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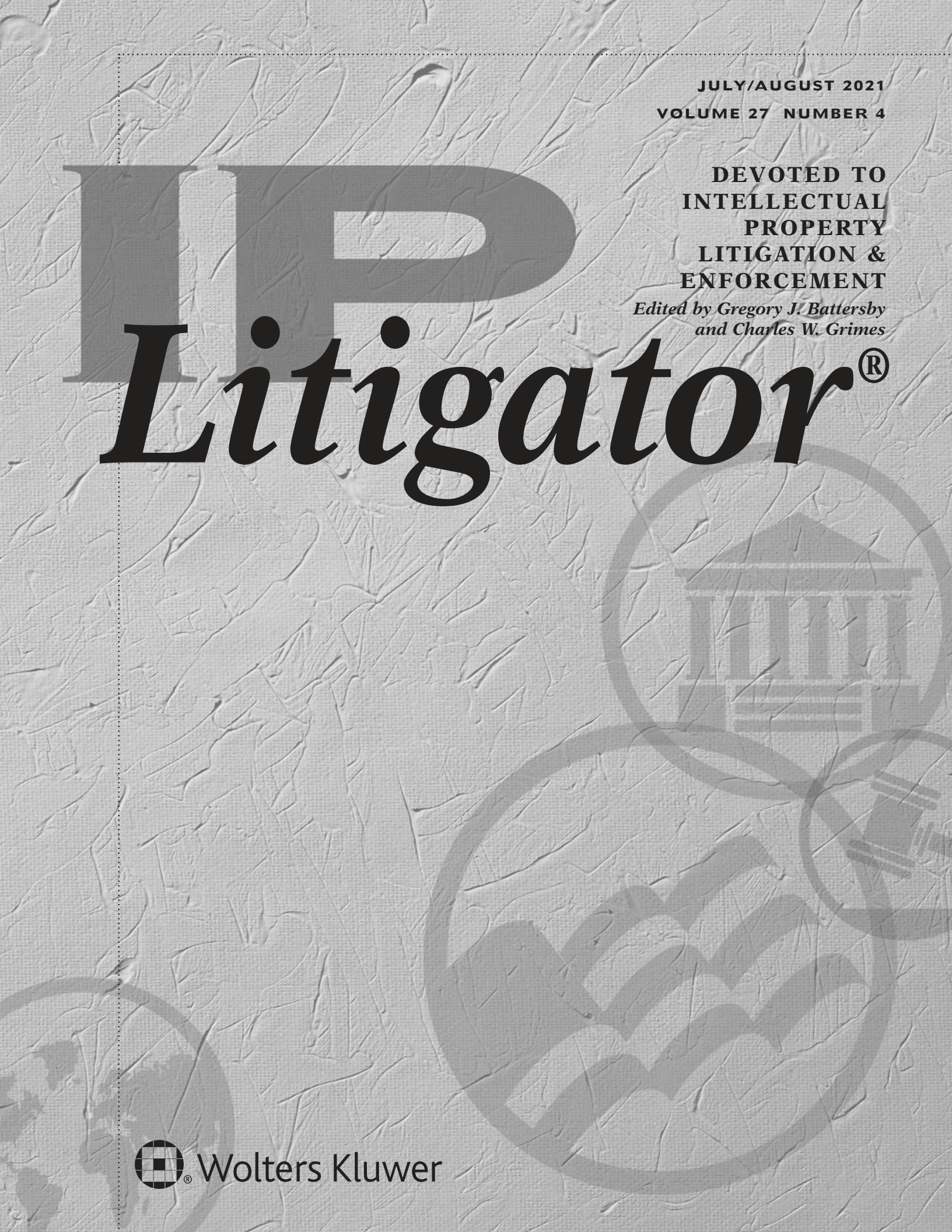

Wolters Kluwer

Federal Circuit Report

Richard Kurz and Nisha Gera

Federal Circuit Affirms Invalidated Decision for Columbia University's DNA Sequencing Patents

