Filed: February 7, 2019

On behalf of **Illumina, Inc.** By: Kerry Taylor (Reg. No. 43,947) Michael L. Fuller (Reg. No. 36,516) William R. Zimmerman (pro hac vice) Nathanael R. Luman (Reg. No. 63,160) KNOBBE, MARTENS, OLSON & BEAR, LLP 2040 Main Street, 14th Floor Irvine, CA 92614 Telephone: 949-760-0404 Facsimile: 949-760-9502 Email: <u>BoxIllumina@knobbe.com</u>

Derek Walter (Reg. No. 74,656) <u>Derek.walter@weil.com</u> Edward R. Reines (pro hac vice) <u>Edward.reines@weil.com</u> <u>Illumina.Columbia@weil.com</u> WEIL, GOTSHAL & MANGES LLP 201 Redwood Shores Parkway Redwood Shores, CA 94065 Telephone: 650-802-3000 Facsimile: 650-802-3100

### UNITED STATES PATENT AND TRADEMARK OFFICE

## **BEFORE THE PATENT TRIAL AND APPEAL BOARD**

### ILLUMINA, INC. Petitioner

v.

## THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK Patent Owner

IPR2018-00291	Patent 9,718,852
IPR2018-00318	Patent 9,719,139
IPR2018-00322	Patent 9,708,358
IPR2018-00385	Patent 9,725,480*

## ILLUMINA MOTION TO EXCLUDE COLUMBIA EVIDENCE

<sup>\*</sup>This identical paper is being filed in each of these four IPRs.

# **TABLE OF CONTENTS**

Exclusion of Exhibit 2116 (Menchen Declaration)1
Exclusion of ¶¶31, 33-34 from Exhibit 2116 (Menchen Declaration)2
Exclusion of ¶¶38-39, 43 from Exhibit 2116 (Menchen Declaration)4
Exclusion of ¶¶94-97 from Exhibit 2116 (Menchen Declaration)5
Exclusion of ¶¶100-106 from Exhibit 2116 (Menchen Declaration)6
Exclusion of ¶109 from Exhibit 2116 (Menchen Declaration)
Exclusion of ¶51 from Exhibit 2116 (Menchen Declaration)8
Columbia selectively cites portions of Dr. Romesberg's deposition transcript (Exhibit 2140) in an incomplete and misleading fashion, and the selective citations should be excluded or read in fuller context under FRE 106, 401-403
Exclusion of Ex. 2140, 146:3-147:24, 148:11-149:179
Exclusion of Ex. 2140, 128:5-1310
Exclusion of Ex. 2140, 160:20-161:511
Exclusion of Ex. 2140, 173:2-6, 178:19-2411
Exclusion of Ex. 2140, 166:25-169:13, 178:19-24, 176:20-2212
Exclusion of Ex. 2140, 130:8-22, 134:1-136:23, 128:25-130:24, 152:8-25
Exclusion of Ex. 2140, 94:10-1513
Exclusion of Ex. 2140, 73:24-2514
Exclusion of Ex. 2140, 184:10-185:6, 186:13-187:7, 188:16-189:10

## TABLE OF CONTENTS (Cont'd)

Page No.

Exclusion of Ex. 2140, 41:22-42:14, 34:4-35:2, 39:16-40:24,	
39:16-39:251	5

# **TABLE OF AUTHORITIES**

Braun v. Lorillard Inc., 84 F.3d 230 (7th Cir. 1996)	2
Delaware Valley Floral Group, Inc. v. Shaw Rose Nets, LLC, 597 F.3d 1374 (Fed. Cir. 2010)	7
<i>General Elec. Co. v. Joiner</i> , 522 U.S. 136 (1997)	8
Pharmastem Therapeutics, Inc. v. ViaCell, Inc., 491 F.3d 1342 (Fed. Cir. 2007)	4

## **OTHER AUTHORITIES**

1	37 C.F.R. § 42.64
	37 C.F.R. § 42.65
passim	Fed. R. Evid. 106
9	Fed. R. Evid. 401
9	Fed. R. Evid. 402
passim	Fed. R. Evid. 403
passim	Fed. R. Evid. 702

Petitioner moves to exclude the following evidence under 37 C.F.R. §42.64.

