Nos. 2022-1594 & 2022-1653

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

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

Appellants,

v.

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

Cross-Appellants.

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

OPENING BRIEF FOR APPELLANTS THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, UNIVERSITY OF VIENNA, EMMANUELLE CHARPENTIER

Sara E. Margolis
Jonathan E. Barbee
MOLOLAMKEN LLP
430 Park Avenue
New York, NY 10022
(212) 607-8160 (telephone)
(212) 607-8161 (fax)

Elizabeth K. Clarke
MOLOLAMKEN LLP
300 N. LaSalle Street, Suite 5350
Chicago, IL 60654
(312) 450-6700 (telephone)
(312) 450-6701 (fax)

Jeffrey A. Lamken
Counsel of Record
Kenneth E. Notter III
MOLOLAMKEN LLP
The Watergate, Suite 500
600 New Hampshire Avenue, N.W.
Washington, D.C. 20037
(202) 556-2000 (telephone)
(202) 556-2001 (fax)
jlamken@mololamken.com

Counsel for The Regents of the University of California, University of Vienna, Emmanuelle Charpentier

Interference 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.

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

A eukaryotic cell comprising a target DNA molecule and an engineered and/or non-naturally 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.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 2022-1594 & 2022-1653

Short Case Caption The Regents of the University of California v. The Broad Institute, Inc.

Filing Party/Entity The Regents of the University of California, University of Vienna, Emmanuelle Charpentier

Instructions: Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box**. Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 09/30/2022

Signature: /s/ Jeffrey A. Lamken

Name: Jeffrey A. Lamken

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☑ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☑ None/Not Applicable
The Regents of the University of California		
University of Vienna		
Emmanuelle Charpentier		

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☑ Additional pages attached

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☐ None/Not Applicable ☑ Additional pages attached

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

CERTIFICATE OF INTEREST
Addendum to Questions 4 and 5

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

The following counsel appeared for Appellants in the originating agency:

STERNE, KESSLER, GOLDSTEIN & FOX PLLC
Eldora L. Ellison
Eric K. Steffe
David H. Holman
Byron L. Pickard
John Christopher Rozendaal
Paul A. Ainsworth
Michael E. Joffre

RINLAURES LLC
Li-Hsien Rin-Laures

MARSHALL GERSTEIN & BORUN LLP
Sandip H. Patel

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). *See also* Fed. Cir. R. 47.5(b).

The Regents of the University of California v. ToolGen, Inc., Patent Interference No. 106,127 (Patent Trial and Appeal Board)

The Regents of the University of California v. Sigma-Aldrich, Co., LLC, Patent Interference No. 106,132 (Patent Trial and Appeal Board)

TABLE OF CONTENTS

Page

INTRODUCTION 1

JURISDICTIONAL STATEMENT 3

ISSUES PRESENTED 3

STATEMENT 3

I. Background 3

A. The Search for Gene-Editing Systems 3

B. CVC Invents a Groundbreaking Programmable Gene-Editing System 4

C. CVC's May 2012 "P1" Application Discloses CRISPR-Cas9 in Eukaryotic Cells 8

D. CVC Discloses Its Invention to Acclaim 10

II. CVC and Five Other Labs Report Actually Reducing CVC's Invention to Practice Within Months of CVC's Disclosure 12

A. CVC's Planned Reductions to Practice 13

B. Multiple Laboratories Promptly Report Reducing CVC's Invention to Practice 14

1. After Obtaining CVC's Chimera A Before Publication, Broad Promptly Reports Reduction to Practice 14

2. Four Other Labs Report Positive Results Within Months of CVC's Invention 17

C. CVC Reduces Its Invention to Practice 18

1. Expression Vectors in Human Cells 19

2. Microinjection in Zebrafish Embryos 21

III. Proceedings Below 22

A. The Earlier '048 Interference 22

B. The Current '115 Interference 23

1. Written Description 24

2. Conception and Reduction to Practice 25

SUMMARY OF ARGUMENT 28

ARGUMENT 30

I. The PTAB's Conception Decision Cannot Be Sustained 30

A. Conception Is Complete When It Is Sufficiently Definite and Permanent that Skilled Artisans Can Construct the Invention 32

B. The PTAB Departed from the Framework Precedent Demands 35

C. The PTAB Erroneously Employed a Subjective Expectation-of-Success Standard 41

II. The PTAB's Decision Flouts the Originality Requirement 44

III. The PTAB's Analysis Fails the APA's Reasoned-Decisionmaking Requirement 47

A. The PTAB's "Must Be Differences" Theory Is Unreasoned and Unsupported 47

B. The PTAB Ignored Rafts of Evidence Contrary to Its Positions 50

C. The PTAB's Analysis of CVC's Microinjection Embodiment Is Arbitrary and Unreasoned 52

IV. The PTAB Erred in Denying Accorded Benefit Based on Lack of Written Description 55

A. P1's Expansive Disclosures Satisfy Written Description 56

B. The PTAB Improperly Engrafted a Burden-To-Convince Requirement onto Written Description 60

1. Written Description Does Not Require Persuasion 61

2. The PTAB Erroneously Converted "Possession" into "Proof".....63

CONCLUSION.....66

TABLE OF AUTHORITIES

Page(s)

CASES

Acromed Corp. v. Sofamor Danek Group, Inc.,
253 F.3d 1371 (Fed. Cir. 2001) 33, 39

Alcon Rsch. Ltd. v. Barr Labs., Inc.,
745 F.3d 1180 (Fed. Cir. 2014) .....*passim*

Allergan, Inc. v. Sandoz Inc.,
796 F.3d 1293 (Fed. Cir. 2015) 61

Alpert v. Slatin,
305 F.2d 891 (C.C.P.A. 1962) 39, 40

Amgen, Inc. v. Chugai Pharm. Co.,
927 F.2d 1200 (Fed. Cir. 1991) 31

Applegate v. Scherer,
332 F.2d 571 (C.C.P.A. 1964) 41, 42, 43, 46

Ariad Pharms., Inc. v. Eli Lilly & Co.,
598 F.3d 1336 (Fed. Cir. 2010) .....*passim*

Barba v. Brizzolara,
104 F.2d 198 (C.C.P.A. 1939) 33, 38, 39

BASF Plant Sci., LP v. Commonwealth Sci. & Indus. Rsch. Org.,
28 F.4th 1247 (Fed. Cir. 2022) 61, 63

Biogen Int'l GMBH v. Mylan Pharms. Inc.,
18 F.4th 1333 (Fed. Cir. 2021) 62

Burroughs Wellcome Co. v. Barr Labs., Inc.,
40 F.3d 1223 (Fed. Cir. 1994) .....*passim*

Cameron & Everett v. Brick,
1871 C.D. 89 (Comm'r Pat.).....31, 33, 37

Capon v. Eshhar,
418 F.3d 1349 (Fed. Cir. 2005) 63

City of Elizabeth v. Nicholson Pavement,
97 U.S. 126 (1877).....41

Cooper v. Goldfarb,
154 F.3d 1321 (Fed. Cir. 1998).....25

Crown Packaging Tech., Inc. v. Ball Metal Beverage Container Corp.,
635 F.3d 1373 (Fed. Cir. 2011).....55, 57, 64

Dana-Farber Cancer Inst., Inc. v. Ono Pharm. Co.,
964 F.3d 1365 (Fed. Cir. 2020).....41

Diamond Rubber Co. of N.Y. v. Consolidated Rubber Tire Co.,
220 U.S. 428 (1911).....58

Dist. Hosp. Partners, L.P. v. Burwell,
786 F.3d 46 (D.C. Cir. 2015).....49

Dolbear v. Am. Bell Tel. Co.,
126 U.S. 1 (1888).....*passim*

Evans v. Eaton,
20 U.S. (7 Wheat.) 356 (1822).....57, 61

Falkner v. Inglis,
448 F.3d 1357 (Fed. Cir. 2006).....56, 63

Field v. Knowles,
183 F.2d 593 (C.C.P.A. 1950).....39

Finch v. Dillenback,
121 F.2d 459 (C.C.P.A. 1941).....46

*Glob. Tel*Link v. FCC*,
866 F.3d 397 (D.C. Cir. 2017).....49

Hedgewick v. Akers,
497 F.2d 905 (C.C.P.A. 1974).....46

Hitzeman v. Rutter,
243 F.3d 1345 (Fed. Cir. 2001).....40, 43

In re Lee,
277 F.3d 1338 (Fed. Cir. 2002) 43

MacMillan v. Moffett,
432 F.2d 1237 (C.C.P.A. 1970) 43

Martek Biosciences Corp. v. Nutrinova, Inc.,
579 F.3d 1363 (Fed. Cir. 2009) 65

Mergenthaler v. Scudder,
11 App. D.C. 264 (1897) 32, 33

Morall v. DEA,
412 F.3d 165 (D.C. Cir. 2005) 48

Music Choice v. Copyright Royalty Bd.,
970 F.3d 418 (D.C. Cir. 2020) 50

Mycogen Plant Sci. v. Monsanto Co.,
243 F.3d 1316 (Fed. Cir. 2001) 43

Nat. Res. Def. Council v. U.S. Nuclear Regul. Comm'n,
879 F.3d 1202 (D.C. Cir. 2018) 42

In re O'Farrell,
853 F.2d 894 (Fed. Cir. 1988) 4, 7

Pers. Web Techs., LLC v. Apple, Inc.,
848 F.3d 987 (Fed. Cir. 2017) 47

Pfaff v. Wells Elecs., Inc.,
525 U.S. 55 (1998) 34

Price v. Symsek,
988 F.2d 1187 (Fed. Cir. 1993) 44

Princeton Vanguard, LLC v. Frito-Lay N. Am., Inc.,
786 F.3d 960 (Fed. Cir. 2015) 50, 51, 54

Provisur Techs., Inc. v. Weber, Inc.,
— F.4th —, 2022 WL 4474941 (Fed. Cir. Sept. 27, 2022) 52, 53, 54, 55

Regents of Univ. of Cal. v. Broad Inst., Inc.,
903 F.3d 1286 (Fed. Cir. 2018) .....*passim*

Rey-Bellet v. Engelhardt,
493 F.2d 1380 (C.C.P.A. 1974) 37

Sewall v. Walters,
21 F.3d 411 (Fed. Cir. 1994) .....*passim*

Sinclair & Carroll Co. v. Interchemical Corp.,
325 U.S. 327 (1945).....34, 39, 44

Sorenson Commc'ns Inc. v. FCC,
755 F.3d 702 (D.C. Cir. 2014).....53

In re Tansel,
253 F.2d 241 (C.C.P.A. 1958) 39

Univ. of Pittsburgh of Commonwealth Sys. of Higher Educ. v. Hedrick,
573 F.3d 1290 (Fed. Cir. 2009) .....*passim*

CONSTITUTIONAL PROVISIONS & STATUTES

U.S. Const. art. I, § 8, cl. 8 46

Administrative Procedure Act, Pub. L. 79-404, 60 Stat. 237 (1946) .....*passim*

Patent Act.....*passim*

35 U.S.C. § 112 .....30, 55

35 U.S.C. § 135(a).....3

35 U.S.C. § 141 3

28 U.S.C. § 1295(a)(4)(A).....3

OTHER AUTHORITIES

U.S. Patent No. 821,393.....34

https://www.nps.gov/articles/roadtofirstflight.htm.....34

W. Robinson, *The Law of Patents for Useful Invention* (1890) 46

STATEMENT OF RELATED CASES

No appeal has previously been taken from the proceedings below. The Court's decision in this appeal may directly affect or be directly affected by the following pending proceedings: *The Regents of the University of California v. ToolGen, Inc.*, Patent Interference No. 106,127 (Patent Trial and Appeal Board), and *The Regents of the University of California v. Sigma-Aldrich, Co., LLC*, Patent Interference No. 106,132 (Patent Trial and Appeal Board).

INTRODUCTION

Jennifer Doudna, Emmanuelle Charpentier, and their colleagues invented a revolutionary technology for editing DNA—the CRISPR-Cas9 gene-editing system. This case concerns who is entitled to patents for using that system to edit genes in ***eukaryotic*** (*e.g.*, plant or animal) cells: Doudna and Charpentier, who invented the technology, announced it to the world, and received the Nobel Prize for it; or a scientist at the Broad Institute who took their design and then (along with many others) promptly reduced it to practice using routine methods.

Doudna and Charpentier, along with co-inventors Martin Jinek and Krzysztof Chylinski (collectively, "CVC"[1]) conceived of and described every element of the invention before Broad's first alleged conception. They developed the invention's design and structure; described how that structure could be placed inside eukaryotic cells using well-known techniques; and explained that their invention was capable of editing DNA in ***any*** cell type, including eukaryotes. Despite all that, the Patent Trial and Appeal Board ("PTAB") awarded priority to Broad because it purportedly reduced the invention to practice first—even though the PTAB never identified ***any*** inventive contribution Broad made. The PTAB reached that backward result through multiple legal errors.

[1] University of **C**alifornia, University of **V**ienna, and Emmanuelle **C**harpentier.

For conception, 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. But the PTAB refused to apply that ***objective*** standard. Instead, it required CVC to ***know*** the invention would work, defying this Court's precedents. It disregarded 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.

The PTAB accorded Broad priority even though it could not identify anything ***inventive***—not a single limitation of the count—that Broad did not get ***from CVC***. That violates the Constitution's admonition that patents must be awarded to original inventors, not followers who reduce others' inventions to practice.

The PTAB's written-description decision is also contrary to precedent. Rather than assess whether CVC's patent disclosures were sufficient to allow skilled artisans to identify the invention, the PTAB demanded more: It required CVC's disclosures to ***persuade*** skeptical artisans the invention would overcome various imagined hurdles to reduction to practice in eukaryotic cells. That defies this Court's instruction that written description "is not about whether the patentee has proven to the skilled reader that the invention works." *Alcon Rsch. Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014).

Finally, the PTAB failed to engage in the reasoned decisionmaking the Administrative Procedure Act demands. That, too, requires reversal.

