Educational Briefing On Interference Proceedings Relating To CRISPR/Cas9 Genome Editing Technology Patents

August 28, 2018

Today's Participants

- Cora Holt, Associate, Finnegan, Henderson, Farabow, Garrett & Dunner, LLP
- José Rivera, Executive Vice President and General Counsel, Intellia Therapeutics
- Lindsey Trickett, Vice President, Investor Relations, Intellia Therapeutics

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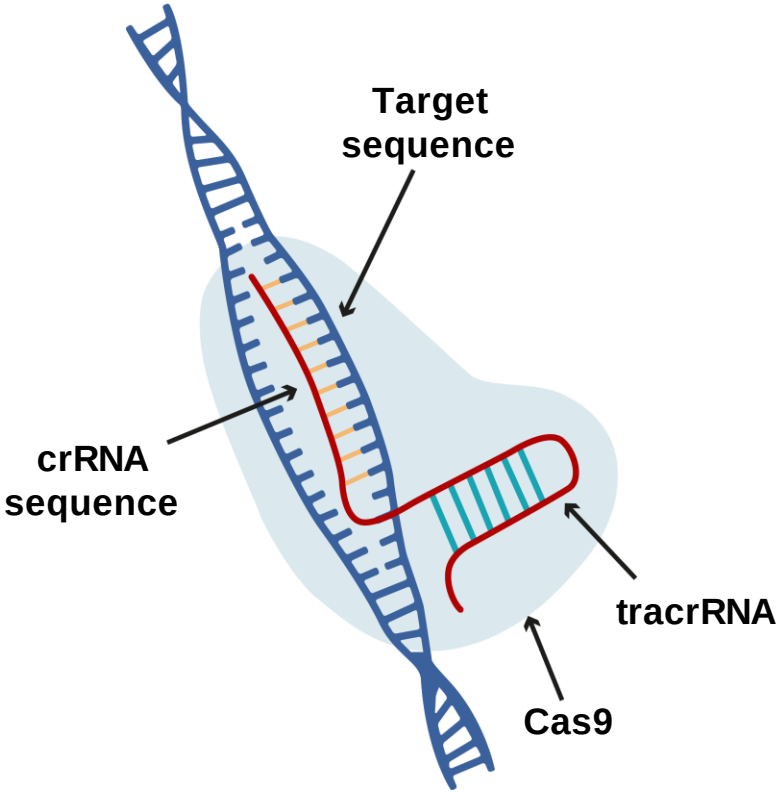
About Finnegan And Speaker Biography

Finnegan, Henderson, Farabow, Garrett & Dunner, LLP is one of the largest IP law firms in the world. From offices in Atlanta, Boston, London, Palo Alto, Reston, Seoul, Shanghai, Taipei, Tokyo and Washington, D.C., the firm practices all aspects of patent, trademark, copyright, and trade secret law, including counseling, prosecution, licensing, and litigation. Finnegan also represents clients on IP issues related to European patents and trade marks, international trade, portfolio management, the Internet, e-commerce, government contracts, antitrust, and unfair competition.

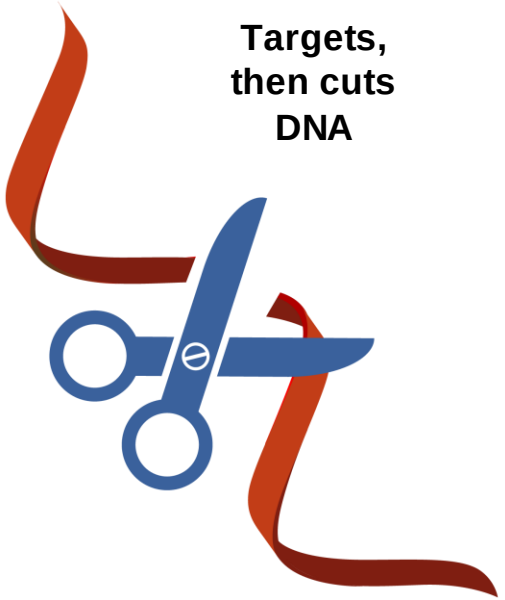
Cora Holt is an experienced litigator at both the trial and appellate levels. She represents clients in patent disputes before federal district courts, the U.S. Court of Appeals for the Federal Circuit, and the U.S. Supreme Court. While Cora handles cases involving a variety of technologies, her practice focuses on the biotechnology, pharmaceutical, and life sciences industries. She has represented clients in cases involving human therapeutic antibodies, chemical compounds, medical devices, drug delivery systems, soybean plants, and engineered microorganisms. Her work also includes significant experience litigating Hatch-Waxman and biosimilars cases. In addition to her patent litigation work, Cora assists clients in portfolio counseling matters and proceedings before the U.S. Patent and Trademark Office. She also devotes significant time to pro bono work, particularly the representation of veterans in cases before the U.S. Court of Appeals for Veterans Claims, the U.S. Court of Federal Claims, and the Federal Circuit.

