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

CORRECTED OPENING 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

Count 1

U.S. Patent No. 8,697,359, Claim 18

The CRISPR-Cas system of claim 15, wherein the guide RNAs comprise a guide sequence fused to a tracr sequence.

Claim 15 recites:

An engineered, programmable, non-naturally occurring Type II CRISPR-Cas system comprising a Cas9 protein and at least one guide RNA that targets and hybridizes to a target sequence of a DNA molecule in a eukaryotic cell, wherein the DNA molecule encodes and the eukaryotic cell expresses at least one gene product and the Cas9 protein cleaves the DNA molecules, whereby expression of the at least one gene product is altered; and, wherein the Cas9 protein and the guide RNA do not naturally occur together.

-OR-

U.S. Patent Application No. 15/981,807, Claim 156

A eukaryotic cell comprising a target DNA molecule and an engineered and/or nonnaturally occurring Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)—CRISPR associated (Cas) (CRISPR-Cas) system comprising

a) a Cas9 protein, or a nucleic acid comprising a nucleotide sequence encoding said Cas9 protein; and

b) a single molecule DNA-targeting RNA, or a nucleic acid comprising a nucleotide sequence encoding said single molecule DNA-targeting RNA; wherein the single molecule DNA-targeting RNA comprises:

i) a targeter-RNA that is capable of hybridizing with a target sequence in the target DNA molecule, and

ii) an activator-RNA that is capable of hybridizing with the targeter-RNA to form a double-stranded RNA duplex of a protein-binding segment, wherein the activator-RNA and the targeter-RNA are covalently linked to one another with intervening nucleotides; and wherein the single molecule DNA-targeting RNA is capable of forming a complex with the Cas9 protein, thereby targeting the Cas9 protein to the target DNA molecule, whereby said system is capable of cleaving or editing the target DNA molecule or modulating transcription of at least one gene encoded by the target DNA molecule.

CERTIFICATE OF INTEREST

Counsel for Cross-Appellants, The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College certifies the following:

1. The full name of every party represented by me is:

The Broad Institute, Inc.

Massachusetts Institute of Technology

President and Fellows of Harvard College

2. The names of the real parties in interest represented by me is:

None

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

None

4. The names of all law firms and the partners or associates who appeared for the parties now represented by me before the Patent Trial and Appeal Board, or are expected to appear in this Court, are:

Zachariah Summers, Quinn Emanuel Urquhart & Sullivan LLP

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal are:

The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College *v.* ToolGen, Inc., Patent Interference No. 106,126 (DK) (PTAB)(suspended pending this appeal)

The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College *v.* Sigma-Aldrich Co., LLC, Patent Interference No. 106,133 (DK) (PTAB)(suspended pending this appeal)

The Regents of the University of California, University of Vienna, and Emmanuelle Charpentier *v.* ToolGen, Inc., Patent Interference No. 106,127 (DK) (PTAB)(suspended pending this appeal)

The Regents of the University of California, University of Vienna, and Emmanuelle Charpentier *v.* Sigma-Aldrich Co., LLC, Patent Interference No. 106,132 (DK) (PTAB)(suspended pending this appeal)

DATE: February 15, 2023 /s/ Raymond N. Nimrod

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTORY AUTHORITIES

RULES AND REGULATIONS

TABLE OF ABBREVIATIONS

Parties

CVC	Regents of the University of California, University of Vienna, and Emmanuelle Charpentier
Broad	The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College

Patents and Applications

B1	Broad's Provisional App. No. 61/736,527 (Appx211-562)
P1	CVC's Provisional App. No. 61/652,086 (Appx563-759)
P2	CVC's Provisional App. No. 61/716,256 (Appx760-1038)
P3	CVC's Provisional App. No. 61/757,640 (Appx1039-1417)
'359 Patent	Broad Patent No. 8,697,359 (Appx17564-17680)

Defined Terms

048 Interference	Interference No. 106,048
115 Interference	Interference No. 106,115
APA	Administrative Procedures Act
Cong 2013	Cong *et al.*, Multiplex Genome Engineering Using CRISPR/Cas Systems, 339(6121) SCIENCE 819-823 (2013) with Supplemental Material (Appx5566-5596)
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CVC I	*Regents of Univ. of California v. Broad Inst., Inc.*, 903 F.3d 1286 (Fed. Cir. 2018)

Jinek 2012	Jinek *et al.*, A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity, 337(6096) SCIENCE 816-821 (2012) (Appx5597-5602)
POSITA	Person of ordinary skill in the art

STATEMENT OF RELATED CASES

No other appeal in or from this Interference was previously before this Court or any other appellate court.

This is, however, the second appeal from a patent interference concerning the same parties, CRISPR-Cas9 subject matter, and many of the same Broad patent claims. The prior interference, Interference 106,048, ended when the PTAB granted Broad's motion for a judgment of no interference-in-fact. This Court affirmed, concluding that substantial evidence supported the PTAB's findings. *Regents of Univ. of California v. Broad Inst., Inc.*, 903 F.3d 1286 (Fed. Cir. 2018)(*CVC I*).

In the present interference, the PTAB held that *CVC I* does not control the outcome here (Appx159), but noted "the relevant facts considered in the prior interference may be similar to and overlapping with the relevant facts" at issue in this interference. Appx82.

Counsel for Cross-Appellants are aware of the following four other Patent Interferences currently pending in the PTAB that may be directly affected by this Court's decision in this appeal:

> The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College v. ToolGen, Inc., Patent Interference No. 106,126 (DK) (PTAB)(suspended pending this appeal)

The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College v. Sigma-Aldrich Co., LLC, Patent Interference No. 106,133 (DK) (PTAB)(suspended pending this appeal)

The Regents of the University of California, University of Vienna, and Emmanuelle Charpentier v. ToolGen, Inc., Patent Interference No. 106,127 (DK) (PTAB)(suspended pending this appeal)

The Regents of the University of California, University of Vienna, and Emmanuelle Charpentier v. Sigma-Aldrich Co., LLC, Patent Interference No. 106,132 (DK) (PTAB)(suspended pending this appeal)

INTRODUCTION

In this Interference, CVC asserted that it was the first to conceive of and reduce to practice the subject matter of Count 1, directed to using engineered CRISPR-Cas9 systems to modify DNA in eukaryotic cells. Substantial evidence supports the PTAB's decision rejecting CVC's assertion.

In an interference, the PTAB determines which party has priority of invention and is entitled to patent claims encompassing the disputed subject matter (the "count"). Pre-AIA, priority goes to the first party to reduce the invention of the count to practice unless the other party can show that it was first to conceive the invention and exercised reasonable diligence toward a later reduction to practice. *See Cooper v. Goldfarb*, 154 F.3d 1321, 1327 (Fed. Cir. 1998). As the Junior Party, CVC had the burden to show that it was entitled to priority over Broad.

As the PTAB found—and CVC does not dispute—Broad had a corroborated actual reduction to practice at least by October 5, 2012, when Dr. Feng Zhang submitted a manuscript to *SCIENCE* describing his successful uses of CRISPR-Cas9 in eukaryotic cells (the October 5 Manuscript). Given this finding, CVC needed to show a complete

conception or reduction to practice before October 5, 2012. CVC failed to do so. Therefore, judgment of priority to Broad was proper.

CVC argued that it had a complete conception by March 1, 2012; but the evidence, including CVC's repeated failures and the inventors' communications regarding those continuing failures in the following months, revealed they lacked any settled plan for how to create the functional eukaryotic CRISPR-Cas9 system of Count 1. Indeed, even by mid-October 2012, CVC's extensive experiments were failing, its scientists and their collaborators were struggling with a plethora of potentially insurmountable problems, and CVC's inventors lacked any plan for overcoming the fundamental problems plaguing their system.

The PTAB recited and applied the correct, objective legal standard for conception: "Conception is complete only when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, *without extensive research or experimentation*." Appx138 (quoting *Burroughs Wellcome Co. v. Barr Lab., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994)).[1] This is exactly the

[1] All emphases in this brief are supplied unless otherwise noted.

standard CVC urged the PTAB to use. Appx66858 (CVC quoting *Burroughs*).

The PTAB made numerous findings under this standard, including the following three key fact-findings:

(1) CVC's inventors and their collaborators, all at least of ordinary skill, engaged in extensive research and experimentation in their failed attempts to implement CVC's hope for a functional eukaryotic CRISPR-Cas9 system (Appx158);

(2) CVC's course of experimentation after their purported conceptions revealed uncertainty that so undermined the specificity of the inventors' idea that it was not a definite and permanent reflection of the complete invention (Appx159); and

(3) CVC's inventors lacked a clear plan for addressing the multiple failures encountered during the long course of experimentation (Appx157; Appx183).

Thus, the PTAB concluded that CVC failed to prove conception as of March 1 or any date before October 5, 2012. Substantial evidence supports the PTAB's finding that CVC lacked a conception.

As to written description, substantial evidence similarly supports the PTAB's findings that neither P1 nor P2 included adequate support under §112 for an embodiment of Count 1. Neither P1 nor P2 disclosed an experiment in eukaryotic cells; nor did they include instructions or disclosures showing that CVC's inventors possessed the invention at issue—a functional eukaryotic CRISPR-Cas9 system—in this highly unpredictable art.

The PTAB's decisions comprise 180-plus pages, hundreds of record citations, and numerous credibility findings; its determinations are the epitome of reasoned decision-making under the APA.

Regarding Broad's conditional cross appeal (which the Court need not address if it affirms the priority decision), the PTAB interpreted Broad's claim term "guide RNA" too narrowly by limiting it to "only a single-molecule RNA configuration," excluding dual-molecule RNA configurations.

JURISDICTIONAL STATEMENT

Broad agrees with CVC's jurisdictional statement; jurisdiction similarly exists over Broad's timely filed cross-appeal.

COUNTER-STATEMENT OF ISSUES

On CVC's Appeal:

1. Whether substantial evidence supports any of the PTAB's dispositive fact-findings on conception, including that:

(1) CVC's inventors and their collaborators, all of at least ordinary skill, engaged in extensive research and experimentation in their failed attempts to implement CVC's hope for a functional eukaryotic CRISPR-Cas9 system;

(2) CVC's course of experimentation after their purported conceptions revealed uncertainty that so undermined the specificity of the inventors' idea that it was not a definite and permanent reflection of the complete invention; and

(3) CVC's inventors lacked a clear plan for addressing the multiple failures encountered during the long course of experimentation.

2. Whether the PTAB's thorough, 180-page analysis satisfies the APA's reasoned-decision making requirement.

3. Whether substantial evidence supports the PTAB's findings that CVC failed to show that either P1 or P2 adequately support the invention of Count 1.

On Broad's Conditional Cross-Appeal:

1. Whether the PTAB erred in giving "guide RNA" a narrow construction rather than the broadest reasonable interpretation.

2. Whether the PTAB erred in denying Broad's Motions 2 and 3 based on this narrow claim construction.

COUNTER-STATEMENT OF THE CASE

I. The 048 Interference

In the 048 Interference, CVC attempted to strip Broad of its eukaryotic CRISPR-Cas9 claims by provoking an interference between CVC's environment-free claims and Broad's eukaryotic claims.[2] In that Interference, the PTAB granted Broad's motion for no interference-in-fact, which this Court affirmed. *CVC I*, 903 F.3d at 1289. As a result, Broad kept its eukaryotic claims and CVC kept its environment-free claims. CVC now has patents—not at issue here—claiming the environment-free subject matter, including sgRNA claims.

In *CVC I*, this Court found that "[i]n light of the record evidence, which includes expert testimony, contemporaneous statements made by skilled artisans, statements by the [CVC] inventors themselves, and prior art failures, we conclude that the Board's fact-finding as to a lack of reasonable expectation of success [in eukaryotic cells] is supported by substantial evidence." *Id*. at 1294. This Court identified numerous categories of substantial evidence supporting the PTAB's findings:

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[2] All of Broad's patents and the application in *CVC I* are at issue here. One additional, later-issued Broad patent—U.S. Patent No. 9,840,713—is also at issue here.

- The "statements by the [CVC] inventors acknowledging doubts and frustrations about engineering CRISPR-Cas9 systems to function in eukaryotic cells and noting the significance of Broad's success." *Id*. at 1293.

- The contemporary observations of CVC's expert Dr. Dana Carroll who, in a September 2012 review of Jinek 2012, raised specific reasons why CRISPR-Cas9 may not work in eukaryotic cells. *Id*. at 1292-93.

- The material differences between eukaryotic and prokaryotic cells that would present potentially insurmountable challenges in adapting the prokaryotic CRISPR-Cas9 system to eukaryotic cell uses. *Id*. at 1292.

- The historical struggles and failures in attempting to adapt other prokaryotic systems, such as Group II Introns, for use in eukaryotes. *Id*. at 1293-94.

The PTAB relied on these same categories of evidence, and more, in its decisions in this Interference.

II. The Challenges Of Engineering Functional Eukaryotic CRISPR-Cas9 Systems

Count 1 requires a CRISPR-Cas9 system with a single-molecule guide RNA (sometimes called "sgRNA"[3]) that functions in eukaryotic cells. Engineering a functional eukaryotic CRISPR-Cas9 system presented myriad, and potentially insurmountable, challenges.