JURISDICTIONAL STATEMENT

The PTAB had jurisdiction under pre-America Invents Act ("AIA") 35 U.S.C. § 135(a). *See* Pub. L. 112-29 § 3(n)(2). The PTAB entered final judgment on February 28, 2022. CVC appealed on March 30, 2022. This Court has jurisdiction under pre-AIA 28 U.S.C. § 1295(a)(4)(A) and 35 U.S.C. § 141. Pub. L. No. 112-274 § 1(k)(3).

ISSUES PRESENTED

1. Whether the PTAB legally erred by failing to apply an objective standard for conception, and/or impermissibly awarded priority without identifying any inventive contribution by the purported inventor.

2. Whether the PTAB's analysis is arbitrary and capricious.

3. Whether the PTAB applied an erroneous legal standard to conclude that CVC's first and second provisional applications lacked written description.

STATEMENT

I. BACKGROUND

A. The Search for Gene-Editing Systems

By early 2012, two technologies had become standard for gene editing: zinc finger nucleases ("ZFNs") and transcription activator-like effector nucleases ("TALENs"). ZFNs and TALENs include two proteins: one that binds to a target

DNA sequence, and another (naturally found in prokaryotes, *i.e.*, single-celled organisms lacking a cell nucleus) that cleaves DNA. Appx65646; Appx67648 (¶67).

To edit genes in eukaryotes (organisms with a cell nucleus), systems like ZFNs and TALENs are delivered into the nucleus, where eukaryotic DNA resides. By early 2012, scientists had developed reliable methods for doing so, including expression-vector-based methods and microinjection. Appx67678-67679 (¶¶136-137); Appx13521 (¶64).[2] Those methods worked in all eukaryotic systems—animals, plants, and humans. Appx65646.

ZFNs' and TALENs' "design principles" were "well-established." Appx65646. But scientists had to design a ***new protein*** for every new target DNA sequence, making these systems too "costly and time consuming" for "widespread use." Appx65649; Appx646 [0001].

B. CVC Invents a Groundbreaking Programmable Gene-Editing System

CVC focused on an "ancient immune system" found in prokaryotic cells, called "CRISPR," which "disarms viruses by cleaving their DNA." Appx64060. They discovered how to leverage the simplest CRISPR system—the Type II system—for gene editing. Appx64060; Appx64098.

[2] An expression vector contains DNA. When the vector is introduced into a cell, the cell synthesizes an RNA strand from the DNA, which may then be used to synthesize a protein. *In re O'Farrell*, 853 F.2d 894, 898-99 (Fed. Cir. 1988).

Scientists had known that, in Type II CRISPR systems, an RNA sequence known as "***crRNA***" guided at least one DNA-cleaving protein to a complementary target DNA sequence, adjacent to a "PAM" sequence. Appx13831; Appx65643; Appx57589.[3] Some hypothesized that the "***Cas9***" protein was involved in DNA cleavage. Appx13855.

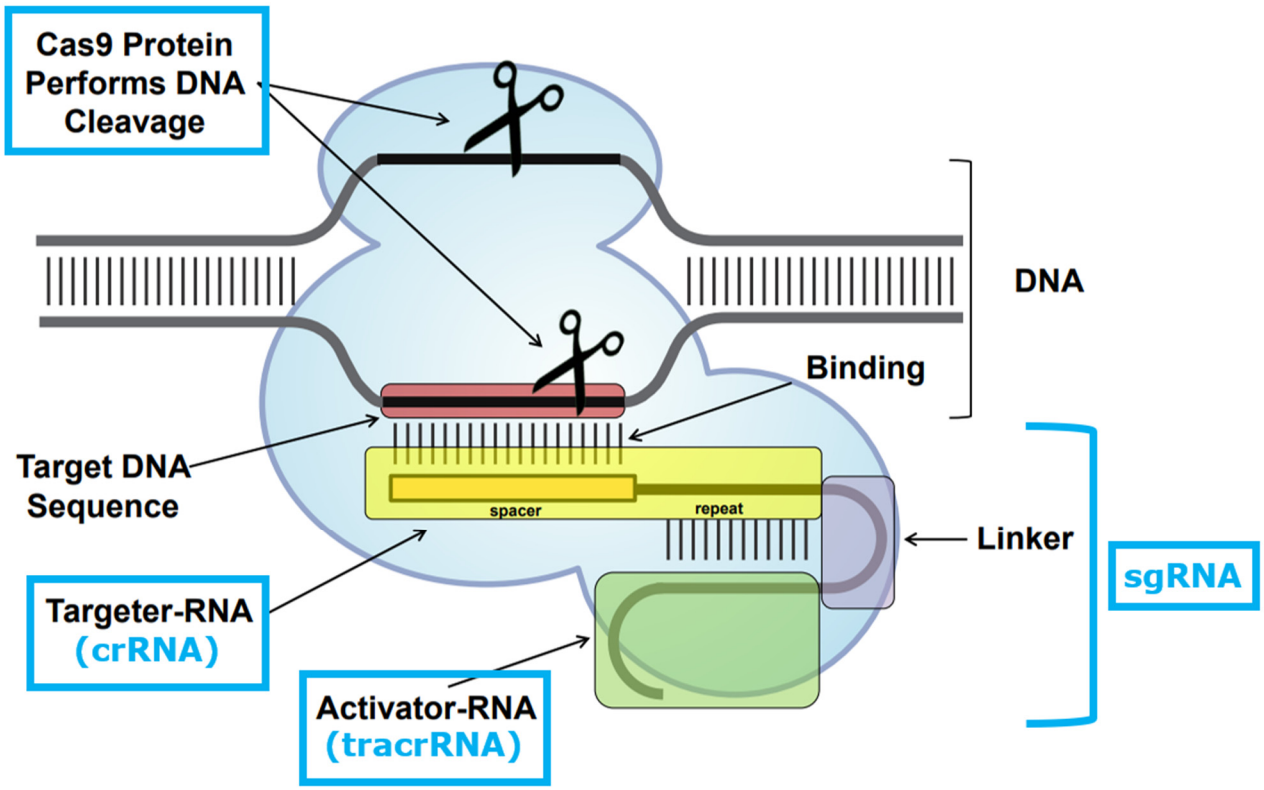
In early 2011, Charpentier's lab published its discovery that another RNA sequence, called "***tracrRNA***," helped convert precursor crRNA strands into their active, mature form. Appx13897-13898. But scientists did not know tracrRNA played an essential role in the final DNA cleavage complex. Appx13900; Appx13813; Appx13832.

CVC's *in vitro* experiments yielded a groundbreaking discovery: ***Mature tracrRNA, mature crRNA, and Cas9*** together achieved targeted DNA cleavage. Appx57592-57593. CVC thus identified, for the first time, the three essential components of the CRISPR-Cas9 DNA cleavage complex. Scientists could cleave DNA simply by combining the two mature RNAs and Cas9, bypassing cumbersome RNA pre-processing steps that occurred in nature. Appx5598-5599. No other proteins or RNAs were needed. Appx5598-5599.

[3] Protospacer-adjacent motifs ("PAMs") allow the CRISPR system to recognize foreign DNA and prevent cleavage of the prokaryotic cell's own DNA. Appx57589.

CVC then made the "crucial" further discovery that tracrRNA and crRNA could be linked to form a single-molecule "chimeric" RNA. Appx57592. This "chimeric RNA" is called "single-guide" RNA or "sgRNA." Appx57592. The single-guide structure simplified gene editing because the crRNA and tracrRNA became one component instead of two. Appx57592-57593.

CVC's single-guide CRISPR-Cas9 cleavage system can be illustrated as follows:



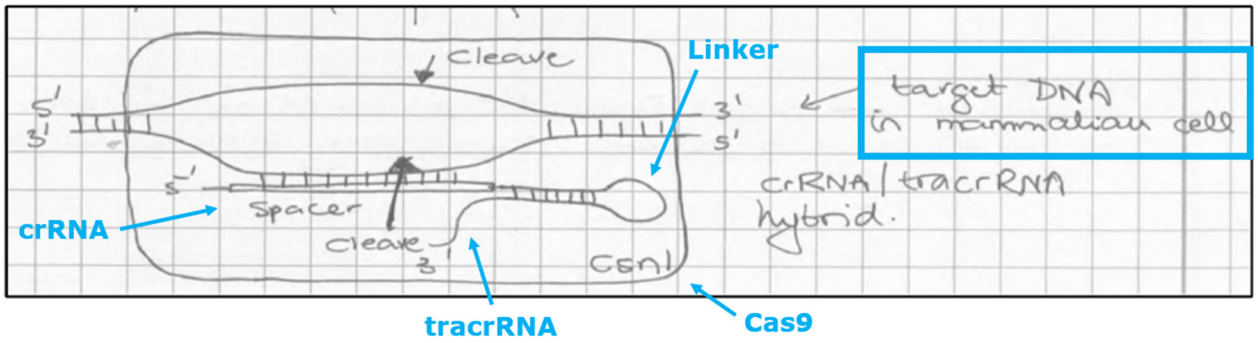
Appx80272 (annotated); Appx5602.

CVC designed an sgRNA ("chimera A"), and tested its CRISPR-Cas9 complex *in vitro* on target DNA, including eukaryotic gene sequences. Appx5602;

Appx67260-67261 (¶¶67-69); Appx67286-67287 (¶127). CVC's complex cleaved the target each time. Appx5602; Appx67260-67261 (¶¶67-69); Appx67286-67287 (¶127). CVC concluded its CRISPR-Cas9 system could "enable targeting of any DNA sequence of interest with few constraints." Appx5602.

The complex exploits nucleic acid hybridization—common to all DNA/RNA—to locate the target DNA sequence. Appx5598. DNA and RNA are both made of four nucleic-acid "bases," represented as A, C, G, and T/U (T in DNA, U in RNA). *O'Farrell*, 853 F.2d at 896-97 & n.5. Each base pairs with its complement—G with C, A with T/U. *See id.* When the bases in a DNA sequence and an RNA sequence are "complementary," the sequences hybridize by binding together. *Id.* In the CRISPR-Cas9 complex, some of the crRNA sequence (yellow above) complements—and thus hybridizes to—the target DNA sequence (red above). *See* Appx5598-5599. That lines up the Cas9 protein to cleave the DNA at the target location. Appx5598-5599. The result is a simpler gene-editing system that can be reprogrammed by changing the crRNA. Appx65646.

In March 2012, Jinek (Doudna's colleague) drew CVC's invention in his lab notebook, recording an embodiment where the "target DNA" was "in [a] mammalian cell":



Appx69009 (annotated); Appx67247 (¶42).

CVC's April 2012 invention disclosure explained the invention's use for "targeted gene insertion in crop plants" and "human gene therapy." Appx65648. CRISPR-Cas9, it stated, could be used "analogous[ly]" to ZFNs and TALENs, but with "superior" accuracy and efficiency. Appx65646-65650. The sgRNA and Cas9 components could be introduced into eukaryotic cells using prior-art techniques like "vectors" or "direct microinjection" that worked for ZFNs and TALENs. Appx65651; Appx65630-65631; *see* p. 4, *supra*. The CVC inventors foresaw "considerable exploitation" of their system "for targeted genome editing in cells of the three kingdoms of life" (bacteria, archaea, and eukaryotes). Appx63811; Appx63759; Appx67442 (¶49).

C. CVC's May 2012 "P1" Application Discloses CRISPR-Cas9 in Eukaryotic Cells

In May 2012, CVC filed its first provisional patent application, "P1" (No. 61/652,086), disclosing CVC's CRISPR-Cas9 system and how to practice it. P1 announces that CVC's system improves on existing gene-editing systems—ZFNs

and TALENs, Appx646[0001]-[0003]; Appx67678-67679(¶137)—and identifies the CRISPR-Cas9 system's three essential components: crRNA and tracrRNA (which could be linked to form sgRNA), and Cas9, Appx646-647[0004]-[0005]; Appx657-658[0047]-[0048]; Appx665[0079].

P1 repeatedly discloses using that system in eukaryotic cells. It identifies "fruit fly," "fish, amphibian, reptile, bird, mammal," and "human" cells—all eukaryotes—as "[s]uitable host cells" and "[t]arget cells of interest." Appx689[00165]; Appx705[00218]. References to "eukaryotic DNA" and "eukaryotic cells" pervade the definitions. Appx652[0027]; Appx655[0038]; *see* Appx652-653[0028]; Appx658[0049]; Appx659[0055]; Appx660-661[0060]-[0061]. P1 includes at least 21 claims for cleaving target DNA in eukaryotic cells. Appx722[claims 61-69]; Appx725-727[claims 93-96, 102-109].

P1 explains why the complex works in any cell, including eukaryotic cells: It exploits universal principles of nucleic-acid hybridization to target specific sites, *see* p. 7, *supra*, and thus can cleave DNA in cells "from any organism," Appx689[00165]. P1 discloses *in vitro* experiments showing that CVC's system cleaved three different target DNA sequences. Appx713-714[00248]-[00251]; Appx565-567[Figs. 3A-3C]; *see* pp. 6-7, *supra*.

The CRISPR-Cas9 system, P1 explains, can be introduced into eukaryotic cells using existing "well-known techniques . . . (*e.g.*, microinjection, electropora-

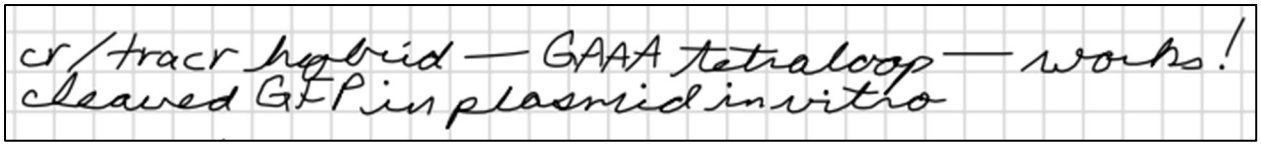
tion, transfection, etc.)." Appx691[00173]; *see* Appx655-656[0039]. P1 lists "examples of suitable eukaryotic promoters" and "suitable expression vectors" "for eukaryotic host cells." Appx679[00127]; Appx684[00149].