In *Trustees of Columbia University v. Illumina, Inc.*, the U.S. Court of Appeals for the Federal Circuit affirmed the Patent Trial and Appeals Board ("PTAB" or "Board") decision to invalidate five patents owned by Columbia, finding them obvious.[1] The patents are related to methods of DNA sequencing covering nucleotide analogs and their use in "sequencing-by-synthesis."[2] The invalidations were the result of inter partes review (IPR) proceedings initiated by Illumina.[3]

This non-precedential opinion concerned Columbia's challenges to the PTAB's factual findings regarding, inter alia, teaching away and whether there would be reasonable expectation of success when evaluating obviousness challenges to the patents.[4] Since these were factual findings, the appeal was considered under the deferential "substantial evidence" standard.[5] Of note, the Federal Circuit explained that a "teaching away" for the purposes of obviousness requires "clear discouragement" from implementing a technical feature present in the prior art.[6] Also, the Federal Circuit opined that for purposes of the obviousness analysis, a "reasonable expectation of success does not require the best of all possible results."[7] Given the deferential standard of review, the Federal Circuit decided not to second-guess the Board's factual findings, determining that the arguments raised on appeal concerning certain references and expert testimony went to the weight of the evidence, and affirmed the Board's decision.[8]

Disputed Patent Claims

The claims are directed to methods for "sequencing by synthesis" (SBS), which is a method of nucleic acid sequencing by using nucleotide analogs.[9] SBS works by "detecting the identity of a nucleotide analogue after the nucleotide analogue is incorporated into a growing strand of DNA."[10] The claims recite analogs of the nucleotide bases adenine, guanine, cytosine, and thymidine.[11] These derivatives were modified by having a unique detectable label conjugated to the base by a cleavable linker, and further used a small, cleavable chemical moiety to block or cap the 3' hydroxyl on the deoxyribose sugar making it nonreactive.[12] The detection of the unique label identifies the sequence identity of the nucleotide, and once the label is removed from the base the polymerase reaction proceeds to the next nucleotide analog.[13] These steps comprise a cycle of the SBS reaction and could be used in automated sequencing regimes.[14]

The appeal was centered on a particular claim limitation: "the use of a capping group that is 'small,' and not a 'ketone group,' 'a methoxy group, or an ester group.'"[15] The prior art references cited by the PTAB to hold the claims obvious encompassed use of an allyl group, which the PTAB determined would satisfy the claim limitation. The prior art disclosed a DNA sequencing method that the PTAB considered to be "equivalent to SBS," but the reference taught that allyl capping groups provided incomplete activity whereas other capping groups demonstrated complete termination of DNA synthesis.[16]

The Court's Reasoning

The Federal Circuit evaluated Board's factual findings for substantial evidence.[17] Since obviousness is a question of law based on factual determinations, the Federal Circuit would have overturned Board's findings if not supported by substantial evidence. But the Federal Circuit affirmed the Board, rejecting in turn the three arguments asserted by Columbia.[18] Columbia's arguments were related to teaching away and the lack of a reasonable expectation of success.

First, Columbia contended that the Board erred in its interpretation of the prior art's teachings, and failed to recognize that those teachings would have constituted a "teaching away" by informing a person skilled in the art that allyl capping groups were not efficient enough for successful SBS since "SBS requires efficient incorporation of nucleotides."[19] The Federal Circuit panel decided that the Board's conclusions were supported by substantial evidence, and stated that teaching away must be shown by "'clear discouragement' from implementing a technical feature."[20] Columbia, according to the panel, had not demonstrated that there was any such clear

discouragement.[21] According to the court, even though the prior art taught that sequencing methods using alternative capping groups were more efficient, a mere existence of "better" alternatives did not negate "inferior" alternatives for purposes of obviousness.[22]

