

IPR2025-01593
Patent 10,278,961

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BONERGE LIFESCIENCE (HUNAN) CO., LTD.,
Petitioner,

v.

NANJING NUTRABUILDING BIO-TECH CO., LTD.,
Patent Owner.

IPR2025-01593
Patent 10,278,961

Before KAREN I. SWEENEY, *Trial Paralegal*

DECLARATION OF DR. QIANG TONG, PH.D.

Patent Owner, Nanjing Nutrabuilding Bio-Tech Co., Ltd., hereby respectfully submits the following Declaration of Dr. Qiang Tong, Ph.D. to the Board in support of Patent Owner's Preliminary Response.

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TABLE OF EXHIBITS

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2076	Curriculum Vitae of Dr. Qiang Tong, Ph.D.
2077	Cheng Z, Chen AF, Wu F, Sheng L, Zhang HK, Gu M, Li YY, Zhang LN, Hu LH, Li JY, Li J. (2010) ‘8,8-Dimethyldihydroberberine with improved bioavailability and oral efficacy on obese and diabetic mouse models.’ <i>Bioorg Med Chem.</i> 18(16):5915-24. doi: 10.1016/j.bmc.2010.06.085. Epub 2010 Jul 1. PMID: 20663675. (“Cheng”)
2078	Arch JR. (2011) ‘Challenges in $\beta(3)$ -Adrenoceptor Agonist Drug Development.’ <i>Ther. Adv. Endocrinol. Metab.</i> 2(2):59-64. doi: 10.1177/2042018811398517. PMID: 23148171; PMCID: PMC3474627. (“Arch”)
2079	Beasley DE, Koltz AM, Lambert JE, Fierer N, Dunn RR. (2015) ‘The Evolution of Stomach Acidity and Its Relevance to the Human Microbiome.’ <i>PLoS One.</i> 10(7):e0134116. doi: 10.1371/journal.pone.0134116. PMID: 26222383; PMCID: PMC4519257. (“Beasley”)
2080	Yang F, Gao R, Luo X, Liu R, Xiong D. (2023) ‘Berberine influences multiple diseases by modifying gut microbiota.’ <i>Front. Nutr.</i> 10:1187718. doi: 10.3389/fnut.2023.1187718. PMID: 37599699; PMCID: PMC10435753. (“Yang”)
2081	Chang C, Roh YS, Du M, Kuo YC, Zhang Y, Hardy M, Gahler R, Solnier J. (2024) ‘Differences in Metabolite Profiles of Dihydroberberine and Micellar Berberine in Caco-2 Cells and Humans-A Pilot Study.’ <i>Int. J. Mol. Sci.</i> 25(11):5625. doi: 10.3390/ijms25115625. PMID: 38891813; PMCID: PMC11171481. (“Chang”)
2082	Chen J, Cao J, Fang L, Liu B, Zhou Q, Sun Y, Wang Y, Li Y, Meng S. (2014) ‘Berberine derivatives reduce atherosclerotic plaque size and vulnerability in apoE(-/-) mice.’ <i>J. Transl. Med.</i> 12:326. doi: 10.1186/s12967-014-0326-7. PMID: 25425200; PMCID: PMC4261588. (“Chen”)
2083	Yu Y, Liu L, Wang X, Liu X, Liu X, Xie L, Wang G. (2010) ‘Modulation of glucagon-like peptide-1 release by berberine: in vivo and in vitro studies.’ <i>Biochem Pharmacol.</i> 79(7):1000-

	6. doi: 10.1016/j.bcp.2009.11.017. Epub 2009 Nov 27. PMID: 19945441. (“Yu”)
2084	Yao Y, Chen H, Yan L, Wang W, Wang D. (2020) ‘Berberine alleviates type 2 diabetic symptoms by altering gut microbiota and reducing aromatic amino acids.’ <i>Biomed Pharmacother.</i> 131:110669. doi: 10.1016/j.biopha.2020.110669. Epub 2020 Sep 13. PMID: 32937246. (“Yao”)
2085	Feig PU, Shah S, Hermanowski-Vosatka A, Plotkin D, Springer MS, Donahue S, Thach C, Klein EJ, Lai E, Kaufman KD. (2011) ‘Effects of an 11 β -hydroxysteroid dehydrogenase type 1 inhibitor, MK-0916, in patients with type 2 diabetes mellitus and metabolic syndrome.’ <i>Diabetes Obes. Metab.</i> 13(6):498-504. doi: 10.1111/j.1463-1326.2011.01375.x. PMID: 21272190. (“Feig”)
2086	Fergusson G, Ethier M, Guévremont M, Chrétien C, Attané C, Joly E, Fioramonti X, Prentki M, Poitout V, Alquier T. (2014) ‘Defective insulin secretory response to intravenous glucose in C57Bl/6J compared to C57Bl/6N mice.’ <i>Mol. Metab.</i> 3(9):848-54. doi: 10.1016/j.molmet.2014.09.006. PMID: 25506550; PMCID: PMC4264561. (“Fergusson”)
2087	Li L, Chang L, Zhang X, Ning Z, Mayne J, Ye Y, Stintzi A, Liu J, Figeys D. (2020) ‘Berberine and its structural analogs have differing effects on functional profiles of individual gut microbiomes.’ <i>Gut Microbes.</i> 11(5):1348-1361. doi: 10.1080/19490976.2020.1755413. Epub 2020 May 6. PMID: 32372706; PMCID: PMC7524264. (“Li”)
2088	Yin J, Xing H, Ye J. (2008) ‘Efficacy of berberine in patients with type 2 diabetes mellitus.’ <i>Metabolism.</i> 57(5):712-7. doi: 10.1016/j.metabol.2008.01.013. PMID: 18442638; PMCID: PMC2410097. (“Yin”)
2089	Zhang X, Zhao Y, Zhang M, Pang X, Xu J, Kang C, Li M, Zhang C, Zhang Z, Zhang Y, Li X, Ning G, Zhao L. (2012) ‘Structural changes of gut microbiota during berberine-mediated prevention of obesity and insulin resistance in high-fat diet-fed rats.’ <i>PLoS One.</i> 7(8):e42529. doi: 10.1371/journal.pone.0042529. Epub 2012 Aug 3. PMID: 22880019; PMCID: PMC3411811. (“Zhang 2012”)
2090	Zhang Y, Gu Y, Ren H, Wang S, Zhong H, Zhao X, Ma J, Gu X, Xue Y, Huang S, Yang J, Chen L, Chen G, Qu S, Liang J,

