Nos. 22-1594, 22-1653

United States Court of Appeals for the Federal Circuit

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

v.

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

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

BRIEF OF AMICI CURIAE SCIENTISTS IN SUPPORT OF APPELLANTS AND REVERSAL

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UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 22-1594, 22-1653

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

Filing Party/Entity Amici Curiae Scientists Thomas R. Cech, Jack W. Szostak, Titia de Lange, Michael S. Levine, and David Jay Segal

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

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

Date: 10/07/2022

Signature: /s/ Ginger D. Anders

Name: Ginger D. Anders

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☑ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☑ None/Not Applicable
Dr. Thomas R. Cech		
Dr. Titia de Lange		
Dr. Michael S. Levine		
Dr. David Jay Segal		
Dr. Jack W. Szostak		

☐ Additional pages attached

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

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

☐ None/Not Applicable ☐ Additional pages attached

Regents of the Univ. of Cal. v. ToolGen, Inc., Patent Interference No. 106,127 (PTAB)		
Regents of the Univ. of Cal. v. Sigma-Aldrich, Co., LLC, Patent Interference No. 106,132 (PTAB)		

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

☑ None/Not Applicable ☐ Additional pages attached

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STATEMENT OF INTEREST OF AMICI CURIAE[1]

Amici curiae are individual scientists who have dedicated their lives to research in cutting-edge scientific fields related to biology and chemistry. Amici have an interest in this matter because they believe the Patent Trial and Appeal Board's decisions fundamentally misunderstand the scientific method and, if upheld, would harm science.

Dr. Thomas Cech is a Distinguished Professor of Biochemistry and the Director of the Interdisciplinary Quantitative Biology PhD Program at the University of Colorado Boulder.[2] For his work in the field of RNA catalysis, Dr. Cech was awarded the 1989 Nobel Prize in Chemistry. His recent research has addressed the question of how telomeric DNA-

[1] In accordance with Federal Rule of Appellate Procedure 29(a)(4)(E), amici confirm that no party or counsel for any party authored this brief in whole or in part, and that no person other than amici or their counsel made any monetary contribution intended to fund the preparation or submission of this brief. All parties have consented to the filing of this brief. "Party" is defined as the Regents of the University of California, the University of Vienna, Emmanuelle Charpentier, the Broad Institute, Inc., the Massachusetts Institute of Technology, and/or the President and Fellows of Harvard College.

[2] Dr. Cech is signing the amicus brief in his individual capacity and not as an employee or agent of HHMI.

binding proteins recruit human telomerase in cells, using CRISPR genome editing and single-molecule live-cell imaging.

Dr. Titia de Lange is the Leon Hess Professor and the Director of the Anderson Center for Cancer Research at Rockefeller University. Her research focuses on the mechanism by which mammalian telomeres are protected from the DNA damage response.

Dr. Michael S. Levine is the Anthony B. Evnin '62 Professor in Genomics, a Professor of Molecular Biology, and the Director of the Lewis-Sigler Institute for Integrative Genomics at Princeton University. His research focuses on how noncoding regions of the genome function to control the differential patterns of gene expression, both spatial and temporal, that define cell behavior.

Dr. David Jay Segal is a Professor in the Department of Biochemistry and Molecular Medicine at the University of California, Davis. His research interests include zinc finger, TALE, CRISPR/Cas genome engineering, and targeted gene regulation for applications in research and therapeutics, especially neurologic disorders.

Dr. Jack W. Szostak is a University Professor in the Department of Chemistry at the University of Chicago.[3] Dr. Szostak's research has focused on nucleic acid biochemistry, including seminal work on DNA repair, telomeres, and telomerase. He was awarded the 2009 Nobel Prize in Physiology or Medicine.

The positions taken in this brief are those of amici alone and should not be attributed to any institution with which amici are or have been affiliated. Amici sign this brief in their individual capacities and not as an employee or agent of any institution.

SUMMARY OF ARGUMENT

In 2020, Dr. Jennifer Doudna and Dr. Emmanuelle Charpentier received the Nobel Prize in Chemistry for the discovery of a powerful new method for genome editing: the CRISPR-Cas9 genetic scissors. As the Nobel Prize committee explained, "[t]here is enormous power in this genetic tool," which has "revolutionised basic science[.]" Appx64060. The committee credited Drs. Doudna and Charpentier's invention with

[3] Dr. Szostak is signing the amicus brief in his individual capacity and not as an employee or agent of HHMI.

having "taken the life sciences into a new epoch . . . bringing the greatest benefit to humankind." Appx64060.

