

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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**PACIFIC BIOSCIENCES OF CALIFORNIA, INC.,**  
Petitioner

v.

**THE CHINESE UNIVERSITY OF HONG KONG,**  
Patent Owner

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PTAB Case No. **IPR2024-00028**  
U.S. Patent No. **11,091,794 B2**

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**PATENT OWNER'S SUR-REPLY**

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## I. INTRODUCTION

As explained in the Patent Owner Response (Paper 15, “POR”), claim 1 of the ’794 Patent recites a specific method for detecting a base modification. That method comprises first “receiving data” and then from that data “creating an input data structure...wherein the input data structure includes” a window, and the properties of each nucleotide in the window including the nucleotide identity, the position of the nucleotide with respect to a target position within the window, the PW, and the IPD. Claim 1 further requires “inputting the input data structure into a model the model trained by: receiving a first plurality of first data structure” and then “determining, using the model, whether the modification is present in a nucleotide at the target position within the window in the input data structure.” POR at 5-7.

In contrast, the first two references of Ground 1, the Flusberg publications, disclose a method that avoids including nucleotide identity as a property in an input data structure as claimed. As Petitioner’s own expert explains, “Flusberg’s specific example *avoids* using sequence context as an express input variable because it is held constant....” EX1002, ¶107 (emphasis added). *See also* EX2037, 87:21-23 (“we can fix the sequence context. And I think this is what they did in this -- in this experiment reported in the Flusberg publications.”). And, as Petitioner’s own expert further explains, the third reference of Ground 1, the PacBio-BAM, does not disclose any method of base modification detection or how to use its content in base

modification detection, let alone suggest that a person of ordinary skill in the art (“POSITA”) should ignore the Flusberg publications’ method and instead include nucleotide identity as a property in an input data structure as follows: “I do not claim that [the PacBio-BAM] teaches how to do base modification detection. This is merely a description of the content of this file.” EX2037, 105:22-24.

In Reply (Paper 19), Petitioner repeats its mantra that any “use” of nucleotide identity renders claim 1 obvious. Nonsense. In fact, Petitioner’s own expert confirmed on cross-examination that the way the claimed method and the Flusberg publications’ method account for nucleotide identity are fundamentally different. POR at 16 (citing EX2037, 109:5-12 (“[Q:] Would a person of skill in the art consider those two methods of taking into account sequence context interchangeable? [A:] I mean, these are different kind of experiments, and the -- so, no, they cannot be viewed interchangeably. It’s quite a different situation.”)). For this reason alone, claim 1 is not obvious over Ground 1.

Moreover, at the time of the ’794 Patent’s earliest filing date, a POSITA would not include PW in an input data structure as claimed. Beginning in 2013 and as co-authors of Flusberg explained, a POSITA would understand that “PW is not as sensitive to shifts in sequence context” and thus would “restrict attention to IPDs” for base modification detection. EX1010, 130; EX2041, ¶141. And that is exactly what the art did until the ’794 Patent. EX2041, ¶141. For example, PacBio’s

kineticsTools did not include PW and instead restricted its focus on IPD utilizing “IPDs observed at each position in the genome” to compare those “IPDs to values expected for unmodified DNA” to detect base modifications. EX1021, 1. Accordingly, by the earliest priority date of the ’794 Patent, a POSITA would not have been motivated to include PW in an input data structure in combination with the other claimed properties as recited in claim 1.

Finally, objective indicia support that claim 1 is not obvious over Ground 1. For example, claim 1’s exceptionally high predictive power to detect a particular nucleotide modification, 5mC, was unexpected compared to the closest prior art method of the Flusberg publications. EX2041, ¶39. But according to Petitioner’s expert, at best a POSITA would have expected the claimed method of including nucleotide identity as a property in the input data structure to have the same level of detection as the Flusberg publications’ method that controls for nucleotide identity. EX2037, 113:8-22. And contrary to Petitioner’s arguments on Reply, there is no requirement that “the unexpected results...be recited in the claims.” *Ex Parte Steven Tierney, Martin Heeney, Weimin Zhang, Simon Higgins, & Iain Liversedge*, APPEAL2011-012142, 2013 WL 5399868 at \*3 (P.T.A.B. Jan. 22, 2013) (citing *In re Merchant*, 575 F.2d 865, 869 (CCPA 1978)).

