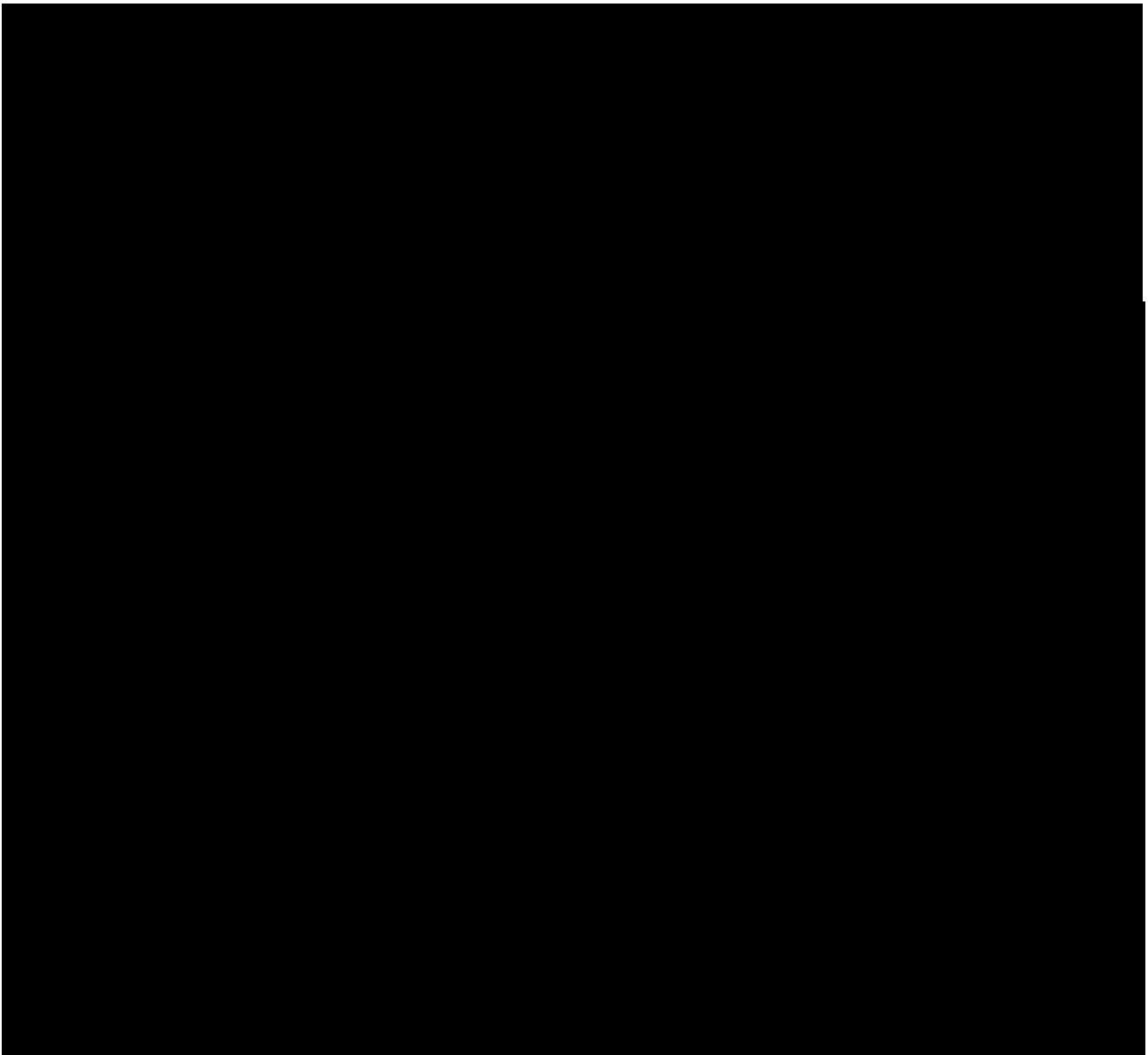
C. Columbia's Patented Sequencing Chemistry is Responsible for Illumina's Commercial Success