	Qin L, Huang Q, Peng Y, Li Q, Wang X, Kong P, Hou G, Gao M, Shi Z, Li X, Qiu Y, Zou Y, Yang H, Wang J, Xu G, Lai S, Li J, Ning G, Wang W. (2020) 'Gut microbiome-related effects of berberine and probiotics on type 2 diabetes (the PREMOTÉ study).' <i>Nat Commun.</i> 11(1):5015. doi: 10.1038/s41467-020-18414-8. PMID: 33024120; PMCID: PMC7538905. ("Zhang 2020")
2091	Kun Wang, Xinchu Feng, Liwei Chai, Shijie Cao & Feng Qiu (2017) The metabolism of berberine and its contribution to the pharmacological effects, <i>Drug Metabolism Reviews</i> , 49:2, 139-157, DOI: 10.1080/03602532.2017.1306544 ("Wang")

DECLARATION OF DR. QIANG TONG, PH.D.

I, Qiang Tong, declare as follows:

I. INTRODUCTION

1. This section contains a summary of my educational background, career history, publications, and other relevant qualifications. My full curriculum vitae is attached as Exhibit 2076 submitted with this declaration.

2. Aside from what is shown in my CV, I completed my postdoctoral training in diabetes research within the Department of Nutrition at the Harvard School of Public Health. From 2022 until my retirement in July 2025, I directed a basic and pre-clinical research program investigating how nutritional interventions—such as caloric restriction, fasting, and high-fat diets—and plant-derived compounds like berberine and resveratrol influence aging and metabolic syndromes. My work focused on the genetic pathways, such as the Sirtuin genes, regulated by these factors, specifically regarding insulin resistance and diabetes, extensively utilizing diet-induced and genetic rodent models of these diseases.

II. COMPENSATION

3. For my efforts in connection with the preparation of this declaration, I am being compensated at an hourly rate of \$400.00. My compensation is not in any way contingent on my performance, the result of this proceeding, or any of the issues involved therein. I am also being reimbursed for expenses incurred as a result of

activities performed as an expert.

III. MATERIALS REVIEWED

4. In preparing this declaration, I have reviewed and/or considered at least the documents cited in the List of Patent Owner's Exhibits above, as well as the documents referenced in this declaration. I have also relied on my own understanding and expertise.

IV. RELEVANT LEGAL STANDARDS

5. I am not a lawyer. I have been provided with an understanding of the legal principles that govern patent validity and claim construction. I have conducted my analysis in conformance with these principles. I set forth those understandings below.

A. Obviousness

6. Patent Owner's counsel has informed me that the issue to contend with in this matter is obviousness, which is governed by Title 35 United States Code ("U.S.C.") § 103. The statute provides that a "patent may not be obtained ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains." I have also been informed that issued patents are presumed to be valid. 35 U.S.C § 282(a).

7. The patent owner's counsel informed me that in an inter partes review, the Petitioner has the burden of proving, by a preponderance of the evidence, that the challenged patent claims would have been obvious based on "prior art" before the effective filing date of the claimed invention (i.e., before April 19, 2016).

8. For purposes of this report, I understand that "prior art" consists of patents, patent applications, and printed publications that existed prior to April 19, 2016, if not prior to April 19, 2015.

9. I have been informed that when a single prior art reference does not contain every limitation or element of a single patent claim, the PTAB can only invalidate the claim if supplying the missing limitations through another prior art reference or modification of the existing prior art would have been obvious to a person of ordinary skill in the art, and doing so without applying hindsight bias (i.e., looking back to prior to April 19, 2016 based on what is currently known so as to recreate the current invention in the prior art through what is now known because of the invention). I have been further informed that a claim is invalid for obviousness only if the differences between the claimed invention and the prior art are such that the claimed invention, as a whole, would have been obvious to a person having ordinary skill in the art before the effective filing date of the claimed invention, again without the benefit of hindsight.

10. As part of the obviousness analysis, I have been informed that prior art

references may be combined to show that a patent claim is invalid as obvious. I also understand that an obviousness evaluation may be based on a single reference or a combination of prior art references. For example, a single reference—when considered in light of the knowledge of a person of ordinary skill in the art—may render a claim obvious. Where a Petitioner attempts to prove obviousness by merely throwing metaphorical darts at a board in hopes of arriving at a successful result where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, hindsight claims of obviousness may be rejected.