CVC's later provisional patent applications, "P2" (filed October 19, 2012) and "P3" (filed January 28, 2013), add more detail. Appx760-1038; Appx1039-1417.

D. CVC Discloses Its Invention to Acclaim

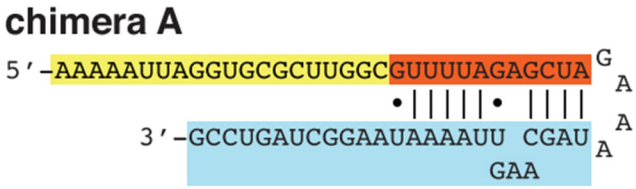
In June 2012, at UC Berkeley's annual invitation-only CRISPR research conference, CVC shared its discovery that the essential components of the CRISPR-Cas9 DNA cleavage complex are crRNA, tracrRNA, and Cas9. Appx65915. Explaining that crRNA and tracrRNA could be linked to form sgRNA, CVC briefly showed—onscreen only—the nucleotide sequence of its "chimera A" sgRNA. Appx65932. CVC described how to program the complex to target a chosen DNA sequence, and presented experimental results demonstrating DNA cleavage *in vitro*. Appx65929-65934.

CRISPR pioneer Rodolphe Barrangou recalled "excitement in the room." Appx80956(¶8); Appx80958(¶16). Attendees understood the invention was a "game changer for genome editing in eukaryotes" because it would allow gene editing "in a fraction of the time and at a fraction of the cost" of prior-art systems. Appx80958(¶16). CRISPR luminary Erik Sontheimer's notes illustrate the surprise and excitement:



Appx80260.

On June 28, 2012, *Science* published CVC's seminal article, *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity* ("Jinek 2012"). Appx5597-5641. The paper explained that CVC's CRISPR-Cas9 system "enable[d] targeting of any DNA sequence of interest with few constraints." Appx5602. It reproduced CVC's "chimera A," and asserted the invention could—like ZFNs and TALENs—be used for "genome-editing":



Appx5602.[4]

Jinek 2012's peer reviewers understood the invention could "be designed to cleave any target DNA sequence, raising the possibility of programmed genome editing." Appx64329. Reviewer Luciano Marraffini realized it could be "re-

[4] The yellow- and orange-highlighted sequences are crRNA; the blue-highlighted sequence is tracrRNA. Appx5602. The yellow DNA-targeting portion of the crRNA can be modified to target different DNA sequences. *See* pp. 6-8, *supra*.

programmed to target essentially any sequence in any genome with a very high specificity," making it a "new, invaluable tool for genome editing." Appx79336.

Awarding Doudna and Charpentier the Nobel Prize in Chemistry, the Nobel Committee hailed the invention's "enormous power," which "not only revolutionised basic science," but "also resulted in innovative crops and will lead to ground-breaking new medical treatments." Appx64060. CVC's "genetic scissors" made it "possible to change the code of life itself," taking life sciences "into a new epoch." Appx64060.

II. CVC AND FIVE OTHER LABS REPORT ACTUALLY REDUCING CVC'S INVENTION TO PRACTICE WITHIN MONTHS OF CVC'S DISCLOSURE

CVC's announcement sparked a frenetic "race" to publish papers demonstrating use of CVC's invention in eukaryotic cells. Appx80008-80009(52:17-53:8). Scientists understood they "would be able to quickly apply" CVC's CRISPR-Cas9 system in eukaryotic cells "because the process for doing so was straightforward and required only routine genome-editing techniques." Appx80972(¶21); Appx80003(31:8-19). The question "was not ***whether*** the CRISPR-Cas9 system would work in eukaryotes"—skilled artisans "all expected it would"—but whether it would "***outcompete*** the existing genome-editing technologies, such as TALENs and ZFNs." Appx80959(¶17) (emphasis added).

A. CVC's Planned Reductions to Practice

By June 2012, CVC pursued two plans to reduce its invention to practice in eukaryotic cells. ***First***, drawing on techniques successfully used with ZFNs, the CVC inventors sought to introduce the complex into human cells using ***expression vectors*** that would cause the cells themselves to synthesize ("express") the complex's components. Appx67370(¶55); *see* p. 4 n.2, *supra*.

By May 2012, Jinek had constructed an sgRNA vector incorporating one of the most common "promoters" for expressing RNA—the "U6 promoter"—to drive the cell's expression of the sgRNA. Appx67283-67284(¶124); Appx80797(¶68). A "strong promoter" would yield "high expression" of sgRNA, helping it form the CRISPR-Cas9 complex inside the cell. Appx79959(69:17-70:2).

By May, Jinek had also designed Cas9 vectors with "a CMV promoter" (a common promoter for expressing proteins) "to drive expression of Cas9" protein inside the cell. Appx67284(¶124). He added one or more nuclear localization signals ("NLSs") to the Cas9 sequence—a "well established" technique to "aid in getting proteins to the nucleus." Appx67270-67271(¶86). By June, Jinek had ordered and was awaiting delivery of a Cas9 sequence that was "codon-optimized" for eukaryotic-cell expression. Appx67293-67294(¶¶151, 155).

Second, by June 22, CVC had decided to recruit a colleague, Florian Raible, to reduce the invention to practice another way: ***microinjecting*** a pre-formed

CRISPR-Cas9 complex—already shown to work *in vitro*, *see* pp. 6-7, *supra*—into the nucleus of zebrafish embryos, Appx66680; Appx67444 (¶56). Because the Cas9 and sgRNA were pre-assembled into a complex outside the cell, there was no "need for in vivo expression of [ ]either RNA [ ]or protein, codon bias optimization and so on." Appx66308. Injecting the complex into rapidly dividing embryonic cells (like zebrafish embryos) would facilitate access to eukaryotic DNA because chromatin—tightly wound eukaryotic DNA structures—unwinds during cell division. Appx67438 (¶32).

B. Multiple Laboratories Promptly Report Reducing CVC's Invention to Practice

Within months, CVC and at least five other labs reported reducing CVC's invention to practice using standard, prior-art techniques.

1. *After Obtaining CVC's Chimera A Before Publication, Broad Promptly Reports Reduction to Practice*

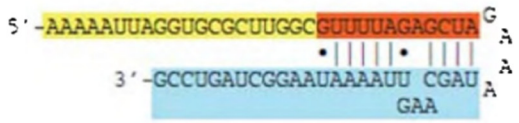
For over a year, Broad's Feng Zhang had attempted—unsuccessfully—to use incomplete CRISPR-Cas9 systems to edit eukaryotic genes. Appx80853-80900 (¶¶A1-A78). Like other scientists, Zhang did not understand that mature ***tracrRNA*** was a necessary third component of the final DNA-cleavage complex. Appx80001 (24:17-25:3); Appx80848-80849 (¶¶156-157). As a result, he had no idea that mature tracrRNA and crRNA could be linked to form sgRNA. Appx80001 (23:15-24:9). Instead, Zhang struggled with experiments using un-

processed RNAs and other extraneous elements, wondering what "other factors need to be identified." Appx80853-80900(¶¶A1-A78); Appx47155.

All that changed on June 26, 2012. Before Jinek 2012 published in *Science*, Zhang received portions of it—including CVC's "chimera A" sgRNA sequence—from his collaborator, Marraffini, who was a peer-reviewer of CVC's manuscript:

From: Luciano Marraffini <marraffini@mail.rockefeller.edu>
Sent: Tuesday, June 26, 2012 4:05 PM
To: Feng Zhang
Subject: RE: CRISPR

Hi Feng. I checked and they provide pre-processed crRNAs to the in vitro reaction, so there is no need for RNAse III in their assays. The minimal tracr/crRNA guide is shown below. Yellow is spacer, orange is repeat and blue is tracrRNA sequence



Let's hope it works. Best,

Luciano

Appx77492; Appx80005(37:17-38:7). Marraffini told Zhang the complex had just three necessary elements—crRNA and tracrRNA (linked to form sgRNA), and Cas9. Appx80002-80003(27:4-16, 29:20-30:3); Appx77492. He told Zhang that CVC used mature ("pre-processed") RNAs. Appx77492. CVC's invention, Marraffini advised, "would be an important tool for genome editing in eukaryotes specifically." Appx80012(68:13-21). Despite years of litigation, including an earlier appeal to

this Court, Broad withheld that communication until discovery ***halfway through the proceedings below***. Appx78889.

Upon receiving chimera A, Zhang abandoned his previous experimental designs. Appx80847-80849(¶¶154-158). He plugged CVC's chimera A sequence into a standard RNA vector he got from a neighboring lab, and the Cas9 sequence into an existing vector he had used with TALENs. Appx77667; Appx64114; Appx75005(¶21); Appx80804-80806(¶¶81-83). Like Jinek, Zhang used the well-known U6 promoter to drive high levels of sgRNA expression, and another common promoter to drive Cas9 expression. Appx75005(¶21); Appx80797(¶68); Appx80804(¶80). Like Jinek, Zhang added one or more NLSs to the Cas9 sequence. Appx79961(78:10-12); Appx80808(¶89). And like Jinek, Zhang codon-optimized his Cas9 sequence using commercially available tools. Appx79963(85:9-13); Appx80806(¶84).

In July 2012—mere weeks after receiving chimera A from Marraffini—Zhang purportedly reduced the invention to practice in mouse cells, supposedly detecting mutations in two of 275 samples (a 0.75% success rate). Appx162-163. Zhang's results were published in a January 2013 paper ("Cong 2013"), which reproduced the precise chimera A that Marraffini got from CVC and shared with Zhang on June 26:

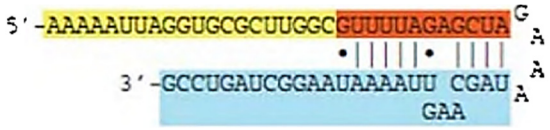


Image shared by Marraffini

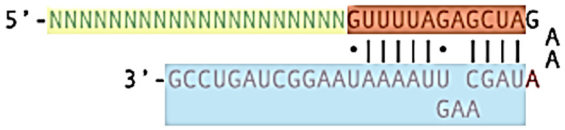


Image in Cong 2013

Appx77492; Appx5568 (highlighting added).[5]

In December 2012, Broad filed a patent application claiming CRISPR-Cas9 for eukaryotic gene editing. Appx563.

2. *Four Other Labs Report Positive Results Within Months of CVC's Invention*

Within months of Jinek 2012's publication, four other labs reported using CVC's CRISPR-Cas9 complex to cleave DNA in eukaryotic cells, employing methods CVC identified in P1 and its invention disclosure. Each introduced the complex into cells using techniques from their earlier published gene-editing experiments:

- By October, Church's group reported cleavage with a delivery method it had used for TALENs. *Compare* Appx80300-80309, *with* Appx53203-53206.
- By November, Kim's lab reported applying CVC's system using methods from its existing ZFNs gene-editing platform. *Compare* Appx79244-79251, *with* Appx15794-15807.
- By December 6, Chen's lab reported cleavage using methods from Chen's existing ZFNs gene-editing platform. *Compare* Appx79062-79092, *with* Appx79043-79044 [0065-0066].

[5] "N" represents any nucleotide. Appx80788 (¶52 n.2).

- By December 18, Joung's lab reported cleavage in zebrafish embryos using methods from an existing TALENs system. *Compare* Appx79217-79243, *with* Appx47104-47127.

Those labs' methods are summarized below (ZFNs/TALENs methods in orange; CRISPR-Cas9 methods in purple):

Research Group	Publication	Months after Jinek 2012	Vector(s)	Cell type/cell line	Delivery method(s)
Feng Zhang (Broad)	Zhang, 2011, Nat. Biotech (TALEs) (Ex. 4620) Sanjana, 2012, Nat. Prot. (TALENs) (Ex.5130)	3+ months until Oct. 5 manuscript submission	• Expression vector with EF1α promoter	HEK293F T cells	Lipofectamine 2000
	Cong, 2013, Science (CRISPR-Cas9) (Ex. 3564)		• Cas9: expression vector with EF1α promoter • sgRNA: expression vector with U6 promoter	HEK293F T cells	Lipofectamine 2000
George Church (Harvard)	Briggs, 2012, Nuc. Acids Res. (TALENs) (Ex. 5281)	4 months until Oct. 26 manuscript submission	• Expression vector with CMV promoter	293T cells	Lipofectamine 2000
	Mali, 2013, Science (CRISPR-Cas9) (Ex. 3623)		• Cas9: expression vector with CMV promoter (Invitrogen) • sgRNA: expression vector with U6 promoter (Invitrogen)	293T cells	Lipofectamine 2000
Jin-Soo Kim (ToolGen)	Kim, July 2012, Genome Res. (ZFNs) (Ex. 5239)	Less than 5 months until Nov. 20 manuscript submission	• "p3," a pcDNA3.0 derivative	293T cells K562 cells	Lipofectamine 2000 (293T cells) Nucleofection (K562 cells)
	Cho, Jan. 2013, Nat. Biotech (CRISPR-Cas9) (Ex. 4076)		• Cas9: "p3s," a pcDNA3.1 derivative • sgRNA: *in vitro* transcribed RNA	293T cells K562 cells	Lipofectamine 2000 (293T cells) Nucleofection (K562 cells)
Keith Joung Collaboration (Harvard; Mass. Gen.)	Sander, 2011, Nat. Biotech. (TALENs) (Ex. 5236)	6.5 months until Dec. 18 manuscript submission	• TALENs: *in vitro* transcribed mRNA	Zebrafish embryo	Microinjection of mRNA
	Hwang, Jan. 2013, Nat. Biotech. (CRISPR-Cas9) (Ex. 4233)		• Cas9: *in vitro* transcribed mRNA • sgRNA: *in vitro* transcribed sgRNA	Zebrafish embryo	Microinjection of RNAs
Fuqiang Chen (Sigma)	Chen, 2011, Nat. Methods (ZFNs) (Ex. 5022)	Less than 6 months until filing of Dec. 6 application	• ZFN: *in vitro* transcribed mRNA	K562 cells	Nucleofection of mRNA or plasmid DNA
	Chen, Appl. No. 61734256 (CRISPR-Cas9) (Ex. 5020)		• Cas9: *in vitro* transcribed mRNA • sgRNA: U6 promoter plasmid or *in vitro* transcribed RNA	K562 cells	Nucleofection of RNAs or plasmid DNA

Appx88237 (highlighting added).

