Nos. 2022-1594 & 2022-1653

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, UNIVERSITY OF VIENNA, EMMANUELLE CHARPENTIER,

Appellants,

v.

THE BROAD INSTITUTE, INC., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, PRESIDENT AND FELLOWS OF HARVARD COLLEGE,

Cross-Appellants.

On Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board, in Interference No. 106,115

RESPONSE AND REPLY BRIEF FOR APPELLANTS THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, UNIVERSITY OF VIENNA, EMMANUELLE CHARPENTIER

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ARGUMENT ON MAIN APPEAL

Broad's brief speaks most loudly through omission. Nowhere does Broad identify anything its "inventor," Zhang, contributed to the count. Nowhere does Broad address binding precedent holding conception is complete when the invention is ready for hand-off to skilled artisans for reduction to practice. Broad does not (and cannot) dispute that many labs reported promptly reducing to practice once CVC disclosed its invention. Nor does Broad address the cases of Alexander Graham Bell and others awarded patents for groundbreaking advances despite their own difficulties proving their inventions worked; it ignores entirely *Dolbear v. American Bell Telephone Co.*, 126 U.S. 1 (1888). And nowhere does Broad explain how the PTAB's bespoke written-description standard differs from the burden-to-persuade-skeptics standard Broad disclaims.

There is a reason neither Broad nor the PTAB identifies anything Zhang invented. Zhang learned of every feature of the count—***CVC's*** discovery of the necessary and sufficient components for CRISPR-Cas9 gene editing, ***CVC's*** then-still-unpublished single-guide RNA sequence, and their use for eukaryotic gene editing—when Zhang's collaborator, Marraffini, gave them to Zhang. That is why Broad cites Marraffini's ***email describing CVC's*** work as evidence of ***Zhang's*** conception. Zhang, like many others, then quickly reported implementing CVC's invention using routine prior-art methods. Broad's contention that Zhang became

the inventor by reducing CVC's invention to practice contravenes settled law. Especially where originality is contested, the patent goes to the inventor "who had the thought," not the mechanic who "merely made the test" to prove it worked. *Applegate v. Scherer*, 332 F.2d 571, 573-74 & n.1 (C.C.P.A. 1964).

This case is not about "substantial evidence." Broad.Br.1. It is about legal standards. Broad, like the PTAB, ignores the controlling, objective standard for conception. Conception is sufficiently firm and definite when the invention can be ***handed off to a skilled artisan*** for reduction to practice—regardless of whether ***the inventor*** succeeds. Broad ignores the controlling standard for written description, which does not require the patent to ***convince*** artisans the invention works. And Broad ignores the APA's requirement of reasoned decisionmaking. The so-called evidentiary "findings" Broad invokes rest on the legal errors Broad attempts to sidestep. Broad offers post-hoc rationales. But this Court cannot affirm on grounds the PTAB never gave.

Broad seeks to wrest credit for a world-changing invention from two Nobel Prize-winning women who did the inventive work—without identifying anything it contributed. Reversal is warranted.

I. THE PTAB'S CONCEPTION DECISION CANNOT STAND

A. The PTAB Failed To Apply Governing Law

This appeal is not about "substantial evidence," Broad.Br.40-41; it is about legal standards. The critical facts are not seriously disputed: Just months after CVC announced its invention, five labs reported reducing it to practice using prior-art techniques. CVC also succeeded within months, just weeks after retaining a different graduate student (of ***less***-than-ordinary skill) to re-run earlier tests. Zhang, meanwhile, claims conception on June 26, 2012, the very day he received an email summarizing ***CVC's*** unpublished work—Broad's only documentary evidence of ***Zhang's*** supposed "conception" of the count's single-guide RNA element. Broad.Br.17-18. Based on legal errors, the PTAB discarded that undisputed evidence as irrelevant.

1. Under the concededly "objective" standard, Broad.Br.2, 30, 35-36, 57, conception is complete when the inventor's idea is sufficiently "definite and permanent" that "***one of ordinary skill*** in the art ***could*** construct the apparatus without unduly extensive research or experimentation," *Sewall v. Walters*, 21 F.3d 411, 415 (Fed. Cir. 1994) (emphasis added). That is, conception is complete when the invention is "ready" for hand-off to the skilled mechanic, *Cameron & Everett v. Brick*, 1871 C.D. 89, 90 (Comm'r Pat.), when implementation does not require further "inventive acts," *Sewall*, 21 F.3d at 416. Thus, in *Dolbear*, the Supreme Court

awarded Bell his patent despite his inability to make the telephone work. The critical fact was that other skilled artisans, using his disclosures, could. CVC.Br.33-34. Broad never mentions, much less distinguishes, *Dolbear* or similar cases. CVC.Br.31-34, 38-44.

Seeking to justify the PTAB's exclusive focus on ***CVC's*** reduction to practice, Broad argues that the PTAB "applied the . . . 'without extensive research or experimentation' conception standard from *Burroughs*" *Wellcome Co. v. Barr Laboratories, Inc.*, 40 F.3d 1223 (Fed. Cir. 1994); it accuses CVC of departing from the standard pressed below, Broad.Br.57-60; *but see* Broad.Br.58 n.8. But saying that an invention may be reduced to practice "without extensive research or experimentation," *Burroughs*, 40 F.3d at 1228, with "only the exercise of ordinary skill," *id.* at 1231, "without any further exercise of inventive skill," *Mergenthaler v. Scudder*, 11 App. D.C. 264, 279 (1897), or that it is ready for hand-off to the "skilled mechanic," *In re Tansel*, 253 F.2d 241, 244 (C.C.P.A. 1958), are all different ways of saying the same thing: Conception is complete when "'the work of the inventor ceases and the work of the mechanic begins.'" *Mergenthaler*, 11 App. D.C. at 277. The absence of need for further invention means a skilled artisan can reduce to practice without "extensive" experimentation; the test looks beyond just the inventors' efforts.

Broad's suggestion that some cases overlook the "'without further invention' formulation," Broad.Br.58-60, misses the mark. In *Acromed Corp. v. Sofamor Da-*

nek Group, Inc., 253 F.3d 1371 (Fed. Cir. 2001), conception was complete because designing a spine plate was "not an ***inventive*** conception," but "'exercise of . . . normal skill.'" *Id.* at 1380 (emphasis added). In *Tansel*, conception was complete because all that remained "'belong[ed] to the department of construction, ***not invention***.'" 253 F.2d at 243-44 (emphasis added). Conceding that *Barba v. Brizzolara*, 104 F.2d 198 (C.C.P.A. 1939), applies the "'without further invention'" standard, Broad dismisses it as an originality contest. Broad.Br.58-59. But the same basic conception standard applies—and originality is at issue here too. *See* pp. 17-25, *infra*.

Broad must change the subject from the controlling standard, and focus solely on ***CVC's*** efforts in reducing to practice, for a reason: Broad cannot identify anything inventive Zhang (or others) added. *See* pp. 17-20, *infra*. But the test is whether "***one*** skilled in the art could understand the invention," such that only "ordinary skill remained to reduce it to practice." *Burroughs*, 40 F.3d at 1228, 1231 (emphasis added). Conception is complete if "one" skilled artisan can reduce to practice with ordinary skill—even if the inventor fails. *Dolbear*, 126 U.S. at 536; CVC.Br.33-34, 38-40. Whether the inventor's experiments "succeeded or failed, or even took place, does not determine whether conception was complete." *In re Jolley*, 308 F.3d 1317, 1325 (Fed. Cir. 2002).

2. The PTAB's disregard of that standard led it to discard robust evidence that CVC's conception was complete by June 2012:

- At least five labs (besides CVC) quickly reported reducing the invention to practice with routine methods following CVC's disclosure. CVC.Br.14-18. As this Court has observed, so many near-simultaneous reductions to practice are "objective evidence that persons of ordinary skill in the art understood the problem and a solution to that problem." *Regents of Univ. of Cal. v. Broad Inst., Inc.*, 903 F.3d 1286, 1295 (Fed. Cir. 2018).

- CRISPR scientists contemporaneously agreed that implementing CVC's invention in eukaryotes would be "straightforward" and "just a matter of trying," "requir[ing] only routine genome-editing techniques." Appx80003 (31:8-19); Appx80972 (¶21); CVC.Br.12. Clearly those "skilled in the art could understand the invention." *Burroughs*, 40 F.3d at 1228.

- Zhang insisted he "conceived" the invention on June 26, 2012—the day he learned of ***CVC's*** gene-editing system from Marraffini, Appx74903—and proclaimed success within weeks using a protein-expression vector from his published TALE work and a common RNA-expression vector borrowed from a neighboring lab, CVC.Br.16.

- CVC used materially the ***same*** methods as Zhang. If Zhang's method was operative, so was CVC's. CVC.Br.37.

Broad denies the PTAB refused to consider other labs' reported success. Broad.Br.34, 52-54. But Broad invokes the portion of the PTAB's opinion where the PTAB ***rejected*** other labs' "activities" as "'evidence of . . . conception.'" Broad.Br.52-53 (citing Appx179-180) (emphasis omitted). Broad does not defend the PTAB's reference to "*nunc pro tunc*" conception as justifying that result. CVC.Br.40. Instead, Broad repeats the PTAB's assertion that Zhang's activities did not "'inure'" to CVC and protests that Zhang and CVC "did not collaborate."

Broad.Br.53. But even non-collaborators' success can show conception is complete. *Dolbear*, 126 U.S. at 535-36.

3. Broad invents new rationales, asserting that two labs reporting success were not "independent of Broad." Broad.Br.56. The PTAB made no such finding, so Broad cannot defend the decision on that ground. *SEC v. Chenery Corp.*, 318 U.S. 80, 93-94 (1943). Broad cites no evidence those labs collaborated with Zhang on CRISPR-Cas9 gene editing. Indeed, all reported success using ***different*** (prior-art) techniques. CVC.Br.17-18. And "independence" is irrelevant; even "one" lab's success suffices. *Dolbear*, 126 U.S. at 536.

Broad says there is no evidence of "how these other labs conducted their research" and whether they had "only ordinary, as opposed to extraordinary, skill." Broad.Br.56-57. The PTAB never invoked that theory, again foreclosing it. *Chenery*, 318 U.S. at 93-94. Besides, CVC put the labs' work into evidence, Appx80300-80309; Appx53203-53206; Appx79244-79251; Appx15794-15807; Appx79062-79092; Appx79012-79061; Appx79217-79243; Appx47104-47127; offered expert analysis of that work, Appx80814-80817(¶¶99-104); and discussed it in briefs, Appx66888-66889; Appx81088-81090; Appx81100; Appx85658. Broad and the PTAB ignore it.

Several labs that reported reducing CVC's invention to practice, moreover, are involved in a string of interferences among themselves. Broad.Br.xiii-xiv.

Broad and the PTAB's standard would award the invention of the century to the lab that was quickest to reduce to practice. That cannot be correct. "Invention is not the work of the hands, but of the brain," *Edison v. Foote*, 1871 C.D. 80, 81 (Comm'r Pat.); patent law rewards "innovation," not "'the work of a mechanic,'" *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 330 (1945). The PTAB's erroneous test would reward speedy mechanical work over innovation.

4. Even examining only CVC's own experiments, alleged "extensive testing" would not disprove conception. *Rey-Bellet v. Engelhardt*, 493 F.2d 1380, 1387 (C.C.P.A. 1974); *Sewall*, 21 F.3d at 415 n.3. Conception may be complete even where "much patience and mechanical skill, and perhaps a long series of experiments" are needed to reduce to practice. *Cameron*, 1871 C.D. at 90. What matters is the "nature" of the experiments—whether they required "more than routine skill," *i.e.*, "inventive acts." *Rey-Bellet*, 493 F.2d at 1387; *Sewall*, 21 F.3d at 416. But the PTAB ignored the experiments' "nature." It refused to consider that, by June 2012, CVC planned to reduce its invention to practice with prior-art techniques; that CVC's plan never changed; and that CVC succeeded with the same design it started with. CVC.Br.13-14, 18-22; Nobel.Scientists.Br.10. Under the proper standard, that ***also*** proves CVC's conception was complete—CVC used only "routine skill" to reduce to practice. *Rey-Bellet*, 493 F.2d at 1387. The PTAB ***never*** found otherwise.

