

Paper No. _

Filed: February 19, 2019

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)¹

**PATENT OWNER'S OPPOSITION TO
PETITIONER'S MOTION TO EXCLUDE**

¹ An identical Paper is being entered into each listed proceeding. Unless otherwise indicated, the citations to Papers herein refer to the IPR2018-00291 Papers.

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Illumina's motion lacks merit. Dr. Menchen's declaration evidences the flaws in Illumina's obviousness arguments. At his deposition, Illumina avoided the evidence of non-obviousness, instead focusing on §112 issues not germane to these proceedings. Illumina now seeks to exclude Dr. Menchen's declaration, which covers **relevant** issues, based on Illumina's allegation that he did not adequately answer deposition questions on **irrelevant** issues. Not only is that allegation off base, but there exists no evidentiary basis to exclude Dr. Menchen's declaration.

Nor is there merit to Illumina's request to ***exclude its own expert's testimony***. Illumina's claim that Columbia's citations are "misleading" has no basis in fact and is not an evidentiary basis to exclude the underlying deposition testimony. Columbia invites review of the testimony and citations thereto, each of which is accurate, unlike Illumina's mischaracterizations. Sur-Reply, 28-29.

Rather than address proper evidentiary issues, Illumina's motion improperly attempts to present new argument. Illumina's Reply, based on new theories, circumvented its word-limit by incorporating almost 3,000 words from a declaration. Sur-Reply, 29-30. Illumina's motion serves as ***yet another*** improper merits brief. Trial Practice Guide, August 2018, 16 ("arguments regarding weight should appear only in the merits documents"); *Liberty Mut. Ins. v. Progressive Cas. Ins.*, CBM2012-00002, Paper 66 at 62 (Jan. 23 2014) (a motion to exclude "is not an opportunity to file a sur-reply"). Illumina's motion should be denied.

Exhibit 2116 Is Admissible

As an initial matter, the motion fails for not identifying “where in the record the objection[s] originally w[ere] made.” Trial Practice Guide, August 2018, 16; 37 C.F.R. §42.64. Illumina’s requests largely seek exclusion under FRE 403/702 based on Dr. Menchen’s alleged lack of expertise and credibility, which in addition to being wrong (as detailed below), is unpreserved. Illumina did not timely object to Ex. 2116 as lacking expertise or credibility. 37 C.F.R. §42.64. Instead, Illumina only previously raised other objections, and only did so for portions of Ex. 2116, despite now seeking to exclude the entire document. IPR2018-00291, Paper 35, at 5-9 (only raising other objections). Moreover, “the proper place” for credibility and weight arguments “is in substantive pleadings...and not a motion to exclude.” *Kinik Co. v. Chien-Min Sung*, IPR2014-01523, Paper 21 at 2 (Aug. 5, 2015).

Regardless, there is no evidentiary basis to exclude Ex. 2116 under FRE 403/702 because Illumina’s accusation that Dr. Menchen “appeared to know very little about the very subjects on which he had opined in that exhibit” is false. While 37 C.F.R. §42.53(d)(5)(ii) limits the scope of cross-examination to “the scope of the direct testimony,” Illumina repeatedly asked outside-the-scope questions largely pertaining to §112 issues (subject to objections). *E.g.*, Ex. 1113, 329:2-330:21 (“Q. [I]s there anything in [the patent-at-issue’s] disclosure that would **enable** the use of allyl groups for the claimed inventions...?”) (Emphases added throughout Paper).

Almost all of the criticized testimony in Illumina's motion pertains to these §112 issues. *See* Ex. 1112, 240:22-241:9 (Q: "Are there any small...chemical groups that would meet R in the claims of the [patent-at-issue] that are disclosed in the specification of the patent?"); Ex. 1113, 383:10-20 (Q: "Would a [POSA] reading the [patent-at-issue] know to use the polymerase that's described in Ju's 2005 article...?"); *see, e.g.*, Ex. 1112, 144:7-151:25, 178:11-179:6, 179:11-180:9, 181:10-15, 235:19-237:18, 239:19-240:21, 248:13-249:14, 252:20-254:11, 262:6-17.