## **Exclusion of Exhibit 2116 (Menchen Declaration)**

Columbia's attorneys spent 8-9 full days preparing Dr. Menchen to be deposed on Exhibit 2116. Ex. 1112, 12:8-13:6. Despite this extensive preparation, Dr. Menchen appeared to know very little about the very subjects on which he had opined in that exhibit. *Id.*, 235:19-237:18, 239:19-240:21, 262:6-17; Ex. 1113, 363:2-14, 374:16-376:8, 379:18-380:16, 381:2-6, 383:10-20. Not only did he not personally know, he claimed he was also unaware of what a POSA would have known in the relevant time frame on these topics. *Id.* Any opinions given on a topic where Dr. Menchen lacked relevant knowledge creates confusion regarding the scope of what he was actually testifying to and does not help a trier of fact decide an issue relevant to the IPR, so should be excluded under FRE 403 and FRE 702(a).

In addition, Dr. Menchen's declaration should be excluded under FRE 702 because his testimony is not based on sufficient facts or data. Columbia's attorneys instructed Dr. Menchen to review small portions of selected documents to form opinions on an overly narrow subset of issues in this proceeding. For example, he avoided forming an opinion on what can meet the claim limitations. Ex. 1112, 144:7-151:25, 248:13-249:14, 252:20-254:11. He avoided forming an opinion on whether any 3'-capping group meets the "small" limitation recited by Columbia's claims. *Id.*, 171:11-177:10, 179:11-180:9, 181:10-15, 240:22-241:9. He was unable to identify

any 3'-capping group that could be efficiently incorporated by a polymerase (id., 286:15-287:17, Ex. 1113, 378:5-380:16) or would meet the requirements of Columbia's patent. Ex. 1113, 323:2-11. He did not know how to determine whether a 3'-capping group is efficiently incorporated because he testified that "efficient" is a relative term. Id., 378:14-19. He admitted that he has no idea if any polymerases would work to incorporate nucleotides falling within Claim 1. Ex. 1112, 178:11-179:6, 239:19-240:21, 286:4-14. Dr. Menchen was instructed to review only a few pages of the prosecution history, and told to ignore other relevant portions of the prosecution history. Ex. 1112, 242:9-245:12. In answering leading questions on redirect, he repeatedly confirmed that he could not provide an opinion on any of these host of issues. Ex. 1113, 394:12-397:25. Columbia improperly put blinders on its testifying witness to prevent him from seeing and forming opinions based on the entire record of this proceeding. Columbia's tactics call into question the credibility of all of Exhibit 2116, and this exhibit should be excluded under FRE 702. See, e.g., Braun v. Lorillard Inc., 84 F.3d 230, 234-35 (7th Cir. 1996).

#### **Exclusion of ¶¶31, 33-34 from Exhibit 2116 (Menchen Declaration)**

Paragraphs 31, 33-34 of Exhibit 2116 should be excluded under FRE 403 and 702 because Dr. Menchen's testimony regarding Metzker's "Termination\*" is not the product of reliable scientific principles and creates the misleading impression that a POSA would believe that 3'-O-allyl nucleotides are inefficiently incorporated

by DNA polymerase. Dr. Menchen directly admitted "I'm not an expert on polymerases." Ex. 1112, 270:2-16. He admitted he's not an enzymologist (*id.*, 141:9-20), has never worked with a polymerase (Ex. 1112, 193:13-18, Ex. 1113, 347:9-25), has never worked with reversibly capped nucleotides (Ex. 1112, 218:13-18), and does not have sufficient knowledge of polymerases to determine whether a polymerase would efficiently incorporate 3'-O-allyl capped nucleotides. *Id.*, 141:21-142:5, 142:21-143:18, 178:22-179:6; 288:16-289:1. Dr. Menchen is not qualified to opine on polymerase-based enzymatic incorporation of nucleotide analogs.