B. The PTAB Erroneously Demanded Certainty of Success

Broad concedes conception does not require inventors to ***know*** the invention will work. Broad.Br.60-61, 67; CVC.Br.41-44. That dooms the PTAB's decision, which demanded CVC have a system it "knew" would work. Appx161-162; Appx183; Appx155. Broad's insistence that the PTAB ***recited*** the correct standard, Broad.Br.60-61, cannot save a decision that ***applies*** the wrong one. This Court "determine[s] which legal standard the tribunal ***applied***, not which standard it recited." *Dell Fed. Sys., L.P. v. United States*, 906 F.3d 982, 992 (Fed. Cir. 2018).

The PTAB held that, "[t]o have conceived," the CVC inventors needed "a definite and permanent idea . . . of a system they ***knew*** would" cleave DNA "in a eukaryotic cell." Appx161-162 (emphasis added); *see* Appx183 (requiring plan to "achieve a ***functional*** . . . system" (emphasis added)). The PTAB rejected CVC's conception of microinjecting zebrafish embryos because it was "not persuaded the CVC inventors ***understood*** that reducing the invention to practice in zebrafish . . . required only routine skill by 28 June 2012"—*i.e.*, they did not ***know*** the June 28 methods ***would work***. Appx155 (emphasis added).

Broad dismisses those statements because some were made to "rebut[]" CVC's arguments. Broad.Br.60-61. But the PTAB applied the wrong standard in its affirmative analysis too. Appx155. And legal error is error wherever it appears.

C. Broad's Purported "Findings" Underscore the PTAB's Legal Errors

The supposed "findings" Broad invokes to defend the PTAB's decision are products of the very legal errors Broad seeks to sidestep. And many are not PTAB findings at all, but Broad's own (mistaken) creations.

1. *Broad's "Extensive Experimentation" Arguments Repeat PTAB Legal Errors (Putative Finding #1)*

Broad invokes the PTAB's finding that CVC engaged in a "'"prolonged period of extensive research, experiment, and modification,"'" deeming it "dispositive." Broad.Br.40-41. But the PTAB erred twice over in holding that alleged "extensive" experimentation defeated CVC's conception.

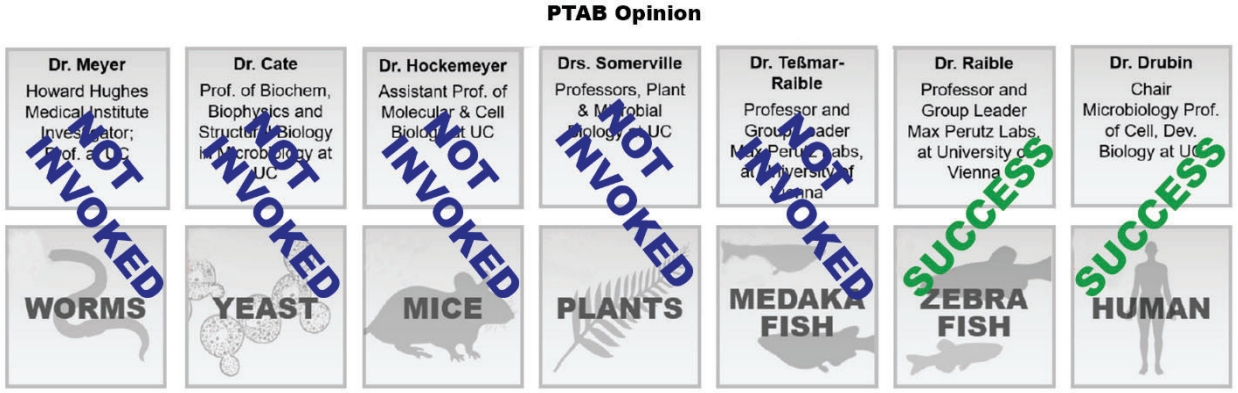
First, the proper standard asks whether a ***skilled artisan*** could succeed with ordinary skill, not whether ***the inventor did***. *See* pp. 3-8, *supra*. CVC's experiments thus are not "dispositive." And the PTAB erred in disregarding evidence that so ***many*** scientists reported reducing CVC's conception to practice so quickly with routine skill. *See* p. 6, *supra*. Focusing on CVC alone, Broad replicates the PTAB's error.[1]

[1] CVC had no such myopic focus below. Broad.Br.61-64. As the PTAB acknowledged, Appx179-180, CVC repeatedly invoked other artisans' reductions to practice, Appx66888-66889; Appx81089-81092; Appx85658-85659. CVC also emphasized artisans' testimony that implementation would be easy. Appx81090; Appx85657.

Second, even focusing on CVC's experiments, deeming them "extensive" is not enough. The PTAB had to consider the experiments' "nature"—whether they required "more than routine skill." *Rey-Bellet*, 493 F.2d at 1387. The PTAB never identified ***what*** about the experiments was non-routine and ignored ample evidence they ***were*** routine. *See* p. 8, *supra.*

Broad repeats the PTAB's erroneous assertion that CVC's collaborators were all "'of at least ordinary skill.'" Broad.Br.40. The CVC graduate students conducting experiments, Cheng and East-Seletsky, concededly were not skilled artisans. CVC.Br.19-20. Broad suggests (without evidence) that Cheng's advisor, Drubin, supervised Cheng. Broad.Br.41, 32. But the PTAB made no such finding. *See Chenery*, 318 U.S. at 93-94. Cheng—working in another lab in another building, Appx83481(310:1-6)—traded emails with Doudna and Jinek, Broad.Br.41, but Broad never explains how that makes Cheng a skilled artisan. The experiments promptly succeeded once moved to Doudna and Jinek's lab. Appx67520(¶15); Appx67397-67400(¶¶126-130).

Unable to defend the PTAB's reasoning, Broad invents new rationales. It invokes seven supposed efforts to reduce to practice, Broad.Br.32, 42-43, but the PTAB mentioned only two—and they succeeded.



Broad cannot defend the PTAB's decision by proffering different rationales. *Chenery*, 318 U.S. at 93-94.

For three of Broad's supposed "failures" (yeast, mice, plants), moreover, no experiments had even begun by October 2012. Appx88170. One (medaka) had indications of success. Appx68381. Two (zebrafish and human cells) succeeded. Appx67397-67400 (¶¶126-130); Appx67122-67123 (¶55). And CVC's system ultimately succeeded in worms. A. Friedland, et al., *Heritable Genome Editing in* C. elegans *via a CRISPR-Cas9 System*, 10(8) Nat. Methods 741 (2013), https://bit.ly/41ZPuwk. Those show conception ***was*** complete.

2. *Broad's "Incomplete Conception" Arguments Repeat PTAB Legal Errors (Putative Finding #2)*

Broad's second "finding" likewise repeats PTAB legal errors. Broad argues that CVC's experiments show "incomplete conception[]." Broad.Br.43-48. But conception is complete when the inventor has the idea of the structure ***of the invention***—the features ***in the count***—and an "operative method" of making it. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991).

Here, the invention is (1) a single-guide CRISPR-Cas9 complex; (2) comprising crRNA, tracrRNA, and Cas9; (3) in a "eukaryotic cell"; (4) "capable of cleaving" "target DNA." Appx1429-1430. It is undisputed that, before Broad's earliest asserted conception date, CVC had produced the complex; tested it *in vitro*; recited all elements in a patent application; and disclosed operative ways to implement it in eukaryotic cells—including microinjection and vector expression. *See* CVC.Br.4-10, 13-14, 18-22. Having structure and means ***is*** conception. *Amgen*, 927 F.2d at 1206.

Because conception must be evaluated "as of the date alleged," moreover, whether "subsequent testing succeeded or failed, or even took place," is not dispositive. *Jolley*, 308 F.3d at 1325; *see Burroughs*, 40 F.3d at 1233 (Lourie, J., concurring-in-part and dissenting-in-part); Regeneron.Br.9-13. Broad would disadvantage inventors who reduce their own inventions to practice compared to those who only file patents. *See Haskell v. Colebourne*, 671 F.2d 1362, 1365-66 (C.C.P.A.

1982) (disclosure sufficient for constructive reduction to practice shows conception); Nobel.Scientists.Br.13-15. And it would make conception a subjective inquiry into inventor confidence, contravening *Jolley* and *Burroughs*.

Broad invokes *Burroughs*' observation that "subsequent . . . experimentation" may undercut conception when it "so undermines the specificity of the inventor's ***idea*** that it is not yet a definite and permanent reflection of the ***complete invention***." 40 F.3d at 1229 (emphasis added). That at most means that, where the ***only*** evidence of reduction to practice is skilled-artisan struggles, the inventor's "idea"—the invention—may be incomplete. *Id.*; *see* CVC.Br.39-40. Here, that so many labs so quickly reported success, using conventional means, shows the invention was complete. CVC.Br.35-37. Refusing to look beyond the inventors' actions alone was legal error. *Dolbear*, 126 U.S. at 535-36.

Burroughs, moreover, asks whether "the inventor's ***idea***" is so "undermine[d]" that "***it***"—the inventive "***idea***"—is "not yet . . . definite and permanent." 40 F.3d at 1229 (emphasis added). That requires uncertainty about the "features" in the count; changes outside the count are irrelevant. *Tyco Healthcare Grp. LP v. Ethicon Endo-Surgery, Inc.*, 774 F.3d 968, 975 (Fed. Cir. 2014); *Sewall*, 21 F.3d at 416; *Barba*, 104 F.2d at 202. The PTAB found no uncertainty about the content of ***the count*** itself: a single-guide CRISPR-Cas9 complex, used to edit DNA in a eukaryotic cell. Appx1429-1430. The inventor statements Broad cites as showing

"lack of a plan," Broad.Br.44-48; *but see* CVC.Br.19-21, confirm the PTAB's error. None relates to the elements of the count; none can show relevant uncertainty. *Tyco*, 774 F.3d at 975.

Broad suggests CVC was "reconsidering" additional elements. Broad.Br.44, 63. Outside the count, those elements are irrelevant. *Tyco*, 774 F.3d at 975. The argument is also *Chenery*-barred: The PTAB never found CVC "reconsider[ed]" those elements. 318 U.S. at 93-94. And Broad is wrong. CVC did not "reconsider[]" codon optimization; it planned to codon optimize all along, Appx67293-67295(¶¶151, 155). CVC never changed promoters, Appx83083(91:1-92:10); Appx67283-67284(¶124); Appx67545-67546(¶¶90-92); never abandoned vector expression, CVC.Br.19-20; never changed its RNA design, CVC.Br.20. If CVC tweaked experimental conditions, *see* Broad.Br.44, the PTAB never found they were part of the count, *Tyco*, 774 F.3d at 975, or that they were "more than routine," *Rey-Bellet*, 493 F.2d at 1387; p. 8, *supra*; Nobel.Scientists.Br.8-10. Any supposed "modification" to unclaimed matters—routine ones at that—hardly undermines conception.

Broad also largely ignores CVC's plan to microinject the complex in zebrafish. The PTAB's conception decision cites no email concerning microinjection, and the PTAB refused to consider whether CVC's zebrafish experiments succeeded. Appx133. That is another failure of reasoning: Success, even if unrecognized,

proves earlier conception complete. *Univ. of Pittsburgh of Commonwealth Sys. of Higher Educ. v. Hedrick*, 573 F.3d 1290, 1298-99 (Fed. Cir. 2009).