What Is CRISPR/Cas9 Genome Editing?

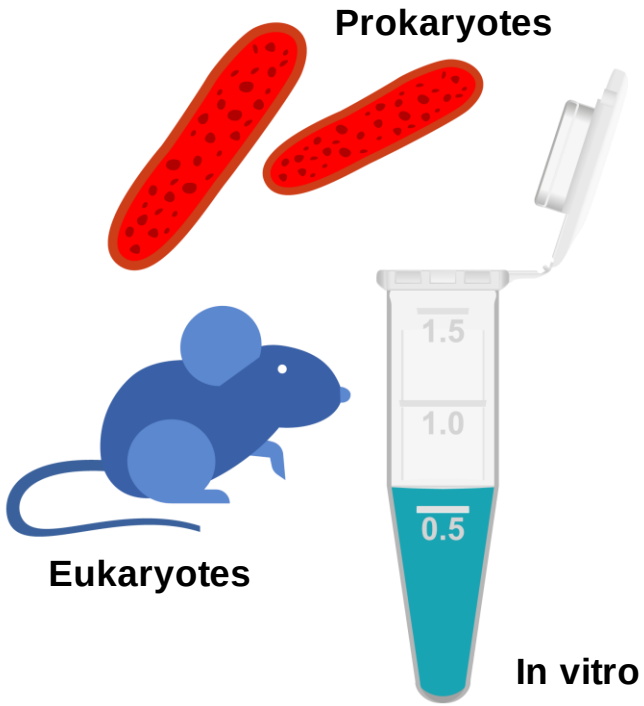
COMPONENTS



USE



SETTINGS



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What Is An Interference?

U.S. Patent and Trademark Office (USPTO) interference proceeding occurs in two stages:

Stage 1: Do the two sets of claims interfere?

To answer this question, the USPTO asks whether the claims are directed to the *"same patentable invention"* by employing a two-way obviousness test: Without considering the other language in the specifications, are the claim sets of the competing patents and applications obvious over each other?

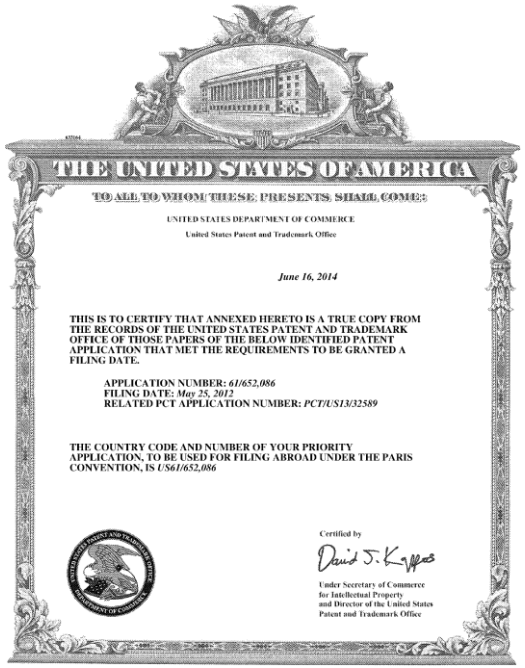
- If the claims interfere, proceed to Stage 2 to determine who invented first.
- If the claims do not interfere, terminate interference without determining who invented first.
  - If terminated at Stage 1, both parties can continue to pursue their applications.

Stage 2: If the two sets of claims overlap, who invented first?

To answer this question, the USPTO looks at both parties' evidence of invention and determines who invented first.

- Only the first inventor may continue to pursue its application.