In rendering his unsupported opinion on polymerase-based incorporation of nucleotide analogs, Dr. Menchen made up a cartoon of a gel banding pattern that supposedly supported his theory that "Termination\*" would have been interpreted as reporting inefficient 3'-O-allyl polymerase incorporation, which he acknowledged was unsupported by Metzker (Ex. 1016). Ex. 1112, 206:3-22, 210:20-23, 213:16-24. Instead, Dr. Menchen relied on Metzker 1998 (Ex. 2131), which he did not cite in his declaration. Ex. 1112, 211:8-212:10. Metzker's 1998 publication demonstrated, and Dr. Menchen agreed, that such a banding pattern is resolved into **efficient and complete** incorporation by modestly increasing nucleotide concentration. Ex. 2131, 816 ("Following enzymatic mop-up, the incorporation of 3'-O-methyl-dATP by AMV-RT shows complete termination without natural nucleotide read-through (Figure 3, lanes B)."); Ex. 1113, 428:17-431:21.

Dr. Menchen's unsupported conclusion that Metzker's "Termination\*" would lead a POSA to believe that 3'-O-allyl-nuclotides were unsuitable for sequencing is contradicted by his own patents. Dr. Menchen admitted he was motivated to include the 3'-O-allyl capping group in his sequencing patents because of Metzker's disclosure. Ex. 1112, 189:5-13. He further admitted that the 3'-O-allyl capping group was a good candidate for polymerase incorporation-based sequencing. Ex. 1112, 61:17-62:6, 64:25-65:12, 69:15-21, 78:17-79:4, 154:22-155:9, 156:4-12.

Dr. Menchen's testimony in paragraphs 31, 33-34 of Exhibit 2116 form the cornerstone of Patent Owner's briefs. POR, 18-21; Sur-Reply, 10. This unqualified and unreliable testimony should be excluded under FRE 702. *See, e.g., Pharmastem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1355 (Fed. Cir. 2007).

## Exclusion of ¶¶38-39, 43 from Exhibit 2116 (Menchen Declaration)

Paragraphs 38-39 and 43 of Exhibit 2116 should be excluded under FRE 403 and 702 due to Dr. Menchen's lack of expertise and his mischaracterization of the polymerase literature. In these paragraphs he hypothesizes that the 1% natural dATP contaminant in Metzker's 3'-O-allyl-dATP polymerase screen would have had no effect on Metzker's results. Dr. Menchen's hypothesis contradicts Dr. Metzker's 1998 publication (a reference that Dr. Menchen reviewed but failed to cite because he allegedly ran out of time). Ex. 1112, 211:8-212:9; Ex. 1113, 426:18-427:25. Metzker 1998 is specifically directed to a method whose sole purpose is removing

contaminant dNTP in order to provide more reliable results when testing modifieddNTPs. Ex. 2131, 814 (Abstract). Metzker 1998 explains that dATP contamination of less than 0.5% "remains sufficiently high that the DNA polymerase selectively incorporates the preferred natural dNTP over the 3'-O-modified-dNTP analog." Ex. 2131, 814. Metzker observed 3'-O-allyl-dATP-mediated termination in the presence of 2.5  $\mu$ M of natural dATP despite the higher background and decreased signal intensity caused by the natural dATP. Ex. 2131, 814; Ex. 1016, 4263. This incorporation in the face of competing natural dATP substrate contamination demonstrates the highly efficient incorporation of 3'-O-allyl-dATP by Vent(exo-) polymerase. Ex. 2126, 129:18-130:4. Dr. Menchen's unqualified and unreliable testimony attempting to ignore this fact by mischaracterizing the state of the art and failing to cite a known reference that undermines his opinion should be excluded.