1. *Graham* Factors

11. Counsel for the Patent Owner has informed me that an obviousness analysis considers a number of factors that consider four factual inquiries underlying obviousness, otherwise known as the *Graham* factors. I have been informed that the inquiries are as follows: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and, (4) objective evidence of nonobviousness (otherwise known as the secondary considerations of non-obviousness).

a. Scope and Content of the Prior Art

12. I have been informed that for a reference to be proper for use in an obviousness rejection, it must be dated prior to April 19, 2016. I also understand

that the prior art should be considered for all that it teaches, and not just be “cherry picked.” I have further been informed that in order to be proper for use in an obviousness challenge, the reference must be “analogous” art to the claimed invention in the patent. Prior art is considered non-analogous unless it is (1) from the same field of endeavor as the claimed invention, or (2) reasonably pertinent to the particular problem faced by the inventor.

b. Differences Between the Claimed Invention and the Prior Art

13. I have been informed that an obviousness analysis requires that the differences between what is claimed in the patent under consideration and the prior art be ascertained.

c. Level of Ordinary Skill in the Art

14. The Patent Owner’s counsel has informed me that my analysis must be performed from the perspective of a hypothetical “person of ordinary skill in the art” (“POSITA”) as of the effective filing date of the patent, which I understand to be April 19, 2016. I understand that a POSITA is a hypothetical person who is presumed to be aware of all pertinent prior art, has ordinary skill in the field of the invention, and is a person of ordinary creativity. I understand that my analysis should not be performed using a present-day perspective, and that I should not use hindsight.

d. Secondary Considerations of Non-Obviousness

15. Patent owner's counsel informed me that evidence of nonobviousness—sometimes called “secondary considerations” or “objective indicia”—must be considered when present. These factors include commercial success, long-felt but unmet need, failure of others, industry praise, unexpected results, copying, licensing or licensing interest, and skepticism of experts.

16. I have been informed that when a prior art reference suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant the prior art referenced may be said to “teach away” from the claimed invention.

2. Motivation to Combine with a Reasonable Likelihood of Success

17. I have been informed that after considering the scope and content of the prior art and identifying the differences between the prior art and the challenged claims, if any, the obviousness inquiry evaluates whether a person of ordinary skill in the art would have been motivated to combine or modify the existing prior art to bridge the differences between the prior art and the claimed invention; and if so, whether a person of ordinary skill in the art would have had a reasonable expectation of likelihood of success in doing so.

a. Motivation to Combine

18. Assuming a challenger demonstrates that all of the elements of the invention are present in the prior art combination and/or modification proposed, the challenger must then also demonstrate that there would be a reason to combine or modify the prior art references to arrive at the claimed invention. I am informed that the question is whether a POSITA would have combined elements from specific references in the way the claimed invention does (i.e., to arrive at the claims' actual limitations). I am further informed that a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Finally, I have further been informed that a motivation to combine must be based on articulated reasoning with some rational underpinning.

b. Reasonable likelihood of Success

19. A reasonable likelihood of success in the combination of prior art references or modification of the prior art is also required to establish obviousness, and this requirement is independent of the motivation to combine.

20. I have been informed that the asserted expectation must be grounded in what the prior art actually teaches, and cannot be based on generalized disclosures, mere possibility, hope, or hindsight reconstruction. I have also been informed that where the art is unpredictable or the petition for inter partes review fails to tie the

prior art to the claimed results, Petitioner has not met its burden to prove reasonable likelihood of success.

V. SUMMARY OF OPINIONS

21. Based on my review of U.S. Patent No. 10,278,961 (Exh. 1001, the “’961 patent”) and its prosecution history (Exh. 1002), the other materials I have considered, and my knowledge and experience, my opinions are as follows:

22. There are differences between the prior art and the challenged claims of the ‘961 patent in that none of the prior art cited by the petitioner shows administration of dhBBR to humans for purposes of managing glucose tolerance at the dosages required by the patent or in the forms required by the patent.

23. The experimental procedures used in the prior art (such as Turner), as I further describe below, compromise the applicability of the results asserted from the prior art cited by the petitioner to a human context, which is non-equivalent for many reasons including, for example, the inbred mice used for the studies in the prior art where such mice (e.g., C57Bl/6J) are known to have genetic mutations affecting glucose metabolism.

24. There is evidence of a lack of transferability of experimental animal data to humans in other not entirely unrelated contexts, which would counsel against a reasonable expectation of success.

25. There are differences in the properties and mechanisms of BBR and

dhBBR, and to the extent the prior art focused on conversion of dhBBR to BBR there are not only mechanistic differences discussed below, but inconsistencies based on the fact that the human stomach is more acidic than the rodent stomach, which would cause the properties of BBR and dhBBR to differ between humans and rodents such that rodent results would not be transferable with a reasonable expectation or success, and perhaps not even be motivated (other than by pure speculation) to try to extend the results from rodents to humans.

26. For these and other reasons discussed below, the prior art teaches scientific uncertainty, mechanistic divergence, and dosing ambiguity all of which preclude a finding of obviousness.

VI. OVERVIEW OF THE '961 PATENT

27. The 961 patent (“Administration of Berberine Metabolites”) describes methods for administering certain metabolites of berberine, such as dihydroberberine and tetrahydroberberine, to humans to manage metabolic functions including reducing fasting blood glucose, improving glucose tolerance, and increasing blood ketone levels, with potential therapeutic applications for conditions like diabetes, metabolic syndrome, dyslipidemia, obesity, and glucose intolerance. The patent explains that these metabolites may be more bioavailable and effective than berberine itself, and may be incorporated in various delivery forms (e.g., capsules, tablets, food or beverage products), alone or in combination with other

compounds such as ketone sensitizers to promote ketosis. The '961 patent also covers dosing ranges (25 mg to approximately 800 mg of dihydroberberine), complex formulations (e.g., microemulsions, liposomes), and co-administration strategies to enhance efficacy and reduce side effects.

