

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HELENA LABORATORIES CORPORATION.,
Petitioner,

v.

SEBIA,
Patent Owner.

Case IPR2024-00801
Patent 7,887,686

PATENT OWNER'S PRELIMINARY RESPONSE

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PATENT OWNER'S EXHIBIT LIST

Exhibit	Description
2001	Declaration of James P. Landers, Ph.D
2002	Curriculum Vitae of James P. Landers, Ph.D

I. INTRODUCTION

The challenged claims of U.S. Patent No. 7,887,686 (the “‘686 patent”) relate to a free solution capillary electrophoresis (alternatively referred to as capillary zone electrophoresis” or “CZE” herein) method for separating and resolving hemoglobin variants (complex structures that can differ by a single amino acid) in a blood sample using a zwitterionic buffer (ZB) and a flow inhibitor (FI). The prior art of record confirms that separating and resolving hemoglobins (alternatively identified as “haemoglobin”, “Hb”, or “Hgb”) in a blood sample to confirm both the presence and absence of a hemoglobin variant (also referred to herein as a “hemoglobin form”) was an art-recognized problem. The ‘686 patent details many failed efforts to resolve various hemoglobin forms from one another, including Shihabi, a primary Petitioner reference.

The ‘686 patent explains that a combination of a ZB and a FI can be used in a CZE method to separate and resolve various forms of hemoglobin in a blood sample. Claim 1 recites that hemoglobins present in a blood sample are separated and resolved and that the hemoglobins are HbA₂ and HbC, HbD, HbE, HbS, HbF or HbA. The prior art known to the Examiner during prosecution included capillary electrophoresis (hereinafter “CE”) methods using a ZB (Tris) that were unsuccessful in separating and resolving certain hemoglobins. *See* for example Shihabi and Sahin discussed in the ‘686 patent. Ex. 1001, 1001-0016. The Examiner relied on

Camilleri for the teaching of the combination of a ZB and a FI (1,4-diaminobutane), but unrelated to separating and resolving hemoglobins. The Examiner ultimately determined after vigorous prosecution that the invention *as a whole* of separating and resolving hemoglobins in a CZE method using a ZB and a FI was patentable over the art of record, including Shihabi and Camilleri relied on by Petitioner.

Petitioner's challenge to the claims fails because Petitioner relies on the same or substantially the same prior art that the Office previously reviewed (*see* 35 U.S.C. § 325(d)) and Petitioner has failed to address § 325(d) or the *Becton, Dickinson* factors¹.

Petitioner relies on primary reference Shihabi in each asserted Ground of Invalidity. However, Shihabi's deficiencies are expressly discussed in the '686 patent and were expressly considered by the Examiner during prosecution of (the '686 patent). Huang, the alternative primary reference in each asserted Ground of Invalidity, is relied on by Petitioner *for the very same teachings* as Shihabi. Huang's teachings, therefore, are the same as or substantially similar to Shihabi.

¹ Petitioner's challenge to the claims relies in part on the Declaration of Dr. Wu (Ex. 1004). Patent Owner's Preliminary Response to the Petition relies in part on the Declaration of Dr. James P. Landers (Ex. 2001) which sets forth his qualifications at ¶¶ 1-23 and his CV (Ex. 2002).

The secondary reference Camilleri in Ground 2, relied on for teaching the combination of a ZB and a FI (1,4-diaminobutane in particular) was also considered by the Examiner. The secondary reference Coufal in Grounds 1, 2 and 3 is relied on *for the very same teaching* of a combination of a ZB and a FI as that of Camilleri. Coufal's teachings, therefore, are the same as or substantially similar to Camilleri. The secondary reference Landers in Ground 3 is relied on *for teaching the very same* 1,4-diaminobutane as Camilleri. Landers' teachings, therefore, are the same as or substantially similar to Camilleri.

Further, Petitioner has not even attempted to "demonstrate a material error by the Office" in issuing the '686 patent over Shihabi and Camilleri. Accordingly, the Board should exercise its discretion to deny the Petition under 35 U.S.C. § 325(d).

Petitioner also failed to present a prima facie case of obviousness based on the three asserted Grounds of Invalidity. The asserted art fails to teach or suggest each claim element, e.g., use of a blood sample and separating and resolving HbA₂ and HbC, HbD, HbE, HbS, HbF or HbA when present in the sample. The prior art failed to achieve such separation and resolution.

Further, Petitioner fails to present facts or law supporting motivation to combine the asserted art with a reasonable expectation of success. Petitioner makes conclusory statements, but provides no evidence of motivation and a reasonable expectation of success. The art demonstrates unpredictability in the use of a

combination of a ZB and a FI to separate and resolve hemoglobins. Accordingly, the Board should deny instituting *inter partes* review.

II. U.S. PATENT NO. 7,887,686

A. Summary of the ‘686 Patent

The ‘686 patent achieves what the prior art failed to accomplish, -- ***separating and resolving*** any normal or abnormal haemoglobins or haemoglobin variants ***in a biological sample*** using a CZE method. Ex. 1001, 1:7-20. The ‘686 patent separates and resolves haemoglobin HbA₂ from other forms of haemoglobin, automatically and in series in a single step analysis without a double coating, and particularly guarantees satisfactory resolution between HbA₂, HbC, HbD, HbE, HbS, HbF and HbA forms. Ex. 1001, 2:5-10. The ‘686 patent teaches that the claimed methods improve the accuracy and precision of qualitative and quantitative analysis of variants compared with analyses carried out using known methods. Ex. 1001, 3:2-4. In particular it teaches the separation and resolution of HbA₂ from HbC or HbE, which could not be accomplished by prior art CZE methods. Ex. 1001, 3:1-5.

The “qualitative” aspects involve peak identification based on a specific migration time or an observed migration time relative to an internal marker. The “quantitative” aspects involve defining the relative amount of a specific component(s) based on either ‘peak height’ or ‘peak area’. The ‘area under the peak’

defines how much of that component is present. A ‘stable’ baseline with ‘low noise’ is important to determining area under a peak. Ex. 2001, ¶¶ 46-47.

The ‘686 patent details limited prior success in the field of separating and resolving certain haemoglobins using CE. According to the ‘686 patent, the “dynamic double coating” method of the Analis kit cannot separate HbA₂, HbC, and HbE fractions well enough rendering quantitative analysis of the HbA₂ fraction impossible when HbC or HbE are present. Ex. 1001, 1:30-43. Further, since HbS and HbD fractions have the same electrophoretic position, complementary analysis in an acidic medium is necessary to determine the type of variant present in the sample. Ex. 1001, 1:30-46. Ishoka uses CE to separate HbC, HbS and HbA using a borate buffer, but provides no indication that its method could separate and resolve other hemoglobin forms. Ex. 1001, 1:52-56. Jenkins (1996), (1997) and (1999) using CE could only provide insufficient resolutions between HbA, HbF and HbS. Ex. 1001, 1:56-59. Sahin using CE and a Tris buffer “obtained deeply unimpressive results for resolution between HbA, HbF, HbS, and HbA₂.” Ex. 1001, 1:59-65. Shihabi using CE and a Tris-arginine buffer “allowed HbA/HbS separation [but] HbC/HbE and HbA₂ fractions were not resolved.” Ex. 1001, 1:65-2:1. Chen U.S. Patent No. 5,202,006 and Chen U.S. Patent No. 5,439,825 using CE could only provide “low resolution” for HbA, HbF, HbS, and HbC, and provided no indication that its method could be used to resolve other hemoglobin forms. Ex. 1001, 2:1-4.

The prior art identified in the '686 patent failed to provide a method to separate and resolve all claimed hemoglobin forms when present in a blood sample, especially resolving HbC, HbE and HbA₂ from each other and resolving HbD and HbS from each other. Ex. 2001, ¶ 48.

The Patentee discovered that the seven forms of hemoglobin, if present in subcombinations in a biological sample, could be separated from other components in the biological sample and resolved into individual peaks by CE *both qualitatively and quantitatively* using an analysis buffer including *a ZB and a FI*. Ex. 1001, 2:11-26, 3:6-10 (“The zwitterionic buffer flow inhibitor associations of the invention are of particular use in analyzing samples in which normal or variant haemoglobins of the HbA₂, HbC, HbD, HbE, HbS, HbF and/or HbA type are present, to detect and/or quantify them.”). The '686 patent emphasizes resolving and quantifying HbA₂ even in the presence of HbC or HbE (Ex. 1001, 3:4-5) which Shihabi could not do. Ex. 2001, ¶ 49; Ex. 1001, Figs. 1-7D, 3:29-44. The '686 patent provided for the first time a method capable of confirming both the presence and absence of any of the seven forms of hemoglobin, if present, in a blood sample. Ex. 2001, ¶ 50.

The electrophoregrams of Figs. 1-5 demonstrate separation and resolution of various hemoglobins in samples with peaks having good separation, good Gaussian shape (no fronting or tailing) and clean baselines, thereby allowing the quantification of the peak area representative of a particular hemoglobin with confidence, as

indicated in each Figure. While the peaks in Fig. 5 for D and S are only partially resolved (the resolution between two peaks (R) is about 0.7), they have good Gaussian shape without fronting, the baseline is clean and a line can be drawn that evenly divides the overlap allowing quantification of the peaks with confidence. While the HbA peaks exhibit a slight tailing effect, in all cases HbA is the dominant Hb form and the pre- and post-HbA peak baseline is the same, hence, quantitative value can be extracted. Ex. 2001, ¶¶ 51-56.

The '686 patent provides a CE method using a ZB and a FI not only for detection and quantification of the presence of hemoglobin forms HbA₂, and HbC, HbD, HbE, HbS, HbF or HbA in a blood sample, but also the confirmation of the absence of a particular hemoglobin form, if not detected in the blood sample. Ex. 2001, ¶ 57.

