Appeal Nos. 2022-1594, 2022-1653

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.

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

REPLY BRIEF FOR CROSS-APPELLANTS

RAYMOND N. NIMROD
MATTHEW D. ROBSON

QUINN EMANUEL
URQUHART & SULLIVAN, LLP
51 Madison Avenue
New York, NY 10010
212-849-7000

STEVEN R. TRYBUS
HUGH S. BALSAM

LOCKE LORD LLP
111 South Wacker Drive
Chicago, IL 60606
312-443-0699

Attorneys for Cross-Appellants,
The Broad Institute, Inc.,
Massachusetts Institute of Technology, and
President and Fellows of Harvard College

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page

Cases

Rules and Regulations

INTRODUCTION

As explained in Broad's Opening Brief, if the Court affirms the judgment of priority to Broad, it need not reach any issue in Broad's conditional cross-appeal.

CVC leads its Response to Broad's cross-appeal with an argument that the Court should not take up the cross-appeal because there were allegedly independent grounds for denying preliminary Motions 2 and 3 that Broad did not address. CVC is wrong for at least two reasons.

First, CVC's argument ignores that the proper construction of the claim term "guide RNA" is inextricably linked to the dispositions of Motions 2 and 3. The PTAB itself addressed the claim construction of "guide RNA" first, as a threshold issue, before proceeding to address Motions 2 and 3. Motions 2 and 3 were directed to aligning the scope of the count of the interference to the scope of the claims—and the scope of the claims turns on the threshold claim-construction issue. Thus, the predicate issue of the scope of "guide RNA" directly impacted the dispositions of Motions 2 and 3. Acknowledging this, even CVC's brief links the decisions on these motions to the construction of "guide RNA."

(*See, e.g.*, CVCRespBr41) (noting that the PTAB "held that Broad's claims reciting 'guide RNA' did not need to be de-designated from the count [the relief sought in Motion 3] because that term meant single-guide RNA").

If, as Broad contends, "guide RNA" is given its proper broadest reasonable construction, it follows that the PTAB should have granted Motion 2 and broadened the scope of the count (and of the relevant priority evidence) to conform to the scope of the involved claims. This would have allowed both parties to rely on their best evidence and would have allowed Broad to introduce evidence of Dr. Feng Zhang's eukaryotic cell work with CRISPR-Cas9 systems using a dual-molecule configuration, pre-dating any of CVC's alleged conceptions. In the alternative, the PTAB should have granted Motion 3 so that the scope of Broad's involved claims was limited, as was Count 1, to only those claims that specify single-molecule RNA configurations.

Second, CVC's "independent grounds" argument ignores the fact that, if the Court addresses the cross-appeal, it has the discretion to address the PTAB's erroneous claim construction even if it believes claim construction did not affect the decisions on Motions 2 or 3. *See, e.g.*,

Thorner v. Sony, 669 F.3d 1362, 1369 (Fed. Cir. 2012) (construing a claim term at the appellant's request to aid ongoing proceedings upon remand).

When CVC finally addresses claim construction, it puts all its eggs in one basket. According to CVC, in one sentence—read in isolation from the rest of the specifications—Broad acted as its own lexicographer and defined the term "guide RNA" as limited to only the single-molecule configuration. But, not only is that sentence devoid of any definitional language, it is expressly limited to "aspects of the invention." It does not purport to address the invention as a whole or *all* aspects of the invention. CVC's argument also ignores the necessary context of the specifications as a whole, including multiple instances where Broad used explicit definitions when it actually wanted to, and did, define other terms.

According to CVC, its (mis)reading of the one sentence it relies on overcomes *all* the evidence in the specifications and elsewhere consistently showing that the broadest reasonable interpretation of the claim term "guide RNA" encompasses both the single- and dual-molecule configurations. That evidence includes: (i) other references in the

specifications to "guide RNA" that encompass both configurations, (ii) clear claim differentiation that the PTAB concluded favored Broad's construction and that CVC never substantively rebuts, and (iii) CVC's own Jinek 2012 publication, which established a plain and ordinary meaning for "guide RNA" as of 2012 that includes both configurations.