Illumina obfuscates this fact by narrowly citing testimony to appear as pertaining to before the priority date, when it actually pertains to §112 issues after that date. For example, Illumina cites 286:4-14 and 286:15-287:17, where Dr. Menchen is asked what a POSA "would do in terms of selecting polymerases[.]" The preceding pages, however, show that the antecedent questions relate to a POSA "*with the [patent-at-issue] in front of them*[.]" Ex. 1112, 285:5-25. The same is true regarding Illumina's misleading citations to 363:2-14. *See* Ex. 1113, 361:19-362:2 ("Turning to the [patent-at-issue]...what is the linker that's described...?"). In response, Dr. Menchen credibly explained that he had not been asked to opine on those issues. *E.g.*, Ex. 1113, 361:19-362:2.

Illumina also claims that Dr. Menchen failed to review the entire file history. But he reviewed the portions of the file history relevant to the issues he opined on,

i.e., construction of the term “chemical linker” (Y). Tellingly, Illumina has not identified any other portion of the file history relevant to that issue.

¶¶31, 33-34 Are Admissible

Illumina seeks exclusion of ¶¶31, 33-34 under FRE 403/702, claiming that Dr. Menchen’s testimony allegedly “creates the *misleading* impression” that “3’-O-allyl nucleotides are inefficiently incorporated by DNA polymerase.” There is no evidentiary basis to exclude ¶¶31, 33-34 because Dr. Menchen’s testimony is not misleading—Metzker 1994 teaches that Vent(exo-) does not efficiently incorporate the 3’-O-allyl-dATP, as even Dr. Metzker himself acknowledged. Ex. 2025, 10 (Metzker 1994 showed 3’-O-allyl-dATP was “not efficiently incorporated by Vent(exo-) polymerase[.]”); Ex. 1017, 6348 (Metzker 1994 showed 3’-O-allyl-dATP was a “poor substrate[.]” with “limited activity”); Ex. 2126, 106:10-107:2; *see* Ex. 2099, 2:21-36 (Jones noting “low efficiency” of Metzker 1994 and others). Columbia’s patents acknowledge Metzker 1994’s statements about 3’-O-allyl-dATP incorporation (*not* efficient incorporation) and nothing more. Ex. 1002, 3:28-30.

Illumina’s motion theorizes that trace contamination caused Metzker to report “Termination*” (*i.e.*, incomplete termination activity) for the 3’-O-allyl-dATP. But as Dr. Menchen and the prior art explained, the result of that contamination is a “readthrough” band (Ex. 1016, 4263; Ex. 2116, ¶¶28, 43), and Metzker’s assays were purposefully “designed to differentiate between the incorporation of the natural

dNTP (read-through) and the 3'-O-modified dNTP (true termination).” Ex. 2131, 817 (citing Metzker 1994). Trace contamination did not cause Metzker to report Termination* for the 3'-O-allyl-dATP, and this is confirmed by the fact that Metzker reported “Termination” (not Termination*) for other nucleotides despite contamination. Ex. 2116, ¶28. In describing Metzker’s assay, Dr. Menchen explained that an inefficiently incorporated nucleotide would result in an extra band (the “efficiency test band”). Ex. 2116, ¶¶30-32. Illumina wrongly concludes that Dr. Menchen “made up” this explanation. But Dr. Romesberg himself relies on efficiency test bands when gauging incorporation rates, which he claims “the field calls N minus 1 bands.” Ex. 2140, 99:4-13, 127:1-128:24; Ex. 1119, ¶87. He also confirmed that Metzker’s Termination* experiments could appear as Dr. Menchen explained (except in two extreme exceptions). Ex. 2140, 127:1-128:24.