B. Free Solution Capillary Electrophoresis of Hemoglobins

CZE is a separation technique that uses an electric potential to cause analytes in a sample (and eventually in the buffer) to “migrate” within a silica capillary. Ex. 2001, ¶ 24. This is referred to as “electrophoretic mobility (μ_{ep})” which represents the migration of a charged analyte under the influence of an applied potential, which is primarily determined by the analyte’s net charge and its mass (size). *Id.* Applying a potential to a capillary filled with a liquid buffer containing electrolytes produces an additional effect, one that is only induced by an electrical field – this is

“electroosmotic flow” (EOF), which refers to the bulk movement or flow of the solution itself within the capillary (μ_{ep}); essentially a “pumping of fluid in one direction powered by an electric field. *Id.* As a result, the overall mobility of a charge species (μ_{app} ; apparent mobility) in a capillary under the influence of an electric field is represented by:

$$\begin{array}{c} \text{Mobility observed} \\ \downarrow \\ \mu_{app} = \mu_{ep} + \mu_{eof} \\ \begin{array}{c} \text{Mobility due to analyte charge (q) and mass (mass)} \\ \downarrow \\ \mu_{ep} \\ \uparrow \\ \mu_{eof} \\ \text{Mobility due to charge on capillary wall} \end{array} \end{array}$$

The sum of the driving force is from the analyte itself and the bulk flow of the fluid. *Id.* Overall movement of charged analytes within the capillary is a result of both electrophoretic and electroosmotic flow. It stands to reason that if the charge on the capillary wall decreases dramatically, the mobility of the analyte is primarily driven by charge and mass of the analyte. *Id.*

Capillaries used for electrophoresis are comprised of fused silica (silicon dioxide; SiO₂). Ex. 2001, ¶ 25. At the appropriate pH, the inner surface of a fused silica capillary in contact with an electrolyte solution is negatively charged due to the presence of silanol groups (SiO⁻). *Id.* When the capillary is uncoated (bare or naked), the negative charge is exposed to the buffer and sample and small, positively-charged ions (e.g., sodium, Na⁺) interact with the negative surface. *Id.* This interaction generates the bulk flow that is EOF. *Id.* In contrast, if, the inner surface of the fused silica capillary is “coated” (covalently-modified) with a

permanent polymeric or other chemical coating, this serves to shield the negative charge on the capillary wall from the buffer components and analytes. *Id.* As a result of reducing the surface negative charge, EOF can be dramatically reduced. Both coated and uncoated (bare or naked) capillaries are used in CE depending on the analytes to be separated. *Id.*

Buffers are commonly used in chemistry/biochemistry to avoid drastic changes in pH usually with two forms of the same compound, one that can buffer ‘acidic’ changes and the other ‘basic’ changes. Ex. 2001, ¶ 26. Because ZBs carry both positive and negative charges, they exhibit properties beneficial to CE, such as stability, low UV absorbance, low conductivity and compatibility with a variety of analytes, including proteins. *Id.* A ZB with at least one amine function, at least one acid function (COOH or SO₃H) and at least one OH in opposite position, are of particular interest for the separation/resolution of the Hb variants listed in claim 1. Ex. 1001, 7:37-41 (Claim 3). Exemplary ZB includes tricine. Ex. 1001, 8:7-10 (Claim 15).

A FI (also known as a flow modifier) electrostatically binds to the negative charges in the silica on the inner surface. Ex. 2001, ¶ 27. When the FI is part of the buffer solution filling the cavity, the effect is “dynamic coating.” *Id.* A FI is often a small positively charged organic molecule. *Id.* This electrostatic interaction (positive charge binds to negative charge) can reduce the wall charge, thus ‘passivating’ it,

and this can result in a decrease in the magnitude of electroosmotic flow. *Id.* While EOF always exists to some extent (i.e., never zero), it can be reduced to negligible levels. *Id.* The '686 patent uses a FI to reduce EOF which lengthens the separation time, and allows the hemoglobin variants, which have very similar electrophoretic mobility, sufficient time to resolve. *Id.* The table below identifies the single amino acid differences between HbA and hemoglobin variants that result in very similar structure and, as a result, very similar electrophoretic mobilities can be expected. *Id.* Consequently, hemoglobin variants are closely migrating proteins. *Id.*

Hb A: $\alpha 2/\beta 2$ chains
Hb A2: $\alpha 2/\delta 2$ chains
Hb S same as Hb A except glutamic acid in position 6 of the β -chain is replaced by valine (neutral).
Hb C same as Hb A except glutamic acid in position 6 of the β -chain is replaced by lysine (basic).
Hb E same as Hb A except glutamic acid in position 26 of the β -chain is replaced by lysine (basic).
Hb D: same as Hb A except glutamic acid in position 121 of the β -chain is replaced by glutamine (neutral).

As shown, HbA, HbS, HbC, HbE and HbD only differ by a single amino acid substitution in a hemoglobin protein complex that includes 4 chains, each around 145 amino acids, thus comprised overall of roughly of 600 amino acids. *Id.* HbC and HbE do not have an amino acid substitution at all, but simply differ by the position of a single lysine in the β -chain. *Id.*

CE can be used to separate proteins without use of a FI. Ex. 2001, ¶ 28. While the CE separation of proteins can be enhanced by FI, this is not always the case. *Id.* In general, a reduction in EOF provides longer 'on-capillary' time and extends the opportunity for closely migrating species to be resolved. *Id.* But, a reduction in EOF

cannot be used to predict successful separation and resolution of particular closely-migrating proteins within a sample. *Id.* The art relied on by Petitioner provided no teaching that the differences among closely-migrating hemoglobin variants would be significant enough for EOF modification to allow resolution. *Id.* Empirical studies are usually required to ascertain whether separation and resolution of a particular protein from other sample components is enhanced by a FI. *Id.*

There is no absolute correlation between a type of FI and the reduction in EOF, and there is no absolute correlation between reducing EOF and protein separation and resolution. The effect of FIs on the magnitude of EOF reduction is not predictable, can be affected by a number of parameters (e.g., buffer type and strength) and must be determined empirically for any given protein variants as to whether a FI will reduce EOF in a manner to allow sufficient separation and resolution of the protein variants. Ex. 2001, ¶ 29.

III. INSTITUTION SHOULD BE DENIED UNDER 35 U.S.C. § 325(d)

“[I]nstitution of *inter partes* review is discretionary.” *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17 (PTAB Dec. 15, 2017) (Designated Precedential Aug. 2, 2019 as to § III.C.5 ¶ 1) (citing *Harmonic Inc. v. Avid Tech, Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) ; *see also* 35 U.S.C. § 325(d).

This discretion includes denying institution of petitions as a whole even when at least one challenged claim meets institution criteria. PTAB Consolidated Trial Prac. Guide (Nov. 2019) at 65 (citing *Deeper, UAB v. Vexilar, Inc.*, IPR2018-01310, Paper 7 (PTAB Jan. 24, 2019) (informative); *Chevron Oronite Co. v. Infineum USA L.P.*, IPR2018-00923, Paper 9 (PTAB Nov. 7, 2018) (informative)). As detailed below, Petitioner's reliance on the same or similar art and the same or similar arguments already reviewed by the Examiner warrants discretionary denial.

There is a two-part framework in evaluating the prior consideration of the same or substantially the same prior art or arguments, to which the *Becton, Dickinson* factors provide useful insight. *Advanced Bionics*, IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020). The first part considers whether the same or substantially the same art or arguments were previously presented to the Office *Id.* at 8. If the first part is satisfied, the Board determines in the second part whether the petitioner has demonstrated that the Office erred in a manner material to patentability. *Id.* at 8-11 (citing *Becton, Dickinson*, Paper 8 at 24).

When considering this two-part framework, the Board considers the following non-exclusive factors:

- (a) the similarities and material differences between the asserted art and the examination's prior art;
- (b) the cumulative nature of the asserted art and the examination's prior art;

(c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;

(d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;

(e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and

(f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

See Becton, Dickinson, IPR2017-01586, Paper 8 at 17–18. Petitioner fails to address this framework and factors.

Above factors (a), (b), and (d) relate to the first part and factors (c), (e), and (f) relate to the second part. *Advanced Bionics*, IPR2019-01469, Paper 6 at 10. If a condition of the first part is satisfied and petitioner fails to show a material error, discretion is generally exercised to not institute *inter partes* review. *Id.* at 8-9.

Also, when the “same or substantially the same prior art or arguments” were presented during original prosecution, the Board has repeatedly denied institution. 35 U.S.C. § 325(d) ; *Dorco Co. v. Gillette Co.*, IPR2017-00500, Paper 7 at 17–18 (PTAB June 21, 2017); *Apple Inc. v. Uniloc USA, Inc.*, IPR2017-00224, Paper 7 at 6-7 (PTAB May 25, 2017).

Here, the Board should deny institution on all grounds because Petitioner’s challenges rely on the same or substantially the same prior art presented during prosecution of the ‘686 patent and Petitioner has not demonstrated a material error by the Office. *Advanced Bionics*, IPR2019-01469, Paper 6 at 10-11.

Petitioner’s asserted grounds of invalidity are as follows.

Claims Challenged	35 U.S.C. §	Art Relied Upon
1, 2, 3, 6, 7, 10-14, 17, 18 and 23	103	Shihabi or Huang and Coufal
15 and 16	103	Shihabi or Huang and Coufal and Camilleri
4, 5, 8, 9, 19-22 and 24	103	Shihabi or Huang and Coufal and Landers

Huang (Ex. 1015) is relied upon in the alternative to Shihabi (Ex. 1011), with Petitioner making no distinction between their teachings.

Shihabi was expressly discussed in the ‘686 patent and expressly considered by the Office having been cited on an IDS. Ex. 1003, 1003-0006, 1003-0042, 1003-0269; Ex. 2001, ¶¶ 58-61, Appendix A, ¶ 2. Huang is redundantly relied on by the Petitioner *for the very same teachings* as Shihabi already considered by the Office and, accordingly, does not save Petitioner. Ex. 2001, ¶¶ 59, 72-74. The secondary reference Camilleri was expressly considered by the Office and Petitioner relies on Coufal and Landers *for the very same teachings* relied on by the Office with

Camilleri during prosecution, i.e. a combination of a ZB and a FI (1,4-diaminobutane in particular). Petitioner provides no explanation of material error by the Office in allowing the ‘686 patent over Shihabi (or the redundant Huang) and Camilleri (or the redundant Coufal and Landers). Accordingly, the Board should exercise its discretion and deny the Petition.

A. The Board Should Deny Institution of Grounds 1, 2 and 3 Based on Shihabi With Coufal Camilleri and Landers under *Becton, Dickinson* Factors (a), (b) and (d)

1. Becton, Dickinson Factor (a)

Shihabi meets the first part of the *Advanced Bionics* test (*i.e.* whether the same art was presented to the Office) in view of *Becton Dickinson* factor (a). Shihabi was expressly described in the ‘686 patent as failing to teach resolution of “HbC/HbE and HbA₂ fractions.” Ex. 1001, 1:65-2:1. Shihabi was also considered by the Examiner during prosecution. Ex. 1003, 1003-0269; Ex. 2001, ¶¶ 60-61. *See Advanced Bionics*, Paper 6 at 7–8 (“Previously presented art [under § 325(d)] includes . . . art provided to the Office by an applicant, such as on an Information Disclosure Statement (IDS).”) (modification in original); *Husky Injection Molding Sys. v. Plastipak Packaging, Inc.*, IPR2020-00428, Paper 24 at 10–11 (PTAB July 28, 2020). Camilleri also meets the first prong of the *Advanced Bionics* test in view of *Becton, Dickinson* factor (a). Camilleri was expressly considered by the office for teaching the combination of a ZB and a FI (1,4-diaminobutane in particular). Ex.

1003, 1003-0418; Ex. 2001, ¶ 75, Appendix A, ¶ 31. Accordingly, *Becton Dickinson* factor (a) is met with respect to Shihabi and Camilleri.

2. Becton, Dickinson Factor (b)

a. Shihabi

Petitioner relies on Shihabi and Coufal for invalidity of claims 1, 2, 3, 6, 7, 10-14, 17, 18 and 23 (Ground 1). Shihabi was already reviewed and its teachings considered by the Examiner. Shihabi teaches separation of hemoglobin variants HbC, HbS, HbF, and HbA using a 9 kV potential and a zwitterionic buffer (Tris). Ex. 1011, Figure 1; Ex. 2001, ¶ 61. Shihabi also teaches separation of HbA₂, HbS and HbA using a lower 6 kV potential. Ex. 1011, Fig. 4; Ex. 2001, ¶ 61.