[3] The term "sgRNA" refers to the single-molecule guide RNA configuration of a CRISPR-Cas9 system. sgRNA is sometimes referred to as RNA with the components "fused" or as "chimeric RNA."

A. CRISPR-Cas9 Systems Occur Naturally Only In Prokaryotic Cells, Which Are Much Simpler Than Eukaryotic Cells

Eukaryotic cells have a nucleus and can make up multi-celled organisms such as plants and animals. In contrast, prokaryotic cells (*e.g.*, bacteria) have no nucleus and are unicellular. Eukaryotic cells are much more complex than prokaryotic cells.

CRISPR-Cas9 systems, which are protein:RNA complexes, occur naturally only in prokaryotes, and serve as defense mechanisms against pathogens. Appx54927(¶30-31). The protein component includes Cas9. The RNA components (crRNA and tracrRNA) hybridize to form an RNA duplex. *Id*; *see also* Appx54931(¶38); Appx54965(¶129). That RNA duplex directs the Cas9:RNA complex to its DNA target, where the system may cleave target DNA in the prokaryotic cell.

As noted, significant differences exist between prokaryotic and eukaryotic cells, stemming from a 1.5-billion-year evolutionary divergence, including:

- Eukaryotic cells have a nucleus protecting genomic DNA, organized into discrete structures, called chromosomes, composed of a protein/DNA complex called chromatin. Appx54963(¶124); Appx54968-54970(¶¶139-43).

- Prokaryotic cells lack nearly all the structural organization found in eukaryotic cells, such as a nucleus and chromatin, that functions to organize and protect DNA. Appx54967(¶136); Appx54969-54970(¶¶140-41).

- Eukaryotic cells employ different cellular machinery and mechanisms to express genes, relying on proteins and complexes not found in prokaryotic cells. Appx54947(¶77). Those proteins and complexes can be essential to the proper transcription and translation of genetic material. Appx54966(¶132).

- Prokaryotic and eukaryotic cells have different environments, including different intracellular temperatures, ion concentrations, and pH. *Id*.

- Prokaryotic systems expressed in eukaryotic cells are often destroyed by native eukaryotic defense mechanisms. Appx54964-54966(¶¶127-30).

Based on those differences, 2012 POSITAs knew there were many obstacles to adapting prokaryotic protein:RNA complexes for use in eukaryotes, including:

(1) delivery into the eukaryotic cell,

(2) expression of the components in the cell,

(3) surviving eukaryotic defense mechanisms,

(4) formation of the protein:RNA complex,

(5) toxicity to the cell,

(6) proper protein folding,

(7) localization in the nucleus,

(8) access to the desired DNA target in the chromatin, and

(9) cleavage of the DNA.

Appx54962-54963(¶124). Illustrating this, prior-art attempts to adapt other prokaryotic systems for eukaryotic use revealed significant obstacles, resulted in largely failed attempts, and exposed a need for a specialized set of conditions for each system to achieve even minimal success. Appx54972-54979(¶¶148-67).

Only one prior attempt of record, Group II introns, included both protein and RNA components, like CRISPR-Cas9. Appx54972-54975(¶¶149-57). The 2012 POSITA knew that, after over 16 years of experimental efforts on Group II introns, researchers ultimately achieved only limited success in modified eukaryotic cells under extremely specialized conditions, including introducing toxic levels of magnesium into the cells. Appx54973(¶153).

B. The CVC Inventors' *In Vitro,* Cell-Free Experiments

CVC's inventors disclosed *in vitro* biochemical studies of CRISPR-Cas9 at a public conference in June 2012. Appx183. These studies—published days later as Jinek 2012—involved CRISPR-Cas9 systems in just cell-free environments, specifically test-tubes containing only the

CRISPR-Cas9 system components and purified DNA targets under simpler and more concentrated conditions than in eukaryotic cells. These studies did not mimic the prokaryotic cell environment, much less address the obstacles presented by eukaryotic cells. Appx54923(¶19). Jinek 2012 disclosed experiments using either dual-molecule RNA or sgRNA. To create the sgRNA, CVC used prior art techniques to link the tracrRNA and crRNA. Appx19480(¶4.35).

Before the interferences, CVC's inventors admitted that it was still unknown after Jinek 2012's *in vitro* experiments whether CRISPR-Cas9 could be adapted to work in eukaryotic cells. For example, Dr. Jennifer Doudna stated, after Jinek 2012 published, that "getting CRISPR to work in human cells" would be "*a profound discovery*." Appx5644. She stated in 2014, after publication of Broad's success in eukaryotes, that "[o]ur [Jinek] 2012 paper was a big success, but there was a problem. We weren't sure if CRISPR/Cas9 would work in eukaryotes—plant and animal cells." Appx49994. Explaining her uncertainty, she said, "[u]nlike bacteria, plant and animal cells have a cell nucleus, and inside, DNA is stored in a tightly wound form, bound in a structure called chromatin." *Id.*

The scientific community similarly doubted that CRISPR-Cas9 could be engineered to work in eukaryotic cells. In September 2012, eukaryotic-genome-editing expert Dr. Dana Carroll, later a CVC expert witness, published a review of Jinek 2012, identifying serious reasons for doubt. Appx49991. For example, he observed that eukaryotic enzymes could degrade the RNA components in CRISPR-Cas9 systems or the systems could fail to overcome chromatin. *Id*.

III. Zhang's Invention Of Functional Eukaryotic CRISPR-Cas9 Systems

Zhang was uniquely situated to become the first scientist to conceive of and reduce to practice engineered CRISPR-Cas9 systems for use in eukaryotic cells. Before 2011, *THE SCIENTIST* called him the "Midas of Methods" for his feat of adapting a pond scum protein to function in eukaryotic cells. Appx88788-88789. As a Junior Fellow at Harvard, he applied TALENs (transcription activator-like effector nucleases) in a new way—to control transcription of genes in human cells. Appx75019(¶¶45-46). By 2010, at just age 27, Zhang had accepted

appointments at Broad and MIT, and founded his Broad laboratory. Appx75020(¶47).

Zhang first learned of prokaryotic CRISPR systems in February 2011, and immediately recognized the potential for repurposing these systems for use in eukaryotic cells. Appx74998(¶5).

A. 2011: Zhang Identifies The Necessary Components For A Functional Eukaryotic CRISPR-Cas9 System

By April 2011, well before Jinek 2012, Zhang recognized the three components of CRISPR-Cas9 necessary as a starting point for engineering the system to work in eukaryotic cells: Cas9, crRNA, and tracrRNA. Appx75028-75034(¶¶66-70). He understood that tracrRNA was a necessary part of the CRISPR complex responsible for cutting DNA. Specifically, he understood from a March 2011 publication (Appx18383-18447) by Dr. Emmanuelle Charpentier and others that tracrRNA formed a persistent duplex with crRNA and that this RNA duplex formed a complex with Cas9—the cutting complex that cleaved DNA. Appx74998-74999(¶6); Appx75028-75034(¶¶66-70); Appx76211-76213(¶5).

In August 2011, Zhang designed and ordered a vector to express tracrRNA and pre-crRNA in eukaryotic cells. Appx75034-75035(¶79).

By late 2011, he successfully used this system, which included his codon-optimized (humanized) Cas9 from *S. thermophilus* bacteria, in proof-of-concept experiments to cleave DNA in human cells. Appx75035-75038(¶¶80-82,84); Appx76210-76216(¶¶3-9).

B. January-June 2012: Zhang Continues To Develop Eukaryotic Dual-Molecule RNA CRISPR-Cas9 Systems

Given his 2011 successes, Zhang included in a January 2012 grant proposal an engineered, eukaryotic dual-molecule RNA CRISPR-Cas9 system. Appx18231; Appx75039-75041(¶¶87-91).

Zhang then started experimenting with a different Cas9 ortholog (SpCas9), from *S. pyogenes* bacteria; but SpCas9 was not expressing as well in human cells as his hStCas9[4] system. Appx75043-75045(¶¶96-98); *see also* Appx75916(¶6). On March 1, 2012, Zhang created a design for a human-codon-optimized version of SpCas9. Appx75045(¶99). Zhang then showed that his engineered hSpCas9 properly expressed and formed an active Cas9:RNA complex to cleave DNA in a eukaryotic cell. Appx75048-75050(¶¶106-08).

[4] An "hStCas9" means Cas9 from *S. Thermophilus* ("St") that has been engineered for translation in human cells via codon optimization ("h" means "humanized").

With this success, Zhang modified the hSpCas9 to facilitate delivery into the nucleus; with improved delivery into the nucleus, the hSpCas9 system could efficiently cut genomic targets. Appx75051-75052(¶¶110-13). Throughout 2012, Zhang continued planning and running successful experiments using dual-molecule RNA hSpCas9 systems in eukaryotic cells. Appx5566–5570.

As part of his 2012 work, Zhang collaborated with Dr. Luciano Marraffini of Rockefeller University. Marraffini focused solely on prokaryotic CRISPR systems; he was not privy to all of Zhang's eukaryotic experiments. Appx75041-75043(¶¶93-95). Neither Marraffini nor his lab performed CRISPR-Cas9 experiments in eukaryotic cells. *Id*.

C. June 26, 2012 Conception Of Count 1: Zhang Adds Single-Molecule RNA (sgRNA) Experiments To His Continuing Dual-Molecule RNA Work

On June 26, 2012, Zhang received an email from Marraffini about a single-molecule version of CRISPR-Cas9 RNA that Marraffini learned about at a public conference. Appx77636; Appx75052-75053(¶114). The email referenced only the bare sgRNA design fusing the crRNA and tracrRNA—RNAs of which Zhang was already aware—into one molecule.

Appx77636-77637. Neither the email nor anyone presenting at the conference discussed any technical solutions for the challenges of creating a functional *eukaryotic* CRISPR-Cas9 system.

After learning of the sgRNA variation, Zhang designed experiments to use sgRNA with his functioning hSpCas9 system, in addition to continuing his work with dual-molecule RNA systems. Appx75005-75007(¶¶19-22); Appx75920-75930(¶¶14-25). Contrary to CVC's false narrative (CVCBr16), Zhang did not merely "plug in" sgRNA into standard vectors and methods from his prior TALENs research. Before CVC's public disclosure of sgRNA, Zhang had already developed vectors and methods specifically tailored for eukaryotic CRISPR-Cas9 systems and had overcome the key challenges for making a functional eukaryotic CRISPR-Cas9 system. Appx74999(¶7); Appx75002(¶13); Appx75024-75062(¶¶59-131). Thus, his eukaryotic CRISPR-Cas9 systems were ready for use, including with an sgRNA. As the PTAB found, Zhang applied his knowledge to formulate a definite and permanent idea of a functioning eukaryotic sgRNA CRISPR-Cas9 system. Appx181-182.

D. July 2012: Zhang Creates A Functional Eukaryotic sgRNA System, Thereby Reducing Count 1 To Practice

By July 20, 2012, Zhang successfully used his sgRNA-hSpCas9 system to cleave a genomic target in eukaryotic (mouse) cells. Appx75066-75072(¶¶140-49); Appx75920-75936(¶¶14-32); Appx76553-76554(¶¶35-36). After receiving the results of a surveyor assay on July 20, 2012, Zhang recognized and appreciated the cleavage product showed success, and immediately directed his student to repeat this experiment, which again confirmed success. Appx75073-75090(¶¶150-69); Appx75935-75958(¶¶31-33); Appx76553-76556(¶¶37-43).

Zhang also enlisted a third-party lab to sequence the DNA from the experiment, which further confirmed successful cleavage. Appx75085-75088(¶¶164-66); Appx75948-75957(¶¶45-58).

E. October 5, 2012: Zhang Submits His Manuscript To *SCIENCE* Evidencing And Corroborating His Actual Reductions To Practice of Count 1

On October 5, 2012, Zhang submitted a manuscript to *SCIENCE*, describing his successes with sgRNA and dual-molecule RNA CRISPR-Cas9 systems in both mouse and human cells. Appx77018-77053; Appx75012-75016(¶¶31-38). After peer review, *SCIENCE* published it online on January 3, 2013, as Cong 2013. Appx5566-5570. At that time,

Doudna described Cong 2013, and an accompanying article published with it in *SCIENCE*, as removing "a huge bottleneck in both research and the development of human therapeutics." Appx82044.

Highlighting the enormous impact of Cong 2013, it is the most highly cited CRISPR article in history. Appx75016(¶39).

