

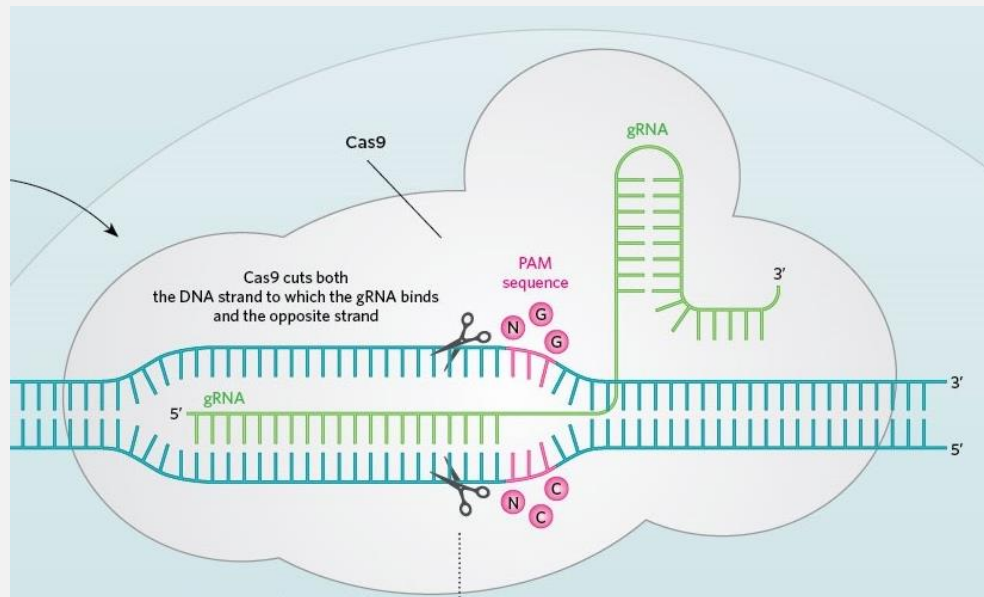
# CRISPR – Editing your Genome

Who invented it and owns the patent?