Because Broad's construction is reasonable in light of all the evidence, and is broader than the construction CVC advocated, the PTAB erred in not adopting Broad's construction. Accordingly, if the Court reaches the cross-appeal, Broad respectfully requests that the Court reverse the PTAB's claim construction, vacate the denials of Motions 2 and 3, and remand this matter for further proceedings under the correct claim construction.

ARGUMENT

Because the PTAB treated the proper construction of "guide RNA" as a threshold issue for its rulings on Broad's preliminary Motions 2 and 3, Broad will proceed likewise here.

I. The PTAB Did Not Give "guide RNA" Its Broadest Reasonable Interpretation

The broadest reasonable interpretation of "guide RNA" should not be narrowly restricted to only the single-molecule RNA configuration, but also properly includes the dual-molecule RNA configuration.

A. CVC Ignores The Broadest Reasonable Interpretation Standard

CVC concedes that the Court must apply the "broadest reasonable interpretation" of the claim at issue (CVCRespBr49), but, after once reciting that standard, never applies it. CVCRespBr49-64.

If *broadest reasonable* interpretation means anything, it means that, at the end of the analysis, if there are different reasonable constructions of a claim term to the POSITA in light of all of the evidence, the Court must adopt the broadest of those constructions. *See Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1301-02 (Fed. Cir. 2015)

(adopting the broader "from among a set of data objects" construction over the narrower "only two" proposed construction); *see also Apple Inc. v. VirnetX Inc.*, IPR2014-00481, Final Written Decision, Paper 35 at 24-25 (PTAB August 24, 2015) (adopting the broader of two competing reasonable constructions), *aff'd,* 671 F. App'x 786, 787 (Fed. Cir. 2016).

Moreover, Jinek 2012 further demonstrates that Broad's construction is reasonable. Broad's specifications used a term that a POSITA, at the time, would have understood to refer to both single- and dual-molecule RNA configurations and was derived from what CVC characterizes as the seminal paper in the field. CVCBr11. A 2012 POSITA would have known that Broad was using the term consistent with Jinek 2012.

Here, Broad's claim construction is both reasonable and broader than CVC's construction. Thus, the PTAB erred in declining to adopt Broad's construction in favor of CVC's narrower construction. Broad's construction is reasonable in light of the intrinsic evidence (as shown below), and that is dispositive.

B. In Late 2012, A POSITA Understood That "guide RNA" Included Both Single-Molecule And Dual-Molecule Configurations

As Broad demonstrated in its Opening Brief, Jinek 2012 (Appx5597-5641) supplied the plain and ordinary meaning of "guide RNA" as of December 2012 (Broad's effective filing date) or, at the very least, is additional evidence supporting Broad's construction. BroadBr84-85. That plain and ordinary meaning encompassed the single-molecule and dual-molecule configurations both disclosed in Jinek's June 2012 publication. Jinek 2012 uses the term "guide RNA" when referring to both configurations. *Compare* Appx5610("[T]he ***dual*** tracrRNA:crRNA structure acts as ***guide RNA*** that directs the endonuclease Cas9 to the cognate target DNA." (emphases added)) *with* Appx5602(referring to single-molecule configuration).

CVC's primary response on this point is circular: it says that any plain and ordinary meaning of "guide RNA" is irrelevant because, CVC says, Broad's specifications provide "an express definition." CVCRespBr60. But, of course, the plain and ordinary meaning of a term is always relevant in claim construction, especially if one needs to

determine whether the patentee has clearly *redefined* the term in the specification from that pre-existing meaning.

Where, as here, a plain and ordinary meaning exists and the specifications as a whole do not clearly provide a different and narrower meaning, the plain meaning controls. *Thorner*, 669 F.3d at 1365; *Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1356-58 (Fed. Cir. 2004).

While in the main appeal CVC treats Jinek 2012 as the foundational, near Promethean reference for the 2012 POSITA's understanding of CRISPR-Cas9 technology (CVCBr11-12), in opposing Broad's cross-appeal CVC dismisses this publication as merely "one prior-art article." CVCRespBr60. Jinek 2012 was the *only* reference published before Broad's effective filing date to include a discussion of the single-molecule RNA configuration of CRISPR-Cas9 systems. All prior CRISPR-Cas9 publications discussed the dual-molecule RNA configuration when discussing the guide RNA component of the system.

