Appeal No. 2017-1907

United States Court of Appeals
for the Federal Circuit

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,

Appellees.

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Interference No. 106,048

BRIEF FOR APPELLEES

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CERTIFICATE OF INTEREST

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

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

The Broad Institute, Inc.

Massachusetts Institute of Technology

President and Fellows of Harvard College

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

None

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

None

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

Thomas J Kowalski and Deborah L. Lu, Vedder Price, PC

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

None

DATE: October 25, 2017 /s/ *Steven R. Trybus*

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TABLE OF ABBREVIATIONS

Parties	
UC	Regents of the University of California, University of Vienna, and Emmanuelle Charpentier, collectively
Broad	The Broad Institute, Inc., Massachusetts Institute of Technology, and President and Fellows of Harvard College, collectively
Patents and Applications	
the '859 Application	Patent Application No. 13/842,859 (UC)
the '086 Provisional	Provisional Patent Application No. 61/652,086 (UC)
the '527 Provision	Provisional Patent Application No. 61/736,527 (Broad)
the Kim Application	U.S. Patent Application No. 14/685,568
Defined Terms	
PTAB	Patent Trial and Appeal Board of the United States Patent and Trademark Office
PTO	United States Patent and Trademark Office
POSA	Person of ordinary skill in the art
Jinek 2012	Jinek *et al.*, A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity, 337(6096) SCIENCE 816-821 (2012) (Appx04798-04842)
Cong 2013	Cong et al., Multiplex Genome Engineering Using CRISPR/Cas Systems, 339(6121) SCIENCE 819-823 (2013) with Supplemental Material (Appx04682-04712)
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
Cas	CRISPR associated
crRNA	CRISPR RNA
tracrRNA	trans-activating crRNA
TALEN	Transcription activator-like effector nuclease
ZFN	Zinc finger nuclease

STATEMENT OF RELATED CASES

No other appeal in or from this interference proceeding was previously before this Court or any other appellate court. Counsel for Appellees are not aware of any case in this or any other court or agency that will directly affect or be directly affected by this Court's decision in this appeal.

JURISDICTIONAL STATEMENT

UC has failed to provide an adequate basis for jurisdiction. UC merely asserts, without discussion, that this Court has jurisdiction under pre-AIA 28 U.S.C. §1295(a)(4)(A), which relates to appeals from decisions of the PTAB. However, this Court's precedent requires UC to set forth its actual injury–in-fact in order to establish jurisdiction for its appeal, yet UC has failed to do so. *Phigenix v. Immunogen*, 845 F.3d 1168, 1175 (Fed. Cir. 2017). That is particularly true here given that UC has publicly asserted that the PTAB's decision actually benefitted, rather than harmed, UC. *See, e.g.*, http://news.berkeley.edu/2017/02/15/berkeley-statement-regarding-patent-boards-decision-on-crispr-cas9-gene-editing-technology/ ("We [UC] are pleased that UC's application, covering the invention and use of CRISPR gene editing in all cells, can move toward issuance as a U.S. patent."). Given this public statement and others like it, UC must set forth its harm in order to justify its allegation of jurisdiction.

In addition, if the Petitioner is successful in *Oil States*, and the Supreme Court holds that patents are private rights that require adjudication in an Article III court, Appellants would not be able to seek to extinguish Appellees' patent rights in an interference in the PTAB.

COUNTER-STATEMENT OF ISSUES

1. Whether substantial evidence supports the PTAB's fact finding that a POSA in 2012 would not have had a reasonable expectation of success in engineering prokaryotic-based CRISPR-Cas9 systems to function in eukaryotic cells.

INTRODUCTION

This appeal turns on the question of whether, based on the record below, substantial evidence—that is, more than a mere scintilla of evidence—supports the PTAB's fact finding that a POSA in 2012 would not have had a reasonable expectation of success that CRISPR-Cas9 systems, occurring only in prokaryotic (bacterial) cells, could be made to function in the fundamentally different setting of eukaryotic (nucleated) cells, such as in animals and plants. It plainly does, and this Court should affirm the PTAB's judgment.

(1) The PTAB relied on five categories of substantial evidence. The PTAB based its finding on five categories of evidence—each of which individually constitutes substantial evidence and collectively provide overwhelming evidence in support of the PTAB's finding of no reasonable expectation of success:

> **Category 1: Contemporaneous statements by the UC Inventors** expressing frustrations and doubts about the ability to make CRISPR-Cas9 systems function in eukaryotic cells. Appx00014-00017.
>
> **Category 2: Contemporaneous statements by skilled artisans,** including a scientific article written by one of UC's experts (Dr. Dana Carroll) stating clear concerns and identifying multiple reasons why CRISPR-Cas9 systems might not function in eukaryotic cells. Appx00017-00023.

Category 3: Evidence of other research groups seeking to engineer CRISPR-Cas9 systems to work in eukaryotic cells demonstrating that, while they were motivated to try, there was no reasonable expectation of success. Appx00023-00025.

Category 4: Extensive scientific evidence of the fundamental differences between prokaryotic and eukaryotic cells that weighs heavily against an expectation that a prokaryotic system could be adapted to function in eukaryotic cells. Appx00029-00035.

Category 5: Extensive evidence of obstacles and failures encountered in prior-art attempts to adapt other prokaryotic systems to eukaryotes. Appx00035-00046.

(2) UC does not refute that the PTAB relied on substantial evidence. To prevail on this appeal, UC would need to establish that the PTAB was not entitled to accord any weight whatsoever to any of these five independent categories of evidence. UC fails to do so, and instead simply disagrees with the PTAB's factual interpretations, its credibility determinations, its inferences drawn from the evidence, and the relative weight it gave to evidence. In short, UC improperly asks this Court to redo the PTAB's fact finding, rather than to assess whether substantial evidence supports it.

Some examples in each category illustrate the nature of UC's arguments:

- **Category 1:** UC complains that the PTAB was "unfair" because it accorded too much "weight" to the contemporaneous evidence of the UC inventors' frustrations and doubts. App.Br. at 57-61. But the PTAB's finding that "*contemporaneous statements* cited by *both parties* persuade us that one of ordinary skill in the art *would not have reasonably expected success* before experiments in eukaryotic cells were done" is strongly supported by extensive evidence that the PTAB reviewed and cited. Appx00023.[1] Certainly, an inventor's statements of frustrations and doubts should not, as UC suggests, be ignored. The PTAB's weighing of these contemporaneous statements is entitled to substantial deference by this Court.

- **Category 2:** UC does not dispute that Dr. Carroll's contemporaneous scientific article expressed doubt about whether CRISPR-Cas9 could be engineered to function in eukaryotic cells. App.Br. at 61. Rather, UC complains that the PTAB should have accorded greater weight to his subsequent expert report (prepared for the Interference) in which he sought to explain away his prior statements. App.Br. at 53-54. The PTAB's credibility determination—favoring Dr. Carroll's contemporaneous statements over his litigation testimony—is entitled to substantial deference.

[1] All emphases are supplied unless otherwise noted.

- **Category 3:** UC complains that the PTAB should have inferred that a POSA would have had a reasonable expectation of success because other groups started efforts in 2012 to repurpose CRISPR to work in eukaryotic cells and eventually achieved some success. App.Br. at 39-43. The PTAB properly found that evidence only showed a motivation, not an expectation of success. Appx00023. Notably, UC does not address the evidence before the PTAB showing that the eventual demonstrations (by Dr. Zhang and others) that CRISPR-Cas9 could actually be engineered to function in eukaryotic cells was regarded as a revolutionary invention (rather than merely the expected outcome from routine exercise of ordinary skill). UC again asks this Court to reweigh the evidence and come to a different conclusion on whether POSA would have had a reasonable expectation of success.

- **Category 4:** UC argues that the many potential obstacles arising from the differences between prokaryotic and eukaryotic cells (for example, that eukaryotic DNA is elaborately embedded in chromatin and that expression of prokaryotic proteins can be toxic to eukaryotic cells) were no longer considered *actual* obstacles as of 2012. App.Br. at 54. In fact, the PTAB made a contrary finding based on substantial evidence—including Dr. Carroll's contemporaneous statement in 2012, in which he specifically identified chromatin and toxicity as potential obstacles. Appx00033. This again constitutes substantial evidence supporting the

PTAB's finding that a POSA would not have had a reasonable expectation of success in 2012.

- **Category 5:** UC argues that the PTAB did not consider UC's four examples of successful adaptations of prokaryotic proteins other than Cas9 to eukaryotes. App.Br. at 52-53. In fact, the PTAB thoroughly addressed those examples, explained the differences, and found that UC's four examples—*out of thousands of prokaryotic proteins*—would not have provided a POSA with a reasonable expectation of success. Appx00041-00046. Rather, the PTAB found that (i) Broad's examples of prior attempts to adapt RNA-based prokaryotic systems were more analogous to the RNA-based CRISPR-Cas9 system and therefore more pertinent and (ii) this evidence clearly showed examples of failures and obstacles. *Id*. This evidence also constitutes substantial evidence supporting the PTAB's finding.

In summary, each of these categories of evidence constitutes substantial evidence supporting the PTAB's finding of no reasonable expectation of success and the judgment should be affirmed.

(3) <u>UC incorrectly claims that the PTAB made three legal errors</u>. Because UC cannot show that no substantial evidence supports the PTAB's finding, UC claims that the PTAB committed three legal errors. None have merit.

Supposed Legal Error 1: UC incorrectly claims the PTAB applied a legally improper standard for assessing reasonable expectation of success by demanding evidence of "certainty" of success. App.Br. at 57-61. The PTAB did no such thing. Its decision explicitly states that expectation of success does *not* require "certainty" or "absolute predictability." Appx00019.

Supposed Legal Error 2: UC also asserts that the PTAB erroneously required, as matter of law, the prior art to teach "*specific instructions*" to deliver success, when it supposedly should have presumed an expectation of success based on the alleged later use of conventional techniques to achieve success. App.Br. at 31-36. However, following this Court's precedent, the PTAB imposed no legal standard requiring specific instructions. Appx00028-00029; Appx00039. Rather, it properly evaluated expectation of success based on the facts of this case. Appx00032-00046.

Supposed Legal Error 3: UC claims that the PTAB committed legal error by not considering the Kim patent application, filed October 23, 2012, as available prior art. App.Br. at 20, 23-24, 44-47. But the Kim application is at best potential §102(e) prior art: it published in May 2014 and so was not available in 2012. The PTAB correctly ruled that consideration of such secret—and (according to UC) potentially interfering in its own right—art is not appropriate for determining interference-in-fact. Appx00046-00048. Indeed, it would be illogical to permit

secret, potentially interfering activities of an *unrelated third party* to somehow qualify UC to participate in an interference with Broad. Regardless, any error here would be harmless because the Kim application is not in fact §102(e) prior art to Broad's invention. As UC admits, Broad previously antedated the October 23, 2012, Kim application based on the undisputed October 5 submission date of the Broad inventors' seminal paper in *Science*. App.Br. at 11; Appx00308.