3. *Broad's "Clear Plan" Argument Fails (Putative Finding #3)*

Broad cites the PTAB's purported finding that CVC lacked a "'clear plan'" because it merely "'hoped'" its system "'would work.'" Broad.Br.48 (emphasis omitted). Insofar as the PTAB denied conception because CVC "'hoped'" (but did not ***know***) its invention would work, Broad agrees that was error. *See* p. 9, *supra.* If the PTAB meant CVC did not have an "operative method of making" its invention, *Amgen*, 927 F.2d at 1206, that was unsupported: CVC planned to use both vector expression and microinjection. CVC.Br.13-14, 18-22; Appx65651; Appx691[00173]. CVC never changed course, and ample evidence proved those methods "operative." CVC.Br.12-22. Indeed, CVC's human-cell methods were materially ***the same*** as Zhang's, which the PTAB found operative. Appx181; CVC.Br.37. The PTAB disregarded that evidence based on its erroneous view that intermediating "doubts" and "failures" render clear plans—even when pursued to success—irrelevant. Appx158; CVC.Br.37-39.[2]

[2] The PTAB never determined CVC's inventors lacked credibility. Broad.Br.50-51. At most, it found isolated statements in Doudna's and Jinek's declarations did not "reflect" certain evidence the PTAB found relevant to its conclusion that CVC lacked a "plan." Appx155-156. CVC's conception case does not rest on those statements.

As to supposed "[o]bstacles" to reduction to practice, Broad.Br.48, the question is whether ***skilled artisans*** could supply a solution without inventive skill—not whether the inventors knew "the location of every nut, screw, and bolt." *Tansel*, 253 F.2d at 243-44 (artisan could identify appropriate circuit); *Barba*, 104 F.2d at 202 (artisan could mount air conditioner); *Acromed*, 253 F.3d at 1380 (artisan could design surgical plate); *Sewall*, 21 F.3d at 416 (artisan could design chip). The PTAB's departure from that standard led it to disregard overwhelming evidence, including reported success from lab after lab. Regardless, CVC's later success with its initial methods shows it knew how to overcome any "obstacles."

Broad's arguments about CVC's conception by March or April 2012, Broad.Br.48-50, are misdirected. On appeal, CVC need only show the PTAB erred in disregarding CVC's conception before the October 5 date the PTAB assigned Broad. Because CVC conceived by June 2012, whether documents show even earlier conception is irrelevant.

II. AWARDING THE INVENTION TO A COPYIST FLOUTS THE ORIGINALITY REQUIREMENT

A. Zhang Contributed Nothing

Broad, like the PTAB, identifies nothing in the count Zhang contributed. That is because Zhang got the ***entire*** count—every feature—from CVC's unpublished work through CVC's peer-reviewer, Marraffini. CVC.Br.15-17. Zhang then proved it worked using routine techniques. CVC.Br.16-17. That is copying, not invention.

CVC is not arguing that "sgRNA is the invention." Broad.Br.64. The ***count*** is the invention. And Zhang got ***every element of the count***—everything claimed as inventive—from CVC through Marraffini, not just sgRNA. Marraffini gave Zhang:

- CVC's discovery of the three necessary and sufficient components of the CRISPR-Cas9 DNA-cleavage complex, including tracrRNA, Appx80001-80003 (24:17-25:3, 27:4-16, 29:20-30:3);
- CVC's use of "pre-processed" RNA, bypassing the processing steps that had mired Zhang's own experiments, Appx77492;
- CVC's chimera A sgRNA sequence, copied from CVC's unpublished manuscript, Appx77492; Appx80005 (37:17-38:7); and
- the insight that CVC's invention would be "an important tool for genome editing in eukaryotes specifically," Appx80012 (68:13-21).[3]

Indeed, Zhang claimed conception on June 26, 2012, the day he got CVC's work from Marraffini. Broad.Br.17-18. Marraffini gave Zhang the whole invention.

Broad's view that Zhang need not have invented anything, Broad.Br.65-66, defies fundamental principles. Patents must be awarded to the "original inventor," not a "borrower or a copyist." 1 W. Robinson, *The Law of Patents for Useful Inventions* § 58 (1890); *see* U.S. Const. art. I, § 8, cl. 8. "[W]here the issue is originality," *MacMillan v. Moffett*, 432 F.2d 1237, 1240 (C.C.P.A. 1970), the question is not

[3] Broad's argument that Zhang got the chimera A sequence from CVC's "public disclosures," Broad.Br.65, is wrong: The sequence was copied from the then-unpublished Jinek 2012 manuscript. Appx80005 (37:17-38:7); CVC.Br.16.

"who merely made the test," but "who had ***the thought***," *Applegate*, 332 F.2d at 574 (emphasis added). Zhang cannot be deemed the inventor without identifying what he invented. Nor can Zhang have "solely conceived the invention" when he concededly got at least one "essential feature"—sgRNA—from CVC. *In re VerHoef*, 888 F.3d 1362, 1367 (Fed. Cir. 2018); *see* Broad.Br.17-18; Appx74903.

Merely "confirming the operability" of another's idea is not invention. *Burroughs*, 40 F.3d at 1230. That is why *Burroughs* awarded the patent to Burroughs Wellcome, which had the idea to use AZT to treat AIDS—not the scientists who "confirmed [its] operability." *Id.* That is why *Barba* awarded the patent to Brizzolara, who "had the idea" of mounting an air conditioner above the train car headroom, not Barba, who worked out "particular means" to mount it "without the exercise of invention." 104 F.2d at 200, 202. That is why *Applegate* awarded the patent to Scherer, who "had the thought" of using the particular chemical on lampreys—not Applegate, "who merely made the test" to prove efficacy. 332 F.2d at 574. And that is why this patent belongs to the CVC inventors, who conceived the Nobel Prize-winning single-guide CRISPR-Cas9 eukaryotic gene-editing complex—not Zhang, who merely reduced it to practice using ordinary skill.

Fundamentally, Broad (like the PTAB) repeats the error rejected in *Applegate* and *MacMillan*, equating reduction to practice with invention where originality is at issue. Zhang spent a year trying to solve a puzzle with the wrong pieces before

jettisoning his experiments, and claiming conception, ***the same day*** Marraffini slipped him the right pieces—every feature of the count—from CVC. CVC.Br.14-15; pp. 20-24, *infra*. The PTAB declared that Zhang's "success"—his reduction to practice—meant he "must have" invented something, without finding anything in the count that came from Zhang. Appx181-182.

But *Applegate* and *MacMillan* hold that, "where the issue is originality or derivation," reducing to practice ideas received from another is not invention. *MacMillan*, 432 F.2d at 1240; *Applegate*, 332 F.2d at 573-74. One must ask whether the party who first reduced to practice invented something, or whether it rapidly implemented another's idea with ordinary skill. *Id.* Rather than identify anything Zhang invented, the PTAB and Broad urge that CVC's efforts to reduce to practice—after its invention was communicated to Zhang—somehow destroy CVC's conception. But once an innovator communicates "the totality of the invention defined in the count"—"whether it be called a 'conception' or by any other name"—she is the inventor, regardless of who reduced to practice first. *Applegate*, 332 F.2d at 573. That is precisely what happened here.

B. Broad's Assertion that It Invented Everything Defies *Chenery* and the Record

1. *Zhang Did Not Invent CRISPR-Cas9 Gene Editing*

Broad paints ***Zhang*** as CRISPR's true inventor, arguing that Zhang understood the three components of the CRISPR-Cas9 DNA-cleavage complex before

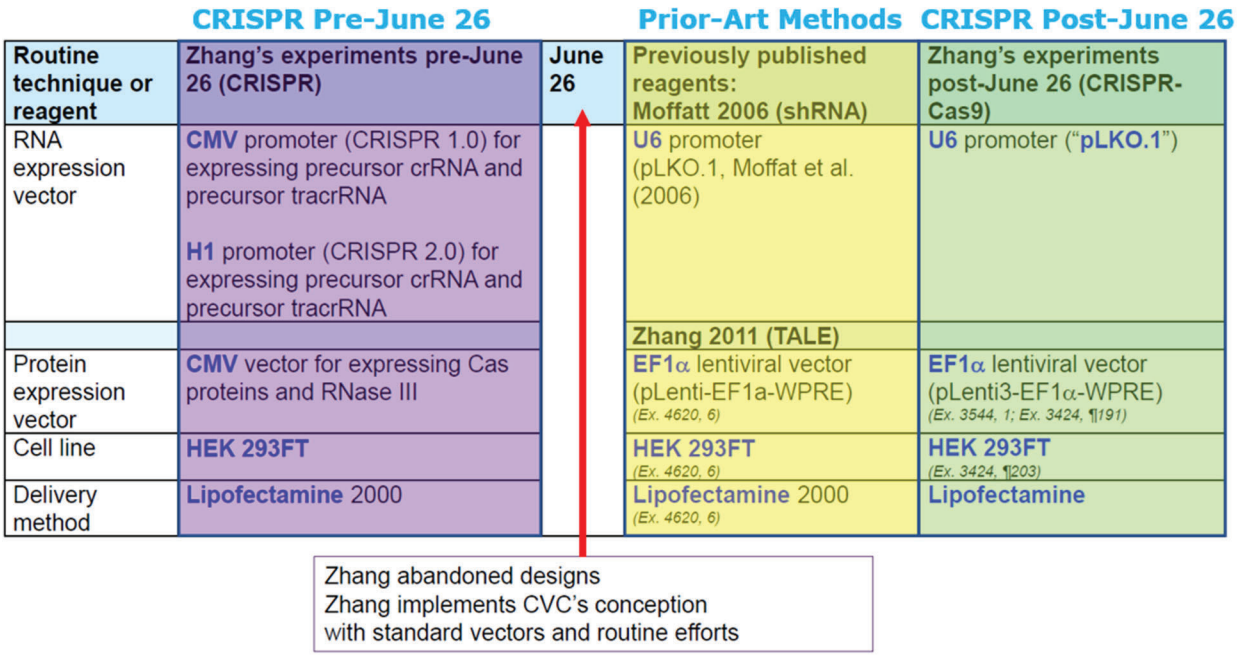
CVC's disclosure, reducing it to practice by "late 2011." Broad.Br.15-16. That argument is both *Chenery*-barred, 318 U.S. at 93-94, and flatly contradicted by the record.

The contention that Zhang "recognized" the role of tracrRNA in the CRISPR DNA-cleavage complex from a Charpentier paper ("Deltcheva") in 2011, Broad.Br.15, is nonsense. Deltcheva taught that tracrRNA was involved in crRNA ***pre-processing***, but dissociated from ***mature crRNA*** after processing. Appx13900. Contemporaneous reviews agreed. Appx13813; Appx13832. Only in 2012 did ***CVC*** announce that ***mature tracrRNA*** was critical to ***the final DNA-cleavage complex***. Appx5598-6000. If Zhang had "recognized" mature tracrRNA's role in the final DNA-cleavage complex in 2011, that would have been monumental—it was one of the "crucial discover[ies]" that won CVC the Nobel Prize. Appx57592. Yet there is no evidence Zhang told ***anyone*** about that supposed realization, or took ***any steps*** to confirm it (such as conducting experiments with processed RNA). *See* Appx5597-5603. Zhang never thought of linking tracrRNA and crRNA to form single-guide RNA—even though Broad says it would be trivial once one realized mature tracrRNA is part of the DNA-cleavage complex. Broad.Br.17-18; Appx75053-75054 (¶¶116-117). And if Zhang knew about mature tracrRNA's role in 2011, why did his collaborator, Marraffini, send him CVC's work in mid-2012 and tell him of its importance?

A December 2011 presentation by Zhang's lab shows tracrRNA ***absent*** from the cleavage complex. Appx76929. Zhang's January 2012 grant application proposed to "***[i]dentify*** the minimal set of genes and RNA elements" for "a functional CRISPR system," characterizing tracrRNA as "facilitat[ing] ***the processing*** of" crRNA. Appx77559 (emphasis added). From April 2011 through June 26, 2012, Zhang unsuccessfully tried to reproduce the natural CRISPR system using elements Deltcheva identified for crRNA ***pre-***processing (RNase III, unprocessed crRNA, and unprocessed tracrRNA)—***not*** mature tracrRNA in the cleavage complex. Appx13900; Appx80876-80900(¶¶A39-A78); Appx76451-76469. In June 2012, Zhang's lab still wondered what "other factors need to be identified in Type II CRISPR." Appx76469; Appx75051(¶111).