Jinek 2012, as the first publication to disclose the single-molecule RNA configuration in a CRISPR-Cas9 system, was uniquely suited to,

and did, provide a 2012 POSITA with the plain and ordinary meaning of "guide RNA."

In fact, when specifically discussing the single-molecule configuration, Jinek 2012 made clear that it was describing the single-molecule configuration as an alternative to the well-known dual-molecule configuration. Jinek 2012 specifically used the terms "single chimeric RNA," "single RNA-guided Cas9," and "chimeric RNA" when limiting its discussion to the single-molecule configuration. Appx5601-5602, Appx5628-5630, Appx5636.

CVC is thus incorrect when it says there was a "dearth of evidence of plain meaning." CVCRespBr63. Jinek 2012 was the *only* reference in the field published before Broad's filing date that discussed both the single- and dual-molecule RNA configurations, and it used the term "guide RNA" to refer to both. The POSITA would review Broad's specifications with this predicate understanding of what a "guide RNA" means. Thus, Jinek 2012 refutes CVC's argument that the term "guide RNA" lacked a plain and ordinary meaning to a 2012 POSITA. CVC

simply ignores the record evidence contrary to its position. CVCRespBr62-63.

C. Broad's Specifications As A Whole Do Not Limit "guide RNA" To The Single-Molecule Configuration

Regardless of whether one looks only to the specifications to establish the meaning of "guide RNA" in the first instance, or for a clear disavowal or re-definition of the plain and ordinary meaning of the term, the result is the same: the broadest reasonable interpretation encompasses both single- and dual-molecule configurations.

1. The Sentence That CVC Argues Is "Definitional" Is Not; And It Actually Supports Broad's Construction Because It Shows "guide RNA" Covers Both Single- And Dual-Molecule RNA Configurations

CVC's entire claim construction argument rests on an invalid premise: that one sentence in the specifications somehow restricted "guide RNA" to only the single-molecule configuration. The sentence CVC seizes upon says:

> *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.

Appx17616(12:6-10)(emphases added).

This sentence supports Broad's, not CVC's, construction, because it states that "guide RNA" comprises three components: "the guide sequence, the tracr sequence and the tracr mate sequence." Thus, "guide RNA" as used in this sentence simply means a system including these three recited RNA sequences. This encompasses both single- and dual-molecule RNA configurations because—as is undisputed—both configurations include the three recited sequences. Appx19468-19489, Appx18383-18447. In this way, far from limiting "guide RNA" to only configurations where the three components are linked into a single molecule, the sentence CVC relies on shows the term covers RNAs with these three components regardless of whether they are covalently linked to one another in a single molecule or not.

That said, for the following reasons, the sentence on which CVC focuses is not definitional in the first place, especially when read, as it must be, in the context of the specifications as a whole.

1. Unlike *many* other sentences in the specifications in which Broad expressly conveyed that it was acting as its own lexicographer, the sentence upon which CVC relies contains no express words of definition. For instance, the sentence does not say "As used herein the term" guide RNA "means"…, as Broad wrote elsewhere in the specifications in the instances when it actually defined terms. *See, e.g.*, Appx17616(12:17-20) ("*As used herein the term* 'wild type' is a term of art understood by skilled persons and *means* the typical form of an organism…."); (12:21-22) ("*As used herein the term* 'variant' *should be taken to mean* the exhibition of qualities that have a pattern…."); (12:26-30) ("*The terms* ["non-naturally occurring" or "engineered"], when referring to nucleic acid molecules or polypeptides *mean* that the nucleic acid molecule or the polypeptide is at least substantially free from at least one other component…."); (12:38-42) ("'Perfectly complementary' *means* that all of the contiguous residues of a nucleic acid sequence will hydrogen bond…."); Appx17617(13:50-52) ("By therapeutic benefit *is meant* any therapeutically relevant improvement…."); Appx17613(5:3-9) ("Within a recombinant expression

vector, 'operably linked' is *intended to mean* that the nucleotide sequence of interest is linked….") (all emphases added).