Yet, based on a fundamental misunderstanding of scientific research, the Patent Trial and Appeal Board ("PTAB") denied Drs. Doudna and Charpentier (along with their collaborators, Drs. Martin Jinek and Krzysztof Chylinski, the "CVC inventors") patents covering a CRISPR-Cas9 complex for editing DNA in eukaryotic cells. The scientific method requires researchers to approach experiments with objectivity, which is precisely what the CVC inventors did here—expressing professional skepticism while confirming their discovery through the routine methods detailed in their patent application. The scientific method also requires the scientific community to exercise professional skepticism before accepting new discoveries. The PTAB, however, treated these elements of the scientific method as evidence that the CVC inventors lacked a definite and permanent idea of how to use CRISPR-Cas9 to modify DNA in eukaryotes. If allowed to stand, the PTAB's decisions will harm science.

ARGUMENT

I. Science Is Trusted, Not Because It Is Perfect, but Because It Is Thorough and Critical

Science is not perfect. A perfectly designed experiment can fail for a host of reasons before subsequent experiments vindicate the underlying theories. Likewise, experiments may succeed (or appear to succeed) even when they are designed using incorrect or incomplete theories. Luck, human error, and unaccounted-for variables all play a role in determining the results of an experiment. It is impossible to control for all of these factors.

We nonetheless trust scientific discoveries because scientists have developed rigorous procedures for testing their initial results and moving past initial failures. Fundamentally, good scientists do "whatever it takes to avoid fooling [themselves] into thinking something is true that is not, or that something is not true that is." Neil deGrasse Tyson, *What Science Is, and How and Why It Works*, HAYDENPLANETARIUM.ORG (Jan. 23, 2016). They challenge observations, even their own expectations, with a "tough, sustained scrutiny" beyond what is commonplace among lay persons. *See* Naomi Oreskes, *Science Isn't Always Perfect—But We Should Still Trust It*, TIME.COM (Oct. 24, 2019). After conceiving of an

idea, scientists move step-by-step through the process of confirming their discovery, collecting and weighing data to determine whether the idea will work. This process, part of the scientific method, is what makes scientific progress possible.

Failure, which may be of two types, is an inevitable part of scientific research. On the one hand, there are mundane failures arising from biological variability, experimental imprecision, and the play of chance. These failures, which are part of day-to-day life at the lab bench, can be fixed through optimization and routine experimentation that ultimately leads to successful implementation of the invention. On the other hand, a fundamental failure occurs when a well-designed and well-executed series of experiments fails to support a scientist's expectations despite efforts to optimize or improve the experimental design and execution, suggesting the scientist has not actually made a discovery.

Without skepticism—including a willingness to recognize, even welcome, failure—scientists risk falling prey to one of the most pernicious problems in science: confirmation bias. *See* Raymond S. Nickerson, *Confirmation Bias: A Ubiquitous Phenomenon in Many Guises*, 2 REV. GEN. PSYCH. 175, 175 (1998) ("If one were to attempt to identify a single

problematic aspect of human reasoning that deserves attention above all others, the *confirmation bias* would have to be among the candidates for consideration."). Driven by the desire to achieve success, they may build a case in favor of a hoped-for outcome, rather than evaluating the evidence objectively. *See id.* Once engaged in case-building, scientists no longer are practicing the "tough, sustained scrutiny" required by the scientific method.

II. The PTAB Misunderstood These Basic Principles, Treating Routine Experimentation and Scientific Skepticism as Fundamental Doubt

The PTAB fundamentally misunderstood how skepticism and failure operate within the scientific method. CRISPR research in particular involves complex biological systems with many variables, and experimental failures are common and are not necessarily indicative of a problem in the underlying theories or experimental design—as evidenced by the fact that the Broad Institute reported only *two* positive results out of 265 sequencing reads in its first "successful" use of the CRISPR-Cas9 system to cleave DNA in eukaryotic cells, a gene modification rate of less than one percent. *See* Appx171-172. Accordingly, CRISPR scientists must remain vigilant—setting aside even their own firmly held

expectations when evaluating experimental data. Unfortunately, the PTAB mistook the CVC inventors' ordinary skepticism for fundamental doubt about the specificity of their inventive idea.