Scientific Community Recognizes Doudna/Charpentier As CRISPR/Cas9 Inventors



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS, SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

June 16, 2014

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *61/652,086*
FILING DATE: *May 25, 2012*
RELATED PCT APPLICATION NUMBER: *PCT/US13/32589*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US61/652,086*

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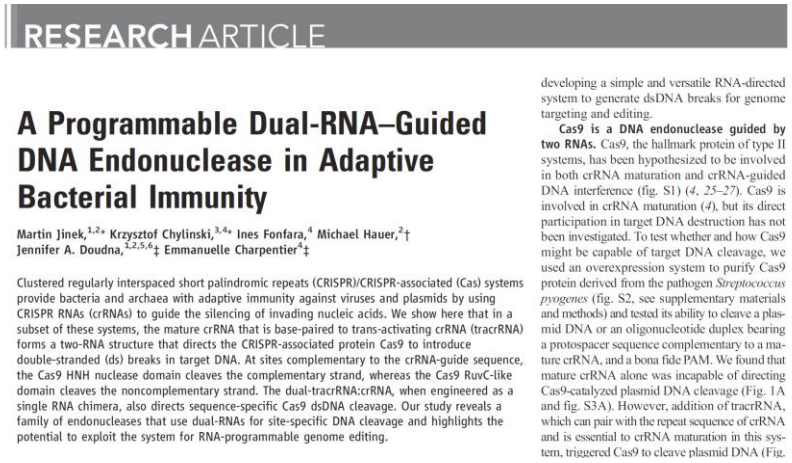
May 25, 2012

UC, Vienna and Charpentier filed their first patent application for the breakthrough technology



RESEARCH ARTICLE

A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity

Martin Jinek,[1,2*] Krzysztof Chylinski,[3,4*] Ines Fonfara,[4] Michael Hauer,[2†] Jennifer A. Doudna,[1,2,5,6‡] Emmanuelle Charpentier[4‡]

Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) systems provide bacteria and archaea with adaptive immunity against viruses and plasmids by using CRISPR RNAs (crRNAs) to guide the silencing of invading nucleic acids. We show here that in a subset of these systems, the mature crRNA that is base-paired to trans-activating crRNA (tracrRNA) forms a two-RNA structure that directs the CRISPR-associated protein Cas9 to introduce double-stranded (ds) breaks in target DNA. At sites complementary to the crRNA-guide sequence, the Cas9 HNH nuclease domain cleaves the complementary strand, whereas the Cas9 RuvC-like domain cleaves the noncomplementary strand. The dual-tracrRNA:crRNA, when engineered as a single RNA chimera, also directs sequence-specific Cas9 dsDNA cleavage. Our study reveals a family of endonucleases that use dual-RNAs for site-specific DNA cleavage and highlights the potential to exploit the system for RNA-programmable genome editing.

developing a simple and versatile RNA-directed system to generate dsDNA breaks for genome targeting and editing.

Cas9 is a DNA endonuclease guided by two RNAs. Cas9, the hallmark protein of type II systems, has been hypothesized to be involved in both crRNA maturation and crRNA-guided DNA interference (fig. S1) (*4*, *25*–*27*). Cas9 is involved in crRNA maturation (*4*), but its direct participation in target DNA destruction has not been investigated. To test whether and how Cas9 might be capable of target DNA cleavage, we used an overexpression system to purify Cas9 protein derived from the pathogen *Streptococcus pyogenes* (fig. S2, see supplementary materials and methods) and tested its ability to cleave a plasmid DNA or an oligonucleotide duplex bearing a protospacer sequence complementary to a mature crRNA, and a bona fide PAM. We found that mature crRNA alone was incapable of directing Cas9-catalyzed plasmid DNA cleavage (Fig. 1A and fig. S3A). However, addition of tracrRNA, which can pair with the repeat sequence of crRNA and is essential to crRNA maturation in this system, triggered Cas9 to cleave plasmid DNA (Fig.

June 28, 2012

UC, Vienna and Charpentier first to publish the necessary components for CRISPR/Cas9 genome editing

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UC Provided Blueprint For Follow-on Patent Applications

ToolGen Application Oct. 23, 2012

Sigma-Aldrich Application Dec. 6, 2012

Broad Application Dec. 12, 2012

Harvard Application Dec. 17, 2012

Broad was the third follow-on party to file a U.S. patent application for the use of CRISPR/Cas9 in eukaryotic cells