From these multiple excerpts, it is evident that the patentees knew how to add definitional language when they wanted to, yet chose not to do so here.

To act as its own lexicographer, a patentee must "clearly set forth a definition of the disputed claim term" and must "clearly express an intent" to redefine the term from its ordinary meaning. *Thorner*, 669 F.3d at 1365 (internal citations omitted). The sentence on which CVC focuses cannot accomplish this heavy lift in view of the teachings of the specifications as a whole, especially when numerous sentences *do* "clearly set forth a definition" of other terms.

2. CVC's argument also depends on the flawed notion that "[t]he most sensible reading of 'used interchangeably' is that all three terms…mean the same thing." CVCRespBr51. But another reasonable reading in context is that the concepts are used interchangeably only in certain contexts, and do not mean the same thing for all purposes.

Further confirming the reasonableness of Broad's construction, the specifications contain numerous examples from which a POSITA would understand that terms that could be used "interchangeably" would most assuredly ***not*** "mean the same thing." For example, the preceding paragraph in the specifications states:

> The terms "polynucleotide", "nucleotide", "nucleotide sequence", "nucleic acid" and "oligonucleotide" are *used interchangeably*.

Appx17616(11:50-52)(emphasis added). A 2012 POSITA reading this sentence would undoubtedly know that "used interchangeably" is not redefining these terms to mean the same thing. A polynucleotide is not a nucleotide, and a POSITA would never have thought that, by calling them "interchangeable," Broad was redefining those terms to mean the same thing. To use a non-scientific example, nails, screws, tape, and glue may sometimes be used interchangeably for certain purposes (*e.g.*, as fasteners), but that does not mean they are the same thing, or that nails "means" screws, etc.

Rather, "interchangeable" as used in Broad's specifications, including in the sentence that is the basis of CVC's argument, denotes

only that sometimes the terms might be substituted for one another, thereby broadening the disclosure to cover different concepts. Tellingly, CVC failed to respond to this point in its brief.

3. CVC also tries to distract the Court from the accepted meaning of the phrase "*aspects* of the invention." Citing no authority, CVC submits that "aspects of the invention" means *every* aspect unless preceded by a modifier like "some" or "several." CVCRespBr53-54.

But "aspects of the invention" *itself* connotes something less than "every aspect" of the invention. For example, the Cambridge Dictionary, https://dictionary.cambridge.org/us/dictionary/english/aspect, defines "aspect" as "*one part* of a situation, problem, subject, etc." The Collins English Dictionary, https://www.collinsdictionary.com/us/dictionary/english/aspect, defines "aspect" as "*one of the parts* of its character or nature." And, the Oxford Languages Dictionary defines "aspect" as "a particular *part* or feature of something." https://www.bing.com/search?q=define+aspect&FORM=DCTSRCCITE (Bing utilizing Oxford Languages Dictionary) (emphases added).

These references show that the meaning of "aspects" is fundamentally at odds with CVC's position that a POSITA would have read "aspects of the invention" as encompassing the *entire* invention because the phrase does not contain a redundant modifier like "some."

4. CVC mistakenly relies on the word "the" in the phrase "*the* polynucleotide sequence comprising the guide sequence, the tracr sequence and the tracr mate sequence" (CVCRespBr51-53) to argue that all three sequences must be in a single molecule. A dual-molecule RNA is a "polynucleotide sequence" just like a single-molecule RNA is. A "polynucleotide sequence" does not mean that any or all of the bases in the sequence are covalently linked into a single molecule, and CVC has not presented evidence to the contrary. Demonstrating the folly of CVC's mis-reading of the phrase "the polynucleotide sequence," the widely used terminology "the nucleotide sequence of the human genome" refers to the roughly 3 billion bases of the 23 human chromosomes, which are not covalently linked to one another, *i.e.*, are not a single molecule.