Similarly, Petitioner’s attempts to dismiss other objective indicia of nonobviousness are contrary to the law. As the Federal Circuit explained in *Rambus*

*Inc. v. Rea*, “[o]bjective evidence of nonobviousness need only be ‘reasonably commensurate with the scope of the claims,’ and we do not require a patentee to produce objective evidence of nonobviousness for every potential embodiment of the claim.” 731 F.3d 1248, 1256-57 (Fed. Cir. 2013) (reciting that “[t]he Board erred when it found that Rambus’s objective evidence of nonobviousness lacked a nexus because it related to unclaimed features”). The ’794 Patent solves an unmet need for direct detection of DNA methylation without bisulfite conversion through its novel method. EX2041, ¶¶54-73. What’s more, Petitioner itself, including in the Flusberg publications, attempted to address that very issue but failed. POR at 49-50. And contrary to Petitioner’s arguments, Claim 1 is commensurate in scope of the holistic kinetic (HK) model as disclosed in Tse (EX2027, 213:19-21; EX2041, ¶¶77-87) which was first praised by Petitioner’s CEO, Christian Henry (EX2017, 5) and then copied by Petitioner (EX2041, ¶¶77-86). Accordingly, that the method of claim 1 produced unexpected results, addressed a long-felt yet unmet need while others tried and failed, received praise from the industry (including Petitioner), and was later copied by Petitioner strongly favors nonobviousness.

## II. CLAIM 1 IS NOT OBVIOUS OVER GROUND 1.

### A. The References of Ground 1 Account for Nucleotide Identity by Holding it Constant and Thus Avoid Including Nucleotide Identity as a Property in an “Input Data Structure.”

When a combination of references does not disclose all the features of a claimed invention, there must be motivation to modify the combination to arrive at the claimed invention. *Apple Inc. v. MPH Techs. Oy*, 28 F.4th 254, 263 (Fed. Cir. 2022) (“Substantial evidence supports the Board’s finding that Apple failed to show a motivation to modify the prior art combination to include substitution.”)

As explained in the POR [*see, e.g.*, POR at 14 *et seq.*] and confirmed by both Patent Owner’s expert [*see, e.g.*, EX 2041, ¶132] and Petitioner’s expert [*see, e.g.*, EX1002, ¶107; EX2037, 87:21-23], the first two Ground 1 references, the Flusberg publications, avoid including nucleotide identity as a property in an input data structure by holding nucleotide identity constant. Specifically, Petitioner’s expert explains that Flusberg “avoids using sequence context as an express input variable because it is held constant – Flusberg’s principal component analysis model is trained on a particular sequence that is varied in methylation state, but not in nucleotide sequence.” EX1002, ¶107. The third Ground 1 reference, the PacBio-BAM, does not disclose any method of modification detection. EX2037, 105:22-24. Petitioner’s other references (which are not relied upon in Ground 1) account for nucleotide identity in the same way as the Flusberg publications, namely, they avoid

including nucleotide identity in an input data structure in combination with the other recited properties as claimed by holding nucleotide identity constant and thus control for it. EX2041, ¶¶135-143; EX2037, 193:11-13 (referring to kineticsTools [EX1021], “[nucleotide identity] is controlled in this case, and, yes, I think this is consistent with the method that is described in the white paper [EX1016] or in the Flusberg publications”).

In Reply, Petitioner ignores its own expert’s testimony<sup>1</sup>—an in fact does not include a single citation to its expert’s declaration—to argue that the any use of nucleotide identity to detect a modification renders obvious the specific method recited in claim 1. But as explained above and as Petitioner’s expert confirms, that the Flusberg publications use or account for nucleotide identity does not disclose or suggest that it should be included as a property in an input data structure as claimed. Indeed, “[t]he selection of features for an input data structure is a fundamental problem in model training.” EX2041, ¶27.

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<sup>1</sup> Petitioner also had the option of filing a reply expert declaration but could not because their own expert does not support Petitioner’s arguments on reply. Having abandoned its own expert’s testimony, Petitioner crafts new positions in reply and quibbles with Patent Owner’s expert without evidence.

And Petitioner provides no motivation for a POSA to modify Flusberg's method that avoids including nucleotide identity in an input data structure to arrive at claim 1. To the contrary, as explained in the POR at 14-17, a POSA would not have been motivated to modify the methods disclosed in the Ground 1 references that "avoid" including nucleotide identity as a property in an input data structure, with the claimed method.