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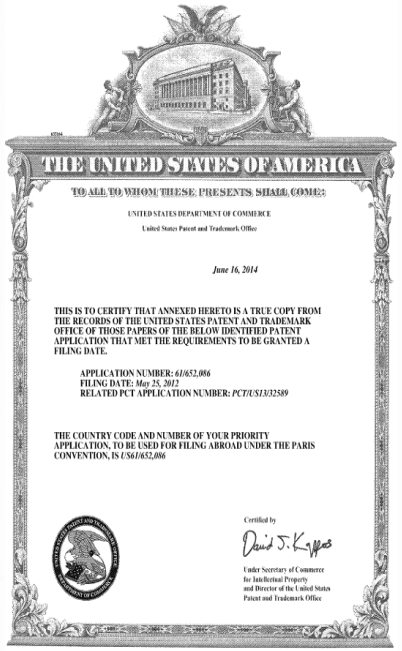
UC Patent Family Identifies CRISPR/Cas9 Invention, Including Its Components And Uses In A Variety of Settings



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CRISPR/Cas9 Genome Editing

In a cell

gRNA **sgRNA**

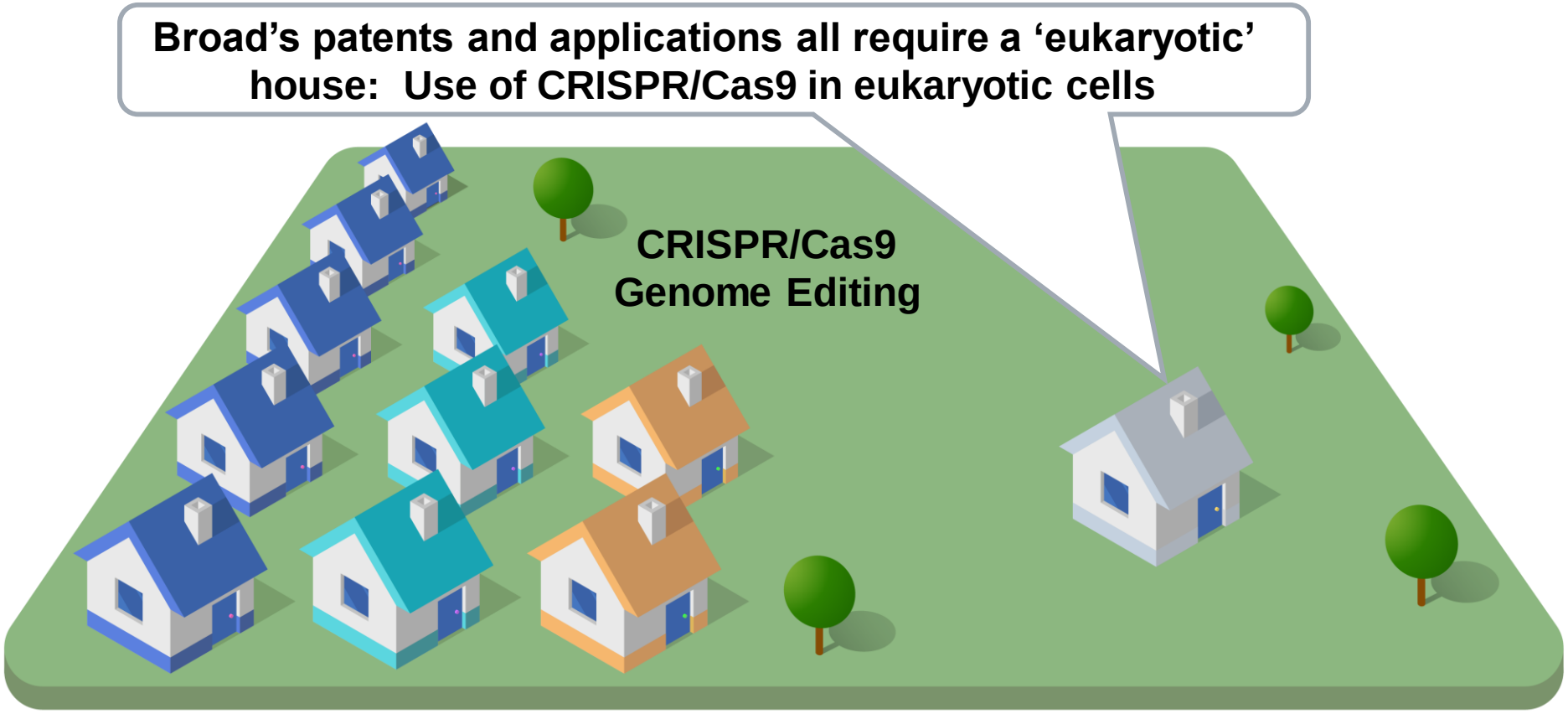
Eukaryotic

INVENTIONS

- CRISPR/Cas9 composition
- CRISPR/Cas9 use in any setting with any guide
- CRISPR/Cas9 use in any setting with single-guide RNA
- CRISPR/Cas9 use in a cell with any guide
- CRISPR/Cas9 use in a cell with single-guide RNA
- CRISPR/Cas9 use in eukaryotic cells with any guide
- CRISPR/Cas9 use in eukaryotic cells with single-guide RNA
- CRISPR/Cas9 use *in vitro* with any guide
- CRISPR/Cas9 use *in vitro* with single-guide RNA
- Single-guide RNA formats
- Other CRISPR/Cas9 inventions

gRNA: guide RNA
sgRNA: single-guide RNA

UC Patent Family Describes The ‘Land’ Plus Types Of ‘Houses’ That Could Be Built



Patent is a <u>right to exclude others</u>