CVC's reliance on the term "the polynucleotide sequence" is further misplaced because it ignores the "[i]n aspects of the invention…" qualifier

earlier in the sentence. It is correct that, in "aspects of the invention" described in the specifications, the "guide RNA" component is in the single-molecule configuration. But, the figures, examples, and disclosures of the specifications also include references where the "guide RNA" component is in the dual-molecule configuration. *See*, *e.g.*, Appx22814-15 (Example 6 titled "Optimization of the Guide RNA for *Streptococcus pyogenes* Cas9" and discussing *both* single- and dual-molecule RNA configurations for the guide RNA); Appx22443(38:33-43) (referring to delivery of "chimeric guide RNA" (single-molecule), a "combination of tracrRNA and crRNA" (dual-molecule), and to both alternatives collectively as "guide RNA"). The question before the Court is whether "guide RNA" must exclusively be read as limited to the single-molecule configuration. Taking the specifications as a whole, the answer to that question is a resounding "no."

The two cases CVC cites regarding the supposed significance of the word "the" are far afield and do not relate to interpreting a discussion from patent specifications. *Rumsfeld v. Padilla,* 542 U.S. 426 (2004), focuses, not on claim construction, but on the word "the" in the habeas

statute while answering the question of who the proper respondent is to a habeas petition. *Id.* at 434-35. In *Shum v. Intel Corp.*, 629 F.3d 1360 (Fed. Cir. 2010), too, the issue was not claim construction, but rather whether the phrase "the prevailing party" in Federal Rule of Civil Procedure 54(d)(1) could be read to encompass multiple prevailing parties where each prevailed on certain issues. *Id.* at 1366-70. Neither *Rumsfeld* nor *Shum*, contrary to CVC's argument, is relevant to the specialized context of Broad's specifications. CVCRespBr52.

For at least these reasons, the sentence on which CVC's entire claim construction argument rests is not definitional.

2. The Broadest Reasonable Interpretation Of "guide RNA" From The Specifications As A Whole Includes The Dual-Molecule RNA Configuration

CVC's brief erroneously dismisses all the intrinsic evidence showing that Broad's construction is the broadest reasonable construction.

1. CVC tries to dismiss Example 6 of the '356 patent as meaningless. CVCRespBr55-56. But that example, entitled "Optimization of Guide RNA for *Streptococcus pyogenes* Cas9," describes

six experiments: three in a dual-molecule configuration and three in a single-molecule ("chimeric") configuration. Appx22814(105:1-106:16). Example 6 thus confirms that "guide RNA" encompasses both configurations, as both configurations are parts of Example 6.

CVC's response ignores the experiments and instead focuses only on the results. According to CVC, because Example 6 reports that the chimeric guide RNA systems worked better than the dual-molecule systems, Example 6 supports limiting "guide RNA" to the single-molecule configuration. CVCRespBr55-56. But the relevant inquiry is not which configuration Example 6 reports was better among those tested, but rather whethera POSITA would have understood that "Guide RNA" in the title encompasses all of the experiments in the example. The results do not change the title, or require the POSITA to ignore the dual-molecule experiments.

2. Regarding claim differentiation, which the PTAB acknowledged "tend[s] to indicate that 'guide RNA' is a generic term" encompassing both configurations (Appx21), CVC once again circularly argues that claim differentiation must give way to the supposed "clear

definition" (CVCRespBr57-59) in the specifications. Relying almost solely on this erroneous assumption, CVC forgoes any substantive response to Broad's points on claim differentiation.

That is, CVC offers no rejoinder to Broad's argument that independent claim 15 of the '359 patent recites "guide RNA" with no particular configuration, but dependent claim 18 adds a limitation: it limits the "guide RNA" of claim 15 to "guide RNAs [that] comprise a guide sequence fused to a tracr sequence," *i.e.*, a single-molecule configuration. Appx3113. Of course, if CVC's construction were correct, claim 18 would be redundant of claim 15 and the supposed words of limitation in claim 18 would have no meaning. That is improper under well-established claim construction principles. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1324 (Fed. Cir. 2005) (*en banc*) ("The inclusion of such a specific limitation on the term [at issue] in [dependent] claim 2 makes it likely that the patentee did not contemplate that the term [at issue] already contained that limitation.") (citing *Dow Chem. Co. v. United States*, 226 F.3d 1334, 1341-42 (Fed. Cir. 2000) (concluding that an independent claim should be given broader scope than a dependent claim to avoid

rendering the dependent claim redundant)); *Karlin Tech. Inc. v. Surgical Dynamics, Inc.*, 177 F.3d 968, 971-72 (Fed. Cir. 1999) ("The doctrine of claim differentiation … is ultimately based on the common sense notion that different words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope ... normally means that limitations stated in dependent claims are not to be read into the independent claims from which they depend.") (internal citations omitted).