Petitioner attempts to distract from its failure to provide motivation to modify the method of the Flusberg publications by arguing for the first time in Reply that a single limitation of claim 1 does not require any use of the nucleotide identity. Reply at 10 ("Element 1.2 does not require 'use' of nucleotide identity."). But, claim 1 expressly recites "inputting the input data structure into a model, the model trained by: receiving a first plurality of first data structures [and] determining, using the model, whether the modification is present in a nucleotide at the target position within the window in the input data structure." And, both parties' experts agree, claim 1 requires that model be trained by a data structure that matches the claimed "input data structure" including nucleotide identity and the other claimed properties. EX2041, ¶44; EX1002, ¶130.

Petitioner next argues that because claim 1 is not limited to a particular "model," so long as nucleotide identity is received by the system and used in any way, then the limitation of creating an input data structure with the required

properties is disclosed. Again, Petitioner's own expert disagrees. EX2037, 108:20-109:12. And regardless of the specific model, claim 1 requires first "receiving data... and obtaining, from the data" values for a set of properties including nucleotide identity, IPD, and PW, then "creating an input data structure... wherein the input data structure includes" the set of said properties. That same input data structure must be used to train a model regardless of the specific model, and then "determining, using the model, whether the modification is present in a nucleotide at the target position within the window in the input data structure." POR at 5-7. Simply receiving the PacBio-BAM with the required data and using it in some way does not disclose or render claim 1 obvious. EX2041, ¶132.

Petitioner next argues for the first time in Reply that claim 1 does not require that the nucleotide identity be a variable and instead can be constant. But Petitioner's own expert explains why that is incorrect, testifying that the Flusberg publications avoid including nucleotide identity in an "input data structure" that is used to train a model precisely because nucleotide identity is held constant as follows: "Flusberg's specific example avoids using sequence context as an express input variable because it is held constant – Flusberg's principal component analysis model is trained on a particular sequence that is varied in methylation state, but not in nucleotide sequence." EX1002, ¶107. In other words, according to Petitioner's expert the

Flusberg publications' method avoids including nucleotide identity in an input data structure precisely because it is held constant. And Dr. Koo agrees. EX2041, ¶106.

Additionally, and contrary to Petitioner's assertion in Reply at 6-7, Patent Owner does not admit that the PacBio-BAM suggests considering nucleotide identity in base modification detection. Petitioner's partial quotation omits the qualifying phrase "[a]t best for Petitioner." POR at 22-23. Regardless, even if nucleotide identity should be considered or accounted for does not motivate a POSITA to modify how nucleotide identity is accounted for in the Flusberg publications.

Next, Petitioner's argument in Reply at 9 regarding the '338 Patent's use of basecalls is incorrect. As the Petitioner admits, the '338 patent discloses that basecalls can be used to detect pausing and that pausing may be "indicative of base modifications." *Id.* at 8-9. That disclosure does not mean nucleotide identity could or should be included in an input data structure as claimed. EX2041, ¶¶124-25. To the contrary, the '338 patent identifies exactly what properties can be used in an input data structure to detect base modifications and nucleotide identity is not one of them. Specifically, the '338 patent discloses that for base modification detection "a set of measurable features might be {pulse width, pulse duration, pulse height, pulse amplitude variability}." EX1007, 66:58-60. The '338 patent further discloses that "it will be clear to one of ordinary skill that the approach can be extended to pulse

metrics other than IPD, such as pulse width, branch rate, mismatch rate, deletion rate, etc.” again omitting any mention of nucleotide identity. EX1007, 67:64-67. Indeed, while the ’338 patent identifies a long list of properties that could be included in an input data structure to detect base modifications, the ’338 patent does not identify nucleotide identity because the Flusberg publications’ method accounts for nucleotide identity in a different way—by keeping it constant. EX1002, ¶107; EX2037, 87:21-23.