Broad's assertion that Zhang had a dual-guide system by "late 2011," Broad.Br.15-16, is similarly fanciful. The "late 2011" experiment Broad invokes lacked the ***mature*** tracrRNA critical to the gene-editing complex. Appx80876-80878(¶¶A39-A40). Zhang agreed the results were "nonspecific"—a failure. Appx79774(165:5-166:10); Appx76459-76460. Broad proclaims success based on an April 2012 picture of unidentified cells. Broad.Br.16; Appx75048-75049(¶107). But in May 2012, Zhang told Marraffini his lab had not produced "***any*** genome modification." Appx77488 (emphasis added).

Nor did Zhang use his prior work to reduce CVC's system to practice. *See* Broad.Br.18, 53-54. Before June 26, 2012, Zhang was using a CMV promoter to express Cas9 and RNase III, and a CMV or H1 promoter to express ***unprocessed*** RNAs (purple column below). Appx76454; Appx76464. The day he obtained CVC's invention from Marraffini, Zhang dumped those designs. He jettisoned RNase III; used an EF1α vector from his TALE experiments to express Cas9; and used a garden-variety RNA vector with a U6 promoter to express CVC's sgRNA (green column). CVC.Br.16. Both vectors were straight from prior art (yellow column), not Zhang's earlier failed CRISPR efforts (purple column). Appx77666-77667.



Appx88308 (blue headers added). That is why Zhang's only documentary evidence of conception on June 26, 2012, is Marraffini's email describing ***CVC's*** work. Broad.Br.17-18. Zhang invented nothing before June 26.

2. *Broad's New Theory Continues a Pattern of Revisionist History*

Broad's revisionist efforts reflect an unfortunate pattern. In 2014, to obtain claims involved in this interference, Broad told the PTO Zhang had successfully tested a CRISPR-Cas9 system that included "guide RNA"—defined to include ***tracrRNA***, Appx23532[0048]—in experiments performed in ***March 2011***. Appx75135-75136(¶¶5.1.4-5.1.5); Appx75026-75027(¶¶63-64). Zhang now admits he did not use ***any*** tracrRNA (even for pre-processing) until reading Deltcheva in ***April 2011***. Appx79752(78:12-17); Appx75030(¶70). Broad now abandons any claim of a March 2011 "success." Broad.Br.15-17.

In 2016, to obtain single-guide RNA claims involved in this interference, Broad told the PTO that Zhang's January 2012 grant application showed his "appreciation that a single RNA"—rather than separate crRNA and tracrRNA strands—could be "used as a guide in the CRISPR-Cas system." Appx46336(¶19); Appx44344. Broad now asserts the application shows a "dual-molecule RNA system," Appx75040(¶89); Appx17332-17333, and admits Zhang learned of single-guide RNA on June 26, 2012. Broad.Br.17-18. Broad's description of pre-June-

2012 material as showing "appreciation" that "a single RNA can be used as a guide" was false.

After a decade of patent prosecution, a prior interference, and an appeal to this Court, Broad finally revealed—halfway through this second interference—that Zhang learned of CVC's invention, including its sgRNA sequence, from Marraffini. Broad concealed that for years. It resisted discovery even after the Marraffini email was revealed. Appx78855-78859. Broad's assertions that Zhang invented everything cannot be credited, let alone for the first time on appeal.

III. THE PTAB'S DECISIONS FAIL APA REVIEW

The PTAB's decisions are inconsistent with the APA's promise of reasoned decisionmaking. CVC.Br.47-55. Broad's contention that CVC failed to argue prejudice, Broad.Br.66, is incorrect. CVC argued it would have prevailed absent those errors. CVC.Br.47-55. Errors that "call[] into question" the agency's conclusions are necessarily "harmful," *In re Chapman*, 595 F.3d 1330, 1339 (Fed. Cir. 2010), so "nothing further need be said," *Shinseki v. Sanders*, 556 U.S. 396, 410 (2009).

A. The PTAB's "Must Be Differences" Logic Is a Fallacy

The PTAB deemed Zhang the inventor, not because it could identify anything Zhang contributed, but because there supposedly "must have been differences" between his efforts and CVC's given that Zhang succeeded while one CVC graduate student didn't. Appx181.

That makes no sense. The PTAB failed to identify any inventive differences between what CVC conceived and what Zhang did. Broad argues that the PTAB identified "technical" differences in the systems. Broad.Br.69-70. The one purported difference the PTAB identified—the U6 promoter—was no difference. Broad concedes CVC ***and*** Zhang used that promoter. CVC.Br.48-49; Broad.Br.70-71. A must-have-been-differences theory without any differences cannot stand. *Morall v. DEA*, 412 F.3d 165, 178 (D.C. Cir. 2005).

Broad nowhere defends the PTAB's refusal to consider obvious alternative explanations. The PTAB never considered that graduate students performed CVC's "failed" experiments; that random chance and low efficiency produce discrepancies in detecting results; or that many of the supposed "failures" were attempts to achieve something beyond the count. CVC.Br.49-50; Nobel.Scientists.Br.7-8. Leaving "obvious alternative[s]" unaddressed violates the APA. *Dist. Hosp. Partners, L.P. v. Burwell*, 786 F.3d 46, 59 (D.C. Cir. 2015).

Rather than address those errors, Broad obfuscates. It argues that CVC "never disputed" the existence of "technical differences." Broad.Br.70. Not so. CVC repeatedly explained that the systems were the same—that Zhang "did not innovate" because he got the invention from CVC. Appx81090-81100.

Broad conceded that Zhang's "adaptations" and "individual technique[s]" were routine. Appx85770(30:8-21). While Broad disputes that characterization as

"unfathomable," Broad.Br.70, CVC describes Broad's position as Broad does—that Broad admitted each technique was "individually" routine and claimed inventiveness only in "selection and combination." *Compare* CVC.Br.48, *with* Broad.Br.70. Regardless, CVC used the ***same*** techniques Zhang did. If there were differences, the PTAB and Broad don't identify them. Nor are any in the count.

B. Broad Cannot Paper over the PTAB's Failure To Consider Contrary Evidence

The APA requires agencies to explain their decisions to consider one set of facts but not others. *Princeton Vanguard, LLC v. Frito-Lay N. Am., Inc.*, 786 F.3d 960, 970 (Fed. Cir. 2015). Broad never defends the PTAB's unexplained choices.

The PTAB ignored that CVC reduced its invention to practice as it originally proposed. CVC.Br.51. Broad repeats the PTAB's conclusory assertion that CVC engaged in "extensive" modifications. Broad.Br.62-63, 69. But the PTAB never identified any modifications to the inventive idea in the count, much less non-routine ones. *See* pp. 13-16, *supra*. Broad does not either. Nor do contemplated modifications change that CVC ultimately succeeded using the same methods CVC initially envisioned.

Broad likewise cannot defend the PTAB's other failures of reasoning, from disregarding five labs' prompt reports of successful reductions to practice following CVC's announcements, to failing to explain why it credited evidence of some subjective beliefs but not others, or its self-contradiction regarding certainty.

CVC.Br.50-51. Broad's response that the CVC inventors lacked a "plan," Broad.Br.69, is irrelevant and wrong, *see* pp. 15-16, *supra.* Most fundamentally, neither the PTAB nor Broad answers why, in this art, four months of experimentation by graduate students is "excessive" or "undue," much less reflects a need for further invention. CVC.Br.50-52.

C. The PTAB's Analysis of Microinjection Underscores the APA Violations

The PTAB never identified actual barriers to implementing CVC's invention through microinjection. CVC.Br. 52-55. Broad argues the PTAB was ***not required*** to address microinjection because the record supposedly shows microinjection did not "overcome the hurdles to eukaryotic uses." Broad.Br.71-72. But the PTAB's decision stands or falls on the PTAB's analysis, not Broad's after-the-fact rationalizations. And the record amply shows that microinjecting a pre-formed complex into rapidly dividing cells obviates Broad's litigation-inspired "obstacles." CVC.Br. 53. The APA required the PTAB to do the analysis. *Provisur Techs., Inc. v. Weber, Inc.*, 50 F.4th 117, 123-24 (Fed. Cir. 2022).

It did not. And Broad provides no response at all on that or other failures of reasoning. *E.g.*, CVC.Br.53-54 (PTAB never addressed whether CVC's microinjection experiments succeeded); CVC.Br.54 (PTAB never explained why artisans might doubt efficacy of microinjection); CVC.Br.54-55 (PTAB erroneously stated

it had considered and rejected that P1 described microinjection). Broad ignores those errors because it cannot defend them.

IV. BROAD IGNORES THE LEGAL ERRORS REGARDING WRITTEN DESCRIPTION

P1 describes the structure of the CRISPR-Cas9 complex and routine techniques to implement it in eukaryotes. It correctly explains why the invention works. Those descriptions amply satisfy the written-description requirement, particularly in an interference on a composition count. CVC.Br.55-60.

A. Broad Cannot Explain How—Under the Correct Standard—P1's Disclosures Lack Written Description

Broad never disputes that P1 describes all the count's components, with experimental data proving the complex cleaves DNA. CVC.Br.56-57. It includes 21 claims for cleaving target DNA in eukaryotic cells, identifies eukaryotic target cells, and explains why the complex works in eukaryotes. CVC.Br.57. And P1 correctly tells artisans only well-known techniques are needed to practice the invention in eukaryotes. Appx646[001]; Appx691[00173]-[00174].

Broad never argues that P1 failed to tell the world what CVC "claims as [its] own invention." *Evans v. Eaton*, 20 U.S. (7 Wheat.) 356, 434 (1822). Anyone reading P1 could "'visualize or recognize the identity'" of CVC's claimed invention. *Alcon Rsch. Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014). Anyone reading P1 could see CVC "had in mind"—that it "possess[ed]"—"the

invention as claimed." *Crown Packaging Tech., Inc. v. Ball Metal Beverage Container Corp.*, 635 F.3d 1373, 1380-81 (Fed. Cir. 2011).

Broad insists the PTAB recited the correct written-description standard. Broad.Br.75-76. But this Court considers the standard the PTAB ***applied***. *Dell*, 906 F.3d at 992. The PTAB confessed its decision "hinge[s] on the lack of a working example" in eukaryotes and lack of "expectation of success." Appx103. The critical difference between P1 and P3 was that the latter included a working eukaryotic example. CVC.Br.64. Broad, like the PTAB, faults P1 ***only*** because it lacks "a working eukaryotic example." Broad.Br.74.

But written description "is not about whether the patentee has proven to the skilled reader that the invention works." *Alcon*, 745 F.3d at 1191. It "does not demand either examples or an actual reduction to practice." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010) (en banc). An inventor need not even "understand or be able to state the scientific principles underlying his invention." *Diamond Rubber Co. v. Consolidated Rubber Tire Co.*, 220 U.S. 428, 435-36 (1911). ***Convincing*** others the invention will work is not part of written description.

Broad's one-sentence misdescription of *Ariad*, Broad.Br.76, illustrates the PTAB's error. *Ariad* rejected the notion that "examples or an actual reduction to practice" are necessary. 598 F.3d at 1352. It hinged on failure to ***describe*** the ***substances*** that "achieve[d] the desired [claimed] result," a "gaping hole[]" in the

disclosure. *Id.* at 1341, 1358. Here, P1 describes the CRISPR-Cas9 complex itself and what artisans need (routine techniques) to use it in eukaryotes. CVC.Br.56-60.

Broad's distortion of *Alcon,* Broad.Br.76, is unavailing. Like the patent there, P1 ***includes*** experimental data. Appx713-714[00248]-[00251]. That P1 lacks "data proving" the invention works is "irrelevant . . . as a legal matter" because it ***describes*** the claimed invention. 745 F.3d at 1190. The PTAB's decision contravenes *Alcon*'s rule that written description is "not about whether the patentee has proven to the skilled reader that the invention works." *Id.* at 1191.

The PTAB insisted P1 must provide "specific instructions or conditions," or state none are necessary. Appx91. But it makes no sense to require that patentees, after providing instructions, say no further instructions are necessary. CVC.Br.65. Broad offers no answer. Regardless, P1 satisfies that made-up standard by telling artisans that "well-known techniques" used successfully with prior-art systems, like TALENs and ZFNs, could be used for the CRISPR-Cas9 system too. Appx691[00173]-[00174]; Appx646[0001]-[0003].