The Examiner asserted that Chen U.S. 5,202,006 taught using CE on hemoglobin A, A₂, S and F and on hemoglobin S. Ex. 1003, pp. 1003-0253-1003-0254; *see also* Ex. 2001, Appendix A, ¶¶ 5-8. These include the same hemoglobin variants separated by Shihabi. Ex. 2001, ¶ 62. The Examiner was also aware that Chen taught separation of HbA, HbF, HbS, and HbC using CZE and a barbituric acid buffer. Ex. 1001, 2:1-5. These are the same hemoglobin variants separated by Shihabi using Tris at 9 kV. Ex. 2001, ¶ 62. The Examiner also relied on Mohammad for teaching capillary isoelectric focusing using an ampholine buffer for identification of the same hemoglobin variants separated by Shihabi using Tris at 9kV. Ex. 1003, p. 1003-0350; *see also* Ex. 2001, ¶ 62, Appendix A, ¶¶ 14-18.

Separation of each of the hemoglobins identified in Shihabi HbC, HbS, HbF, and HbA (Tris and 9 kV) and HbA₂, HbS and HbA (Tris and 6 kV) was already known, albeit using different buffer conditions and/or isoelectric focusing. Ex. 2001, ¶ 62.

During prosecution, Sahin (Ex. 1007) was reviewed and considered by the Examiner (Ex. 1001, 1001-0001; Ex. 1003, 1003-0269) and is described in the ‘686 patent for teaching “deeply unimpressive results for resolution between the HbA, HbS and HbA₂ fractions for Tris buffer.” Ex. 1001, 1:63-66. The Examiner was well aware beyond Shihabi that the ZB Tris was described as being used in CE of samples including Hb variants HbA, HbS and HbA₂ and that the same Hb variants separated by Shihabi were disclosed in the prior art as being separated. Ex. 2001, ¶ 63. Shihabi is not a new reference as it was reviewed and considered by the Examiner. Additionally, Shihabi is cumulative of and provides no better teaching than Chen and Mohammad, and Sahin. *Id.* Petitioner has provided no explanation of why Shihabi is a better reference than Chen, Mohammad, or Sahin

b. Coufal

In Ground 1, Petitioner relies on Coufal (Ex. 1013) for teaching a combination of a ZB (particularly Tris) and a FI (particularly an aliphatic diamine). *See* Petition, pp. 22 (claim 1), 43 (claim 23). The Examiner relied on Camilleri for teaching a combination of a ZB and a FI (1,4-diaminobutane). Ex. 1003, 1003-0418; Ex. 2001, ¶ 64, Appendix A, ¶¶ 26-32. 1,4-diaminobutane is an aliphatic diamine just like the

ethylenediamine of Coufal. Ex. 2001, ¶ 64. Camilleri, in general, teaches the use of cationic amines as a FI, of which the ethylenediamine of Coufal is one. Ex. 1020, 1020-0002; Ex. 2001, ¶ 64. Petitioner has provided no explanation of how or why Coufal is a better reference than Camilleri with respect to claims 1 and 23 of Ground 1 for the teaching of a ZB and a FI and Coufal's teachings for the use of ZB and FI are the same as Camilleri. Ex. 2001, ¶ 64.

In Ground 1, Petitioner has relied on Coufal for teaching the additional limitations of claims 6, 12, 17, and 18. *See* Petition, pp. 27, 30, 38, and 40. The Examiner considered Shihabi (Claim 12) and relied on Sunzeri (Claims 6, 12) and Nouadje (Claims 17 and 18) for teaching these limitations. Ex. 1003, 1003-0416-1003-0419, 1003-0251; Ex. 2001, ¶¶ 66, 69-71, Appendix A, ¶ 5. Petitioner has provided no explanation of how or why Coufal is better than Sunzeri, Shihabi, or Nouadje with respect to the teachings of claims 6, 12, 17, and 18 and Coufal's teaching of these limitations is substantially the same as Sunzeri, Shihabi, or Nouadje that were already considered by the Examiner. Ex. 2001, ¶¶ 66, 69, 70, 71.

In Ground 1, Petitioner has also relied on Coufal for teaching the capillary tube limitations of claims 10 and 11. Petition, pp. 30, 32. However, Coufal is not a better reference than the '686 patent discussion that these limitations were known. Petition, pp. 30-32; Ex. 2001, ¶¶ 67-68. Petitioner has provided no explanation of how or why Coufal is a better prior art reference than the '686 patent's discussion

and Coufal's teaching of these limitations is the same as or substantially the same as '686 patent discussion of these limitations. Ex. 2001, ¶ 67-68.

Petitioner also relies on Coufal's ethylenediamine in Ground 3 for teaching the particular FI of claims 4, 5, and 24. *See* Petition, pp. 49 (claim 4), 51 (claim 5), and 64 (claim 24). Camilleri teaches 1,4-diaminobutane, which is an aliphatic diamine just like Coufal's ethylenediamine. Ex. 2001, ¶ 65. Petitioner has provided no explanation of how or why Coufal is a better reference than Camilleri with respect to teaching the aliphatic diamine of claims 4, 5 and 24 of Ground 3 and Coufal's teachings for the use of a ZB and an aliphatic diamine FI are the same as Camilleri. *Id.*

c. Camilleri

Camilleri (Ex. 1020) is relied on by Petitioner only for teaching the ZB (tricine) of claims 15 and 16. Petition, pp. 46-47; Ex. 2001, ¶ 75. Camilleri was expressly considered by the Examiner for teaching the combination of a ZB and FI 1,4-diaminobutane, but was not relied upon for teaching tricine. Ex. 1003, 1003-0418; Ex. 2001, ¶ 75. Appendix A, ¶ 31. The Examiner reviewed and understood that Camilleri taught tricine. *Id.* However, the Examiner relied on Sunzeri for teaching tricine. Ex. 1003, 1003-0415-1003-0417; Ex. 2001, ¶¶ 66, 75, Appendix A, ¶ 27. Camilleri's teaching of a ZB (tricine) relied on by Petitioner is cumulative of Sunzeri's teaching of a ZB (tricine). Ex. 2001, ¶ 75.

d. Landers

In Ground 3 Landers is relied on by Petitioner for teaching 1,4-diaminobutane as the aliphatic diamine of claims 4, 5 and 24, the 1,4-diaminobutane of claims 19-22, and the FI concentration of claims 8 and 9. Petition, pp. 50 (claim 4), 52 (claim 5), 54 (claim 8), 56 (claim 9), 58 (claim 19), 59 (claim 20), 61 (claim 21), 62 (claim 22), and 65 (claim 24); Ex. 2001, ¶ 76. Camilleri was cited by the Examiner. Ex 1003, 1003-0418. Camilleri teaches specific concentrations of 1,4-diaminobutane, which is an aliphatic diamine. Ex. 2001, ¶¶ 76-78. Petitioner has provided no explanation of how or why Landers is a better reference than Camilleri with respect to a teaching of the aliphatic diamine of claims 4, 5 and 24 or a teaching of 1,4-diaminobutane of claims 19-22, and the specific FI concentrations of claims 8 and 9. Landers's teaching of the use of the aliphatic diamine and specific concentrations of 1,4-diaminobutane is the same as Camilleri. Ex. 2001, ¶¶ 76-78.

Petitioner relies on Coufal and Landers for the very same teachings of Camilleri relied on by the Office during prosecution, e.g. a combination of a ZB and a FI (1,4-diaminobutane in particular) and are therefore cumulative of Camilleri. *See* Petition, pp. 3 (comparing teachings of already-considered Camilleri and Coufal for a ZB and FI), 17-18 (comparing already-considered Camilleri, Coufal and Landers for a ZB and FI (1,4-diaminobutane, in particular)). “A reference is cumulative when it teaches no more than what a reasonable examiner would consider to be taught by

the prior art already before the PTO.” *Roku, Inc. v. Universal Electronics, Inc.*, IPR2019-01619, Paper 11 at 16) (quoting *Regeneron Pharm., Inc. v. Merus N.V.*, 864 F.3d 1343, 1350 (Fed. Cir. 2017)).

Accordingly, Coufal and Landers present essentially the same teachings as, and are cumulative of, Camilleri. *Liberty Mut. Ins. Co. v. Progressive Casualty Ins. Co.*, CBM2012-00003, Paper 7 (PTAB Oct. 25, 2012). “Because the references are not identical, each reference has to be better in some respect or else the references are collectively horizontally redundant.” *Id.* at 3. At no point does the Petitioner provide any reason why Coufal or Landers would be preferable to Camilleri.

Petitioner has simply not offered any distinction between the relative strengths and weaknesses of its application of the prior art to one or more claim elements compared to Shihabi and Camilleri already before the Office. *See EMC Corp. v. PersonalWeb Techs., LLC*, IPR2013-00087, Paper 25 at 3–4 (PTAB June 5, 2013); *Liberty Mut.*, CBM2012-00003, Paper 7 at 2–3.

3. Becton, Dickinson Factor (d)

Petitioner argues that certain teachings were missing from the prior art during prosecution of the ‘686 patent, namely:

- a) Hemoglobin variant separation by CE alone or with ZB;
- b) Any CE separation using both ZB and FI.
- c) Any CE separation recognizing the need to reduce EOF.

d) Any CE separation using ZB and FI to reduce EOF.

Petition, p. 3. Petitioner is wrong for each of a)-d).

Regarding a): The Examiner found during prosecution that Chen taught CE separation of hemoglobin variants A, A2, and F alone and variants A, F, S, and C with a ZB (baritunic acid). Ex. 1003, 1003-0253-1003-0254; Ex. 2001, ¶ 82; Appendix A, ¶¶ 6-7; Ex. 1016, 5:33-36, 6:1-4.

Regarding b): The Petition itself belies this argument. Petition, p. 11 (“The Examiner indicated that Camilleri ...taught the combination of a ZB (tricine) ...[and] a FI...”). Camilleri describes CE separation using both a ZB and a FI. Ex. 2001, ¶ 83; Ex. 1020, 1020-0002.

Regarding c) Preventing a protein-capillary surface interaction would be understood to reduce electroosmotic flow (EOF), therefore Camilleri contemplated reducing EOF in a CE separation. Ex. 2001, ¶ 84.

Regarding d): Camilleri, contemplated CE separation using ZB and FI to reduce EOF. Ex. 2001, ¶ 85; Ex. 1020, 1020-0003(“**[p]rotein adsorption may also be reduced** by addition of cationic surfactants ... to the buffer. Increasing the concentration *first reduces*, then eliminates, and finally reverses the charge on the capillary surface... (the latter condition also causes **a reversal of the EOF**).” (Emphasis added).

Furthermore, the art of record provides the very same teachings that Petitioner says was absent during prosecution. Because Petitioner relies upon prior art that is “the same or substantially the same art previously . . . presented to the Office,” the first step set forth in *Advanced Bionics* is satisfied. The Board should proceed to the second step – “whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.” *See Advanced Bionics*, IPR2019-01469, Paper 6 at 8.

Petitioner relies on the prior art for the same reasons the Examiner relied on the art of record. Shihabi is not substantially different from the teachings of Chen U.S. 5,202,006, Mohammad, and Sunzeri or Sahin all before the Examiner.