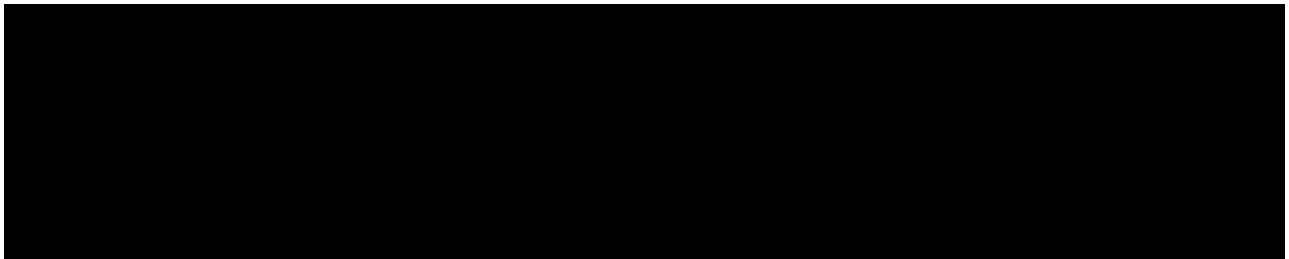
A showing of commercial success requires a nexus between the success of the commercial product and the claimed invention. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). Moreover, “[i]f the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus.” *Id.*