Unable to dispute Dr. Menchen’s analysis, Illumina questions his qualifications by citing vague snippets of testimony and ignoring evidence of his extensive expertise. Ex. 2116, ¶¶3-5; Ex. 2066. For example, Illumina overstates Dr. Menchen’s testimony that he is “not an expert on polymerases[.]” Motion, 2-3. Dr. Menchen actually testified that he could not interpret polymerase crystal structure calculations because he is “not a crystallographer” or “an expert on polymerases,” so he “can’t really evaluate...that analysis” himself. Ex. 1112, 269:15-270:16 (referring to analysis at Ex. 1009, 56-58). Evaluation of crystal

structure calculations is *not* relevant to this case. Similarly, Illumina's citation to Dr. Menchen's testimony that he does not work with polymerases *himself* (Ex. 1112, 193:13-18) ignores that his CV shows decades of experience leading and participating in teams designing and testing labeled nucleotides as polymerase terminators. Ex. 2066; Ex. 1112, 218:19-21. Dr. Menchen is highly qualified to opine on the relevant issues.

Illumina's remaining arguments rely on mischaracterizations previously addressed by Columbia. Sur-Reply, 7-8, 28-29. In brief, Illumina claims that Dr. Menchen's Sanger sequencing patents, which use the term "allyloxy," contradict his alleged position that 3'-O-allyl-dATP was "unsuitable for *sequencing*[".]” Motion, 4. However, Metzker taught the 3'-O-allyl-dATP was “not suitable for *SBS*” due to inefficient incorporation. Ex. 2116, ¶33. Sanger and SBS have different requirements. *E.g.*, Ex. 2140, 149:1-17. Similarly, Dr. Menchen did not testify that he included “allyloxy” in his Sanger patents because of Metzker's disclosures. Ex. 1112, 164:9-16 (“I don't remember correlating the Metzker article with what we wrote here.”). Illumina's citations do not show otherwise. Asked about identifying “allyl groups” and “suitable modifier[s],” Dr. Menchen responded by referencing allyl nomenclature (“He calls it allyl in the [1994] paper”), not suitability, and he consistently testified that Metzker's 3'-O-allyl-dATP lacked suitability for SBS. *E.g.*, Ex. 1112, 189:5-13, 289:11-290:10. Nor did Dr. Menchen testify that the allyl

capping group was “a good candidate[.]” Motion, 4. He testified to the opposite effect. Ex. 1112, 64:16-68:4. Last, Dr. Menchen did not rely on and did not fail to cite Metzker 1998 as proof of the efficiency test band. Metzker 1994 itself shows the efficiency test band. Ex. 2116, ¶32. At the deposition, Illumina wrongly theorized that a readthrough band and efficiency test band cannot “co-exist[.]” Ex. 1112, 210:13-19, 211:8-14. Dr. Menchen correctly identified Metzker 1998 as an example disproving Illumina’s theory, which Illumina has now dropped.

¶¶38-39, 43 Are Admissible

Illumina seeks exclusion of ¶¶38-39, 43 under FRE 403/702 for being inconsistent with the “fact” that Termination* “demonstrates the *highly efficient* incorporation of 3’-O-allyl-dATP by Vent(exo-) polymerase.” Illumina’s purported fact is directly contradicted by the literature, as explained above, which reports that the 3’-O-allyl-dATP was “*not efficiently incorporated*” by Vent(exo-).

Illumina also argues that the evidence contradicts Dr. Menchen’s alleged position that contamination has “no effect on Metzker’s results[.]” But that is not Dr. Menchen’s position. Contamination *does* produce a readthrough band, which decreases gel band intensity, but *does not* affect the results in Metzker’s Table 2 (*i.e.*, Termination vs. Termination*). Ex. 2116, ¶¶28, 39, 44. Illumina also misreads Metzker 1998 as stating that contamination was problematic for the 1994 screening assays. To the contrary, Metzker 1998 confirms that those assays were “designed to

differentiate between” contamination and incorporation. Ex. 2131, 817. The Metzker 1994 screening assays examined whether the nucleotides could perform a *single base addition step*. See Ex. 1016. As Metzker 1998 teaches, contamination becomes an obstacle in “*subsequent base addition steps*[.]” Ex. 2131, 814.