(4) UC incorrectly asserts that the PTAB failed to consider evidence and arguments in two areas.

Supposed Failure 1: UC incorrectly asserts that the PTAB failed to consider evidence and arguments on simultaneous invention as secondary indicia of obviousness as shown by the publications of several research groups. App.Br. at 36-47. However, UC never argued to the PTAB that the activity of other research groups showed simultaneous invention or was a secondary consideration and thus the PTAB had no opportunity to address the argument. Appx00231-00295. The PTAB did address the evidence related to other research groups on the merits in the context of UC's actual arguments below, devoting an entire section of its opinion to this subject. Appx00023-00025.

Supposed Failure 2: UC asserts that the PTAB failed to consider prior art dated after December 12, 2012 in assessing no interference-in-fact. App.Br. at 61-

64. But UC presented no such prior art in its opposition to Broad's motion. Appx00231-00295.

In summary, the PTAB did not incorrectly apply any legal standards or fail to consider any evidence or arguments.

Conclusion. Because the PTAB's judgment was supported by substantial evidence and in full conformity with the law, it should be affirmed.

COUNTER-STATEMENT OF THE CASE

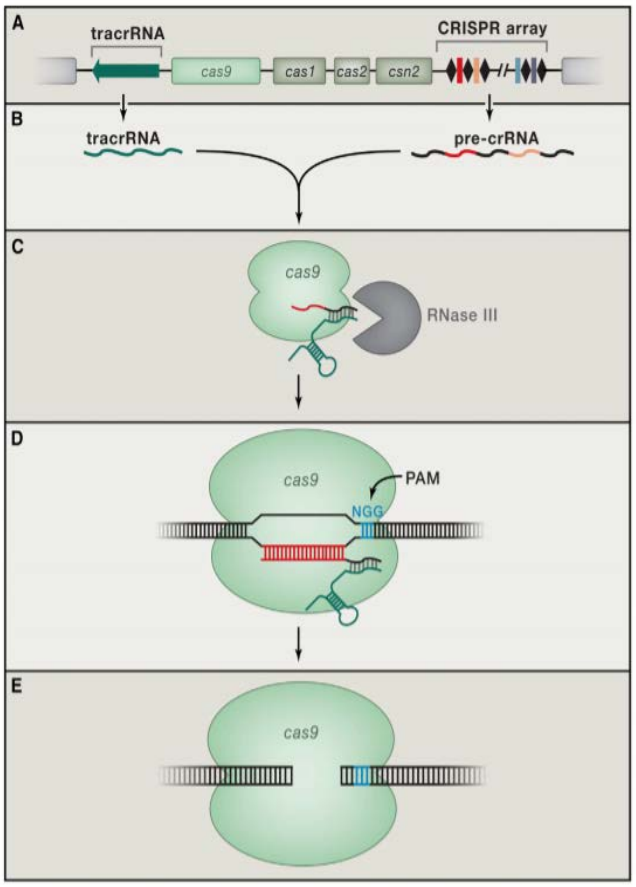
I. THE DEVELOPMENT OF CRISPR FOR EUKARYOTIC GENOME EDITING

A. CRISPR Is a Naturally-Occurring System Present Only in Prokaryotes (Bacteria and Archaea)

CRISPR[2] systems occur naturally only in prokaryotes, such as some bacterial species and most archaea. Appx05488, ¶2.1. Natural CRISPR systems serve as defense mechanisms against a pathogen (such as a virus) by acquiring a short piece of the pathogen's DNA, which provides immunity against subsequent exposure to the pathogen. Appx05488-05490, ¶¶2.2-2.9. There are various types of CRISPR systems, categorized at the time relevant here as Type I, II, and III systems. Appx05489, ¶2.8. The invention at issue concerns Type II systems, which are sometimes referred to as CRISPR-Cas9 systems. *Id*.

[2] "Cas9" refers to a particular protein, a nuclease, that is a component of the CRISPR-Cas9 system.

CRISPR-Cas9 systems in nature include protein and RNA components, specifically, four Cas proteins, one of which is Cas9, CRISPR RNA (crRNA) and trans-activating crRNA (tracrRNA). Appx05489-05490, ¶2.9. Each of the components of the CRISPR-Cas9 system is encoded at a locus within the prokaryote's genome. *Id*. The figures below illustrate the natural process that occurs including transcribing the CRISPR-Cas9 components, forming the active Cas9 protein-RNA complex, and cutting DNA within the prokaryotic cell:



Appx09311.

The CRISPR locus is shown in Figure A and, upon transcription of the CRISPR locus, tracrRNA and a long pre-crRNA molecule are produced, as shown in Figure B. Appx09311. The pre-crRNA, which is encoded by a CRISPR array, comprises fragments of foreign DNA (shown in red and orange and referred to as "spacers") that had been incorporated into the genome of the prokaryote and are interspersed between repeating sequences (referred to as "direct repeats" and shown in black). *Id*.

Figure C shows the formation of the protein-RNA complex. Appx09311. The pre-crRNA and tracr-RNA associate by a process called hybridization to form a duplex, and the pre-crRNA is shortened into individual units (crRNA) by Cas9 and another enzyme, RNaseIII. *Id*. Then the crRNA/tracrRNA duplex complexes with the Cas9 protein. *Id*.

Figure D shows a crRNA:tracrRNA:Cas9 complex that has identified a target DNA sequence that is complementary to the spacer sequence shown in red and is adjacent to a Protospacer Adjacent Motif (PAM) sequence. Appx09311. The complex functions like a pair of molecular scissors to create a double-stranded break in the DNA. Appx09311; Appx05489-05490, ¶2.9. Figure E shows the resulting blunt cut in both strands. Appx09311.

The long scientific path of discovery that led to this characterization of naturally occurring CRISPR systems took approximately 20 years and involved study of several different types of bacterial CRISPR systems. Appx09311.

In 1993, Dr. Francisco Mojica recognized that a locus with a distinctive structure (consisting of a series of palindromic repeats separated by unique "spacer" sequences of a fixed size) is present in diverse species of bacteria. Appx07964-07972; Appx05488, ¶2.3; Appx09310. The term **C**lustered **R**egularly **I**nterspaced **S**hort **P**alindromic **R**epeats (CRISPR) was eventually coined to describe these loci. Appx09311. Dr. Mojica later discovered, in 2003, that the spacer sequences corresponded to pathogens that infected the bacteria. Appx05488, ¶2.3; Appx09312-09313.

Further developments by other researchers included:

- 2007 – Experimental evidence showing that CRISPR was an adaptive bacterial immune system. Appx07953-07956.
- 2008 – Showings that long pre-crRNA is cleaved into individual crRNAs and that a CRISPR system acts upon DNA targets. Appx09683-09688; Appx07957-07960.
- 2010 – Demonstration that CRISPR-Cas9 cuts both strands of viral DNA at precise positions and that Cas9 is the only Cas protein required for this activity. Appx07939-07944.

All of this research was focused exclusively on CRISPR systems in bacterial cells, their natural environment.

B. As Early as 2008, Researchers Speculated on the Possibility of Engineering a CRISPR System to Function in the Different Environment of Eukaryotic Cells, But No Success Was Achieved

As early as 2008, two separate research groups speculated on the possible use of CRISPR in eukaryotic cells. Appx09603-09631; Appx08074. Both groups filed patent applications on their bacterial CRISPR work and disclosed conventional techniques possibly applicable to engineer the CRISPR systems to function in the vastly different milieu of eukaryotic cells; neither resulted in an issued patent. *Id*.

The significant differences between prokaryotic and eukaryotic cells stem from an evolutionary divergence 1.5 billion years ago. Over that time, eukaryotic cells became increasingly complex and ultimately formed multicellular organisms, whereas prokaryotic cells remained simple, single-celled organisms. The many differences include:

- Eukaryotic cells developed a protective nucleus housing the organism's genomic DNA. Appx05533-05534, ¶¶6.28-6.29.
- In the nucleus, eukaryotic DNA is organized into discrete structures, called chromosomes, composed of a protein/DNA complex called chromatin. *Id*. In chromatin, strands of DNA are wrapped around proteins

called histones thereby forming a complex, tightly packed structure. Appx05533, ¶6.29; Appx05880. In contrast, prokaryotic cells lack nearly all of the structural organization found in eukaryotic cells that functions to organize and protect DNA, such as a nucleus and chromatin. Appx05533, ¶6.29; *see also* Appx00030.

- Eukaryotic cells also employ a different cellular machinery and mechanisms than prokaryotic cells to express genes, relying on proteins and complexes not found in prokaryotic cells. Appx05528-05535, ¶¶6.14-6.35. Those proteins and complexes can be essential to the proper transcription and translation of genetic material. *Id*.

- Prokaryotic and eukaryotic cells also have different environments, such as different intracellular temperatures, ion concentrations, and pH. Appx05533, ¶6.28; *see also* Appx00029-00030. The different environment of a eukaryotic cell might prevent a prokaryotic protein from properly folding or forming protein-RNA complexes, either one of which might prevent the protein-RNA system from functioning in a eukaryotic cell. Appx05533-05535 ¶¶6.28-6.35; *see also* Appx00030-00031.

- Prokaryotic systems expressed in eukaryotic cells are often degraded by native eukaryotic defense mechanisms, which might prevent a

prokaryotic system from forming or might degrade a formed system so quickly that it cannot carry out its intended functions. *Id*.

In sum, potential obstacles to adapting prokaryotic protein-RNA complexes for use in eukaryotes included at least whether: (1) the components could be delivered into the cell, (2) the components would express properly, (3) the components would survive the eukaryotic defense mechanisms, (4) the components would not be toxic to the cell, (5) the protein would fold properly, (6) the complex would localize in the nucleus, (7) the complex would be able to access the desired DNA target in the chromatin, and (8) the complex would function. Appx05525-05535, ¶¶6.6-6.35; Appx09304; *see also* Appx00029-00031.

The art included prior attempts to adapt other natural protein-only prokaryotic systems to eukaryotes, but success was reported for only a few of the thousands of prokaryotic proteins. Appx05536, ¶6.40. Attempts to adapt prokaryotic RNA-based systems revealed significant obstacles, largely failed attempts, and the requirement to find a unique set of modifications in each instance to achieve success where possible. Appx05537-05538, ¶¶6.44-6.47.

Only one prior attempt of record, the prokaryotic Group II intron system, included both protein and RNA components, like the CRISPR-Cas9 system. Appx05535-05536, ¶¶6.36-6.39. Adapting Group II introns to eukaryotes required

expressing both components while surviving the eukaryotic cell's defense mechanisms, their assembling into the appropriate protein-RNA complex with proper protein folding, and their accessing and altering the eukaryotic target. Appx08653-08656, ¶¶1.44-1.51. After 16 years of experimental efforts, researchers ultimately achieved only limited success in modified eukaryotic cells using a specialized set of conditions. *Id*.

