

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*

**PATENT OWNER NANJING NUTRABUILDING BIO-TECH CO., LTD.'S
OBJECTIONS TO PETITIONER'S EVIDENCE SUBMITTED IN REPLY**

Pursuant to 37 C.F.R. § 42.64(b)(1), Patent Owner, Nanjing Nutrabuilding Bio-Tech Co., Ltd. hereby respectfully submits its Objections to Petitioner's Evidence Submitted in Reply.

PATENT OWNER’S OBJECTIONS TO PETITIONER’S EVIDENCE

SUBMITTED IN REPLY

Patent Owner Nanjing Nutrabuilding Bio-Tech Co., Ltd. (“Patent Owner” or “NNB”) submits the following objections to Petitioner Bonerge Lifescience (Hunan) Co., Ltd.’s (“Petitioner” or “Bonerger”) evidence submitted with its Reply Brief (Paper No. 23). The objections are made pursuant to 37 C.F.R. §§ 42.61-42.65, as well as the Federal Rules of Evidence pursuant to 37 C.F.R. § 42.62.

Patent Owner’s current objections to certain evidence submitted with Petitioner’s Reply Brief are set forth in the following Table:

PETITIONER’S REPLY EXHIBIT	GROUND FOR OBJECTIONS
Exh. 1021 - Ni Yanxia et al., Therapeutic effect of berberine on 60 patients with Type II diabetes mellitus and experimental research. CJIM (1988) (with English Abstract).	Introduces new or belated arguments. Exhibit 1021 (“Ni”) constitutes new evidence and/or argument for unpatentability first added in reply brief, which is improper. 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding opposition”); Consolidated Trial Practice Guide at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”); <i>see also Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.</i> , 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (new theories of unpatentability introduced by petitioner in reply improper). At the top portion of page 9

	of Petitioner’s Reply (Paper 23), Petitioner, for the first time, cites to newly submitted Ni as a basis for supporting unpatentability. If Ni was cited in a reference Petitioner included in its Petition, there was nothing stopping Petitioner from including it as part of its Petition and presenting it in a ground of unpatentability. Petitioner did not do that. Accordingly, Petitioner should not be permitted to rely on Ni for any purpose related to unpatentability, and Ni should be stricken from the record. FRE 901, 902 – Lack of Authentication. Ni is objectionable for a lack of authentication. It is of unknown origin, no chain of custody is provided, and there is no information about the alleged translator of the portion of the document shown in English, when the translation was made, if it is an accurate or certified translation. Petitioner has not proffered sufficient information or evidence to show what this document is, how it was created, and how it was translated (in part). <i>Apator Miitors ApS v. Kamstrup A/S</i>, 887 F.3d 1293, 1295 (Fed. Cir. 2018); <i>Kolcraft Enters., Inc. v. Graco Children’s Prods., Inc.</i>, 927 F.3d 1320, 1324 Fed. Cir. 2019). Thus, Ni is also objectionable for a lack of foundation, in addition to a lack of authentication. FRE 801, 802 - Hearsay. Ni constitutes hearsay. It is an out of court statement offered for the alleged
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	truth (of unknown origin or translation, as noted in the authentication objection above) contained therein, as set forth at the top of page 9 of Paper 23. FRE 1002 – Not the Best Evidence. Ni is objectionable under the best evidence rule, and the requirement of an original should be imposed here because Ni is of unknown origin, unknown translation, and incomplete translation.
Exh. 1023 – Supplemental Declaration of Dr. Ronald J. Shebuski, Sr.	General. NNB objects to the Supplemental Declaration of Dr. Ronald J. Shebuski, Sr. (Exh. 1023) because each paragraph is <i>ipse dixit</i> – as these paragraphs lack foundation and are not based in sufficient facts or data pursuant FRE 702. <i>See Cephalon, Inc. v. Watson Pharms., Inc.</i>, 707 F.3d 1330, 1338 (Fed. Cir. 2013). As a result, Petitioner has not established these paragraphs are relevant pursuant FRE 401, and the Board should exclude them as inadmissible under FRE 402, 403. General – Claim Construction. Dr. Shebuski does not address “glucose tolerance” consistent with a proposed construction that entails fasting or postprandial glucose. Rather, he refers generally to “glucose tolerance” without specifying whether he is referring to fasting or postprandial glucose. This flaw renders all such paragraphs where he does so (<i>see e.g.</i> ¶¶ 116, 117, 118, 120, 121, 124, 125,