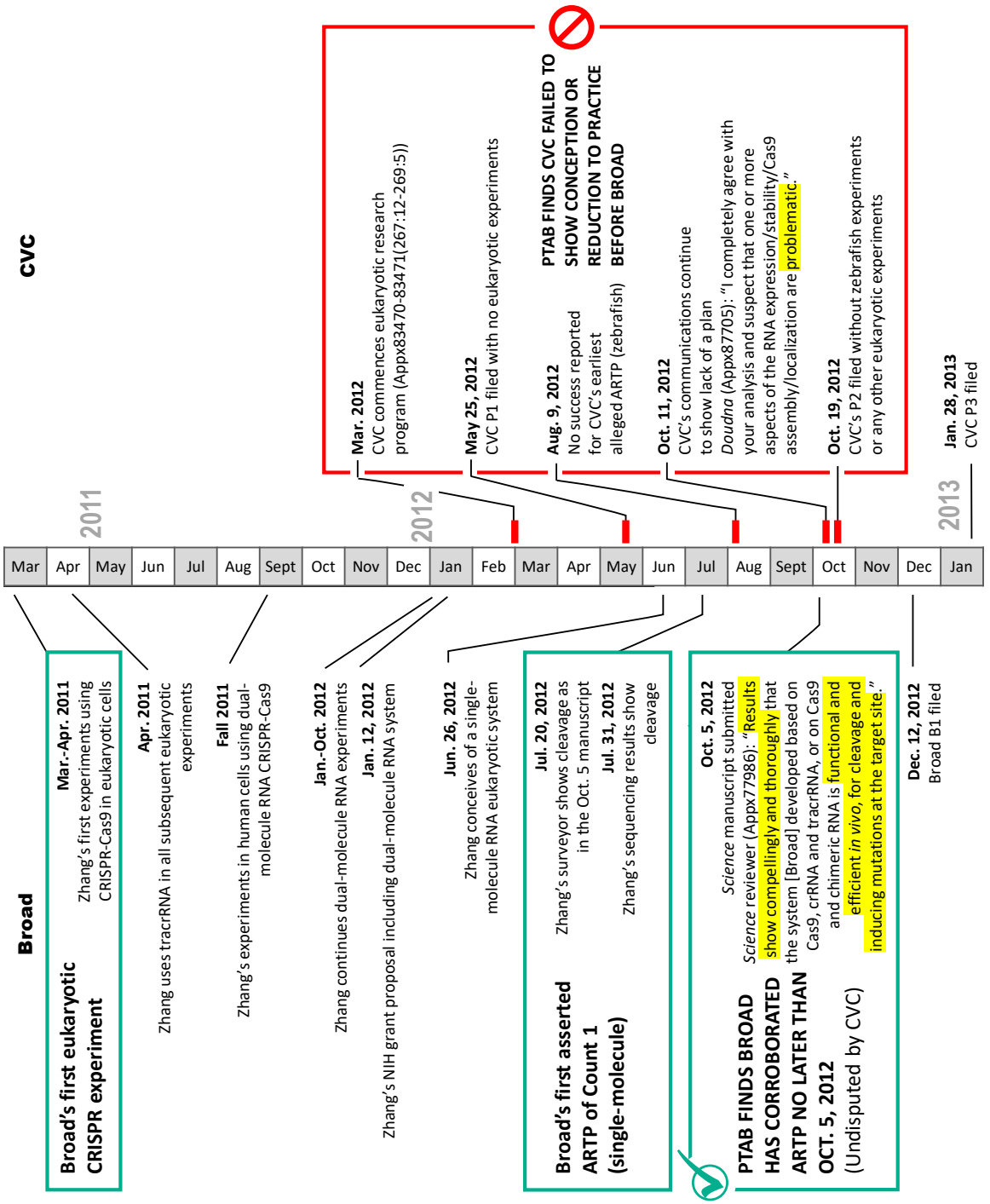
Zhang's laboratory became a leader of the resulting CRISPR revolution, distributing his engineered eukaryotic reagents to more than 2,800 institutions located in 71 countries in response to more than 57,000 requests. Appx75016-75018(¶¶39-42).

F. Summary Timeline

A timeline contrasting Zhang's experiments, starting with his dual-molecule RNA experiments in 2011 and his sgRNA experiments in mid-2012, with CVC's work follows:[5]

[5] Broad created this timeline for this brief to summarize the record evidence.

Timeline of Key Dates



It was Zhang's work, starting well before CVC's alleged conception, that allowed him to determine the technical features of an operable CRISPR-Cas9 eukaryotic system. As the PTAB found, "determination of those features indicated that the Broad inventors had a definite and permanent idea of a system in eukaryotic cells, which lead them to an actual reduction to practice earlier than the CVC inventors." Appx182.

IV. The Decision On Preliminary Motions

Interferences proceed in two phases, a preliminary-motions phase and a priority phase. The preliminary-motions phase may address issues that determine who will be the Junior Party and the Senior Party when determining priority in the second phase. Each party has the burden of persuading the PTAB by a preponderance of the evidence to grant the relief sought in its motions (both preliminary and for priority). *See* 37 C.F.R. § 41.121(b).

In its Motion 1, CVC sought the benefit of the filing date of P1, its earliest provisional application, as its effective filing date; alternatively CVC sought benefit of P2 or P3. If CVC succeeded in showing P1 or P2 was a constructive reduction to practice of Count 1, it would have been the Senior Party. CVC did not.

The PTAB found that CVC failed to show that P1 or P2 adequately described an embodiment of Count 1, in part because P1 and P2 reported only an *in vitro*, cell-free test tube experiment and unsupported assertions that the system would work in far more complicated eukaryotic cells. *See, e.g.*, Appx81; Appx102-105; Appx15679-15680; Appx15682-15683.

The PTAB recognized that where, as here, there is significant unpredictability in the art, many known obstacles, and prior art failures with similar systems, more in the way of description is required (*e.g.*, "specific instructions or conditions" or eukaryotic experiments). Appx90-91. The PTAB ultimately determined that "a preponderance of the evidence indicates possession would not have been understood" based on the disclosures of P1 or P2. The PTAB awarded CVC benefit only of the January 28, 2013 filing date of P3, which included a eukaryotic experiment. Appx102-103.

These rulings impacted the proceedings in two ways relevant to this appeal:

First, CVC remained the Junior Party with the burden of proof on priority.

Second, because it is undisputed on appeal that Broad had a corroborated actual reduction to practice no later than October 5, 2012, the sole issue now is whether substantial evidence supports the PTAB's findings that CVC failed to prove conception or reduction to practice before October 5, 2012.

V. The Decision On Priority

In the priority phase, the motions relevant to CVC's appeal are Broad's Motion 5 for Priority and CVC's Motion 2 for Priority. As to Broad's motion, the PTAB found that Broad showed a corroborated actual reduction to practice at least as early as October 5, 2012, when Zhang submitted the manuscript to *SCIENCE*.[5]

CVC's priority motion argued conceptions of Count 1 as of March 1, April 11, May 28, and June 28, 2012, and further asserted actual reductions to practice by August 9, 2012 in zebrafish cells and October 31, 2012 in human cells. The PTAB denied CVC's motion finding: (1) CVC did not show the zebrafish experiments were an actual reduction to

[5] Because the PTAB found that Broad's October 5, 2012 date predated any conception or reduction to practice by CVC, it did not resolve whether Broad reduced to practice by July 20, 2012. Appx169.

practice, and (2) CVC did not establish conception before October 5, 2012.[6]

A. CVC Failed To Show Conception Before October 5, 2012

The PTAB examined CVC's evidence allegedly showing that its inventors had complete conceptions of a CRISPR-Cas9 system that functioned in eukaryotic cells as of CVC's proffered conception dates and found that CVC had not proven conception as of any of its alleged dates, nor any time before October 5, 2012.

The PTAB found that CVC's inventors and the scientists collaborating with them—all "of at least ordinary skill"—engaged in a "prolonged period of extensive research, experiment and modification." Appx158-159. The PTAB found that CVC's inventors' communications surrounding their experiments reflected "uncertainty that so undermines the specificity of the inventor's idea that it [was] not yet a definite and permanent reflection of the complete invention as it [would] be used in practice." *Id.*

[6] Given these determinations, the PTAB did not need to address CVC's alleged October 31, 2012 reduction to practice. Appx137.

The PTAB also found that CVC's inventors lacked any definite and permanent idea for achieving a functioning eukaryotic system. Appx157. The PTAB found, instead, that CVC's inventors merely had a system they "hoped would work in eukaryotic cells." Appx159.

The PTAB also made multiple credibility determinations adverse to CVC. *E.g.*, Appx155. Moreover, the PTAB rejected CVC's argument that success of other independent researchers, including Zhang, who were unconnected to CVC's inventors and who did not have CVC's alleged plan in hand, somehow proved CVC's conception. Appx179-180.

Thus, the PTAB found that CVC did not show a complete conception.

B. CVC Failed To Show An Actual Reduction To Practice In Zebrafish

The PTAB rejected CVC's argument that its zebrafish experiments were an actual reduction to practice. It is noteworthy that CVC *did not even allege* that its zebrafish experiments were a success during the earlier 048 Interference; rather CVC's earliest alleged eukaryotic actual reduction to practice was October 29, 2012, corresponding to its human cell experiments. Appx18286. CVC's reliance on the zebrafish

experiments is a litigation-inspired resurrection of a failed experiment that never saw the light of day before this Interference.

The PTAB made numerous adverse fact-findings and credibility determinations regarding to the zebrafish experiments. For example, the PTAB noted that, "the apparent importance of the experiments" made it "unclear why [CVC's collaborator Dr. Florian Raible] abandoned them if he believed the CRISPR-Cas9 system designed by the CVC inventors was producing positive results in fish cells." Appx135. Weighing the evidence, the PTAB found "[i]t seems more likely that Dr. Raible's abandonment of the project indicates that he did not recognize any success in 2012," particularly given that after unsuccessful experiments, he "abandoned the project, despite, in his words the 'massive interest' in field." Appx135-136. The PTAB found that CVC failed to point "to contemporaneous evidence showing that Dr. Raible considered the results of the 9 August 2012 experiment to have been successful." Appx125.

The PTAB recognized that successful use of the CRISPR-Cas9 system in zebrafish would have been news about which Doudna and Dr. Martin Jinek would have been told, *and* would have remembered.

Appx132. "Dr. Doudna testified that getting the genome editing [] CRISPR-Cas9 system to work in a fish cell would have been of broad interest and would be publication-worthy in a high impact journal in 2012." *Id.* The PTAB found that "[i]t is unlikely that Dr. Doudna and Dr. Jinek [were] told of results understood by Drs. Chylinski and Charpentier to be the first successful gene modification in a eukaryotic cell by a CRISPR-Cas9 system and forgot it." Appx131. In light of this evidence, the PTAB found that "CVC over-emphasizes isolated words by its inventors to argue that they recognized and appreciated Dr. Raible's results." *Id.*

The PTAB further noted that the zebrafish results were never published, nor even mentioned in CVC's P2 or P3 applications, both filed after the zebrafish experiment. Appx132.

The PTAB was not persuaded by CVC's declaration testimony, finding that contemporaneous lab records contradicted testimony that the experiment was recognized as a success. For example, Dr. Krzysztof Chylinski's August 9, 2012 email to Charpentier merely stated that "there is a hint it might work but we shouldn't be overexcited now." Appx126. As to this "hint," the PTAB found it was unclear if the email

even referred to zebrafish. Appx127. The PTAB also did not credit Chylinski's declaration testimony that contradicted the contemporaneous documents. Appx129.

VI. The PTAB's Determinations Relevant Only To Broad's Conditional Cross-Appeal

The PTAB denied Broad's Motion 2, which sought to broaden the count to enable Broad to present proofs regarding Zhang's dual-molecule RNA research and also denied Broad's Motion 3, which sought to designate certain claims as not corresponding to the sgRNA-limited Count 1. In doing so, the PTAB first addressed a claim-construction issue related to both motions: ascertaining the broadest reasonable interpretation of Broad's claim term "guide RNA."

The PTAB acknowledged that Broad presented persuasive evidence that "guide RNA" includes both single- *and* dual-molecule configurations, but ultimately said it was unable to conclude, after reviewing certain extrinsic evidence, "that the term 'guide RNA' was well known in the art to mean either a single or a dual RNA molecule configuration." Appx26. Relying on one non-definitional sentence in Broad's specification, the PTAB limited "guide RNA" to "only a single-molecule RNA configuration." *Id.*

SUMMARY OF ARGUMENT

The PTAB correctly recited and applied the legal standard from *Burroughs*, 40 F.3d at 1228, that conception "is complete only when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, *without extensive research or experimentation*." Appx138. In contrast, a "conception *is not complete* if the subsequent course of experimentation, especially experimental failures, *reveals uncertainty that so undermines the specificity of the inventor's idea* that it is not yet a definite and permanent reflection of the complete invention *as it will be used in practice*." *Burroughs*, 40 F.3d at 1229; Appx138-139. At both parties' urging, the PTAB applied this objective standard and used it to make many findings adverse to CVC, including three key fact-findings:

Finding #1: The PTAB found that CVC's inventors and collaborating scientists "were of *at least ordinary skill*" and that they engaged in a "prolonged period of *extensive research, experiment, and modification*," in contrast to the exercise of ordinary skill *without extensive* research and experimentation. Appx158-159 (quoting *Burroughs*, 40 F.3d at 1230). Based on this finding, the PTAB

determined that CVC's inventors failed to establish a complete conception. *Id.* This finding alone would warrant affirmance.