C. CVC Reduces Its Invention to Practice

Within months, CVC likewise reduced to practice using the techniques envisioned at the outset.

1. *Expression Vectors in Human Cells*

By October 2012, CVC reduced its invention to practice in human cells using expression vectors. Appx67700(¶181). Because Doudna's laboratory was ill-equipped for human-cell experiments, CVC borrowed graduate student Aaron Cheng (not a POSA) from a neighboring lab. Appx59222; Appx67346(¶10).

Cheng began experiments in July 2012, Appx67467(¶24), and quickly obtained promising results. On August 9, Cheng detected what he, Doudna, and Jinek believed to be "very exciting" evidence of cleavage. Appx67385-67387(¶¶98-101); Appx67302(¶179). Cheng immediately proceeded to experiments that attempted homology-directed repair ("HDR")—cleaving DNA and inserting a donor gene. Appx67387(¶101). Later that month, Cheng emailed Doudna and Jinek reporting "unfortunate results"—no evidence of HDR. Appx68467. Doudna suggested trying again "with improved Cas9 expression." Appx68467.

In August and September, Cheng continued focusing on HDR. Appx67488-67493(¶¶71, 76-87). In parallel, he attempted cleavage using newly arrived codon-optimized Cas9 vectors. Appx67489(¶75); Appx67493-67499(¶¶88-102); p. 13, *supra*. In mid-September, Cheng reported "no cleavage." Appx68081. Doudna counseled him to "tak[e] a step back" and make sure the August results were replicable before modifying other parameters. Appx68081. Because there were "so many variables in these experiments," Doudna instructed the graduate student to

"move forward in a stepwise fashion as much as possible" to correlate variables with results. Appx68081.

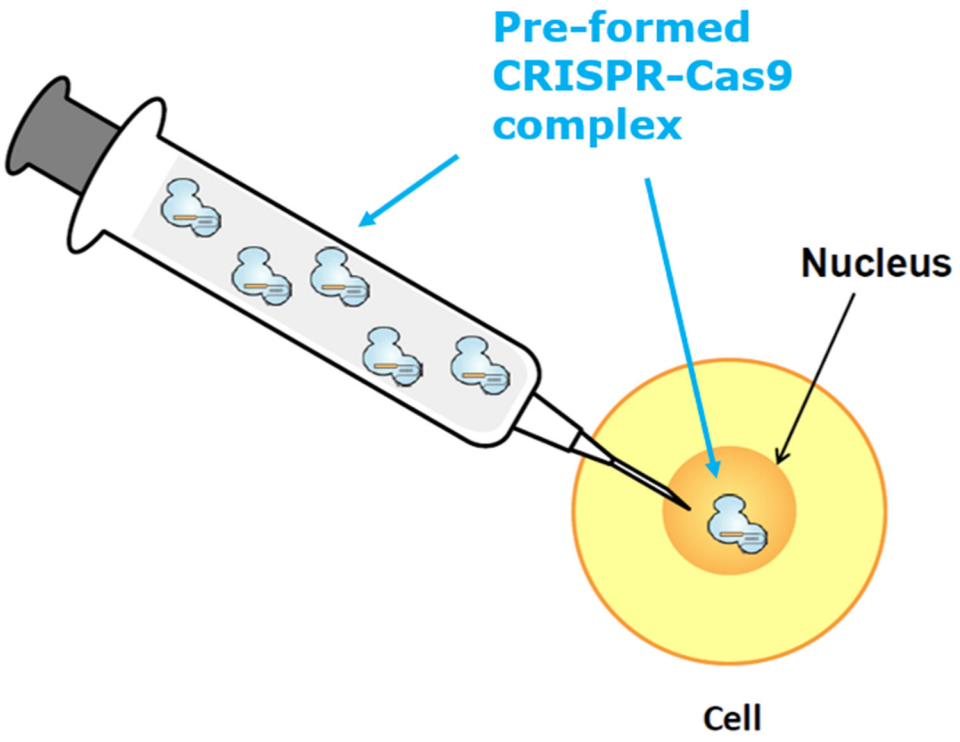
By late September, Doudna and Jinek transitioned Cheng's work to first-year graduate student Alexandra East-Seletsky (also not a POSA). Appx67315(¶¶216-217); Appx67568(¶4). East-Seletsky initially worked with Cheng to replicate his early experiments. Appx67520(¶¶17-18). When initial attempts failed, Doudna described the results as "disappointing." Appx67318(¶225); Appx67067. Although Doudna and Jinek posited the possibility of tweaking their sgRNA design, Appx66847, they did not. They instructed East-Seletsky to work to replicate the team's earlier apparent success. Appx67396-67397(¶¶123-124).

On October 29—just weeks after joining Doudna's lab and only four months after CVC's first human-cell experiments—East-Seletsky detected cleavage using the same basic vectors Jinek designed by June: an sgRNA vector with a U6 promoter, and a codon-optimized Cas9 vector with a CMV promoter and an NLS. Appx67397-67398(¶¶126-127); Appx67701-67702(¶¶182-185). East-Seletsky replicated the result several times. Appx67399-67400(¶¶128-130); Appx67330(¶251). CVC succeeded not after changing its design or methods, but after changing its graduate student.

Doudna and Jinek published those results in a January 2013 article and disclosed them in CVC's third provisional patent application, "P3." Appx67406 (¶143); Appx18723; Appx67708-67709 (¶199).

2. *Microinjection in Zebrafish Embryos*

Raible's parallel efforts drew on both CVC's successful *in vitro* experiments and Raible's prior work with ZFNs and TALENs in zebrafish. Appx67445 (¶58); Appx67106 (¶7); Appx67230-67232 (¶¶16-17). Raible microinjected a pre-formed CRISPR-Cas9 complex—like the one CVC used for its successful *in vitro* experiments—directly into zebrafish cell nuclei, as he had done with prior-art gene-editing systems. Appx66680.



Appx80268 (annotated).

Performing experiments in July and August 2012, Appx67210-67212 (¶¶117-123); Appx67214-67215 (¶127), Raible reported on August 9 that he had produced a mutant fish—one of roughly 30 fish. Appx67122 (¶55). Given the system's "stunning efficiency" *in vitro*, however, he had hoped for results "suggesting that the efficiency of CRISPR-Cas9 *in vivo* could compete with" existing gene-editing technologies. Appx66680; Appx67128 (¶74). "[O]ther labs with more resources," he said, would likely generate higher efficiency first, making a "high-impact" publication unlikely. Appx67128 (¶74). The PTAB took Raible's decision not to publish as "indicat[ing] that he did not recognize any success." Appx135-136.

III. PROCEEDINGS BELOW

A. The Earlier '048 Interference

In 2015, CVC suggested an interference between its Patent Application No. 13/842,859, which claimed an sgRNA CRISPR-Cas9 complex without reference to cell-type or environment, and Broad patents claiming a CRISPR-Cas9 system in eukaryotic cells. *See* Appx5093; Appx5522-5523.

The PTAB declared Interference No. 106,048, but later terminated it for lack of interference-in-fact. Appx5561. Interference-in-fact turned on whether CVC's generic-environment ***claims*** in the '859 application, if deemed prior art, would render Broad's eukaryote-specific ***claims*** obvious. *See* Appx5521. The PTAB ruled that disclosure of a "CRISPR-Cas9 system in a generic environment" would not have

led skilled artisans to reasonably expect success in eukaryotic cells. Appx5524. The PTAB did not consider CVC's ***applications*** as prior art—only the '859's ***generic-environment claims***; it never considered P1's teachings on how to cleave DNA in eukaryotic cells or its eukaryote-specific claims. Appx5559.

This Court affirmed. *Regents of Univ. of Cal. v. Broad Inst., Inc.*, 903 F.3d 1286, 1291 (Fed. Cir. 2018) ("*CVC I*"). The Court agreed that the "prior art contained a number of techniques that had been used for adapting prokaryotic systems for use in eukaryotic cells," and that "obstacles adopting other prokaryotic systems had been overcome." *Id.* at 1294. "[S]ix research groups," moreover, had "independently applied CRISPR-Cas9 in eukaryotic cells within months of [CVC's] disclosures." *Id.* at 1295. That near-simultaneous reduction to practice was "evidence of the level of skill in the art" and "objective evidence that persons of ordinary skill in the art understood the problem and a solution to that problem." *Id.* But the Court concluded that, "[g]iven the mixture of evidence in the record," substantial evidence supported the PTAB's ruling that eukaryotic-cell claims were nonobvious over generic-environment claims. *Id.* at 1292.

B. The Current '115 Interference

The current interference concerns CVC's and Broad's competing claims to the CRISPR-Cas9 DNA-cleavage complex in eukaryotic cells. Count 1 recites a "eukaryotic cell" containing a single-guide CRISPR-Cas9 complex—comprising

"covalently linked" crRNA and tracrRNA, and "Cas9 protein"—that is "capable of cleaving or editing" a "target DNA molecule." Appx1429-1430.

1. *Written Description*

The PTAB addressed whether CVC should be accorded benefit of its P1 application. To be accorded benefit, an application must "describe[ ] and enable[ ]" "one embodiment within the count." Appx67. The PTAB found the 168-page P1 lacked adequate written description. Appx82. It agreed P1 describes the single-guide CRISPR-Cas9 DNA-cleavage complex. Appx80; Appx94. It agreed P1's experimental data proved the complex was "capable of cleaving . . . a target DNA molecule *in vitro*." Appx80. And it agreed P1 repeatedly recited using the complex to cleave DNA in eukaryotic cells. Appx81.

The PTAB asserted, however, that artisans might doubt the CRISPR-Cas9 system would work in eukaryotic cells. Appx90-91. Noting that P1 did not report *in vivo* results, the PTAB cited theoretical hurdles to introducing the CRISPR-Cas9 complex into eukaryotic cells using expression vectors—RNA degradation, potential need for nuclear localization signals and codon optimization, and chromatin access. Appx86-87; Appx95-103. It rejected CVC's argument that patent applications need not address "all theoretical" adaptations that prove "***unnecessary*** for practicing the invention" or are known in the art. Appx89. The PTAB never identified which (if any) of those theoretical hurdles would prevent skilled artisans from implemen-

ting the count, or which (if any) corresponding adaptations were unknown in the prior art. Nor did it identify anything inventive Broad contributed to overcome putative hurdles. *See* pp. 44-47, *infra.*

The PTAB concluded that, absent successful *in vivo* results, disclosure of "specific instructions or conditions necessary" to overcome theoretical hurdles, or an explicit statement that "no specific instructions or conditions were necessary," skilled artisans would not believe CVC "possess[ed]" the invention. Appx90-91; Appx103. It therefore held that CVC's disclosures lacked sufficient written description until P3 disclosed CVC's successful "eukaryotic experiments." Appx106.

2. *Conception and Reduction to Practice*

After discovery, the PTAB considered conception and reduction to practice. The party that first conceives an invention is entitled to priority—even if others reduce to practice first—so long as it diligently pursued its own reduction to practice. *Cooper v. Goldfarb*, 154 F.3d 1321, 1327 (Fed. Cir. 1998). CVC claimed conception between March and June 2012. Appx146. Broad argued that Zhang conceived on June 26, 2012, Appx178—the day Zhang received CVC's single-guide CRISPR-Cas9 system.

CVC's Conception and Reduction to Practice. Conception occurs when the inventor has a "definite and permanent idea of the complete and operative invention" that is "so clearly defined . . . that only ordinary skill would be necessary to reduce

the invention to practice." *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994). The PTAB thus observed that inventors "need not know that the invention will work for conception to be complete"; "reasonable expectation of success" is irrelevant. Appx138; Appx159.

The PTAB nonetheless held CVC could not have conception absent a "definite and permanent idea" of "a system they ***knew***" would cleave DNA in eukaryotic cells. Appx162 (emphasis added). The PTAB did not dispute that CVC had disclosed the CRISPR-Cas9 complex's structure and announced it would cleave DNA in eukaryotic cells well ***before*** Zhang's claimed conception date. The PTAB held, however, that CVC lacked conception because, in reducing the invention to practice, it "encountered multiple experimental failures before [it] recognized any success." Appx159. The PTAB invoked Jinek's and Doudna's emails about Cheng's human-cell experiments as evidence CVC did "'not yet'" have "'a definite and permanent'" idea "'of the complete invention.'" Appx150-163. The PTAB "acknowledge[d]" evidence that "only routine materials and techniques" were needed to reduce the invention to practice, but held that CVC's supposed difficulties precluded conception. Appx150-163.

The PTAB did not mention that CVC never changed its invention in any material way. It did not address that Cheng's successor, East-Seletsky, reduced the invention to practice just weeks after the purported "failures," using the ***same*** vector

design and methods CVC originally identified. The PTAB dismissed as irrelevant evidence that, once CVC disclosed its invention to the world, myriad ***other*** skilled artisans—including Zhang—swiftly reported reduction to practice using prior-art methods. Appx161; Appx180.

Regarding microinjection, the PTAB did not identify any difficulties requiring more than routine skill to solve. But it was "not persuaded that the CVC inventors ***understood*** that reducing the invention to practice" "using this design would have required only routine skill." Appx154-155 (emphasis added). It faulted the CVC inventors for not "provid[ing] Dr. Raible with specific instructions that would have produced positive results." Appx157.

The PTAB never found whether Raible's experiments in zebrafish succeeded. Appx133. It ruled that, even assuming Raible obtained "positive results" on August 9, those would not count as actual reductions to practice because CVC did not "recognize[ ] and appreciate[ ] the results." Appx131-135.

Broad's Reduction to Practice. The PTAB did not award Zhang a conception date or decide when Zhang supposedly conceived the invention. It instead ruled that Zhang reduced the invention to practice no later than October 5, 2012, when he submitted the Cong manuscript to *Science*. Appx176-177. Having concluded that CVC failed to establish conception before October 5, the PTAB awarded priority to Broad. Appx184.