	126, 128, 130, 131, 136, 150, 171) irrelevant under FRE 401, 402, as well as lacking in foundation). Introduces new or belated arguments. Exh. 1023 contains extensive untimely discussion, argument, and analysis that constitutes new evidence and/or argument for unpatentability first added in reply brief, which is improper. 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding opposition”); Consolidated Trial Practice Guide at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”); <i>see also Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.</i>, 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (new theories of unpatentability introduced by petitioner in reply improper). Paper 23 (Petitioner’s Reply) cites to Exh. 1023 no less than 24 times. More specifically, Patent Owner objects as follows to specific paragraphs in Exh. 1023 (with the paragraph number followed immediately by the objections): ¶ 112 – Dr. Shebuski refers to “the terms of my compensation” from ¶ 5 of his original declaration (Exh. 1003), but in ¶ 5 of Exh. 1003, Dr. Shebuski stated, “For my efforts in connection with the preparation of this declaration, I am being compensated at my standard
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	hourly rate for my time”; yet, Dr. Shebuski did not state his hourly rate. Fed.R.Civ.P. 26(a)(2)(B)(vi) requires an expert to disclose “a statement of the compensation to be paid for the study and testimony in the case.” Dr. Shebuski failed to disclose his “standard hourly rate” or a “statement of the compensation to be paid” for his work on this matter. Such information should be provided forthwith. ¶ 116 (last sentence – so general as to be irrelevant under FRE 401, 402). ¶ 117 (so general it is not helpful to the trier of fact, nor relevant under FRE 401, 402, 702(a)). ¶ 118 (“likely the active moiety” is speculation – lack of personal knowledge – FRE 602; last sentence is a straw man in that this is not the argument made by Patent Owner’s experts, and is thus irrelevant under FRE 401, 402; this is the <i>ipse dixit</i> of the expert and lacks foundation). ¶ 120 (lack of foundation; speculation as to “Therefore, the results from an intraperitoneal test on diabetic mouse treated with dihydroberberine (“dhBBR”) and the results from an oral test on diabetic patients treated with dhBBR likely will yield similar results” and Turner at 1416 says “similar effect” not the “same mechanism,” as Dr. Shebuski asserts without further support – and this is a new argument reply brief as well – lack of personal
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	knowledge – FRE 602). Additionally, Dr. Shebuski asserts, without citation to any portion of Turner, that Turner teaches that the mechanism of action of berberine and dhBBR “is the same mechanism by which diabetic drug metformin exerts its effects on humans,” but Turner itself hedged by stating that “[t]hese data highlight the importance of complex I as a diabetes target. Inhibition of complex I is likely the main mechanism by which BBR activates AMPK.” Thus, Dr. Shebuski’s assertion in this regard is the <i>ipse dixit</i> of the expert and lacks foundation). ¶ 121 (FRE 401, 402 – lack of relevance because this mechanism of action is not at issue; ambiguous and lacking in foundation because Dr. Shebuski failed to define “glucose tolerance” nor address the arguments that controvert his assertion at Paper 18, p. 34-36). ¶ 126 (FRE 401, 402 – lack of relevance; this is the <i>ipse dixit</i> of Dr. Shebuski in terms of what a person of skill in the art would have believed; speculative – Dr. Shebuski did not squarely address Patent Owner’s criticism that overnight fasting of a nocturnal animal created a stressed state, including the fact that Turner did not control for this issue, and instead Dr. Shebuski misdirected with mechanistic information about metformin, a drug he did not mention in his original declaration (Exh. 1003)
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	that failed to address Patent Owner’s point about the issues with an overnight fast; finally, by attempting to equate dhBBR and metformin to imply a reasonable expectation of success, an argument not raised by Petitioner in its Petition nor by Dr. Shebuski in his original declaration, Petitioner has improperly submitted new evidence and/or argument in reply, which is improper). ¶ 129 (FRE 602 – lack of personal knowledge – Dr. Shebuski asserts without basis that the mice in Turner were cross-referenced only to Molero and not also to Ye; his <i>ipse dixit</i> assertion also lacks foundation and is speculative). ¶ 131 (FRE 401, 402 – lack of relevance; <i>ipse dixit</i> of expert; lack of foundation – Dr. Shebuski frames the issue in an irrelevant manner, because 486 mg/day dhBBR was not administered to a human in any of the art cited by Petitioner; and, Dr. Shebuski mischaracterizes the issue because Patent Owner extensively criticized Shaw and the FDA Guidance for determining human effective dosage, which functions as a criticism of the 486 mg/day dhBBR alleged human dose because it rejects the calculation used to arrive at 486 mg/day). Thus, Dr. Shebuski’s statements in ¶ 131 are entirely irrelevant). ¶¶ 134-136 (Introduces new or
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	belated arguments. Paragraphs 134-136 constitute new evidence and/or argument for unpatentability first added in reply brief, which is improper. 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding opposition”); Consolidated Trial Practice Guide at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”); <i>see also Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.</i>, 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (new theories of unpatentability introduced by petitioner in reply improper). More specifically, Dr. Shebuski is framing and characterizing the issue in a manner not previously stated; in fact, the reference to Turner suggesting that Turner taught 560 mg/kg/day improved glucose tolerance in mice is based on “data not shown” by Turner – <i>see</i> Exh. 1004, p. 3, left column), thus rendering Dr. Shebuski’s assertion as lacking in foundation and lacking in personal knowledge, FRE 602); and Dr. Shebuski’s reliance on Feng is similarly lacking in foundation inasmuch as Feng did not study human beings and the concentration of dhBBR it used were ~2.43 times higher than the upper end of the range claimed in claim 1 of the ‘961 Patent – <i>see</i> Paper 18 at 44 and at 46-47, citing Exh. 2108 at ¶ 78)); <i>see also</i> the objections to ¶ 131 which apply equally to ¶¶ 134-136. ¶ 137 – (FRE 401, 402 – lack of
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	relevance; <i>ipse dixit</i> of expert; lack of foundation – Dr. Shebuski frames the issue in an irrelevant manner, because 486 mg/day dhBBR was not administered to a human in any of the art cited by Petitioner; and, Dr. Shebuski mischaracterizes the issue because Patent Owner extensively criticized Shaw and the FDA Guidance for determining human effective dosage, which functions as a criticism of the 486 mg/day dhBBR alleged human dose because it rejects the calculation used to arrive at 486 mg/day). Thus, Dr. Shebuski’s statements in ¶ 137 are entirely irrelevant). ¶ 138 (FRE 401, 402 – lack of relevance, <i>ipse dixit</i> of expert, lack of foundation for at least the reasons stated above in connection with ¶ 131; – 1500 mg/day of berberine is not part of the patent claim; Introduces new or belated arguments. New evidence relied on in reply (Ni – Exh. 1021) is improper – 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding opposition”); Consolidated Trial Practice Guide at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”); <i>see also Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.</i>, 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (new theories of unpatentability introduced by petitioner in reply improper). Ni was available to
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	Petitioner and Dr. Shebuski prior to the filing of the original petition, and neither Petitioner nor Dr. Shebuski relied on it at all. They should be precluded from doing so now; FRE 602 – lack of personal knowledge and lack of foundation in that Dr. Shebuski has not shown (without the use of new, improper evidence in Exh. 1021 (Ni)) the basis for the assertions made; FRE 801, 802 – hearsay and multiple hearsay in that Dr. Shebuski relies upon Zhang, which itself relies further upon other out-of-court statements, including the “[s]everal clinical investigations ...” mentioned in this paragraph of Dr. Shebuski’s supplemental declaration); <i>see also</i> the objections to ¶ 131 which apply equally to ¶ 138 in terms of the 486 mg/day. Introduces new or belated arguments. New argument, as here in ¶ 139, is improper – 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding opposition”); Consolidated Trial Practice Guide at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”); <i>see also Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.</i>, 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (new theories of unpatentability introduced by petitioner in reply improper). ¶ 139 (FRE 401, 402 – lack of relevance, and lack of foundation, in that the FDA Guidance, Exh. 1008, p. 6
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	(as labeled; FDA numbering p. 3) says, “The recommended process for selecting the MRSD is presented in Appendix E and described in this section. The major elements (i.e., the determination of the no observed adverse effect levels (NOAELs) in the tested animal species, conversion of NOAELs to HED, selection of the most appropriate animal species, and application of a safety factor) are all discussed in greater detail in subsequent sections.” There is no evidence that any of the references cited by Petitioner or Dr. Shebuski followed the recommended process of the FDA, and Petitioner has shown no such reliance. None of Dr. Shebuski’s comments address the issues with the FDA Guidance highlighted by Patent Owner in Exh. 2157 (Blanchard) and detailed in Paper 18 at 18-22, 30, 32. This is also the foundation-less, <i>ipse dixit</i> of Dr. Shebuski in that he notes the following in ¶ 139 (emphasis added): “The FDA Guidance thus suggests that human equivalent dosage “can be derived from a PAD.” The suggestion to compare MRSD (“Maximum Recommended Starting Dose”) to HED, further implies HED is derivable from PAD and can be useful in drug development. Because Turner discloses dosages based on <i>in vivo</i> mouse studies, a POSITA would have reasonable expectations that the 486 mg/day HED dosage would provide the “same degree of effect” on