Broad's insistence that the art is "unpredictable and nascent," Broad.Br.75-76, changes nothing. P1 explicitly describes every purportedly "nascent" or "unpredictable" aspect of the count—the CRISPR-Cas9 complex's components and exact sgRNA sequence. CVC.Br.8-10. The rest was well-known and routine. As P1 ***correctly*** and ***explicitly*** teaches, artisans needed only use well-known and routine

methods they successfully used with TALENs and ZFNs. CVC.Br.8-10, 56-60. Moreover, unpredictability is typically relevant when determining whether a patent's disclosure supports the full ***scope*** of a broad genus where each claimed embodiment is ***not*** explicitly described. *Capon v. Eshhar*, 418 F.3d 1349, 1358-60 (Fed. Cir. 2005). In an interference on a composition count, the patent need only describe "'one embodiment within the scope of the count.'" *Falkner v. Inglis*, 448 F.3d 1357, 1362 (Fed. Cir. 2006). P1 does that, leaving nothing for prediction.

B. Broad's "Substantial Evidence" Argument Is a Strawman

1. Broad argues that "substantial evidence" supports the PTAB's "finding" that artisans would have rejected P1's disclosures without "eukaryotic experiments or specific instructions." Broad.Br.77-82. But written description is "an objective inquiry into the four corners of the specification." *Ariad*, 598 F.3d at 1351. And patents need not ***convince*** skeptical artisans the invention works when they describe the invention ***and*** teach that only well-known techniques are required. CVC.Br.61-66. Whether artisans are convinced is irrelevant. CVC.Br.65-66.

Broad's reliance on supposed prior failures with Group II introns, Broad.Br.79, is unavailing. P1 directs artisans to TALENs and ZFNs, which had been successfully implemented in eukaryotes. Appx646[0001]-[0003]; Appx67678-67679(¶137). P1 ***correctly*** directs artisans to ***those*** well-known tools and methods to implement CRISPR-Cas9 in eukaryotes, Appx679[00127]; Appx685[00152];

Appx691-693[00173]-[00178], not Group II introns. The many labs that reported reducing the invention to practice looked to those well-known tools, not Group II introns. CVC.Br.17-18. Broad cannot go ***beyond*** the four corners of the patent to manufacture obstacles in defiance of the patent's directions. *See Ariad*, 598 F.3d at 1351.

Nor can Broad rely on other supposed "obstacles" like chromatin access, codon optimization, and PAM sequences. Broad.Br.77-82. Pointing to those hypothetical obstacles merely repeats the PTAB's legal error—discarding P1's ***disclosures*** for speculation about reasons why artisans might not ***believe*** those disclosures. CVC.Br.63-64. Regardless, chromatin access is no obstacle. CVC.Br.53. Nor is codon optimization or PAM—P1 addresses codon optimization and depicts known PAM sequences adjacent to the target sequences. CVC.Br.59-60.

Finally, Broad argues that the CVC inventors' expressions of scientific caution—what Broad calls self-doubt—trump P1's disclosures. Broad.Br.80. But private communications outside the patent are ***never*** relevant to written description; the inquiry is confined to the patent's four corners. No authority suggests that inherent scientific uncertainty or subjective doubt somehow renders the specification's ***correct*** description of the invention inadequate. Such a rule would award patents only to those sufficiently arrogant to never confess doubt.

2. Broad's invocation of "substantial evidence" is ironic: Broad concealed critical evidence during the prior interference (including the appeal to this Court) and first half of this interference. It was not until ***after*** the PTAB's decision on written description that Broad finally confessed that Marraffini—a reviewer on CVC's paper—gave Zhang CVC's invention, including its sgRNA sequence. *See* pp. 17-18, *supra*; CVC.Br.15-16.

Before that evidence came to light, Broad persuaded the PTAB that P1's disclosures were insufficient because supposed impediments might cause artisans to doubt CVC's complex would work. Appx87-96. But Marraffini (and others) did not doubt it would work; he told Zhang it would. CVC.Br.15-16. Zhang had no doubts. He claimed conception the day he received Marraffini's email. Appx74872. Zhang's (and everyone else's) experiments then proved there were no barriers to implementation in eukaryotes. Broad's hypothesized uncertainties were just that—hypothesized. And Broad knew it all along. The PTAB's decision must be overturned.

CONCLUSION

The PTAB's judgment should be reversed.

RESPONSE TO CROSS-APPEAL

Before the PTAB, Broad moved to (1) expand the interference count beyond ***single-guide*** RNA CRISPR-Cas9 systems or, alternatively, (2) ***remove certain claims*** from the interference. The PTAB properly rejected each of Broad's motions on multiple, independent grounds. Broad's cross-appeal, however, challenges only one ground for each decision, ignoring alternative grounds. That dooms the cross-appeal. A party appealing only one of multiple, independent grounds for decision has failed to show an entitlement to relief. Nor may that party challenge omitted grounds for the first time on reply.

Broad's challenge lacks merit regardless. Broad argues the PTAB erred in construing "guide RNA" in Broad's claims to mean "single-guide RNA." The specifications of Broad's own patents, however, explicitly define "guide RNA" as "single guide" RNA. They use singular language, excluding multiple-molecule configurations. Neither Broad's isolated counterexamples, nor its appeal to a single prior-art reference, overcome the specifications' text.

COUNTER-STATEMENT OF ISSUES PRESENTED ON CROSS-APPEAL

1. Whether Broad's challenge to the PTAB's denial of Broad's Motions 2 and 3 must be rejected because Broad failed to challenge the PTAB's independently sufficient grounds for denying those motions.

2. Whether the PTAB correctly construed Broad's claim term "guide RNA" in denying Motions 2 and 3.

COUNTER-STATEMENT OF THE CASE ON CROSS-APPEAL

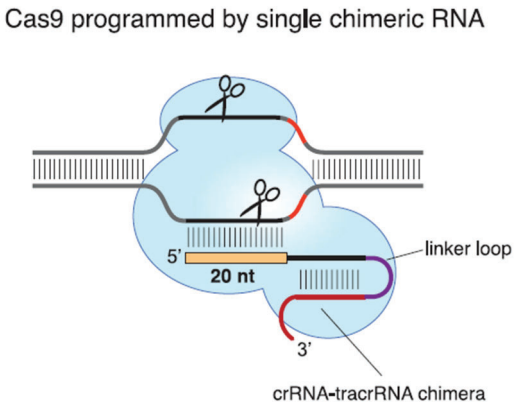
Broad's cross-appeal concerns the scope of the interference proceedings below. Broad insists the PTAB abused its discretion (1) in refusing to expand the interference beyond "single-guide" CRISPR-Cas9 systems and (2) in identifying which of Broad's claims should be included in the interference.

I. THE PTAB DECLARES A SINGLE-GUIDE INTERFERENCE

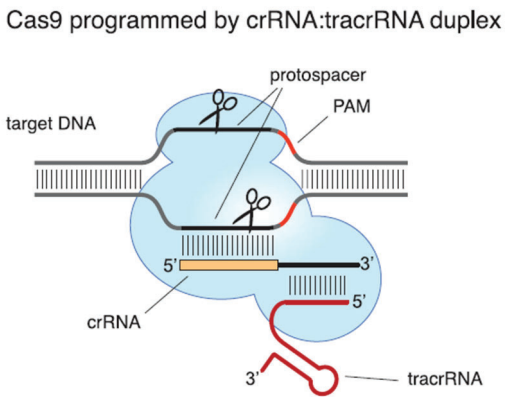
In conducting interferences, the PTAB assesses which party was the first to invent the subject matter recited in the "interference count." That count is the PTAB's "description of the interfering subject matter that sets the scope of admissible proofs on priority." 37 C.F.R. § 41.201. This cross-appeal concerns whether the PTAB was permitted to adopt an interference count addressing the invention of a ***single-guide*** CRISPR-Cas9 gene-editing system in eukaryotic cells, or whether it was required to adopt a "generic" count that also includes ***dual-guide*** (or "dual-molecule") configurations.

In a "single-guide" (or "single-molecule") CRISPR system, the tracrRNA and crRNA components are linked to form a single RNA molecule. *See* CVC.Br.6; Appx1429-1430. By contrast, in a "dual-guide" (or "dual-molecule") configuration,

the tracrRNA and crRNA are separate RNA molecules. Appx16. The two configurations are illustrated below:



Single-guide RNA



Dual-guide RNA

Appx5602. A so-called "generic" count would encompass both configurations. Appx18.

The PTAB declared this interference with a single-guide count. Appx118. The PTAB designated specific claims from each party's patents and patent applications as "corresponding" to that count (and thus involved in the interference). Appx1432-1433. A claim "corresponds to a count" if the count, treated as prior art, "would have anticipated or rendered obvious the subject matter of the claim." 37 C.F.R. §41.207(b)(2). In an interference, all claims designated as "corresponding" to the count "are presumed to stand or fall together" for purposes of priority and derivation. *Id.* §41.207(b)(1).

II. THE PTAB REJECTS BROAD'S MOTIONS TO REPLACE THE SINGLE-GUIDE COUNT WITH A GENERIC COUNT AND TO DE-DESIGNATE VARIOUS BROAD CLAIMS

During the interference, Broad moved to broaden the count to include both single-guide RNA ***and*** dual-guide RNA. In that motion ("Motion 2"), Broad asserted that the single-guide count did not reflect the "full scope of the interfering subject matter" because some of its involved claims—particularly those reciting "guide RNA"—do not require a particular RNA configuration. Appx36-39. Broad asked the PTAB to broaden the count to a "generic" count that did not specify the RNA configuration. Appx33-35. Broad also filed a contingent motion ("Motion 3") asking that, if the single-guide count were retained, Broad's allegedly generic claims be de-designated and removed from the interference. Appx41-42.

A. The PTAB Denies Broad's "Motion 2" To Replace the Single-Guide Count with a Generic Count on Two Grounds

The PTAB denied Broad's "Motion 2" on two, independent grounds. Appx33-41.

First, although Broad had argued for a count that was generic as to RNA configuration, Broad's proposed count differed from the PTAB's existing single-guide count in additional, important ways. Appx34-35. For example, Broad's proposed count was "directed to a method," whereas the PTAB's count was "directed to a system or a eukaryotic cell." Appx35. Broad's count eliminated the requirement that tracrRNA be present in the DNA-cleavage complex. Appx47666. And it dis-

pensed with the requirement that the cleavage complex cause the "alter[ation]" of "at least one gene product," Appx47664-47665; Appx47669. Broad did not explain why those additional changes were appropriate or necessary. Appx35.

The PTAB held that those unexplained, additional changes themselves were independent grounds for denying Broad's motion to substitute its proposed "generic" count for the existing single-guide count. Appx34-35. The PTAB explained that a party seeking to change the count must show a "compelling reason to do so." Appx33. Broad, the PTAB pointed out, proposed—without justification—several modifications unrelated to RNA configuration. Appx35. Broad "d[id] not explain why these other changes [were] necessary," and the PTAB was not inclined to "make a change in the count 'for change's sake.'" Appx35 (quoting *Louis v. Okada*, 59 U.S.P.Q.2d 1073, 1076 (B.P.A.I. 2001) (precedential)). The PTAB denied Broad's Motion 2 on "th[at] basis ***alone***." Appx35 (emphasis added).

Second, in the alternative, the PTAB held that expanding the count was unnecessary. Appx35-41. The PTAB disagreed with Broad's argument that the "'vast majority'" of Broad's claims in the interference were generic. Appx37-39. Broad argued that its claims reciting "guide RNA" were generic, but the PTAB found that "guide RNA" meant ***single-guide*** RNA. Appx14-33. The PTAB then held that Broad's Motion 2 "fail[ed] to identify" any other generic claims. Appx39.

Because Broad's motion identified no generic claims, the PTAB held that a broader count was not needed. Appx36-41.

