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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTELLIGENT BIO-SYSTEMS, INC.

Petitioner,

v.

ILLUMINA CAMBRIDGE LTD.

Patent Owner.

Case IPR2013-00266 (LMG)

U.S. Patent 8,158,346

**PATENT OWNER ILLUMINA'S REPLY TO PETITIONER'S
OPPOSITION TO ILLUMINA'S MOTION TO AMEND**

Columbia Exhibit 2030
Illumina, Inc. v. The Trustees of Columbia
University in the City of New York
IPR2018-00322

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I. IBS Seeks To Avoid The Intended Purpose Of Its Own References

IBS' argument that the claimed methods are not patentable disregards the cleavage efficiency required for SBS. Paper 37, 1-2. IBS and its expert agree that the intended purpose of the closest prior art was sequencing-by-synthesis ("SBS"). Ex. 2030, 106:5-23; Paper 37, 2-3. It is undisputed that <90% cleavage efficiency would not work for SBS. Ex. 2017, 3:5-8; Ex. 2031 ¶ 27. In fact, the efficiency needed to be >97%. *Infra*, Section III. A skilled artisan would not combine *Church* or *Rabani* with *Ju* or *Tsien* to remove a disulfide linkage and a 3'-protecting group under a single set of conditions because the expected cleavage efficiency would not work for the intended purpose of SBS. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009). Because a person of skill in the art would not combine these references, the Proposed Claims are patentable irrespective of whether $\geq 90\%$ efficiency is itself a consideration.

II. IBS Distorts Church To Assert An Unreasonable Expectation Of Success

IBS argues that *Church* (Ex. 1019), Fig. 6 shows disulfide cleavage with "high efficiency." Paper 37, 2. IBS' reliance on Ex. 1019, Fig. 6 is misplaced because the image quality is too poor to accurately show the data. Dr. Branchaud admitted he is "not an expert in" interpreting these images (Ex. 2032, 54:4-9), that visual analyses are inaccurate (*id.*, 108:8-109:2), and he "cannot say" whether Fig. 6 accurately shows the cleavage results (Ex. 2030, 74:6-22). Dr. Branchaud's bias

is demonstrated by his testimony that he could not tell that Ex. 1019, Fig. 6 was worse than Ex. 1030, Fig. 6. Ex. 2030, 69:8-78:22. In contrast, IBS' attorneys (Ex. 2032, 64:10-20), Dr. Romesberg (Ex. 1022, 229:1-4), and the Patent Office (Ex. 2033, 2), all confirm what is apparent to anyone—Ex. 1019, Fig. 6 is a poor image. Church submitted better quality replacement figures. Ex. 2033, 3. Indeed, any objective comparison of the images shows that Ex. 1030, Fig. 6 is more accurate.

Dr. Romesberg correctly determined that *Church's* cleavage efficiency was unquantifiable. Ex. 1022, 230:15-231:8. The evidence shows that 10% fluorescence can look identical to 0%. Ex. 2032, 106:23-107:11; Ex. 2034, 3; Ex. 2035, Fig. 1B & 1D; *see also* Ex. 2032, 94:10-15 (saying Ex. 2036, Fig. S5(C) is 100% converted, but Fig. S5(D) shows 7.5% unconverted). Dr. Branchaud could not say if Fig. 6 even shows >50% cleavage. Ex. 2030, 83:4-20. Thus, Church's cleavage data provides no expectation that cleavage efficiency for a disulfide linker and a 3'-OH protecting group under a single set of conditions would be different than *Ruby* and *Herman*, which teach unacceptable efficiency. Paper 31, 10-13.

III. Ruby, Herman, And Pierce Did Not Provide An Expectation Of Sufficient Cleavage For The Claimed Sequencing Method

IBS and its expert rely on numerous assumptions to assert that *Ruby* and *Herman's* disulfide cleavage efficiencies were “much higher” than the reported 86-87%. Paper 37, 8-9; Ex. 1021 ¶ 37. Despite over 150 speaking objections and constant coaching by IBS' counsel during deposition (*see, e.g.*, Ex. 2030, 76:6-12,

129:20-131:21, 145:16-146:1, 154:15-16, 199:8-14, 243:3-12, 313:15-314:7), Dr. Branchaud admitted that he failed to account for several important aspects of these references. *Id.*, 141:21-145:9, 150:16-154:8, 161:17-162:16, 164:20-24, 197:1-15. Dr. Romesberg accounted for the omitted aspects and concluded that the reported 86-87% accurately reflects the cleavage efficiencies obtained by *Ruby* and *Herman*. Ex. 2037 ¶ 14, 16; Ex. 2019, 7:35-50. Thus, a skilled artisan would be dissuaded from pursuing the claimed methods by *Ruby* and *Herman*. Paper 31, 10-13.