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	humans.” Dr. Shebuski’s statement “same degree of effect” neglects to disclose that the HED “is usually used to refer to the human equivalent dose of the NOAEL.” Exh. 1008, p. 18. “NOAEL” stands for “No observed adverse effect level (NOAEL): The highest dose tested in an animal species that does not produce a significant increase in adverse effects in comparison to the control group. Adverse effects that are biologically significant, even if not statistically significant, should be considered in determining an NOAEL.” <i>Id.</i> Dr. Shebuski also failed to lay a foundation to show that the claimed 486 mg/day from Turner and the FDA Guidance complies with the definitions for HED and NOAEL in the FDA Guidance. Because he failed to do so, his testimony lacks foundation and is irrelevant. ¶ 140 (Introduces new or belated arguments. New argument, as here in ¶ 140, is improper – 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding opposition”); Consolidated Trial Practice Guide at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”); <i>see also Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.</i>, 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (new theories of unpatentability introduced by petitioner
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	in reply improper). Petitioner did not present these arguments in its Petition, nor did Dr. Shebuski these arguments in his original declaration. They certainly did not present them in this manner. This is new argument. In fact, the FDA Guidance was not identified as a reference in Grounds 1-4 in the Petition. <i>See</i> Paper 2 at 2. Patent Owner also objects to “See above” as vague and ambiguous in that it is unclear as to which of the dozens of paragraphs above Dr. Shebuski refers). ¶¶ 142-148 (FRE 401, 402 – lack of relevance – What Dr. Shebuski claims Zhang concludes is of no relevance to the challenge to the quality of data in Zhang. Whether or not NNB’s experts have identified a publication questioning Zhang is not the standard, but a straw man from Dr. Shebuski. The fact is that Zhang has chosen to represent its data in an unusual manner that seems directed to depicting less error in graphical form than is shown in the data in tabular form. <i>Why do that?</i> To mask substantial spread in the data. Zhang also used berberine, not dhBBR. Introduces new or belated arguments. New arguments, as here in ¶¶ 142-148, is improper – 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding opposition”); Consolidated Trial Practice Guide at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to
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	make out a prima facie case of unpatentability.”); <i>see also Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.</i>, 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (new theories of unpatentability introduced by petitioner in reply improper). Here, Dr. Shebuski presented a series of calculations regarding the data in Zhang that were not presented in the Petition, although they could have been). ¶ 150 (Introduces new or belated arguments. New assertions and arguments, as here in ¶ 150, is improper – 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding opposition”); Consolidated Trial Practice Guide at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”); <i>see also Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.</i>, 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (new theories of unpatentability introduced by petitioner in reply improper). Here, Dr. Shebuski gratuitously claims that Zhang corroborates other clinical studies, none of which were included in the Petition. This is a new assertion, and also an irrelevant assertion under FRE 401, 402). Dr. Shebuski’s reference to Ni, Xie, and Wei are improper and should be stricken. Also, Patent Owner also objects to “See above” as vague and ambiguous in that it is unclear as to which of the dozens of paragraphs
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	above Dr. Shebuski refers). ¶¶ 151-155 (FRE 1002 – not the best evidence. What Feng teaches or does not teach is best determined from Feng itself, not Dr. Shebuski’s characterization of Feng. Similarly, Dr. Shebuski’s new characterization of Feng introduces new or belated arguments. New assertions and arguments, as here in ¶¶ 151-155, is improper – 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding opposition”); Consolidated Trial Practice Guide at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”); <i>see also Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.</i>, 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (new theories of unpatentability introduced by petitioner in reply improper); Dr. Shebuski’s new characterization of Feng is also irrelevant under FRE 401, 402 because Feng used a large dose of dhBBR that Dr. Shebuski does not address. Feng conducted <i>in vitro</i> studies on cell lines and rodents at large, out-of-the-claimed-range dosages rendering its relevance to humans <i>nil</i>. <i>See</i> Paper 18, p. 44 (citing Exh. 2108 at ¶ 78); Lack of Foundation/Ipse Dixit of Expert – Dr. Shebuski’s assertion in ¶ 153 that “[t]he anerobic condition mimics human gastrointestinal tract” is without citation or support, lacks foundation, and is also new argument in
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	Petitioner’s Reply. Dr. Shebuski’s assertion in ¶ 155 that “[i]ncubation with air exposure can mimic the condition of dhBBR crossing the intestinal epithelium – from the apical / anerobic intestinal lumen side to the basolateral / blood circulation side” is also is without citation or support, lacks foundation, and is also new argument in Petitioner’s Reply). ¶¶ 158-159 (Lack of Foundation/<i>Ipse Dixit</i> of Expert – Dr. Shebuski did not engage with the Patent Owner’s criticisms of extrapolating motivations to combine or reasonable expectations of success – <i>see</i> Paper 18 at 47-49 and Exhs. 2175 (p. 1, 4, 5), 2176 (p. 14), 2108 (¶ 80), 2183 (¶ 227) – rather, Dr. Shebuski ignored Patent Owner’s criticisms, claimed in ¶ 158 that Caco-2 cells are widely used (the general proposition for which is not relevant to this particular issue, FRE 401, 402), and without cogent basis or reasoning, particularly in light of Patent Owner’s un rebutted criticisms of how Petitioner used Caco-2 cell data in its Petition, simply proclaimed that a “POSITA reading Maubon and Sun will not be discouraged from using Caco-2 cells for human drug absorption studies.” That is a straw man because it is such a general proposition untethered to the issues here that is meaningless and irrelevant. The question to be asked of Dr. Shebuski and his assertion is, “based on what?” Dr. Shebuski then continued in ¶ 159 with additional foundation-less, overly general,
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	unsupported statements that are solely <i>ipse dixit</i> – namely, “[n]either Maubon nor Sun would persuade a POSITA to question what Feng teaches ...” and “[a] POSITA would have reasonable expectations that Feng’s finding that dhBBR is more bioavailable is true clinically, not just true at lab studies. Again, “based on what?” Neither Maubon nor Sun directly address Feng. Feng used such a high dose of dhBBR (1945 mg/kg/day) that the dosage itself would teach away from higher absorption. If the absorption of dhBBR is so high, why is such a high dose needed? Feng is not relevant and does not support a finding of unpatentability at all). ¶¶ 160-162 (FRE 401, 402 – lack of relevance. Dr. Shebuski has not engaged with Dr. Hartung’s points, but simply identified in argumentative form, what Dr. Hartung did not say. This is an irrelevant straw man that Dr. Shebuski uses as a springboard to offer new, improper opinions in reply in ¶ 163). ¶ 164 (FRE 401, 402 – lack of relevance. Again, Dr. Shebuski does not engage with, nor contest, the core principle stated by Dr. Tong (<i>see</i> Exh. 2109 at ¶ 37) that “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.” Rather, Dr. Shebuski erects another straw man and
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	states that Dr. Tong never analyzed why the studies failed. This is not relevant. The fact is, the studies failed, and that is why, according Dr. Tong, after citing three (3) additional examples in Exh. 2109 at ¶¶ 38-40, concludes in ¶ 41 that, “[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.” Dr. Shebuski’s straw man statement in ¶ 164 is irrelevant). He then piggy-backs on his irrelevant straw man to offer improper new opinion and argument in ¶ 165 that does not respond to anything in Patent Owner’s Response. ¶ 165 (Introduces new or belated arguments. New evidence relied on in reply (Ni – Exh. 1021) is improper – 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding opposition”); Consolidated Trial Practice Guide at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”); <i>see also Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.</i>, 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (new theories of unpatentability introduced by petitioner in reply
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	improper). Ni was available to Petitioner and Dr. Shebuski prior to the filing of the original petition, and neither Petitioner nor Dr. Shebuski relied on it at all. They should be precluded from doing so now. Additionally, the follow-on argument in the remainder ¶ 165 is gratuitous in that it does not appear to respond to anything in Patent Owner’s Response. FRE 602/FRE 801, 802 – lack of personal knowledge/hearsay – Dr. Shebuski’s reference to Feng’s assertion that “[t]he therapeutic effect of BBR on lipid- and glucose related metabolic disorders are recently confirmed in a large number of patients by independent clinical groups both in and outside China” is hearsay and Dr. Shebuski lacks the personal knowledge to attest to such statements in Feng. The final sentence of ¶ 165 is also <i>ipse dixit</i>. ¶¶169-175 (Introduces new or belated arguments. New evidence or argument relied on in is improper – 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding opposition”); Consolidated Trial Practice Guide at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”); <i>see also Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.</i>, 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (new theories of unpatentability introduced by petitioner in reply
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	improper). In ¶¶ 169-175, Dr. Shebuski interprets marketing documents in Exh. 2115 (and he has no known expertise in marketing, so his opinions lack foundation and constitute improper expert opinions of a lay witness FRE 701(c) and are thus irrelevant, FRE 401, 402). They are further irrelevant (FRE 401, 402) and improper new arguments in reply because, if used to controvert a nexus for commercial success, Dr. Shebuski focuses on the bioavailability issue, whereas Patent Owner, in its response (<i>see</i> Paper 18 at 64), cited Exh. 2115 as supporting a nexus as to glucose management, glucose tolerance, and blood sugar control, not bioavailability.
Exh. 1025 – Ex Parte Bernstein, Appeal No. 2014-007316, Appl. No. 13/197,581 (P.T.A.B. Aug. 27, 2015) (Decision on Appeal)	Introduces new or belated arguments. Exhibit 1025 constitutes new evidence and/or argument for unpatentability first added in reply brief, which is improper. 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding opposition”); Consolidated Trial Practice Guide at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”); <i>see also Wasica Fin. GmbH v. Cont’l Auto. Sys., Inc.</i>, 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (new theories of unpatentability introduced by petitioner in reply improper). Because the decision in <i>Ex Parte Bernstein</i> was available to Petitioner at the time it