Against this backdrop, two groups proposed the possibility of engineering prokaryotic CRISPR systems to function in eukaryotic cells in 2008. Appx08074; Appx09603-09631. However, neither group reported any success as of 2012. Appx00306.

C. In February 2011, Broad's Dr. Feng Zhang Began Engineering Successful CRISPR-Cas9 Systems to Function in Eukaryotic Cells

In early 2011, Broad inventor Dr. Feng Zhang began engineering CRISPR systems that would successfully function in eukaryotic cells. In February 2011, Dr. Zhang filed an Invention Disclosure memorandum disclosing numerous applications of an engineered form of a CRISPR-Cas9 system that would function in eukaryotic cells. Appx09597-09602. Dr. Zhang thereafter designed several CRISPR-Cas9 systems for use in eukaryotic cells. Appx09599; Appx09632-09662. Dr. Zhang reported the generation and successful testing of CRISPR-Cas9 constructs reflecting his designs in human (eukaryotic) cells. *Id*.

In January 2012, five months prior to the publication of the Jinek 2012 article discussed below, Dr. Zhang submitted a grant proposal to the NIH that set forth the "design of a mammalian CRISPR expression system" using four components—Cas9, a pre-crRNA, tracrRNA, and RNase III. Appx09529. Dr. Zhang's subsequently published article, Cong *et al*. 2013, reported success with this CRISPR-Cas9 system. Appx04682-04712. The Cong *et al*. 2013 article has become the most frequently cited CRISPR publication. Appx05493-05494, ¶2.14.

Dr. Zhang filed his first patent application on the invention, U.S. Provisional Application No. 61/736,527, on December 12, 2012. Appx05573-05877. Within three years, this application led to a dozen issued U.S. patents relating to CRISPR-Cas9 systems engineered for use in eukaryotic cells. Appx00083-00089. The PTAB's decision recites in full, claim 1 of USPN 8,697,359 as Broad's representative claim for its analysis. Appx00011. Claim 1 requires "an engineered, non-naturally occurring" CRISPR-Cas9 system introduced "into a eukaryotic cell" and "operable in a eukaryotic cell," whereby the Cas9 protein cleaves a DNA target. Appx00221.

II. EXPECTATIONS IN THE ART AFTER PUBLICATION OF THE JINEK 2012 PAPER BY THE UC INVENTORS

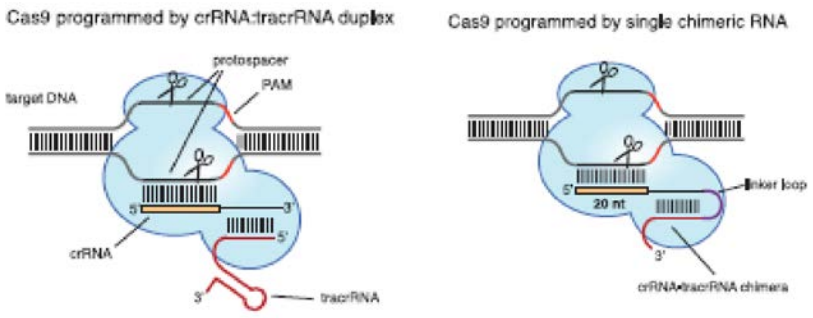
A. The UC Inventors' *In Vitro* Experiments and Engineered Chimeric Molecule

In June 2012, while Dr. Zhang was continuing his successful experiments with CRISPR systems in eukaryotic cells, the UC inventors published Jinek 2012 with results of their experiments using a CRISPR system. Appx04798-04842.

For their studies, the UC inventors removed the CRISPR-Cas9 system from the prokaryotic cell environment to study it in an extremely simple cell-free "in vitro" environment—that is, a test-tube containing only the components of the CRISPR system and a purified DNA target sequence. Appx04801. Thus, UC's studies were neither in prokaryotic nor in eukaryotic cells. Using that test-tube environment, UC's scientists endeavored to determine the minimal system required for CRISPR function. Appx04801.

In addition, the UC scientists altered the RNAs from the natural system by using a covalent linker to join the tracrRNA and crRNA into a single RNA molecule. Appx04802-04803. UC referred to this linked RNA molecule as a "chimeric" RNA. *Id.* The figures reproduced below from Jinek 2012 show the difference between the natural system and their chimeric RNA system. Appx04803. The figure on the left shows the natural system with the crRNA and tracrRNA hybridized as a duplex, while the figure on the right shows chimeric

RNA with a covalent linker loop (shown in the lower right hand portion of the figure) between the two RNA sequences.



Id.

The UC scientists designed two types of chimeric RNA with the covalent linker loop, both with substantially shorter tracrRNA sequences than in natural tracrRNA. Appx04803. The Jinek 2012 paper reported that the "Chimera A" version worked efficiently *in vitro*, while the even shorter "Chimera B" version did not. *Id*.

On May 25, 2012, shortly before the publication of Jinek 2012, UC's inventors filed the '086 Provisional disclosing the results of their *in vitro* experiments and their chimeric RNA molecules. Appx00771-00944. A chimeric RNA molecule, with its covalent linking, is not required by the count. The UC patent application at issue in the interference, the '859 Application, claims the benefit of the '086 Provisional. Appx00415. All of UC's involved claims are directed to use of a CRISPR-Cas9 system with chimeric RNA in any environment.

Appx00010-00011. None of UC's involved claims recite a eukaryotic limitation. Appx00011.

The PTAB's decision recites in full claim 165 of the '859 Application as UC's representative claim for its analysis. Appx00010. The claim requires a CRISPR-Cas9 system wherein "the activator-RNA and the targeter-RNA are covalently linked to one another" (UC's claims use "targeter-RNA" instead of crRNA and "activator-RNA" instead of tracrRNA). *Id*.

B. Contemporaneous Observations of the UC Inventors and Skilled Artisans after Publication of the Jinek 2012 Paper

The Jinek 2012 paper speculated on the possibility that the CRISPR system might be an alternative to ZFNs and TALENs, two known systems for cleaving DNA in eukaryotic cells. Appx04803. However, Jinek 2012's *in vitro* experiments in a defined test-tube environment provided no guidance concerning how POSA might, if at all possible, engineer CRISPR systems to function in eukaryotic cells. Appx05525-05528, ¶6.6-6.13.

Dr. Dana Carroll, who would later serve as UC's expert in the interference, published a contemporaneous article in September 2012 (a few months after the June publication of Jinek 2012) and cited serious reasons for doubt as to whether CRISPR-Cas9 could be engineered to work in eukaryotic cells. Appx04765-04797; *see also* Appx00017-00018. Among other things, Dr. Carroll pointed out that prior experiences with ZFNs and TALENs could not resolve key questions

about whether CRISPR-Cas9 could function in eukaryotic cells. *Id*. One important reason cited was that the ZFNs and TALENs systems were based on proteins that naturally function in eukaryotic cells (and thus are adapted to the complex chromatin structure of eukaryotic cells), whereas CRISPR systems naturally function only in prokaryotic cells. *Id*.

Dr. Carroll's paper also highlighted many scientific unknowns reflected in the scientific literature. Appx04797. For example, he observed that the RNA components of the CRISPR-Cas9 system could be degraded by eukaryotic enzymes called ribonucleases. Appx04797; *see also* Appx00017-00018. Dr. Carroll additionally expressed doubt over whether engineering of CRISPR-Cas9 in eukaryotic cells could be achieved at all, stating that "[g]ene editing through base pairing had been attempted many times and is still being pursued," even though the efficiency of even those systems that work "remains discouragingly low in most cases." *Id*.

Public remarks made by the UC inventors Drs. Jennifer Doudna and Martin Jinek reinforced the uncertainty. Appx05878-05881; Appx05905-05909; Appx05910-05914; *see also* Appx00015. For example, Dr. Doudna stated in a 2014 interview:

> Our [Jinek] 2012 paper was a big success, but there was a problem. We weren't sure if CRISPR/Cas9 would work in eukaryotes—plant and animal cells.

Appx05880; *see also* Appx00015.

Dr. Doudna also stated that, after the publication of Jinek 2012, "getting *CRISPR to work in human cells"* would be "*a profound discovery***.**" Appx05907-05908. These contemporaneous statements directly conflict with UC's representation to the PTAB (and repeated in this appeal) that the publication of Jinek 2012 rendered such a discovery "obvious" (rather than "profound"). Appx00238-00243.

C. Attempts to Adapt CRISPR to Eukaryotes by Research Groups after Jinek 2012

After the June 2012 publication of the Jinek paper, the Broad team continued their work with the system outlined in Dr. Zhang's January 2012 NIH proposal. Appx09522-09529. UC's asserts, without any record support, that Broad's inventors "took UC's disclosures in Jinek 2012 as their jumping off point," using the "single-guide chimeric RNA that Jinek 2012 disclosed." App.Br. at 41.

Broad actually reported in Cong 2013 that it successfully used the *dual-molecule* RNA (*i.e.*, crRNA:tracrRNA duplex described in Dr. Zhang's NIH proposal) prior to work with the (chimeric) single-guide RNA. Appx04683. Broad's data not only demonstrated that the single-guide RNA was not necessary

for eukaryotic uses, but that dual-molecule approach was *superior* in eukaryotic cells compared to the Jinek chimeric RNA. Appx04683.

Other scientists affiliated with Broad also conducted research related to CRISPR-Cas9 systems engineered for eukaryotic cells, including Dr. George Church at Harvard and Dr. Keith Joung at the Harvard Hospitals. Appx08585, ¶11.111. Drs. Church and Joung were members of the Broad, which is a community including scientists from Harvard, Harvard Hospitals and MIT. *Id*. Drs. Church and Zhang also co-advised Dr. Cong, who was the lead author on Broad's Cong 2013 publication. *Id*. Dr. Joung (like Dr. Doudna) explicitly acknowledged assistance from Dr. Church in his subsequent publication, the Hwang 2013 paper. Appx04770; Appx04763.

UC asserts that the work of these Broad scientists and Dr. Jin-Soo Kim of ToolGen bears on the understanding and expectations of ordinary skilled artisans. App.Br. at 39. But all of these researchers had significantly more than ordinary skill with gene editing in eukaryotic cells. *See* Appx08430-08433.

Moreover, Drs. Church, Kim and Joung each sought patent protection for their respective eukaryotic work, reflecting their belief that the work was *not routine* and *not obvious*, but rather inventive. *See* Appx05325-05481. Similarly, the UC inventors themselves expressed surprise when they confidentially learned that the Church laboratory had achieved success in eukaryotes. Appx05908.

UC suggests that, based on the *in vitro* results of Jinek 2012 and with knowledge of conventional techniques, POSA could easily and readily have adapted its CRISPR system with chimeric RNA to function in eukaryotes. App.Br. at 4, 42-43. But the contemporaneous evidence shows that UC's inventors *themselves* (who, having done the work reported in Jinek 2012, had advance knowledge compared to other teams) actually experienced "many frustrations" trying to make CRISPR work in eukaryotes, as Dr. Doudna publicly acknowledged. Appx05908.