Moreover, the ’338 patent does not investigate or explain how pausing might be used in base modification detection, instead simply theorizing that it might be useful as follows: “if sequencing of a modification is known to increase the likelihood of pausing, then this information can be incorporated into a Bayesian likelihood model for identifying modified bases.” EX1007, 65:14-15. But, a POSITA would recognize that pausing is not useful. EX1049, 144:5-9. (“I don’t think this pausing has any relationship to IPD - - to the methylation or - - or to modifications.”). And in fact, Petitioner’s own reference confirms that pausing is not useful for methylation detection as follows: “Our current understanding is that pauses do not carry useful information about the methylation state of the DNA.” EX1021, 2. *See also* EX1049, 142:4-22. So, the ’338 patent’s suggesting that pausing might be useful in base modification detection does not suggest or motivate a POSITA to include nucleotide identity as a property in the claimed input data

structure, particularly where the '338 Patent discloses accounting for nucleotide identity in a different way, keeping it constant.

Petitioner's arguments on Reply at 7-9 regarding the disclosure of the Flusberg publications further support that claim 1 is not obvious. According to Petitioner, the '338 Patent discloses that a "combination of [its reaction data] can serve as a signal for the presence of a modification in the template nucleic acid" [Reply at 8], and that reaction data includes "pulse features [that] include the identities of each nucleotide in the sequence, as well as PW and IPD for each nucleotide" [*Id.*]. Yet, the Flusberg Publications avoid including the nucleotide identity in an input data structure as claimed. EX1002, ¶107; EX2037, 87:21-23. In other words, the authors of the Flusberg publications had access to all the information in the PacBio-BAM including nucleotide identity, yet disclosed a method that avoids including nucleotide identity in an input data structure. That the PacBio-BAM includes nucleotide identity adds nothing to the disclosure of Flusberg publications and would not motivate a POSA to modify Flusberg's methods. EX2041, ¶131.

Petitioner's argument in Reply at 10 that Patent Owner's expert asserted the prior art does not suggest to a POSA how "to use nucleotide identity" is false. Dr. Koo testified that the prior art, including the Flusberg publications, taught a POSA exactly how to use nucleotide identity, namely control for it and thus avoid including

it as a property in an input data structure as claimed. EX2041, ¶114 (“the disclosure does not suggest to a person of ordinary skill in the art to use nucleotide identity as property in an input data structure as claimed. To the contrary, a POSA would not modify a method that controls for nucleotide identity by keeping it constant and thus eliminating it a variable, and instead introduce an addition[al] property into the input data structure....”).

Moreover, Petitioner’s criticism on Reply at 11 of Dr. Koo’s interpretation of Fig. 14 is misplaced. Dr. Koo explained that Figure 14 is a “depiction of the artist” and that it omits actual data. EX1049, 99:25-100:5. Regardless, Figure 14 simply confirms that the Flusberg publications had the same data as PacBio-BAM, yet disclosed a method that avoids including nucleotide identity in an input data structure as claimed.

Moreover, Petitioner’s citations on Reply at 11-13 that nucleotide identity is used to align sequences in the prior art does not disclose or suggest including nucleotide identity as property in an input data structure as claimed. Indeed, Petitioner’s own expert recognized that kineticsTools includes sequence alignment [EX1002, ¶37], but testified that kineticsTools does not disclose including nucleotide identity as a property in an input data structure just like the Flusberg publications [EX2037, 193:11-13].

And, contrary to Petitioners assertion, the '794 Patent's discussion of Feng does not recite that Feng describes an input data structure including sequence context. To the contrary, the '794 Patent expressly recites that Feng has "attempted to take into account the sequence context" [EX1001, 19:3], which just like for the Flusberg publications, does not mean that Feng discloses including nucleotide identity as a property in an input data structure as claimed.

Petitioner further tries to confuse the difference between sequence context and nucleotide identity. Reply at 9-10. However, a POSITA will readily recognize, as Petitioner's own expert did, that these two properties are in fact not the same. Petitioner's expert testified that sequence context means "the signal and the identity of the bases that are surrounding a particular modification...." EX2037, 80:19-20. So, according to Petitioner's own expert, sequence context includes far more than nucleotide identity.

Accordingly, Petitioner has failed to demonstrate that claim 1 is obvious under Ground 1.

**B. A POSA Would Not Have Included PW in an Input Data Structure as Claimed.**

As explained in the POR, at the presumed time of the invention in 2019, the well-understood use of PW in base modification detection was to exclude it as

property in an input data structure and instead focus on IPD alone. POR at 31, *et seq.* (citing EX2041, ¶151).