Originality. The PTAB rejected CVC's originality challenge. Appx177-184. For the first time in almost a decade of patent prosecution and litigation, Broad disclosed—halfway into this interference—that Zhang received confidential information from CVC's 2012 manuscript through a peer reviewer before publication. Specifically, Zhang's collaborator sent Zhang an image of CVC's chimera A, clipped from CVC's confidential manuscript before publication, and Zhang used chimera A in his alleged reduction to practice. *See* pp. 15-17, *supra*.

The PTAB identified no limitation of the count that Zhang contributed. It identified no reagent, technique, or "technical feature[]" Zhang contributed beyond what CVC had disclosed. Appx182. The PTAB instead speculated that "CVC's failures before Broad's success by 5 October 2012 indicate there must have been differences." Appx181. Despite identifying nothing Zhang contributed, the PTAB rejected CVC's originality challenge because CVC purportedly lacked prior conception. Appx183-184.

SUMMARY OF ARGUMENT

I. Conception occurs—and an invention merits protection—once the inventor's idea is complete enough for a skilled artisan to put the invention into working form. The PTAB erred in departing from that objective standard. It disregarded unrebutted objective evidence that CVC's invention was ready to be handed off to skilled mechanics by June 2012. Indeed, at least five labs reported

reducing the invention to practice using standard techniques just months after Jinek 2012's disclosure. The PTAB, however, looked solely to CVC's own purported "uncertainty" while reducing to practice. But the PTAB could not explain why CVC's purported failures preclude conception when CVC succeeded within months using the same design it initially identified.

The PTAB also erroneously required expectation of success. While nominally disclaiming any such requirement, the PTAB nonetheless required more—that CVC ***know*** its invention would work. That defies precedent.

II. The PTAB erroneously rejected CVC's originality challenge. Patent law rewards ***inventors***, not artisans who test another's invention to find it works. The PTAB identified nothing Zhang added that CVC had not already conceived, much less anything in the count. For good reason: Zhang obtained the blueprint for CVC's invention—including CVC's chimera A sequence and the use of the invention in eukaryotes—from CVC's unpublished manuscript. Zhang cannot be the inventor when he added nothing but instead (improperly) obtained every limitation of the count from CVC.

III. The PTAB fell short of the standards imposed by the Administrative Procedure Act. It failed to connect its conclusions to its findings, and repeatedly ignored relevant evidence. For CVC's microinjection embodiment, for example, the PTAB asserted it had previously made findings ***it never made***. Especially for an

invention of such magnitude, the PTAB's rationale fell well short of reasoned decisionmaking.

IV. The PTAB applied the wrong legal standard for written description. CVC's P1 did what §112 requires: It provided "a written description of the invention" that allows skilled artisans to identify the invention. P1 describes the essential components of the CRISPR-Cas9 DNA cleavage system; shows it can cleave DNA *in vitro*; directs artisans to well-known techniques for using it in eukaryotes; and repeatedly claims it in eukaryotic cells.

The PTAB rejected that as insufficient because, in its view, P1 would not ***convince*** artisans the invention would work in eukaryotes. The PTAB demanded that P1 disclose experimental data, rebut hypothetical obstacles with specific instructions, or recite that no adaptations are required. Written description requires none of that. The inventor's obligation is to tell artisans what she invented, not convince skeptics the invention will work.

ARGUMENT

I. THE PTAB'S CONCEPTION DECISION CANNOT BE SUSTAINED

CVC conceived of every limitation in the count before Broad's first ***alleged*** conception date of June 26, 2012. By then, the CVC inventors had developed the structure recited in Count 1 with its critical elements: crRNA and tracrRNA linked to form sgRNA, and Cas9 protein. Appx1429-1430; pp. 5-6, *supra*. They had de-

scribed how the CRISPR-Cas9 complex could be placed in a "eukaryotic cell," Appx1430, using well-known techniques like expression vectors and microinjection, regularly used with TALENs and ZFNs, *see* pp. 8-10, *supra*. They had even designed the vectors for expressing sgRNA and Cas9 used in their later actual reductions to practice. *See* p. 13, *supra*. And they had explained that the complex was "capable of" finding and cleaving "target DNA" in any cell, including eukaryotic cells, using nucleic acid hybridization to guide Cas9 to target DNA. Appx1430; pp. 9-10, *supra*.

The PTAB's decision denying CVC conception rests on twin legal errors. For over a century, the law has recognized that "conception" occurs once "the inventor is ready to instruct the mechanic in relation to putting [the invention] in working form." *Cameron & Everett v. Brick*, 1871 C.D. 89, 90 (Comm'r Pat.). The idea is sufficiently "definite and permanent" if the inventors had "both the idea of the invention's structure and possession of an operative method of making it." *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991).

Disregarding that objective standard, the PTAB did not ask whether CVC's invention was sufficiently "definite and permanent" that a skilled artisan could "construct" it. *Sewall v. Walters*, 21 F.3d 411, 415 (Fed. Cir. 1994). The PTAB deemed it irrelevant that, promptly after CVC's announcement of its invention, at least five labs reported successfully using CVC's CRISPR-Cas9 complex to cleave

DNA in eukaryotic cells—powerful and uncontested evidence that skilled artisans "could construct" and use the invention without undue experimentation. *Id.* Instead, the PTAB looked only to the CVC inventors' own purported failures (in fact, a graduate student's) while ignoring that CVC's experimental design never materially changed. That defies settled law. Whether ***the inventor*** succeeds promptly is irrelevant when the evidence shows the invention is sufficiently firm, definite, and developed that ***skilled mechanics*** can do so—and the evidence shows they did.

The PTAB also legally erred by insisting that inventors must ***know*** their invention would work for conception to be complete. Conception does not require even an "expectation" the invention will work, much less ***knowledge*** it will. *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994); *Univ. of Pittsburgh of Commonwealth Sys. of Higher Educ. v. Hedrick*, 573 F.3d 1290, 1299 (Fed. Cir. 2009).

Standard of Review. Conception is a legal question reviewed *de novo*, while underlying factual findings require substantial evidence. *Sewall*, 21 F.3d at 415.

A. Conception Is Complete When It Is Sufficiently Definite and Permanent that Skilled Artisans Can Construct the Invention

For more than a century, this Court and its predecessors have applied the conception standard articulated in *Mergenthaler v. Scudder*, 11 App. D.C. 264 (1897). Conception is the "formation, in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is thereafter to be ap-

plied in practice." *Id.* at 276 (emphasis omitted). The "'true date'" of conception is "'the point where the work of the inventor ceases and the work of the mechanic begins.'" *Id.* at 277. Conception thus is complete when "[a]ll that remains to be accomplished . . . belongs to the department of ***construction***, not invention," *id.* at 276 (emphasis added)—that is, "***when one of ordinary skill in the art could construct*** the apparatus without unduly extensive research or experimentation," *Sewall*, 21 F.3d at 415 (emphasis added); *see Burroughs*, 40 F.3d at 1228 (idea "definite and permanent enough that one skilled in the art could understand" it); *Mergenthaler*, 11 App. D.C. at 279 (once "others skilled in the art" could "reduce the conception to practice").

Conception can be complete even if "much patience and mechanical skill, and perhaps a long series of experiments," are required to reduce the invention to practice. *Cameron*, 1871 C.D. at 90. The question is whether "means to carry out" the invention "could be worked out by one skilled in the art without the exercise of invention." *Barba v. Brizzolara*, 104 F.2d 198, 202 (C.C.P.A. 1939); *see Acromed Corp. v. Sofamor Danek Group, Inc.*, 253 F.3d 1371, 1380 (Fed. Cir. 2001).

For example, in *Dolbear v. American Bell Telephone Co.*, 126 U.S. 1 (1888), the Supreme Court held that Alexander Graham Bell was entitled to patent the telephone, even though—despite his inventive genius—Bell himself could not ***construct*** a telephone that "transmitted . . . spoken words." *Id.* at 535. What

mattered was that those following Bell's disclosure succeeded, proving that a "good mechanic, of proper skill in matters of the kind," could use Bell's ideas to make a functioning telephone. *Id.* at 535-36. Bell's own struggle was irrelevant: "[I]t is enough" if an inventor "describes his method with sufficient clearness and precision to enable those skilled in the matter to understand what the process is, and if he points out some practicable way of putting it into operation." *Id.* at 536. That makes sense. Patent law rewards "innovation"—the person who conceived the invention—not "'the work of a mechanic skilled in the art'" who puts it into operation. *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 330 (1945).

History is replete with similar examples. The Wright brothers applied for a patent on their "flying machine" nearly a year before their first successful flight and—despite an intervening series of discouraging tests—the patent was granted. *See* U.S. Patent No. 821,393; https://www.nps.gov/articles/roadtofirstflight.htm. The inventors of treating AIDS using AZT conceived their invention before showing the drug actually worked. *Burroughs*, 40 F.3d at 1227-30.

Those cases illustrate a fundamental point: An "invention" under the Patent Act—which "refers to the inventor's conception rather than to a physical embodiment of that idea," *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 60 (1998)—is complete when ready for ***skilled artisans*** to reduce it to practice, not when the ***inventor herself*** successfully does so.

B. The PTAB Departed from the Framework Precedent Demands

The PTAB reached the wrong result by asking the wrong question. Rather than ask whether CVC's invention was ready for hand-off to skilled mechanics, it asked whether the CVC inventors ***themselves*** immediately succeeded in reducing their invention to practice without experimentation or "'uncertainty.'" Appx159. It thus dismissed as irrelevant overwhelming, unrebutted evidence that CVC's invention was ready for hand-off to skilled artisans by June 2012—the prompt reporting of success by five other labs. It focused solely on CVC's purported struggles in reducing its invention to practice, and only for one method—expression vectors. That was legal error.

1. Declining to ask whether CVC's invention was ready to be handed off to skilled artisans, the PTAB refused to examine overwhelming evidence on that question. It is undisputed that, within six months of CVC's June disclosure, at least ***five*** other skilled artisans—Church, Kim, Chen, Joung, and Zhang—reported success, all using routine techniques and readily available reagents culled from their previously published ZFNs and TALENs work. *See* pp. 14-18, *supra*. It is hard to imagine more powerful, objective, real-world evidence that conception was "complete"—that "one of ordinary skill in the art could construct the apparatus without unduly extensive research or experimentation"—than the fact that so many actually did, so quickly after learning of CVC's invention. *Sewall*, 21 F.3d at 415.

As this Court observed, such rapid and near-simultaneous reductions to practice in the wake of CVC's announcement are "objective evidence that persons of ordinary skill in the art understood the problem and a solution to that problem." *CVC I*, 903 F.3d at 1295.[6] Yet, to the PTAB, that widespread success was irrelevant.

The PTAB also nowhere mentioned evidence that, once the CVC inventors announced their invention, skilled artisans understood implementation would be "straightforward," "just a matter of trying." Appx80003 (31:8-19); Appx80972 (¶21). The PTAB ignored that attendees at the CRISPR conference, where the invention was announced, immediately recognized it as a "game changer for genome editing in eukaryotes." Appx80958 (¶16). It did not address that Marraffini, a peer-reviewer of CVC's groundbreaking *Science* article, was so excited that he told Zhang CVC's invention "would be an important tool for genome editing in ***eukaryotes specifically***." Appx80012 (68:13-21) (emphasis added). Nor did it consider the significance of Zhang's alleged conception on ***June 26, 2012***, the very day he learned of CVC's invention. *See* Appx178.

[6] In *CVC I*, this Court upheld the PTAB's finding that Broad's eukaryotic ***claims*** were nonobvious over CVC's ***generic-environment claims***. 903 F.3d at 1290-91. But that obviousness determination turned on expectation of success, which is irrelevant here. *Id.* at 1296; *see Burroughs*, 40 F.3d at 1228-29; pp. 41-44, *infra*. *CVC I* also considered only CVC's generic ***claims*** in light of prior art. *CVC I*, 903 F.3d at 1291-92. It did ***not*** address CVC's patent applications, its other disclosures, or a wealth of evidence in ***this*** record, nor account for CVC's plans for reducing the invention to practice by late June 2012. *CVC I*, 903 F.3d at 1291-92; Appx82.

Indeed, Zhang reportedly reduced to practice within weeks of CVC's disclosures using the same routine techniques CVC planned ***before*** June 26. Like CVC, Zhang used the common U6 promoter to drive RNA expression. Appx75096(¶¶180-181); Appx80797-80801(¶¶68-73). Like CVC, Zhang codon-optimized his Cas9 sequence using commercially available techniques. Appx79963(85:9-13); Appx80806(¶84). And like CVC, Zhang added an NLS to his Cas9 protein. Appx79961(78:10-12); Appx80808(¶89). The PTAB identified ***nothing*** Zhang contributed that CVC did not already have. Appx181; *see* pp. 44-47, *infra.* That the PTAB ignored all that objective evidence—every shred of evidence proving that artisans understood the invention and how to implement it—confirms its failure to apply the proper standard.

2. Rather than ask whether CVC's invention was objectively ready for hand-off to skilled artisans, the PTAB focused on whether the CVC inventors expressed subjective "uncertainty" on ***their way*** to reducing to practice. Appx159; *see* Appx154; Appx158-160. That is doubly wrong.

First, even setting aside other scientists' prompt successes, the "existence of research or experimentation"—even "a long series of experiments"—does not itself prove conception incomplete. *Sewall*, 21 F.3d at 415 n.3; *Cameron*, 1871 C.D. at 90. Instead, the "nature" of the experiments—whether they required "more than routine skill"—is determinative. *Rey-Bellet v. Engelhardt*, 493 F.2d 1380, 1387

(C.C.P.A. 1974). The PTAB never found that, following CVC's disclosures, "more than routine skill" was required to implement either of CVC's methods. CVC's vector-expression experiments, performed by non-POSA graduate students, were routine: The CVC inventors never strayed from their basic designs, persisting with their original vectors until they succeeded. *See* pp. 18-22, *supra*. Similarly, for microinjection, there is no evidence CVC strayed from their original design, nor any finding the zebrafish experiments failed. Appx133.