D. The Enthusiastic Scientific Reaction to the Cong 2013 Article

The reaction of the scientific community to the Cong 2013 article confirms that the adaption of CRISPR for eukaryotic cells was considered exciting and groundbreaking work, not merely routine, expected results. Appx05493-5494, ¶2.14; Appx09513. Indeed, that paper has become the most-cited CRISPR article, acknowledging the first successful demonstration that CRISPR could be engineered to work in a eukaryotic environment. *Id*.

UC's Dr. Doudna described the Cong article and the accompanying article by Dr. Church as removing "a huge bottleneck in both research and the development of human therapeutics" and concluded that "it's possible that this technique will completely revolutionize genome engineering in animals and plants." Appx05911. Since the publication of the Cong article and continuing to

the present, the Zhang laboratory has become a significant leader of that revolution, distributing their reagents in response to tens of thousands of requests by other laboratories. Appx05493-05494, ¶2.14.

III. THE INTERFERENCE PROCEEDINGS

A. UC Requests an Interference Based on the Premise That UC's *In Vitro* CRISPR System Was Readily and Easily Applicable to Eukaryotic Cells

On January 28, 2013, the UC inventors filed a provisional patent application that included eukaryotic CRISPR experiments. Appx01218-01574. UC submitted claims to eukaryotic CRISPR-Cas9 systems, but UC's earliest alleged actual reduction to practice in eukaryotic cells occurred after the October 5, 2012, submission date of Broad's Cong 2013 article. UC therefore made a strategic decision to seek an interference with Broad's eukaryotic claims using UC's environment-free claims, rather than suggest an interference between UC's eukaryotic claims and Broad's eukaryotic claims.

On April 13, 2015, UC filed a Suggestion for Interference arguing that there was no patentable distinction between UC's environment-free claims and Broad's eukaryotic-specific claims. Appx08240-08353. The basic premise of UC's argument was that the *in vitro* system of Jinek 2012 "was readily applicable" to eukaryotic cells and this "would have been predicted and expected by persons of ordinary skill in the art." Appx08334. UC made these allegations despite the

inventors' open acknowledgements, discussed above, of uncertainty and their internal struggles and frustrations to get CRISPR to work in eukaryotes. *See, e.g.*, Appx05908.

B. UC's Proposed Count Is Rejected by the PTAB When It Institutes the Interference

On January 11, 2016, the PTAB declared Interference No. 106,048 between UC's pending application and Broad's issued patents. Appx00081-00097. It defined the count to be a method of using the CRISPR-Cas9 system in *eukaryotic* cells. Appx00090-00091; Appx08269, Appx08297-08298. It then identified all of the more than 400 claims in Broad's 12 patents, as well as the allowed claims in UC's '859 application, as corresponding to the Count. Appx00091-00093.

C. UC's Premise for the Interference Unravels During The Interference and the PTAB Grants Broad's Motion 2 Finding No Interference-in-Fact

The interference revealed that the fundamental premise of UC's suggestion of interference was fatally flawed. The record revealed that not only would a POSA have had no reasonable expectation of successfully engineering CRISPR for eukaryotes after Jinek 2012, but further, neither did UC's inventors nor UC's expert. *See, e.g.*, Appx04797; Appx05908. The PTAB granted Broad's Motion 2 for judgment of no interference-in-fact based on its finding of no reasonable expectation of success. Appx00049.

The PTAB considered and judged the relative weight of the evidence in the five categories discussed above. *See* Appx00001-00051. Based on its evaluation of the evidence, including credibility of witnesses, the PTAB made the affirmative finding that "***contemporaneous statements*** cited by both parties persuade us that one of ordinary skill in the art ***would not have reasonably expected success*** before experiments in eukaryotic cells were done." Appx00023.

The PTAB also found that the "differences between prokaryotic and eukaryotic systems would make use of CRISPR-Cas9 in a eukaryotic system unpredictable even though it was known to work endogenously in prokaryotes." Appx00029-00030. The PTAB also considered the parties' evidence of prior attempts to adapt prokaryotic systems for use in eukaryotes and found the RNA-based examples to be more pertinent. Appx00034-00044. The PTAB explained that those systems "each require a unique set of conditions, tailored to the particular system, to achieve any level of success in eukaryotic cells." Appx00039.

The PTAB also considered but rejected UC's argument that the allegedly "immediate" success realized by other allegedly independent research groups evidenced a reasonable expectation of success. Appx00023-00025. The PTAB factually determined that the interest expressed by a number of groups demonstrated a motivation to adapt CRISPR-Cas9 for eukaryotic cells, but did not demonstrate an expectation of success. Appx00023.

The PTAB concluded with the factual finding that the "preponderance of the evidence, including the contemporaneous statements of the inventors and others in the field, as well as the knowledge of ordinarily skilled artisans, demonstrates that one of ordinary skill would not have had a reasonable expectation of success that CRISPR-Cas9 could be used in a eukaryotic cell." Appx00048–00049. Because it found no interference-in-fact, the PTAB terminated the interference.

SUMMARY OF ARGUMENT

The PTAB's decision should be affirmed because substantial evidence supports its fact finding that a POSA in 2012 would not have had a reasonable expectation of success in engineering CRISPR-Cas9 systems to function in eukaryotic cells. The PTAB record includes five distinct categories of evidence supporting that determination—each of which individually constitutes substantial evidence and which together provide compelling evidence.

UC has not rebutted the substantial evidence in any of the categories. Instead, UC simply disputes the PTAB's factual interpretations, credibility determinations, inferences drawn from the evidence, and the relative weight the PTAB gave to different pieces of evidence. In short, UC improperly asks this Court to redo the PTAB's fact finding, rather than to judge whether substantial evidence supported the finding.

Because UC cannot meet the standard of review—there is substantial evidence that supports the PTAB's finding—UC contends that the PTAB committed three legal errors and failed to consider UC's evidence and arguments in two areas. None of these contentions have any merit.

UC's first claim of legal error has no merit. *See* App.Br. at 27-30. UC asserts that the PTAB erroneously demanded evidence of "certainty" of success, but the PTAB's decision shows that it did no such thing.

UC's second claim of legal error is that the PTAB erroneously required, as a matter of law, the prior art to teach "*specific instructions*" to deliver success. App.Br. at 31-36. However, following this Court's precedent, the PTAB imposed no *legal* requirement for specific instructions, and instead evaluated expectation of success *based on the facts* of this case. *See* Appx00025-00046.

UC's third claim of legal error is that the PTAB did not consider the Kim patent application as available prior art. App.Br. at 44-47. However, the PTAB correctly ruled that consideration of such secret—and potentially interfering (according to UC) in its own right—art is not appropriate for the interference-in-fact inquiry. Appx00046-00048. Regardless, the Kim application is not §102(e) prior art to Broad's invention. Broad previously antedated the October 23, 2012, Kim application during prosecution based on the undisputed October 5, 2012, submission date of the Broad inventors' Cong 2013 paper. Appx00308.

UC incorrectly asserts that the PTAB failed to consider UC's evidence and arguments on simultaneous invention as secondary indicia of obviousness. App.Br. at 43-47. According to UC, the PTAB supposedly held, as a matter of law, that simultaneous invention can never show reasonable expectation of success. The PTAB made no such ruling and did not even address the issue because UC did not raise it below. The PTAB did not reject the underlying evidence relating to other research groups as a matter of law; rather, the PTAB analyzed the evidence, on the merits, and found that it did not support a finding of a reasonable expectation of success. Appx00023-00025.

Finally, UC asserts that the PTAB failed to consider prior art dated after December 12, 2012, in assessing interference-in-fact, but UC presented no such prior art in its opposition to Broad's motion. App.Br. at 61-64.; Appx00231-00295.

STANDARD OF REVIEW

"In order for an interference-in-fact to exist" between claims of non-identical scope, the PTAB must find "two-way" unpatentability—"invention A must anticipate or make obvious invention B, and invention B must anticipate or make obvious invention A." *Noelle v. Lederman*, 355 F.3d 1343, 1350-51 (Fed. Cir. 2004)(quoting *Eli Lilly & Co. v. Bd. of Regents of Uni. Of Wash.*, 334 F.3d 1264, 1268 (Fed. Cir. 2003)). An obviousness determination requires a factual

finding "that the skilled artisan would have had a reasonable expectation of success." *In re Stepan Co.*, 868 F.3d 1342, 1345-46 (Fed. Cir. 2017); *Ariosa Diagnostics v. Verinata Health, Inc*., 805 F.3d 1359, 1366 (Fed. Cir. 2015).

This Court reviews the PTAB's legal determinations *de novo* and its factual findings for substantial evidence. *Ariosa*, 805 F.3d at 1366; *In re Huang*, 100 F.3d 135, 138 (Fed. Cir. 1996). Substantial evidence "means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938). The PTAB's decision must be affirmed so long as the evidence below amounts to "more than a mere scintilla of evidence." *In re Warsaw Orthopedic, Inc*., 832 F.3d 1327, 1329 (Fed. Cir. 2016). "[T]he possibility of drawing two inconsistent conclusions from the evidence does not prevent an administrative agency's finding from being supported by substantial evidence." *In re Gartside*, 203 F.3d. 1305, 1312 (Fed. Cir. 2000)(citing *Consolo v. Federal Maritime Comm'n*, 383 U.S. 607, 620 (1966)).

ARGUMENT

I. SUBSTANTIAL EVIDENCE SUPPORTS THE PTAB'S FACTUAL FINDING THAT A POSA WOULD NOT HAVE HAD A REASONABLE EXPECTATION OF SUCCESS

As a factual prerequisite to any obviousness determination, a person of ordinary skill in the art must have had a reasonable expectation of achieving success in making the claimed invention. *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1344 (Fed. Cir. 2013). An evaluation of reasonable expectation of success "must be narrowly tailored to the facts of each individual case." *Pfizer, Inc. v. Apotex, Inc*., 480 F.3d 1348, 1366 (Fed. Cir. 2007). Facts relevant to this inquiry include "the characteristics of the science or technology, its state of advance, the nature of the known choices, the specificity or generality of the prior art, and the predictability of results in the area of interest." *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008).

Here, the PTAB methodically considered and assessed such evidence and found that, in 2012, a POSA would not have had a reasonable expectation of success in engineering CRISPR-Cas9 to function in eukaryotic cells. Appx00002.

The PTAB's decision addressed five categories of evidence in support of its finding of no reasonable expectation of success, each of which—by itself—would provide far more than a mere scintilla of evidence. To prevail on appeal, UC

needed to demonstrate that each one of these five independent categories of evidence should be accorded no weight whatsoever. UC failed to do so.