VII. LEVEL OF ORDINARY SKILL IN THE ART FOR THE '961 PATENT

28. I have been asked to offer my opinion regarding the level of ordinary skill in the art as of the effective filing date, which I understand to be April 19, 2016 for the '961 Patent. I have considered the types of problems encountered in the art, the prior solutions to those problems found in prior art references, the rapidity with which innovations are made, the sophistication of the technology, the level of education of active workers in the field, and my own experience working with those of skill in the art at the time of inventions.

29. Based on my education and experience, as described above and in my CV (Exh. 2076), as well as consistent with the subject matter of the '961 Patent and the prior art described below, it is my opinion that a person of ordinary skill in the art ("POSITA") during the relevant period would have held a Ph.D or equivalent degree in pharmaceutical sciences, physiology, translational medicine, preclinical drug development, or a related biomedical field. Alternatively, a POSITA could be a person with a master's degree with at least 2–3 years of experience in preclinical drug development. Such a person would have been familiar with "prior art", such as

the limitations of extrapolating efficacy, pharmacokinetics, and dosing from rodent models to humans. A POSITA would know that the metabolism of berberine and its derivatives involves the digestive tract and gut microbiota, which differ between species.

VIII. CLAIM CONSTRUCTIONS UNDER C.F.R. § 42.104(b)(3)

30. For purposes of this proceeding only, Petitioner contends that, except for the claim term “managing glucose tolerance” from claim 1 being included as an element of the claim, no formal claim constructions are necessary.

IX. RESPONSE TO CHALLENGED CLAIMS

A. GROUND 1: Claims 1, 2, 5, 6, and 7 Are Not Obvious over Turner in View of Shaw

1. **Claim 1: A method of managing glucose tolerance in an individual comprising administering a pharmaceutically effective amount of dihydroberberine, wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine**

31. Based on reports that dihydroberberine (dhBBR) improved insulin resistance in rodent models (e.g., Turner, Exh. 1004), a POSITA might generally contemplate whether dhBBR merited further investigation. However, when viewed through the lens of the relevant prior art as a whole, multiple factors existing at or before the filing of the '961 patent would have **materially disincentivized** a

POSITA from advancing dhBBR into human clinical trials. Accordingly, the prior art does not provide sufficient motivation to pursue the claimed invention with a reasonable likelihood of success.

32. A POSITA's motivation is further informed by the degree of independent validation and clinical interest reflected in the scientific record. Here, the lack of human clinical investigation of dhBBR prior to and following the filing of the '961 patent evidences limited enthusiasm for its translation to humans.

33. Furthermore, a review of the U.S. clinical trial registry (<https://clinicaltrials.gov/>) reveals only four dhBBR-related trials, of which two were sponsored by the '961 patent holder. All trials were initiated after 2020 after the effective filing date of the application for the '961 patent in April of 2016. No independent clinical results have been listed for these trials. The lack of independent clinical investigation prior to the filing of the '961 Patent underscores that development of the compound was neither routine nor predictable at that time and supports the conclusion that a person of ordinary skill in the art would not have had a reasonable expectation of success in pursuing the claimed invention.

34. Similarly, I conducted a PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) search combining the terms "dihydroberberine," "glucose," and "human" and only identified three scientific publications (Cheng 2010 in Exh 2077 and a Zhang publication from 2026), as well as a study sponsored by the Patent Owner in this

matter (Moon 2021). However, a search of the Cheng publication for the word “human” does not result in any “hits.” Zhang being newly published rodent study and well after the ‘961 patent application filing date is not relevant. And, Moon in 2021, which also post-dates the ‘961 patent application filing date, shows that the Patent Owner itself was performing human studies with dhBBR. As such, the absence of meaningful, translatable human studies demonstrates that the content of the ‘961 patent was not obvious and a POSITA would not have had a reasonable likelihood of success at the time of filing. Standalone rodent or cell culture studies do not adequately bridge the significant gap between the ‘961 Patent and the alleged prior art at the time of filing.

35. The **absence of independent human trials or confirmatory studies** strongly suggests that skilled researchers did not view dhBBR as a compelling candidate for clinical development. This lack of follow-on work weighs against the notion that a POSITA would have been motivated to pursue dhBBR for human diabetes treatment.

36. Even assuming that a POSITA was motivated to test dhBBR in humans, the prior art would not have provided a **reasonable expectation of success**, as required for obviousness.

37. The metabolic disease literature is replete with examples where rodent efficacy failed to translate into clinical benefit in humans, including within the

treatment of metabolic disorders. For example, β 3-adrenergic receptor agonists showed robust anti-obesity and anti-diabetic effects in rodents but failed in humans (Arch 2011, Exh. 2078).

38. Another example is the 11β -HSD1 inhibitors, which improved glucose levels and insulin resistance in rodents, but clinical studies in humans showed minimal improvements in glucose control (Feig 2011 Exh. 2085).

39. Furthermore, King (Exh. 1011) discusses that mutations in KCNJ11 caused hyperinsulinemic hypoglycemia in humans yet produced glucose intolerance and reduced insulin secretion in mice. Exh. 1011, at p 8.

40. Lai 2014 teaches that while mice lacking the ZnT8 gene were predisposed to Type 2 diabetes, loss-of function mutations in humans protected humans from developing Type 2 diabetes (*see* Exh. 2020 at p. 005).

41. A POSITA, who is aware of all existing prior art, would know that rodent studies showing some initial indicia of promise are far from a guarantee (or even likelihood) of success when translated to humans. Instead, a POSITA would know that significant number of treatments that are effective in treating a disease in rodents fail when given to humans. Specifically, as addressed above, many rodent studies of metabolic disorders and diabetes have historically exhibited limited and unpredictable translational value in human applications. Without any human data or prior art successfully demonstrating how to actually translate this rodent data to

human treatment, the invention disclosed in the '961 Patent was not obvious and a POSITA would not have been motivated to combine the existing prior art with any likelihood of success.