CVC's only response is to offer the *ipse dixit* that claim differentiation is not a "strict rule" (pointing to a claim not at issue here) and the erroneous argument that the doctrine must "give way" here to the imagined "clear definition in the specifications." CVCRespBr59. But, unlike the cases CVC cites, including *GPNE Corp. v. Apple Inc.*, 830 F.3d 1365 (Fed. Cir. 2016), dependent claim 18 of the '359 patent differs from independent claim 15 *only* in that it requires the guide sequence and tracr sequence to be "fused," *i.e.*, in the single-molecule configuration. Moreover, again unlike in CVC's cited cases (*GPNE*, 830 F.3d at 1371 ("the specification and the prosecution history so consistently describe

'nodes' as pagers,'…")), here the specifications do not define "guide RNA" as limited to the single-molecule configuration. *See also Hill-Rom Services, Inc. v. Stryker Corp.*, 755 F.3d 1367, 1374 (Fed. Cir. 2014) ("However, nothing in this specification or prosecution history rebuts the presumption established by the doctrine of claim differentiation.").

3. CVC's discussion (CVCRespBr56) of Column 38 of the '308 patent is beside the point. Of course, there are references in the specification in which the "guide RNA" is in the single-molecule configuration—that is one of the aspects of the disclosed invention. But the relevant question is whether the specifications *limit* "guide RNA" to only the single-molecule RNA configuration for the invention as a whole, not whether that configuration is disclosed in the specifications.

4. CVC stands the law on its head when it says that a preferred embodiment "sheds no light" on the meaning of "guide RNA." CVCRespBr57. CVC overlooks the case law establishing that a construction like the PTAB's here that reads out embodiments, especially preferred embodiments, is "rarely, if ever, correct." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996); *MBO Labs., Inc.*

v. Becton, Dickinson & Co., 474 F.3d 1323, 1333 (Fed. Cir. 2007); *Oatey Co. v. IPS Corp.*, 514 F.3d 1271, 1276 (Fed. Cir. 2008) ("We normally do not interpret claim terms in a way that excludes embodiments disclosed in the specification.") (internal citations omitted).

For these reasons, the specifications as a whole show that the broadest reasonable interpretation of "guide RNA" is not limited to the single-molecule configuration.

3. Broad's Construction Is Supported By Dr. Zhang's Earliest CRISPR-Cas9 Work Because That Work Was Directed To Dual-Molecule RNA Systems

Many of Broad's claims are broader than the single-molecule configuration of the CRISPR-Cas9 systems, also encompassing dual-molecule configuration CRISPR-Cas9 systems for use in eukaryotic cells; Dr. Zhang had been working with the dual-molecule configuration since early 2011.

Broad's earliest work on CRISPR-Cas9 systems in eukaryotic cells—and its best proofs on the interfering eukaryotic subject matter—date to early 2011 and included experiments with the dual-molecule RNA configuration. Appx19366-19370(¶¶7.1-7.13). In February 2011, Zhang

began repurposing CRISPR-Cas9 systems to edit genes in eukaryotic cells. Appx19366-19367(¶7.2). Thereafter, in 2011 and 2012, Zhang designed several CRISPR-Cas9 systems for gene editing in eukaryotic cells using the dual-molecule RNA configuration. Appx19367-19370(¶¶ 7.3-7.13); *see also* Appx19337-19353(¶¶5.97-5.146).