### **Exclusion of ¶¶94-97 from Exhibit 2116 (Menchen Declaration)**

Paragraphs 94-97 of Exhibit 2116 should be excluded under FRE 702 because Dr. Menchen's testimony that a POSA would not have expected Vent(exo-) to incorporate 5-substituted pyrimidines (thymine/cytosine) or 7-substituted 7-deazapurines (adenine/guanine) does not reliably apply scientific principles to the facts of this case. Dr. Menchen ignores that Vent polymerase had been demonstrated in the prior art to incorporate nucleotides having labels attached at the 5-position of thymine/cytosine and 7-position of 7-deaza-adenine/guanine. Ex. 1040, 3228, 3230;

Ex. 1041, 4832-33; Petition, 31. Dr. Menchen further ignores Vent(exo-) variants that were known in the prior art to be even more tolerant toward incorporation of nucleotides with substituted bases and modified 3'-groups. Ex. 1122, 2552. It is not surprising that Dr. Menchen failed to address the Vent(exo-) polymerase incorporation literature because he openly and repeatedly admitted that he is not an expert in this area. Ex. 1112, 141:19-142:9, 142:21-143:9, 143:10-18, 178:22-179:6, 193:13-18, 270:2-16, 288:16-289:2. His unqualified opinion is contrary to the significant weight of evidence regarding Vent(exo-) polymerase incorporation, and his repeated disclaimer of any knowledge in this field—including knowledge about what a POSA would know or do—confirms that his opinions would not help the trier of fact. This testimony should be excluded under FRE 702.

#### **Exclusion of ¶¶100-106 from Exhibit 2116 (Menchen Declaration)**

Paragraphs 100-106 of Exhibit 2116 should be excluded under FRE 702 due to the unreliability of Dr. Menchen's testimony. He opines that Tsien's disclosure of the 3'-O-allyl capping group is a "large genus of compounds," or perhaps the "vinyl ether" instead of the allyl ether. Dr. Menchen's opinion in this proceeding is contradicted by Patent Owner's previous expert, Dr. Trainor, who affirmed that Tsien discloses the small 3'-O-allyl ether blocking group as meant by Patent Owner's patents (Ex. 1098, 107:12-108:20) and that such a small blocking group would not interfere with polymerase recognition. *Id.*, 154:10-156:6. Dr. Menchen's

opinion in this proceeding directly contradicts the established definition of "allyl" in Ex. 1099, 13, 305 (the IUPAC definition of "allyl" is "–CH<sub>2</sub>-CH=CH<sub>2</sub>"), as is further confirmed in numerous industry handbooks and textbooks recognizing that "allyl" refers to "–CH<sub>2</sub>-CH=CH<sub>2</sub>" such as Ex. 1101, 67; Ex. 1102, 2-71; Ex. 1103, 24; Ex. 1039, 503; Ex. 1104, 254; Ex. 1105, 209. Dr. Menchen never explains why Tsien's teachings should be interpreted contrary to the established definition of "allyl."

Dr. Menchen's basis for concluding that Tsien meant vinyl rather than the "allyl" as expressly stated by Tsien is not based on a reliable principle or method. Dr. Menchen argues that Gigg only applies Hg to cleave vinyl ethers in acetone/water, so Tsien must have meant vinyl, not allyl. In doing so, he willfully ignores that Gigg describes a 2-step deprotection of allyl ethers, where isomerization to vinyl was an intermediate step to removing the allyl, something he noted himself earlier in his own declaration. Ex. 2116 ¶54.