A. Category 1: Contemporaneous Statements of the Inventors Support the PTAB's Finding

The first category of evidence includes contemporaneous public statements of the inventors regarding their actual expectations after the publication of Jinek 2012. Broad submitted evidence of contemporaneous statements by UC's inventors acknowledging their doubts and frustrations about engineering CRISPR-Cas9 systems to function in eukaryotic cells. Appx00204; Appx00213-00214. The PTAB weighed these statements against other inventor statements cited by UC in an attempt to show alleged expectation of success. Appx00013-00017. The PTAB found the statements cited by UC simply identified the "potential," "promising" "possibility" of CRISPR "theoretically" working in eukaryotes, but did not establish any basis for expecting success. *See* Appx04799; Appx04803; Appx00014-00017. Based on its analysis of this evidence, the PTAB found "the contemporaneous statements cited by both parties persuade us that one of ordinary skill in the art would not have reasonably expected success before experiments in eukaryotic cells were done." Appx00023.

UC now complains that "the PTAB placed enormous weight on the statements by [UC inventor] Dr. Doudna" and that the PTAB "disregarded abundant evidence of actual success in the field in favor of post-hoc inventor

statements." App.Br. at 34, 60. But, a plain reading of the PTAB's decision makes clear that the PTAB considered all the evidence, including the evidence of alleged success. Appx00025-00026; Appx00045-00046. UC's real argument is that its alleged *inferential evidence* of an expectation of success (based on later success) should have been given greater weight than the *direct evidence* of what skilled artisans thought and said before they conducted the experiments and the results were known. But this Court, of course, cannot reweigh this evidence. *In re NTP, Inc.*, 654 F.3d 1279, 1292-93 (Fed. Cir. 2011).

Moreover, the "significant weight" given to the inventors' statements is entirely consistent with this Court's instruction that "[c]ontemporaneous evidence of what skilled artisans thought at the time of the invention help[s] inform [the] inquiry into whether the expectation of success was reasonable." *NanKwest, Inc. v. Lee*, 686 Fed. Appx. 864, 875 (Fed. Cir. 2017). As the PTAB noted, "if the inventors themselves were uncertain, it seems that ordinarily skilled artisans would have been even more uncertain." Appx00017.

UC also argues that the PTAB's "characterization [of the inventors' statements] is unfair." App.Br. at 57-61. UC argues, as it did before the PTAB, that the inventors' statements merely indicate that "confirmatory experimentation was necessary." App.Br. at 53-54. But, the PTAB considered these exact

arguments and found that "none of them express[ed] an expectation that such results would be successful." Appx00017.

In response, UC again falls back on the inventors' reports of later success. App.Br. at 58-60. Yet, even after obtaining successful results, and with the benefit of hindsight, UC's inventors clearly stated that prior to the experiments, "it was not known whether [CRISPR-Cas9] would function in eukaryotic cells," "there was a problem[,] [w]e weren't sure if CRISPR-Cas9 would work in eukaryotes," and implementing CRISPR in eukaryotes was a "huge bottleneck." Appx04756-05457; Appx05880; Appx05911.

Finally, UC seeks to neutralize the evidence of its inventors' statements by arguing that "the only conclusion the PTAB ultimately drew from the statements" was that they did not indicate an expectation of success one way or another. App.Br. at 58. Here, UC simply misstates the record; the PTAB unequivocally found that "*contemporaneous statements* cited by both parties persuade us that one of ordinary skill in the art *would not have reasonably expected success* before experiments in eukaryotic cells were done." Appx00023.

The evidence of the inventors' contemporaneous statements constitutes substantial evidence in support of the PTAB's finding. UC failed to rebut this evidence.

B. Category 2: Contemporaneous Statements of UC's Expert Support the PTAB's Finding

The second category of evidence consists of the contemporaneous statements of skilled artisans after the publication of Jinek 2012—specifically, the statements of UC's expert, Dr. Carroll, in a September 2012 article. Appx00017-00019; *see* Appx04796-04797. Dr. Carroll's statements were highly probative because they specifically addressed the impact (or lack thereof) of the *in vitro* experiments described in Jinek 2012—what UC claims was the linchpin of success by other groups in implementing CRISPR in eukaryotic cells. Appx04795-04797.

Instead of confirming UC's linchpin theory, Dr. Carroll published a litany of concerns why, despite the disclosures provided by the Jinek 2012 paper, the bacterial CRISPR-Cas9 system could not reasonably be expected to be successfully adapted for use in eukaryotic cells. Appx04797. For example, Dr. Carroll explained that CRISPR-Cas9 might be degraded by nucleases in the cell; that toxicity could result from introducing it into eukaryotes; and that "[t]here is no guarantee that Cas9 will work effectively on a chromatin target or that the required DNA-RNA hybrid can be stabilized in that context…." *Id*. Based on these concerns, Dr. Carroll repeatedly expressed doubt that CRISPR-Cas9 would work in eukaryotes, and instead observed that "[w]hether the CRISPR system will provide the next generation of targetable cleavage reagents *remains to be seen*…." *Id*. As he aptly concluded in his paper, "[o]nly attempts to apply the system in

eukaryotes will address these concerns." Appx04797; *see also* Appx00017-00019. It is hard to conceive of a more clear expression that there was no "reasonable expectation of success."

After an extensive analysis of Dr. Carroll's 2012 article and his testimony in the interference, the PTAB found that "we do not discern any expectation that it would work before results of the actual studies were known" and "the only conclusion we draw from Dr. Carroll's statement [in 2012] is that at the time, he did not have a reasonable expectation that the system would work." Appx00018-00019. In so doing, the PTAB properly exercised its discretion in accepting the contemporaneous evidence from 2012 over Dr. Carroll's conflicting testimony as an expert witness. *See Velander v. Garner*, 348 F.3d 1359, 1371 (Fed. Cir. 2003). This is a classic example of a fact-finder assessing credibility; it should not be disturbed on appeal.

Dr. Carroll's 2012 article also illustrated the limited value of the allegedly "well-known conventional techniques" UC so heavily relies on in its brief. UC asserts that Dr. Carroll's 2012 paper "described in detail how those very techniques could be used to implement CRISPR-Cas9 in eukaryotes" and that he "accurately predicted precisely how CRISPR-Cas9 could be implemented in eukaryotic cells, providing detailed instructions." App.Br. at 33, 61. But Dr. Carroll actually makes no such prediction in the article, nor does he provide any detailed instructions.

Instead, he explains the uncertainty surrounding those same techniques, stating, for example, that a key issue "is how delivery to the target cells or organisms will be accomplished" and notes that "direct injection" of RNA has been used in embryos of some animals, but makes no prediction of whether that technique would work for CRISPR. Appx04797.

Dr. Carroll's 2012 article documenting his contemporaneous doubts after considering UC's Jinek 2012 paper—with full knowledge of the "well-known conventional techniques" is highly probative and compelling evidence on the question of reasonable expectation of success. *See Noelle*, 355 F.3d at 1353(relying on state of art as described by expert witness to find no reasonable expectation of success). Because this substantial evidence supports the PTAB's finding of no reasonable expectation of success, it too warrants affirmance.

C. Category 3: Substantial Evidence Relating to Work by Research Groups after Jinek 2012 Supports the PTAB's Finding

The third category of evidence relates to the work of research groups after Jinek 2012, which UC advanced as evidence that a POSA would have had a reasonable expectation of success in 2012. Appx0023-0025. Before the PTAB and again here, UC asks this Court to infer that a POSA would have had a reasonable expectation of success from the fact that other, supposedly independent groups began work to engineer CRISPR to work in eukaryotes in 2012 and eventually achieved some success, albeit after Broad. In effect, UC is asking this

Court to make this inference anew from the evidence, and find it more probative than the actual, contemporaneous views expressed by UC's inventors and expert, and by other individuals with skills far above those of a POSA.

The PTAB rejected UC's argument below, finding that while the evidence showed motivation, it did not show that a POSA would have had an "*expectation* of success before the results from these experiments were known." Appx00023. Consistent with the PTAB's finding, the evidence showed that even highly skilled researchers in other groups considered the results surprising and to represent a major advance in the field, contrary to UC's current assertion that this was simply an expected result from the exercise of routine skill. Appx5908; Appx00023-00024. For example, UC relies on the eukaryotic CRISPR work of three researchers, Drs. Church, Kim, and Joung, as supposedly evidencing an expectation of success. However, each sought patent protection for their respective eukaryotic work, reflecting their belief that the work was *not routine* and *not obvious*, but rather inventive. *See* Appx05180-05199.

UC also relies on the later success of its own inventors as evidencing a pre-experiment expectation of success. App.Br. at 39-40. But the contemporaneous evidence shows the opposite. As the PTAB noted, one UC inventor stated that getting CRISPR to work in human cells, would be "***a profound discovery***," not an expected and unsurprising result. Appx05908. Thus, the PTAB properly

determined that the evidence showed motivation, but not an expectation of success. Appx00023.

Moreover, UC's expert testified that each of the lead scientists on the submissions identified by UC—Drs. Zhang, Church, Hwang, and Kim—were of *extraordinary* skill. Appx08430-08433; Appx00307-00308; *see also* Appx08586-08585, ¶¶11.112-11.111(Broad's expert testifying to same). In fact, they were named as inventors on earlier gene editing inventions (*e.g.*, TALEN-based) systems by 2012. *See, e.g.*, Appx09322-09409; Appx09410-09495; Appx09496-09512. Similarly, as UC admitted below—and the PTAB agreed—the UC inventors were not persons of ordinary skill. Appx00017. Thus, even if any of these extraordinarily skilled scientists had an expectation of success, that would not be evidence that a POSA would likewise have had a reasonable expectation of success.

In fact, the reaction of the scientific community to the Cong 2013 article demonstrates that POSAs considered the adaption of CRISPR for eukaryotic cells exciting groundbreaking work, not merely routine, expected results. The Cong 2013 paper became the most cited CRISPR article. Appx05493-05494, ¶2.14.

The PTAB thus correctly rejected UC's attempt to convert the efforts of highly skilled scientists to engineer CRISPR to work in eukaryotic cells into an *inference* that a POSA would have had an expectation of success. On the contrary,

substantial evidence from this category supported the PTAB's finding regarding no reasonable expectation of success, especially for a POSA.

D. Category 4: Substantial Evidence Relating to the Differences Between Prokaryotic and Eukaryotic Cells Supports the PTAB's Finding

The fourth category of evidence relates to the significant differences between prokaryotic and eukaryotic cells and the resulting reasons why a natural bacterial system for prokaryotic immunity might not function to edit DNA in eukaryotic cells. Appx00029-00034. Both parties' experts opined that the differences between the two types of cells would have raised numerous questions that a skilled person could not answer in 2012 absent experiments successfully performed in eukaryotic cells. Appx05524-05535 ¶¶6.5-6.35; Appx04797; *see also Noelle*, 355 F.3d at 1353.