As the coauthors of Flusberg explained in Schadt in 2013:

Given the high degree of regulation involved in the base incorporation process, PW is not as sensitive to shifts in sequence context induced by modifications as IPD (Flusberg et al. 2010). Therefore, for the purposes of developing an initial model of kinetic variation, we restrict attention to IPDs.

EX1010, 130. *See also* EX2041, ¶141.

Following that understanding of a POSA, all of Petitioner's references after the '338 Patent focus on IPD and exclude PW. *See* POR at 35. Even up until a few months prior to the '794 patent, the art (including Petitioner itself) followed that path by excluding PW and focusing on IPD for base modification detection. EX2038, 159.

Petitioner's argument that Clark mentions PW in 2011 [Reply at 15] is not relevant. The only reference other than the Flusberg publications cited by Petitioner on Reply as purportedly including PW in base modification detection is Clark, which was published in 2011. EX1008, 1. But as explained above, two years later in 2013, two of the same authors of the Clark reference, T. Clark and J. Kornack, published in Schadt that "PW is not as sensitive" as IPD such that one should "restrict attention to IPDs." EX1010, 130. *See also* EX2041, ¶137.

Accordingly, regardless of what the Flusberg publications (or Clark) disclose regarding PW, by the time the '794 Patent was filed, a POSA would not have included PW as a property in an input data structure, in addition to the other claimed properties.

### **III. OBJECTIVE INDICIA SUPPORT NONOBVIOUSNESS**

Petitioner fails to overcome the objective indicia favoring the nonobviousness of claim 1. Contrary to Petitioner's assertions, the evidence demonstrates a clear nexus between the claims and the objective indicia of nonobviousness. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373-74 (Fed. Cir. 2019) (“[T]he patent owner is still afforded an opportunity to prove nexus by showing that the evidence of secondary considerations is the ‘direct result of the unique characteristics of the claimed invention.’”) (quoting *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996)).

Dr. Koo testified that claim 1 provided a significantly improved method to detect DNA modifications because of the claims specific “input data structure” as follows: “[t]he reason the method of claim 1 has such a high AUC is because the inventors discovered, by systematically probing the predictive power of features, an optimal feature set to construct an input data structure that could accurately detect base modification.” EX2041, ¶39. Dr. Koo continued, “[t]hose features are a window, and the properties of each nucleotide in the window, namely, the nucleotide identity, the position of the nucleotide with respect to a target position within the

window, the PW, and the IPD.” *Id.* That testimony is un rebutted and establishes a nexus to why claim 1’s method achieved unexpected results, received praise, was copied by others, and why others, including Petitioner, tried but failed.

Accordingly, the objective indicia are a direct result of the unique characteristics of the claimed invention and thus strongly favor nonobviousness.

**A. Unexpected Results**

The claimed invention achieved superior and unexpected results compared to the prior art, particularly in detecting modifications like 5mC. Petitioner’s focus on whether the unexpected results encompass every aspect of the claim or align perfectly with its broad scope is misplaced. There is no requirement that unexpected results relied upon for patentability be recited in the claims. *Ex Parte Steven Tierney, Martin Heeney, Weimin Zhang, Simon Higgins, & Iain Liversedge*, 2013 WL 5399868 at \*3. Moreover, “[i]t is sufficient that the claim recites an element, which is not in the closest prior art, that causes the unexpected result.” *Id.*

Here, a POSITA would not have expected the improved detection of methylation by including nucleotide identity as a property in the input data structure with the other claimed properties. EX2041, ¶161. Petitioner’s own expert explains that the expectation would have been the same level of detection, not better. EX2037, 113:8-114:1. Ultimately, the ’794 Patent demonstrated an unexpectedly better detection of 5mC, achieving a prediction accuracy of 0.94 compared to the 0.55

accuracy of the Flusberg method. Moreover, the claimed method's ability to detect 5mC is on par with detection using bisulfite sequencing, the stated goal of both Flusberg and the '794 Patent. EX2041, ¶162. Those unexpected results strongly favor that claim 1 is not obvious.