This early dual-molecule guide RNA work is reflected in the specifications and in the Cong 2013 reference. Appx19366-19369(¶¶7.2-7.6). For instance, Cong 2013 (Appx5566-5596) describes experiments in which the RNA components were expressed separately—a dual-molecule RNA configuration. Figure 1B illustrates this concept. Appx5569.

After Cong 2013 sets forth the dual-molecule work, it discloses that Broad "explored the generalizability of RNA-guided genome editing in eukaryotic cells" by, among other things, "adapt[ing] a chimeric crRNA-tracrRNA hybrid," *i.e.*, a single-molecule RNA construct. Appx5567. Cong 2013 reported eukaryotic function for the CRISPR-Cas9 systems that Zhang engineered using both the dual-molecule and the single-molecule configurations. Appx17467-17469, Appx19367-19370(¶¶7.3-7.13), Appx5569, Appx18231 (Fig4B). And Broad, unlike CVC, was the

first to achieve success in a eukaryotic system, and did so with both configurations of RNA. These successes were both disclosed in the patent specifications and are encompassed within the scope of the relevant claims.

D. If The Court Reaches The Cross-Appeal Issues, It Has Discretion To Address Claim Construction Even If The Construction Would Not Affect The Decisions On Preliminary Motions 2 And 3

This Court has the discretion to construe claim terms even if they do not affect the judgment on appeal. *See, e.g.*, *Thorner*, 669 F.3d at 1369 (construing a term at the appellant's request). There are two interferences, Nos. 106,126 and 106,133, currently pending before the PTAB that may be impacted by the construction of the term "guide RNA." In fact, the PTAB has stayed both interferences pending this Court's decision in this appeal. Thus, if the Court reaches the cross-appeal issues, it would serve the public interest and ultimately conserve judicial resources for the Court to review the PTAB's erroneous claim construction in this proceeding. Doing so would allow all proceedings to operate under the proper construction moving forward. Claim

construction is, of course, a question of law, and the parties' briefs both here and before the PTAB fully address it.

II. CVC's "Independent Bases" Argument Is Meritless

As noted in the Introduction, CVC contends that grounds other than claim construction independently support the PTAB's decisions on Motions 2 and 3. CVCRespBr43-49. Broad disagrees. The PTAB should be permitted to resolve that dispute with the benefit of this Court's guidance regarding the true scope of Broad's claims.

A. The PTAB Correctly Treated Claim Construction As The Threshold Issue For Preliminary Motions 2 And 3

The PTAB treated claim construction as the threshold issue and devoted 20 pages of detailed analysis to the construction of "guide RNA" *before* taking up and then deciding Motions 2 and 3. Appx14-33.

In these circumstances, the PTAB's incorrect claim construction necessarily impacted the decisions on Motions 2 and 3. Confirming this, the PTAB's decision expressly links claim construction to the decisions on the two motions. *See, e.g.*, Appx39-40(39:22-40:1) ("Because Broad fails to persuade us that a majority of its claims are generic as to RNA

configuration, we are not persuaded by the argument that the interference is only about eukaryotic CRISPR-Cas9 systems."); Appx40(40:6-8) ("Although Broad characterizes its 'best proofs' as including the use of a dual-molecule guide RNA, Broad fails to persuade us in Motion 2 that its claims, properly interpreted, encompass this subject matter."); Appx43(43:6-9) ("Rather, our denials of Broad Motions 1 and 2 are based on a failure of Broad to meet its burdens. For example, in Motion 2 Broad failed to meet its burden of persuading us of its argument that the majority of its claims are properly interpreted as encompassing a generic configuration of RNA molecules.").

CVC contends that, even if Broad ties the claim construction errors to the decisions on Motions 2 and 3, the PTAB would need a "compelling reason" to change the count (Motion 2). CVCRespBr39. But, what could be more compelling than a change in the claim construction that shows that Count 1 is limited in a way that the majority of Broad's claims are not? CVC also concedes that the PTAB denied Motion 3 because "'guide RNA' did not need to be de-designated from the count because that term meant single-guide RNA." CVCRespBr41.

The PTAB's incorrect and overly narrow construction of "guide RNA" plainly influenced its decisions on Motions 2 and 3. Importantly, Broad is not seeking an outright reversal of the PTAB's rulings on the motions; it seeks only to vacate the decisions and to correct the claim construction so that the PTAB can decide the issues in the motions on remand in light of the proper claim construction.