The Examiner asserted that Chen U.S. 5,202,006 taught separation of HbA₂, HbA and HbF as part of normal blood (col. 1, lines 26-30) and also HbS (col. 2, lines 1-5). Ex. 1003, 1003-0254. The Examiner was also aware that Chen taught separation of HbA, HbF, HbS, and HbC using CZE and a barbituric acid buffer. Ex. 1001, 2:1-5; Ex. 1003, 1003-0254, 1003-0309. The Examiner relied on Mohammad for teaching separation of HbC, HbS, HbF, and HbA. Ex. 1003, 1003-0350. Accordingly, separation of each of the hemoglobins identified in Shibahi was already known to be separated, albeit using different buffer conditions.

The Examiner relied on Sunzeri for teaching separation using a zwitterionic buffer (tris). Ex. 1003, 1003-0415-1003-0417. Sahin was expressly considered by

the Examiner and is described in the ‘686 patent for teaching “deeply unimpressive results for resolution between the HbA, HbS and HbA₂ fractions for Tris buffer”. Ex. 1001, 1:59-61; Ex. 1007, 1007-0001-1007-0002. The Examiner was well aware beyond Shihabi that the zwitterionic buffer Tris was described in Sahin as being used in capillary electrophoresis of samples including Hb variants.

Since Petitioner is making the same or similar arguments based on Shihabi and Camilleri as were made by the Examiner during prosecution (i.e., separation of haemoglobins using a Tris zwitterionic buffer were known, and the combination of a zwitterionic buffer and a flow inhibitor was known), *Becton, Dickinson* factor (d) weighs in favor of discretionary denial.

B. Petitioner Has Not Demonstrated Material Error by the Office

Petitioner fails to demonstrate a material error by the Office as required by the second step of *Advanced Bionics*, which consists of an evaluation of *Becton, Dickinson* factors (c), (e), and (f). Therefore, the Board should exercise its discretion to deny institution of *inter partes* review.

1. Becton, Dickinson Factor (c)

Factor (c) weighs in favor of the Board exercising its discretion because the Examiner considered Shihabi and Camilleri, even though Shihabi was not used expressly for a rejection. *Alarm.com Inc. v. Vivint, Inc.*, IPR2015-01967, Paper 12 at 15, 21 (March 30, 2016). The Examiner was well aware of Shihabi because

Shihabi was described in the '686 patent as using a zwitterionic buffer to separate HbA and HbS but that "HbC/HbE and HbA₂ fractions were not resolved." Ex. 1001, 1:65-2:1; *see also* Ex. 1003, 1003-0269 (IDS which was initialed by the Examiner. Camilleri was expressly relied upon by the Examiner for teaching a zwitterionic buffer and a flow inhibitor (1,4-diaminobutane in particular)). Ex. 1003, 1003-0418; Ex. 2001, ¶ 64, Appendix A, ¶ 31.

Accordingly, Factor (c) weighs in favor of the Board exercising its discretion.

2. Becton, Dickinson Factor (e)

Petitioner has not pointed out how the Examiner erred in the evaluation of Shihabi and Camilleri. Therefore, factor (e) weighs in favor of the Board's exercise of discretion. Petitioner fails to provide any explanation of why the '686 patent should not have been allowed by the Examiner in view of Shihabi and Camilleri. Petitioner simply provides the same or similar arguments advanced by the Examiner and hopes for a different conclusion.

Petitioner provides no explanation of what material error was made by the Examiner with respect to the teachings of either Shihabi or Camilleri that warrants the Board to revisit patentability of the '686 patent claims based on Shihabi and Camilleri or the redundant references Coufal or Landers. Because Petitioner fails to "point[] out sufficiently how the Examiner erred in its evaluation of the asserted

prior art,” factor (e) favors the Board’s exercise of its discretion. *See Becton, Dickinson*, IPR2017-01586, Paper 8 at 18; 24–25.

3. Becton, Dickinson Factor (f)

Shihabi and Camilleri were presented to the Office. Coufal and Landers are relied on by the Petitioner for the same teachings as Camilleri and factor (f) weighs heavily in favor of the Board’s exercise of its discretion. Importantly, Petitioner did *not* submit any experimental data or scientific explanation in support of its Petition. Therefore, there is no additional evidence or science to consider. And although Petitioner provided a declaration in support of its Petition, that declaration is largely repetitive of the asserted references, references described in the ‘686 patent, references cited by the Examiner during prosecution, and otherwise includes conclusory statements regarding motivation and predictability found in the Petition. *See Universal Imaging Indus.*, IPR2019-01383, Paper 7 at 8-9, 31. Accordingly, the Board should exercise its discretion under § 325(d) to deny institution. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 8 (citing *Becton, Dickinson*, Paper 8 at 24).

C. The Board Should Deny Institution of Grounds 1, 2 and 3 Based on Huang as Being Redundant to Shihabi With Coufal, Camilleri and Landers

Huang meets the first prong of *Advanced Bionics*, i.e. whether substantially the same art was previously presented to the Office under *Becton, Dickinson* factors (a), (b) and (d). Huang (Ex. 1015) is relied on by Petitioner for the very same

teachings as Shihabi. *See* Petition, pp. 16, 19-21 treating Shihabi and Huang as identical, interchangeable prior art references and making no distinction between their teachings. But, even Petitioner admits that Shihabi and Huang fail to teach “the FI to enhance separation, a feature that is expressly taught by Coufal for CE.” Petition, p. 20.

The Petitioner identifies no reason how or why Huang is a better teaching than Shihabi. The Petitioner treats Huang (which separates HbF, HbA, HbS and HbC) as interchangeable with Shihabi (which also separates HbF, HbA, HbS and HbC). *See NXP USA, Inc. v. Impinj, Inc.*, IPR2020-00519, Paper 7 at 7–12 (PTAB Aug. 17, 2020) (patent substantially the same where Petitioner did not “identify any specific information . . . that is ‘additional’ to or ‘different’ than” the combination of other previously considered references). Huang’s teachings are the same as or substantially similar to Shihabi’s teachings relied on by Petitioner. Ex. 2001, ¶ 73. Huang is also cumulative of and provides no better teaching than Chen and Mohammad and Sahin which were considered by the Examiner. Ex. 2001, ¶ 74. Petitioner has provided no explanation of why Huang is a better reference than Chen, Mohammad, or Sahin. *Id.*

The above analysis of *Becton Dickinson factors* (a), (b) and (d) with respect to Shihabi in combination with Coufal, Camilleri and Landers therefore apply equally to Huang in combination with Coufal, Camilleri and Landers in favor of

discretionary dismissal. As with Shihabi, Petitioner has not demonstrated any material error by the Office and therefore fails to satisfy the second step of *Advanced Bionics*. The above analysis of *Becton Dickinson factors* (c), (e) and (f) with respect to Shihabi in combination with Coufal, Camilleri and Landers therefore apply equally to Huang's cumulative teachings in combination with Coufal, Camilleri and Landers in favor of discretionary dismissal.

Accordingly, the Board should exercise its discretion and deny Petition Grounds 1, 2 and 3 based on combinations of Huang, Camilleri, Coufal or Landers.

IV. PETITION FAILS TO MEET ITS BURDEN UNDER 35 U.S.C. § 314(a)

Petitioner's Grounds of Invalidity 1, 2, and 3 each (1) fail to teach all of the claim limitations, and (2) fail to teach motivation to modify a primary reference with any reasonable expectation of success. Accordingly, Petitioner has failed to present a prima facie case of obviousness. Ex. 2001, ¶¶ 79-140.

A. Petitioner Has Failed to Meet Its Burden to Establish a Prima Facie Case of Obviousness on Ground 1

1. Relevant Art

Petitioner's and Dr. Wu's characterization of the relevant art are not only both in error, but also inconsistent with each other.

First, Petitioner mischaracterizes Dr. Wu's description of the relevant art as being "analytical chemistry, ... separation by CE, but not limited to separation of

hemoglobin variants by CE (Ex. 1004 ¶ 61, page 1004-0032 and ¶ 82, page 1004-0038).” Petition, p. 19.

Dr. Wu admits that “the ‘686 patent relates to separating hemoglobin (HbA₂) in a blood sample from other hemoglobin variants such as HbA, HbF, HbS, in that same blood sample by capillary electrophoresis (CE) and then quantifying the amount of HbA₂.” Ex. 2001, ¶ 92; Ex. 1004, ¶ 27. Dr. Wu also admits that the particular problem in the art was in separating hemoglobins using CE. Ex. 1004, ¶¶ 28-30. Dr. Wu also admits that “prior art is from the same field of endeavor or interest as addressed in the ‘686 patent, namely *hemoglobin variant separation by capillary electrophoresis*” or “the prior art is *reasonably pertinent to hemoglobin variant separation by capillary electrophoresis*...” Ex. 2001, ¶ 93; Ex. 1004, ¶ 3 (emphasis added). Despite these admissions, Dr. Wu then goes on to describe that the “relevant art is not limited to hemoglobin separation by capillary electrophoresis, rather, the relevant art is capillary electrophoresis *per se*.” Ex. 1004, ¶ 82.

In this description of the relevant art, Dr. Wu ignores his own admission above that the claims as a whole are directed to free solution capillary electrophoresis for separating and resolving hemoglobins and that the primary references Shihabi and Huang he relies on are directed to capillary electrophoresis of hemoglobins and disregards the particular problem with which the invention was involved. Ex. 2001, ¶¶ 91, 94. Dr. Landers disagrees that “the relevant art is capillary electrophoresis

per se” since this ignores the particular problem with which the invention was involved (i.e., the separation of hemoglobins using capillary electrophoresis) and therefore the relevant art is the separation of hemoglobins using capillary electrophoresis. Ex. 2001, ¶¶ 90-95.

Further, Petitioner defines the relevant art as “analytical chemistry, i.e., determining the chemical composition and structure of materials and the quantitative and qualitative evaluation of the amounts of those materials and, for example, separation by CE, but not limited to separation of hemoglobin variants by CE.” Petition, p. 19. However, this definition is inconsistent with Dr. Wu’s definition of the relevant art. Dr. Wu defines the relevant art as including analytical **biochemistry** as an alternative to analytical chemistry. Ex. 1004, ¶ 61.

Further, Dr. Wu “more specifically” defines the relevant art as “separation by capillary electrophoresis” as compared to Petitioner who distances capillary electrophoresis as a mere “example.” Compare Ex. 1004, ¶ 61 with Petition, p. 19. Further, Dr. Wu expressly includes separation of hemoglobin variants by capillary electrophoresis within the definition of “relevant art”, while Petitioner distances by stating that the relevant art is “not limited to separation of hemoglobin variants by CE.” In essence, Petitioner has attempted to reserve the entire field of analytical chemistry as “relevant art” while Dr. Wu has a more limited opinion. *See* Ex. 2001,

¶¶ 97-98. The table below compares Petitioner’s definition of “relevant art” with Dr. Wu’s definition of “relevant art”.