Contrary to Petitioner's assertion otherwise, "[c]onsistent with the rule that all evidence of nonobviousness must be considered when assessing patentability, the PTO must consider comparative data in the specification in determining whether the claimed invention provides unexpected results." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (reversing final rejection of claims). "[W]hen an applicant demonstrates substantially improved results...and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary." *Id.* at 751. Petitioner implies without any evidence that the inventors of the '794 patent intentionally failed when evaluating the Flusberg publications' method. But the data presented in Figure 29 was obtained and analyzed well before any dispute arose between the parties and should not be dismissed just because Petitioner's attorneys say so. Petitioner cites no evidence casting any doubt on the comparison with the Flusberg method set forth in the '794 Patent. Thus, Figure 29 demonstrates the unexpected results achieved by the novel base modification detection method, surpassing the effectiveness of the previously available Flusberg publications' method.

Regardless, others in the field have confirmed the '794 Patent's unexpected results compared with the Flusberg method. *See* EX2039 at 16 (explaining that compared to Clark [EX1008], which follows the Flusberg method [EX2041, ¶135], “the HK model dramatically improved 5mC detection rates by 90% at 94% specificity” such that “the HK model constitutes a new, viable approach for studying epigenetic modifications in molecular diagnostic applications”).

Accordingly, the unexpected improvement in 5mC detection confirms that claim 1 is not obvious.

**B. Long-Felt but Unmet Need**

Petitioner erroneously contends that the satisfaction of a previously unmet need for detecting 5mC without bisulfite treatment lacks a nexus because claim 1 is not limited to 5mC or does not exclude bisulfite treatment. Reply at 16. But, in *Rambus Inc. v. Rea*, the Federal Circuit held that, “[t]he Board erred when it found that Rambus’s objective evidence of nonobviousness lacked a nexus because it related to unclaimed features,” explaining that “[o]bjective evidence of nonobviousness need only be reasonably commensurate with the scope of the claims, and we do not require a patentee to produce objective evidence of nonobviousness for every potential embodiment of the claim.” 731 F.3d at 1256-57 (quotation omitted). Here, claim 1’s method allows for the direct detection of 5mC without the drawbacks of bisulfite treatment—a significant advancement that directly relates to

the claims. EX2041, ¶¶152-159. The claims do not need to recite this advantage in order to be “reasonably commensurate with the scope of the claims.” *Id.*

Petitioner’s argument that claim 1 does not explicitly exclude bisulfite treatment prior to sequencing is irrelevant and mischaracterizes the significance of the claimed invention. An important aspect of claim 1 lies in its ability to enable the reliable detection of nucleotide modifications, including 5mC, without relying on bisulfite treatment. Both the ’794 Patent and the Flusberg publications explain that same long felt need. EX1001, 2:8-31; EX1007, 3:10-13. The asserted claims satisfy it. As a third-party authored journal article recognized in 2022, “[t]he overall methylation level analyzed by the HK model [citing Tse] highly correlated with bisulfite sequencing results (99%) [and thus] constitutes a new, viable approach for studying epigenetic modifications in molecular diagnostic applications.” EX2039 at 16.

Finally, Petitioner overlooks that multiple researchers in the art, including Petitioner, have acknowledged the significant challenges of directly detecting DNA methylation through SMRT sequencing. *See* POR at 44-45. The method of claim 1 represents a breakthrough as it provides a solution to this longstanding issue without requiring these additional steps or excessive sequencing depth. Petitioner’s attempt to dismiss this evidence is unfounded, as it overlooks the established difficulties in the field that the claim effectively addresses.

**C. Failure of Others**

While the Flusberg Publications sought to enable direct detection of methylation without bisulfite sequencing, both demonstrably failed to achieve this goal. Petitioner mischaracterizes statements from Dr. Dessimoz's deposition, claiming that "PO's own lawyer even argued this as an 'advantage' of both Flusberg publications." Reply at 19. First, Patent Owner's cross-examination questions are not evidence. Regardless, three years after the Flusberg publications, Petitioner's own reference, Schadt, referred to Flusberg and explained that "no statistical framework has been proposed to identify kinetic variation events from SMRT sequencing data that can serve as a surrogate for chemical modifications of DNA or RNA sequences." EX1010, 130. So, while Flusberg and the '338 patent raised the idea that such modifications might be detectable, no viable approach had been developed until the '794 Patent. EX2041, ¶157.