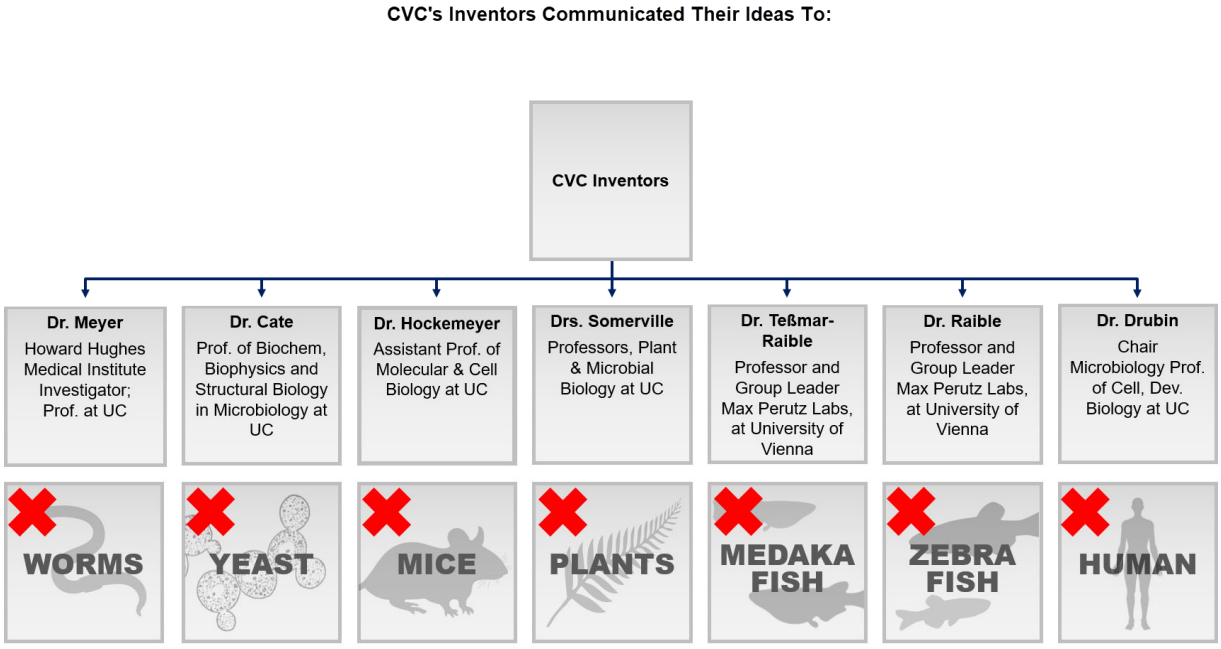
Finding #2: The PTAB found that CVC's inventors' idea fell squarely within *Burroughs*'s category of incomplete conceptions:

> [W]e are persuaded that *the communications surrounding these experiments* reflect "*uncertainty that so undermines the specificity of the inventor's idea* that it [was] not yet a definite and permanent reflection of *the complete invention as it [would] be used in practice*."

Appx158-159 (quoting *Burroughs*, 40 F.3d at 1230 (revisions to *Burroughs*'s quotation original to the PTAB)).

The PTAB's fact-finding was supported by the objective, contemporaneous evidence that many groups of scientists working with or at CVC's behest and armed with CVC's alleged plan were unable to achieve an actual reduction to practice without extensive research, experimentation, and modification. Specifically, CVC enlisted a veritable who's-who of eukaryotic-genome-editing experts—working with cells from worms, yeast, mice, plants, medaka fish, zebrafish, and humans—with the hope that one might find a path to success:[6]

[6] Broad created this demonstrative for this brief to summarize the record evidence.



See Appx83470(267:22-268:7); Appx83851(107:6-22); Appx70024-70025; Appx68835. Although they had CVC's alleged plan in hand, *none* of these world-class labs reported any success before October 5, 2012. And this was no ordinary project. These extraordinarily skilled scientists knew that there would be "massive interest" in any success and publication in a "high-impact" journal. Appx135.

CVC attempts to downplay the struggles and failures of these expert groups and its own inventors, contending that in "only four months" CVC was able to actually reduce the invention to practice by October 31. CVC misses the point in two key regards. *First*, the PTAB found that CVC engaged in extensive *research, experiment, and*

modification during that period. *Second*, regardless of how long they took (and the PTAB did not find it took only four months), the inventors' communications during that period revealed that they lacked a settled plan before conducing the ill-fated experiments and did not have a definite and permanent idea of how to address the obstacles they encountered. Appx156-157.

Finding #3: The PTAB also found that "CVC does not direct us to evidence that any of the inventors had a definite and permanent idea of an sgRNA CRISPR-Cas9 system that would work to edit DNA in eukaryotic cells, particularly when they encountered what was perceived as design problems in their system at that time." Appx157. The PTAB found, instead, that CVC's inventors merely had a system they "hoped would work in eukaryotic cells." Appx159.

The PTAB made multiple credibility determinations—such as finding that the contemporary evidence contradicted CVC's present-day declaration testimony. For example, the PTAB rejected the inventors' testimony that they had definite plans for a functional CRISPR-Cas9 system, finding that "their statements prepared for this proceeding do not reflect these contemporaneous communications." Appx155.

Unable to dispute the substantial evidence supporting the PTAB's findings, CVC accuses the PTAB of "disregard[ing] unrebutted objective evidence that CVC's invention was ready to be handed off to skilled mechanics" based on the success of five other unrelated labs, including Broad. CVCBr28-29, 35-37. CVC's accusation is false; the PTAB squarely addressed this evidence of other labs' alleged success in the context of CVC's conception argument:

> CVC attempts to shift our focus to the *activities of other, competing inventors*, rather than on the activities of its own inventors. We are not persuaded that these other activities are evidence of the *CVC inventors' ideas or of their conception*.

Appx179-180. The PTAB rightfully rejected CVC's argument that alleged success of other researchers, unconnected to CVC's inventors and without CVC's alleged plan in hand, somehow proved CVC's conception.

In rejecting CVC's reliance on the success of Broad's Zhang, the PTAB found that "[t]he Broad inventors' activities and ideas do not inure to CVC, at least because CVC never submitted anything to the Broad inventors for testing." Appx180. Instead, the PTAB found that Zhang already had independently determined the "technical features necessary to achieve success" and that "determination of those [technical] features indicated that the Broad inventors had a definite and permanent idea of

a system in eukaryotic cells, which lead them to an actual reduction to practice earlier than the CVC inventors." Appx182.

CVC incorrectly accuses the PTAB of making two legal errors.

Purported Legal Error on Conception #1: CVC asserts that "this Court's precedents required the PTAB to determine whether CVC's invention was sufficiently complete that it was ready for skilled artisans to reduce it to practice *without further invention*." CVCBr2. But, CVC never raised this as the legal standard for conception before the PTAB and so it is inappropriate for CVC to assert the PTAB erred on a point never brought before it. Before the PTAB, CVC advanced the "without extensive research or experimentation" legal standard, citing *Burroughs*. Appx66858(quoting *Burroughs*, 40 F.3d at 1228). It appears that CVC now advances this new formulation because it cannot overcome the PTAB's findings, including that CVC and its collaborators engaged in "*extensive research, experiment, and modification*."

Purported Legal Error on Conception #2: CVC argues that the PTAB "legally erred by insisting that inventors must know their invention would work for conception to be complete." CVCBr32. The PTAB did no such thing. Nowhere in the 23-plus pages of discussion and

application of the *Burroughs* objective standard does the PTAB state any requirement that the inventor "know" the invention would work. Appx137-160. The PTAB explicitly stated the opposite: "The inventor *need not know* that the invention will work for conception to be complete" (Appx138) and "[w]e do not base our decision on a lack of reasonable expectation of success by the CVC inventors" (Appx159).

CVC's entire argument on this point is based on two paragraphs (Appx161-162) that were not part of the PTAB's affirmative bases for finding CVC did not prove conception (Appx137-160) but rather were in a portion of the PTAB's decision rebutting CVC's incorrect argument that conception was complete when CVC's inventors knew of bare CRISPR-Cas9 components. The PTAB rejected this argument because CVC ignored the functional eukaryotic system limitation in an effort to strip Count 1 down to simply sgRNA.

Purported APA Violation: CVC's APA argument is based on mischaracterizations of the PTAB's detailed findings, which are supported by extensive record citations and easily meet the APA standard.

CVC prominently touts the fact that Doudna and Charpentier won the Nobel Prize for their contributions to the field of CRISPR-Cas9 technology. But, however notable CVC's *in vitro,* cell-free research was, CVC failed to conceive of the *subject matter of Count 1*, a CRISPR-Cas9 system that operates in the trickier and unpredictable milieu of eukaryotic cells, before Zhang did. Unlike the PTAB, the Nobel committee did not consider or reach any conclusion about invention of the eukaryotic subject matter of Count 1 under U.S. patent law.

Purported Error in Denying Motion For Benefit: CVC wrongly accuses the PTAB of improperly requiring a working example or a reasonable expectation of success when it found P1 and P2 lacked adequate written description. The PTAB stated that it was not requiring, as a matter of law, a working example or a reasonable expectation of success. Appx103. Rather, the PTAB made a factual determination based on a 2012 POSITA's understanding and the state of the art, which the PTAB found to be "highly unpredictable." *Id.* Based on that unpredictability, the failures of similar prior-art systems, and the paucity of information in P1, the PTAB found P1 "did not disclose specific instructions or conditions necessary for CRISPR-Cas9 activity in a

eukaryotic cell, or indicate that no specific instructions or conditions were necessary." Appx91. Thus, CVC did not persuade the PTAB that a POSITA "would have considered there to be possession, given the experiences in the art with the similarly complex Group II intron RNA/protein system." *Id.*

* * *

The Court need not address Broad's conditional cross-appeal if it affirms the priority judgment as discussed above. But if it does:

On claim construction, the broadest reasonable interpretation of "guide RNA" as shown by its plain and ordinary meaning, the doctrine of claim differentiation, and the specifications is not limited to "only a single-molecule RNA configuration" but rather includes both single- and dual-molecule RNA configurations.

If the Court agrees with Broad's construction of "guide RNA," it should vacate and remand the PTAB's decisions denying Broad's Motions 2 and 3, which both relied on its incorrect and narrow interpretation.

STANDARD OF REVIEW

Because CVC was the Junior Party, CVC had the burden to show a reduction to practice of Count 1 earlier than Broad or an earlier conception with diligence leading to a reduction to practice.

"Conception is a legal conclusion premised on various underlying facts." *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052, 1063 (Fed. Cir. 2005). "The principles are legal, but the conclusions of law focus on the evidence, for which the [PTAB's] factual findings are reviewed for support by substantial evidence." *In re Steed*, 802 F.3d 1311, 1316 (Fed. Cir. 2015).

Written description is a fact question that this Court reviews for substantial evidence. *Q.I. Press Controls, B.V. v. Lee*, 752 F.3d 1371, 1380 (Fed. Cir. 2014).

ARGUMENT ON CVC'S APPEAL

I. The Court Should Affirm The PTAB's Priority Judgment Because CVC Failed To Prove Conception Before Broad's Undisputed Actual Reduction To Practice

On priority, the PTAB relied on substantial evidence and applied the correct legal standards to hold that CVC failed to show conception before Broad's undisputed, corroborated reduction to practice at least as early as October 5, 2012. CVC wrongly focuses on whether substantial evidence supports its conception arguments. But, the relevant inquiry is whether substantial evidence supports the findings that the PTAB made; it does, and that is dispositive.

A. Substantial Evidence Supports The PTAB's Finding That The CVC Inventors Lacked Prior Conception

The PTAB made three key fact-findings.

1. Finding #1: Persons Of At Least Ordinary Skill Were Unable To Reduce The CVC Inventors' Ideas To Practice Without Extensive Experimentation

First, the PTAB found that CVC's inventors and the scientists collaborating with them were "of at least ordinary skill," yet they "engaged in a 'prolonged period of extensive research, experiment, and modification' following the alleged conception…" Appx158. Whether "only the exercise of ordinary skill, rather than extensive

experimentation" would have been required is a factual determination, reviewed for substantial evidence. *In re Jolley*, 308 F.3d 1317, 1324 (Fed. Cir. 2002). This fact-finding is dispositive under *Burroughs*, as the PTAB found. Appx138(quoting *Burroughs*, 40 F.3d at 1229).

Substantial evidence fully supports the PTAB's findings. CVC's inventors enlisted many collaborating scientists, including, for example, Dr. David Druben and his graduate student Aaron Cheng "to test sgRNA CRISPR-Cas9 in human cells." Appx149. The PTAB found that they suffered "several months of failed experiments and doubt with human cells," as shown in extensive email correspondence with Doudna documenting their failures. Appx158. And this was not a lone graduate student making simple experimental errors as CVC suggests—Doudna was in near-constant communication with Cheng, directing him on exactly what experiments to perform and setting the parameters.[7] There can be no dispute that Cheng was under CVC's inventors' direction and

[7] For examples of the scores of emails between Doudna/Jinek and Cheng regarding the failed human cell experiments from April to October 2012, see: Appx66249-66250; Appx66836; Appx67067-67087; Appx68465; Appx69428-69447; Appx59222-59228.

control—CVC contended to the PTAB that Cheng's work inures to CVC's inventors. Appx66886.

CVC's inventors also enlisted Raible, "to test sgRNA CRISPR-Cas9 in zebrafish cells." Appx149. He used techniques from his prior TALENs genome-editing work, such as microinjection, but did not recognize any success. Appx154-155.

The PTAB's fact-findings that all these skilled artisans—Drubin, Cheng, Doudna, Charpentier, Jinek, Chylinski, Raible—were unable to actually reduce the invention to practice without extensive research, experiment, and modification is powerful, objective evidence that CVC's inventors' "idea" was *not* ready to be handed off to POSITAs for reduction to practice.