Petition — Relevant Art	Dr. Wu — Relevant Art
“The relevant art is analytical chemistry, i.e., determining the chemical composition and structure of materials and the quantitative and qualitative evaluation of the amounts of those materials and, for example, separation by CE, but not limited to separation of hemoglobin variants by CE.”	“[T]he relevant art would be analytical chemistry or analytical biochemistry, i.e., determining the chemical composition and structure of materials and the quantitative and qualitative evaluation of the amounts of those materials and, more specifically, separation by capillary electrophoresis, including separation of hemoglobin variants by capillary electrophoresis.”

2. Level of Ordinary Skill in the Art

Factual indicators of the level of ordinary skill in the art include the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field. *Orthopedic Equip. Co., v. U.S.*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros., Inc. v. United States*, 512 F.2d 1065 (Ct. Cl. 1975)). The prior art itself can reflect the appropriate level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

Petitioner’s definition of the POSITA differs notably from Dr. Wu’s definition. Petition, p. 18. The table below compares Petitioner’s definition of the POSITA with Dr. Wu’s definition of the POSITA. Ex. 2001, ¶ 99.

Petition — POSITA	Dr. Wu — POSITA
“A POSITA at the relevant time frame, would (1) have a baccalaureate degree in Chemistry, (2) be actively seeking (or have already received). an advanced related scientific degree, and (3) have at least two years of experience in the capillary electrophoresis, or many years of experience in the art and less formal education.”	“One of ordinary skill in the art of the ‘686 Patent, at the relevant time frame, would have (1) a baccalaureate degree in Chemistry or Biochemistry, and (2) be actively seeking (or have already received) an advanced related scientific degree, and (3) have at least two years of experience in the capillary electrophoresis.”

Dr. Wu’s definition alternatively includes a baccalaureate degree in biochemistry. Petitioner makes no explanation of why the art of analytical biochemistry or the baccalaureate degree in biochemistry is excluded by Petitioner’s definitions of a POSITA, especially when the claimed subject matter is directed to the biochemical application of separating hemoglobins within a blood sample. Indeed, it is unclear whether Dr. Wu has any experience in separating hemoglobins using free solution capillary electrophoresis, despite that being the focus of the claims. Ex. 2001, ¶ 100.

Furthermore, Dr. Wu states that “the ‘686 Patent, in general terms, describes the limitations of prior art techniques that were known to the inventors for separating HbA₂ from other variants (such as HbA, HbC, HbE, HbD, HbF, HbS).” Ex. 1004, ¶ 29. Dr. Wu recognizes these variants as being clinically significant and that “a clinical laboratory scientist would know which of the hemoglobin forms are relevant and justify the need for separate hemoglobin A (wildtype) from hemoglobin A2

(found in a patient with beta-thalassemia), S and C (sickle cell disease and trait), F (fetal form), D and E (rare hemoglobinopathies that causes anemia) for analysis and test reporting purposes.” Dr. Wu concludes that “[t]his is more the medical diagnostic part and is neither part of, nor required for, the ‘686 patent.” Ex. 1004, ¶ 55. Having reviewed the prosecution history, Dr. Wu, however, is well aware that claim 1 was amended to expressly select the seven forms of hemoglobin he identifies as being clinically significant for separation. Ex. 1003, 1003-0396; Ex. 2001, ¶ 101. Appendix A, ¶¶ 19-30. Dr. Wu attributes the selection of the seven forms of hemoglobin to a clinical laboratory scientist, yet provides no requirement that the POSITA have any clinical laboratory experience. Dr. Wu provides no explanation for this notable discrepancy between his definition of the POSITA (and that of the Petitioner) other than to say the claim includes a “medical diagnostic part”. What is clear is that Dr. Wu has relied on no actual laboratory experience of his own, clinical or otherwise, in identifying hemoglobin variants and grouping them for analysis using capillary electrophoresis. Ex. 2001, ¶ 101.

Petitioner’s and Dr. Wu’s definitions of the POSITA are in agreement that one of skill is required to have “(3) have at least two years of experience in the capillary electrophoresis.” Compare Ex. 1004, ¶ 63 with Petition, p. 18. However, Dr. Wu does not explain how one of skill obtains at least two years of experience. Presumably, this experience may be obtained in post-graduate research or industry.

However, Dr. Wu's basis for alleging this requirement is entirely based on (1) the work of others cited in the '686 patent, (2) his own undergraduate or graduate education experience, (3) his teaching experience, and (4) mentoring or advising others. Ex. 1004, ¶ 63. Dr. Wu cites to no *actual and significant* capillary electrophoresis experience of his own on which to base his definition of a POSITA. Again, it is not at all clear whether Dr. Wu, himself, has ever used free solution capillary electrophoresis to separate hemoglobins or whether he has even observed such a method or reviewed experimental data resulting from such a method. Ex. 2001, ¶ 102.

The Petition fails regardless of how Petitioner characterizes the relevant art (Petition, p. 19) or the level of skill of a POSITA (Petition, p. 18). The Board need not resolve the relevant art or the precise required level of skill in order to deny the Petition. Ex. 2001, ¶¶ 103-104. As such, Petitioner reserves the right to address the definitions of relevant art and a POSITA later in this proceeding should it be instituted.

3. Problems in the Art of Resolving Hemoglobins

The '686 patent is directed to *separating and resolving* hemoglobins *in a biological sample* using a CE method. The art of record during prosecution of the '686 patent recognized the problem of separating hemoglobins, but was unsuccessful in obtaining separation and resolution of HbA₂ and also HbC, HbD, HbE, HbS, HbF

or HbA when those hemoglobin variants are present in the sample. Dr. Wu states that there were “limitations of the prior art techniques that were known to the inventors for separating HbA₂ from other variants (such as HbA, HbC, HbE, HbD, HbF, HbS) in terms of low resolution of the fractions” (Ex. 1004, ¶ 29) and confirms that some of those problems are described in the ‘686 Patent (Ex. 1004, ¶ 30). Dr. Landers agrees. Ex. 2001, ¶¶ 30-45. Exemplary limitations and/or problems are summarized below.

a. Camilleri

Camilleri (Ex. 1020) recognized that “the separation of protein species varying only in subtle structural differences would be difficult, if not impossible, to achieve.” Ex. 1020, 1020-0002.

b. Chen U.S. 5,202,006

Chen (Ex. 1016) recognized that “hemoglobins present in a normal adult are Hemoglobin A ($\alpha_2\beta_2$) which comprises about 97% of the total hemoglobin, Hemoglobin A₂ ($\alpha_2\delta_2$) and Hemoglobin F ($\alpha_2\delta_2$), which comprise the remaining 3%.”

Ex. 1016, 1:26-30. Chen further discloses:

The α chains comprise 141 amino acids and the non- α chains comprise 146 amino acids. The exact type, number and precise sequence of these amino acids is characteristic for each type of globin chain; any alteration in the sequences gives rise to an abnormal globin chain, resulting in the production of abnormal hemoglobin. Abnormal hemoglobins are part of a group of inherited disorders collectively referred to as the “hemoglobinopathies.”

Ex. 1016, 1:41-49.

Chen further teaches that “[w]ith reference to structural defects, approximately 400 structural abnormalities of the globin chain have been described.” Ex. 1016, 1:62-64. Chen identifies HbS, HbH, and HbF as being clinically significant. Ex. 1016, 2:1-50. Chen, however, teaches that “unequivocal separation of hemoglobin variants, and in particular hemoglobin variants A, F, S and C, has not been demonstrated using open CZE protocols.” Ex. 1016, 4:57-60. Chen teaches that “[g]iven to benefits associated with open CZE, and the necessity for screening for hemoglobin variants, it would be advantageous to have an open tube CZE protocol for analyzing hemoglobin variants.” Ex. 1016, 4:61-64.

Chen’s proposed solution is to use a barbituric acid buffer with CZE using an untreated capillary column. Ex. 1016, 4:66-5:15. The result of that proposed solution is reproduced below as Fig. 1.

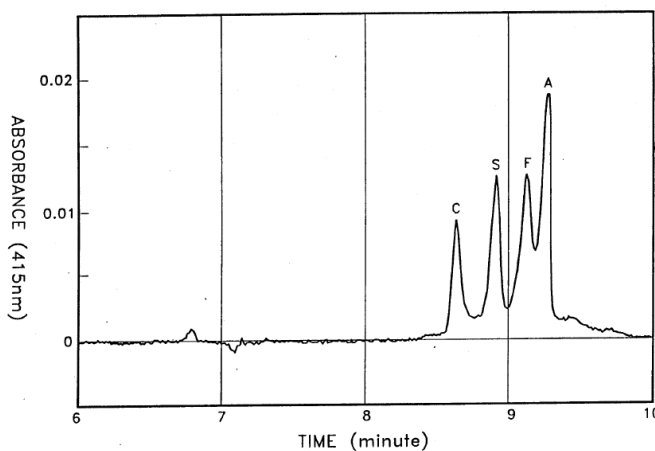


FIG. 1

The '686 patent recognized that Chen “could only produce low resolutions between the principle haemoglobins, namely HbA, HbF, HbS and HbC.” Ex. 1001, 2:1-4. Chen does not mention, much less propose a solution for separating and resolving samples containing HbA₂, HbE, or HbD variants and Chen’s only solution demonstrates insufficient separation and resolution of HbA, HbF, HbS and HbC variants in a control sample with these hemoglobins. Ex. 1016, Fig. 1; Ex. 2001, ¶ 35.

Resolution – how well two peaks are separated - can be defined numerically (as discussed in Huang) by a value that indicates how much ‘peak overlap’ exists. Peaks that are baseline resolved have a resolution (R) of 1.5, while peaks that are only partially resolved have an R of less than that. Factors allowing quantitative information to be extracted about two closely-migrating species are: 1) ‘resolution’ (how much overlap), 2) the Gaussian nature of the peaks, 3) how ‘clean’ the baseline is (stability and noise) between peaks. Ex. 2001, ¶ 36. While separation for the C and S peaks of Chen Fig. 1 is good, separation between the F and A peaks is low, with poor Gaussian shape and uncertain baseline. *Id.*

c. Sahin

Sahin (Ex. 1007) acknowledges that “hundreds of Hb variants, some producing no symptomatic disease, have been identified by various analytical methods.” Ex. 1007 at 1007-0001. Sahin teaches that “[t]he Hb S and C variants are

isoelectric variants as a result of single amino acid changes in one of the globin chains (β), and such changes induce alterations in the structural-functional relationships of the Hb subunits to one another...” Ex. 1007 at 1007-0001. Sahin proposed using CZE with uncoated capillaries and different buffers to separate hemoglobin variants, explaining that

[t]he basis for the separation of the Hb variants using CZE is the charge differences in the globin polypeptides. The structure of all variants are such that they possess a net negative charge, under the conditions of CZE separation, and thus the inherent electrophoretic mobility of the Hb species will be directed to the anode.

Ex. 1007 at 1007-0002. Sahin further discloses that mobility of the Hb variants is ultimately directed towards the cathode because of electro-endosmotic flow (EOF) generated by the electric current and buffer conditions. *Id.*

Sahin counsels that “[s]atisfactory separation of analyte using CZE is highly dependent on a suitable electrophoresis buffer-electrolyte” and that “[s]everal different buffers have been used for haemoglobin separations in traditional free zone electrophoresis applications” including Tris. Ex. 1007 at 1007-0002. Sahin further teaches that “[t]he variant Hb F has no significant charge difference from Hb A1 (only 0.05 pH unit separates these variants), and this presents the most difficult challenge to manipulating conditions to separate common variants.” Ex. 1007 at 1007-0003.