42. Petitioner relies heavily on the Turner (Exh. 1004) study in their obviousness arguments, citing that preliminary rodent studies could provide a POSITA with a reasonable likelihood of success. However, Turner's data suffers from multiple translational limitations, including exclusive use of young male rodents and the use of intraperitoneal injection of glucose into C57Bl/6J mice with a known mutation predisposing mice to glucoregulatory defect (Fergusson 2014, Exh. 2086).

43. In Paragraph 46 of the Petitioner's expert's report, Petitioner's expert claims that based on the King reference (Exh. 1011) published in 2012, "the high-fat diet mice model is one of the most common animal models to research type two diabetes, especially for treatments to improve insulin resistance." Petitioner's expert argues that Turner followed the same high-fat diet model as described in King when it used the C57Bl/6 mice. . Lai 2014 teaches that "Dietary modification in rodents appears to have limited translatable benefit for understanding and treating human obesity and diabetes due—at least in part—to divergent dietary compositions, species/strain and gender variability, inconsistent disease penetrance, severity and duration and lack of resemblance to human obesogenic pathophysiology." (*see* Exh.

2020 at p. 002).

44. Fergusson (Exh. 2086), published in 2014, prior to the filing date of the provisional application for the '961 Patent, investigated the presence of a five-exon deletion in the *Nnt* gene, which caused a defective insulin secretory response to intravenous glucose (which bypasses the gut, like the intraperitoneal glucose injection utilized in Turner) in C57Bl/6J ("Bl/6J") mice (like those utilized in Turner). *Id.* at p. 001-002. The study found that Bl/6J mice have impaired GSIS [Glucose-Stimulated Insulin Secretion] compared to Bl/6N when glucose is administered intravenously during both a tolerance test and hyperglycemic clamp." *Id.* at p. 005. The researchers concluded that the defect included "impairment of both first and second phase insulin secretion, as well as its potentiation by arginine, **without changes in whole body insulin sensitivity,**" *Id.* (emphasis added). This indicates that the mice used in Turner (Exh. 1004), who were given glucose in a manner which bypasses the gut, carried the *Nnt* gene mutation which can cause impaired insulin production unrelated to insulin resistance and glucose tolerance in non-physiological glucose administrations. *Id.*

45. Additionally, all the mice utilized in Turner were young male mice (Exh. 1004 at p. 002). As disclosed in Fergusson (Exh. 2086), the GSIS of these Bl/6J mice was only measured in male mice. *Id.* at p. 004. Because of the "well-documented insulinotropic action of estrogens," it is possible that female 6J mice

have an improved or normal response to glucose. *Id.* However, Turner only used male mice and therefore dhBBR may not improve glucose homeostasis in high-fat fed female BI/6J mice.

46. The methodology utilized in Turner (Exh. 1004), including the use of an intraperitoneal glucose injection and male BI/6J mice significantly hinders its translational value to humans. In Fergusson (Exh. 2086), the researchers conclude that the “test and experimental conditions used to assess beta-cell function and/or glucose homeostasis has a **significant impact on the results and their interpretations.**” *Id.* at p. 006 (emphasis added). The study found that this insulin secretion defect is most significant during intravenous glucose administration as well as with use of a hyperglycemic clamp in BI/6J mice, but not during oral glucose tolerance tests. *Id.* Based on this data, Fergusson teaches that when testing beta-cell function in rodents, “one would advise to perform an OGTT [Oral Glucose Tolerance Test] plus an IVGTT [Intravenous Glucose Tolerance Test] or hyperglycemic clamp to accurately assess beta cell function in rodents.” *Id.* at p. 006.

47. Further, the authors in Fergusson showed a strong preference for the hyperglycemic clamp due to it allowing researchers to measure two phases of insulin secretion and C-peptide release. *Id.* Turner (Exh. 1004) did not perform any oral glucose tolerance tests or use the “gold standard” hyperglycemic clamp test

discussed in Fergusson on the mice or rats in the study. *See* Exh. 2086 at p. 002. Instead, Turner used male BI/6J mice with known *Nnt* mutation causing impaired GSIS, and only one glucose tolerance test, intraperitoneal glucose injection. Intraperitoneal glucose injections like the ones utilized in Turner bypass the gut and are non-physiological much like intravenous injections. *See* Exh. 1004 at p. 4.

48. A POSITA would have been aware that similar non-physiological tests like intravenous injections were known to cause skewed insulin secretion results in BI/6J mice due to the NNT defect, and that these methodologies make the mouse data from the Turner study unreliable such that it would not motivate extending the results to humans or create a reasonable expectation of success in a POSITA. A POSITA would consider the fact that Turner does not include an oral glucose tolerance test using dhBBR, and uses a non-physiological, gut-bypassing glucose administration method on BI/6J male mice with a known GSIS mutation in similar situations, when weighing the value of the Turner study, and conclude that Turner's results are of limited value, particularly with respect to translating such results to human physiology.

49. Turner also reported plasma berberine (BBR) levels peaking before dhBBR levels peaked following oral dhBBR administration (*see* Exh. 1004, Supplementary Fig. 2C), contradicting the asserted absorption-conversion sequence.