Columbia's second argument, which was that a person skilled in the art would not have had a reasonable expectation of success in achieving sequencing using nucleotides comprising allyl-capped groups, was also deemed unpersuasive by the panel.[23] Columbia argued that teachings from the prior art reference would not have provided an expectation that allyl-capped groups would be capable of achieving at least twenty cycles of sequencing.[24] The Board, however, had found that a combination of prior art references provided an expectation that at least twenty sequencing cycles could be performed.[25] According to the Federal Circuit, a "reasonable expectation of success" does not require "the best of all possible results."[26] Further the court explained that "[s]uccess may not have only one definition."[27] The court decided that the Board's finding concerning a reasonable expectation of success was supported by substantial evidence and refused to consider "reweighing the evidence" on appeal.[28]

Finally, the court explained that "the specification of Columbia's patents provide further evidence that a person of ordinary skill would have had a reasonable expectation of success in using allyl capping groups for SBS."[29] Columbia tried to persuade the panel that a prior art reference was "discouraging," but the court explained that the patent specification cited the same reference "as evidence that allyl groups can be used … using well-established synthetic procedures."[30] The Federal Circuit noted that the admissions in the specification regarding prior art are binding on the patentee, and no data was shown that would discourage such use.[31]

Conclusion

The Federal Circuit panel decided that "[i]n sum ... Columbia has not pointed to any flaw in the Board's analysis."[32] The panel noted that the Board was given "two alternative theories" of whether the person skilled in the art would have had a reasonable expectation of success in using allyl capping groups in SBS methods.[33] The Board apparently chose one of them and the Federal Circuit declined to upset that decision, explaining that "[o]ur task is not to determine which theory we find more compelling."[34] The court decided that substantial evidence supported the Board's decisions.[35] While the opinion was non-precedential, it provides guidance for how the Federal Circuit evaluated the facts concerning the teaching away and reasonable expectation of success arguments that were presented to the Board when viewed under the deferential standard of review that was applicable for the appeal.

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1. *Trs. of Columbia Univ. v. Illumina, Inc.*, No. 19-2302 (Fed. Cir. Feb. 1, 2021) (Slip Op.), *available at http://www.cafc.uscourts.gov/sites/default/files/opinions-orders/19-2302.OPINION.2-1-2021_1726127.pdf*; *see also Trs. of Columbia Univ. v. Illumina, Inc.*, No. 19-2302, 2021 WL 317661 (Fed. Cir. Feb. 1, 2021).
2. Slip op. at 2.
3. *Id.*
4. *Id.*at 8.
5. *Id*. at 7 (citing *In re Elsner*, 381 F.3d 1125, 1126 (Fed. Cir. 2004) and *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000)).
6. *Id.* at 9.
7. *Id.* at 11.
8. *Id.* at 13.
9. *Id.* at 2.
10. *Id.* at 3.
11. *Id.* at 5.
12. *Id.* at 3.
13. *Id.*
14. *Id.*
15. *Id.* at 5.
16. *Id.* at 6.
17. *Id.* at 7.
18. *Id.* at 15.
19. *Id.* at 8–9.
20. *Id.* at 9 (citing *Univ. of Md. Biotechnology Inst. v. Presens Precision Sensing GmbH*, 711 F. App'x 1007, 1011 (Fed. Cir. 2017)).
21. *Id.* at 9–10.
22. *Id.* at 10 (citing *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012)).
23. *Id.* at 10–11.
24. *Id.*
25. *Id.* at 10.
26. *Id.* at 11.
27. *Id.*
28. *Id.* at 13 (citing *Celgene Corp. v. Peter*, 931 F.3d 1342, 1352 (Fed. Cir. 2019)).
29. *Id.*
30. *Id.* (quotation and emphasis omitted).
31. *Id.* (citing *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007)).
32. *Id.* at 14.
33. *Id.*
34. *Id.* (quotation omitted).
35. *Id.* at 15.