Broad's expert, Dr. Simons, identified concerns relating to the nature of the chromatin structure of eukaryotic DNA, potential instability and degradation of the CRISPR-Cas9 complex in the eukaryotic environment, potential toxicity, and other variables, such as protein folding and intercellular ion concentrations, that would each contribute to the unpredictability of using prokaryotic systems in eukaryotes in 2012. Appx05527-05543, ¶¶6.13-6.60; Appx09304-09309(teaching degradation of misfolded proteins); Appx09297-09303(teaching toxicity of prokaryotic protein Cre in eukaryotic environments); *see also* Appx00029-00031. Dr. Carroll, in his

2012 article, identified many of these same concerns, including the chromatin structure, instability, degradation, and toxicity. *See* Appx04797. These concerns implicated several obstacles, choices, and variables that would need to be identified and resolved in order to successfully implement CRISPR in eukaryotes. *See In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

To counter this extensive evidentiary record, UC relies on the PTAB's recognition that some techniques that might be tried as part of an effort to engineer CRISPR-Cas9 to function in eukaryotic cells (the codon optimization, direct injection, and targeting techniques) were routine and well-known. App.Br. at 32, 35, 49-50; *see* Appx00035. Based solely on this observation, UC argues "[t]he prior art provided ample guidance concerning a finite number of approaches to applying CRISPR-Cas9 in eukaryotes" and thus "there was no need for a skilled artisan to 'vary all the parameters' or 'explore a new technology.'" App.Br. at 49-50. However, UC identifies only three of "a number of techniques" that a POSA could select from to begin engineering prokaryotic systems to operate in eukaryotes, without any identification of the other required techniques and without any indication that these techniques would cause the adaptation of CRISPR in eukaryotic cells to be successful. *See* Appx08764-08765.

More importantly, none of the three techniques UC focuses on address the concerns about differences between prokaryotic and eukaryotic cells that might

prevent CRISPR-Cas9 from functioning, such as the obstacles of chromatin, instability, degradation, and toxicity. Appx05533-05535, ¶¶6.28-6.35; Appx04797. Tellingly, Dr. Carroll in 2012 published his doubts and concerns with full knowledge of the three techniques identified by UC. Appx04797. For example, Dr. Carroll identified concerns that, even if delivery could be achieved using one of those techniques, the chromatin structure could be an insurmountable obstacle in implementing CRISPR-Cas9 in eukaryotes. Appx09111-09112; *see also* Appx00030; Appx05533, ¶6.29. Similarly, the delivery techniques would not answer the questions about assembly, degradation or toxicity.

UC argues that, by 2012, uncertainties regarding chromatin "had long been overcome" based on four prokaryotic protein examples. App.Br. at 53, n.14. The PTAB found that argument "to be less persuasive" because Dr. Carroll's August 2012 article identified chromatin as a concern for implementation of CRISPR systems in eukaryotic cells. Appx00033-00034. Further, Dr. Carroll admitted during deposition that those examples merely indicated that "the next prokaryotic protein that somebody was studying *might or might not* work in a chromatin context." Appx09111; *see also* Appx00034. Weighing this evidence, the PTAB found that these examples "would not have provided those of ordinary skill with a reasonable expectation that any of the thousands of prokaryotic system[s],

including the CRISPR-Cas9 system, would work in the context of eukaryotic chromatin." Appx00034.

Next, UC argues that "the PTAB focused on *potential* obstacles that could *theoretically* have affected CRISPR-Cas9, while ignoring what actually happened." App.Br. at 54. UC argues that "potential toxicity" would not have been "*actual* concerns to skilled artisans considering applying CRISPR-Cas9." *Id*. However, Dr. Carroll's 2012 article identified potential toxicity as an actual concern. Appx04797(referring to "the potential side effect of inducing breaks at multiple regions of transcription"). Dr. Carroll's article also identified concerns over two other potential obstacles that the PTAB noted, including whether the "required DNA–RNA hybrid" could be stabilized in the eukaryotic cell and whether the natural mechanisms in a eukaryotic cell for "removal of RNA primers during DNA replication" would destroy the CRISPR RNA. *Id*.

The PTAB properly found that the multitude of variables and concerns would bear heavily on whether POSA would have had a reasonable expectation of success of using CRISPR-Cas9 in eukaryotic cells. Appx00028-00034; *Institut Pasteur*, 738 F.3d at 1345-46. Thus, this fourth category of evidence constitutes further substantial evidence in support of the PTAB's finding, which UC has failed to rebut.

E. Category 5: Substantial Evidence Relating to Prior Art Attempts to Adapt Prokaryotic Systems to Eukaryotes Supports the PTAB's Finding

The fifth category of evidence relates to the failures and obstacles encountered in prior attempts to adapt other prokaryotic systems to function in eukaryotes. Appx00035-00046. Broad presented evidence of three such systems: riboswitches, ribozymes, and Group II introns, all of which skilled artisans struggled to implement in eukaryotic cells. Appx00211-00213. Each illustrated that existence of conventional techniques did not suffice to provide success and each "required specific tailoring of conditions." Appx00036-00039. Based on this evidence, the PTAB determined that "one skilled in the art would have expected that CRISPR-Cas9 would have also required its own set of unique conditions." Appx00039.

The Group II introns are the most analogous system to CRISPR-Cas9; both systems contain an RNA component complexed with a protein component. Appx00038. Despite 16 years of effort, and with full knowledge of the conventional techniques that UC cites on appeal, researchers were not able to implement Group II Introns in natural eukaryotic cells. Appx08653-08656, ¶¶1.45-1.51; Appx05915. UC noted that Group II Introns were eventually implemented in one circumstance; but, that required altering a eukaryotic cell to contain an excessive level of magnesium, effectively creating a biologic test tube.

Appx09222-09223; Appx5915. Such evidence does not show success, and Dr. Carroll admitted that such a system would not be of use as a genetic engineering tool. Appx09225-09226. Moreover, the limited success achieved by that particularized solution required 16 years of research efforts, which would hardly instill a POSA with a reasonable expectation of success regarding another prokaryotic protein-RNA based system. Appx00038-00039.

The unique obstacles researchers encountered with Group II introns, as well as with ribozymes and riboswitches, along with the necessity of developing tailored sets of solutions to achieve any success with each system, illustrates that the prior art provided, at most, only general guidance to a POSA that would not have been sufficient to establish a reasonable expectation of success in implementing the novel CRISPR technology in eukaryotes. *See Kubin*, 561 F.3d at 1359; *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

UC relies on a handful of other prokaryotic examples that supposedly would have provided the guidance necessary to give POSA an expectation of success. App.Br. at 31-32. But none of UC's examples involve systems analogous to CRISPR-Cas9 and are therefore not relevant. *See Velander*, 348 F.3d at 1374(finding an expectation of success based on prior successes with "*proteins with similar characteristics*"). For example, UC relied on the prokaryotic proteins, but the PTAB credited Dr. Simons's unrebutted testimony that the smaller, less

complex nature of those prokaryotic proteins, such as Cre, would not have informed the expectation of success with the larger CRISPR-Cas9 complex. Appx05546, ¶¶6.67-6.68; Appx04870; Appx04856; *see also* Appx00042-00043. And none of them included an RNA component or an RNA-protein complex as in the CRISPR-Cas9 system.

Likewise, the PTAB also evaluated UC's evidence surrounding the prior art ZFN or TALEN gene editing systems. Appx00039-00041. UC admitted that the ZFN and TALEN systems have origins in eukaryotic domains, while CRISPR-Cas9 is a strictly prokaryotic system. *See* Appx08258-08261. Based on this undisputed difference, Dr. Simons testified that the experience with ZFNs and TALENs would not bear on the use of CRISPR-Cas9 in eukaryotes. Appx05546-05547, ¶¶6.69-6.72; *see also* Appx00040. Dr. Carroll noted the same difference in his August 2012 article. Appx04796-04797. The PTAB weighed this evidence and found that the ZFN and TALEN systems were not "analogous or relevant to the question of whether CRISPR-Cas9 would work in eukaryotic cells." Appx00041.

UC also argues that the PTAB made its determinations "without any analysis" and that the PTAB erred by analyzing these examples "in isolation." App.Br. at 55-56. UC ignores that the PTAB extensively analyzed the unique difficulties encountered in engineering each of these prokaryotic protein-RNA

complexes to operate in eukaryotes. Appx00036-00044. The PTAB properly determined that each prior art system "required specific tailoring of conditions" to have any success in eukaryotic cells. Appx00039.

Thus, this fifth category of evidence constitutes further substantial evidence supporting the PTAB's finding, which UC has failed to rebut.

* * * *

Each of the five categories of evidence—even alone—provides substantial evidence in support of the PTAB's finding and UC has failed to rebut any of them. Taken together, Broad respectfully submits that this evidence compels affirmance.

II. UC ERRONEOUSLY ASSERTS THAT THE PTAB COMMITTED LEGAL ERRORS IN ITS INTERFERENCE-IN-FACT ANALYSIS

In the face of the substantial evidence supporting the PTAB's fact finding of no reasonable expectation of success, UC argues that the PTAB committed three legal errors in its interference-in-fact analysis. First, UC claims that the PTAB applied a "certainty" standard for assessing expectation of success. App.Br. at 27-30. Second, UC claims that the PTAB required, as a matter of law, the prior art to teach "*specific instructions*" to deliver success. App.Br. at 31-36. Third, UC claims that the PTAB improperly rejected the Kim Application as available prior art. App.Br. at 42-47. None of UC's legal arguments has any merit.

A. UC Erroneously Claims that the PTAB Applied an Incorrect Legal Standard Requiring Certainty of Success

UC asserts the PTAB applied an incorrect legal standard by requiring pre-experimentation "certainty" to find a reasonable expectation of success. App.Br. at 22. But the PTAB did no such thing. The PTAB stated the opposite, noting that "the case law makes clear that a *certainty* of success is not required." Appx00012. The PTAB further noted that "[o]bviousness does not require absolute predictability of success … [A]ll that is required is a reasonable expectation of success." Appx00012-00013. The PTAB consistently applied a reasonable expectation standard, not a certainty standard, as UC argues. *See, e.g.,* Appx00017; Appx00032; Appx00039.

For example, when evaluating Dr. Carroll's contemporaneous statements, the PTAB explicitly acknowledged that "there need not be absolute predictability for a conclusion of obviousness." Appx00019. The PTAB observed that "Dr. Carroll's statement highlights some specific reasons why the CRISPR-Cas9 system might fail in eukaryotes" and concluded that Dr. Carroll "did not have a *reasonable expectation* that the system would work" in 2012. *Id*. The PTAB also found significant UC's failure to present any contemporaneous evidence from those in the field "that the system was 'expected' to work or that it ***would 'likely' work***." Appx00023. The reasoning employed by the PTAB demonstrates that it

was not demanding certainty, but only a reasonable expectation of success consistent with the law.