from making, using, offering for sale or selling the covered inventions

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Claims At Issue In The CRISPR/Cas9 Interference

UC

- CRISPR/Cas9 composition
- CRISPR/Cas9 use in any setting with any guide
- **CRISPR/Cas9 use in any setting with single-guide RNA**
- CRISPR/Cas9 use in a cell with any guide
- CRISPR/Cas9 use in a cell with single-guide RNA
- CRISPR/Cas9 use in eukaryotic cells with any guide
- CRISPR/Cas9 use in eukaryotic cells with single-guide RNA
- CRISPR/Cas9 use *in vitro* with any guide
- CRISPR/Cas9 use *in vitro* with single-guide RNA
- Single-guide RNA formats
- Other CRISPR/Cas9 inventions

VS

Broad

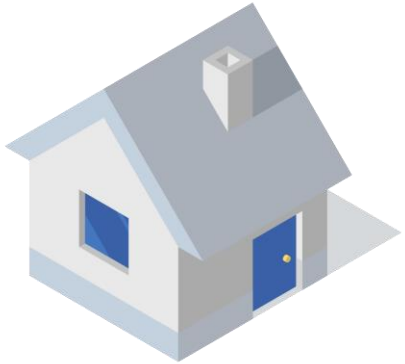
CRISPR/Cas9 use in eukaryotic cells with any guide

Interference scope:

Patent Trial and Appeal Board (PTAB) decision focused on whether use of CRISPR/Cas9 in eukaryotic cells was obvious in view of UC's invention of CRISPR/Cas9 technology and its use in any setting

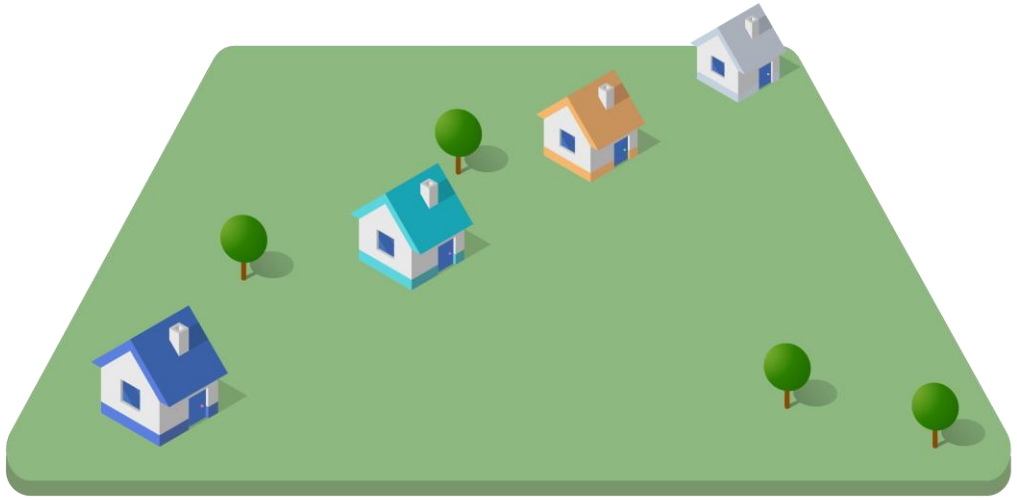
UC Patent Family Covers All Types Of CRISPR/Cas9 Settings