	filed its Petition, Petitioner should be barred from relying upon it (and the references Petitioner cites from the <i>Ex Parte Bernstein</i> decision) in its Reply. Effectively, Petitioner is not relying upon the <i>Ex Parte Bernstein</i> decision, or solely the <i>Ex Parte Bernstein</i> decision, but the references discussed therein, including Murdock and Freireich, which Petitioner explicitly references in its Reply Brief. <i>See</i> Paper 23 at 8. Petitioner should have presented these references in its Petition, but failed to do so. Accordingly, Petitioner should be precluded from using the <i>Ex Parte Bernstein</i> decision (or the references cited therein) effectively as new grounds of unpatentability presented for the first time in reply, and Exh. 1025 should be stricken from the record. FRE 401, 402 – Lack of Relevance. Undesignated Board decisions in ex parte appeals have no precedential value in subsequent, unrelated matters, particularly adversarial proceedings with expert witnesses such as inter partes review. <i>See Ford Motor Co. v. Neo Wireless LLC</i>, No. IPR2023-00763, 2025 WL 3728020, at *15 (PTAB Sept. 3, 2025) (rejecting Petitioner’s reliance on non-precedential ex parte appeal – “The <i>McBrady</i> case cited by Petitioner is not a precedential decision but a routine ex parte appeal decision of a patent application.”). District courts have also questioned the precedential value of ex
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	parte patent application proceedings in a collateral estoppel context as well. <i>See e.g. Realvirt, LLC v. Lee</i>, 179 F. Supp. 3d 604, 607 (E.D. Va. 2016), <i>aff'd sub nom., Realvirt, LLC v. Iancu</i>, 734 Fed. App'x 755 (Fed. Cir. 2018).
Exh. 1026 – Appellant's Appeal Brief, U.S. Patent Application No. 13/197,581 (Ex parte Bernstein), with Exhibits A-G	Introduces new or belated arguments. Exhibit 1026 constitutes new evidence and/or argument for unpatentability first added in reply brief, which is improper. 37 C.F.R. § 42.23(b) (“A reply may only respond to arguments raised in the corresponding opposition”); Consolidated Trial Practice Guide at 73 (“Petitioner may not submit new evidence or argument in reply that it could have presented earlier, e.g. to make out a prima facie case of unpatentability.”); <i>see also Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.</i>, 853 F.3d 1272, 1286-87 (Fed. Cir. 2017) (new theories of unpatentability introduced by petitioner in reply improper). Because the appeal brief in <i>Ex Parte Bernstein</i> was available to Petitioner at the time it filed its Petition, Petitioner should be barred from relying upon it (and the references Petitioner cites from the <i>Ex Parte Bernstein</i> appeal brief) in its Reply. Effectively, Petitioner is not relying upon the <i>Ex Parte Bernstein</i> appeal brief, or solely the <i>Ex Parte Bernstein</i> appeal brief, but the references discussed therein, including Murdock and Freireich, which Petitioner explicitly references in its Reply Brief. <i>See</i> Paper 23 at 8.