A. Objective Experimentation Is Not Fundamental Doubt

First, the PTAB found that certain experimental failures after March 1, 2012, undermined conception—that is, whether the invention was fully formed, and ready for implementation by skilled artisans without further inventive effort. *See, e.g.*, Appx162. Mainly, the PTAB relied on a series of internal communications among the CVC inventors and researchers attempting to reduce their invention to practice. For example, it quoted a few emails saying:

- "Shucks! I guess it would have been too easy of it worked the first time . . . I'll think on this and get back to you - my quick take is maybe try again with improved Cas9 expression?" Appx151.
- "Since there are so many variables in these experiments I think we have to try to move forward in a stepwise fashion as much as possible." Appx151.
- "As for Cas9 in mammalian cells I completely agree with your analysis and suspect that one or more aspects of the RNA expression/stability/Cas9 assembly/localization are problematic. It would be great to test some alternate designs of the guide RNA in vitro." Appx153.
- "Based on the latest set of results, I suspect we have a problem with our RNA design. Either we are not targeting

> the right piece of DNA (due to chromatin structure etc), or the problem lies with the RNA design per se. Given that the ZFN has no problems cleaving the same region (+/- 30 bp), the former is probably the lesser concern at this point. On the other hand, there could be a number or reasons for the latter including . . . ." Appx152.

The PTAB also pointed out how it took some months—between five and eight—for the CVC scientists to successfully reduce their invention to practice. Appx158; Appx160. Based on the passage of time as well as internal communications about a handful of experimental missteps, the PTAB concluded that the CVC inventors had fundamental doubts about whether CRISPR-Cas9 would work in eukaryotic cells. Appx158.

But this conclusion mistakes mundane failures—part of everyday lab work—for fundamental failures—which might suggest the inventive idea is inoperative or incomplete. The CVC inventors' joke that "it would have been too easy [i]f it worked the first time" reflects the fact that, in these delicate experiments where CRISPR-Cas9 systems are introduced into living cells, experiments often do not work the first time. The CVC inventors had to eliminate variables one-by-one in a stepwise manner, as is normal and natural for research at this level, especially in an academic lab staffed by students. The emails cited by the PTAB demonstrate that throughout this process the CVC inventors remained objective and open-

minded in considering whether they needed to tweak their experimental design. Refusing to entertain that possibility during the course of experimentation would not have been evidence of conception, as the PTAB seemed to expect. It would have been evidence of an irresponsible departure from the scientific method.

Critically, despite initial setbacks, the inventors eventually reduced to practice their invention—in the form in which they had conceived of it—using only those routine materials and techniques known to persons of ordinary skill in the art. Appx161. That is, the eventual working invention relied on the same RNA design the CVC inventors first sketched out in the P1 patent application, with the RNA sequence fine-tuned using only conventional methods. Appx146; Appx159-160; Appx.85648. This evidence shows the CVC inventors never *fundamentally* doubted their invention; their expression of uncertainty was just ordinary scientific skepticism. In short, they achieved success after engaging in good science, remaining vigilant and careful while testing their pre-existing expectations.

B. Scientific Skepticism Is Not Fundamental Doubt

Second, the PTAB faulted CVC for not providing experimental results in its first provisional patent application ("P1") that a CRISPR-Cas9 system would work in eukaryotic cells. *See, e.g.*, Appx102-103. In the absence of a working example in the P1 patent application, the PTAB held that the application must explain to a person of ordinary skill how to overcome theoretical obstacles to implementation that a skeptical scientist might have raised prior to CVC's actual reduction to practice, *see* Appx102-103, or explain that no specific instructions or conditions were necessary, Appx91. Indeed, the PTAB collected from one scientist—Broad's expert Dr. Chad Mirkin—a list of potential reasons why a person of ordinary skill in the art (i.e., a skeptical scientist) might have believed, prior to the successful implementation of CRISPR-Cas9 systems in eukaryotic cells, that routine laboratory techniques might not work due to theoretical obstacles such as RNA degradation in eukaryotic cells, differences in the environment of eukaryotic and prokaryotic cells, and toxic effects of prokaryotic RNAs on eukaryotic cells. *See* Appx86-105. Based on this list of theoretical obstacles, the PTAB found that, even if the P1 patent application in fact described all that was needed to use the

CRISPR-Cas9 system in eukaryotes, a skeptical scientist reviewing the application would not have understood the inventors to have adequately described their invention in P1. Appx105.