The '686 patent states that Sahin “obtained deeply unimpressive results for resolution between HbA, HbF, HbS and HbA₂” using a borate or barbitol buffer, “and also deeply unimpressive results for resolution between the HbA, HbS and HbA₂ fractions for Tris buffer.” Ex. 1001, 1:59-65. The Sahin figures below show poor Hb variant separation efficiency. More specifically, visual inspection indicates problems with non-Gaussian peak shape (Fig. 4), significant peak overlap (poor resolution) and, an inherent inability to rationally define the baseline for any set of peaks (Figs. 1-3). This is particularly notable with the inability to cleanly resolve HbF from HbA (Fig 3). Ex. 2001, ¶ 40.

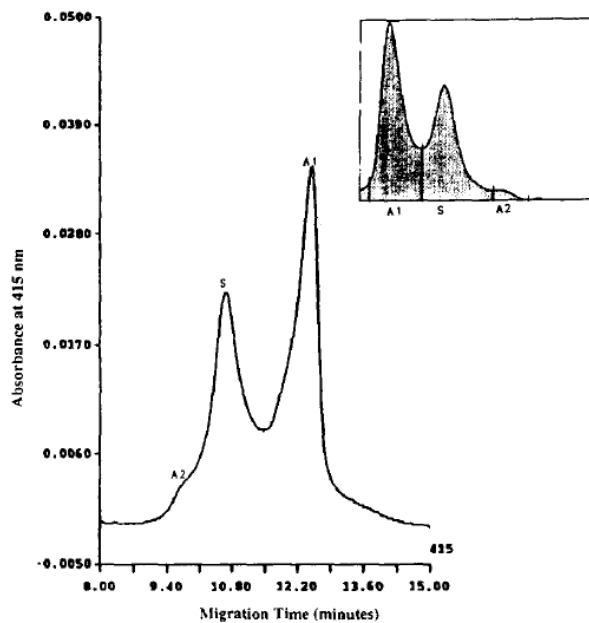


Fig. 1. Electropherogram of a sample from a patient with sickle-cell disease. Electrolyte, 1.0 M Tris-HCl (pH 8.0). Other conditions as described under Experimental.

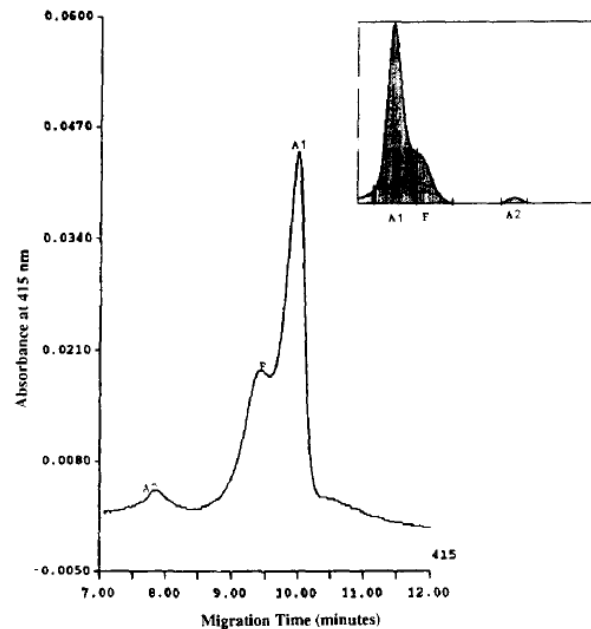


Fig. 2. Electropherogram of a patient's sample with a significant Hb F fraction. Electrolyte, veronal (sodium barbitol) (pH 8.5).

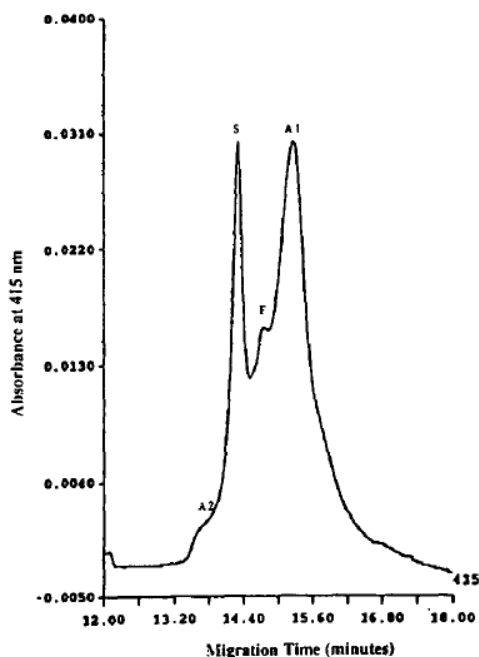


Fig. 3. Electropherogram of a patient's sample containing significant proportions of variants Hb A1, A2, S and F. Buffer, sodium borate (pH 8.5).

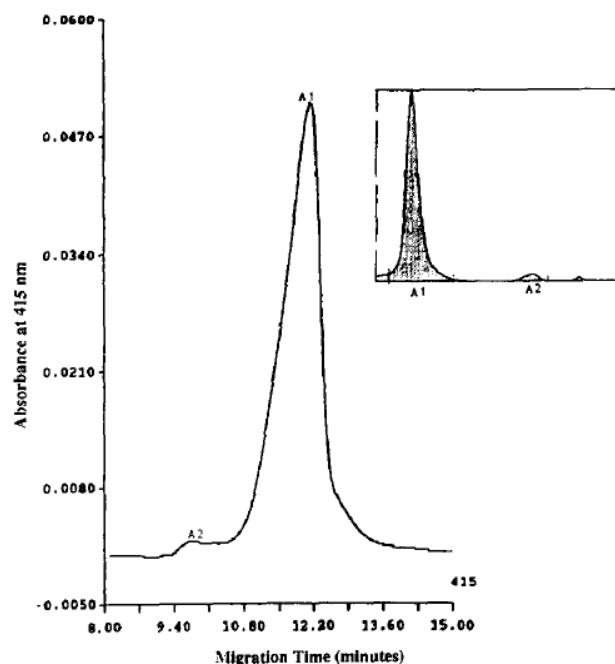


Fig. 4. Electropherogram of a sample obtained from a healthy adult. Buffer, veronal (pH 8.5).

d. Shihabi

Shihabi (Ex. 1011) teaches the clinical importance of HbA₂.

An elevated HbA₂ level, in the presence of a normal serum level, is used clinically to aid in the diagnosis of β -thalassemia. [Citation omitted]. HbA₂ can also increase slightly in other clinical disorders such as in hyperthyroidism, hemoglobin S (Hb S) trait, and megaloblastic anemia in absence of β -thalassemia.

Ex. 1011, 1011-0001. Shihabi, however, teaches that separating HbA₂ (being a small peak) is problematic in the presence of a very large peak due to overlap.

However, the two major problems in HbA₂ are the accuracy and the reproducibility of the quantification of a very minor peak ($\sim 2\%$) in the presence of a very large peak. The precision of the HbA₂ should be $< 6\%$ for clinical diagnosis. . . . The quantification of a minor small peak in the presence of a large one is problematic in most separation methods and especially CE. In CE, several factors affect the precision and

accuracy of such quantification, e.g., sample size, wall interaction, integrator software, and voltage [internal citations omitted].

Ex. 1011, 1011-0001. While Shihabi states that “it is demonstrated that the major hemoglobin variants A, F, S, C, and A₂ can be separated well by CE in an arginine-Tris buffer.” Ex. 1011, 1011-0001. Figure 1 of Shihabi below shows poor Hb variant separation efficiency. More specifically, visual inspection indicates problems with poor separation of A from F, and an inherent inability to rationally define the baseline for quantitation of any of peaks C, S, F and A. Further, in Shihabi Fig. 1 HbA₂ was not identified as a peak.

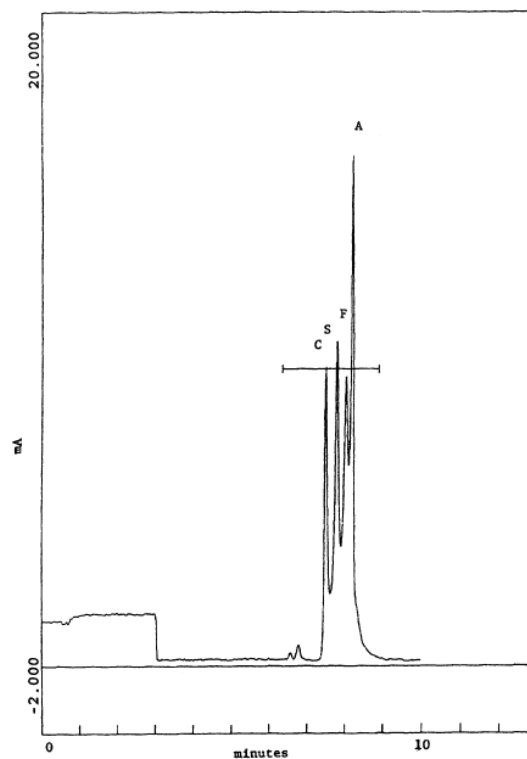


Figure 1. Separation of the major hemoglobin variants by CE at 9 kV.

Ex. 2001, ¶ 43.

While a lower applied voltage improved the overall separation of HbA₂, Figure 4 (Ex. 1011, 1011-0002) shows poor Hb variant separation efficiency.

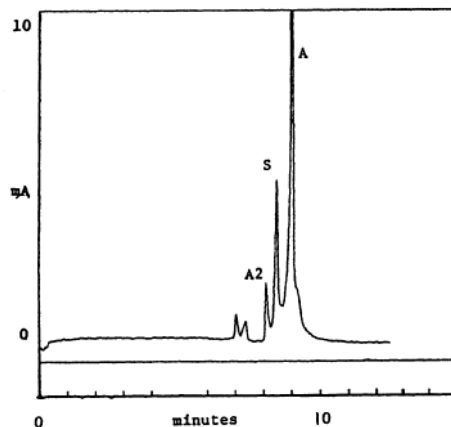


Figure 4. HbA₂ from (top) a normal patient; (middle) a patient with β -thalassemia with a low MCV, and (bottom) a patient with S trait.

Visual inspection indicates problems with non-Gaussian peak shape for the A2 and S peaks with fronting and tailing of the A peak especially, and, an inherent inability to rationally define the baseline for any of peaks A2, S and A. Ex. 2001, ¶ 45.

4. Resolution

At Petition p. 2, Petitioner defines “low resolution” as “insufficient separation.” Dr. Landers agrees, especially with respect to the references discussed in the ‘686 patent such as Chen ‘006, i.e. Chen “could only produce low resolutions between the principal haemoglobins, namely HbA, HbF, HbS and HbC.” Ex. 1001, 2:3-4; Ex. 2001, ¶ 80. Factors contributing to a qualitative and quantitative separation and resolution of two components are: 1) the amount of overlap, 2) a Gaussian peak shape, and 3) a ‘clean’ the baseline (stable, low noise) between peaks.