	Petitioner should have presented these references in its Petition, but failed to do so. Accordingly, Petitioner should be precluded from using the <i>Ex Parte Bernstein</i> appeal brief (or the references cited therein) effectively as new grounds of unpatentability presented for the first time in reply, and Exh. 1026 should be stricken from the record. FRE 401, 402 – Lack of Relevance. In addition to the fact that undesignated Board decisions in ex parte appeals have no precedential value in subsequent, unrelated matters, particularly adversarial proceedings with expert witnesses such as inter partes review (<i>see Ford Motor Co. v. Neo Wireless LLC</i>, No. IPR2023-00763, 2025 WL 3728020, at *15 (PTAB Sept. 3, 2025) (rejecting Petitioner’s reliance on non-precedential ex parte appeal – “The <i>McBrady</i> case cited by Petitioner is not a precedential decision but a routine ex parte appeal decision of a patent application.”))), and the fact that district courts have also questioned the precedential value of ex parte patent application proceedings in a collateral estoppel context as well (<i>see e.g. Realvirt, LLC v. Lee</i>, 179 F. Supp. 3d 604, 607 (E.D. Va. 2016), <i>aff’d sub nom., Realvirt, LLC v. Iancu</i>, 734 F. App’x 755 (Fed. Cir. 2018))), Petitioner here is relying on a party’s appeal brief as evidence notwithstanding the fact that the appeal brief pertains to an entirely unrelated matter, and thus, has
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	no evidentiary value or relevance to this proceeding. FRE 801, 802 – Hearsay. Exhibits A-G attached to Appellant’s Appeal Brief constitute hearsay, and/or multiple hearsay.
Exh. 1028 – Bonerge Brochure - Berberine and Dihydroberberine Ver-1.0, NF00034-NF00042 (attachment to NF00028) (HIGHLY CONFIDENTIAL – ATTORNEYS’ EYES ONLY; to be filed under seal)	FRE 401, 402 - Lack of relevance. Petitioner notes that Feng’s bioavailability data was “in vitro” (Paper 23 at 20) (“In vitro, they discovered that DHB’s internal absorption rate was five times greater than BBR’s.”), making it irrelevant to <i>whole body</i>, in vivo patent claims under consideration here: “administering, to an individual, a pharmaceutically effective amount of dihydroberberine” <i>See</i> Exh. 1001, p. 11 (claim 1), which claims the administering of dhBBR to an individual (a person), not in vitro. Petitioner’s assertion of confidentiality as to Exhibit 1028 (at the Attorneys’ Eyes Only level, no less) calls into question whether Exhibit 1028 should even be considered, and is even relevant, inasmuch as it does not appear to be a public document.
Exh. 1029	Limited Objection – FRE 401, 402 – Lack of Relevance. Exhibit 1029 is not relevant to the question of bioavailability or cardiovascular support inasmuch as it is not prior art,