Dr. Menchen's unreliable testimony in paragraphs 100-106 of Exhibit 2116 is misleading, contrary to Patent Owner's prior expert's testimony, unsupported by the vast weight of the evidence, and should be excluded under FRE 403 and 702, and by estoppel. *Delaware Valley Floral Group, Inc. v. Shaw Rose Nets, LLC*, 597 F.3d 1374, 1381 (Fed. Cir. 2010) ("[W]hen a party has given clear answers to unambiguous questions which negate the existence of any genuine issue of material fact, that party cannot thereafter create such an issue with an affidavit that merely

contradicts, without explanation, previously given clear testimony.").

## **Exclusion of ¶109 from Exhibit 2116 (Menchen Declaration)**

Paragraph 109 of Exhibit 2116 should be excluded under FRE 702 because it is unsupported by any facts and is not the product of reliable scientific principles. Dr. Menchen provides a conclusory assertion that Illumina's Dower-based ground fails for the same reasons as the Tsien-based ground. Dr. Menchen fails to provide any facts or explanation supporting such a conclusion. He also does not provide any analysis of Dower's unique disclosures. Dr. Menchen's superficial treatment of Dower is not an expert opinion—it is simply unsupported argument. "[N]othing in either *Daubert* or the Federal Rules of Evidence requires a [] court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert." *General Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). Expert opinion must be based on sufficient facts, not conclusory assertions. 37 C.F.R. §42.65. Dr. Menchen's unsupported testimony should be excluded.

#### **Exclusion of ¶51 from Exhibit 2116 (Menchen Declaration)**

Dr. Menchen's ¶51 argues that labeled nucleotides were inefficiently incorporated by Vent (exo-) polymerase. This paragraph should be excluded under FRE 403 and 702 as misleading and unreliable. Dr. Menchen cites only a 1992 publication describing a CircumVent<sup>TM</sup> sequencing kit to allegedly support his position. Dr. Menchen, however, admitted he has no idea what a CircumVent<sup>TM</sup>

sequencing kit is. Ex. 1112, 186:24-187:11. Further, Dr. Menchen never cited Gardner (Ex. 1122), which in 1999 described that Vent polymerase "variants are [] more tolerant toward incorporation of nucleotides with substituted bases []." Ex. 1122, 2552. Dr. Menchen was not even aware of any modified polymerases (Ex. 1113, 347:9-25) or methods of screening polymerases. *Id.*, 344:23-345:23. Dr. Menchen never addressed the evidence presented in the petition that demonstrated incorporation of base-modified nucleotides using Vent polymerase. Ex. 1040, 1041. His opinion based only on a single outdated strawman reference should be excluded.

## <u>Columbia selectively cites portions of Dr. Romesberg's deposition transcript</u> (Exhibit 2140) in an incomplete and misleading fashion, and the selective citations should be excluded or read in fuller context under FRE 106, 401-403

**Exclusion of Ex. 2140, 146:3-147:24, 148:11-149:17:** Columbia uses Exhibit 2140 at 146:3-147:9, 148:11-149:17 to assert that "Dr. Romesberg conceded that Sanger and SBS have fundamentally different <u>termination</u> efficiency requirements." Sur-reply, 6 (emphasis supplied); *id.*, 7 (citing Ex. 2140, 146:3-147:24, 148:11-149:17). Columbia misuses this testimony to argue that its own witness's (Dr. Menchen's) prior art disclosures of 3'-O-allyl capping groups for polymerase-based Sanger sequencing are not relevant to polymerase-based SBS sequencing. *Id.* Dr. Romesberg's complete testimony explains that Sanger has a different <u>termination</u> efficiency requirement relative to SBS, but Sanger nevertheless has a high <u>incorporation</u> efficiency requirement in order to accurately perform

Sanger sequencing. For example, Dr. Romesberg explains that the 3'-modified nucleotides and natural nucleotides used in Sanger sequencing are required to be competitively incorporated by the polymerase so that at least some termination occurs at every position of the oligonucleotide being sequenced. Ex. 2140, 146:3-16; Ex. 1119 ¶¶72, 98-101. Columbia's distortion of Dr. Romesberg's testimony to misleadingly denigrate its own witness's prior art teaching that 3'-O-allyl capped nucleotides are useful for polymerase-based sequencing is improper and prejudicial, and this testimony should either be excluded or read in its proper context. FRE 106.