50. A POSITA would therefore understand that rodent metabolic efficacy,

standing alone, does not reliably predict human therapeutic success. Turner's rodent data (Exh. #1004) would provide, at most, a possible research hypothesis with several variables and inconsistencies, not a reasonable expectation that dhBBR would succeed in reducing glucose levels in humans, clinically or otherwise. I believe that the petitioner's assertions concerning Turner and its combination with other references are governed by hindsight – petitioner is reconstructing the patented invention based on current knowledge, not what was known at that time about dhBBR in humans, which was very little. Furthermore, the existing data (not speculation) about dhBBR prior to April 19, 2016 had a number of variables and inconsistencies that a POSITA would understand as rendering such data highly inconclusive about the effects of dhBBR on glucose metabolism in humans.

51. The petitioner's reliance on a 10× safety factor is misplaced because the factor applies to NOAEL-based toxicology extrapolations, not pharmacologically active or effective doses. *See* Exh. 1008. That dose is designed only as an initial safety dose or the “No Observed Adverse Effect Levels.” *Id.* The '961 patent's disclosed dosing range is addressed to pharmaceutically effective doses, not toxic thresholds; therefore, applying a safety factor to the dosing ranges in Turner (Exh. 1004) is completely irrelevant and does not support a finding of obviousness.

52. In my opinion, petitioner overlooked or ignored significant experimental design issues in Turner that compromise its applicability to humans, and in doing so,

petitioner more or less “cherry-picked” the prior art, as opposing to considering the prior art as a whole, which I understand is how the obviousness analysis is supposed to be performed.

2. Claim 2 - The method of claim 1 wherein the administration of dihydroberberine reduces fasting glucose levels

53. As stated above in paragraphs 37-52, a POSITA would understand that the rodent glucoregulatory effect of dhBBR demonstrated in Turner (Exh. 1004), standing alone, does not reliably predict human therapeutic success in humans given dhBBR. A POSITA would not have a reasonable likelihood of success in administering dhBBR to reduce fasting glucose levels in humans based on limited rodent data which was achieved under the noted problematic experimental design conditions. And, the petitioner fails to provide additional prior art that would motivate the extending of what Turner’s data shows in terms of the glucoregulatory effects seen in rats to humans, let alone with a reasonable expectation of success.

54. There are further questions about Turner’s experimental design beyond those noted above in terms of whether fasting rodents at night (when they tend to be most active given that they are nocturnal) was appropriate. In Turner (Exh. 1004, p. 2) the methods reference two additional papers, including reference 10 – Molero. I checked Molero, and on page 3412 of the journal (page 2 of the article), reference is made to overnight fasting of mice prior to the glucose tolerance test. When humans

are tested for glucose levels, they typically fast overnight when they are at rest. Combined with the fact the rodents have a much higher metabolic rates than humans, overnight fast is much more stressful for rodents than for humans (“Lai”, Exh. 2020 at p. 005). So, I believe Turner suffers this additional flaw that limits its ability to motivate extending its teachings to humans or provide a reasonable and legitimate expectation of success (as opposed to mere speculation).

3. Claim 5 - The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet

55. Not only is claim 5 nonobvious based on its dependent relationship to claim 1, but Turner (Exh. 1004) teaches that BBR and dhBBR were provided in the high-fat diet fed to the rodents (*see Id.* at p. 4), not as a stand-alone capsule or tablet as stated in claim 5 of the ‘961 Patent. The petitioner does not disclose any prior art that demonstrates the administration of dhBBR as a capsule. A POSITA would not have been motivated to administer dhBBR in a capsule or tablet based on the prior art relied upon by the petitioner.

56. Notably, when BBR or dhBBR is incorporated into rodent feed, dosing is effectively continuous and dependent on both the frequency and quantity of food consumed by the animals. As a result, daily intake of BBR or dhBBR may vary from day to day and from animal to animal. Besides, rodents also consume some feed during daytime, which is equivalent to the nighttime for humans. In contrast,

administration via a capsule represents a discrete, one-time dosing event, with drug delivery characteristics that differ substantially, including the fact that the compound would be provided in capsule or tablet form which can be taken close to a meal or between meals.

4. Claim 6 - The method of claim 1 wherein the dihydroberberine is orally administered as at least one of a food product or beverage product

57. Not only is claim 5 nonobvious based on its dependent relationship to claim 1, but Turner (Exh. 1004) does not teach dhBBR or BBR delivery in a liquid/beverage product, as claimed in the '961 patent. Turner teaches the administration of dhBBR within the high-fat diet of rodents. *Id.* Turner does not teach the administration of dhBBR as a beverage, nor the administration of dhBBR to a human at all. *Id.* A POSITA would not have a reasonable likelihood of success in orally administering dhBBR as a food product or beverage to a human.

5. Claim 7 - The method of claim 1 wherein the dihydroberberine is administered at least once daily

58. Because Turner (Exh. 1004) added dhBBR in the high-fat diet, the dosing is continuous as rodents consume the diet. It would not be obvious to a POSITA in light of Turner to administer the medication once a day.

B. GROUND 2: Claim 5 Is Not Obvious Over Turner in View of Shaw and Zhang

1. Claim 5 - The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet

59. In addition to what has already been said in connection with claim 1 and Ground 1, which applies here, Turner (Exh. 1004) teaches that BBR and dhBBR were provided in the high-fat diet, not as stand stand-alone capsule or tablet as stated in Claim 5. Zhang (Exh. 1006) teaches the oral administration of BBR, not dhBBR. As I elaborate below in Paragraphs 60-69, there are significant differences between BBR and dhBBR. It would not be obvious to a POSITA to administer dhBBR orally by capsule or tablet based on Turner where rodents are fed dhBBR in their food and Zhang, in which BBR, a different substance, is administered.