	but dated August 31, 2026 as shown directly on the exhibit. The exhibit may be relevant to commercial success, and the nexus issue because “healthy metabolism” would naturally include healthy <i>glucose</i> metabolism. A standard biochemistry textbook such as Principles of Biochemistry by Lehninger, Nelson, and Cox (see attached) supports this notion inasmuch as it defines “metabolism” as “[t]he entire set of enzyme-catalyzed transformations of organic molecules in living cells; the sum of anabolism and catabolism” and “glycolysis” as “[t]he catabolic pathway by which a molecule of glucose is broken down into two molecules of pyruvate.”
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Date: September 8, 2026

Respectfully submitted,

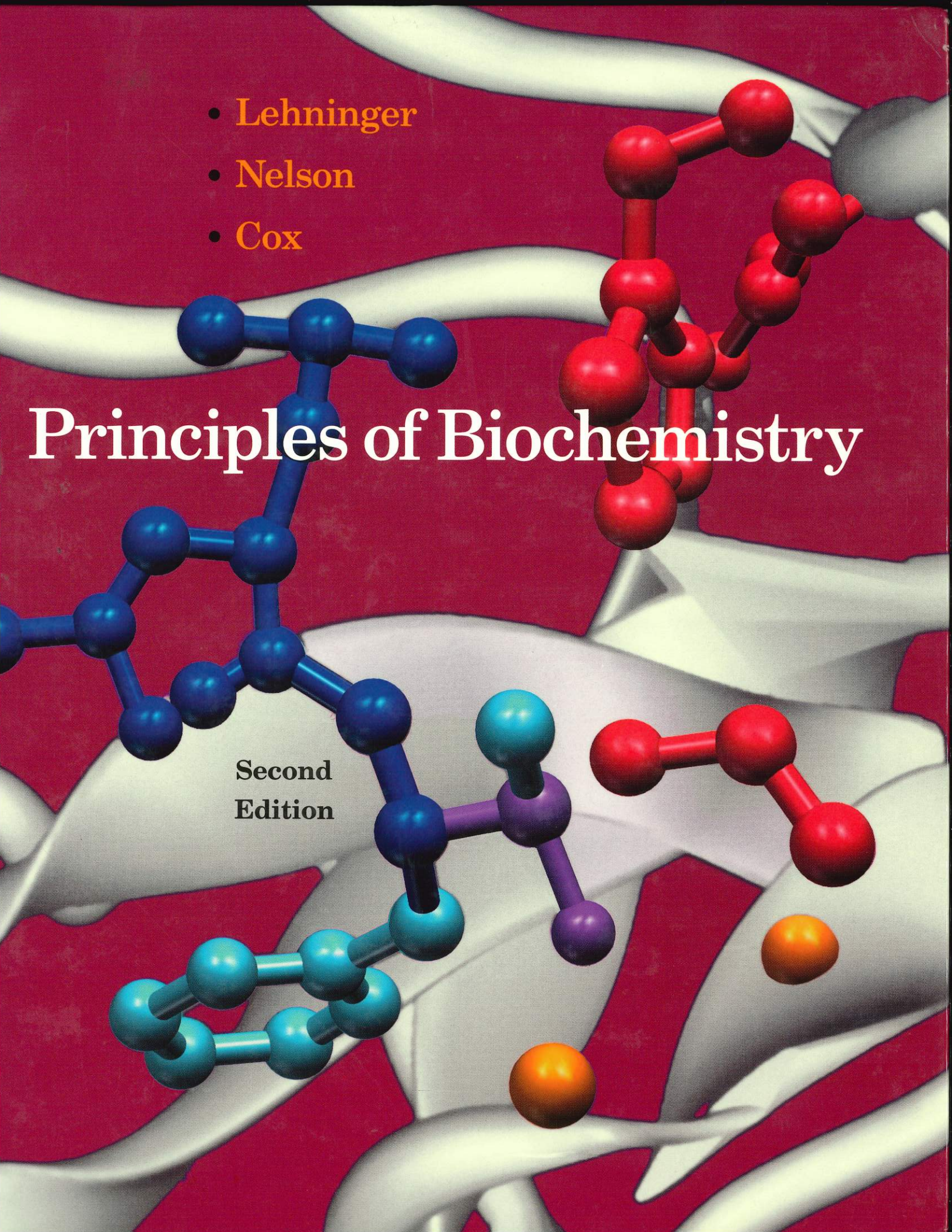
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- Lehninger
- Nelson
- Cox

Principles of Biochemistry

Second
Edition



Principles of Biochemistry

Second Edition

Albert L. Lehninger, David L. Nelson, and Michael M. Cox

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Cover: The active site of the proteolytic enzyme chymotrypsin, showing the substrate (blue and purple) and the amino acid residues (red and orange) critical to catalysis. Determination of the detailed reaction mechanism of this enzyme (described on pp. 223–226) helped to establish the general principles of enzyme action.

Frontispiece: A view of tobacco ribulose-1,5-bisphosphate carboxylase (rubisco). This enzyme is central to photosynthetic carbon dioxide fixation; it is the most abundant enzyme in the biosphere. Different subunits are shown in blues and grays. Important active site residues are shown in red. Sulfates bound at the active site (an artifact of the crystallization procedure) are shown in yellow.