Ex. 2001, ¶¶ 3, 36. Certainly, “insufficient separation” or any of the above would at least make quantitative analysis of hemoglobins challenging. Ex. 2001, ¶ 80.

5. Flow Inhibitor Does Not Need to Be Construed

A FI is a chemical used in a CZE method that interacts with the capillary to alter the charge on the inner surface wall of the capillary. This interaction affects electroosmotic flow. Ex. 2001, ¶¶ 86-87.

The Patentee argued that the claimed FI was different from the antibody of Sunzeri because it did not bind to the target analyte. Ex. 1003, 1003-0458-1003-0460. In this context, the claimed FI “is not specific for a particular analyte or complex to be separated”, because the claimed FI is not an antibody used to bind to an analyte. Because the explanation was based on Sunzeri’s antibody, the language that “the flow inhibitor is not specific for a particular analyte or complex to be separated” is not definitional. Ex. 2001, ¶ 88.

Patent Owner submits that the Board need not construe this term to deny institution. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011); *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999); *See also* Ex. 2001, ¶ 89. Patent Owner reserves its rights to assert constructions should trial be instituted.

6. Detailed Analysis of U.S. 7,887,686

According to the plain wording, claims 1, 23 and 24 of the '686 patent each require a CZE method for separating and resolving haemoglobins in a blood sample by migration using a ZB and at least one FI. Ex. 1001, 7:22-34, 8:39-64; Ex. 2001, ¶¶ 105-106.

a. Separating and Resolving HbA₂ and at Least One Other Form of Haemoglobin

Claim 1 further requires that said haemoglobins are a haemoglobin HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA haemoglobin. Accordingly, from among the haemoglobins in a blood sample, claim 1 requires separation and resolution of haemoglobin variant HbA₂ and, if present, claim 1 further requires separation and resolution of hemoglobin variants HbC, HbD, HbE, HbS, HbF or HbA, when present in a blood sample. Ex. 2001, ¶¶ 107-110.

b. Separating and Resolving in a Blood Sample

Claims 1, 23 and 24 each require separating and resolving haemoglobins in a blood sample. Ex. 2001, ¶¶ 111-112.

c. Analysis Buffer of the Zwitterionic Type and At Least One Flow Inhibitor

Claims 1, 23 and 24 each require use of a ZB and at least one FI. Ex. 2001, ¶¶ 113-119.

7. Ground 1: Shihabi or Huang and Coufal Fail to Teach All of the Claim Limitations of Claims 1, 2, 3, 6, 7, 10, 11, 12, 13, 14, 17, 18 and 23 Requiring Capillary Electrophoresis Using a Blood Sample

Claim 1 of the '686 patent, and accordingly, dependent claims 2, 3, 6, 7, 10, 11, 12, 13, 14, 17, 18 and 23 each require a CZE method using a blood sample. Shihabi, Huang and Coufal each fail to teach or suggest a CZE method *using a blood sample*.

Shihabi teaches using red blood cells (only a part of blood) and not a blood sample which includes components other than red blood cells. Ex. 1011, 1011-0002. Huang teaches using “[m]ixtures of Hb C, S, F, and A, of Hb A and F, and of Hb A and S” and not a blood sample. Ex. 1015, 1015-0001. Coufal fails to teach or suggest any biological sample. Ex. 2001, ¶¶ 120-121. Accordingly, since the combination of Shihabi or Huang and Coufal fails to teach or suggest a CZE method *using a blood sample*, Petitioner has failed to demonstrate a prima facie case of obviousness.

8. Ground 1: Shihabi or Huang and Coufal Fail to Teach All of the Claim Limitations of Claims 1, 2, 3, 6, 7, 10, 11, 12, 13, 14, 17, and 18 Requiring Resolution of HbA₂ and HbC, HbD, HbE, HbS, HbF or HbA

Claim 1 of the '686 patent, and accordingly, dependent claims 2, 3, 6, 7, 10, 11, 12, 13, 14, 17, and 18 each require separating and resolving haemoglobin HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA haemoglobin if present in the sample. Shihabi and Huang fail to teach or suggest separating and resolving

haemoglobin HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA haemoglobin. Coufal fails to teach any hemoglobin separation. Ex. 2001, ¶ 122.

Shihabi teaches the problem of separating a small peak such as with HbA₂ with larger peaks using capillary electrophoresis and recognizes that “HbA₂ comigrates with HbC.” Ex. 1011, 1011-0002, 1011-0003. As the Petitioner acknowledges, Shihabi also does not teach a FI. Petition, p. 3; Ex. 1011, 1011-0001-1011-0002; Ex. 2001, ¶ 123.

Shihabi has no discussion or example of separation efficiency with hemoglobin variants HbD and HbE and, further, has no teaching or description of being able to separate and resolve HbA₂ from these variants. Shihabi’s Figure 1 shows poor Hb variant separation efficiency between hemoglobin variants HbC, HbS, HbF and HbA at 9kV using the Tris buffer. Ex. 1011, 1011-0002, Fig. 1. Shihabi was not able to separate and resolve HbA₂ from variants HbC, HbS, HbF and HbA at 9kV using the Tris buffer, insofar as no HbA₂ peak is identified. Ex. 2001, ¶ 124.

Shihabi recognizes that HbC and HbE comigrate with HbA₂ in its capillary electrophoresis method. Ex. 1011, 1011-0003; Ex. 2001, ¶ 125. In order to identify a peak corresponding to HbA₂, Shihabi teaches to reduce the voltage to 6kV. Ex. 1011, 1011-0002. However, when the voltage was reduced to 6kV to separate HbA₂, Shihabi does not show peaks for HbC or HbE. Only peaks attributable to HbS and

HbA are identified. *See* Ex. 1011 at 1011-0003 (Fig. 4); Ex. 2001, ¶ 126. Shihabi does not teach or suggest using a FI with the Tris buffer to separate and resolve HbA₂. Petition, p. 3.

At 9kV, Shihabi was unable to separate and resolve HbA₂. Ex. 2001, ¶ 126. At 6 kV, Shihabi was unable to show peaks for HbC or HbE. Ex. 2001, ¶ 127. Accordingly, Shihabi does not teach a method that separates and resolves HbA₂ and other variant haemoglobins present in the blood sample, unlike the claimed method for separating and resolving HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA haemoglobin, when present in a blood sample. Ex. 2001, ¶ 127.

Huang (Ex. 1015) has no discussion, or identification, of peaks for HbD or HbE in any model mixture. Ex. 2001, ¶ 128. Huang identifies peaks for HbC, HbS, HbF and HbA (Ex. 1015, 1015-0002(Fig. 1)), identifies peaks for HbF and HbA (Ex. 1015, 1015-0002 (Fig. 2a)) and identifies peaks for HbS and HbA (Ex. 1015, 1015-0002 (Fig. 2b)) in model mixtures. Ex. 2001, ¶ 128. However, several problems are apparent, including non-Gaussian peak shape (‘fronting’ and ‘tailing’), significant peak overlap (poor resolution) and, an inherent inability to rationally define the baseline for any given peak. Ex. 2001, ¶ 128. Huang does not teach the claimed method for separating and resolving HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA hemoglobin when present in a blood sample. Ex. 2001, ¶ 128.

Coufal fails to teach or suggest resolution of any hemoglobin variant. Ex. 2001, ¶ 128.

Accordingly, since the combination of Shihabi or Huang and Coufal fails to teach or suggest separating and resolving hemoglobin HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA hemoglobin, Petitioner has failed to demonstrate a prima facie case of obviousness.

9. Ground 1: Petitioner Fails to Demonstrate a Motivation to Combine Shihabi or Huang with Coufal with Any Reasonable Expectation of Success

Obviousness requires “a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Petitioner must demonstrate “that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016) (citations omitted). Conclusory “assertion[s] that it would have been so” and “unsupported statement[s]” that the combinations are “within the skill” of a skilled artisan and “well-known and predictable” do not meet Petitioner’s burden. *Johns Manville Corp. v. Knauf Insulation, Inc.*, IPR2018-00827, Paper 9 at 13–14 (PTAB Oct. 16, 2018) (informative). A Petition devoid of citation or analysis

to support its contentions is also fatally flawed. *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-00582, Paper 34 at 28–30 (PTAB Aug. 5, 2019) (informative).

Whether a patent claiming the combination of prior art elements would have been obvious is determined by whether the improvement is more than the predictable use of prior art elements according to their established functions. *KSR*, 550 U.S. at 417. To support this conclusion, however, it is not enough to show merely that the prior art includes separate references covering each separate limitation in a challenged claim. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). Rather, obviousness additionally requires that a person of ordinary skill at the time of the invention “would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention.” *Id.* In determining whether there would have been a motivation to combine prior art references to arrive at the claimed invention, it is insufficient to simply conclude the combination would have been obvious without identifying any reason why a person of skill in the art would have made the combination. *Metalcraft of Mayville, Inc. v. Toro Co.*, 848 F.3d 1358, 1366 (Fed. Cir. 2017). “To the extent an art is unpredictable, as the chemical arts often are, *KSR*’s focus on [] ‘identified, predictable solutions’ may present a different hurdle because potential solutions are

less likely to be genuinely predictable.” *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 996 (Fed. Cir. 2009).

Moreover, in determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 164 (Fed. Cir. 1985); *see also Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1537 (Fed. Cir. 1983).

The Petitioner admits that both Shihabi and Huang fail to teach use of a FI. Petition, pp. 16, 19. The Petitioner relies on Coufal for teaching “various ZB/FI combinations and FI buffer additives to reduce EOF and thus increase the separation of components of the sample.” Petition, p. 19; Ex. 2001, ¶ 129.

The Petitioner concludes without any citation or analysis that “[b]ecause adding FI yields the predictable results of reducing EOF and thus increasing separation of the components of the sample, the claims merely set forth old steps and old components, with each performing the same function it had been known to perform and yielding no more than one would expect from such an arrangement.” Ex. 2001, ¶ 130.

Petitioner provides no justification for modifying either Shihabi or Huang to include a FI other than “the claims merely set forth old steps and old components.”

Petitioner merely identifies elements of the claims in the prior art and concludes motivation to combine without identifying any reason why a person of skill in the art would have made the combination, and without any reason why one of skill would have believed that using the combination of a ZB and a FI would have separated and resolved hemoglobins in a blood sample using capillary electrophoresis with a reasonable expectation of success. This is clearly deficient under *KSR*, *Unigene Labs*, and *Metalcraft of Mayville*. *Procter & Gamble* expressly recognizes the chemical arts as being unpredictable and requiring more than a mere recitation of “old steps and old components” in support of predictability.