C. GROUND 3: Claims 1,2,5, And 7 Are Not Obvious Over Zhang in View of Feng

1. Claim 1: A method of managing glucose tolerance in an individual comprising administering a pharmaceutically effective amount of dihydroberberine, wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine

60. The petitioner relies on Zhang in view of Feng to assert that dhBBR would predictably succeed in humans because it acts as a prodrug for BBR. The petitioner attempts to equate the known effects of BBR and dhBBR, but there are several

notable differences between dhBBR and BBR, as detailed below.

61. First, Cheng, published in 2010, teaches that dhBBR readily oxidizes to BBR under acidic conditions (*see* Exh. 2077 at p. 003). Beasley teaches that human gastric pH (~1.5) is substantially lower than rodent gastric pH (~3.8–4.4) (*see* Exh, 2079 at p. 005-006). Accordingly, a POSITA would reasonably expect that orally administered dhBBR in humans would undergo **extensive pre-absorptive conversion to BBR in the stomach**, eliminating the purported bioavailability advantage of dhBBR observed in rodents. As a result, dhBBR would not meaningfully improve systemic exposure relative to oral BBR in humans, and doses extrapolated from rodent studies would likely be subtherapeutic once converted to BBR. Here, a POSITA would expect that while dhBBR is cited as being more readily absorbable than BBR *in rodents*, the greater acidity of the human stomach would lead to a significant portion of the dhBBR being converted to BBR before it is absorbed *in humans*. This predictable chemical behavior further diminishes any reasonable expectation of success.

62. Second, BBR's asserted anti-diabetic effects occur substantially in the intestinal lumen. BBR is characterized by extremely low systemic exposure. Zhang 2012 (Exh. 2089 at p. 002) reports: Rat C_{max} of ~4 ng/mL following 100 mg/kg oral BBR; Human C_{max} of ~0.4 ng/mL following a single 400 mg dose; In vitro efficacy of BBR is at concentrations higher than microgram/mL levels. These data

strongly suggest that BBR's therapeutic effects are mediated largely through **local intestinal actions**. The following data indicate that BBR's glucose-lowering effects arise substantially from **intestinal mechanisms**, including the inhibition of intestinal glucose absorption, GLP-1 stimulation, and gut microbiota modulation, none of which were as of April of 2016 or are now presently established as to dhBBR.

63. Inhibition of Intestinal Glucose Absorption: BBR inhibits carbohydrate digestion and glucose absorption by reducing intestinal disaccharidase activity (Liu, Exh. 1010). In both diabetic and normal rats, BBR suppressed postprandial glucose levels following oral glucose loading. *Id.* at p. 4. Human clinical evidence supports the conclusion that BBR exerts its primary glucose-lowering effects within the gastrointestinal tract. Zhang (Exh. 1006 at p. 3) reported improvements in fasting glucose and oral glucose tolerance test (OGTT) outcomes, both of which involve glucose administered via the oral route and processed through the gut; however, no statistically significant improvement over placebo was observed in glucose disposal during hyperinsulinemic euglycemic clamp testing, which delivers glucose directly into the bloodstream and therefore bypasses intestinal involvement. *Id.* at p. 4. Consistent with this finding, Zhang also reported no significant changes in systemic insulin sensitivity markers, including HOMA and circulating insulin levels. *Id.* at Table 1. These results indicate that BBR's efficacy is largely dependent on its presence and activity within the gastrointestinal tract rather than on systemic

exposure in humans. In contrast, dhBBR does not remain localized in the gastrointestinal tract and is instead absorbed and converted to BBR after oral uptake, making its pharmacological effects dependent on post-absorption metabolism. Because there are no data demonstrating that dhBBR shares BBR's gut-localized mechanism of action, a POSITA would not have had a reasonable expectation of success in extrapolating BBR-focused findings to dhBBR, rendering dhBBR's therapeutic effects inherently unpredictable in humans.

64. GLP-1 Stimulation. Glucagon-like peptide-1 (GLP-1) is a hormone secreted from intestinal cells in response to nutrient intake. *See* Exh. 2083. GLP-1 has strong anti-diabetes and other beneficial effects in clinical use. *Id.* BBR promotes GLP-1 biosynthesis and secretion from intestinal cells. *Id.* at p. 001. The petitioner has provided no evidence that dhBBR reproduces this effect. A POSITA at the time of filing would have no reason to believe that dhBBR would behave in a similar way to BBR with relation to GLP-1 stimulation.

65. Gut Microbiota Modulation. BBR modulates gut microbiota to influence glucose homeostasis by enrichment of SCFA-producing bacteria (Zhang 2012, Exh. 2089), inhibition of DCA biotransformation in humans (Zhang 2020, Exh. 2090), and reduced glucoregulatory efficacy when microbiota is disrupted by antibiotics (Yao 2020, Exh. 2088). In Zhang 2012, the researchers observed a significant reduction in the diversity of gut microbiota in berberine-treated rats. *See*

Exh. 2089 at p. 001.

66. The prior art cited by the petitioner does not teach that dhBBR reproduces BBR's intestinal effects in rodents or humans. Even if it did, dhBBR would be expected to be **less effective** due to rapid absorption with reduced luminal exposure and lower intended dosing than BBR, as one proposed advantage of dhBBR is its higher bioavailability than BBR. A POSITA would therefore not reasonably expect dhBBR to recapitulate BBR's clinical efficacy.