And, as shown above, CVC's inventors and their colleagues failed to achieve a timely reduction to practice before October 5, 2012 not only in zebrafish and human cells. As the chart on page 32 shows, they also set out to implement CVC's system in worms, yeast, mice, plants, and medaka fish—all with no reported success in 2012. See Appx83470(267:22-268:7); Appx83851(107:6-22); Appx70024-70025.

The lack of reported success with worms is particularly telling. CVC's inventors communicated their alleged conceptions to worm-genome-engineering expert Dr. Meyer, who proceeded to struggle for months. Appx67578; Appx69997. Jinek lamented after failed efforts that there were just "too many parameters to optimize." Appx65777; *see also* Appx83854-83855(120:10-121:21).

The worm experiments did not succeed in 2012; to the contrary, a 2013 publication by Doudna and Meyer acknowledged that it was not until they obtained guidance from Broad's Cong 2013 article—and used Zhang's eukaryotic CRISPR-Cas9 system with the *dual-molecule* RNA configuration—that they achieved any success. Appx82059.

2. Finding #2: CVC's Inventors Expressed Uncertainty That So Undermined The Specificity Of Their Idea That It Was Not A Definite And Permanent Reflection Of The Complete Invention

Second, the PTAB found that CVC's conception evidence fell squarely within *Burroughs*'s category of incomplete conceptions:

> [W]e are persuaded that the communications surrounding these experiments reflect "*uncertainty that so undermines the specificity of the inventor's idea* that it [was] not yet a definite and permanent reflection of the complete invention *as it [would] be used in practice*."

Appx158-159 (quoting *Burroughs*, 40 F.3d at 1230).

The PTAB relied upon CVC's inventors' many communications in the months following their alleged conceptions where they expressed uncertainty, doubt, and confusion, and proposed ever-shifting plans to try to overcome their failures. Throughout March-October 2012, CVC's inventors were reconsidering all aspects of their system (delivery method, NLS design, RNA design, selection of appropriate promotors, codon optimization, and more). Appx83080(79:9-17)(changing expression strategy); Appx83083(92:11-19)(changing plasmid concentration); Appx83083-83084 (92:20-93:6)(trying codon optimized Cas9); Appx83084(94:8-14)(varying temperatures); Appx83100(158:17-159:3)(harvesting cells after different time periods); Appx83099(156:3-10)(staggering transfections); Appx83081(81:6-20; 82:8-15); Appx87729-87731 (changing promoters).

Even by October 11, 2012—after Broad's date and many months after CVC's alleged conception—Jinek and Doudna were still uncertain even as to what problem(s) were causing their failures:

> I still think the problem may be with the assembly and localization of the Cas9 RNP - either due to degradation of the

> guide RNA, failure to assemble with Cas9, or failure of the RNP nuclear localization.

Appx67067.

Jinek had no proposed solution. Instead, in an October 11 email to Doudna, he identified *still further* potential problems, including a potential problem "with the RNA design per se" (*i.e.*, the sgRNA configuration reported in Jinek 2012) and listing "a number or [*sic*] reasons" for this, including:

> -RNA is not made at sufficient levels
>
> -*RNA is expressed strongly but turns over too fast* to associate with Cas9 posibly [*sic*] due to degradation by exonucleases
>
> -*RNA is stable but does not associate with Cas9 at the right place and at the right time*.

Appx67063. Doudna's response reflects that she did not know which of the many modes of failure was occurring:

> I completely agree with your analysis and *suspect that one or more aspects of the RNA expression/stability/Cas9 assembly/localization are problematic*.

Appx67062. These were not minor problems or thoughts to optimize a definite and permanent idea—they are fundamental obstacles to achieving a functional eukaryotic system. Moreover, CVC's inventors' contemporaneous statements reveal their lack of any plan, much less the

settled plan required for conception, for overcoming these obstacles. The table below illustrates just some of those statements showing CVC's inventors' lack of a plan for addressing obstacles including RNA degradation, formation of a stable complex, toxicity, and navigating the complex eukaryotic cellular milieu, including challenges presented by the nucleus and chromatin.

Obstacles in Eukaryotic Cells	**CVC Inventors' Statements Showing Their Lack Of A Settled Plan For Overcoming The Obstacles**
RNA Degradation	"I still think that the problem may be with the assembly and localization of the Cas9 RNP - either due to *degradation of the guide RNA*, failure to assemble with Cas9 or failure of the RNP nuclear localization." Appx67065(Doudna, 10/11/12). "RNA is expressed strongly, but turns over too fast to associate with Cas9 - *posibly [sic] due to degradation by exonucleases*." Appx67063(Jinek, 10/11/12).
Formation and Persistence of Components and Complex	"I do wonder if *the Cas9:RNA complex is either falling apart* during or after injection, or if the concentration is too low." Appx68463(Doudna, 8/20/12). "[W]e probably have an RNA expression/stability or *complex assembly problem*." Appx67901(Jinek, 10/23/12). "RNA is stable but *does not associate with Cas9 at the right place and at the right time*." Appx67063(Jinek, 10/11/12).

Toxicity	"*Pretty high toxicity* observed (death or misdevelopment)." Appx68381(Chylinski, 8/31/12). "An issue not touched by this is the question of off-site targets. This is obviously a big concern in human applications (along with *toxicity*)…." Appx66312(Raible, 6/28/12).
Failure to Act in Complex Eukaryotic Milieu on Chromatin-Bound DNA in the Nucleus	"I think *we're hoping that the Cas9 protein binds the RNA* such that the RNP is *transported into the nucleus*." Appx68085(Doudna, 9/14/12). "I wonder if having a too-efficient NLS on Cas9 is actually counterproductive, if it means that *Cas9 is transported before it has a chance to find and bind the guide RNA*… Thoughts?" *Id.* "I wonder if it's possible that Cas9 is cleaving the DNA but not releasing it? If this were true, perhaps altering (lowering) ***the salt concentrations*** in the experiment would make a difference." Appx68012(Doudna, 8/28/12). "Either we are *not targeting the right piece of DNA (due to chromatin structure* etc), or the problem lies with the RNA design per se." Appx67063(Jinek, 10/11/12).

The PTAB correctly found that these contemporaneous statements revealed the unsettled nature of CVC's purported plans. It was not only the massive program upon which CVC embarked, the numerous failed experiments, or their length of time, but it was also the nature of the

"communications surrounding these experiments" that evidenced a lack of a definite and permanent idea. Appx159.

3. Finding #3: CVC's Inventors Lacked A Clear Plan For Overcoming The Many Obstacles To Achieving A Functional Eukaryotic System

The PTAB reinforced its holding on CVC's lack of conception by finding a "lack of a clear plan by the CVC inventors to achieve a functional system." Appx183. While CVC attempted to rely on litigation-inspired declarations to show the inventors had a plan, the PTAB found that the witness "statements prepared for this proceeding do not reflect [the] contemporaneous communications." Appx155. The PTAB found that CVC failed even to "direct us to evidence that any of the inventors had a definite and permanent idea of a sgRNA CRISPR-Cas9 system that would work to edit DNA in a eukaryotic cell, particularly when they encountered what was perceived as design problems in their system at that time." Appx157. Ultimately the PTAB found that, "[a]lthough the CVC inventors developed a system on 1 March 2012 that they *hoped* would work in eukaryotic cells, the preponderance of the evidence demonstrates that they did not have a definite and permanent idea of how to achieve that result…." Appx159.

These findings are supported by the contemporaneous lab records that CVC itself introduced to try to show conception. For example, to support its March 1, 2012 alleged conception, CVC relied on Jinek's lab notebook entry of that date. But that entry provides only a cartoon of a chimeric RNA without any detail, bearing the hopeful note "New idea: adapt the [Cas9] system as a gene-targeting tool in mammalian cells." Appx69007. There is no indication of how they intended to accomplish that adaptation or whether they had even considered the challenges of accomplishing such a feat. Jinek even admitted that their "plan" was to consider "multiple approaches and multiple organisms." Appx83929(272:16-17). Addressing such generic plans, the PTAB noted that "CVC does not direct us to more explanation or details of the processes that the CVC inventors understood, at the time, would be needed to achieve a functional sgRNA CRISPR-Cas9 system in a eukaryotic cell." Appx148.

Over a month later, CVC's inventors still had no idea which of a multitude of techniques, if any, might lead to a successful eukaryotic CRISPR-Cas9 system. CVC relied on an April 11, 2012 Invention Disclosure Form ("IDF") to show conception, but that form merely

contains a laundry-list of techniques that one might use in a research project attempting to deliver CRISPR-Cas9 to eukaryotic cells. The PTAB made a finding that the IDF "does not provide many details of how the inventors envisioned such a system would be operable." *Id.*

CVC also offered documents in an attempt to show that as of May 28, 2012 they had plans to use sgRNA CRISPR-Cas9 systems in human cells and from June 28, 2012 showing plans in zebrafish cells. But, as discussed above, the PTAB found this "not persuasive evidence of a definite and permanent idea of the invention by the CVC inventors due to the, at least perceived, subsequent experimental failures of this design." Appx155. And, as to sgRNA constructs in human cells, the PTAB found that they simply led to "several months of failed experiments and doubt." Appx158.

4. The PTAB Made Multiple Credibility Determinations Adverse To CVC

The PTAB made multiple credibility determinations, which on appeal are "virtually unassailable." *Charles G. Williams Const., Inc. v. White*, 326 F.3d 1376, 1381 (Fed. Cir. 2003). For example, the PTAB found that "CVC cites to the inventors' declarations as evidence that they

had a plan to address the issues they encountered, but *their statements prepared for this proceeding do not reflect these contemporaneous communications*." Appx155. Based on Doudna's contemporaneous statements, the PTAB specifically discredited her declaration statements that she understood how to make a functional eukaryotic CRISPR-Cas9 system:

> *But her contemporaneous statements* on 11 October 2012 that "one or more aspects of the RNA expression/stability/Cas9 assembly/localization are problematic" ([Appx67059]) or that there was contamination from controls ([Appx67067]), as well as suggestions to "test some alternate designs of the guide RNA" ([Appx67059]), *does not indicate she knew how to solve this problem to make a functional system at the time.*

Appx156. Likewise, the PTAB declined to accept Jinek's declaration testimony that was contradicted by his contemporaneous statements:

> But, *his contemporaneous statements on 11 October 2012 … do not* indicate he had a definite and permanent idea of a function [*sic*] system at the time.

Id.

Substantial evidence supports the PTAB's findings that CVC's inventors did not have a conception before October 5, 2012.

B. CVC Falsely Accuses The PTAB Of Disregarding The Success Of Other Researchers Independent Of CVC

CVC accuses the PTAB of "disregard[ing] copious unrebutted evidence that artisans understood exactly how to reduce CVC's invention to practice using routine techniques—and that five separate labs (besides CVC) promptly did." CVCBr2. CVC's claim is demonstrably false because the PTAB addressed this argument in multiple pages of its opinion, making several adverse fact-findings and rejecting CVC's argument on labs independent of CVC. Appx179-184.

For context, this argument does not relate to the labs that collaborated with CVC and were given CVC's alleged plan, but rather labs unconnected to and independent from CVC, such as Broad.

1. The Work Of The Independent Labs Did Not Establish A CVC Conception

The PTAB did not ignore the evidence; the PTAB addressed CVC's conception argument based on the work of those labs and rejected it:

> CVC attempts to *shift our focus to the activities of other, competing inventors*, rather than on the activities of its own inventors. We are not persuaded that these other activities are evidence of the *CVC inventors' ideas or of their conception*.

Appx179-180. Specifically with respect to Broad, the PTAB rejected CVC's argument that Broad's independent, "quick" reduction to practice somehow supported CVC's conception:

> [W]e are not persuaded by CVC's argument that because the Broad inventors were able to reduce to practice an embodiment of Count 1 "quickly and easily," *the CVC inventors had a complete conception*. (*See* [Appx 81076] CVC Opp. 5, Paper 2567, 6:1-6:12.)

Appx180. Weighing the evidence, the PTAB found that regardless of *Broad's* success, *CVC* itself lacked a definite and permanent idea:

> [R]egardless of any success of the Broad inventors, the preponderance of the evidence presented by the parties demonstrated that the CVC inventors' experimental failures reveal uncertainty undermining a definite and permanent idea of an sgRNA system that edits or cleaves DNA in a eukaryotic cell.

Id.

Moreover, the PTAB found that "[t]he Broad inventors' activities and ideas do not inure to CVC" because "CVC never submitted anything to the Broad inventors for testing." *Id*. This is correct—Broad and CVC did not collaborate on eukaryotic CRISPR-Cas9. As noted above, Zhang had been conducting experiments with his dual-molecule RNA system for more than a year before Jinek 2012, and he succeeded with sgRNA

quickly because he had already done the hard work of determining what was needed for a functional CRISPR-Cas9 eukaryotic system before Jinek 2012.

2. The PTAB Rightly Rejected CVC's Argument That sgRNA Was All That Was Needed To Reduce The Count To Practice

CVC argues that Zhang "took chimera A [an sgRNA] from CVC's still-unpublished manuscript and proved the invention works." CVCBr47. CVC goes so far as to state, incredibly, that "[t]he PTAB all but conceded that, had CVC hired Zhang to reduce its invention to practice, CVC—not Zhang—would have been the inventor; every inventive feature came from CVC," apparently suggesting that the whole of the invention is simply the sgRNA component disclosed in Jinek 2012. CVCBr46 (citing Appx180-181). But the PTAB made no such concession or finding. To the contrary, the PTAB "decline[d] to accept CVC's argument that Dr. Zhang contributed nothing to the invention of Count 1." Appx181. The PTAB further rejected CVC's attempt to focus on the sgRNA limitation, finding that CVC's "argument discredits the limitation in Count 1" that requires functionality in eukaryotic cells. Appx181-182.