B. The PTAB Rejects Broad's Alternative "Motion 3" To De-Designate Its Supposedly Generic Claims

At the same time it moved to broaden the count, Broad filed a separate, contingent motion (Motion 3). Broad requested that, if Motion 2 were denied, the PTAB de-designate and remove Broad's purportedly generic claims from the interference.[4] According to Broad, such "'generic'" claims did not "'correspond[] to'" the single-guide count. Appx41. Nearly all the claims Broad argued were "generic" for purposes of Motion 3, however, recite "guide RNA," which the PTAB construed as encompassing only single-guide RNA. Appx44. Claims 15 and 26 of the '713 patent were the only two claims Broad argued were "generic" that do not recite "guide RNA." Appx45-46.[5]

To demonstrate that claims do not "correspond[] to" a count, a party must show that the count, if "treated as prior art," would not "anticipate[]" those claims or "render[]" them "obvious." 37 C.F.R. §41.207(b)(2). Broad thus had to show

[4] Broad asked the PTAB to de-designate Broad's "generic" claims ***only***, Appx17344, even though CVC also had generic claims involved in the interference. CVC argued that the PTAB could not grant Broad's request without also de-designating CVC's generic claims. Appx48273.

[5] The PTAB considered claims 15 and 26 for Motion 3 only, Appx45-46; it declined to consider them for Motion 2 because Broad failed to timely raise them in that motion, Appx39 (citing 37 C.F.R. §§41.121(b), 41.122(b)).

that the PTAB's single-guide count, treated as prior art, would not anticipate or render obvious the generic claims; in other words, the generic claims would have to be separately patentable over single-guide claims. Appx43.

Although Broad (as the movant) had the burden of proof, 37 C.F.R. §41.208(b), Broad did not affirmatively argue that the generic claims would be patentable over the single-guide count. Appx47-53. Instead, Broad "assume[d]" that, if the PTAB denied Motion 2, it would do so by finding that the single-guide and generic RNA configurations were "separate patentable invention[s]," establishing (in Broad's view) lack of correspondence. Appx17327.

The PTAB rejected Broad's request. Appx53. It held that Broad's claims reciting "guide RNA" did not need to be de-designated from the count because that term meant single-guide RNA. Appx44. The PTAB recognized that Motion 3 targeted two claims for de-designation that do not recite the term "guide RNA." Appx47. And it found that those claims—15 and 26 of the '713 patent—***were*** generic. Appx47. But Broad failed to make its case even as to those claims because it made no "clear argument" that generic claims do not "correspond[ ] to" the single-guide count. Appx52. Broad simply did not argue that a single-guide count, treated as prior art, would not anticipate or render obvious a "generic" claim.

Further, the PTAB observed, Broad's argument rested on a faulty assumption. Broad "assume[d]" the PTAB would deny Motion 2 ***because*** single-guide and

generic CRISPR-Cas9 were "separate[ly] patentable," Appx17327 (emphasis omitted), but the PTAB did not invoke that rationale, Appx43. Given Broad's failure to argue a lack of claim correspondence under 37 C.F.R. §41.207(b)(2), the PTAB found Broad "failed to meet its burden of showing that these claims were not properly designated as corresponding to Count 1." Appx52.

SUMMARY OF ARGUMENT

I. The PTAB denied Broad's Motions 2 and 3 on multiple, independent grounds. Broad's opening brief, however, challenges the same single ground for each motion: the PTAB's construction of Broad's claim term "guide RNA." Because Broad failed to challenge the other, independent grounds, it is not entitled to relief. Overturning one ground cannot alter the result when the decision below rests on independent grounds not challenged on appeal. That alone forecloses Broad's cross-appeal.

II. On the merits, the PTAB properly construed "guide RNA" to mean single-guide RNA. Broad's specifications define "guide RNA" as single-guide RNA and clearly use singular language to describe the guide. Broad's counterexamples and claim differentiation arguments cannot overcome that clear definition. Broad points to a single prior-art use of the term "guide RNA" for support. But where, as here, the specification is clear, resort to that reference is inappropriate. Regardless, substantial evidence supports the PTAB's finding that Broad's prior-art

reference did not show the term "guide RNA" included dual-guide RNA at the time of the invention. The PTAB's correct claim construction dooms both Motion 2 and Motion 3.

ARGUMENT ON CROSS-APPEAL

I. BROAD'S FAILURE TO ADDRESS INDEPENDENT GROUNDS FOR THE PTAB'S DECISION DOOMS ITS CROSS-APPEAL

It is settled law that a party appealing a ruling must, in its opening brief, challenge ***each*** independent ground on which the ruling rests. *See, e.g.*, *LSI Corp. v. Regents of Univ. of Minn.*, 43 F.4th 1349, 1355 (Fed. Cir. 2022). Broad's opening cross-appeal brief does not. That is fatal.

A. Broad Fails To Challenge the PTAB's Independent Rationale for Denying Motion 2

The PTAB gave two rationales for rejecting Broad's motion to broaden the count (Motion 2). First, although Broad urged the PTAB to modify the count from a single-guide to a "generic" count, Broad's proposed revision to the count included multiple changes unrelated to RNA configuration. Appx35. For example, it changed a composition to a method, Appx47663, and dispensed with various limitations, Appx47663-47666; Appx47669; *see* Appx35; pp. 38-39, *supra*. The PTAB observed that Broad did not explain why there was a genuine need for those further proposed changes, *see* Appx35—even though Broad, as the movant, had the burden to do so, *Louis*, 59 U.S.P.Q.2d at 1076. Broad just slipped them in. The PTAB denied Motion 2 "***on th[at] basis alone***." Appx35 (emphasis added). Second, in the

alternative, the PTAB held that Broad failed to prove any of its involved claims were generic because the PTAB found Broad's "guide RNA" claims were single-guide RNA claims. Appx36-39.

Broad's brief nowhere challenges the PTAB's first ground for denying Motion 2. It omits any mention of that basis for the PTAB's ruling—the inclusion of unjustified changes in the proposed substitute count—in its fact section or argument. *See* Broad.Br.29, 83-92. It does not mention the many ways it had, without justification, attempted to change the count apart from RNA configuration. And it does not argue the PTAB somehow abused its discretion in ruling that, because Broad's proposed substitute count was riddled with unexplained changes, the PTAB was entitled to reject Broad's motion "on th[at] basis alone." Appx35.

Broad's failure to address an "independent ground" for the PTAB's denial of Motion 2 in its opening brief forecloses Broad's challenge to that denial on appeal. *See LSI Corp.*, 43 F.4th at 1355 (affirming the PTAB's decision without reaching the merits where appellants failed to challenge an independent ground in their opening brief on appeal); *Acceleration Bay LLC v. 2K Sports, Inc.*, 15 F.4th 1069, 1076 (Fed. Cir. 2021) (similar). It is "well established that arguments not raised in the opening brief are waived." *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1319 (Fed. Cir. 2006). Broad cannot challenge the PTAB's independent grounds for the first time on reply. *See LSI Corp.*, 43 F.4th at 1355.

B. Broad Fails To Challenge the PTAB's Independent Rationale for Denying Motion 3

Broad's opening brief likewise did not challenge an independent ground for denying Motion 3. Motion 3 sought to designate supposedly generic claims as not corresponding to the count. To prevail on that motion, Broad had to show that the count, treated as prior art, would not anticipate or render obvious the claims' subject matter. 37 C.F.R. §41.207(b)(2). The PTAB denied Motion 3 as to Broad's claims reciting "guide RNA" (the vast majority of the claims at issue) because it had previously found that "guide RNA" means single-guide RNA—and thus those claims were not generic. Appx44.

But the PTAB also found that Broad failed to justify de-designation—it failed to show lack of correspondence—***even*** for generic claims. According to the PTAB, two of Broad's claims—claims 15 and 26 of the '713 patent—***were*** generic. Appx47. To disprove claim correspondence, Broad needed to show that the single-guide count, treated as prior art, would not "anticipate[]" or "render[] obvious" a generic claim. 37 C.F.R. §41.207(b)(2). The PTAB denied Broad's motion as to claims 15 and 26 because Broad never made a "clear argument" that generic claims do not "correspond[] to" a single-guide count. Appx52. The PTAB therefore held that Broad failed to meet its burden of disproving claim correspondence even for generic claims. Appx52-53.

Broad never mentions that ruling. Broad nowhere denies that it made no meaningful argument to the PTAB that the single-guide count, if treated as prior art, would neither anticipate a generic claim nor render it obvious. Any such argument would have to contend with the settled rule that a species falling within a genus ordinarily anticipates the genus. *See, e.g.*, *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 971-72 (Fed. Cir. 2001). Given that rule, Broad had to offer some reason why the single-guide species would not anticipate the genus of generic RNA claims. The PTAB found Broad made no such effort, Appx52-53—and Broad never says otherwise.

Broad's opening brief ignores the PTAB's determination that Broad never made the showing required to de-designate even generic claims. That defeats Broad's appeal as to Motion 3 entirely, without regard to which claims the PTAB or Broad deems "generic." Any putative additional generic claims beyond claims 15 and 26 would meet the same fate as concededly generic claims 15 and 26. Broad never attempted to show generic claims—which encompass both single-guide and dual-guide configurations—would not be obvious in light of or anticipated by the single-guide configuration. Nor does Broad argue that its "guide RNA" claims, even if deemed "generic," differ from generic claims 15 and 26 for purposes of claim correspondence. Quite the opposite. To the extent Broad made any arguments at all about claim correspondence below, it argued that its "non-limited" (*i.e.*, generic)

claims should all "be designated as not corresponding to Count 1," without distinguishing among them, much less between claims 15 and 26 and the "guide RNA" claims. *See* Appx51-52.

The PTAB's holding that Broad failed to raise any coherent claim-correspondence argument thus disposes of any and all claims Broad would characterize as generic. Broad's opening brief fails to challenge that independent ground supporting the PTAB's decision. Broad.Br.83-92. That ground thus stands. *See SmithKline*, 439 F.3d at 1319. And it binds Broad here and before the PTAB. Issues not raised on appeal may not be raised "on remand or in any future proceedings," *Tronzo v. Biomet, Inc.*, 236 F.3d 1342, 1349 (Fed. Cir. 2001); the law "'forecloses [further] litigation of issues decided [below] but foregone on appeal,'" *Doe v. United States*, 463 F.3d 1314, 1327 (Fed. Cir. 2006).

Consequently, wholly apart from the PTAB's claim construction, its decision on Motion 3 cannot be overturned. The PTAB ruled that Broad failed to prove—failed even to attempt to prove—that any generic claims do not "correspond to" the count; Broad's failure to challenge that ruling forecloses appeal. *Hurley v. Beech Aircraft Corp.*, 355 F.2d 517, 522-23 (7th Cir. 1966) (failure to challenge determination that would preclude success on remand precludes relief on appeal).[6] There is

[6] In *Hurley*, plaintiffs brought a two-count complaint relating to an aircraft accident. 355 F.2d at 518-19. The trial court dismissed the first count, an implied-warranty claim. *Id.* After a bench trial on the second count, negligence, the trial court ruled

nothing left to remand because Broad cannot prevail in light of the PTAB's ruling that Broad never challenged. *See A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1489 (D.C. Cir. 1995) (citing *NLRB v. Wyman-Gordon Co.*, 394 U.S. 759, 766-67 n.6 (1969)); *In re Watts*, 354 F.3d 1362, 1369-70 (Fed. Cir. 2004).