¶¶94-97 Are Admissible

There is no evidentiary basis to exclude ¶¶94-97 under FRE 702. Those paragraphs are based on Metzker’s data showing that no polymerase capable of incorporating a 3’-O-modified *adenine* was also capable of incorporating a 3’-O-modified *thymine*. Given that data, the fact that Vent(exo-) inefficiently incorporated a 3’-O-allyl adenine provided no expectation of incorporation for thymine, cytosine, or guanine nucleotides. Ex. 2116, ¶¶94-97. And in fact, 3’-O-allyl thymine is *not* incorporated by Vent(exo-). Ex. 1116, 89. Illumina’s motion criticizes Dr. Menchen for allegedly “ignor[ing]” the existence of Vent(exo-) variants, but Illumina’s petition relied solely on Vent(exo-) as used in Metzker 1994, and Dr. Romesberg testified that a POSA “would not have known” whether other variants would incorporate 3’-O-allyl nucleotides. Ex. 2140, 130:8-22, 134:5-14 (“I don’t think I said that [those variants] would be more tolerant of the O-allyl substituent.”). *Leo Pharm. Prods. v. Rea*, 726 F.3d 1346, 1356 (Fed. Cir. 2013) (obvious-to-try theory inappropriate when prior art “at best gives only general guidance as to the particular form of the claimed invention or how to achieve it”).

¶¶100-106 Are Admissible

There is no evidentiary basis to exclude ¶¶100-106, which explain that Tsien’s “allyl ethers” refers to a genus. Tsien cites Gigg, and Dr. Romesberg admits that Gigg teaches a genus of allyl ethers. Ex. 2126, 212:18-214:13. He also conceded that scientists “common[ly]” use “allyl ethers” to refer to a genus (Ex. 2113, 127:6-17, 130:1-25), which is confirmed by the prior art (Response, 53), and Illumina’s Reply concedes that allyl ethers is a genus. Reply, 5-6 (calling “[t]he 3-carbon allyl ether” species the “simplest allylic ether”). Contrary to Illumina’s motion, Dr. Trainor did not testify otherwise, instead merely testifying to the size of allyl ethers. Ex. 1098, 107:12-108:20.

Illumina’s motion also disagrees that a POSA would “contemplate that Tsien may have intended to refer to vinyl ethers” instead of allyl ethers. Ex. 2116, ¶102. But as Illumina notes, “Gigg describes a 2-step deprotection of allyl ethers,” the first step being conversion of the allyl to vinyl using strong base, the second being cleavage of the vinyl using Hg(II) in acetone/water. Tsien only describes the conditions for cleaving the vinyl. Ex. 1013, 24 (“Hg(II) in acetone/water”).

¶109 Is Admissible

Illumina seeks exclusion of ¶109 under FRE 702 for failing “to provide any facts or explanation” for why Illumina’s Dower-based Ground fails. There is no evidentiary basis to exclude ¶109, which lists six reasons why that Ground fails, and

provides citations to earlier in the declaration where those reasons are detailed. Like Tsien, Dower is SBS (Ex. 2126, 25:15-17) and thus has the stringent SBS requirements (*e.g.*, Ex. 2113, 54:5-22; Ex. 2126, 72:7-73:1; Ex. 2116, ¶¶14-16).

¶51 Is Admissible

Illumina seeks exclusion of ¶51 under FRE 403/702 for citing Ex. 2084, which discusses a sequencing kit for which Dr. Menchen allegedly had limited familiarity. There is no evidentiary basis to exclude ¶51, and the details of Ex. 2084's kit are irrelevant. As ¶51 explains, a *labeled* 3'-O-allyl nucleotide would incorporate less efficiently than an *unlabeled* 3'-O-allyl nucleotide, which Metzker 1994 showed was not efficiently incorporated. Ex. 2084 supports this conclusion, as Dr. Romesberg agreed, noting that he himself was unfamiliar with the contents of the kit. Ex. 2126, 124:25-125:6, 127:25-128:9.

Dr. Romesberg's Deposition Testimony is Admissible

Illumina seeks exclusion *of its own expert's testimony* (Ex. 2140), under FRE 106, 401-403, on the basis that Columbia "selectively cites" that testimony. FRE 106 is relevant where a portion of a recorded statement is submitted, whereas here, Ex. 2140 provides the *entirety* of the deposition transcript. If anything, to comply with FRE 106, the entire transcript must be admitted, not partially excluded as Illumina requests. Further, FRE 401-403 go to general admissibility and the exclusion of evidence that is a waste of time. Illumina cannot seriously contend that

the testimony of its own expert is irrelevant or a waste of time. Lacking any evidentiary basis to exclude Ex. 2140, it appears that Illumina simply does not want the Board to consider its own expert's admissions. Columbia addresses the specifics of Illumina's arguments, which are not proper evidentiary challenges, below.