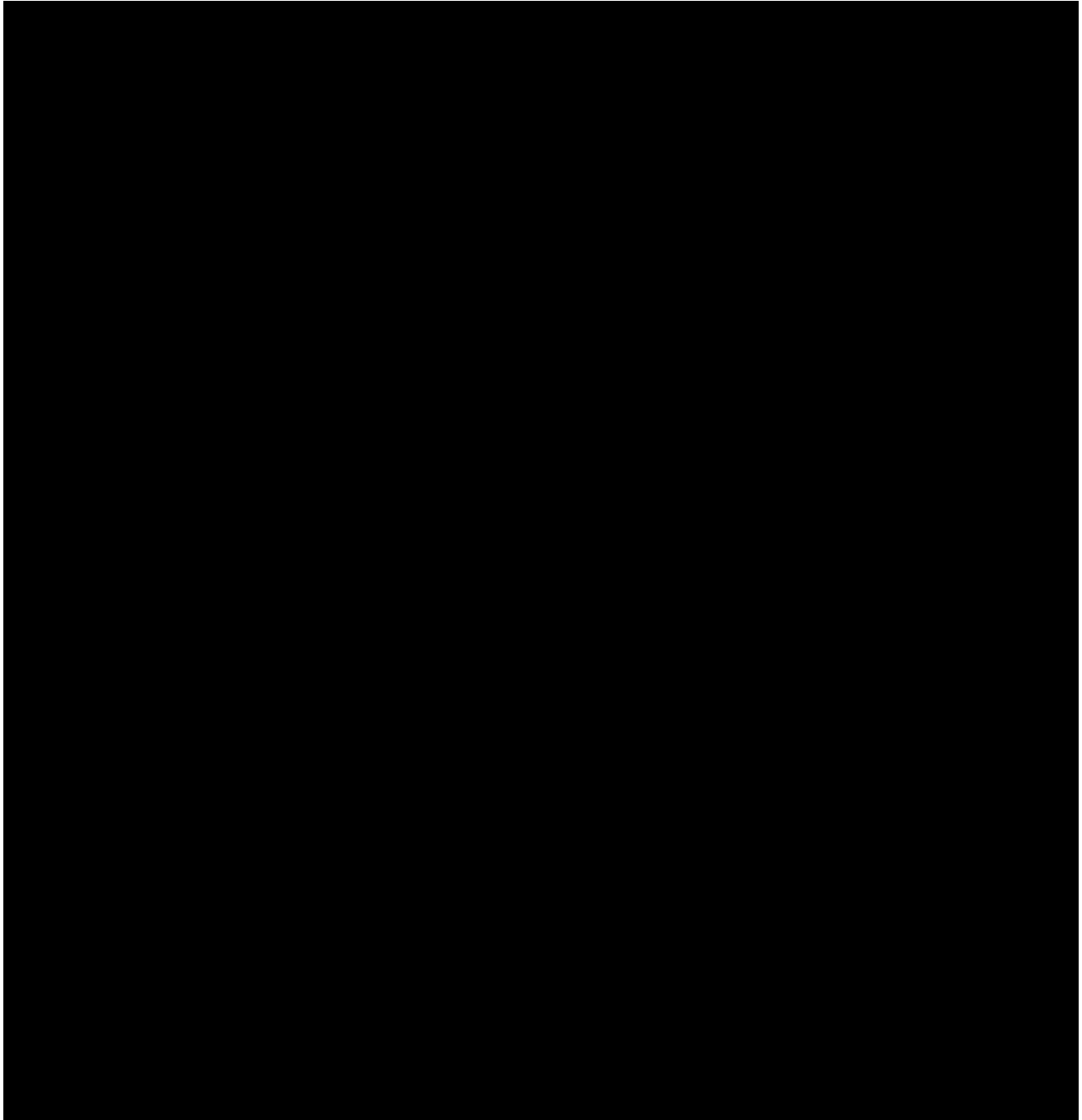








**D. Objective Evidence Permits a Strong Inference