Broad argues that it is "fundamentally unfair" to include generic claims in an interference with single-molecule proofs. Broad.Br.91. But it was Broad that sought an unfair advantage, demanding de-designation of ***only*** Broad's generic claims from the interference, not CVC's. Appx17344. And there is no unfairness because Broad made a strategic decision not to present argument how a single-guide claim would not render obvious or anticipate a generic-guide claim that, being generic, necessarily includes the single-guide configuration. There is no unfairness when Broad strategically chose not to challenge the PTAB's finding on that point. *See* pp. 45-48, *supra*. And there is no unfairness because the PTAB properly denied the motions

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for the defendant. *Id.* The plaintiffs did not appeal the decision on the negligence count, appealing only the dismissal of the implied-warranty count. *Id.* On appeal, the parties and the appellate court ***agreed*** that the trial court's dismissal of the implied-warranty claim was error. *Id.* at 519, 522. But the Seventh Circuit ruled for the defendant anyway because the unappealed negligence ruling prevented plaintiffs from succeeding on the implied-warranty count in any event. *Id.* at 522-23. The same result follows *a fortiori* here. Even if the PTAB's claim construction decision on the "guide RNA" claims were error (which it is not), the PTAB's independent ruling—that Broad never showed or attempted to show that generic claims lack correspondence to the count—prevents Broad from succeeding in its challenge in any event.

on the merits—the PTAB correctly construed Broad's claim term "guide RNA" to mean single-guide RNA. *See* pp. 49-64, *infra*.

II. THE PTAB'S CONSTRUCTION OF "GUIDE RNA" WAS CORRECT

For the above reasons, this Court need not reach the PTAB's claim construction in connection with Motions 2 or 3; Broad cannot prevail regardless. In the event the Court reaches Broad's claim-construction argument anyway, the PTAB properly rejected Broad's argument that the Broad patent claims reciting "guide RNA" are "generic." While Broad insists the term "guide RNA" encompasses single- and dual-guide configurations, the PTAB properly construed "guide RNA" as Broad's patents define it—as meaning "a ***single***-molecule RNA configuration." Appx36 (emphasis added). Broad's specifications clearly define "guide RNA" as "single-guide RNA." Neither Broad's claim differentiation arguments nor its resort to a single prior-art reference overcomes that clear definition. And contrary to Broad's arguments, the term "guide RNA" did not have ***any*** fixed meaning in the art at the time of Broad's patent filings.

Standard of Review. The broadest reasonable interpretation standard applies to claim construction in interference proceedings. *See Dionex Softron GmbH v. Agilent Techs., Inc.*, 56 F.4th 1353, 1358 (Fed. Cir. 2023). Claim construction is reviewed *de novo*, "as are the intrinsic-evidence aspects of a claim-construction analysis." *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 801, 808 (Fed. Cir. 2021). Under-

lying factual determinations concerning extrinsic evidence, such as "extra-patent usage," are reviewed for substantial evidence. *Id.*; *ULF Bamberg v. Dalvey*, 815 F.3d 793, 796 (Fed. Cir. 2016).[7]

A. The Specifications Control the Meaning of "Guide RNA"

Broad asks this Court to turn claim construction on its head. It demands the Court ignore clear definitions in Broad's specifications in favor of one prior-art reference. Broad.Br.83-85. That disregards settled law. The specification is "the single best guide to the meaning of a disputed term." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc). When a patentee defines a term, that "lexicography" governs, even in the face of contrary customary meaning in the art (and there is none here). *Id.* at 1316.

The specifications of Broad's patents define "guide RNA" as "***the*** polynucleotide sequence"—a ***singular*** sequence—that "compris[es] the guide sequence, the tracr sequence and the tracr mate sequence." *See, e.g.*, Appx22771 (emphasis added).[8] And they state that the term "guide RNA" is "used interchangeably" with

[7] Broad omits the standard of review for its cross-appeal arguments. *Contrast* Fed. R. App. P. 28(a)(8)(B), *and* Fed. Cir. R. 28(a)(9), *with* Fed. Cir. R. 28.1(d), *and* 28(b).

[8] "'[G]uide sequence'" and "'tracr mate' sequence" are "sub-portions of crRNA." Appx15. The tracr sequence, or tracrRNA, hybridizes with crRNA to form a crRNA:tracrRNA complex. Appx15.

the term "single guide RNA." *See, e.g.*, Appx22771. Such definitions govern over any other evidence.

1. *The Specifications' Definition of "Guide RNA" Is Clear and Unambiguous*

Reviewing the specifications of Broad's patents, the PTAB correctly found that they "dictate[]" the meaning of "guide RNA," limiting it to single-guide RNA. Appx29-30; Appx38. Each of Broad's involved patent specifications states:

> In aspects of the invention the terms 'chimeric RNA', 'chimeric guide RNA', 'guide RNA', '***single guide RNA***' and 'synthetic guide RNA' are ***used interchangeably*** and ***refer to the polynucleotide sequence comprising the guide sequence, the tracr sequence and the tracr mate sequence***.[9]

That definition is unambiguous. For one thing, it states that "guide RNA" is "used interchangeably" with "single guide RNA" and "chimeric RNA." The most sensible reading of "used interchangeably" is that all three terms—"guide RNA," "single guide RNA," and "chimeric RNA"—mean the same thing. And because "single guide RNA" obviously does not mean dual-guide RNA, neither does "guide RNA."

Moreover, the definition is clear: It says "guide RNA . . . ***refer[s] to the polynucleotide sequence*** comprising"—*i.e.*, made of—"the guide sequence, the

[9] Appx3049 ('359 patent); Appx16334 ('945 patent); Appx3269 ('965 patent); Appx23109 ('406 patent); Appx26260 ('445 patent); Appx22771 ('356 patent); Appx22435 ('308 patent); Appx17735 ('616 patent); Appx28647 ('814 patent); Appx18024 ('839 patent); Appx18149 ('233 patent); Appx30982 ('641 patent); Appx30217 ('713 patent); Appx31413 ('551 application). Emphasis is added.

tracr sequence and the tracr mate sequence." The patents thus declare that "guide RNA" "refer[s] to ***the*** polynucleotide ***sequence***"—a singular item, one "sequence." *See Rumsfeld v. Padilla*, 542 U.S. 426, 434 (2004) (use of definite article "the" before singular noun indicates a singular item); *Shum v. Intel Corp.*, 629 F.3d 1360, 1367 (Fed. Cir. 2010) (same). That clearly indicates single-guide RNA—one RNA "sequence" linked in a single strand.

The remainder of the definition makes that clearer still. It says "the"—singular—"polynucleotide sequence comprising" three items: "the guide sequence, the tracr sequence and the tracr mate sequence." That, too, means single-guide RNA, in which the different components (the crRNA, comprising guide and tracr mate sequences; and the tracrRNA) are linked together to form "the" (singular) "polynucleotide sequence." *See* Appx5602.

If the specifications' definition were meant to encompass two ***separate*** polynucleotides—as in a dual-guide configuration—it would read differently. It would not "refer" to "the polynucleotide sequence," singular; it would say "polynucleotide sequence or sequences." *See* Appx29-30.[10] Broad's specifications thus

[10] Indeed, Broad's patents use that formulation elsewhere. *See, e.g.*, Appx22771 ("'Hybridization' ***refers to*** a reaction in which ***one or more polynucleotides*** react to form a complex that is stabilized via hydrogen bonding between the bases of the nucleotide residues." (emphasis added)).

clearly define "guide RNA" as ***single-guide*** RNA. *See Phillips*, 415 F.3d at 1316 ("definition given to a claim term by the patentee" in the specification "governs").

Broad argues that the introductory phrase "in aspects of the invention" limits the definition to "certain embodiments." Broad.Br.89-90. That cannot be reconciled with the definition's plain language or other parts of the specifications. When Broad's specifications address only "certain embodiments," they say just that, using phrases like "in ***some*** embodiments" and "in ***certain*** embodiments."[11] Similarly, limiting language such as "***several*** aspects" or "***some*** aspects" indicates when not ***every*** "aspect" of the invention is encompassed.[12] The absence of such language

[11] *See, e.g.*, Appx22764 ("In ***some embodiments***, the CRISPR complex comprises one or more nuclear localization sequences . . . ." (emphasis added)); Appx22774 ("In ***some embodiments***, an enzyme coding sequence encoding a CRISPR enzyme is codon optimized for expression in particular cells . . . ." (emphasis added)); Appx22776 ("In ***an embodiment*** of the invention, the transcript or transcribed polynucleotide sequence has at least two or more hairpins." (emphasis added)); Appx22778 ("In ***certain embodiments***, the organism or subject is a plant. In ***certain embodiments***, the organism or subject or plant is algae." (emphasis added)).

[12] *See, e.g.*, Appx22762 ("In ***one aspect***, the invention provides a vector system comprising one or more vectors." (emphasis added)); Appx22773 ("In ***an aspect*** of the invention the recombination is homologous recombination." (emphasis added)); Appx22772 ("***Several aspects*** of the invention relate to vector systems comprising one or more vectors, or vectors as such." (emphasis added)); Appx22777 ("In ***some aspects***, the invention provides methods comprising delivering one or more polynucleotides, such as or one or more vectors as described herein, one or more transcripts thereof, and/or one or proteins transcribed therefrom, to a host cell." (emphasis added)).

here indicates that Broad's "guide RNA" definition is not limited to "certain embodiments."

Broad cites other uses of "in aspects of the invention," but those prove CVC's point. *See* Broad.Br. 90. For example, one specification states: "In aspects of the invention, nickases ***may be used*** for genome editing via homologous recombination." Appx17619 (emphasis added). If the phrase "in aspects of the invention" were already limiting, the phrase "may be used"—which itself indicates that nickases might be employed in some but not all embodiments—would be extraneous. So, too, with Broad's other example, which states: "In aspects of the invention, an exogenous template polynucleotide ***may be referred to*** as an editing template." Appx17737 (emphasis added). Again, if "aspects of the invention" were already limiting, then use of "may" would be extraneous.

The placement of the definition of "guide RNA" in Broad's specifications confirms its breadth. The "guide RNA" definition appears at the beginning of the "Detailed Description of the Invention" section, in the midst of other definitions intended to apply to the invention as a whole. *See, e.g.*, Appx22771. Embodiment-specific discussions do not appear until ***after*** the paragraphs setting forth those general definitions. *See, e.g.*, Appx22772. The "guide RNA" definition's placement among general definitions confirms that it applies generally.

"[C]laim terms," moreover, "are normally used consistently throughout the patent." *Phillips*, 415 F.3d at 1314. It is not clear how the phrases "guide RNA," "chimeric RNA," and "single guide RNA" could be "used interchangeably" in some embodiments, but not others. Nor does Broad point to examples where the specification clarifies whether the terms are being "used interchangeably," or identifies some other meaning for them. The only construction that comports with common sense and the patents as a whole is the one that the specifications provide: The term "guide RNA" means "***the*** polynucleotide sequence," singular—"single guide RNA."

2. *Other Portions of the Specifications Do Not Help Broad*

To avoid the patents' clear definition of "guide RNA," Broad cites three examples that supposedly illustrate "generic" uses of "guide RNA." Broad.Br.88. None helps Broad.

Broad first argues that Example 6 of the '356 patent uses the term "guide RNA" to refer to both single- and dual-guide RNA. Broad.Br.88 (citing Appx22814). But Example 6 uses the term "guide RNA" interchangeably with "chimeric guide RNA" (*i.e.*, single-guide RNA). Appx22814. It uses a different term, "tracrRNA and direct repeat sequences," to refer to dual-guide RNA. Appx22814. The term "Guide RNA" in the title of Example 6—"Optimization of the Guide RNA for *Streptococcus pyogenes* Cas9"—likewise refers only to chimeric, or ***single-guide***, RNA. Appx22814. Example 6 reports the results of

optimizing chimeric guide RNA, which "work[ed] better" than optimizing dual-guide RNA. Appx22814. The title therefore refers to the "optimiz[ed]" RNA, *i.e.*, the single-guide RNA. Appx22814.

Broad also urges that Column 38 of the '308 patent refers to dual-guide RNA ("combination of tracrRNA and crRNA") and single-guide RNA ("chimeric guide RNA") collectively as "guide RNA." Broad.Br.88 (citing Appx22443). But Column 38 states: "Cas9 and its chimeric guide RNA, or combination of tracr-RNA and crRNA. [sic] can be delivered either as DNA or RNA." Appx22443. As the PTAB noted, this sentence "clearly includes a typographical error." Appx31. That is confirmed by the as-filed specification of the application leading to the '308 patent, which contains a comma in the middle of the sentence instead of a period. Appx26531. Properly read, Column 38 reads: "Cas9 and its chimeric guide RNA, or combination of tracr-RNA and crRNA, can be delivered either as DNA or RNA." Appx26531. Separated from the rest of the sentence with commas, the phrase "or combination of tracrRNA and crRNA" thus clarifies that the preceding term, "chimeric guide RNA," means a single sequence that combines both tracrRNA and crRNA—that is, ***single-guide*** RNA. Appx31-32. As the PTAB properly found, Column 38 thus "describes a single molecule chimeric RNA only, not a dual molecule guide RNA." Appx31.

