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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 No. IPR2012-00007
U.S. Patent No. 7,790,869

PETITIONER ILLUMINA'S REPLY TO PATENT OWNER COLUMBIA'S RESPONSE TO PETITION

Columbia Ex. 2039
Illumina, Inc. v. The Trustees of Columbia University in the City of New York

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Columbia does not defend the validity of the original claims, essentially admitting unpatentability of the original challenged claims. Proposed claims 34-54 are unpatentable for the reasons in Illumina's Petition, and for the reasons below.

I. COLUMBIA'S "STARTING POINT" ANALYSIS IS IRRELEVANT AND IMPROPER

Instead of addressing Illumina's invalidity analysis, Columbia inappropriately tries to shoehorn the proposed claims into a pharmaceutical "lead compound" analysis for rebuttal. However, unlike the "starting point" case Columbia cited, the claims here are directed to sequencing methods, not pharmaceutical compounds. Columbia's "starting point" analysis is thus inapplicable to the claims at issue. Moreover, Illumina has not asserted a "structural similarity" obviousness-type analysis, so the lead compound cases would not be relevant even if the Columbia claims were considered to be pharmaceutical compounds. Finally, even if a "starting point" analysis were appropriate, Columbia's emphasis on a *single* starting point (3'-OH labeled dNTPs) is not. USPTO guidelines at 75 F.R. 53643, at 53652, col. 3 ("[i]t should be noted that the lead compound cases do not stand for the proposition that identification of a single lead compound is necessary in every obviousness rejection of a chemical compound.") Instead, a "starting point" is any compound that would be "a natural choice for further development efforts." *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). Tsien's base-

labeled dNTPs are a natural choice for further development efforts in view of Tsien's teachings about label positioning and enzymatic competence, and Dr. Trainor himself agreed that a labeled base was a preferred embodiment of Tsien. Ex. 2094 at 237:19-239:9; Ex. 1002 at 27:35-30:36.

Nor are the straw man changes proposed by Dr. Trainor realistic. For example, Dr. Trainor posits that one of skill in the art would need to convert a ddNTP to a dNTP. *See*, *e.g.*, Ex. 2033 ¶ 65, 80. Not only is this wrong (both Tsien and Prober I/Hobbs disclose dNTPs), but no one of skill in the art would "convert" a ddNTP to a corresponding dNTP. Ex. 1053 ¶ 73. Rather, they would synthesize the dNTP from an appropriate starting material. *Id.* Also, contrary to Dr. Trainor's declaration (*see*, *e.g.*, Ex. 2033.¶¶ 61-63), the prior art as of 1999 provided express reasons to adopt the base-labeled approach for 3'-blocked nucleotides. Ex. 1045 at 956; Ex. 2094 at 349:20-350:21, 352:11-25; Ex. 1053 ¶¶ 60 & 98-109.

Thus, a lead compound analysis is not appropriate to analyze these claims, and, even if it were, Tsien's base labeled nucleotides would be a proper starting point. Tsien and other prior art expressly teach that base labeled nucleotides were a natural choice for further development at the time the '869 patent was filed.

II. CLAIMS 34-54 DO NOT REQUIRE INCORPORATION BY A POLYMERASE

Dr. Trainor's opinions are based on the incorrect premise that the *claims* require that the nucleotide analogue can be incorporated by a polymerase. *See*, *e.g.*,

Ex. 2033, ¶¶ 33, 39, 68(8), 108(4). No such requirement exists in claim 34, and no separate argument is present with respect to any dependent claim. Ex. 1053 ¶ 85. Claim 43 requires that the nucleotide is "incorporated onto a primer," but does not specify that incorporation is performed by a polymerase. *Id.* Claim 49 requires only that the "cleavable chemical group does not interfere with the recognition of the nucleotide by a polymerase." *Id.* Dr. Trainor admitted that this property is met by any 3' blocking group that allows incorporation by a polymerase. Ex. 2094 at 154:10-156:22. For example, Tsien discloses an allyl 3' blocking group, which would not interfere. Ex. 1002 at 24:29-30; Ex. 2094 at 106:14-108:21.

III. CLAIMS 34-54 ARE OBVIOUS OVER TSIEN AND PROBER I

Illumina's Petition demonstrated that Tsien in view of Prober I disclosed all limitations of Claims 35-54. Petition at 21-29. Columbia does not dispute this, instead raising motivation to combine, expectation of success, and secondary considerations.

A. Motivations Existed to Make the Single Change to Tsien (in view of Prober I) to Meet All Limitations of the Challenged Claims

Columbia asserts that a skilled artisan would have had to make "7 [sic] changes" to the "starting point" in Tsien to arrive at the proposed claims. Paper 78 at 18; Ex. 2033 at ¶ 92. But Dr. Trainor admitted that all but two (#1 & #2) of the 8 "changes" are not changes at all – they are expressly disclosed in Tsien.

Specifically, Dr. Trainor agreed that Tsien teaches: (#3-5) chemically

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