The Petition’s conclusory motivations to combine are “nothing more than a restatement of basic tests identified by the Supreme Court for determining whether an invention would have been obvious” that “cannot substitute for specific application of those principles to the facts.” *NJOY, Inc. v. Fontem Holdings I B.V.*, IPR2015-01301, Paper 16 at 11 (PTAB Dec, 8, 2015); *Kinetic Tech., Inc. v. Skyworks Sols., Inc.*, IPR2014-00529, Paper 8 at 15 (PTAB Sept. 23, 2014); *Whole Space Indus. Ltd. v. Zipshade Indus. (B.V.I.) Corp.*, IPR2015-00488, Paper 14 at 17 (PTAB July 24, 2015) (“[C]onclusory labels do not substitute for a fact-based analysis” for motivation to combine). Petitioner’s conclusory, unsupported “design choice” and “routine, customary, or obvious” choice motivations for grounds 1-3

thus legally cannot support institution. *Johns Manville Corp.*, IPR2018-00827, Paper 9 at 13–14 (PTAB Oct. 16, 2018).

Dr. Landers disagrees with Petitioner’s conclusory statement. Ex. 2001, ¶ 131. There is no direct correlation between a FI and magnitude of effect on EOF. Ex. 2001, ¶ 132. Furthermore, even if a FI reduces the EOF in a CZE system analysis of a blood sample, it is not reasonably predictable that HbA₂ will be separated and resolved, and nor is it reasonably predictable that an HbC, an HbD, an HbE, an HbS, an HbF or an HbA haemoglobin will also be separated and resolved, when present in a blood sample. *Id.* Hb variants often stem from very small changes, e.g., a single amino acid substitution, having a negligible effect on mass, and often such changes do not change the overall charge. An even more challenging situation surfaces when the only change between HbC and HbE is the location of an identical amino acid substitution. More specifically, relative to HbA, both variant, HbC and HbE, have a glutamic acid substituted by lysine, however, in the HbC variant this occurs at position 6, while that in HbE occurs at position 26. *Id.* This is important because separation in CZE is based on differences in charge/mass (q/m) ratio. Hence, Hb variants would be expected to have very similar, if not identical mobilities, and therefore difficult to separate. *Id.* Dr. Wu has provided no analysis of the electrophoretic mobilities of hemoglobin variants and how they may be affected by a reduction of EOF. *Id.*

Before the invention date of November 18, 2004, it was simply unknown how the hemoglobin variants may react to a reduction in EOF in terms of separation and resolution. Ex. 2001, ¶ 133. Dr. Wu has provided no evidence of the function of a FI on hemoglobin separation and resolution before the invention date of November 18, 2004. *Id.* Dr. Wu has provided no evidence that reducing EOF will increase the separation and resolution of hemoglobins before the invention date of November 18, 2004, especially whether reducing EOF will separate and resolve HbA₂ and also whether HbC, HbD, HbE, HbS, HbF or HbA will be separated and resolved, when present in a blood sample. *Id.* Dr. Landers states that this would have to be done empirically. *Id.*

Petitioner provides no scientific justification for asserting that adding a FI in the systems of Shihabi or Huang will predictably separate and resolve HbA₂ and also an HbC, an HbD, an HbE, an HbS, an HbF or an HbA, when present in a blood sample. Simply reducing the EOF does not provide a reasonable expectation that HbA₂ will be separated and resolved and also that an HbC, an HbD, an HbE, an HbS, an HbF or an HbA will also be predictably resolved, when present in a blood sample. Ex. 2001, ¶ 134. This is because hemoglobin variants are complex proteins having the same or similar electrophoretic mobility, and there is no basis identified by Dr. Wu or the prior art, for a conclusion that a FI reducing EOF will facilitate separation

and resolution of hemoglobins that have the same or similar electrophoretic mobility. *Id.*

Shihabi provides no basis for one of skill to conclude that adding a FI will result in separation and resolution of HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA haemoglobin when present in a blood sample. Ex. 2001, ¶ 135. The Petitioner provides no analysis of the structure of the claimed haemoglobins from which one of skill could predict that adding a FI to reduce electroosmotic flow will result *in a degree of EOF reduction that will be sufficient to resolve* HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA haemoglobin when present in a blood sample. *Id.* The Petitioner provides no evidence of the effect of a FI on electroosmotic flow that could be used to extrapolate predictable qualitative and quantitative separation and resolution of peaks attributable to HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA haemoglobin if present in a blood sample. *Id.* Shihabi teaches that “Hb C behaves similarly to hemoglobin HbA₂ in migration in this method” and that “[h]emoglobin E . . . comigrated with Hb C and also with HbA₂”. Ex. 1011, 1011-0003. Shihabi itself teaches that different voltages affecting electroosmotic flow result in different haemoglobins being resolved. Ex. 2001, ¶ 135. Shihabi provides no direct relationship between electroosmotic flow and any of the claimed haemoglobin variants, such that use of a FI would predictably resolve

HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA haemoglobin when present in a blood sample. *Id.*

Camilleri teaches that “the separation of protein species varying only in subtle structural differences would be difficult, if not impossible, to achieve.” Ex. 1020, 1020-0002. Coufal, unrelated to separation of any proteins let alone hemoglobins, teaches that “[i]t is difficult to control EOF through fused silica capillaries satisfactorily; EOF is very often unstable over a period of time.” Ex. 1013, 1013-0001. Landers expressly states that any effect 1,4-diaminobutane may have to reduce EOF and enhance resolution of proteins “appears to be specific to glycoproteins, at least for the case of ovalbumin and pepsin.” Ex. 1026, 1026-0008. Landers further states that “separation of a similar nonglycosylated protein ***is not enhanced under the same conditions.***” Ex. 1026, 1026-0009. These prior art teachings relied on by Petitioner demonstrate unpredictability of the use of a FI based on the nature of the protein. Ex. 2001, ¶ 136. There is no scientific reason provided by Petitioner to justify that adding a FI to the method of Shihabi would predictably result in separation and resolution of HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA haemoglobin when present in a blood sample. *Id.* In Dr. Landers opinion, any results are empirical and are not predictable. *Id.*

There is no basis for Dr. Wu’s conclusory statement that “because adding the flow inhibitor yields the predictable results of reducing EOF and thus increasing

separation of the components of the sample, the claims merely set forth old steps and old components, with each performing the same function it had been known to perform and yielding no more than one would expect from such an arrangement.” Ex. 1004, ¶ 104. Camilleri teaches that separation of structurally-close proteins is unpredictable. Coufal teaches that controlling EOF is unpredictable. Landers teaches that separation of glycosylated proteins versus similar non-glycosylated proteins using 1,4-diaminobutane is unpredictable. Accordingly, there is no reasonable expectation as evidenced by the art relied on by Petitioner that a FI would separate and resolve hemoglobins in general and, in particular, separate and resolve HbA₂ and HbC, HbD, HbE, HbS, HbF or HbA, when present in a blood sample. Ex. 2001, ¶ 137.

Huang teaches separation of haemoglobins A, F, S and C using “a neutral, hydrophilic coated capillary with no electroosmotic flow.” Ex. 1015, 1015-0001; Ex. 2001, ¶ 72. Accordingly, Huang itself teaches that a FI is not needed or desired with its method since there is no EOF to reduce. Ex. 2001, ¶ 72.

Yet, Petitioner asserts that one of skill would nonetheless be motivated to add a FI to reduce electroosmotic flow. Petitioner is clearly wrong because Huang operates with “no electroosmotic flow.” Ex. 2001, ¶ 138. Accordingly, adding a FI to reduce EOF would make no sense, and with the appropriate FI, might even reverse the EOF, which was taught by Sunzeri, and over which the Examiner allowed the

application. *Id.* There is no scientific reason provided by Petitioner to justify that adding a FI to the method of Huang would predictably result in separation and resolution of HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA haemoglobin when present in a blood sample. *Id.* Any results are empirical and are not predictable. *Id.*

Accordingly, Petitioner has failed to demonstrate any motivation to combine Shihabi or Huang with Coufal with a reasonable expectation of successfully separating and resolving HbA₂ and HbC, HbD, HbE, HbS, HbF or HbA when present in a blood sample.

10. Ground 2: Claims 15 and 16 Depend from Claim 1 and Camilleri Does Not Provide Teachings Lacking in Shihabi or Huang and Coufal

Dependent claims 15 and 16 are directed to specific ZBs and depend from claim 1. As discussed above with respect to claim 1, the combination of Shihabi or Huang and Coufal fails to teach (1) capillary electrophoresis using a blood sample, and (2) separating and resolving hemoglobin HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA hemoglobin. As set forth above with respect to claim 1, Petitioner has failed to demonstrate any scientific basis for asserting that adding a FI to Shihabi or Huang would predictably result in separation and resolution of HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA hemoglobin when present

in a blood sample. Camilleri provides no teaching that would cure the above deficiencies of Shihabi or Huang and Coufal. Ex. 2001, ¶ 139.

11. Ground 3: Claims 4, 5, 8, 9 and 19-22 Depend from Claim 1 and Landers Does Not Provide Teachings Lacking in Shihabi or Huang and Coufal and Shibabi or Huang and Coufal and Landers Does Not Render Claim 24 Obvious

Dependent claims 4, 5, 8, 9 and 19-22 are directed to various aspects of FIs and depend from claim 1. As discussed above, the combination of Shihabi or Huang and Coufal fails to teach (1) capillary electrophoresis using a blood sample, and (2) separating and resolving hemoglobin HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA hemoglobin. Petitioner has failed to demonstrate any scientific basis for asserting that adding a FI to Shihabi or Huang would predictably result in separation and resolution of HbA₂ and an HbC, an HbD, an HbE, an HbS, an HbF or an HbA hemoglobin when present in a blood sample. Landers (Ex. 1026) provides no teaching that would cure the above deficiencies. Ex. 2001, ¶ 140.

Claim 24 is directed to a CZE method for a blood sample. As discussed above in Section IV(A)(7), Shihabi or Huang and Coufal each fail to teach or suggest a CZE method using a blood sample. Landers does not teach using a blood sample and provides no teaching that would cure the deficiencies of Shibabi, Huang, and Coufal in this respect. Ex. 2001, ¶ 141. Claim 24 also includes a FI. As discussed above in Section IV(A)(9), Petitioner fails to demonstrate a motivation to combine Shihabi or Huang with Coufal with any reasonable expectation of success that a FI would

separate and resolve hemoglobins in general when present in a blood sample. Ex. 2001, ¶ 142. Accordingly, claim 24 is not obvious in view of Shihabi or Huang and Coufal and Landers for at least these reasons. Ex. 2001, ¶¶ 141-142.

V. CONCLUSION

The Petition's overlapping, and redundant grounds are an attempt to rehash previously considered art and arguments both warrant discretionary denial. If that were not enough, the merits of the Petition are also so flawed that Petitioner has not shown that it is more likely than not to prevail on even one claim. For all of these reasons, the Petition should be denied.

Dated: July 25, 2024

By: /Robert F. Altherr, Jr./

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the portions of the above-captioned PATENT OWNER'S PRELIMINARY RESPONSE specified in 37 C.F.R. § 42.24 has 13,563 words in compliance with the 14,000-word limit in 37 C.F.R. § 42.24(b)(1)(2) as counted by the Word Count feature of Microsoft Word.

Dated: July 25, 2024

By: /Robert F. Altherr, Jr./

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CERTIFICATE OF SERVICE

The undersigned certifies service on the Petitioner, under 37 C.F.R. § 42.6(e) by electronic (e-mail) delivery of a true copy of the foregoing PATENT OWNER'S PRELIMINARY RESPONSE to the attorneys of record for Petitioner:

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