146:3-147:24, 148:11-149:17 Are Admissible: Columbia's citations accurately show that "Dr. Romesberg concedes that Sanger and SBS have fundamentally different termination efficiency requirements." Illumina now argues that while Sanger requires low "termination efficiency," it requires high "incorporation efficiency." This is not an evidentiary argument; further, it makes no sense. Termination efficiency and incorporation efficiency are the same thing. Dr. Romesberg testified that "incomplete termination" is "inefficient incorporation[.]" Ex. 2126, 128:10-24. ***Incorporation*** of a 3'-O-capped-dNTP into a DNA strand results in ***termination*** of synthesis. For Sanger, 3'-O-capped-dNTPs must be incorporated into/terminate synthesis of a ***few*** strands (*e.g.*, 0.8%), whereas for SBS, they must be incorporated into/terminate synthesis for ***all*** strands. Sur-Reply, 5-7. Sanger and SBS are fundamentally different. *Id.*

128:5-13 Is Admissible: Illumina inaccurately claims that Columbia "misquote[d]" Dr. Romesberg's testimony that inefficient termination "describes a property." The testimony is clear. Ex. 2140, 128:5-13 ("[I]nefficient termination is -- describes a property."). He also testified that this property can "manifest[]" itself

as incomplete incorporation (*id.*), which is what Metzker's Termination* result reports. Having to "force" incorporation with high concentrations does not change a nucleotide's properties (*i.e.*, inefficient), it instead reaffirms that the nucleotide may not be a "very efficient chain terminator[.]" Ex. 2031, 3; Ex. 2081, ¶17.

160:20-161:5 Is Admissible: Columbia did not "mischaracterize" Dr. Romesberg's testimony that a POSA would use nucleotides efficient enough to be used at the "lowest possible concentration[.]" Ex. 2140, 160:20-161:5, 177:1-14 ("clearly, the lower the better"). That testimony comports with his testimony that SBS requires a "concentration that d[oes] not cause loss in fidelity," *i.e.*, "moderate to low concentrations," as "mutation rates increase with a function of increasing concentration." Ex. 2081, ¶17 ("polymerases lose the ability to accurately replicate a DNA strand at high nucleotide concentrations"); Ex. 2140, 162:1-11, 169:3-5, 173:2-6, 174:22-23, 176:20-22, 178:19-24. Dr. Romesberg agreed that Tsien's use of 30 μ M is consistent with those requirements. Ex. 2126, 101:5-102:1.

173:2-6, 178:19-24 Are Admissible: Contrary to Illumina's assertions, Dr. Romesberg conceded that increasing nucleotide concentration results in increased misincorporation. Ex. 2140, 169:3-5, 173:2-6, 174:22-23; Ex. 2081, ¶17. That testimony contradicts Illumina's belated theory that concentrations can be raised to achieve high incorporation without loss in fidelity. Motion, 11-13. That theory also contradicts the prior art, which shows that Canard's nucleotides were unable to

achieve high incorporation levels below concentrations that would “result in significant misincorporation.” Ex. 2081, ¶17; Ex. 2082, 74:16-74:20.

166:25-169:13, 178:19-24, 176:20-22 Are Admissible: Columbia’s citations accurately show that Dr. Romesberg previously relied on prior art (Fersht) in *defending an Illumina SBS patent* (Ex. 2081, ¶17), which teaches that 202 μ M nucleotide concentration results in increased mutation rates. Illumina now tries to criticize the very data Dr. Romesberg previously relied on, alleging it is not representative of SBS. *Compare* Ex. 2081, ¶17 (relying on Fersht) and Ex. 2082, 67:10-24, 74:4-7 (same) *with* Motion, 12 (criticizing Fersht).