That Illumina Copied Dr. Ju's Nucleotide Analogues**

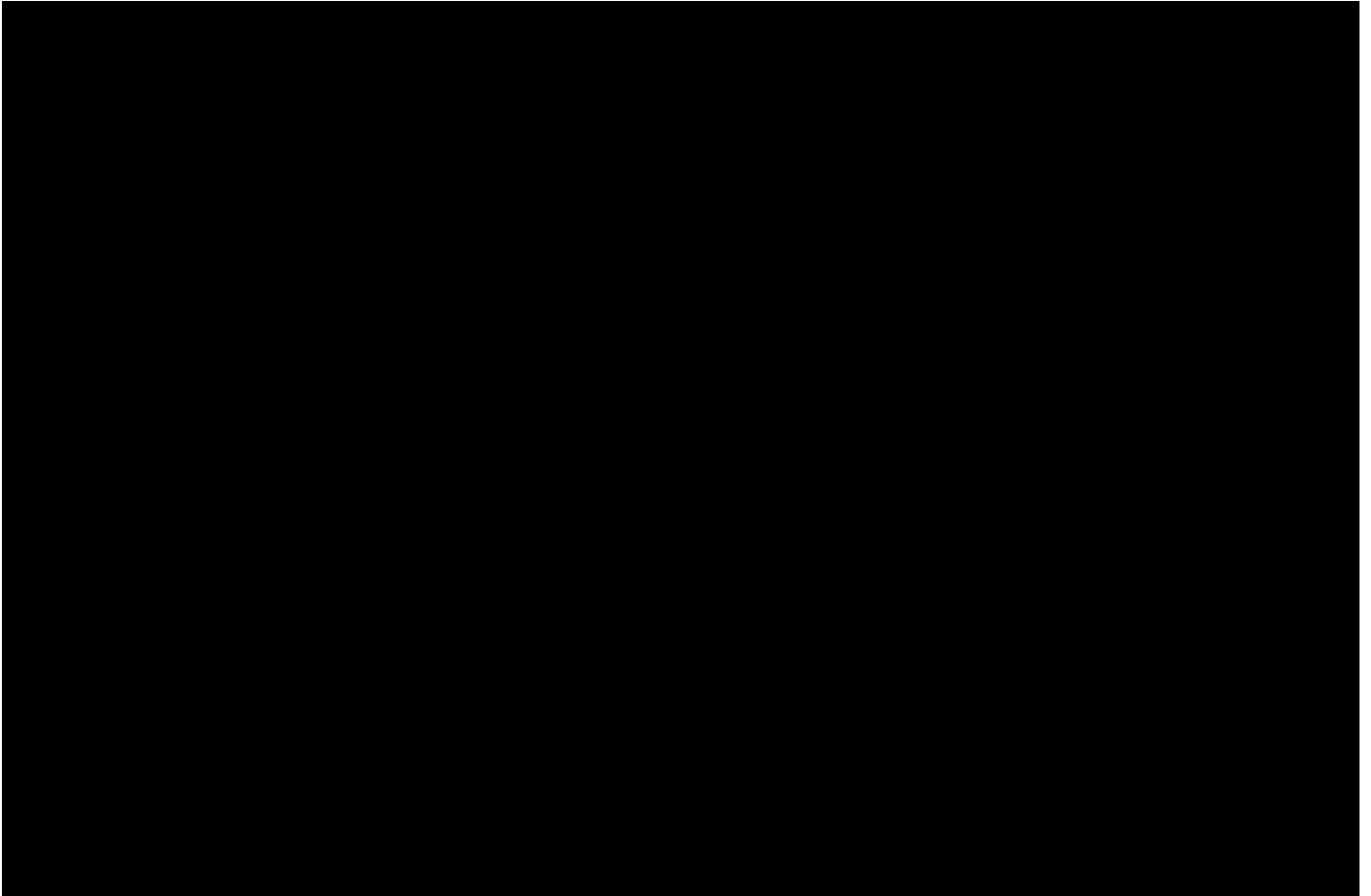