MIT or the University of California

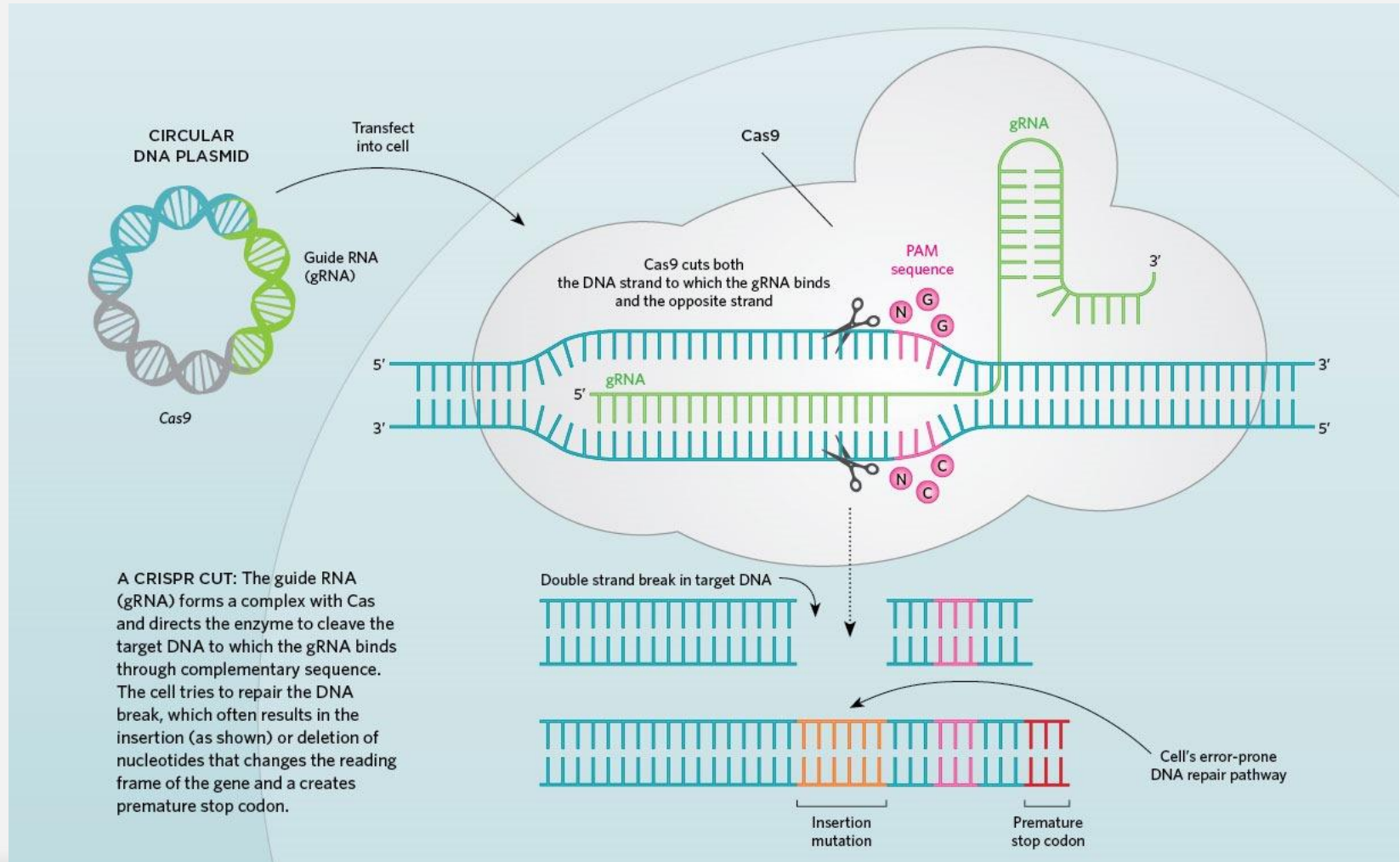
Dr. Jack M. Wilson

Distinguished Professor of Higher Education, Emerging Technologies, and Innovation



# CRISPR

- Clustered Regularly Interspersed Short Palindromic Repeats Array



# CRISPR – a way to edit the genome of living creatures

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- The CRISPR interference technique has enormous potential application, including altering the germline of humans, animals and other organisms, and modifying the genes of food crops.
  - <https://en.wikipedia.org/wiki/CRISPR>
- By delivering the Cas9 protein and appropriate guide RNAs into a cell, the organism's genome can be cut at any desired location.
- Genetic material may be removed and/or inserted.
- There are many potential benefits to being able to remove and insert genetic material.
  - Diseases may be cured
  - Genetic disabilities and/or predispositions may be fixed
  - Agricultural crops can be engineered and changed much faster than using selective breeding.
- There are huge financial implications to all of these.
- There are also strong ethical concerns about the use of this technology and those concerns become particularly powerful when the technology is used in human being.

# The Nobel Prize awarded for CRISPR's discovery in 2020

- Jennifer Doudna and Emmanuelle Charpentier were awarded the Nobel Prize in October 2020 for their discovery of CRISPR. This discovery is providing a key to addressing many diseases that have proven resistant to treatment.
- There is also a back story here that does not appear. They left out the scientist who actually got the patent! At MIT, Feng Zhang took their work and extended it for the first time into living systems.
- In a shock to the scientific community he was awarded the patent for CRISPR. This ignited a huge legal (and scientific) battle that rages until today -but is trending toward Doudna and Charpentier.
- Apparently, the Nobel Committee does not recognize Zhang as deserving credit for the discovery.
- <https://www.nobelprize.org/prizes/chemistry/2020/summary/>



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Emmanuelle Charpentier

Prize share: 1/2



© Nobel Media. Ill. Niklas Elmehed.