The PTAB also properly rejected UC's argument that a researcher's decision to undertake experiments automatically proves an expectation of success. Appx00245("These groups would not have undertaken the use of UC's Type-II CRISPR-Cas system in eukaryotic cells unless there was sufficient motivation and expectation of success."). The PTAB noted that "[i]nstead of creating a presumption of obviousness when researchers attempt experiments to advance a field," that "[e]ach case must be decided in its particular context." Appx00025(quoting *Abbott*, 544 F.3d at 1352).

The PTAB noted that under *KSR*, a reasonable expectation of success can exist where "there are a finite number of identified, predictable solutions" which "leads to the anticipated success." Appx00025(quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)). Focusing on the requirement for "anticipated" success, the PTAB observed that the fact that multiple groups conducted successful experiments does not mean that "an ordinary skilled artisan would have necessarily expected these experiments to be successful." Appx00024. In the context of this field, the PTAB made the fact finding, citing the contemporaneous statements of the inventors and skilled artisans, that a POSA would not have reasonably expected success before experiments in eukaryotic cells were done. Appx00023. UC

provided no evidence of "anticipated success" and the PTAB agreed with Broad's evidence to the contrary.

B. UC Incorrectly Claims that the PTAB Applied a Legal Standard Requiring Specific Instructions

The second legal error UC claims is that the PTAB improperly required, as a matter of law, that the prior art teach "*specific instructions*" for this system to be successfully employed in eukaryotic cells. App.Br. at 22-23. UC further asserts that the PTAB should have presumed an expectation of success because actual success was later achieved using supposed conventional techniques. App.Br. at 30. UC's arguments erroneously portray the PTAB's decision and misstate the law.

Contrary to UC's argument, the PTAB never held that "specialized instructions" are required as a matter of law. Rather, UC is improperly attempting to recast a PTAB fact finding relating to the prior art into a statement of law. In particular, the PTAB found that, based on the evidence of prior experiences with RNA-based systems, a POSA would have needed specialized instructions to have an expectation of success with respect to a eukaryotic CRISPR system:

> Instead, the evidence cited by Broad shows that because each of the riboswitch, ribozyme, and Group II intron RNA based systems required specific tailoring of conditions, one skilled in the art would have expected that the CRISPR-Cas9 system would have also required its own set of unique conditions.

Appx00039.

The PTAB made this fact finding after surveying eleven Federal Circuit cases that analyzed reasonable expectation of success in different situations. Appx00025-00028. The PTAB noted that in some situations, general instructions sufficed when, for example, prior success was achieved with similar systems. Appx00028. The PTAB noted, for example, that in *Velander*, 348 F.3d at 1379, a reasonable expectation of success "was found because all of the elements were known in the prior art and it was known that several other proteins had been produced in a similar way." Appx00026. Similarly, in *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014), a reasonable expectation of success was found where the relevant "technology had become fairly reliable and had produced consistent results." Appx00026.

The PTAB contrasted those examples with situations where the "availability of only generalized instructions and evidence of failures with similar subject matter have indicated [no reasonable expectation of success]." Appx00028. The PTAB noted that in *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003), no reasonable expectation of success was found "because the prior art reported failure with other viruses." Appx00027.

After its review of the case law, the PTAB addressed the factual inquiries of whether "there were instructions in the prior art that would be specifically relevant to CRISPR-Cas9" and also "whether there are examples in the prior art of the

success or failure of similar systems." Appx00028-00029. The PTAB found that each relevant prior art attempt to adapt a similar prokaryotic system to function in a eukaryotic cell encountered different kinds of obstacles and each required a unique set of modifications to achieve even limited success. Appx00035-00044. Accordingly, the PTAB made the fact finding that a POSA would have expected CRISPR to require its own unique set of solutions. *Id*.

The PTAB also properly rejected UC's argument that when success is eventually achieved using "well-known conventional techniques," the claimed invention must be found to have been obvious, regardless of "*ex ante* uncertainty about whether such routine efforts will succeed." App.Br. at 30. Contrary to UC's argument, "*KSR* did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try,' without considering the nature of the science or technology." *Abbott*, 544 F.3d at 1352.

An obviousness determination requires finding "that the skilled artisan would have had a reasonable expectation of success." *Stepan*, 868 F.3d at 1345. Thus, as UC admits, even when the prior art teaches a "finite number of approaches," there still must be "*reason to anticipate success*." App.Br. at 29. The reference in *KSR* to "predictable solutions" and "anticipated success" accords this Court's "longstanding focus on whether a person of ordinary skill in the art

would, at the relevant time, have had a 'reasonable expectation of success.'" *Institut Pasteur*, 738 F.3d at 1344. Thus, even when conventional or routine techniques are supposedly available,[3] the fundamental inquiry remains the same—whether a POSA would have had a reasonable expectation of success in view of the art, including those techniques.

Finally, even if UC's argument were correct, it would *not* apply to the first and second categories of evidence—the contemporaneous statements of the inventors and skilled artisans—which the PTAB analyzed without imposing any requirement of "specific instructions" in the prior art. Rather, those contemporaneous statements were direct evidence of the expectations of the inventors and skilled artisans at the relevant time who plainly had knowledge of the conventional techniques known in the art. That evidence of contemporaneous beliefs independently and persuasively support the PTAB's conclusion that there was no expectation of success in 2012, and directly refutes UC's proposition that a pre-experiment reasonable expectation of success existed simply because actual success was later achieved through the use of allegedly conventional techniques.

[3] Contrary to UC's implications, the PTAB *did not* make any factual finding that "conventional techniques" were used to make the invention. Rather, when the PTAB discussed the alleged "conventional techniques," it was explaining UC's argument, not adopting that position. *See* Appx00044.

C. UC Incorrectly Asserts the PTAB Committed Legal Error by Not Considering the Unpublished Kim Application as Prior Art for the Interference-in-fact Analysis

UC's third legal argument is that the PTAB committed error by not considering the Kim Application to be available prior art under 35 U.S.C. §102(e) for purposes of the interference-in-fact analysis. App.Br. at 42-47. As discussed below, however, the PTAB properly rejected UC's attempt to use the putatively inventive—and potentially interfering in their own right (according to UC)—activities of an *unrelated third party* to somehow qualify UC to participate in an interference with Broad. Appx00046-00048. In addition, the Kim Application does not qualify as §102(e) prior art because its October 23, 2012, filing date does not come before Broad's invention dates, as confirmed by the October 5, 2012, submission date of the Broad inventors' seminal Cong 2013 *Science* paper. Appx04686.

1. The Kim Application Is Not Within the Knowledge of a POSA in 2012 for Purposes of an Interference-in-Fact Inquiry

UC does not dispute that the Kim Application was not public in 2012. UC therefore relies on §102(e), which provides that a patent application, which remains a secret disclosure at the time of its filing, can become retroactive prior art upon its subsequent publication. UC cites *Hazeltine Research, Inc. v. Brenner*, 382 U.S. 252, 254-55 (1965), but that case addressed the use of such art for an

invalidity analysis, not an interference-in-fact analysis. Indeed, the *Hazeltine* Court expressly pointed out that priority was not at issue in that case (*i.e.*, the §102(e) reference was not potentially interfering subject matter).[4] *Hazeltine*, 382 U.S. at 256("There is . . . no question of priority of invention before us.").

UC cites no case supporting its argument that secret prior art under §102(e) is to be considered when assessing interference-in-fact.[5] The PTAB correctly ruled that consideration of such secret; and (according to UC) potentially interfering, prior art is not appropriate when considering interference-in-fact. Appx00046-00048. The purpose of a patent interference is "to determine whether two parties claim the same patentable invention, and if so, who under the law is entitled to priority of invention." *Noelle v. Lederman,* 355 F.3d 1343, 1350 (Fed. Cir. 2004). The UC inventors cannot reasonably assert that they invented the same subject matter as Broad based on secret prior art not available to them.

Indeed, in the analogous context of inventorship disputes under 35 U.S.C. §256, this Court recently ruled that secret prior art under §102(e) is *not* to be

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[4] UC cites *In re Bartfield*, 925 F.2d 1450, 1451 n.4 (Fed. Cir. 1991), which concerned an invalidity determination, not an interference-in-fact determination. App.Br. at 47.

[5] UC argues that for an interference-in-fact inquiry, one must consider the "universe of prior art," citing *Alarm.com v. iControl Networks, Inc*., 2015 WL 1871503, at *24 (PTAB Mar. 31, 2015) and *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1167 (Fed. Cir. 2006). App.Br. at 46. Neither case addresses the question of using secret, potentially interfering prior art under §102(e).

considered as available prior art. *CardiAQ Valve Tech. v. NeoVasc*, No. 2017-1302, 2017 WL 3833209 (Fed. Cir. Sept. 1, 2017). In *CardiAQ*, the district court added two would-be inventors as joint inventors on an issued patent. *Id.* On appeal, the original patent owner asserted that the two would-be inventors contributed nothing more than what was disclosed in a publication indisputably meeting the requirements of §102(e). *Id.* at 3.

This Court agreed with the general proposition that "[a] contribution of *information in the prior art* cannot give rise to joint inventorship because it is not a contribution to conception." *CardiAQ*, 2017 WL 3833209, at *3. The Court noted, however, that "Neovasc has not pointed to any invocation of that proposition in a case involving secret, § 102(e) art," and ruled that such secret prior art should not be considered for purposes of determining inventorship. *Id*. The Court instead restricted the analysis to *public* prior art that "could readily have been acquired by the named inventor independently." *Id.*

The same principle applies here. UC should not be permitted to use secret, potentially interfering, prior art, unavailable to the UC inventors to fill in the gap between its claimed invention and Broad's claimed invention, to assert UC claims the "same patentable invention" as Broad.

Contrary to UC's position, not all categories of prior art under §102 are appropriate or relevant to an interference-in-fact inquiry. For example, secret prior

art of a third party's potentially interfering activities under §102(g) would not be appropriate for such an inquiry between two other parties. Rather, such a third party could potentially have its own interfering claims that might be placed in interference, but it would be illogical to permit one party to continue in the interference based on the putatively inventive activities of a third party.

Similarly, it would be illogical to use the Kim Application as prior art under §102(e) justifying UC's participation in an interference with Broad's inventors. UC asserts that the Kim Application qualifies as prior art and that it discloses the complete eukaryotic CRISPR-Cas9 invention at issue. Appx00238-00240; App.Br. at 44-47. Following the logic of UC's argument, the Kim Application combined with anything would render the Broad claims obvious—because the Kim Application supposedly discloses the same invention as Broad claims. Appx00238-00240. Thus, the scope of UC's involved claims would become irrelevant to the interference-in-fact analysis. It is therefore not surprising that UC identifies no case of this Court nor any PTAB decision supporting the use of such secret and (allegedly) potentially interfering §102(e) art in an interference-in-fact analysis.