**D. Industry Praise and Copying**

Again, contrary to Petitioner's assertions, praise and copying need only be "reasonably commensurate" with the scope of the claims, not coextensive in every detail. *Rambus Inc.*, 731 F.3d at 1256-57. Accordingly, Petitioner's overly narrow view of nexus is unsupported and would undermine the purpose of secondary considerations.

Here, the HK model disclosed in Tse represents the inventive contribution of the '794 patent, including the claimed input data structure, and is commensurate with the scope of claim 1. Petitioner's own expert testified that Tse corresponds with claim 1 of the '794 patent. EX2037, 213:19-21 ("I believe that the patent -- '794 patent, claim 1, is -- corresponds to the model, this clause in that paper."). Dr. Koo confirms that Tse embodies all the elements of claim 1. EX2041, ¶¶86; EX2054. The significance of Tse lies in the claimed combination of properties that satisfy a long-felt need and advance the field of base modification detection. Attempts to minimize this evidence by focusing on the particular model do not rebut the nexus between the Tse's HK model and the inventive features of the '794 patent.

Moreover, as established in *Rambus*, copying does not require exact replication. 731 F.3d at 1256-57. Rather, the focus is whether meaningful aspects of the invention were adopted by others, signaling recognition of its value. *Id.* In this case, the adoption of Tse's HK model by Petitioner reflects deliberate copying of the inventive features of the '794 patent including the claimed "input data structure". The minor differences pointed out by Petitioner (Reply at 22) do not change that Tse's HK model was copied. For example, Petitioner points to the 5-nucleotide difference in the nucleotide window which would not be considered critical by a POSITA. EX2041, ¶¶83, 86. Petitioner also alleges a different CNN, (TensorFlow vs. Keras) but a POSITA would recognize the two are both substantially the same

given they are both CNN's and Keras could be used within TensorFlow. EX1049, 81:2-4. Those differences are not relevant as the meaningful aspects of the HK model were copied including an input data structure included the claimed combination of properties.

Moreover, widespread praise of the invention included recognition from Petitioner's own President and CEO, who highlighted the novelty of the '794 method as "the method for highly accurate simultaneous determination of DNA sequence and CPG methylation in one go." EX2017 at 5. That statement acknowledges a key innovative feature of the claimed method: the ability to achieve "highly accurate" detection "in one go," *i.e.*, without the need for additional steps like bisulfite sequencing. Others have also praised claim 1 as set forth in Tse. EX2050 at 7 ("[r]ecently, a neural network was used to identify 5mC in native DNA, which significantly improved detection generating 99% agreement with bisulfite sequencing data.[citing Tse]"); EX2044 at 2 ("The augmented 5-base HiFi-GS platform allows single molecular resolution of mCpG...with the potential to detect allele-specific events at an order of magnitude increased efficiency as compared to WGBS [whole-genome bisulfite sequencing].") Such recognition underscores not only the technical breakthrough of claim 1 but also its significant practical impact in advancing the field. Accordingly, the substantial evidence of copying and praise strongly supports nonobviousness.

The objective indicia of nonobviousness including satisfaction of a long-felt need, industry praise, copying, and unexpected results are supported by substantial evidence and establish a nexus to the claims. Petitioner's arguments to the contrary are unsupported by the evidence and based on improper legal standards. Those secondary considerations strongly favor of nonobviousness and confirm the patentability of the challenged claims.

#### **IV. CONCLUSION**

For the reasons set forth in the POR and the foregoing reasons Patent Owner requests a finding that no challenged claims are unpatentable.

Dated: December 9, 2024

Respectfully submitted,

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**CERTIFICATE OF WORD COUNT UNDER 37 CFR § 42.24(d)**

Under 37 C.F.R. § 42.24(d), the undersigned certifies that the word count for this Patent Owner's Sur-Reply totals 5,124 excluding the parts exempted by 37 C.F.R. § 42.24(a). The word count was made using the built-in word count function in the Microsoft® Word software used to prepare this document.

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Respectfully submitted,

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**CERTIFICATE OF SERVICE**

The undersigned hereby certifies that service on Petitioner was made as follows, in accordance with 37 CFR 42.6(e):

*Date of service:* December 9, 2024

*Manner of service:* 1. Electronic submission through the USPTO Patent Trial and Appeal Board P-TACTS System  
2. Electronic mail

*Document(s) served:* **PATENT OWNER'S SUR-REPLY**

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