Exclusion of Ex. 2140, 128:5-13: Columbia excerpts and combines two snippets from Exhibit 2140 at 128:5-13 to create the appearance that Dr. Romesberg testified that a POSA would not increase 3'-O-allyl nucleotide concentrations because a "POSA would know that 'inefficient termination' 'describes a property' of a nucleotide." Sur-reply, 12. Columbia misquotes Dr. Romesberg. His testimony is not that inefficiency is a property of a nucleotide. The transcript shows that Dr. Romesberg sought clarification regarding an unclear question from Columbia's counsel. Ex. 2140, 128:5-17. Dr. Romesberg's actual testimony on the subject of increasing 3'-modified nucleotide concentration thoroughly explains how the prior art demonstrates increased nucleotide concentration results in increased incorporation efficiency. Ex. 2140, 206:8-207:14, 59:7-19; Ex. 1119 ¶[75-77, 85-87, 93 (citing Ex. 1016, Fig. 4B; Ex. 2131, Fig. 3; Ex. 1013, 20:17-22). Columbia's

attempt to distort Dr. Romesberg's testimony, and failure to include his full explanation on this topic, creates an incomplete and misleading impression, and the snippets of testimony cited by Columbia should be excluded or read in context.

**Exclusion of Ex. 2140, 160:20-161:5:** Columbia uses a series of ellipses to manufacture a quotation from Exhibit 2140 at 160:20-161:5 to assert that "Dr. Romesberg admits that a POSA 'would want an analog ... or sufficient efficiency ... that is ... sufficient enough to be used *at the lowest possible concentration*." Sur-reply, 13 (emphasis and ellipses in original). Dr. Romesberg's complete testimony explains that a POSA would have been motivated to identify a concentration of sufficient efficiency to incorporate, but would <u>not</u> be motivated to further increase the concentration above the concentration at which the nucleotide is efficiently incorporated. Ex. 2140, 160:20-161:19, 177:1-14; Ex. 1119 ¶¶95-97. Columbia's attempt to mischaracterize Dr. Romesberg's testimony is misleading, and this testimony should be excluded or read within its proper context. FRE 106.

**Exclusion of Ex. 2140, 173:2-6, 178:19-24:** Columbia uses Exhibit 2140 at 173:2-6 and 178:19-24 to assert that Dr. Romesberg conceded "a POSA understood that increasing concentration results in increased misincorporation rates in SBS." Sur-reply, 13. Dr. Romesberg's complete testimony explains that while efficient incorporation of 3'-modified nucleotides occurs at higher concentrations due to a larger Km (weaker binding), this merely results in a shift of the window between

efficient correct incorporation and misincorporation, but the concentration window still separates a lower concentration at which there is accurate and efficient concentration from a higher concentration at which misincorporation begins to occur. Ex. 2140, 212:23-215:23; Ex. 1119 ¶¶96-97. Dr. Romesberg's testimony should either be excluded or read within the proper context. FRE 106.

Exclusion of Ex. 2140, 166:25-169:13, 178:19-24, 176:20-22: Columbia uses Exhibit 2140 at 166:25-169:13 to argue that a POSA would not use a concentration of 202 µM because it would result in "a 40-fold increase in mutation rates (due to misincorporation)." Sur-reply, 13; id. at 14 (citing Ex. 2140, 178:19-24, 176:20-22). Columbia's citations fail to include the full answer provided by Dr. Romesberg, which spans 169:7-170:1. There, Dr. Romesberg explained that the reference being discussed (Ex. 2134) included approximately 10<sup>6</sup> copies (1,000,000) copies) of the oligonucleotide being sequenced. Ex. 2140 at 169:7-170:1. Then he explained that a 40-fold increased mutation rate would cause only 100 of the 1,000,000 copies to have a mutation, and this small number of mutated copies would not cause a problem for detecting the correct sequence among the remaining 999,900 correctly sequenced copies. Id., 171:24-172:12. Nor were the *in vivo* systems there representative of what occurs with in vitro SBS reactions. Id., 172:14-173:21. Dr. Romesberg further testified that Metzker used SBS concentrations up to 5 and 10 mM that still demonstrated acceptable fidelity for SBS. Ex. 2140, 100:3-10; Ex.