FICTION



✗ **The current interference proceeding will determine the ownership of the one and only CRISPR/Cas9 'house'**

FACT

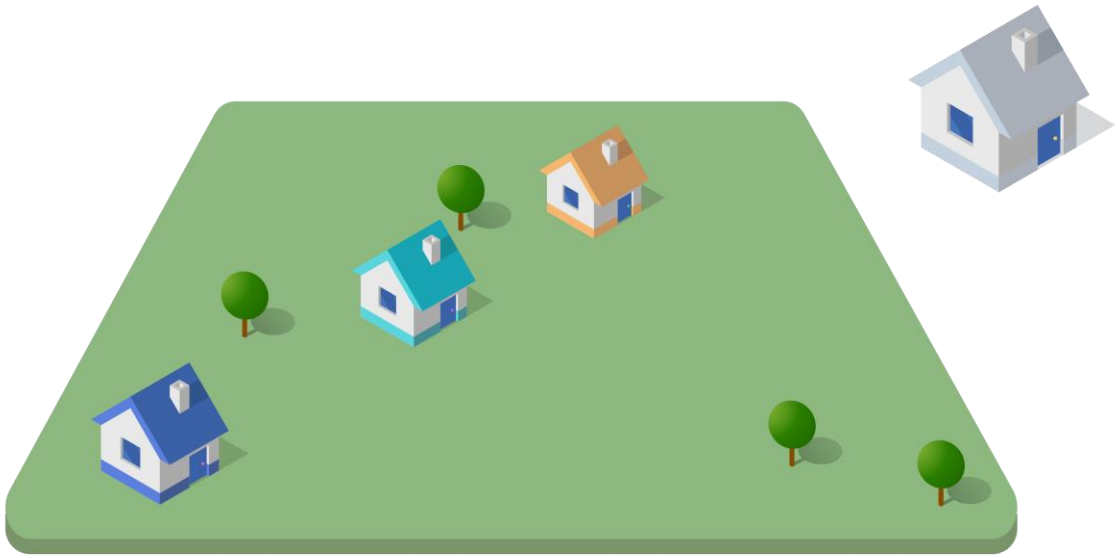


✓ **Use of CRISPR/Cas9 in eukaryotic cells is a subset of the total patent landscape**

✓ **UC patent family covers the 'land' and all the different 'houses'**

UC Patent Family Covers All Relevant CRISPR/Cas9 Components

FICTION



✗ **Anything covered in Broad's claims is outside the UC patent family**

FACT

✓ **Broad's patent claims are NOT outside <u>or</u> separate from UC patent family**

Path From USPTO To Federal Circuit: How We Got Here

PTAB

- Jan. 2016: Grants UC's request for interference
- Feb. 2017: Grants Broad's motion to terminate interference at Stage 1*, finding Broad's claims non-obvious over UC's claims
  - Specification of UC's application is not considered for this analysis

Never reached Stage 2* to determine who invented first; thus, both parties can continue to pursue their own applications

Federal Circuit Court of Appeals

Question Presented:

Was PTAB correct that Broad's claims are non-obvious over UC's claims?

DECISION EXPECTED

* Refer to "What is an Interference?" slide for a definition of Stages 1 and 2

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Federal Circuit Will Only Address The Issues Before It

Will the Federal Circuit address…	
Who is the inventor of CRISPR/Cas9?	✗
Who receives all the patent rights to CRISPR/Cas9?	✗
Who ultimately is entitled to the patent rights for the use of CRISPR/Cas9 in eukaryotes?	✗
What happens to the pending CRISPR/Cas9 patent applications not in the interference?	✗
Whether the PTAB correctly terminated the interference after ruling that the Broad's claims do not interfere with UC's claims?	✓

One Of Three Potential Federal Circuit Rulings Expected

VACATE AND REMAND

(Back to PTAB – Stage 1*)

- PTAB erred in its obviousness analysis and needs to reconsider the Stage 1* question.
- Remand for PTAB to reconsider Stage 1* (whether Broad's claims are obvious over UC's claims).