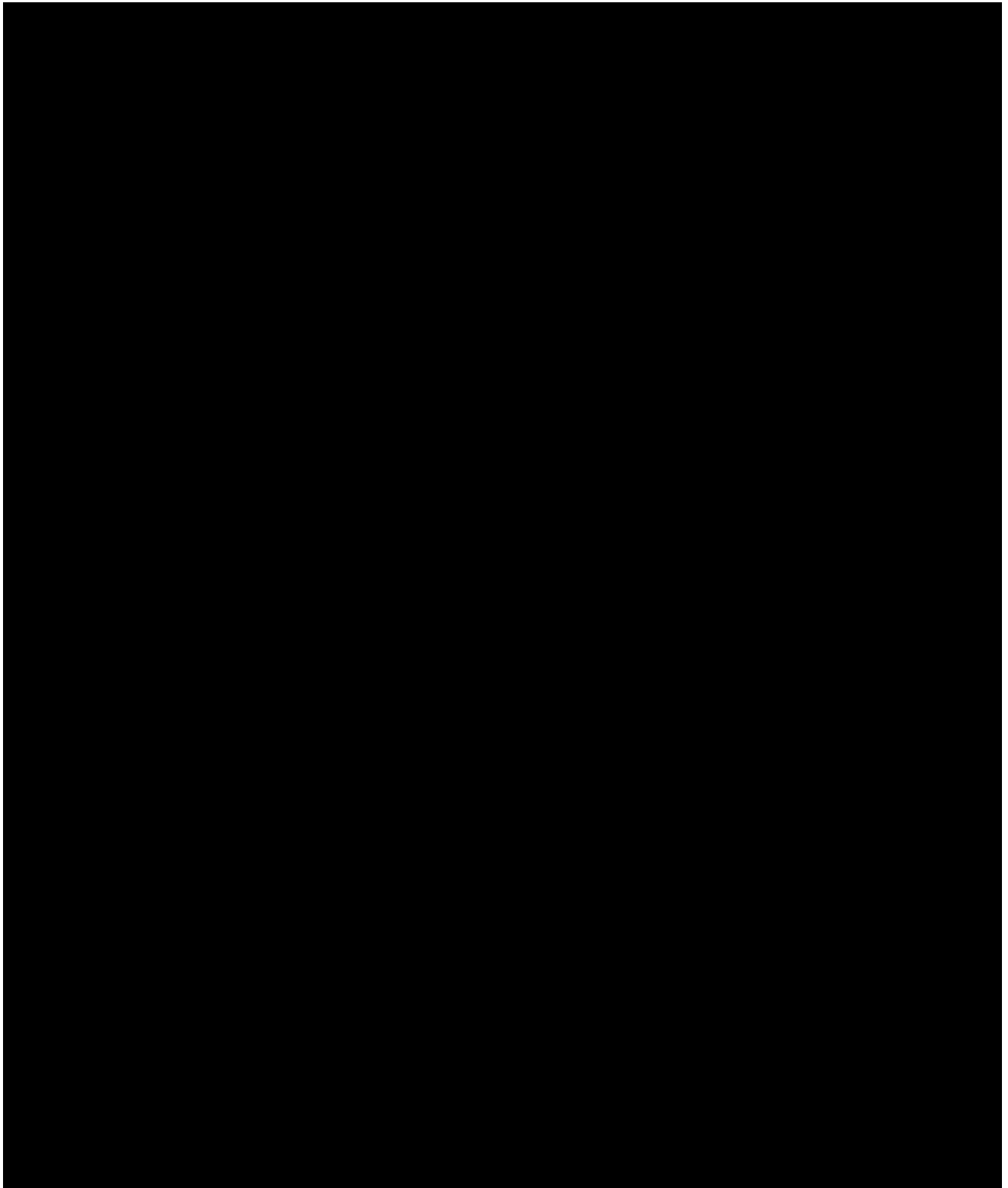
E. Others in the Field Were Skeptical that SBS Could Work