67. Third, dhBBR does not fully replicate BBR function. Chen, published in 2014, demonstrated that oral BBR (10 mg/kg/day) reduced cholesterol in ApoE-deficient mice, whereas **dhBBR at the same dose** did not (Table 2), despite higher bioavailability. *See* Exh. 2082 at p. 007. This finding confirms that dhBBR cannot be assumed to function as a simple surrogate or prodrug for BBR and underscores the **unpredictability** of its biological effects. *Id.* As such, a POSITA would be aware that BBR and dhBBR do not always share the same physiological effects, and therefore a POSITA could not blindly assume the established metabolic benefits of BBR administration equally apply to dhBBR with a reasonable likelihood of success.

68. Fourth, not all BBR derivatives act via conversion to BBR. Cheng, published in 2010, showed that Di-Me remained structurally intact in plasma yet retained glucose-lowering activity. *See* Exh. 2077 at p. 003-006. In addition, BBR undergoes extensive metabolism, and its metabolites, other than dhBBR, contribute

meaningfully to efficacy. See Exh. 2091 at p. 012-013 and generally.

69. Oral administration of dhBBR results in higher proximal gastrointestinal exposure of dhBBR than what is converted from BBR, which primarily occurs in the more distal intestine. See Exh. 1007 at p. 2 (Figs. 1c, 1d therein)). This is based on a higher dhBBR level in the ileum in Fig.1C and more efficient dhBBR conversion by the rat large intestine bacteria versus small intestine bacteria (as shown in Exh. 1007 at Fig.1d-U vs, 1d-M). In addition, dhBBR exhibits distinct biological activities - including stronger pancreatic lipase inhibition and enhanced anti-inflammatory effects - raising the possibility of **uncharacterized side effects of dhBBR**. Since dhBBR administration results in higher plasma BBR levels than BBR treatment, elevated plasma BBR levels could reasonably be expected to increase the likelihood or severity of adverse effects not observed in prior BBR clinical studies. See Exh. 2082 and Exh. 2087. Therefore, a POSITA could not assume that dhBBR shared BBR's safety profile in humans absent dedicated clinical evaluation, undermining a reason to combine and modify the prior art to extend it to humans, but certainly also any reasonable expectation of success.

2. Claim 2 - The method of claim 1 wherein the administration of dihydroberberine reduces fasting glucose levels

70. As stated above in Paragraphs 60-69, a POSITA would understand that there are substantial differences between dhBBR and BBR. Therefore, the

glucoregulatory efficacy of BBR demonstrated in Zhang (Exh. 1006) does not reliably predict human therapeutic success for dhBBR. Additionally, Feng (Exh. 1007) does not teach that dhBBR reduces fasting glucose levels in humans. The administration of dhBBR to reduce fasting glucose levels was not obvious and a POSITA would not have had a motivation to try this method with a reasonable likelihood of success in light of the prior art.

3. Claim 5 - The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet

71. . As stated above, a POSITA would understand that there are substantial differences between dhBBR and BBR. Therefore, the glucoregulatory efficacy of BBR tablet demonstrated in Zhang (Exh. 1006) does not reliably predict human therapeutic success for dhBBR tablet or capsule. The administration of dhBBR by capsule or tablet was not obvious and a POSITA would not have had a motivation to try this method with a reasonable likelihood of success in light of the prior art.

4. Claim 7 - The method of claim 1 wherein the dihydroberberine is administered at least once daily

72. Prior art teaches twice-daily dosing of BBR in humans (Exh. 1006 at p. 2), as well as continuous dosing in mice and rats (Exh. 1004 at p. 4), which are inconsistent with what claim 7 would cover in terms of a once-daily regimen. The administration of dhBBR once a day was not obvious and a POSITA would not have

had a motivation to try this method with a reasonable likelihood of success in light of the prior art.

D. GROUND 4: Claim 6 Is Not Obvious Over Zhang in View of Feng Further in View of Turner

1. Claim 6 - The method of claim 1 wherein the dihydroberberine is orally administered as at least one of a food product or beverage product

73. As addressed above, Zhang, Feng, and Turner do not teach the administration of dhBBR as a food or beverage product in humans. Zhang teaches the administration of only BBR. Turner does not teach dhBBR or BBR delivery in a liquid/beverage product, as claimed in the '961 patent. Additionally, Turner does not teach the administration of dhBBR to humans. The administration of dhBBR as a food or beverage was not obvious and a POSITA would not have had a motivation to try this method with a reasonable likelihood of success in light of Feng, Zhang, and Turner.

X. RIGHT TO SUPPLEMENT

74. I reserve the right to supplement my opinions in the future to respond to any arguments that Petitioner raises. This declaration represents only those opinions that I have formed to date. I reserve the right to revise, supplement, and/or amend my opinions stated herein based on new information that becomes available to me and on my continuing analysis of the materials already provided. I may utilize the

documents cited and/or listed herein, or portions of those documents, as exhibits at any hearing or trial in this proceeding. I may further prepare and use exhibits that summarize portions of my testimony or key terms or concepts presented therein, or other demonstrative exhibits, at any hearing or trial in this proceeding.

75. I reserve the right to supplement my testimony and this report in response to any judicial determinations, in response to the arguments expressed by Petitioner or the opinions of Petitioner's experts in this proceeding, and/or in light of additional evidence or testimony brought forth at trial or otherwise brought to my attention after the date of my signature below.

XI. CONCLUSION

76. For the foregoing reasons, it is my opinion that the prior art neither motivated a POSITA to advance dhBBR into human trials or administration nor provided a reasonable expectation that such trials or administration would succeed. On the contrary, the prior art teaches scientific uncertainty, mechanistic divergence, dosing ambiguity, and superior alternative compounds, all of which preclude a finding of obviousness.

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77. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed on: January 5, 2026

A handwritten signature in black ink, appearing to read 'Qiang Tong', written over a horizontal line.

Dr. Qiang Tong