REVERSE AND REMAND

(Back to PTAB – Stage 2*)

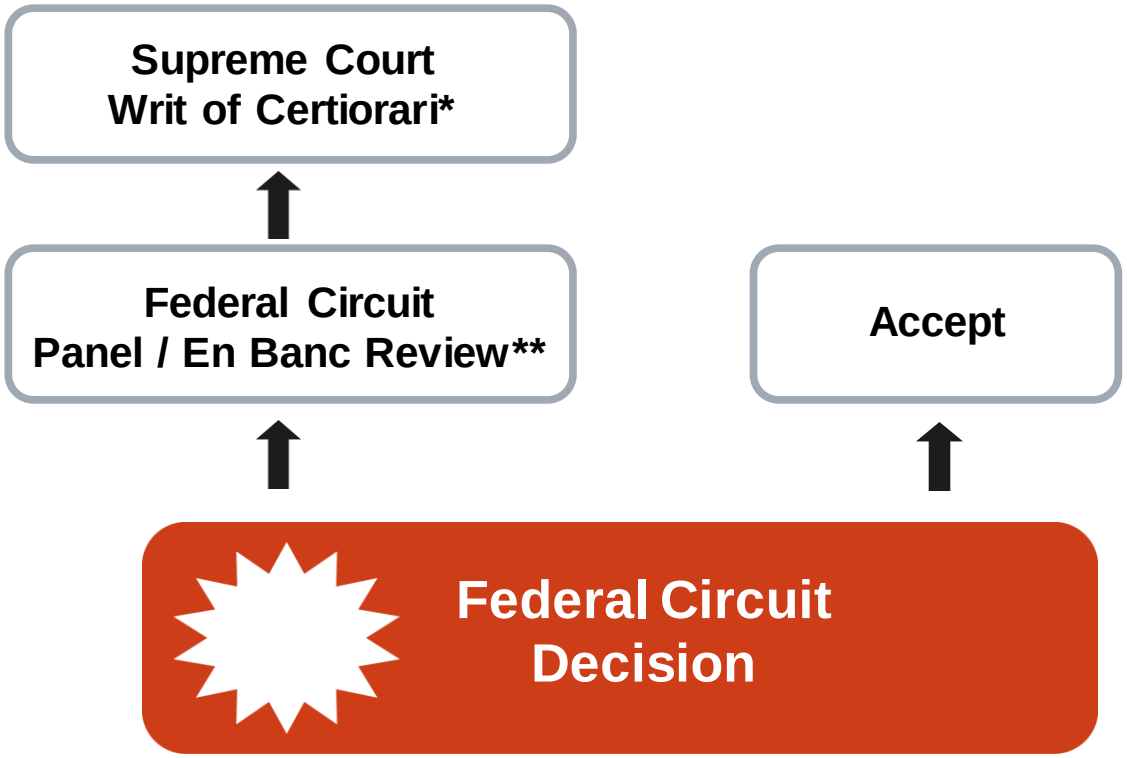
- PTAB erred in its obviousness analysis, and it is clear that Broad's claims are obvious over UC's claims.
- Remand for PTAB to move on to Stage 2* after non-dispositive motions decided (who invented first).

AFFIRM

- PTAB was correct; interference remains terminated.
- Both parties may continue to pursue their own applications and maintain their patents, subject to future challenges.