Illumina’s motion also wrongly asserts that Metzker used “SBS concentrations up to 5 and 10 mM.” Metzker’s sole SBS (BASS) experiment used 3’-O-(2-nitrobenzyl)-dATP at 250 μ M. Ex. 1016, 4266 (Figure 5B and text). All of Metzker’s other experiments were for potential usefulness of modified nucleotides for SBS or Sanger. For SBS, he only used up to 250 μ M. *See* Ex. 1016, Table 2. For Sanger, he used higher concentrations. Ex. 1016, Abstract (noting 3’-O-methyl-dNTP testing was done for Sanger, not SBS), 4262 (noting M13mp19 assay is Sanger, not SBS). Moreover, Illumina’s newest position that a POSA would use 10 mM concentrations is contradicted by Dr. Romesberg’s concession that 1 mM is too high to be useful for SBS. Ex. 2081, ¶17 (POSA dissuaded from nucleotides requiring 1 mM for SBS), Ex. 2082, 74:16-19 (“1 millimolar concentration will

result in significant misincorporation”); Ex. 2140, 156:17-157:2 (“I would certainly worry about fidelity” at 1 mM).

130:8-22, 134:1-136:23, 128:25-130:24, 152:8-25 Are Admissible:

Columbia did not “distort” Dr. Romesberg’s admission that a POSA “would not have known” whether other polymerases would incorporate 3’-O-allyl-dATP. The cited testimony is clear.

94:10-15 Is Admissible: Columbia did not mischaracterize Dr. Romesberg’s testimony that Metzker tested 3’-O-allyl-dATP at a 50,000-fold excess. And contrary to Illumina’s assertion, Metzker 1994 contains no data showing higher incorporation rates at 500 μ M versus **250 μ M**. Illumina points to an example where 500 μ M of 3’-O-methyl-dNTP showed more incorporation than **100 μ M**. Such a five-fold increase for the 250 μ M 3’-O-allyl-dATP would be 1.25 mM, a concentration higher than the 1 mM that Dr. Romesberg conceded is incompatible with SBS for “result[ing] in significant misincorporation[.]” Ex. 2082, 74:16-19; Ex. 2081, ¶17; Ex. 2140, 156:17-157:2. Moreover, Metzker’s 3’-O-methyl-dNTP experiments related to Sanger, not SBS. Ex. 1016, 4259 (noting methyl testing done for Sanger, not SBS).

73:24-25 Is Admissible: Columbia does not improperly use Dr. Romesberg’s testimony against Hiatt. Hiatt deals with template-independent polymerases which cannot be used for SBS (Ex. 1106, Title), and it does not demand SBS requirements

(e.g., efficient incorporation and deprotection requirements). Illumina's new reliance on Klenow fails as the single mention of it pertains to synthesizing DNA strands using *natural* dNTPs. Hiatt does not suggest that Klenow can incorporate 3'-O-capped nucleotides, let alone achieve efficient incorporation of them as required for SBS.

184:10-185:6, 186:13-187:7, 188:16-189:10 Are Admissible: Columbia's citations accurately show that Dr. Romesberg admitted that the Genet references relate to alloc cleavage, not allyl ether cleavage. Ethers were known to be hard to cleave under SBS-compatible conditions. Ex. 2031, 4; Ex. 2033, 3; Ex. 2032, 37; *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963) ("a compound and all of its properties are inseparable"). Illumina provided no evidence that Genet's cleavage conditions for alloc result in rapid, quantitative cleavage of ethers under mild conditions. Dr. Romesberg's further testimony that Dr. Ju figured out the Genet conditions could be modified to be useful simply highlights the hindsight-driven analysis that Illumina consistently employs.

41:22-42:14, 34:4-35:2, 39:16-40:24, 39:16-39:25 Are Admissible: Columbia's citations accurately show that Dr. Romesberg testified that allyl ethers as linkers form a genus. As explained above, the same is true regarding allyl ethers as blocking groups: they define a genus.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing **PATENT OWNER'S OPPOSITION** is being served on February 19, 2019, via email to Counsel for Petitioner at the email addresses below:

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