Invoking isolated emails, the PTAB declared that CVC encountered "months of failed experiments" in human cells. Appx158. But it did not explain why "months" was too long when most of CVC's experiments were performed by graduate students, not POSAs. Appx84928 (¶20); Appx67632 (¶26); Appx67463 (¶3); Appx67517 (¶¶3-4); *see* pp. 19-20, *supra*.

Second, the question is not how the inventors or their collaborators fared, or what they said along the way. It is whether the inventors' idea was sufficiently firm and definite that reduction to practice could be performed by "one skilled in the art without the exercise of invention." *Barba*, 104 F.2d at 202; *Sewall*, 21 F.3d at 415-16. Bell could not construct a working telephone, but others could; Bell was still the inventor. *Dolbear*, 126 U.S. at 535. The researchers in *Hedrick* were not "certain" they had made adipose-derived stem cells. 573 F.3d at 1298. But this Court found conception because their lab notebooks "sufficiently described to those skilled in the

art" how to proceed. *Id.* at 1299. The inventor need not know "the location of every nut, screw, and bolt" so long as a skilled artisan could supply those details without further "invention." *In re Tansel*, 253 F.2d 241, 243-44 (C.C.P.A. 1958) (mechanic could identify appropriate flash circuit with basic research); *Barba*, 104 F.2d at 202 (skilled mechanic could work out means to mount air conditioner); *Field v. Knowles*, 183 F.2d 593, 603 (C.C.P.A. 1950) (dismissing patentee's inability to make inventive feature of his refrigeration unit work); *Sewall*, 21 F.3d at 416 (circuit design was "simply the exercise of the normal skill expected of an ordinary chip designer"); *Acromed*, 253 F.3d at 1380 (surgical plate design could be accomplished with ordinary skill). The PTAB's contrary approach—which ignores the skilled artisan's perspective in favor of counting failures—wrongly rewards ordinary skill in reducing to practice over "substantial innovation." *Sinclair*, 325 U.S. at 330.

3. Nothing supports the PTAB's singular focus on inventor success. The PTAB invoked *Alpert v. Slatin*, 305 F.2d 891 (C.C.P.A. 1962), for the proposition that, "'where results at each step do not follow as anticipated,' there has not been a conception." Appx138. But the problem in *Alpert* was not that ***the inventor*** encountered failures or displayed "uncertainty" while other skilled artisans succeeded. Appx138-139. It was that the ***only*** available evidence—the inventor's own unsuccessful experiments—demonstrated that the idea was objectively "incomplete." *Burroughs*, 40 F.3d at 1229 (discussing *Alpert*). As far as the evidence

showed, Alpert ***never*** succeeded. *Alpert*, 305 F.2d at 894. The PTAB cited not one case holding that an inventor's efforts alone preclude conception in the face of clear evidence that, shortly after the invention's announcement, so many skilled artisans so quickly reported successful implementation. Overwhelming evidence showed skilled artisans could reduce the invention to practice—and in fact reported doing so—within months.

The PTAB dismissed those other scientists' successes on the theory that conception cannot be "*nunc pro tunc*." Appx161. But this is not a case where CVC "possessed a claimed device . . . but failed to recognize" it. *Hitzeman v. Rutter*, 243 F.3d 1345, 1358 (Fed. Cir. 2001). CVC does not seek to substitute "what others might have understood later" for its own idea. Appx161. CVC points to other scientists' reported success, shortly after learning of CVC's invention, using similar published prior-art techniques, as powerful objective evidence that CVC's idea was "definite and permanent enough" that skilled artisans could "construct" the working invention "without unduly extensive research or experimentation." *Burroughs*, 40 F.3d at 1228; *Sewall*, 21 F.3d at 415. The PTAB's dismissal of that evidence as "*nunc pro tunc*" conception reflects its misapprehension of the correct legal standard.

For similar reasons, the PTAB's statement that Zhang's "activities and ideas do not inure to CVC," Appx180, is a non sequitur. CVC's point is not that Zhang's

activities "inure" to CVC to establish CVC's priority. It is that Zhang's reported success using CVC's invention, like other scientists', proves that the invention was ready for hand-off to skilled artisans, as only ordinary skill was needed to implement ***CVC's*** conception.

C. The PTAB Erroneously Employed a Subjective Expectation-of-Success Standard

The PTAB legally erred in yet another way: It demanded the inventors ***know*** their invention would work. It held that the CVC inventors lacked conception of the expression-vector embodiment until they had "a system they ***knew***" would cleave DNA in a eukaryotic cell. Appx161-162 (emphasis added); Appx183. As to micro-injection, the PTAB held it was "not persuaded the CVC inventors ***understood*** that reducing the invention to practice in zebrafish would have required only routine skill." Appx155 (emphasis added).

That defies binding precedent. In *City of Elizabeth v. Nicholson Pavement*, 97 U.S. 126 (1877), the Supreme Court held that an inventor had "made his invention"—had conceived—even though he was then "not sure" his invention worked. *Id.* at 130, 136. This Court has repeatedly held that expectation the invention will work is "irrelevant" to conception, even in an "experimental" field. *Burroughs*, 40 F.3d at 1228-29; *see Applegate v. Scherer*, 332 F.2d 571, 573 (C.C.P.A. 1964); *Dana-Farber Cancer Inst., Inc. v. Ono Pharm. Co.*, 964 F.3d 1365, 1372 (Fed. Cir. 2020). "'The determinative inquiry is not whether [the inventor's]

disclosure was phrased certainly or tentatively, but whether the idea expressed therein was sufficiently developed to support conception of the subject matter'"—that is, the idea was ready for "'those skilled in the art to make the invention.'" *Hedrick*, 573 F.3d at 1299. The PTAB recognized as much, proclaiming it did not "base [its] decision on a lack of reasonable expectation of success by the CVC inventors." Appx159.

But the PTAB contradicted that standard as quickly as it articulated it. Citing the count's requirement that the CRISPR-Cas9 system be "'capable of cleaving'" target DNA, the PTAB required not just an ***expectation*** of success, but that the inventors "***kn[o]w***" the invention would work. Appx161-162 (emphasis added).[7] But reciting a capability does not change the rule that an inventor's "belief" the invention will work is "irrelevant to conception." *Burroughs*, 40 F.3d at 1228. The claims in *Burroughs* recited specific results—"***treating*** a human having an HTLV III virus infection" and administering an "***effective*** HTLV III treatment amount." *Id.* at 1225 n.3 (emphasis added). This Court held the inventors did not need to know the compound would work to have conception. *Id.* at 1228-29. Similarly, in *Applegate*, the count recited using a chemical for "controlling sea lamprey[]" reproduction. 332 F.2d at 571. The Court held the inventor did not need to know

[7] That contradiction dooms the PTAB's decision: Such "internal[] inconsisten[cies]" defy APA requirements. *Nat. Res. Def. Council v. U.S. Nuclear Regul. Comm'n*, 879 F.3d 1202, 1214 (D.C. Cir. 2018).

his invention would actually control lamprey reproduction to establish conception. *Id.* at 573. And in *Hedrick*, the claims recited a stem cell "that can differentiate into two or more" cell types. 573 F.3d at 1295. The inventors did not need to know their methods produced such cells to have conception. *Id.* at 1299. The PTAB's requirement that CVC "kn[o]w" the invention would work, Appx161-162; Appx183, defies those precedents.[8]

Nor does *Hitzeman* make "uncertainty in the mind of the inventor" a barrier to conception. *See* Appx159; Appx162. *Hitzeman* ***agreed*** that expectation of success is irrelevant. 243 F.3d at 1357-58. *Hitzeman* at most required that, when an inventor claims a specific physical composition, she must expect to be able to "produce" that composition—she must have in mind a way of making it. *Id.* at 1358. Here, the CVC inventors had already "produced" the CRISPR-Cas9 complex claimed in the count by Broad's earliest conception date; they had constructed it and tested it *in vitro* to show its "stunning efficiency." Appx66680. They disclosed ***two*** ways to practice the invention in eukaryotes—vectors and microinjection—and had

[8] The PTAB's holding CVC could not have conception until it had "a system [it] ***knew***" would work smacks of the "so-called doctrine of simultaneous conception and reduction to practice." *Burroughs*, 40 F.3d at 1228. But that "rare[ly]" applied doctrine, *Mycogen Plant Sci. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001), ***cannot*** be invoked where (as here) originality is at issue, *MacMillan v. Moffett*, 432 F.2d 1237, 1240 (C.C.P.A. 1970). Regardless, the PTAB's failure to rely on it—and explain why it would apply—precludes its assertion on appeal. *In re Lee*, 277 F.3d 1338, 1344-45 (Fed. Cir. 2002).

designed specific tools to use. *See* pp. 13-14, *supra*. The PTAB legally erred in demanding CVC ***know*** that, once introduced into the cell (using routine techniques), the complex would work to cleave DNA.

II. THE PTAB'S DECISION FLOUTS THE ORIGINALITY REQUIREMENT

This case fundamentally concerns ***who*** invented Count 1. The PTAB declared Zhang the inventor based on his putative October 2012 reduction to practice, rejecting CVC's argument that Zhang was not an "original" inventor. Appx183-184. But the PTAB identified ***nothing*** that Zhang actually invented. Appx181-182. It found no "adaptation" or "technical element" that Zhang added but CVC or skilled artisans would have lacked. It identified ***nothing at all in the count***—the invention—Zhang did not get from CVC. Any test that awards inventorship to a party without identifying the inventive element he contributed cannot be right. Patent law rewards "innovation," not "'the work of a mechanic'" in reducing others' inventions to practice. *Sinclair*, 325 U.S. at 330.

Standard of Review. Originality is a factual question reviewed for substantial evidence. *Price v. Symsek*, 988 F.2d 1187, 1190 (Fed. Cir. 1993).

1. The PTAB's entire analysis of Broad's purported contribution reduces to a few sentences. The PTAB asserted that it "need not" determine what Broad added because "CVC's failures" "before Broad's success . . . indicate there ***must have been differences***." Appx181 (emphasis added). As discussed below (pp. 47-

50), that ipse dixit is unexplained and inexplicable. The PTAB ***agreed*** that CVC was first to identify the elements of the count: the structure of the sgRNA CRISPR-Cas9 complex, placed in a "eukaryotic cell," and "capable of cleaving" DNA in that cell. *See* Appx145; Appx1430.

Any "differences" between Zhang's work and CVC's were "outside the scope of the count" and thus "not relevant" to conception. *Sewall*, 21 F.3d at 416. Regardless, the PTAB never addressed whether any assumed "differences" reflected different ***inventive*** approaches, or simply mechanical skill or luck. *See* pp. 47-50, *infra* (addressing graduate-student efforts); *e.g.*, *Dolbear*, 126 U.S. at 535. The PTAB did not mention that Zhang reduced to practice using the ***same*** techniques CVC identified before Zhang's alleged June 26 conception. *See* pp. 14-17, *supra*. And it did not address that many ***others*** reported success using similar—but not identical—combinations of known techniques, proving there was nothing magical about Zhang's methods. *See* pp. 17-18, *supra*; *CVC I*, 903 F.3d at 1295. The PTAB's "must have been differences" assertion thus does not answer whether Zhang added anything ***inventive*** or was just a more efficient (or luckier) ***mechanic***.

2. The PTAB could not find anything Zhang added because Zhang got the invention from CVC. Halfway through this case—after a decade of patent prosecution and litigation—Broad finally admitted that Zhang got CVC's invention from a peer-reviewer two days ahead of Jinek 2012's publication. *See* Appx183. On June

26, Zhang received CVC's sgRNA sequence from Marraffini, Appx80005(37:17-38:7); he learned tracrRNA's previously unknown role in the final DNA cleavage complex, Appx80001-80003(24:17-25:3, 29:20-30:3); and he was told that CVC used processed RNA, obviating the need to replicate cumbersome pre-processing steps, Appx77492. Zhang was also told that CVC's invention would be "an important tool for genome editing in eukaryotes specifically." Appx80012(68:13-21). Indeed, Zhang purports to have conceived the ***very day*** he learned of CVC's discovery from Marraffini. Appx178.

The PTAB's decision flouts the requirement that patents be awarded to an "original inventor"—not a "borrower or a copyist." 1 W. Robinson, *The Law of Patents for Useful Inventions* §58 (1890); *see* U.S. Const. art. I, §8, cl. 8 (patents for "Inventors"). One who confirms another's idea using "ordinary skill" is not an "original" inventor. *Applegate*, 332 F.2d at 573-74.[9] In *Applegate*, Scherer's contractor did not become the inventor simply because he tested Scherer's idea and proved it worked. *Id.* at 573. The 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, not Zhang. Appx180-181. The result should not be different simply because Zhang, instead of being hired by CVC,

[9] That is true even if something less than a "prior, complete conception" was communicated to the copyist. *Hedgewick v. Akers*, 497 F.2d 905, 908 n.4 (C.C.P.A. 1974); *see Finch v. Dillenback*, 121 F.2d 459, 466 (C.C.P.A. 1941).

took chimera A from CVC's still-unpublished manuscript and proved the invention works. Patent rights to the invention of the century should not be awarded based on a footrace to implement it using routine techniques.

III. THE PTAB'S ANALYSIS FAILS THE APA'S REASONED-DECISIONMAKING REQUIREMENT

The PTAB's decisions require reversal for another, independent reason: Both its conception and written-description decisions repeatedly fail the Administrative Procedure Act's reasoned-decisionmaking requirement.

Standard of Review. Under the APA, agency decisions are reviewed to "ensure that they are not 'arbitrary, capricious,'" "'otherwise not in accordance with law,'" or "'unsupported by substantial evidence.'" *Pers. Web Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 992 (Fed. Cir. 2017).

A. The PTAB's "Must Be Differences" Theory Is Unreasoned and Unsupported

As explained above (pp. 44-47), the PTAB deemed Broad the inventor without identifying any inventive element Broad contributed that CVC was missing. It asserted that CVC lacked "technical features," but never identified what "technical features" were lacking (for vectors or microinjection). Appx181-182. "CVC's failures" using vectors "before Broad's success," the PTAB declared, "indicate there ***must have been differences***." Appx181 (emphasis added). That res-ipsa reasoning

commits twin cardinal sins of the APA—adopting a conclusion inconsistent with the record and failing to address obvious alternative explanations.