1119 ¶¶91, 97. Columbia is effectively trying to use this testimony to suggest Dr. Romesberg agreed that the concentration needed for efficient misincorporation is lower than the concentration needed for efficient correct incorporation, a concept Dr. Romesberg soundly rejected. Ex. 2140, 212:23-215:23; Ex. 1119 ¶¶96-97. Columbia takes Dr. Romesberg's testimony out of context to create a misleading impression, and this testimony should be excluded or read within its proper context.

Exclusion of Ex. 2140, 130:8-22, 134:1-136:23, 128:25-130:24, 152:8-25: Columbia distorts Ex. 2140 in asserting that Dr. Romesberg admitted a POSA "would not have known" whether other polymerases would incorporate 3'-O-allyldATP based on Exhibit 2140 at 130:8-22, 134:5-14 and 128:25-130:24, 134:1-136:23, 152:8-25. Sur-reply, 16. Dr. Romesberg's complete testimony explains that Metzker's data provided predictability for successful incorporation by polymerases that are related to Vent(exo-). Ex. 2140, 114:21-115:14, 116:6-14, 118:16-120:21. He further explained that Vent(exo-) mutants were known in the prior art that enhanced incorporation of 3'-modified and base-substituted nucleotides. *Id.*, 130:12:-22; Ex. 1119 ¶¶79-80. Columbia takes Dr. Romesberg's testimony out of context to create a misleading impression, and this testimony should be excluded.

**Exclusion of Ex. 2140, 94:10-15:** Columbia improperly uses Dr. Romesberg's testimony that Metzker's 250  $\mu$ M concentration of 3'-O-capped nucleotides were provided at a 50,000-fold excess relative to the primer to argue that

a POSA would not have raised the concentration of 3'-O-capped nucleotides above 250  $\mu$ M. Sur-reply, 15 (citing Ex. 2140, 94:10-15). Dr. Romesberg's complete testimony explains that further increases in concentration would be expected to enhance incorporation based on Le Chatelier's Principle and entropy (Ex. 2140, 206:8-207:14, 59:7-19), and that Metzker's data in Figure 4B demonstrated that increasing concentrations even moderately to 500  $\mu$ M (which would be a 100,000-fold excess) provided efficient incorporation. Ex. 1119 ¶¶75-77, 91. Columbia takes Dr. Romesberg's testimony out of context to create a misleading impression, and this testimony should be excluded or read in context. FRE 106.

**Exclusion of Ex. 2140, 73:24-25:** Columbia improperly uses Dr. Romesberg's testimony to assert that Hiatt (Ex. 1106) does not relate to DNA sequencing because Hiatt discloses a template-independent polymerase. Sur-reply, 6 (citing Ex. 2140, 73:24-25). Columbia directed Dr. Romesberg to a few select sentences in Hiatt (a document that Dr. Romesberg had not previously reviewed), and asked questions based solely on the selected sentences. Columbia failed to mention Hiatt's disclosure of the Klenow fragment of DNA polymerase I (Ex. 1106, 19:11-17), which is a template-dependent polymerase. Furthermore, Columbia's use of Dr. Romesberg's testimony to assert that Hiatt is completely unrelated to DNA sequencing is belied by its own patent—Hiatt is cited on the face of Columbia's patent, leaving no doubt that Columbia believes this reference is relevant

to its patent. Ex. 1001, page 2. Columbia takes Dr. Romesberg's testimony out of context, and this testimony should be excluded or read in context. FRE 106.