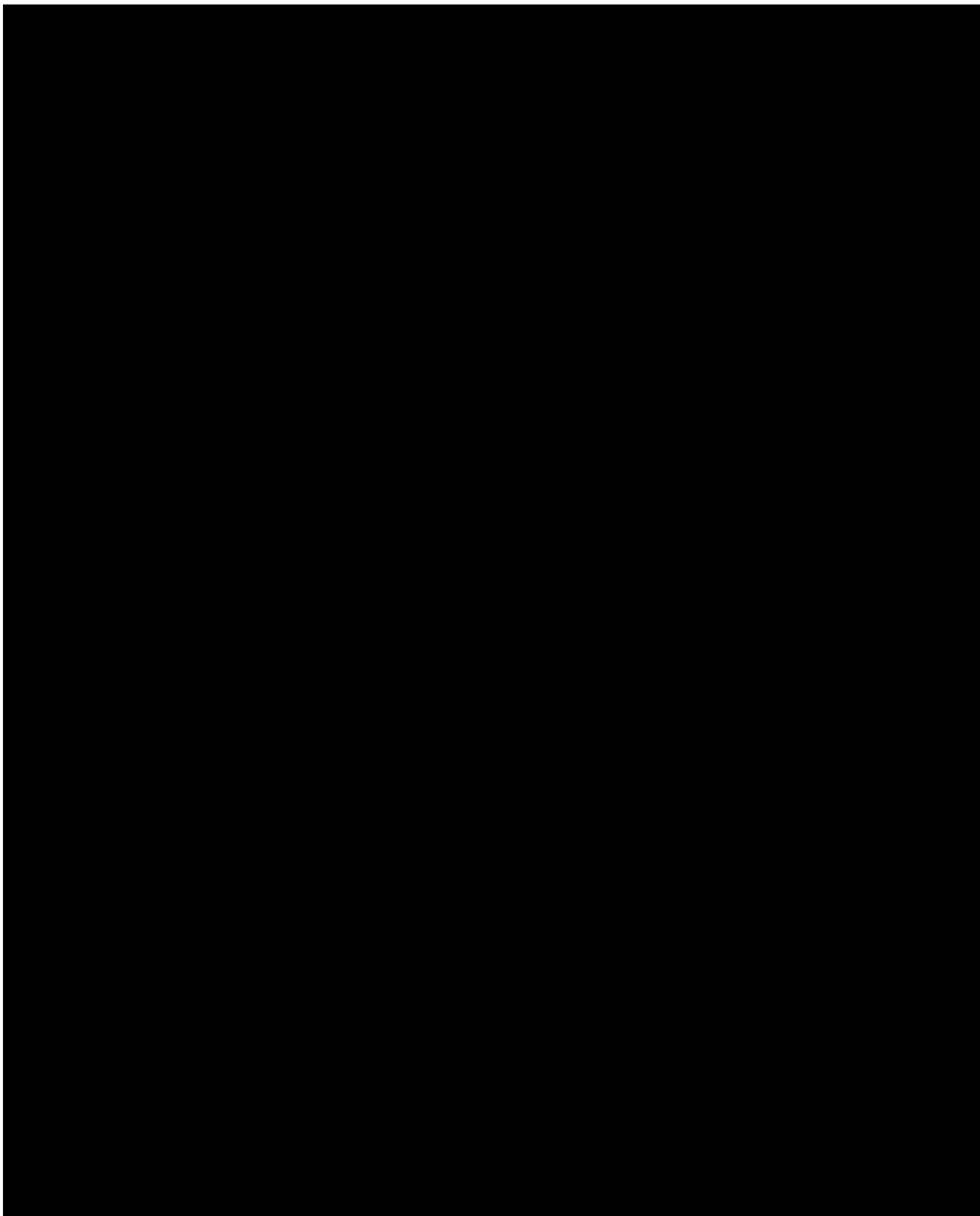


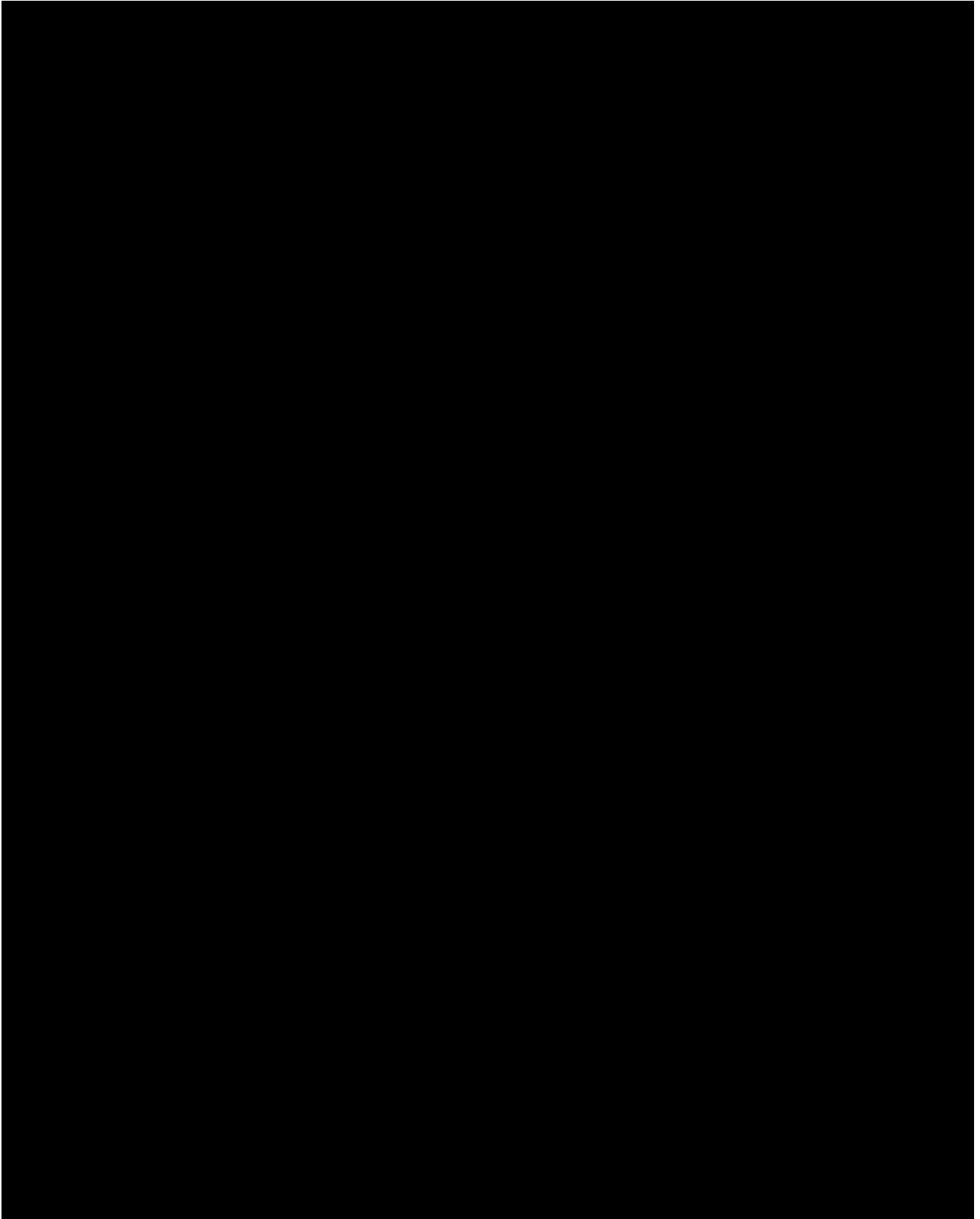
Such skepticism weighs in favor of nonobviousness.