2. The Kim Application Is Not §102(e) Prior Art to Broad's Invention in Any Event

UC's argument on the Kim Application fails for the additional reason that the Kim Application does not qualify as §102(e) prior art to the Broad's invention

in any event. As evidenced by the undisputed submission date of the manuscript for the Cong 2013 *Science* paper, Broad's invention date precedes the filing date of the Kim Application and thereby eliminates its availability as prior art under §102(e). Appx00308. In fact, Broad removed the Kim Application as a reference during prosecution on this basis. *Id*.

Dr. Kim filed his application on October 23, 2012; subsequent to the October 5, 2012, submission date of Broad's manuscript for Cong 2013. Appx00308; Appx04686. UC reasons that the date the various authors submitted their papers for publication to scientific journals is a surrogate for the date of an actual reduction to practice of using CRISPR-Cas9 in eukaryotic cells. App.Br. at 39. Under that reasoning, the Kim Application is not prior art to the Broad patents, as the Broad inventors submitted their paper for publication nearly three weeks before the Kim Application was filed. UC certainly was aware of this fact; the patent examiner accepted that precise explanation in finding that the Kim Application was not prior art to the Broad patents during examination, a point acknowledged by UC when it filed its request for this interference. Appx08342.

Thus, the PTAB's conclusion—that the Kim Application is not prior art under §102(e) to Broad's invention and cannot be portrayed as knowledge that would have been held by a skilled person—is supported by substantial evidence and is consistent with the law.

III. UC INCORRECTLY ASSERTS THAT THE PTAB FAILED TO CONSIDER CERTAIN EVIDENCE AND ARGUMENTS BELOW

UC also argues that the PTAB failed to consider UC's evidence and arguments in two specific areas. First, UC asserts that the PTAB failed to consider UC's evidence and arguments on simultaneous invention as secondary indicia of obviousness as shown by the publications of several research groups. App.Br. at 36, 38. Second, UC argues that the PTAB did not make a finding on Broad's entitlement to a December 12, 2012, priority date and therefore failed to consider later prior art. App.Br. at 61-64.

The PTAB, however, did not fail to consider any evidence or address any arguments made by UC about these points. Rather, UC did not make those arguments to the PTAB. Further, even if made, the PTAB would have rejected those arguments.

A. UC Erroneously Argues that the PTAB Rejected, as a Matter of Law, Its Argument about Evidence of Simultaneous Invention and Secondary Considerations

UC asserts that the PTAB committed legal error by failing to consider UC's arguments and evidence relating to simultaneous invention as "objective evidence of the fourth *Graham* factor—secondary considerations." App.Br. at 36. As discussed below, however, UC did not present a simultaneous invention/secondary consideration argument to the PTAB. Rather, UC argued that the work by allegedly independent research groups evidenced an expectation of success—an

argument that the PTAB fully considered, addressed and, ultimately, rejected. Appx00023-00025.

3. The PTAB Did Not Fail to Address a Simultaneous Invention Argument; Rather, UC Did Not Make It

UC complains that the PTAB disregarded "overwhelming evidence of simultaneous invention"—citing the evidence of other research groups. App.Br. at 43(quoting *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014)). But UC offered this evidence below in support of an entirely different argument—namely, that the decision to undertake experiments necessarily shows an expectation of success. *See* Appx00245("These groups would not have undertaken the use of UC's Type-II CRISPR-Cas system in eukaryotic cells unless there was sufficient motivation and expectation of success.").

UC now tries to repurpose this evidence in its appeal as evidence of "simultaneous invention" and a secondary consideration of obviousness. App.Br. at 36, 43-47. But UC never made a simultaneous invention/secondary consideration argument before the PTAB. Tellingly, UC's opposition brief in the PTAB nowhere even mentions the terms "simultaneous invention" or "secondary considerations," nor is there any mention of the *Graham* factors. Appx00231-00295.

Because UC did not make a simultaneous invention/secondary consideration argument before the PTAB, it cannot now fault the PTAB for failing to address the argument. *See CardiAQ*, 2017 WL 3833209, at *4. As this Court has repeatedly made clear, the failure to press a legal argument below waives a litigant's ability to raise it on appeal. *See, e.g.*, *Sage Prods., Inc. v. Devon Indus., Inc.*, 126 F.3d 1420, 1426 (Fed. Cir. 1997)("appellate courts do not consider a party's new theories, lodged first on appeal."). That is exactly what happened here. UC's failure to make any simultaneous invention/secondary consideration argument at the PTAB means that Broad had no reason to address this argument (with evidence or otherwise), and deprived the PTAB of any opportunity to consider it in the first instance.

4. The PTAB Considered, on the Merits, the Evidence Relating Other Research Groups in the Context of UC's Arguments Below

UC also erroneously argues that the PTAB dismissed as legally irrelevant the underlying evidence relating to the allegedly independent research groups, as shown by their manuscripts and published papers. App.Br. at 36, 43-44. On the contrary, the PTAB addressed the underlying evidence on the merits, devoting an entire section of its opinion to this evidence and UC's corresponding argument. Appx00023-00025.

After reviewing the evidence relating to other research groups, the PTAB made the finding that it demonstrated a substantial motivation to try to achieve the use of CRISPR-Cas9 in eukaryotic cells, but *not* an expectation of success. Appx00023; *see Nat 7 Steel Car, Ltd. v. Canadian Pac. Ry, Ltd.*, 357 F.3d 1319, 1337-39 (Fed. Cir. 2004)(concluding contemporaneous invention "can be understood to suggest that [a POSITA] would have been motivated to combine" the prior art). Thus, far from ignoring UC's evidence, the PTAB determined it was relevant to the obviousness inquiry—but did not support a finding of a reasonable expectation of success in the context of this art.

The evidence discussed by the PTAB in that section of its decision included the Cho *et al.* manuscript, reporting CRISPR related work from Dr. Kim's research group. Appx00023. UC argues that the PTAB erroneously refused to consider the Kim Application as "compelling evidence of simultaneous invention." App.Br. at 45. UC, however, did not present the Kim Application as anything other than §102(e) prior art, as the discussed in the section above. In the proceedings below, UC relied on Kim's manuscript (the Cho paper) for what it now calls simultaneous invention evidence. Appx00244-00246. The PTAB fully considered the Kim work set forth in the Cho paper in connection with its analysis of other "independent research groups." Appx00023.

UC also incorrectly criticizes the PTAB's reliance on *Life Technologies, Inc. v. Clontech Laboratories, Inc.*, 224 F.3d 1320 (Fed. Cir. 2000). The PTAB cited *Life Technologies* for the unremarkable proposition that a researcher's ultimate success, using conventional techniques, does not mean that there necessarily was a pre-experiment expectation of success. Appx00032.

5. Even if UC Had Raised the Issue of Alleged Simultaneous Invention, the Argument Would Have Had No Impact on the PTAB's Obviousness Analysis

Even if UC has presented to the PTAB its newfound argument that simultaneous-invention evidence "provides valuable insight into the level of skill around the time of the invention," the argument would have had no impact on the PTAB's obviousness analysis. App.Br. at 44. The parties never raised any dispute over the level of skill in the art before the PTAB. *Compare* Appx07084-07085, ¶¶70-72(Carroll), *and* Appx06213-06214, ¶¶76-78(Greider), *with* Appx05496, ¶4.1(Simons). UC also asserts that simultaneous invention "demonstrates what others in the field actually accomplished," citing *Trustees of Columbia Univ. in City of N.Y. v. Illumina, Inc*., 620 Fed. App'x 916, 930 (Fed. Cir. 2015). App.Br. at 37. But the parties did not dispute what others in the field actually accomplished.

The disputed issue before the PTAB was whether there was a reasonable expectation of success *before* the experiments were conducted. UC apparently

seeks an *inference* that the groups undertook the experiments because they had an expectation of success. That inference is entirely unwarranted here in view of *direct* and *contemporaneous* evidence to the contrary.

Regardless, UC misapprehends the relevant legal inquiry on appeal because, even if the evidence supported UC's "simultaneous invention" theory, that would simply be one of *many* types of evidence the PTAB considered. Other evidence before the PTAB constitutes far more than a mere scintilla of evidence and thus substantial evidence supports the PTAB's finding and hence its decision.

B. UC Erroneously Asserts that the PTAB Failed to Consider Prior Art Dated After December 12, 2012

UC also asserts that the PTAB erred by failing to determine if Broad was entitled to an effective filing date of December 12, 2012, and therefore failing to consider prior art arising after that date. UC asserts that the "PTAB never decided the appropriate cut-off date, but instead appears to have assumed without analysis that December 12, 2012 was the cut-off date" and that the "PTAB's decision and the record contain no basis on which to conclude that Broad's effective filing date for all its claims is December 12, 2012." App.Br. at 63.

But, before the PTAB, UC submitted no argument related to interference-in-fact based on prior art after December 12, 2012, nor did it identify any additional later dated prior art that should be considered. Indeed, UC itself accepted Broad's December 12, 2012, priority date as the cut-off date for prior art that would be

relevant to the question of Broad's no interference-in-fact motion. *See, e.g.*, Appx00239. UC's opposition brief acknowledged that the work reported in Broad's seminal Cong 2013 *Science* paper was completed before October 5, 2012. Appx00238-00239.

UC never suggested any need for the PTAB to resolve a dispute regarding the cut-off date to decide Broad's motion 2 for no interference-in-fact. *See Wallace v. Dep't of the Air Force*, 879 F.2d 829, 832 (Fed. Cir. 1989)("Ordinarily, appellate courts refuse to consider issues not raised before an administrative agency…. [T]he issue must be raised with sufficient specificity and clarity that the *tribunal is aware that it must decide the issue*,…"). Thus, the PTAB used the December 12, 2012, cut-off date because both parties used that date.

In these circumstances, UC has waived any objection to the PTAB's use of December 12, 2012 as the date for the interference-in-fact determination. *See Google v. SimpleAir*, 682 F. App'x 900, 903-904 (Fed. Cir. 2017)(finding waiver where Google did not specifically ask the PTAB to construe a term differently and on multiple occasions expressly assented to the construction used by the PTAB); *In re Nuvasive, Inc.*, 842 F.3d 1376, 1380-814 (Fed. Cir. 2016)(finding party waived arguments before PTAB where challenged before but not after institution of IPR and therefore PTAB did not need to address issue in final written decision).

CONCLUSION

For the foregoing reasons, the PTAB's judgment of no interference-in-fact should be affirmed.

Respectfully submitted,

Dated: October 25, 2017

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CERTIFICATE OF SERVICE

I hereby certify that on this 25th day of October, 2017, I caused the foregoing brief to be filed with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit through the Court's CM/ECF system.

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

/s/ Steven R. Trybus
Steven R. Trybus

CERTIFICATE OF COMPLIANCE

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

The undersigned further certifies that the brief is proportionally spaced and contains 13,763 words exclusive of the certificate required by Circuit Rule 28(a)(1), table of contents, table of authorities, signature lines, and certificates of service and compliance. The undersigned used Microsoft Word 2013 to compute the count.

/s/ Steven R. Trybus
Steven R. Trybus