Exclusion of Ex. 2140, 184:10-185:6, 186:13-187:7, 188:16-189:10: Columbia improperly uses Dr. Romesberg's testimony to assert that the Genet references (Exs. 1094, 1114, 1115) are inapplicable to the cleavage of allyl ethers. Sur-reply, 18 (citing Ex. 2140, 184:10-185:6, 186:13-187:7, 188:16-189:10). Columbia omits Dr. Romesberg's explanation that Genet's work is directly applicable to allyl ether cleavage because the cleavage mechanisms include identical steps by the exact same palladium chemistry. Ex. 2140, 188:1-15; Ex. 1119 ¶¶40-43. Columbia takes Dr. Romesberg's testimony out of context. FRE 106.

Exclusion of Ex. 2140, 41:22-42:14, 34:4-35:2, 39:16-40:24, 39:16-39:25: Columbia improperly uses Dr. Romesberg's testimony to assert that "[a]s linkers, Tsien's 'allyl ethers' undisputedly refers to a genus of groups that can include allyl groups but does not describe the 3-carbon allyl capping group of the challenged claim." Sur-reply, 20-21 (citing Ex. 2140, 41:22-42:14, 34:4-35:2, 39:16-40:24, 39:16-39:25). Columbia uses this testimony in an incomplete and misleading manner to confuse allyl ether linkers with the 3'-allyl ether capping group. Dr. Romesberg's full testimony explains that allyl ether linkers include the 3-carbon allyl group. Ex. 2140, 31:10-15, 34:13-16, 39:23-24. This testimony should be excluded or read within its full context. FRE 106. Respectfully submitted,

Dated: February 7, 2019	By: <u>/Kerry Taylor/</u>
	Kerry Taylor (Reg. No. 43,947)
	Michael L. Fuller (Reg. No. 36,516)
	William R. Zimmerman (pro hac vice)
	Nathanael R. Luman (Reg. No. 63,160)
	KNOBBE, MARTENS, OLSON & BEAR, LLP
	Derek Walter (Reg. No. 74,656)
	Edward R. Reines (pro hac vice)
	WEIL, GOTSHAL & MANGES LLP
	Attorneys for Petitioner ILLUMINA, INC.

## **CERTIFICATE OF SERVICE**

I hereby certify that a true and correct copy of the foregoing ILLUMINA MOTION TO EXCLUDE COLUMBIA EVIDENCE is being served on February 7, 2019, via e-mail to counsel for the Trustees of Columbia University, at

the email addresses below:

John P. White jwhite@cooperdunham.com Gary J. Gershik ggershik@cooperdunham.com ColumbiaIPR@cooperdunham.com COOPER & DUNHAM, LLP 30 Rockefeller Plaza, 20th Floor New York, NY 10112

Justin J. Oliver VENABLE | FITZPATRICK VENABLE LLP joliver@venable.com 600 Massachusetts Ave. Washington, D.C. 20001 John D. Murnane Robert S. Schwartz Zachary L. Garrett VENABLE | FITZPATRICK VENABLE LLP jmurnane@venable.com rschwartz@venable.com zgarrett@venable.com 1290 Avenue of the Americas New York, NY 10104

Respectfully submitted,

Dated: February 7, 2019	By: /Kerry Taylor/
	Kerry Taylor (Reg. No. 43,947)
	Michael L. Fuller (Reg. No. 36,516)
	William R. Zimmerman (pro hac vice)
	Nathanael R. Luman (Reg. No. 63,160)
	KNOBBE, MARTENS, OLSON & BEAR, LLP
	Derek Walter (Reg. No. 74,656)
	Edward R. Reines (pro hac vice)
	WEIL, GOTSHAL & MANGES LLP
	Attorneys for Petitioner
	-

ILLUMINA, INC.