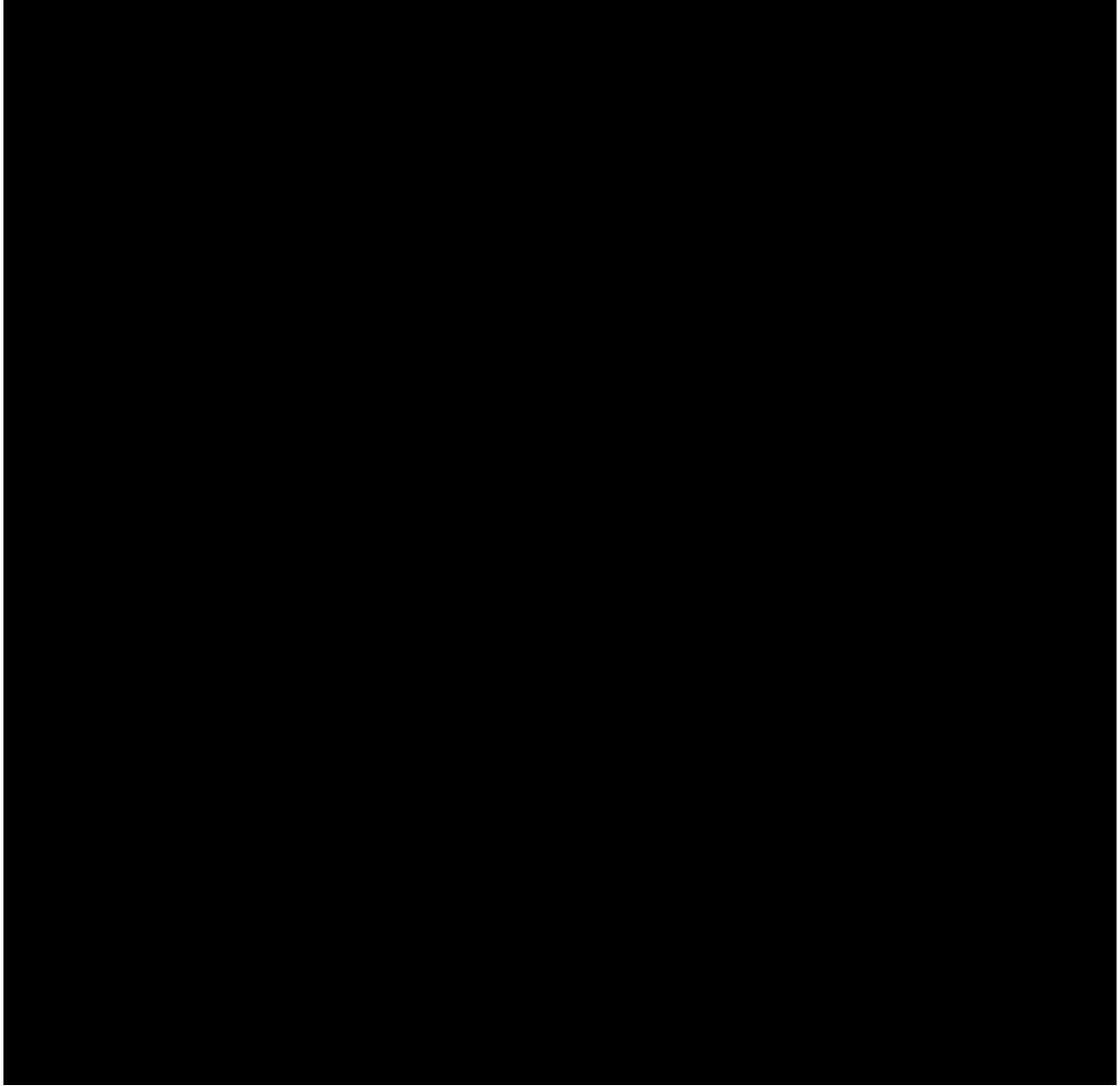
F. Illumina Attempted to License the Challenged Patents