1. Agency decisions must be grounded in evidence. *Morall v. DEA*, 412 F.3d 165, 178 (D.C. Cir. 2005). Here, the PTAB did not identify any relevant difference between CVC's conception and Zhang's reduction to practice—because the record would not support any. Zhang used the same tools CVC had selected by June 2012 to reduce the invention to practice: expression vectors; standard promoters, including the U6 promoter; NLSs; and codon optimization. *See* pp. 14-17, *supra*. The PTAB, moreover, did not explain how any of those techniques could make a difference: Broad ***conceded*** that none required more than ordinary skill. Appx85770(30:8-21). Broad touted the "combination" as inventive, but never meaningfully disputed that CVC identified the ***same*** combination first. Appx85770(30:8-21).

The closest the PTAB came to identifying a difference was a parenthetical reference to Zhang's use of the U6 promoter, Appx181, which inherently results in an sgRNA strand that is four nucleotides longer than the sequence CVC disclosed in Jinek 2012, Appx80801-80803(¶¶74-76). But the vectors used in CVC's human-cell experiments—which CVC designed and built before June 2012—***also*** incorporated the U6 promoter, and ***also*** produced an sgRNA strand that was four nucleotides longer. Appx80801-80803(¶¶74-76); Appx67271(¶87). Invocation of the U6 pro-

moter as a relevant "difference" between CVC's conception and Broad's reduction to practice "makes no sense" when the record shows both CVC ***and*** Broad employed it. *Glob. Tel*Link v. FCC*, 866 F.3d 397, 413 (D.C. Cir. 2017).[10]

2. Courts cannot "uphold agency action if" the agency decision "fails to consider 'significant and viable and obvious alternatives.'" *Dist. Hosp. Partners, L.P. v. Burwell*, 786 F.3d 46, 59 (D.C. Cir. 2015). That precisely describes the PTAB's decision here. The PTAB's "must have been differences" rationale ignores myriad explanations for CVC's supposed "failures" (which in fact were rapidly followed by successes). CVC's experiments were conducted by graduate students, who did ***not*** meet the standard for being skilled in the art. *See* pp. 19-20, *supra*. The PTAB erroneously implied they did. Appx158-159.

Moreover, Zhang claimed success based on an experiment showing a 0.75% modification rate. *See* Appx171. With efficiency that low, many experiments may fail to demonstrate cleavage due to random chance. There are also human error, equipment quality, and measurement failures. Indeed, the line between CVC's supposed failures and its successes was not drawn by a change in techniques. It followed a change in graduate students. One moved on and, within a month of joining Doudna's lab, East-Seletsky—a first-year graduate student—achieved

[10] Nor did the PTAB ever identify anything in Zhang's prior work that explained what Zhang added—unsurprisingly, because Zhang's prior experiments were all failures using the wrong components.

success. The PTAB's "must have been differences" rationale simply fails to address those alternative explanations for CVC's purported experimental failures.

The PTAB also ignored that some supposed failures were attempts to achieve something beyond the count. Because CVC believed Cheng had achieved cleavage by early August, Cheng moved on to attempt HDR following cleavage. Appx67301-67302 (¶178). The PTAB's decision ignores that the different outcomes reflect that CVC sought to achieve results the count does not require. The PTAB's ipse dixit that CVC's failures show Broad must have had something CVC lacked is not the evaluation of all the evidence the APA demands. *Music Choice v. Copyright Royalty Bd.*, 970 F.3d 418, 429 (D.C. Cir. 2020).

B. The PTAB Ignored Rafts of Evidence Contrary to Its Positions

To meet the APA's requirements, the PTAB must address the evidence ***for*** and ***against*** the results it reached. *Princeton Vanguard, LLC v. Frito-Lay N. Am., Inc.*, 786 F.3d 960, 970 (Fed. Cir. 2015). Time and again the PTAB failed to consider the contrary evidence:

- The PTAB failed to consider evidence from CRISPR luminaries Barrangou, Sontheimer, and Marraffini that skilled artisans contemporaneously understood implementation of CVC's invention would be "straightforward," "just a matter of trying." Appx80972 (¶21); Appx80003 (31:8-19); Appx80959 (¶17). Even if CVC's subjective state of mind is relevant, so too is evidence that other skilled artisans contemporaneously understood the invention would work.
- The PTAB failed to consider evidence that five labs reported successful reductions to practice shortly after CVC announced its invention. *See* pp. 14-

18, *supra*. That failure is particularly troubling given ***this Court's*** recognition that those labs' near-simultaneous actual reductions to practice are "objective evidence that persons of ordinary skill in the art understood the problem and a solution to that problem." *CVC I*, 903 F.3d at 1295.

- The PTAB failed to consider evidence of the stability of CVC's conception: CVC reduced to practice using the ***same*** methods it initially proposed. *See* pp. 18-22, *supra*. That CVC never changed course shows stability and permanence, not lack of firm conception.
- The PTAB failed to consider evidence that CVC subjectively believed its invention would work in eukaryotic cells. The inventors were secure enough in their conception to publish their results and file repeated patent applications claiming the invention for use in eukaryotic cells, in May 2012, October 2012, and January 2013. *See* pp. 8-12, *supra*. The PTAB never addressed why CVC's purported doubts—reflected in emails among researchers—override CVC's confidence.

"Just as [the PTAB] may not short-cut its legal analysis," it "may not short-cut its consideration of the factual record before it." *Princeton*, 786 F.3d at 970. The PTAB did just that here.

Finally, the PTAB failed to consider evidence that CVC actually reduced its invention to practice using vectors in October 2012, only ***four months*** after it began experiments in July. *See* pp. 18-21, *supra*. The PTAB never explained why a four-month reduction to practice amounts to "'perplexing'" difficulties "'every step of the way.'" *See* Appx157. The Wright brothers took nearly a year after their patent application to make their famous flight with disappointment after disappointment in between; Bell struggled to make his telephone work until others succeeded. *See* pp. 33-34, *supra*. Nowhere did the PTAB explain why the inventors awarded the Nobel Prize for probably the most stunning advance of the century should be disqualified

because their graduate students initially stumbled but ultimately succeeded in just four months. That lack of reasoned explanation is arbitrary and unsustainable.

C. The PTAB's Analysis of CVC's Microinjection Embodiment Is Arbitrary and Unreasoned

The PTAB's treatment of CVC's microinjection embodiment fares worse still. In dealing with conception and written description, the PTAB simply refused to engage with evidence that there is "something different about microinjection" that "negates" the purported hurdles that (according to the PTAB) might prevent implementing the count with vectors. Appx57065(17:3-9). The PTAB's failure to respond meaningfully to arguments and evidence about microinjection "violates the APA." *Provisur Techs., Inc. v. Weber, Inc.*, — F.4th —, 2022 WL 4474941, at *4-5 (Fed. Cir. Sept. 27, 2022).

1. The PTAB's conception ruling barely addressed whether CVC ***conceived*** of implementing the count by ***microinjecting*** the pre-formed CRISPR-Cas9 complex into rapidly dividing cells. The PTAB nowhere disputed that CVC agreed to engage Raible to do just that before June 26. The PTAB instead asserted conception was absent because it was "not persuaded the CVC inventors understood that reducing the invention to practice in zebrafish . . . would have required only routine skill." Appx155. But CVC was not required to "underst[and]" that reduction to practice "required only routine skill"—it was enough that only routine skill in fact was required. *Burroughs*, 40 F.3d at 1228; *see* pp. 41-44, *supra*.

Regardless, the PTAB's assertion is just that—a bare assertion without "substantial evidence," or any evidence, behind it. While the PTAB listed putative obstacles to the successful use of ***vectors***, it did not address—much less dispute—that ***microinjecting*** a pre-formed complex into rapidly dividing cells like zebrafish embryos obviates most, if not all, of them. Concerns about whether the sgRNA and Cas9 components could meet, form a complex, and localize to the cell's nucleus do not apply when the complex is ***pre-formed*** outside the cell and injected into the nucleus. *See* Appx67677-67678 (¶¶132-135). Purported worries about chromatin access are addressed by injecting the complex into rapidly dividing cells with dynamic chromatin, like embryos. Appx67438 (¶32). The evidence shows the CVC inventors knew all that. Appx66308; *see* pp. 13-14, *supra*. The PTAB cannot invent doubts that are unsupported by the record. *Sorenson Commc'ns Inc. v. FCC*, 755 F.3d 702, 707 (D.C. Cir. 2014). To reject CVC's argument about microinjection, the PTAB needed (at the very least) to address those facts and explain why CVC's position was incorrect. *See Provisur*, 2022 WL 4474941, at *4-5. It did not.

The PTAB also restated its earlier conclusion that it was "not persuaded that the CVC inventors[] recognized and appreciated the result of Raible's zebrafish experiments." Appx154. Whether the CVC inventors appreciated the ***result*** of a potentially successful experiment proves nothing about conception, which does not require successful results or an expectation of success. *See* pp. 41-44, *supra*. The

PTAB also refused to resolve whether microinjection ***succeeded***. If it did—and the evidence showed it did, Appx67777-67793 (¶¶45-82)—that underscores that only ordinary skill was required, whether or not success was recognized, *Hedrick*, 573 F.3d at 1299. The PTAB's refusal to consider ***any*** of that renders its conception decision arbitrary and capricious. *Princeton*, 786 F.3d at 970.

2. The PTAB made nearly the same mistake in its written-description decision. As explained below, the PTAB's written-description decision—like its conception decision—hypothesized obstacles to using ***vectors*** to express the CRISPR-Cas9 complex in eukaryotes. It then held P1 lacked written description because skilled artisans might doubt the invention would work. *See* pp. 60-66, *infra*. But the PTAB nowhere disputed those obstacles do not apply when the pre-formed complex is microinjected into rapidly dividing cells. It thus nowhere explained why skilled artisans would doubt the efficacy of microinjecting a pre-formed complex into rapidly dividing cells, as P1 proposed. *See* Appx104-105. That failure of explanation renders its decision arbitrary and capricious. *See Provisur*, 2022 WL 4474941, at *4-5.

The PTAB instead declared that it need not address whether P1 ***enables*** microinjection of a pre-formed complex, because it had already "determined that the P1 disclosure does not sufficiently ***describe*** an embodiment of Count 1." Appx104-105 (emphasis added). But the PTAB had ***never ruled*** that P1's disclosure of

microinjection was deficient or that skilled artisans would have doubted the method (even if such doubts were relevant). Reasoning that rests on a prior determination the PTAB never made is by definition arbitrary and capricious. *Provisur*, 2022 WL 4474941, at *4-5.

IV. THE PTAB ERRED IN DENYING ACCORDED BENEFIT BASED ON LACK OF WRITTEN DESCRIPTION

The PTAB held that CVC's May 2012 "P1" application could not establish priority because it did not meet the written-description requirement. Appx104. But the PTAB again applied the wrong standard. A written description must allow skilled artisans "to visualize or recognize the identity" of the claimed invention and reasonably convey "that the inventor possessed the claimed invention." *Alcon Rsch. Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014).[11] "[P]ossession" means mental possession—that the inventor "had ***in mind*** the invention as claimed." *Crown Packaging Tech., Inc. v. Ball Metal Beverage Container Corp.*, 635 F.3d 1373, 1380-81 (Fed. Cir. 2011) (emphasis added). The test looks to "'the four corners of the specification from the perspective of a person of ordinary skill.'" *Id.* at 1380 (quoting *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)). For interferences, describing even "'one embodiment within

[11] CVC preserves its position that 35 U.S.C. § 112's text requires written description sufficient to enable others to make and use it—not "possession." *See* Pet. for Writ of Cert., *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, No. 21-1566 (U.S.), filed June 13, 2022.

the scope of the count'" satisfies the written-description component of constructive reduction to practice. *Falkner v. Inglis*, 448 F.3d 1357, 1362 (Fed. Cir. 2006).

Here, P1 ***describes*** the system of Count 1—a "eukaryotic cell" containing a single-guide CRISPR-Cas9 complex "capable of cleaving or editing" a "target DNA molecule." Appx1429-1430. P1 explains both ***why*** the complex can cleave DNA in any cell, including eukaryotes, and ***how to use*** the complex in eukaryotes. It even tells artisans that no special adaptations are necessary by saying only routine techniques are needed. But the PTAB demanded more—that P1's disclosures ***convince*** skilled artisans the invention would work. That was error.

Standard of Review. Whether a claim satisfies written description is reviewed for substantial evidence, but interpretation of precedent regarding the written-description requirement is reviewed *de novo*. *Falkner*, 448 F.3d at 1363.

A. P1's Expansive Disclosures Satisfy Written Description

1. No one denies that P1 describes—for the first time ever—the essential components of the CRISPR-Cas9 system. *See* Appx80; Appx116. P1 identifies and depicts the Cas9 protein. Appx647[0005]; Appx713[00248]; Appx564[Fig. 2]. It describes and depicts mature crRNA and tracrRNA, and explains they can be linked to form an sgRNA. Appx646-648[0004], [0009]; Appx666-667[0083]-[0084]; Appx677-678[00119]. And it proves—with experimental data—that CVC's com-

plex cleaves target DNA. Appx713-714[00248]-[00251]. With the same disclosures and more, Appx760-1038, P2 satisfies written description for the same reasons.

P1's disclosure of eukaryotic cells is unmistakable. It repeatedly recites the CRISPR-Cas9 system's capacity to cleave target DNA in eukaryotic cells. Appx80-82; Appx148. It lists eukaryotic cells, including "fruit fly," "fish," and "human" cells, as "[t]arget cells of interest." Appx689[00165]. References to "eukaryotic" cells outstrip "prokaryotic" two to one. Appx563-759. P1 includes ***21 claims*** to using the CRISPR-Cas9 complex to edit DNA in eukaryotic cells. Appx722[claims 61-69]; Appx725-726[claims 93-96, 102-109]. The specification explains that the complex can "induce DNA cleavage" in "a cell from any organism," Appx689[00165], and advises that artisans can exploit that versatility "to disrupt"—edit—particular ***human*** (eukaryotic) genes, Appx686[00158].