As the PTAB found, it was Zhang who identified the "necessary features of a functional eukaryotic system as recited in Count 1," not CVC. Appx182. And "determination of those features indicated that the Broad inventors had a definite and permanent idea of a system in eukaryotic cells, which led them to an actual reduction to practice earlier than the CVC inventors." Appx182. Zhang succeeded with his own plan because he had already determined the technical features for creating a functional eukaryotic system, not because of sgRNA (which Zhang demonstrated is not necessary for a functional system). *Id*.

CVC also accuses the PTAB of committing a "cardinal sin" by allegedly not identifying specific technical differences between the parties' respective systems. CVCBr48. It is incredible that CVC accuses the PTAB given that CVC *did not dispute* Broad's evidence on the technical differences to the PTAB. The PTAB found that:

> (i) Broad "raises technical reasons why the Broad inventors had success when other eukaryotic CRISPR-Cas9 systems failed" and that
>
> (ii) "CVC fails to dispute the difference between these technical details of the parties' systems."

Appx181. In light of CVC's evidentiary failure, there was no reason for the PTAB to identify specific technical differences.

The PTAB also found that "CVC's failures before Broad's success by 5 October 2012 indicate there must have been differences." *Id.* This finding is based on the eminently reasonable inference that the PTAB drew from Broad's success in contrast to CVC's many months of abject experimental failures.

3. CVC's Reliance On Independent Labs Suffers From Other Defects

CVC's reliance on independent labs as purportedly establishing a CVC conception also suffers from other defects.

First, CVC offered no evidence that these labs were independent of Broad. In fact, three of the other research groups included scientists affiliated with Broad. Appx81507(¶68).

Second, CVC offered no evidence or argument as to whether the scientists at the five labs were of only ordinary, as opposed to extraordinary, skill. That *extraordinarily* skilled artisans achieved a feat says nothing about whether a POSITA could have done so.

Third, CVC offered no evidence regarding how these other labs conducted their research, what challenges they encountered, or how they overcame them.

C. The PTAB Did Not Commit Legal Error

CVC's brief concocts two purported legal errors. Both lack merit.

1. The PTAB Applied The Correct Legal Standard For Conception

As discussed above, CVC erroneously argues that the PTAB "refused" to apply the correct "objective standard" for conception. CVCBr2; *see also infra* p.60-61. But, as noted above, the PTAB applied the well-established "without extensive research or experimentation" conception standard from *Burroughs*. This Court has repeated this standard on numerous occasions. *See, e.g.*, *Bard Peripheral Vascular, Inc. v. W.L. Gore & Assocs., Inc.*, 776 F.3d 837, 845 (Fed. Cir. 2015); *Univ. of Utah v. Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften E.V.*, 734 F.3d 1315, 1323 (Fed. Cir. 2013); *Dawson v. Dawson*, 710 F.3d 1347, 1352 (Fed. Cir. 2013).

This "without extensive research or experimentation" standard is exactly what CVC urged to the PTAB. Appx66858 (CVC quoting

Burroughs). CVC never presented its "without further invention" formulation as the legal standard for conception.[8] It is inappropriate to fault the PTAB for not applying a legal standard CVC did not urge below.

CVC relies primarily on two cases, neither of which it cited before the PTAB, for its "without further invention" formulation, *Acromed Corp. v. Sofamor Danek Grp., Inc.*, 253 F.3d 1371 (Fed. Cir. 2001) and *Barba v. Brizzolara*, 104 F.2d 198, 202 (C.C.P.A. 1939). CVC seems to contend that *Application of Tansel*, 253 F.2d 241, 244 (C.C.P.A. 1958), also supports this formulation. None warrant deviation from this Court's controlling precedent in *Burroughs* and its progeny.

Nowhere does *Acromed* recite a "without further invention" standard for conception. To the contrary, the portion of *Acromed* that CVC relies on cites *Sewall,* which instructs that "[c]onception is complete when one of ordinary skill in the art could construct the apparatus

[8] CVC in its reply argument, after reciting the *Burroughs* "without extensive research or experimentation" standard for conception, asserted that CVC "achieve[ed] multiple actual reductions to practice in a matter of months and requiring *no further inventive steps*." Appx85642(CVC's emphasis). As to the conception standard, however, CVC repeatedly and consistently recited the *Burroughs* standard, even in its reply.

without unduly extensive research or experimentation." *Sewall v. Walters*, 21 F.3d 411, 415 (Fed. Cir. 1994); *see Acromed*, 253 F.3d at 1380 (citing *Sewall*). This is the standard the PTAB applied. Appx157.

Barba addressed a different form of priority contest than here. In *Barba*, the junior and senior parties worked *jointly* on the same subject matter, and, there, "the issue [was] one of originality; independent conceptions of the invention by the respective parties [were] not involved." 104 F.2d at 199-200. The *Barba* court's comment that "[t]he particular means to carry out [senior party's] conception, we think, could be worked out by one skilled in the art without the exercise of invention" was merely the court dismissing the purported contribution of the junior party as not inventive in the context of their joint work. *Id.* at 202. *Barba* did not address a situation where, as here, there are two independent groups.

Application of Tansel, if anything, supports the *Burroughs* standard. *Tansel* instructs that, for a complete conception, "[i]t is sufficient if the inventor is able to make a disclosure which would enable a person of ordinary skill in the art to construct the apparatus *without*

extensive research or experimentation." *Application of Tansel*, 253 F.2d at 243.

2. The PTAB Expressly Declined To Adopt A Legal Standard For Conception That Requires The Inventor To "Know" The Invention Will Work, As CVC Alleges

CVC next argues that the PTAB "legally erred by insisting that inventors must *know* their invention would work for conception to be complete." CVCBr32(emphasis in original). As noted above, however, nowhere in the PTAB's 23 pages discussing and applying the objective *Burroughs* standard (Appx137-160) does the PTAB state any requirement that the inventor "know" the invention would work. To the contrary, the PTAB starts its discussion of the law of conception by stating "*[t]he inventor need not know* that the invention will work for conception to be complete." Appx138. The PTAB stated that "[w]e do not base our decision on a lack of reasonable expectation of success by the CVC inventors." Appx159. The PTAB then fully set forth its affirmative bases for finding that CVC did not prove conception.

CVC's strained argument that the PTAB required knowledge is based entirely on two paragraphs *rebutting* one of CVC's (incorrect)

arguments. The PTAB had already applied the correct legal standards and found against CVC at Appx137-160, before the two-paragraph rebuttal at Appx161-162 that CVC mischaracterizes. As discussed above at 36, the PTAB made this statement in the context of rejecting CVC's attempt to ignore the Count's requirement for a *functional* eukaryotic system.

D. The Remainder Of CVC's Objections Regarding Conception Fail

The remainder of CVC's objections do not overcome the substantial evidence supporting the priority judgment.

1. CVC's Criticism Of The PTAB For Finding The CVC Inventors' Failed Eukaryotic Experiments Relevant To Conception Is Legally Incorrect

CVC criticizes the PTAB for analyzing in depth CVC's inventors' and their colleagues' statements and experiments following CVC's alleged conceptions. This criticism is unwarranted and unfair because CVC asked the PTAB to rely on these activities: *CVC's central argument* before the PTAB on priority was that its inventors had a complete conception *because* of the alleged "speed and ease" with which they allegedly achieved "straightforward actual reductions to practice" in

zebrafish and human cells. *See, e.g.*, Appx66855-66856; Appx66880. Indeed, the section of CVC's priority motion titled "reduction to practice required only ordinary skill" cites *only* to the activities of the CVC inventors in purportedly achieving reductions to practice in zebrafish and human cells with ease.

Given CVC argued for its conception based on its inventors' alleged ease in achieving actual reductions to practice, the PTAB analyzed the evidence of CVC's purported reductions and found that CVC's inventors *did not* achieve straightforward actual reductions to practice but instead encountered multiple failures.

2. CVC's Assertion That Its Design Never Changed From Its Alleged Conception To Its Alleged Reductions To Practice Is Contrary To The PTAB's Findings, All Supported By Substantial Evidence

CVC faults the PTAB because it "did not mention that CVC never changed its invention in any material way." CVCBr26; *see also id*. at 32. But CVC ignores that the PTAB affirmatively found the *opposite*—that the CVC inventors engaged in a "prolonged period of extensive research, experiment, and *modification*" following the alleged March 2012 conception.

The evidence supports the PTAB's finding of extensive modification. Over the course of these many failures, CVC's inventors changed a myriad of experimental features in a futile effort to get the system to work. *See* Appx83080(79:9-17); Appx83083(92:11-19); Appx83083-83084(92:20-93:6); Appx83084(94:8-14); Appx83100(158:17-159:3); Appx83099(156:3-10); Appx83081(81:6-20; 82:8-15); Appx87729-87731.

CVC's attempt to blame the graduate student working with Doudna on the human cell experiments is unavailing. Cheng operated under the supervision of Doudna and Jinek and with constant communication from April to October 2012 (*see supra* fn.7); Doudna and Jinek were directing Cheng what to try next.

3. There Is No Basis For Ignoring The Inventors' Contemporaneous Communications That Document Their Lack Of A Plan

CVC's *amici* allies (with ties to Doudna)[9] urge the Court to ignore CVC's inventors' contemporaneous communications so as not to somehow

[9] Dr. Thomas Cech, on the Amicus Brief of Scientists, was Doudna's mentor when she was a postdoctoral student in his lab. https://www.britannica.com/biography/Jennifer-Doudna.

impede the scientific process. Dkt18 at 13. But, it was *CVC itself* that introduced these email communications from its lab into the record—as purported evidence of corroboration and diligence.

Unfortunately for CVC, the emails show that CVC's inventors had no definite plan in the first place; and the PTAB agreed:

> *CVC does not directly address these e-mail statements in its Reply Brief*, arguing only that Broad "cites correspondence with its colleagues as evidence of CVC's reasonable diligence, which . . . Broad barely challenged." ([Appx85659]CVC Reply 2, Paper 2744, 18:15-17.) *CVC does not provide any reason why these communications are not also evidence [of] the inventors' thoughts and understandings around CVC's asserted conception date*.

Appx154.

II. The PTAB Correctly Rejected CVC's Originality Challenge

CVC's originality challenge is based on its argument that sgRNA is the invention, Zhang contributed nothing inventive, and that the PTAB "identified nothing at all in the count—the invention—Zhang did not get from CVC." CVCBr44. This argument again relies on an incorrect

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Regeneron, which submitted the other amicus brief, is heavily invested in, collaborates with, and licenses patent rights from a CRISPR-Cas9 company Doudna founded. https://ir.intelliatx.com/news-releases/news-release-details/regeneron-and-intellia-therapeutics-expand-collaboration-develop.

characterization of the invention as simply the use of an sgRNA. For the reasons discussed above on pages 54-56, this argument is incorrect.

Viewing all the limitations of Count 1, including the required eukaryotic functionality, the record shows that Zhang had possession of all features of the count by October 5, 2012, and that he possessed the most fundamental features even earlier. He determined the "necessary technical features" to achieve a functional eukaryotic system. Appx182. The *only* element of Count 1 Zhang learned from CVC's public disclosures in June 2012 was the sgRNA species—a configuration that is neither necessary nor sufficient for a functional eukaryotic system.

Ultimately, CVC ignores that it, not Broad, had the burden of proving its own earlier conception (and diligence to a later reduction to practice). In an interference, unlike a contest involving alleged co-inventors, the PTAB does not compare the parties' "inventive" contributions. Rather, "priority of invention goes to the first party to reduce an invention to practice unless the other party can show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing that invention to practice." *Goldfarb*, 154 F.3d at 1327. CVC's attempts to create an additional requirement that the

first party to reduce the invention to practice needs to *prove* its contributions were inventive is not the law.

III. CVC's APA Challenge Fails Because It Rests On False Claims That The PTAB Ignored Evidence

The PTAB's decisions comprise 180-plus pages, hundreds of record citations, and numerous credibility findings. They easily pass the APA's reasoned decision-making requirement. CVC's long-shot arguments to the contrary highlight the weakness of its appeal.

Broad addresses CVC's specific objections below; but the Court need not reach them—CVC's APA argument fails at the outset as it was CVC's burden to demonstrate that any alleged APA violations were not harmless. 5 U.S.C. § 706; *see, e.g.*, *Shinseki v. Sanders*, 556 U.S. 396, 406, 409 (2009). CVC did not even attempt to address this issue, and CVC cannot address this necessary element for the first time in its reply. *See Atlanta Gas Light Co. v. Bennett Regul. Guards, Inc.*, 33 F.4th 1348, 1356, fn. 3 (Fed. Cir. 2022) ("Arguments raised for the first time in a reply brief are not properly before this court."). That failure alone warrants rejection of CVC's APA argument.