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FAD (flavin adenine dinucleotide):

The coenzyme of some oxidation-reduction enzymes; it contains riboflavin.

fatty acid: A long-chain aliphatic carboxylic acid found in natural fats and oils; also a component of membrane phospholipids and glycolipids.

feedback inhibition: Inhibition of an allosteric enzyme at the beginning of a metabolic sequence by the end product of the sequence; also known as end-product inhibition.

fermentation: Energy-yielding anaerobic breakdown of a nutrient molecule, such as glucose, without net oxidation; yields lactate, ethanol, or some other simple product.

fibroblast: A cell of the connective tissue that secretes connective tissue proteins such as collagen.

fibrous proteins: Insoluble proteins that serve in a protective or structural role; contain polypeptide chains that generally share a common secondary structure.

fingerprinting: See peptide mapping.

first law of thermodynamics: The law stating that in all processes, the total energy of the universe remains constant.

Fischer projection formulas: See projection formulas.

5' end: The end of a nucleic acid that lacks a nucleotide bound at the 5' position of the terminal residue.

flagellum: A cell appendage used in propulsion. Bacterial flagella have a much simpler structure than eukaryotic flagella, which are similar to cilia.

flavin-linked dehydrogenases: Dehydrogenases requiring one of the riboflavin coenzymes, FMN or FAD.

flavin nucleotides: Nucleotide coenzymes (FMN and FAD) containing riboflavin.

flavoprotein: An enzyme containing a flavin nucleotide as a tightly bound prosthetic group.

fluid mosaic model: A model describing biological membranes as a fluid lipid bilayer with embedded proteins; the bilayer exhibits both structural and functional asymmetry.

fluorescence: Emission of light by excited molecules as they revert to the ground state.

FMN (flavin mononucleotide): Riboflavin phosphate, a coenzyme of certain oxidation-reduction enzymes.

footprinting: A technique for identifying the nucleic acid sequence bound by a DNA- or RNA-binding protein.

frame shift: A mutation caused by insertion or deletion of one or more paired nucleotides, changing the reading frame of codons during protein synthesis; the polypeptide product has a garbled amino acid sequence beginning at the mutated codon.

free energy (G): The component of the total energy of a system that can do work at constant temperature and pressure.

free energy of activation ($\Delta G^\ddagger$): See activation energy.

free-energy change (ΔG): The amount of free energy released (negative ΔG) or absorbed (positive ΔG) in a reaction at constant temperature and pressure.

free radical: See radical.

functional group: The specific atom or group of atoms that confers a particular chemical property on a biomolecule.

furanose: A simple sugar containing the five-membered furan ring.

fusion protein: (1) A family of proteins that facilitate membrane fusion. (2) The protein product of a gene created by the fusion of two distinct genes.

futile cycle: A set of enzyme-catalyzed cyclic reactions that results in release of thermal energy by the hydrolysis of ATP.



ΔG° : See standard free-energy change.

gametes: Reproductive cells with a haploid gene content; sperm or egg cells.

gangliosides: Sphingolipids, containing complex oligosaccharides as head groups; especially common in nervous tissue.

gel filtration: A chromatographic procedure for the separation of a mixture of molecules on the basis of size; based on the capacity of porous polymers to exclude solutes above a certain size.

gene: A chromosomal segment that codes for a single functional polypeptide chain or RNA molecule.

gene expression: Transcription and, in the case of proteins, translation to yield the product of a gene; a gene is expressed when its biological product is present and active.

gene splicing: The enzymatic attachment of one gene, or part of a gene, to another.

general acid-base catalysis: Catalysis involving proton transfer(s) to or from a molecule other than water.

genetic code: The set of triplet code words in DNA (or mRNA) coding for the amino acids of proteins.

genetic information: The hereditary information contained in a sequence of nucleotide bases in chromosomal DNA or RNA.

genetic map: A diagram showing the relative sequence and position of specific genes along a chromosome.

genome: All the genetic information encoded in a cell or virus.

genotype: The genetic constitution of an organism, as distinct from its physical characteristics, or phenotype.

geometric isomers: Isomers related by rotation about a double bond; also called cis and trans isomers.

germ-line cell: A type of animal cell that is formed early in embryogenesis and may multiply by mitosis or may produce, by meiosis, cells that develop into gametes (egg or sperm cells).

globular proteins: Soluble proteins with a globular (somewhat rounded) shape.

glucogenic amino acids: Amino acids with carbon chains that can be metabolically converted into glucose or glycogen via gluconeogenesis.

gluconeogenesis: The biosynthesis of a carbohydrate from simpler, noncarbohydrate precursors such as oxaloacetate or pyruvate.

glycan: Another term for polysaccharide; a polymer of monosaccharide units joined by glycosidic bonds.

glycerophospholipid: An amphipathic lipid with a glycerol backbone; fatty acids are ester-linked to C-1 and C-2 of glycerol, and a polar alcohol is attached through a phosphodiester linkage to C-3.

glycolipid: A lipid containing a carbohydrate group.

glycolysis: The catabolic pathway by which a molecule of glucose is broken down into two molecules of pyruvate.

glycoprotein: A protein containing a carbohydrate group.

glycosaminoglycan: A heteropolysaccharide of two alternating units: one is either *N*-acetylglucosamine or *N*-acetylgalactosamine; the other is a uronic acid (usually glucuronic acid). Formerly called mucopolysaccharide.

glycosidic bonds: Bonds between a sugar and another molecule (typically an alcohol, purine, pyrimidine, or sugar) through an intervening oxygen or nitrogen atom; the bonds are classified as *O*-glycosidic or *N*-glycosidic, respectively.

glyoxylate cycle: A variant of the citric acid cycle, for the net conversion of acetate into succinate and, eventually, new

motif involved in protein-protein interactions in many eukaryotic regulatory proteins; consists of two interacting α helices in which Leu residues in every seventh position are a prominent feature of the interacting surfaces.

eukotrienins: A family of molecules derived from arachidonate; muscle contractants that constrict air passages in the lungs and are involved in asthma.

levorotatory isomer: A stereoisomer that rotates the plane of plane-polarized light counterclockwise.

ligand: A small molecule that binds specifically to a larger one; for example, a hormone is the ligand for its specific protein receptor.

light reactions: The reactions of photosynthesis that require light and cannot occur in the dark; also known as the light-dependent reactions.