P1 tells the world exactly what CVC "claims as [its] own invention." *Evans v. Eaton*, 20 U.S. (7 Wheat.) 356, 434 (1822). It describes the single-guide CRISPR-Cas9 system of Count 1; proves the system's ability to cleave target DNA *in vitro*; and recites the system's capacity to cleave DNA in eukaryotic cells. Those disclosures clearly convey that CVC "had in mind" a three-component single-guide CRISPR-Cas9 system "capable" of cleaving target DNA in "eukaryotic cell[s]." *Crown*, 635 F.3d at 1381; Appx1430.

2. Although a patent need not "state the scientific principles underlying [the] invention," P1 does. *Diamond Rubber Co. of N.Y. v. Consolidated Rubber Tire Co.*, 220 U.S. 428, 435-36 (1911); *see Alcon*, 745 F.3d at 1190. It explains ***why*** the CRISPR-Cas9 complex's crRNA can target DNA in any cell: The nucleic-acid hybridization it exploits for targeting is universal to all life. *See* Appx650[0018]; p. 7, *supra*. "Because the DNA-targeting RNA provide specificity by hybridizing to target DNA," the CRISPR-Cas9 complex can "induce DNA cleavage" in "a cell from any organism." Appx689[00165].

P1 also guides artisans in ***how to use*** the CRISPR-Cas9 complex to edit DNA in eukaryotes. P1 explains up front that CVC's invention improves on the "[t]wo major technologies"—ZFNs and TALENs—used to edit eukaryotic DNA. Appx646[0001]; Appx67678-67679(¶137). P1 discloses that the same "well-known techniques" used to introduce ZFNs and TALENs into eukaryotic cells—like microinjection and vector-expression—can also introduce CVC's single-guide CRISPR-Cas9 complex. Appx691[00173]-[00174]. CVC's invention inspired such excitement because artisans immediately recognized that applicability "for genome editing in eukaryotic cells" would be "straightforward and require[] only routine genome-editing techniques." Appx80972(¶21).

P1 discloses microinjection, a "well-known technique." Appx691[00173]; Appx692-693[00177]-[00178]. By May 2012, scientists routinely microinjected

RNA, proteins, and multicomponent complexes directly into rapidly dividing cells—a technique the PTAB recognized was "known to be useful in achieving activity of prokaryotic proteins in eukaryotic cells." Appx5547. P1 explains that micro-injection had been successfully used in fruit flies with ZFNs. Appx4338[00174].

P1 next discloses expression vectors, by then also routine. *See* Appx655[0035]; Appx661[0063]. Before 2012, scientists introduced ZFNs and TALENs into human cells using expression vectors. Appx67678-67679(¶137). P1 recites doing the same with the CRISPR-Cas9 complex. Appx678-679[00120]-[00127]; Appx683-684[00145]-[00150]; Appx690-691[00167]-[00172].

P1 discloses techniques for vector expression already known to work in "adapting prokaryotic systems for use in eukaryotic cells." *CVC I*, 903 F.3d at 1294. Picking "the appropriate vector and promoter," P1 explains, "is well within the level of ordinary skill in the art." Appx679[00127]; Appx685[00152]. Before 2012, the U6 promoter was commonly used to express RNA from vectors in eukaryotic cells. Appx67696(¶171); Appx69071-69077.[12] P1 describes codon optimization—a routine "genetic engineering technique[]" used to enhance expression in eukaryotic cells. App654[0033]; *see* Appx5547; Appx67668-67669(¶¶109-112). It identifies well-known NLSs to facilitate localization to the nucleus. Appx676[00115]; *see*

[12] That Broad has previously dismissed P1's proposed implementations as "laundry lists" of routine techniques proves the point: P1 teaches that only routine techniques are required and, if anything, discloses more than was required.

Appx67664-67668(¶¶99-108). Figure 3C depicts known PAM sequences adjacent to the target sequences. Appx567[Fig. 3C]; *see* Appx93 (Broad agreeing role of PAM sequences was known in the art).

Those disclosures together described, for the very first time, a programmable single-guide CRISPR-Cas9 system and provided evidence it could cleave target DNA. They describe ***why*** the CRISPR-Cas9 system can cleave target DNA in any cell, including eukaryotic cells. And they describe ***how*** to implement the system in eukaryotic cells using routine methods like microinjection and vectors. P1 thus not only describes the ***what***—the composition in Count 1—but also the ***why*** and the ***how***. It equips artisans with everything necessary "'to visualize or recognize'" embodiments of Count 1 and teaches artisans how to use those embodiments. *Alcon*, 745 F.3d at 1190.

B. The PTAB Improperly Engrafted a Burden-To-Convince Requirement onto Written Description

The "hallmark of written description is disclosure," *Ariad*, 598 F.3d at 1351, not persuasion. Written description "is about whether the skilled reader of the patent disclosure can recognize that what was claimed corresponds to what was described." *Alcon*, 745 F.3d at 1191. Consequently, this Court has warned, it "is ***not*** about whether the patentee ***has proven*** to the skilled reader that the invention ***works***, or how to make it work." *Id.* (emphasis added).

The PTAB committed the error *Alcon* warns against. Rejecting P1's undisputed ***disclosure*** of a CRISPR-Cas9 system capable of cleaving DNA in eukaryotic cells, the PTAB demanded "results," Appx81, such as "a working example" or proof of a prevailing "expectation of success," Appx103. After reciting putative obstacles to successful implementation using vectors, the PTAB required that P1 ***either*** identify specific instructions or conditions to overcome them, ***or*** state that none were required. Appx86-104. That was legal error.

1. *Written Description Does Not Require Persuasion*

The PTAB's written-description decision applied the wrong legal test. A patent's disclosures need not convince the "skilled reader that the invention works." *Alcon*, 745 F.3d at 1191. Written description "does not demand" "examples," data, or "prior experimental work." *Ariad*, 598 F.3d at 1352; *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1309 (Fed. Cir. 2015). An inventor's own "delay" producing the invention—even for "years"—does not "negate" written description because "actual reduction to practice is not a requirement of possession." *BASF Plant Sci., LP v. Commonwealth Sci. & Indus. Rsch. Org.*, 28 F.4th 1247, 1267 (Fed. Cir. 2022). Instead, written description is satisfied if the disclosure communicates the inventor's visualized invention to the public. *Evans*, 20 U.S. (7 Wheat.) at 434. Whether some skeptic would be convinced that the invention works is irrelevant.

Precedent makes that clear. When Bell "applied for his patent[,] he had never transmitted telegraphically spoken words so that they could be distinctly heard and understood at the receiving end of his line"; his experiments failed. *Dolbear*, 126 U.S. at 535. But he had discovered "the right principle" and worked to implement "that true theory." *Id.* It was enough that he had "describe[d] his method with sufficient clearness and precision to enable those skilled in the matter ***to understand what the process is***." *Id.* at 536 (emphasis added). Whether that description convinced artisans the telephone would work did not matter.

Where this Court has found written description lacking, the problem was not that the specification failed to ***persuade*** artisans that the claimed compound would achieve the result. It was that the specification failed to identify—to ***describe***—the composition required by the claim. *See, e.g.*, *Ariad*, 598 F.3d at 1341, 1354-55 (genus method claims encompassed "all substances that achieve the desired result" but specification never described ***which*** substances would do so); *Biogen Int'l GMBH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1343-44 (Fed. Cir. 2021) (method claim covered treatment with "therapeutically effective" 480-mg dose of DMF but specification lacked "a specific reference to DMF480" and did "not list[ ]" DMF480 as an independent "therapeutically efficacious dose").[13] The disclosure is not

[13] This Court's "blaze marks" cases make the same point. *See Ariad*, 598 F.3d at 1350. Where a specification explicitly describes the claimed invention, no blaze

inadequate where—as here—the patent describes every element and reduction to practice is reported in a matter of months using the very methods the patent discloses.

2. *The PTAB Erroneously Converted "Possession" into "Proof"*

a. P1 undeniably describes the CRISPR-Cas9 complex, recites its use in eukaryotic cells, and claims methods for cleaving DNA in eukaryotes. P1 expressly asserts that CVC's complex is "capable of" cleaving DNA in eukaryotic cells, and shows it works *in vitro*. *See* pp. 9-10, *supra*. That should have ended the inquiry. *Falkner*, 448 F.3d at 1362.

The PTAB erroneously demanded ***persuasion***. Focusing on theoretical "concerns" about impediments—nowhere in the count—to cleaving DNA in eukaryotic cells, the PTAB queried whether artisans would believe CVC's complex would work given concerns about cell temperature, ionic strength, codon optimization, NLSs, and RNA degradation. Appx87-96. The PTAB declared that, given the art's "experiences" "with . . . Group II intron[s]," Appx91—mentioned nowhere in P1—artisans might not be "sure" that "CRISPR-Cas9 systems would work in

---

marks are needed, even in unpredictable arts. *Alcon*, 745 F.3d at 1190-91; *see Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005) (explaining "unpredictability" is relevant in genus claims for "determining the ***scope*** of the coverage to which the inventor is entitled" (emphasis added)). Similarly, this Court's precedents relating to claims involving a functionally defined genus, *see, e.g.*, *BASF*, 28 F.4th at 1268, are inapplicable here, where disclosure of only ***one*** embodiment is needed for priority, *see* p. 56, *supra*.

eukaryotic cells," Appx100-102. The PTAB therefore demanded evidence to convince dubious readers the system works in eukaryotic cells, such as:

- Disclosing data from "eukaryotic experiments," Appx82, or concrete "results from a CRISPR-Cas[9] system in . . . eukaryotic cells," Appx81;
- Explaining how to overcome all "possible difficulties," Appx88;
- Providing "specific instructions or conditions necessary for CRISPR-Cas9 activity in a eukaryotic cell" or "indicat[ing] that no specific instructions or conditions were necessary," Appx91; or
- Convincing skeptics they should not "doubt" the *in vitro* experiment results, Appx91-92.

In sum, the PTAB required CVC's disclosures to prove it had "a ***functional*** CRISPR-Cas9 system in eukaryotic cells." Appx102 (emphasis added).

None of that, however, is necessary to describe ***the invention***, which is set forth in the claims and specification. The PTAB never doubted that P1 conveyed to artisans that CVC had "in mind" the composition of Count 1, or that P1 discloses the routine techniques needed to practice the invention. *Crown*, 635 F.3d at 1381. Instead—contrary to *Alcon*—the PTAB insisted CVC's disclosure must "***prove***[ ] to the skilled reader that the invention works." 745 F.3d at 1191.

The PTAB's differential treatment of P1 and P3 confirms the error. The only difference the PTAB identified between those two disclosures was that P3 included a working ***example*** "in eukaryotic, human cells." Appx106. But written description "does not demand" such "examples." *Ariad*, 598 F.3d at 1352. Nor does it demand "actual reduction to practice." *Id.* Requiring otherwise was legal error.

b. Even if a disclosure were required to provide specific instructions or conditions to overcome possible obstacles, or explain that no such instructions or conditions were necessary, P1 does so. P1 ***told*** artisans no further instructions or conditions were necessary: Throughout the specification, P1 says the same "well-known techniques" used to introduce ZFNs and TALENs into eukaryotic cells can be used for the CRISPR-Cas9 system. Appx691[00173]-[00174]; pp. 8-10, *supra*. Saying ***routine*** techniques are needed is the same as stating that no ***special*** instructions are necessary. *See Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1371 (Fed. Cir. 2009) (describing "conditions generally suitable for all disclosed strains" indicated all embodiments could be treated similarly). If no further instructions are necessary, there is no reason to force inventors to superfluously state that none are required.

Moreover, there is no evidence that specific instructions or conditions were required to overcome any obstacles for CVC's microinjection implementation. P1 proved CVC's CRISPR-Cas9 complex functioned *in vitro*, Appx713-714[00248]-[00251]—with "stunning efficiency," Appx66680. And there is no evidence artisans would have expected the complex to suddenly lose ***all*** activity merely because it is introduced into eukaryotic cells. The PTAB itself has acknowledged that microinjection was a routine technique "known to be useful in achieving activity of prokaryotic proteins" like the CRISPR system "in eukaryotic cells." Appx5547. And

the PTAB never identified any obstacle to implementation by microinjection that would have required specific instructions or conditions to overcome—because artisans understood there were none. *See* pp. 52-55, *supra*. P1's specific instructions for implementing the microinjection embodiment should be more than enough (even under the PTAB's erroneous standard).

No inventor can anticipate and preempt with instructions ***every single*** litigation-inspired hypothetical problem that can be conjured. Lawyers can always imagine 1,001 reasons an invention might not work. Paid experts can invent still more. "'[W]hen the question is whether a thing can be done or not, it is always easy to find persons ready to show how not to do it.'" *Dolbear*, 126 U.S. at 536. For groundbreaking inventions like this, it is easier still to hypothesize why they might fail. But written description is description of the invention, not proof it works. "Possession" means possession of the idea, not construction of a working example. The patent system does not punish inventors of breathtaking innovations by saddling them with the burden of convincing putative skeptics their invention will work.

CONCLUSION

The PTAB's judgment and underlying findings should be vacated, and this Court should reverse, or, alternatively, remand.

September 30, 2022

Respectfully submitted,

/s/ Jeffrey A. Lamken

Jeffrey A. Lamken
Counsel of Record
Kenneth E. Notter III
MOLOLAMKEN LLP
The Watergate, Suite 500
600 New Hampshire Avenue, N.W.
Washington, D.C. 20037
(202) 556-2000 (telephone)
(202) 556-2001 (fax)
jlamken@mololamken.com

Sara E. Margolis
Jonathan E. Barbee
MOLOLAMKEN LLP
430 Park Avenue
New York, NY 10022
(212) 607-8160 (telephone)
(212) 607-8161 (fax)

Elizabeth K. Clarke
MOLOLAMKEN LLP
300 N. LaSalle Street, Suite 5350
Chicago, IL 60654
(312) 450-6700 (telephone)
(312) 450-6701 (fax)

Counsel for The Regents of the University of California, University of Vienna, Emmanuelle Charpentier