A. The PTAB Considered And Expressly Rejected The Evidence CVC Erroneously Claims The PTAB Ignored

CVC asserts that the PTAB "failed to consider evidence from CRISPR luminaries Barrangou, Sontheimer and Marraffini that skilled artisans" would have had an expectation of success implementing CRISPR-Cas9 in eukaryotic cells. CVCBr50. CVC introduced this evidence to the PTAB only in a reply brief. Appx85663-85665(CVC Reply 2 at 22:18-24:6). Nevertheless, the PTAB expressly cited this evidence and rejected it as irrelevant to conception because, as CVC itself urged, a POSITA's expectation of success is irrelevant to conception. *See* Appx159 ("[W]e are not persuaded by either party's evidence of what those in the art expected at the time. (*See* [Appx81220-81226]Broad Opp. 2, Paper 2569, 18:23-24:12; *see* [Appx85663-85665]CVC Reply 2, Paper 2744, 22:18-24:6.")).

CVC also asserts that the PTAB erred by "fail[ing] to consider evidence that CVC subjectively believed its invention would work in eukaryotic cells" and their "confidence" they could achieve such a system. CVCBr51. But, as *Burroughs* instructs, an inventor's subjective belief that their invention will work is irrelevant to conception. Following this

law, the PTAB properly *did not* base its conception determination on the inventors' subjective beliefs as to whether they could achieve a functional system, but rather "on the facts of how specific and settled the inventor's ideas were at the time asserted." Appx138. With its focus thus correctly trained on whether CVC's ideas were *settled*, the PTAB found that CVC's inventors' contemporaneous expressions of doubt and uncertainty as to how to proceed "indicate[] to us they had sufficient uncertainty that undermines CVC's arguments of a definite and permanent idea of an sgRNA CRISPR-Cas9 system to be used in a eukaryotic cell." Appx160.

CVC's contention appears to be that its inventors' alleged confidence they would one day succeed should have offset the contemporaneous evidence of their uncertainties regarding how to do so. Rejecting CVC's argument does not violate the APA. Here, substantial evidence of CVC's inventors' doubts, uncertainties as to how to overcome their failures, and ever-shifting plans—all corroborated by contemporaneous documentary evidence—demonstrate the lack of any definite and permanent idea for an operable system.

CVC also argues that the "PTAB never explained why a four-month reduction to practice amounts to 'perplexing' difficulties 'every step of the

way.'" CVCBr51. But, as discussed above, CVC misses the point that it was not just the length of time the CVC inventors failed, it was also the corresponding communications showing the lack of any plan. *See supra* p.47-48.

CVC asserts that the PTAB failed to consider evidence of the five independent and unrelated labs that reported successful eukaryotic experiments. As discussed earlier, p.52-56, the PTAB expressly considered this evidence but still found against CVC.

Finally, CVC asserts the PTAB failed to consider the fact that CVC's plans never changed. Quite to the contrary, the PTAB considered this issue but found CVC engaged in extensive modification. *See* p.62-63.

B. CVC Did Not Dispute Before The PTAB Broad's Evidence That There Were Material Technical Differences Between The Parties' Systems; It Cannot Do So Now

CVC accuses the PTAB of committing "cardinal sins" by allegedly not identifying specific technical differences between the parties' respective systems. The attack fails on multiple levels.

First, as discussed above (p.55-56), the PTAB considered the technical differences between the two systems and found that Broad

identified differences between the parties' systems and that "CVC fail[ed] to dispute the difference between these technical details of the parties' systems." Appx181. And because CVC never disputed the technical differences, it cannot do so on appeal for the first time.

Second, CVC's argument relies on a false contention that "Broad *conceded* that none [of the adaptations Zhang made] required more than ordinary skill." CVCBr48(CVC's emphasis). Broad made no such concession. Indeed, Broad said the opposite: "Zhang *Did Not Use Only 'Ordinary Skill'* And 'Routine Techniques' In Creating His Eukaryotic CRISPR-Cas9 System." Appx85770. Broad explained that CVC itself had identified no fewer than 12 adaptations Zhang made to the natural system to achieve eukaryotic functionality. It further explained that "*whether allegedly routine or not*" individually, the selection and combination of techniques was certainly not routine. *Id.* It is unfathomable how CVC could argue Broad "conceded" the point.

Third, CVC's appeal brief now points to various aspects of a eukaryotic CRISPR-Cas9 system, such as specific types of promoters, NLSs, codon optimization strategies, vectors, and other adaptations that CVC may have attempted at different times, mixing and matching them,

over the course of its failed experiments. CVCBr48-49. CVC ignores that it was Zhang who had a specific plan for engineering a *functional* eukaryotic CRISPR-Cas9 system using specific techniques and CVC did not, as the PTAB found.

C. It Was Not Arbitrary And Capricious For The PTAB To Reject CVC's Microinjection Arguments

Lastly, CVC asserts that the PTAB "faile[d] to respond meaningfully to arguments and evidence about microinjection," including evidence allegedly showing that this delivery method "obviates most, if not all" the obstacles to use of CRISPR-Cas9 in eukaryotic cells. CVCBr52-53. This is wrong on two levels.

First, the PTAB acknowledged that microinjection was one of many different potential delivery methods presented in the laundry-list of delivery techniques in CVC's IDF. Appx147. But, as the PTAB found, the IDF "does not provide many details of how the inventors envisioned such a system would be operable." Appx148.

Second, the PTAB did not need to address CVC's facially implausible argument that microinjection was a magical cure-all for the challenges of eukaryotic cells. *Synopsys, Inc. v. Mentor Graphics Corp.*,

814 F.3d 1309, 1322 (Fed. Cir. 2016) (the Board is not required "to address every argument raised by a party or explain every possible reason supporting its conclusion."). In fact, the real-world failures using microinjection in worms and zebrafish demonstrate that microinjection *did not* overcome the hurdles to eukaryotic uses. Indeed, after certain microinjection worm experiments failed in 2012, Doudna wrote to her team that she "wonder[ed] if the Cas9:RNA complex is either falling apart during or after injection, or if the concentration is too low." Appx68463. Tellingly, none of P1, P2, or P3 include an example using microinjection to deliver a functional CRISPR-Cas9 system into a eukaryotic cell.

The record also includes Broad's expert's testimony explaining the difficulties of microinjection. Appx50575-50578(¶¶193-98). As Mirkin explained, prior-art attempts to use microinjection to deliver Group II introns (a prokaryotic system) to eukaryotic cells failed. *Id*., ¶197. Indeed, researchers struggled for decades attempting to implement that system in eukaryotic cells, despite their use of microinjection. Appx81372(¶14).

CVC also criticizes the PTAB for "refus[ing] to resolve whether microinjection *succeeded*," even if the CVC inventors did not recognize the success, because a finding of success in zebrafish might somehow help CVC's conception argument. CVCBr54. But, as the PTAB found, *even if* the CVC inventors had achieved an unrecognized success, it was the communications around these experiments that showed the CVC inventors *did not have a settled plan* for achieving a successful eukaryotic system. The lack of a settled plan is dispositive on conception, regardless of whether there was an unrecognized success. The PTAB explained that "at best, the CVC inventors encountered one unrecognized positive result" but their communications nonetheless reflected "uncertainty that so undermines the specificity of the inventor's idea that it [was] not yet a definite and permanent" one. Appx159.

IV. Substantial Evidence Supports The PTAB's Finding That P1 And P2 Lacked Written Description Support For Count 1

Substantial evidence supports the PTAB's findings that neither P1 nor P2 included a written description sufficient for a POSITA to conclude that CVC's inventors possessed the invention of Count 1.

Consistent with CVC's lack of a clear plan and months of struggles, neither P1 nor P2 disclosed a working eukaryotic example. Notably, while CVC alleges it had a complete conception in March 2012 (and a zebrafish reduction to practice in August), P2, filed October 19, 2012, still contained no working examples in eukaryotic cells. It is undisputed that P1 and P2 disclose merely the same cell-free test tube experiments in Jinek 2012.

The PTAB extensively evaluated the evidence to determine whether, despite the lack of a working eukaryotic example, P1 or P2 nevertheless described the invention of Count 1 "in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought." *Lockwood v. Am. Airlines, Inc.,* 107 F.3d 1565, 1572 (Fed. Cir. 1997); *see* Appx90. The PTAB assessed the thousands of pages of expert testimony and underlying evidence and found that a POSITA would not so conclude:

> Broad has persuaded us that absent results of a successful working example, the lack of discussion of PAM sequences, or sample target DNA sequences, the lack of special instructions or conditions necessary to accommodate the eukaryotic cellular environment, and the lack of a discussion of whether access to chromatin could hinder CRISPR-Cas activity would have indicated to those of ordinary skill in the art that the P1

> applicants were not in possession of an embodiment of Count 1.

Appx102-103.

CVC does not challenge any of the PTAB's findings on possession. Instead, CVC once again falsely accuses the PTAB of applying an erroneous legal standard.

A. The PTAB Applied The Correct Written Description Possession Standard

CVC erroneously asserts that the PTAB demanded as a matter of law "a working example," proof of "expectation of success," or "specific instructions." CVCBr25, 61, 64-66. Incredibly, CVC makes this accusation even though the PTAB explicitly stated that it was not imposing any such legal requirements. Appx103. Rather, the PTAB made its determination based on the facts of this case, including the nature of the subject matter at issue here and the highly unpredictable nature of the art:

> The answer may hinge on the lack of a working example or on whether there was an expectation of success, but would reflect *the nature of the subject matter and the art—highly unpredictable—not a general requirement for such things*.

Id. In support of this fact-based conclusion, the PTAB cited *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1357-58 (Fed. Cir. 2010)(*en banc*), where this Court found a lack of written description support because, as here, there were no working examples and "the state of the art at the time of filing was 'primitive and uncertain' with an insufficient supply of prior art knowledge to fill the gaping holes in its disclosure." Appx103 (citing *Ariad*, 598 F.3d at 1357-58).

Contrary to CVC's contention, nowhere did the PTAB require CVC to prove that the written description would "convince skeptics the invention will work." CVCBr30, 60-62. Rather, the PTAB correctly found that, in this unpredictable and nascent art, a *2012 POSITA* would have required more than what P1 and P2 disclose to show possession of the eukaryotic invention of Count 1.

CVC's reliance (CVCBr2, 55, 58, 60) on *Alcon Research Ltd. v. Barr Laboratories, Inc.,* 745 F.3d 1180 (Fed. Cir. 2014) is misplaced. There, in a more predictable art, the patent contained experimental data (unlike the lack of any eukaryotic example here) and, there, the challenger "adduced no evidence" regarding lack of possession (unlike Broad's substantial evidence here as detailed below). *Id.* at 1191-92.

B. Three Categories Of Substantial Evidence Support The Findings That Neither P1 Nor P2 Shows Possession

The PTAB relied on multiple categories of substantial evidence in finding that CVC failed to show possession.

1. Evidence That The 2012 POSITA Would Have Been Aware Of Many Reasons Why Prokaryotic CRISPR-Cas9 Systems Might Not Work In Eukaryotic Cells

The PTAB relied on extensive evidence showing that the 2012 POSITA would have been aware of multiple reasons why CRISPR-Cas9 systems might not work in eukaryotic cells even though it functioned *in vitro*. For example, as Mirkin explained, it was well-known by 2012 that eukaryotic cells target and degrade foreign double-stranded RNAs (like that in CRISPR-Cas9). Appx86-87. Accordingly, the POSITA would have been concerned that RNA degradation of the CRISPR-Cas9 system would have rendered it inoperable. "CVC does not present evidence to contradict Mirkin's testimony about the concerns one would have had, given the lack of discussion of RNA degradation in P1." Appx87.

Mirkin also testified that a POSITA would be aware of many other obstacles, such as chromatin blocking access to the cell's DNA. Appx50556-50558(¶¶139-43). Contemporaneous statements from

experts in the field confirmed that a POSITA would have required the results of eukaryotic experiments or specific instructions to address the numerous known obstacles. Appx50547-50548(¶¶116-17); Appx50572-50573(¶¶183-85). For example, the PTAB relied on the 2012 review of Jinek 2012 by CVC's expert Carroll in which he "stated that actual experiments were necessary to address concerns about chromatin structure and RNA stability and to determine if CRISPR-Cas9 systems would work in eukaryotic cells." Appx100. Based on this evidence, the PTAB concluded:

> Thus, [Carroll's] statements shift the preponderance of the evidence towards Broad's argument that *without at least a discussion of the role of chromatic access in P1*, those of ordinary skill in the art would not have considered the P1 applicants to have had possession of an embodiment of Count 1.

Id.

The lack of discussion in P1 or P2 addressing these concerns is substantial evidence supporting the PTAB's finding of lack of possession.

2. Evidence Of Failures Encountered In Prior Attempts To Adapt Similar Prokaryotic Systems For Use In Eukaryotes

The PTAB also relied on evidence of the failure of others in prior attempts to adapt other prokaryotic systems for use in eukaryotes. For example, Group II introns—a prokaryotic RNA/protein complex (like CRISPR-Cas9)—had been proposed for gene targeting in eukaryotic cells and had been the subject of years of experiments. Appx88. But, as explained earlier, technical issues plagued attempts to adapt this system to eukaryotic cells and "efficient group II intron-based gene targeting [had] not been demonstrated in eukaryotes." Appx89. A 2012 POSITA, knowing this history of Group II introns, would have thought that the similar CRISPR-Cas9 systems likewise would *not* work in eukaryotes without some specific instructions or conditions.