Jennifer A. Doudna

Prize share: 1/2

# CRISPR –Bayh-Dole-First to Invent or File?

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- In 2016 we were seeing one of the epic fights over intellectual property. The potential monetary implications were huge!
  - <http://www.statnews.com/2016/03/08/crispr-patent-fight/>
- Who invented CRISPR?
  - Feng Zhang of MIT's Broad Institute? He presently received the patent.
  - Jennifer Doudna of the University of California Berkeley? She was the first to file –but she did it on March 15, 2013.
  - MIT filed on behalf of Zhang in October 2013
- MIT paid for an expedited review of their patent claim
- UC did not.
- The Broad was granted about a dozen CRISPR patents for genome editing.
- UC claimed that it, and not the Broad, was entitled to those patents.
- And now the dispute is in the courts.
- Who will win?
  - First: <http://www.statnews.com/2016/03/18/crispr-patent-dispute/>
  - Later: <https://www.statnews.com/2017/02/16/crispr-patent-decision-six-takeaways/>
  - Now: <https://www.the-scientist.com/news-opinion/uc-berkeley-team-to-be-awarded-crispr-patent-65453>

# Patents

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Patents are often the first thing that scientists or engineers think of when dealing with intellectual property.

- Patents
  - A patent is a grant from the federal government conferring the rights to exclude others from making, selling, or using an invention for the term of the patent as many as 20 years.
- To obtain a patent, an invention must:
  - Be novel
    - It must be something that is completely new. If others have done it before and disclosed that, then it cannot be patented.
  - Not be obvious to a person of ordinary skill in the field
    - This is often the point around which patents disputes start. If one can show that an idea would be obvious to anyone skilled in the field then it cannot be patented. Sometimes that can be in heavy dispute.
  - Be useful
    - You cannot patent something that does not have an obvious immediate use.

# Patents are useful, but they require vigorous defense

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- Patents are not that hard to obtain, but they can be very difficult to defend.
- It often costs far more to defend a patent than to obtain a patent.
- In this case it is two large Universities, MIT and the University of California, with very deep pockets doing the fighting
- There are two major issues in this case which are important to understanding intellectual property cases of this kind:
  - The Bayh-Dole act grants Universities the ownership of intellectual property created in federally funded research.
  - In 2013, the patent law was changed from first to invent to first to file

# How patents became the rocket fuel of technological entrepreneurship

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- Bayh-Dole Act -1980 (named for Senators Birch Bayh (D) and Robert Dole (R))
  - Gave the patent rights for intellectual property created in university research funded by the federal government to Universities.
  - Prior to Bayh-Dole, the rights went to the Federal Government.
- In order for a patent to be valuable enough to cause an organization to invest the money to commercialize it, that industry needs to be assured that they have rights to use the IP and that others cannot easily imitate their work.
- Prior to Bayh-Dole, an enterprise could not be assured that they had protected rights to intellectual property.
  - Prior to the enactment of Bayh-Dole, the U.S. government had accumulated 28,000 patents, but fewer than 5% of those patents were commercially licensed.
- After Bayh-Dole, Universities got very good at licensing IP to industries. This gave the industries the protected rights that they needed and it also created a significant revenue stream for Universities and Government labs.



# Key patent issues

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- In 2013 the US patent law was changed dramatically
- US converted from “First to Invent” to “First to file” in 2013.
  - For this reason you should be careful not to follow materials written under the old law, since that could invalidate your patent opportunities.
  - Before 2013, there was a lot of work being done to establish who first invented any particular patent. That was why documentation was so important.
  - Now this is no longer relevant. If you invent something and keep it secret and someone else finds out about it and files the patent, you will find it difficult to stop them.
  - The patent priority will go to the first to file.
- US recognizes any filing in any WTO country as establishing the same priority as if it was filed in the US.
  - Title 35 USC Section 119 (a) An application for patent for an invention filed in this country by any person who has, or whose legal representatives or assigns have, previously regularly filed an application for a patent for the same invention in a foreign country which affords similar privileges in the case of applications filed in the United States or to citizens of the United States, or in a WTO member country, shall have the same effect as the same application would have if filed in this country on the date on which the application for patent for the same invention was first filed in such foreign country, if the application in this country is filed within twelve months from the earliest date on which such foreign application was filed.