Lineweaver-Burk equation: An algebraic transform of the Michaelis-Menten equation, allowing determination of $V_{\max}$ and K_m by extrapolation of $[S]$ to infinity.

linking number: The number of times one closed circular DNA strand is wound about another; the number of topological links holding the circles together.

lipases: Enzymes that catalyze the hydrolysis of triacylglycerols.

lipid: A small water-insoluble biomolecule generally containing fatty acids, sterols, or isoprenoid compounds.

lipoate (lipoic acid): A vitamin for some microorganisms; an intermediate carrier of hydrogen atoms and acyl groups in α -keto acid dehydrogenases.

lipoprotein: A lipid-protein aggregate that serves to carry water-insoluble lipids in the blood. The protein component alone is an apolipoprotein.

low-energy phosphate compound: A phosphorylated compound with a relatively small standard free energy of hydrolysis.

lyases: Enzymes that catalyze the removal of a group from a molecule to form a double bond, or the addition of a group to a double bond.

lymphocytes: A subclass of leukocytes involved in the immune response. B lymphocytes synthesize and secrete antibodies; T lymphocytes either play a regulatory role in immunity or kill foreign and virus-infected cells.

lysis: Destruction of a cell's plasma membrane or of a bacterial cell wall, releasing the cellular contents and killing the cell.

lysogeny: One of two outcomes of the infection of a host cell by a temperate

phage. It occurs when the phage genome becomes repressed and is replicated as part of the host DNA; infrequently it may be induced, and the phage particles so produced cause the host cell to lyse.

lysosome: A membrane-bounded organelle in the cytoplasm of eukaryotic cells; it contains many hydrolytic enzymes and serves as a degrading and recycling center for unneeded components.



macromolecule: A molecule having a molecular weight in the range of a few thousand to many millions.

mass-action ratio: For the reaction $aA + bB \rightleftharpoons cC + dD$, the ratio: $\frac{[C]^c [D]^d}{[A]^a [B]^b}$.

matrix: The aqueous contents of a cell or organelle (the mitochondrion, for example) with dissolved solutes.

meiosis: A type of cell division in which diploid cells give rise to haploid cells destined to become gametes.

membrane transport: Movement of a polar solute across a membrane via a specific membrane protein (a transporter).

messenger RNA (mRNA): A class of RNA molecules, each of which is complementary to one strand of DNA; carries the genetic message from the chromosome to the ribosomes.

metabolism: The entire set of enzyme-catalyzed transformations of organic molecules in living cells; the sum of anabolism and catabolism.

metabolite: A chemical intermediate in the enzyme-catalyzed reactions of metabolism.

metalloprotein: A protein having a metal ion as its prosthetic group.

metamerism: Division of the body into segments; in insects, for example.

micelle: An aggregate of amphipathic molecules in water, with the nonpolar portions in the interior and the polar portions at the exterior surface, exposed to water.

Michaelis-Menten constant (K_m): The substrate concentration at which an enzyme-catalyzed reaction proceeds at one-half its maximum velocity.

Michaelis-Menten equation: The equation describing the hyperbolic dependence of the initial reaction velocity, V_0 , on substrate concentration, $[S]$, in many enzyme-catalyzed reactions: $V_0 = \frac{V_{\max}[S]}{K_m + [S]}$.

Michaelis-Menten kinetics: A kinetic pattern in which the initial rate of an enzyme-catalyzed reaction exhibits a hyperbolic dependence on substrate concentration.

microbodies: Cytoplasmic, membrane-bounded vesicles containing peroxide-forming and peroxide-destroying enzymes; include lysosomes, peroxisomes, and glyoxysomes.

microfilaments: Thin filaments composed of actin, found in the cytoplasm of eukaryotic cells; serve in structure and movement.

microsomes: Membranous vesicles formed by fragmentation of the endoplasmic reticulum of eukaryotic cells; recovered by differential centrifugation.

microtubules: Thin tubules assembled from two types of globular tubulin subunits; present in cilia, flagella, centrosomes, and other contractile or motile structures.

mitochondrion: Membrane-bounded organelle in the cytoplasm of eukaryotes; contains the enzyme systems required for the citric acid cycle, fatty acid oxidation, electron transfer, and oxidative phosphorylation.

mitosis: The multistep process in eukaryotic cells that results in the replication of chromosomes and cell division.

mixed-function oxidases (oxygenases): Enzymes, often flavoproteins, that use molecular oxygen (O_2) to simultaneously oxidize a substrate and a cosubstrate (commonly NADH or NADPH).

modulator: A metabolite that, when bound to the allosteric site of an enzyme, alters its kinetic characteristics.

molar solution: One mole of solute dissolved in water to give a total volume of 1,000 mL.

mole: One gram molecular weight of a compound. See Avogadro's number.

monoclonal antibodies: Antibodies produced by a cloned hybridoma cell, which therefore are identical and directed against the same epitope of the antigen.

monolayer: A single layer of oriented lipid molecules.

monoprotic acid: An acid having only one dissociable proton.

monosaccharide: A carbohydrate consisting of a single sugar unit.

mRNA: See messenger RNA.

mucopolysaccharide: An older name for a glycosaminoglycan.

multienzyme system: A group of related enzymes participating in a given metabolic pathway.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.105(b), the undersigned hereby certifies that a copy of this **PATENT OWNER NANJING NUTRABUILDING BIO-TECH CO., LTD.'S OBJECTIONS TO PETITIONER'S EVIDENCE SUBMITTED IN REPLY** has been served on September 8, 2026 upon the following litigation counsel via electronic means:

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Date: September 8, 2026

Respectfully submitted,

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