The PTAB also relied on Mirkin's uncontradicted testimony regarding the difficulties encountered when scientists endeavored to adapt prokaryotic RNA riboswitch and ribozyme systems to work in eukaryotic cells. The PTAB found his testimony persuasive and corroborated and that "CVC fails to direct us to evidence that contradicts Dr. Mirkin's interpretations of these reports." Appx92-93.

3. Contemporaneous Statements Of CVC's Inventors "indicating doubt that a CRISPR-Cas9 system would work in eukaryotic cells"

The PTAB further relied on the contemporaneous statements of CVC's inventors admitting that, even after the *in vitro* experiments in P1 and P2, "it was not known whether such a bacterial system would function in eukaryotic cells." Appx101. The inventors also stated that, while Jinek 2012 (which disclosed the *in vitro* examples of P1 and P2) "was a big success, [] there was a problem." Namely, CVC's inventors "weren't sure if CRISPR-Cas9 would work in eukaryotes." The PTAB found that "even the CVC inventors, who could be considered to have had more skill than the ordinary artisans, were not sure if the eukaryotic chromatin would allow for a functional CRISPR-Cas9 system in a eukaryotic cell." Appx102.

C. The PTAB Appropriately Rejected CVC's Attempt To Stitch Together An Embodiment

CVC's brief highlights a number of techniques it says P1 discloses, such as codon optimization, PAM sequences, etc. CVCBr59-60. But CVC ignores the substantial evidence supporting the PTAB's finding that none of those disclosures, standing alone or taken together, were adequate.

See, e.g., Appx94("[W]e agree with Broad that P1 fails to disclose how PAM sequences should be used with non-natural targets in a eukaryotic CRISPR-Cas9 system"). P1 contains only lists of routine biological methods a POSITA could potentially use to attempt to adapt CRISPR-Cas9 to eukaryotic cells. CVC asserted that these methods may be employed to use CRISPR-Cas9 in eukaryotic cells, without any explanation of how to successfully employ such methods alone or in combination. Appx689[0165].

As to how to deliver CRISPR-Cas9 systems into such cells, the POSITA encounters yet another long list devoid of meaningful guidance or context. Appx680[129]. The PTAB accepted the testimony of Broad's expert that P1 does "not provide any guidance or preference suggesting a POSITA should use particular techniques in combination with specific cells to adapt and deliver [a] CRISPR system." Appx50542(¶97).

The PTAB further found that P2 fares no better than P1. Based on numerous facts discussed throughout its opinion, the PTAB found, "We are unpersuaded that expression of Cas9 protein in the prokaryote *E. coli* or general information about PAM sequences [that CVC argued were

added in P2] cures the deficiencies discussed above in regard to P1." Appx105.

In sum, substantial evidence supports the PTAB's findings on lack of written description.[10]

[10] Not only do P1 and P2 lack written description support, they also lack an enabling disclosure. But, the PTAB did not rule on enablement given the lack of written description. Appx104-105.

ARGUMENT ON BROAD'S CONDITIONAL CROSS-APPEAL

If the Court affirms the judgment of priority, it need not reach Broad's conditional cross-appeal.

I. The PTAB Erroneously Construed "guide RNA" As Limited To "only a single-molecule RNA configuration"

Broad's claims use the term "guide RNA". This term had a plain and ordinary meaning in the art by December 2012 and Broad's specifications do not define it more narrowly, nor do they contain any clear disavowal of that meaning. Thus, Broad is entitled to the full scope of its "guide RNA" claim language, including both single- and dual-molecule configurations.

In an interference, claim terms receive their broadest reasonable interpretation. *Dionex Softron GmbH v. Agilent Technologies, Inc.*, 56 F.4th 1353, 1358 (Fed. Cir. 2023). The patentee may deviate from plain meaning only by including "expressions of *manifest exclusion or restriction*, representing a *clear disavowal* of claim scope." *Thorner v. Sony Computer Entertainment Amer. LLC*, 669 F.3d 1362, 1366 (Fed. Cir. 2012). "Absent a *clear disavowal or contrary definition* in the specification or the prosecution history, the patentee is entitled to the full

scope of its claim language." *Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1358 (Fed. Cir. 2004).

A. Jinek 2012 Gave "guide RNA" A Plain And Ordinary Meaning To A 2012 POSITA

The plain and ordinary meaning to a POSITA in the CRISPR art in December 2012 of "guide RNA" included both single- and dual-molecule RNA configurations. Jinek 2012, co-authored by CVC's inventors, was the most recent CRISPR-Cas9 art available to the POSITA on this point.

Jinek 2012 disclosed two alternate CRISPR-Cas9 system configurations: (1) a dual-molecule configuration, with the crRNA and tracrRNA as separate RNA molecules and (2) a single-molecule RNA configuration covalently linking crRNA and tracrRNA with intervening nucleotides. Importantly, Jinek 2012 was the first disclosure of sgRNA in CRISPR-Cas9 systems and referred to both the sgRNA and the dual-molecule configurations as "guide RNA." Appx5610. Thus, Jinek 2012 established the meaning of "guide RNA" in the CRISPR-Cas9 context in mid-2012 that Broad advocates.

In deciding that "guide RNA" did not have a plain and ordinary meaning despite the clear teachings in Jinek 2012, the PTAB cited

publications in which the term "guide RNA" was used "but not for a complex of the crRNA and tracrRNA." Appx27. These publications all pre-dated Jinek 2012, the initial article that disclosed sgRNA for CRISPR-Cas9. Thus, those earlier references shed no light on the plain and ordinary meaning of "guide RNA" to a post-Jinek 2012 POSITA. And, those references employed the term "guide RNA" in different contexts, while Jinek 2012 specifically defined the term in the context of the RNA configurations for CRISPR-Cas9 systems. *See Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001) ("The claims are directed to the invention that is described in the specification; they do not have meaning removed from the context from which they arose.").

Because these supposed counterweights to Jinek 2012 are irrelevant to the meaning of "guide RNA" to the 2012 POSITA, no evidence supports a conclusion that "guide RNA" lacked a plain, ordinary meaning.

B. Claim Differentiation Confirms That "guide RNA" Is Not Limited To "only a single-molecule RNA"

Broad's claims differentiate between the generic term "guide RNA" and the sgRNA species (referred to as "fused" or "chimeric" in Broad's

claims), further supporting Broad's construction. For example, independent claim 15 in Broad's '359 patent recites "guide RNA" with no indication that it is limited to a particular configuration:

> An engineered, programmable, non-naturally occurring Type II CRISPR-Cas9 system comprising a Cas9 protein and at least one *guide RNA* that targets and hybridizes to a target sequence of a DNA molecule in a eukaryotic cell….

Appx17680. In contrast, dependent claim 18—half of Count 1—explicitly narrows and limits the guide RNA of claim 15 to "fused" guide RNAs (sgRNA):

> The CRISPR-Cas system of claim 15, wherein the *guide RNAs* comprise a guide sequence *fused to* a tracr sequence.

Id.

If "guide RNA" is limited to the sgRNA species, claim 18 is redundant of claim 15. But, the "presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." *Phillips v. AWH Corp.,* 415 F.3d 1303, 1314-15 (Fed. Cir. 2005)(*en banc*). No evidence overrides that presumption.

Other Broad claims that recite "guide RNA" allow the crRNA and the tracr RNA to be delivered on "different vectors." *See, e.g.*, Appx18221,

cl. 3. CVC did not dispute Broad's evidence that delivery on different vectors would result in a "guide RNA" with a dual-molecule configuration. Appx19491-19492; Appx48276. Allowing for delivery of the guide RNA on different vectors resulting in a dual-molecule configuration is nonsensical if "guide RNA" must be sgRNA.

The PTAB acknowledged that claim differentiation was persuasive evidence that "guide RNA" includes single- and dual-molecule configurations. *See* Appx21 (noting '359 patent claims 15 and 18 "tend to indicate that 'guide RNA' is a generic term, which could be limited to single-molecule RNA configuration by the term 'fused' in a dependent claim."). But, the PTAB concluded the presumption was "overcome by Broad's specification." Appx32. That conclusion is legal error; Broad's specifications do not contain a clear disavowal of the plain and ordinary meaning of "guide RNA."

C. The Specification Confirms "guide RNA" Is Not Limited To Single-Molecule RNA

Regardless of whether one starts with Broad's specifications to determine if there is a clear disavowal of the plain and ordinary meaning of "guide RNA" or to supply the term's definition in the first instance, the

result is the same—the broadest reasonable interpretation of "guide RNA" encompasses both single- and dual-molecule configurations.

For instance, Example 6 of the '356 patent uses the term "guide RNA" to encompass both single-molecule and double-molecule guide RNA. Example 6 is entitled "Optimization of the Guide RNA for *Streptococcus pyogenes* Cas9" and refers to both dual-molecule ("tracrRNA and direct repeat sequences") and single-molecule ("chimeric guide RNA") RNA as "guide RNA." Appx22814. Likewise, the '308 patent refers to dual-molecule ("combination of tracrRNA and crRNA") and single-molecule ("chimeric guide RNA") collectively as "guide RNA." Appx22443.

Consistently, the specifications disclose dual-molecule RNA systems as preferred embodiments. For instance, the first "preferred embodiment" in Broad's '359 patent is a dual-molecule RNA embodiment. A construction, like the PTAB's here, that entirely reads out preferred embodiments "is rarely, if ever, correct." *MBO Labs., Inc. v. Becton, Dickinson & Co.*, 474 F.3d 1323, 1333 (Fed. Cir. 2007).

The PTAB did not explain in detail why it was (wrongly) persuaded by CVC's argument that one sentence from Broad's specification narrowly defined "guide RNA":

> *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.

Appx27-28 (quoting Appx17616(12:6-16)). There are several problems with the PTAB's conclusion regarding this intrinsic evidence.

First, the sentence refers only to "aspects of the invention," not the invention as a whole. Thus, the most natural reading of the sentence is that it is not definitional, but instead refers to certain embodiments, some of which are sgRNA embodiments. In contrast, when Broad wanted to specifically define a term, it used "as used herein" "means" language, such as:

> *As used herein the term* "wild type" is a term of the art understood by skilled persons and *means* the typical form of an organism, strain, gene or characteristic as it occurs in nature as distinguished from mutant or variant forms.

Appx17616.

Broad's specification uses the term "aspects of the invention" in a non-limiting manner not to define the invention as a whole. For example, the specification states "[i]n aspects of the invention, nickases may be used for genome editing via homologous recombination" and "[i]n aspects of the invention, an exogenous template polynucleotide may be referred to as an editing template." Appx17619; Appx17737.

Second, the specification shows that "used interchangeably" does not mean the "interchangeable" terms have the same meaning. Consider, for example, the preceding paragraph in the specification:

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

Appx17616. A POSITA reading this sentence would undoubtedly know that "used interchangeably" does not mean that a polynucleotide is a nucleic acid or is a nucleotide; rather "interchangeable" means that, where appropriate, the terms may be substituted, broadening the disclosures to cover different concepts.

Similarly, "used interchangeably" in the one sentence cited by the PTAB does not mean that guide RNA is chimeric RNA; rather, it means that for certain—but not all—"aspects of the invention," the concepts can

be interchangeable in that the CRISPR-Cas9 system has a "guide RNA," whatever the configuration of the RNA.

The totality of the relevant intrinsic evidence is therefore, like the plain and ordinary meaning, consistent only with a broadest reasonable interpretation of "guide RNA" that encompasses both single- and dual-molecule RNA configurations. The Court should accordingly reverse the PTAB's overly narrow construction of "guide RNA."

II. If The Court Agrees "guide RNA" Is Not Limited To Single-Molecule RNA, It Should Vacate The Denials Of Broad Motions 2 And 3

The PTAB denied Broad Motion 2 (to broaden the count beyond sgRNA) and Broad Motion 3 (to designate certain claims that are not limited to sgRNA as corresponding to Count 1) largely based on its incorrect construction of "guide RNA."

It is undisputed that Broad currently has hundreds of involved claims that use the term "guide RNA" and, thus, using the broadest reasonable interpretation, these claims cover both dual- and single-molecule configurations. Count 1, however, is limited to single-molecule RNA systems. It would be fundamentally unfair to put these broader claims at risk in the interference while simultaneously prohibiting Broad

from introducing priority proofs of significant earlier work with dual-molecule RNA.

Accordingly, if the Court agrees that "guide RNA" is not limited to the single-molecule configuration, it should vacate the PTAB's decisions on Broad's Motions 2 and 3 and direct the PTAB to reconsider those motions *de novo* under the proper construction. Awarding priority to claims that are generic as to the RNA based on priority evidence that is limited to only the sgRNA species of Count 1 would violate the "primary purpose of an interference," which is to make a "determination of priority as to *[e]ach* of the common [patentably distinct] inventions claimed by the parties." *Godtfredsen v. Banner*, 598 F.2d 589, 592 (C.C.P.A. 1979).

CONCLUSION

For all these reasons, the Court should affirm the PTAB's judgment of priority to Broad. If the Court reaches Broad's conditional cross-appeal, the Court should reverse the PTAB's construction of "guide RNA" and vacate the PTAB's decisions on Broad's Motions 2 and 3.

Respectfully submitted,

February 15, 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 15th day of February, 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 16,467 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