B. Preliminary Motions 2 And 3 Sought To Ensure That The Scope Of The Count Corresponded To The Scope Of Broad's Claims

At the end of the day, the point of Motion 2 and Contingent Motion 3—together—was to bring the scope of the count of the interference in line with the scope of the involved claims, under the proper claim construction. It is undisputed that Count 1 is limited to single-molecule RNA systems; but, as shown above, Broad has involved claims that are not so limited.

1. Motion 2 Sought To Broaden The Count To Encompass All Of Broad's Claims

Motion 2 thus sought to broaden the count to encompass both the single- and dual-molecule configurations of CRISPR-Cas9 systems for

use in eukaryotic cells because Broad's work, and its involved claims, encompassed both configurations. This was Broad's preferred relief because it would not only give the count and the claims the same scope, but would also allow both parties to use their best proofs on priority.

Thus, granting Motion 2 and broadening the count would have allowed the interference to proceed on even grounds by allowing proofs on CRISPR-Cas9 work in eukaryotic cells with both the dual-molecule RNA configuration ***and*** the single-molecule RNA configuration.

2. Motion 3 Sought To Remove Broad's Generic Claims If The Interference Remained Limited To The Single-Molecule Configuration

Contingent Motion 3 sought to achieve fairness in a different way. If the PTAB decided to deny Motion 2 and retain Count 1, then Motion 3, in relevant part, asked that the PTAB remove from the interference those claims reciting "guide RNA" that were not clearly limited to the single-molecule configuration. This way too, the involved claims would be commensurate with the scope of the count of the interference.

3. The PTAB Erred In Not Granting Either Motion 2 Or Motion 3

By simultaneously retaining Count 1 (denying Motion 2), while keeping Broad's generic RNA claims in the interference (denying Motion 3), the PTAB created a disconnect: Count 1 was not commensurate in scope with the involved claims and this worked a significant unfairness to Broad. Under the PTAB's decision, the interference was not fulfilling its "primary purpose" of determining priority over "the common inventions claimed by the parties." *Godtfredsen v. Banner,* 598 F.2d 589, 592 (C.C.P.A. 1979) (overruled on other grounds).

CVC responds only by complaining that Broad sought an "unfair advantage" by not also seeking to have CVC's generic claims removed from the interference. CVCRespBr48. But CVC is no stranger to PTAB practice and could have itself sought any relief that it deemed appropriate, including moving contingently. Regardless of whether CVC's generic claims remained in the interference, a narrow count with a much broader set of Broad's involved claims was legally improper and unfair to Broad.

CONCLUSION

For the foregoing reasons, as well as the reasons set forth in Broad's Opening Brief, if the Court considers the cross-appeal it should reverse the PTAB's improperly limited claim construction, give "guide RNA" its proper broadest reasonable interpretation, and vacate the decisions on Motions 2 and 3 for the PTAB to consider anew on remand under the proper claim construction.

Respectfully submitted,

July 24, 2023

/s/ Raymond N. Nimrod
Counsel for Cross-Appellants, The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College

CERTIFICATE OF SERVICE

I hereby certify that on this 24th day of July 2023, I caused the foregoing brief to be filed with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit through the Court's CM/ECF system.

Participants in this case who are registered CM/ECF users will be served by the appellate CM/ECF system.

/s/ Raymond N. Nimrod

CERTIFICATE OF COMPLIANCE

In accordance with Circuit Rule 32(a)(5) and Rule 32(a)(7)(B) of the Federal Rules of Appellate Procedure, the undersigned certifies that the accompanying brief has been prepared using 14-point Century Schoolbook typeface, and is double-spaced (except for headings and footnotes).

The undersigned further certifies that the brief is proportionally spaced and contains 5,233 words exclusive of the certificate required by Circuit Rule 28(a)(1), table of contents, table of authorities, signature lines, and certificates of service and compliance. The undersigned used Microsoft Word 365 to compute the count.

/s/ Raymond N. Nimrod