Here, the PTAB misinterpreted the ordinary skepticism the scientific community would have had in the absence of empirical data as a reason to deprive the CVC inventors of patent rights. When presented with a discovery (such as the use of CRISPR-Cas9 to cleave eukaryotic DNA *in vitro*, as disclosed in P1), responsible scientists will reserve judgment that the discovery works in other slightly different situations (such as eukaryotic cells) until experimental results demonstrate that it *actually works*. That demand is just the sort of "tough, sustained scrutiny" required by the scientific method, and it does not mean the scientific community lacks the information necessary to recognize the discovery and implement it as described to determine whether it will work. And as Dr. Mirkin's testimony shows, it is easy to come up with a list of any number of theoretical obstacles to reducing to practice an invention—especially in a field as complex as CRISPR research. But that does not mean that clearing those obstacles requires additional disclosures or anything more than routine methods. Moreover, ordinary

skepticism in the scientific community about whether an invention actually will work should not throw into question the inventor's patent rights when the patent application in fact describes all that is needed to practice the invention.

III. If the PTAB's Decisions Are Left Standing, They Will Encourage Bad Science and Chill Open Discourse

If left standing, the PTAB's decisions, to the extent they reflect a mistaken understanding of the roles of skepticism and failure in the scientific method, will discourage collaboration, slow scientific progress, and reward confirmation bias.

Increasingly, science has become a team sport. Gone are the days of a brilliant individual toiling away in isolation. Modern labs depend on the teamwork of scientists, each playing a role in the scientific process. And as is true with all teams, open communication is key. Yet the PTAB's decisions—which relied upon internal communications among team members to strip the CVC scientists of their invention—will discourage the free flow of communication between collaborators. To avoid jeopardizing future patent rights, scientists may choose not to speculate openly with their colleagues about why an experiment failed or brainstorm next steps. Researchers in academic labs also may be less

open to discussing failed experiments with their students, crippling scientific education. By chilling open communication among collaborators, the PTAB's decisions have the potential to slow scientific progress and discourage the types of risk-taking critical to innovation.

Similar concerns about the effect of communication on patent rights may discourage open discourse within the scientific community as a whole. Science is a conversation: an iterative process that allows for one idea to build and shape the next through refinement of the last. Sharing experimental results with the wider scientific community can launch a slew of new research. But in view of the PTAB's decisions, scientists will feel pressure to secret away their inventions until they can muster enough evidence to convince others that their inventions will work. Indeed, if after filing the P1 patent application the CVC inventors had chosen to conceal their discovery that the single-guide CRISPR-Cas9 system could cleave eukaryotic DNA *in vitro* (at least until publication of P1 18 months later), they might well have been the first to demonstrate use of the CRISPR-Cas9 system in eukaryotic cells and obtained the patents covering such use. On the other hand, keeping their invention secret would have delayed the progress of CRISPR-Cas9 research within

the broader scientific community, because, as the Nobel Prize committee observed, Drs. Charpentier and Doudna's work led to many other "important discoveries," not only in basic research, but also in the treatment of human disease and crop science. Appx64060.

Finally, the PTAB's decision will encourage bad science. If the minor missteps and changes in strategy characteristic of routine bench work can later be used as evidence that an inventor lacked a definite and permanent idea of the invention, as the PTAB found here, scientists will avoid rigorously testing their own settled expectations. Instead, they will be tempted to look for evidence that supports their view, building a case in favor of their invention for fear that proceeding objectively will result in denial of valuable intellectual property rights. Such confirmation bias is antithetical to the very core of the scientific method, which demands steadfast skepticism.

CONCLUSION

For the foregoing reasons, amici urge the Court to correct the PTAB's mistaken understanding of objectivity in the scientific method by reversing the PTAB's decisions.

DATED: October 7, 2022

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Federal Circuit Rule 29(b). The body of the brief contains 2882 words, excluding the portions exempted by rule.

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6), because it has been prepared in a proportionally spaced typeface using Microsoft Word 2016 in New Century Schoolbook 14-point font.

DATED: October 7, 2022 By: /s/ *GINGER D. ANDERS*
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CERTIFICATE OF SERVICE

I hereby certify that on October 7, 2022, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit through the Court's CM/ECF system. A copy has been served on all parties by electronic means.

DATED: October 7, 2022 By: /s/ *GINGER D. ANDERS*
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