Finally, Broad argues that the first "preferred embodiment" of the '359 patent is a dual-molecule RNA embodiment. Broad.Br.88. But the PTAB correctly found that embodiment was irrelevant, because the portion of the patent describing it does not "use the term 'guide RNA.'" Appx32; *see* Appx3065-3066. As the PTAB aptly put it, "[e]ven if single- or double-molecule RNA configurations are preferred embodiments, whether or not Broad ***claims*** these embodiments depends on the language of ***the claims***." Appx32 (emphasis added); *see Novo Nordisk of N. Am., Inc. v. Genentech, Inc.*, 77 F.3d 1364, 1369 (Fed. Cir. 1996) ("While claims are to be interpreted in light of the specification, all that appears in the specification is not necessarily within the scope of the claims."). The "preferred embodiment" of the '359 patent thus sheds no light on the meaning of claims that use the term "guide RNA."

3. *Claim Differentiation Does Not Help Broad*

Nor does claim differentiation overcome the specifications' clear definition. Claim differentiation is "a guide, not a rigid rule." *Howmedica Osteonics Corp. v. Zimmer, Inc.*, 822 F.3d 1312, 1323 (Fed. Cir. 2016). Any presumption raised by claim differentiation "will be overcome" where—as here—"the specification . . . dictates a contrary construction." *GPNE Corp. v. Apple Inc.*, 830 F.3d 1365, 1371 (Fed. Cir. 2016).

Broad invokes claim 3 of its '233 patent, Broad.Br.86-87, which recites a "vector system" wherein a "guide sequence," a "Cas9 protein," and a "tracr sequence" are "located on same or different vectors." Appx1759-1761. Broad contends that, because claim 3 permits the "guide sequence" and "tracr sequence" to be located on different vectors, it allows them to be transcribed as separate molecules. Broad.Br.87. But the claim does not ***require*** those sequences to be on different vectors. The PTAB thus found that claim 3 "could be interpreted differently than Broad asserts." Appx21. This ambiguity in claim 3 cannot overcome the clear definition in the specifications indicating that "guide RNA" means "single guide RNA." *See Mukherjee v. Lai*, 1 F.3d 1253 (Table), 1993 WL 217180, at *2 (Fed. Cir. 1993) (declining to adopt construction based on claim differentiation where the "specification explicitly define[d]" the term differently); *B.E. Tech., L.L.C. v. Sony Mobile Commc'ns (USA) Inc.*, 657 F. App'x 982, 990 (Fed. Cir. 2016) (similar).

Broad's argument that two other claims distinguish between "guide RNA" and "'guide RNA[] compris[ing] a guide sequence fused to a tracr sequence,'" Broad.Br.86 (quoting Appx17680) (emphasis omitted), suffers a similar defect. Even if those claims could be interpreted as Broad argues, they cannot overcome the "contrary construction" dictated by the definition in the specifications. *GPNE*, 830 F.3d at 1371.

Indeed, other claims illustrate why claim differentiation cannot dictate the result Broad seeks. For example, claim 1 of the '945 patent recites a "CRISPR associated (Cas) system comprising . . . a . . . guide RNA." Appx1711. Claim 4, which depends on claim 1, provides that "the CRISPR-Cas system comprises a trans-activating cr (tracr) sequence." Appx1711.[13] If claim differentiation were a strict rule, claim 1 would be construed as encompassing a CRISPR-Cas9 system ***not requiring*** a tracrRNA. That is both inconsistent with its originating specification and scientifically nonsensical: Functional CRISPR-Cas9 systems ***require*** tracrRNA to achieve DNA cleavage. *See* Appx17902 ("In general, 'CRISPR system' refers collectively to transcripts and other elements involved in the expression of or directing the activity of CRISPR-associated ('Cas') genes, including sequences encoding . . . a tracr (transactivating CRISPR) sequence . . . ."); Appx5599 (demonstrating tracrRNA is necessary for CRISPR-Cas9 DNA cleavage). Broad cannot selectively invoke claim differentiation when the application of that doctrine would render its other claims nonsensical. Claim differentiation, in any event, must give way to the clear definition in the specifications.

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[13] *See* Appx1713 ('945 patent claim 14); Appx1722 ('406 patent claim 4); Appx1723 ('406 patent claim 16); Appx1727 ('445 patent claim 3); Appx1729 ('445 patent claim 15); Appx1731 ('445 patent claim 28); Appx1733 ('356 patent claim 4); Appx1734 ('356 patent claim 16); Appx1736 ('356 patent claim 25); Appx1738 ('308 patent claim 5); Appx1740 ('308 patent claim 17); Appx1748 ('814 patent claim 4); Appx1750 ('814 patent claim 17); Appx1751 ('814 patent claim 26); Appx1768 ('641 patent claim 4); Appx1769-1770 ('641 patent claim 15).

B. Broad's Resort to a Prior-Art Reference Is Inappropriate and Does Not Support Broad's Construction Regardless

1. *Broad's Use of a Prior-Art Reference To Define "Guide RNA" Is Inappropriate*

The specification is the "best guide" to the meaning of "guide RNA"—and it provides an express definition here. Broad nonetheless insists that, absent "'a clear disavowal or contrary definition,'" the term's "ordinary meaning" must be determined by reference to a solitary use in one prior-art article, Broad.Br.83-85 (emphasis omitted).

That is upside down. Before the PTAB, both parties characterized the prior art Broad invokes, Jinek 2012, as extrinsic evidence. Appx17346; Appx48277. The PTAB did as well. Appx26. Broad did not argue otherwise before the PTAB. Appx17346-17348. And it does not argue otherwise here, Broad.Br.83-92, accepting the PTAB's determination that Jinek 2012 is extrinsic, Broad.Br.29, 91. *See Rueter v. Dep't of Com.*, 63 F.4th 1357, 1366 n.4 (Fed. Cir. 2023) (issues raised neither below nor in opening brief "doubly forfeited"); *SmithKline*, 439 F.3d at 1319.

That has consequences. "The ordinary meaning of a claim term is not 'the meaning of the term in the abstract.'" *Eon Corp. IP Holdings LLC v. Silver Spring Networks, Inc.*, 815 F.3d 1314, 1320 (Fed. Cir. 2016). "The ***only*** meaning that matters in claim construction is the meaning in the context of the patent." *Trs. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1363 (Fed. Cir. 2016) (emphasis

added). That is why the words in the specification—chosen specifically by the patentee as the "lexicography" of the patent—are the "'single best guide'" to a disputed term's meaning. *Phillips*, 415 F.3d at 1315-16. Sources "not 'created by the patentee in attempting to explain and obtain the patent,'" even sources cited in the patent, thus "merit[ ] less weight than the evidence of the patentee's own words" in the patentee's specification. *Acumed LLC v. Stryker Corp.*, 483 F.3d 800, 809 (Fed. Cir. 2007). And where the patentee's own words actually ***define*** the disputed term, those words should be given even more weight. *Phillips*, 415 F.3d at 1316.

For those reasons, this Court—acting en banc in *Phillips*—rejected the framework Broad proposes: It overruled a line of cases that consulted the specification "only after" an assessment of the "abstract meaning of words . . . divorced from the intrinsic evidence." 415 F.3d at 1320-21. That methodology, the Court held, "improperly restricts the role of the specification in claim construction" and "will systematically cause the construction of the claim to be unduly expansive." *Id.* Contrary to Broad's suggestion, Broad.Br.83-85, this Court thus "does not require explicit redefinition or disavowal" of usage suggested by extrinsic sources. *Trs. of Columbia Univ.*, 811 F.3d at 1363.

Broad made the same argument below, attempting to elevate prior art over the guidance provided by Broad's own specifications. Appx17345-17346. The PTAB correctly rejected that attempt. Appx27. This Court should do the same. Because

Broad's own specifications clearly define "guide RNA" to mean "single-guide RNA," this Court need not look beyond that definition. *Seabed Geosolutions (US) Inc. v. Magseis FF LLC*, 8 F.4th 1285, 1287 (Fed. Cir. 2021).

2. *Jinek 2012 Did Not Establish a Plain and Ordinary Meaning of "Guide RNA"*

Jinek 2012 changes nothing in any event. Broad's only basis for urging that "guide RNA" had a plain meaning in December 2012—and that the meaning encompassed dual-guide RNA—is a solitary use of the phrase in Jinek 2012, the first-ever published disclosure of a CRISPR-Cas9 DNA-cleavage complex (with either RNA configuration). Broad.Br.84-85. The PTAB properly rejected Broad's argument that one use in one publication established that the "clear meaning" of "guide RNA" covered dual-guide RNA in December 2012, when Broad's patents were filed. Appx27.

Jinek 2012 does not define the term "guide RNA." It uses that phrase four times. Appx5597-5641. Three of those uses—including the only two in the body of the article itself—refer to single-guide RNA. Appx5602; Appx5630. In 21 other places, Jinek 2012 uses variations on a ***different*** term—"tracrRNA:crRNA duplex"—to refer to dual-guide RNA. Appx5600-5602; Appx5606-5608; Appx5612-5613; Appx5617; Appx5623-5625 (*e.g.*, "RNA duplex"; "duplexed tracrRNA:crRNA-sp2"). The only place Jinek 2012 supposedly uses the term "guide

RNA" to include dual-guide RNA is in the caption of a single figure in the paper's supplementary materials. Appx5610.

Broad's one prior-art example of use of the term "guide RNA" in one figure in supplementary materials hardly shows that the term always encompasses a dual-molecule complex. The PTAB found no evidence that, by December 2012, skilled artisans had generally seized on such a stray use to shape their understanding of the term "guide RNA." Broad.Br.84-85. Broad cites no case holding that an isolated use in one document establishes plain meaning in the art. Broad offers no evidence that Zhang used the term that way, despite the opposite meaning provided in Broad's own patents. Given the dearth of evidence of plain meaning, the PTAB's finding that "guide RNA" had no clear meaning in the art was at least supported by substantial evidence.

3. *The PTAB Did Not Consider Pre-Jinek 2012 Publications*

Broad accuses the PTAB of considering publications that predate Jinek 2012. Broad.Br.84-85. But the PTAB ***declined*** to consider those publications as evidencing plain meaning. If the PTAB had considered them, Broad invited any error.

First, Broad misreads the record. The PTAB found that the uses of "guide RNA" in "articles published before 2012" were not "relevant to the issue of whether the term 'guide RNA' in Broad's claims [is] limited to a single-molecule RNA configuration." Appx25-26. The PTAB reasoned that it was "not clear" that the term

"guide RNA" in those publications—which predated Jinek 2012's disclosure that the CRISPR-Cas9 cleavage complex required both crRNA and tracrRNA—"refer[red] to a complex of RNAs comparable to the RNA configurations of Broad's claims." Appx26. In other words, the PTAB found that "those earlier references" in "different contexts" "shed no light on the plain and ordinary meaning of 'guide RNA.'" Broad.Br.84-85; *see* Appx26. It thus did exactly what Broad says it should have done.

Second, Broad would have invited any error. The PTAB discussed pre-2012 publications only because ***Broad's*** expert cited them as evidence of the meaning of the term "guide RNA." Appx24-26; *see* Appx19498-19499 (¶¶5.24-5.25). If there was any error, Broad invited it and "cannot complain on appeal." *Chem. Eng'g Corp. v. Essef Indus., Inc.*, 795 F.2d 1565, 1572 (Fed. Cir. 1986).

CONCLUSION

This Court should affirm the PTAB's denial of Broad's Motions 2 and 3.

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Respectfully submitted,

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