IBS misrepresents Dr. Romesberg's testimony to re-write *Herman's* cleavage efficiency as 92.2%. Paper 37, 9; Ex. 1022, 193:6-194:13. But even IBS' inflated efficiency is too low to motivate a skilled artisan to use a 3'-OH protecting group that has the same efficiency as *Herman's* linker for SBS—sequencing even a short 20 nucleotide sequence requires that each cycle proceeds with ~96.5% efficiency (*i.e.*, $0.965^{20} \approx 50\%$). Ex. 1008, 2:1-27 (97% is insufficient for SBS); Ex. 1022, 252:6-9 (overall efficiency required for SBS is 50%); Ex. 2032, 174:9-12 (a read length of 20 nucleotides was “short”).

IBS cites a different Herman article (Ex. 1027, “*Dawson*”) that lacks data to support “virtually complete cleavage” of a disulfide linker. Paper 37, 9. IBS omitted that two years later, Herman/Dawson reported that only “approximately one-half” of the same linker was cleaved. Ex. 2038, 166. Others reported variable cleavage results and abandoned this linker. Ex. 2039, 9594; Ex. 2040, 6:61-64.

IBS' reliance on the "quantitative" DTT cleavage reported for one disulfide protein crosslinking reagent in *Pierce* is misplaced. Paper 37, 10-11 (*citing* Ex. 1026, 181); Ex. 2032, 122:22-129:21. Unlike proteins, DNA contains a negatively charged phosphate backbone that repulses the negatively charged reactive thiolate form of DTT. Ex. 2041, 1175; Ex. 1031, 4057. Thus, DTT cleavage efficiency for proteins is not expected to apply to DNA. IBS admits that *Ruby* and *Herman's* cleavage efficiencies are more applicable to DNA than *Pierce*. Paper 37, 10-11.

IBS argues that it was desirable to decrease the number of reaction steps with disulfides. Paper 37, 11. But, in 2010, IBS said the opposite. Ex. 2042 ¶ 371.

IV. IBS' Proposed 3'-Groups Would Not Have Been Expected To Work

Despite indications that would discourage selection of an azidomethyl group (Ex. 2043, 5; Ex. 2030, 212:22-213-21; Ex. 2044, 202:10-203:10, 152:9-14), IBS provides no rationale for selecting this group from the myriad of other groups. Paper 37, 12; Ex. 1035, 17-23. Instead, IBS used impermissible hindsight to select this group. Ex. 2032, 169:9-172:22, 186:19-189:2; Ex. 2044, 198:2-203:10.

IBS argues that a skilled artisan would select a 2,4-dinitrobenzenesulfonyl ("2,4-DNBS") group for the claimed methods. Paper 37, 12-13. But 2,4-DNBS would have been considered too large for incorporation by a polymerase. Ex. 2037 ¶ 17-20; Ex. 2030, 240:6-242:8; Ex. 2011, 4263; Ex. 1002, 2:31-59. Furthermore, a 2,4-DNBS group would not have been expected to cleave with sufficient efficiency

for SBS. Ex. 2037 ¶ 24; Ex. 2030, 232:10-233:2. Thus, a skilled artisan would not have expected this group to work for the claimed method. Ex. 2037 ¶ 20, 24.

V. IBS' Secondary Considerations Arguments Also Lack Merit

IBS asserts that Illumina's unexpected results are insufficient. Paper 37, 13-14. Illumina showed superior results at 307,302 reaction centers for 150 cycles. Ex. 2023 ¶¶ 14-15. These results are more than sufficient. *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

IBS asserts simultaneous invention by others. Paper 37, 7-8. But each of IBS' exhibits (Exs. 1023-1025) lack nucleotides having a 3'-OH protecting group and a disulfide linker. Thus, IBS' exhibits do not disclose the claimed invention. *Frazier v. Roessel Cine Photo Tech, Inc.*, 417 F.3d 1230, 1238 (Fed. Cir. 2005).

Finally, IBS incorrectly asserts that unexpected results are inapplicable since they relate to a latent property of a known compound. Paper 37, 15. The Vermaas Declaration, however, shows unexpected results for the disulfide linkage and the protecting group of a previously **unknown** compound. These unexpected properties cannot be ignored. *In re Sullivan*, 498 F.3d 1345, 1353 (Fed. Cir. 2007).

VI. Conclusion

Illumina demonstrated that the substitute claims are patentable over the prior art. Thus, Illumina requests entrance of substitute Claims 20-26 for the '346 Patent.

IPR2013-00266
IBS v. Illumina

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PATENT OWNER ILLUMINA'S REPLY TO PETITIONER'S OPPOSITION TO ILLUMINA'S MOTION TO AMEND** is being served on March 21, 2014, via email pursuant to 37 C.F.R. § 42.6(e) per agreement of the parties, to counsel for Intelligent Bio-Systems, Inc., at the addresses below:

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