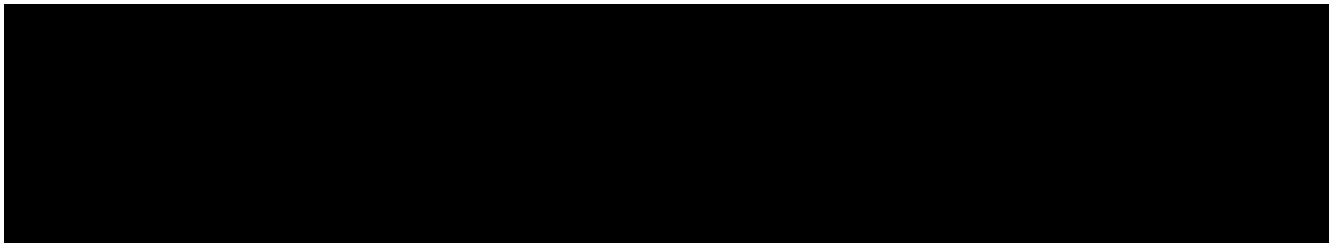


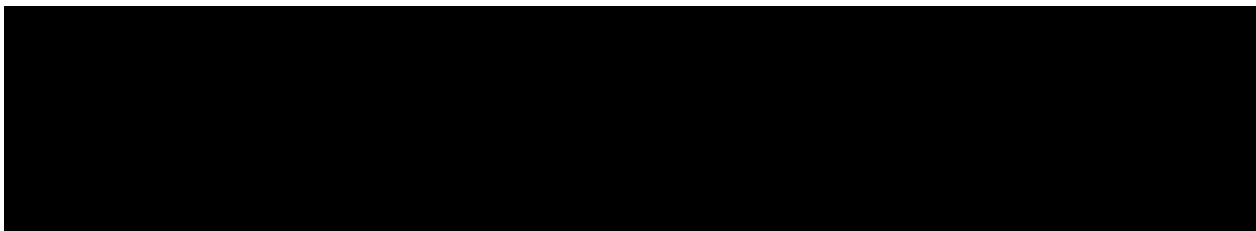






* * *





Case IPR2012-00007
U.S. Patent 7,790,869

Respectfully submitted,

Dated: June 25, 2013

/Donald J. Curry/

Donald J. Curry
Fitzpatrick, Cella, Harper & Scinto
1290 Avenue of the Americas
New York, NY 10104
Tel: (212) 218-2100
Fax: (212) 218-2200
ColumbiaIPR@fchs.com

John P. White (Reg. No. 28,678)
Lead Counsel for Patent Owner
Cooper & Dunham LLP
30 Rockefeller Plaza
New York, NY 10112
Tel: (212) 278-0421
Fax: (212) 391-0525
jwhite@cooperdunham.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ILLUMINA, INC.

Petitioner,

v.

Patent of THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF
NEW YORK
Patent Owner.

Case IPR2012-00007
U.S. Patent 7,790,869

CERTIFICATE OF SERVICE

I hereby certify that a SUBSTITUTE COLUMBIA PATENT OWNER RESPONSE UNDER 37 C.F.R. §42.120 in connection with IPR2012-00007 was served on this 30th day of August 2013 by electronic mail to Reinhart, Boerner, Van Deuren s.c., Counsel for Petitioner, at illuminaiprs@reinhartlaw.com, having a postal address at:

Reinhart, Boerner, Van Deuren s.c.
1000 North Water St., Suite 1700
Milwaukee, WI 53202

Dated: August 30, 2013

/Siew Yen Chong/
Siew Yen Chong