* Refer to "What is an Interference?" slide for a definition of Stages 1 and 2

Federal Circuit Ruling Is Not The Final Say. Doors Remain Open For Both Parties

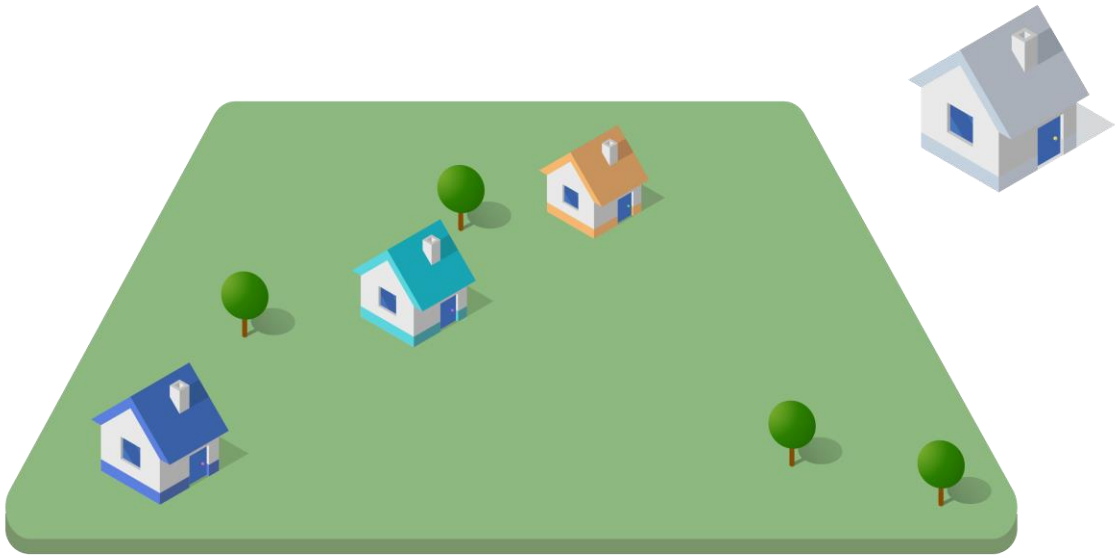


Whether and what kind of further review is granted is entirely within the discretion of the reviewing court

* For Writ of Certiorari – 90 days to file petition
** For Panel/En Banc Review – 30 days to file petition

UC Has Many Options And Can Also Pursue Pending Patent Applications

FICTION



✗ **Anything covered in Broad's claims is outside the UC patent family**

FACT

✓ **Broad's patent claims are NOT outside <u>or</u> separate from UC patent family**

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Key Takeaways For Upcoming Federal Circuit Ruling

- Federal Circuit is not deciding who invented or is entitled to the rights to CRISPR/Cas9 genome editing technology

- Federal Circuit is also not deciding who invented or is ultimately entitled to the rights to the use of CRISPR/Cas9 in eukaryotes

- Federal Circuit decision will not determine the scope of UC's patent rights
  - CRISPR/Cas9 patent landscape is much larger than current interference
  - UC has numerous other applications and patents on CRISPR/Cas9 technology, both within the U.S. and ex-U.S.

- **Federal Circuit will <u>only</u> determine whether the PTAB correctly terminated the interference after ruling that the Broad's claims do not interfere with UC's claims**

Appendix

VACATE And REMAND – Back To PTAB For Stage 1*

Federal Circuit finds PTAB erred in its obviousness analysis, and remands the case to PTAB to re-consider Stage 1 (whether Broad's claims are obvious over UC's claims).

UC's Options

Accept the Federal Circuit ruling

Broad's Options

(1) Accept decision; case returns to PTAB for reconsideration of Stage 1; or

(2) Challenge decision by filing a petition for:

- **Rehearing by the Federal Circuit panel and/or *en banc* court (30 days)**
- **Writ of certiorari before the Supreme Court (90 days)**

Whether to consider these petitions is entirely within the discretion of the court and, if rejected, the case is returned to the PTAB

* Refer to "What is an Interference?" slide for a definition of Stage 1 and 2
All options noted above are possibilities and not a prediction of either the Federal Circuit's decision or any of the parties' probable actions.

REVERSE And REMAND – Back To PTAB For Stage 2*

Federal Circuit finds PTAB erred in its obviousness analysis and that Broad's claims are obvious over UC's claims; remands for PTAB to move to Stage 2 (who invented first).

UC's Options

Accept the Federal Circuit ruling

Broad's Options

(1) Accept decision; case returns to PTAB and moves to Stage 2; or

(2) Challenge decision by filing a petition for:

- **Rehearing by the Federal Circuit panel and/or *en banc* court (30 days)**
- **Writ of certiorari before the Supreme Court (90 days)**

Whether to consider these petitions is entirely within the discretion of the court and, if rejected, the case is returned to the PTAB

* Refer to "What is an Interference?" slide for a definition of Stage 1 and 2
All options noted above are possibilities and not a prediction of either the Federal Circuit's decision or any of the parties' probable actions.

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AFFIRM – Interference Remains Terminated; No Determination On Inventorship

Federal Circuit finds PTAB was correct and affirms termination of interference.

UC's Options

(1) Accept decision
- This interference is over, leaving UC and Broad free to pursue their applications at issue in this interference, as well as other applications
- Note: UC has other pending patent claims which expressly interfere with Broad's claims and may be cause for another interference

(2) Seek further review by filing a petition for:
- Rehearing by the Federal Circuit panel and/or *en banc* court (30 days)
- Writ of certiorari before the Supreme Court (90 days)

Whether to consider these petitions is entirely within the discretion of the court and, if rejected, the case is returned to the PTAB

Broad's Options

Accept the Federal Circuit ruling

All options noted above are possibilities and not a prediction of either the Federal Circuit's decision or any of the parties' probable actions.


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