# CRISPR –Bayh-Dole-First to Invent or File? MIT vs U. California!

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- In 2016 we were seeing one of the titanic fights over intellectual property. The potential monetary implications were huge!
  - <http://www.statnews.com/2016/03/08/crispr-patent-fight/>
- As we saw earlier there are two claims to be the inventor of CRISPR?
  - MIT: Feng Zhang of MIT's Broad Institute received the patent.
  - UC Berkeley" Jennifer Doudna of the University of California Berkeley was the first to file –but she did it on March 15, 2013 –before the law changed from first to invent to first to file.
  - Remember that the law changed from first to invent to first to file on March 16!!!!
  - MIT filed on behalf of Zhang in October 2013
- MIT paid for an expedited review of their patent claim
- UC did not.
- The Broad was granted about a dozen CRISPR patents for genome editing.

# Jennifer Doudna and Emmanuelle Charpentier

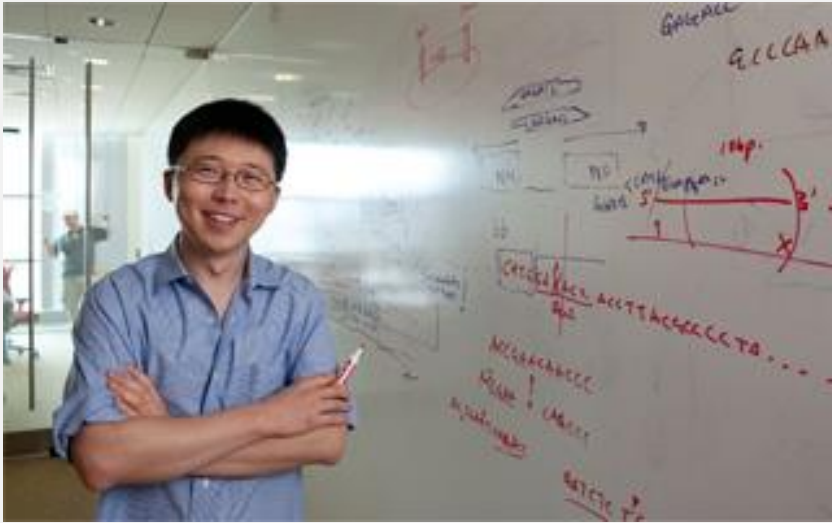
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“Jennifer Doudna and Emmanuelle Charpentier had independently been exploring CRISPR-associated proteins to learn how bacteria use spacers in their immune defenses.[37] They jointly studied a simpler CRISPR system that relies on a protein called Cas9. They found that bacteria respond to an invading phage by transcribing spacers and palindromic DNA into a long RNA molecule. The cell then uses tracrRNA and Cas9 to cut this long RNA molecule into pieces called crRNAs.” -<https://en.wikipedia.org/wiki/CRISPR>



Their study proposed that such synthetic guide RNAs could be used for gene editing.

# Feng Zhang at the Broad Institute at MIT



Feng Zhang: the W. M. Keck Career Development Professor of Biomedical Engineering in the departments of Brain and Cognitive Sciences and Biological Engineering at the Massachusetts Institute of Technology.

<https://www.broadinstitute.org/blog/five-questions-feng-zhang>

“Based on previous work by the Sylvain Moineau Lab, Dr. Zhang began work to harness and optimize the CRISPR system to work in human cells in 2011. While Zhang's group was optimizing the Cas9 system in human cells, the collaborating groups of Emmanuelle Charpentier and Jennifer Doudna reported a biochemical characterization of the CRISPR-Cas9 system, including the design of a single, chimeric guide RNA (sgRNA) capable of facilitating cleavage of DNA using purified Cas9 protein and sgRNA. Zhang's group further optimized this Doudna/Charpentier sgRNA design for expression in mammalian cells and subsequently reported the first application of Cas9 for genome editing in human cells the following year.” -Wikipedia

# And then! Virginijus Šikšnys

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- In June of 2018, Virginijus Šikšnys of Vilnius University was awarded the very prestigious Kavli Prize jointly with Doudna and Charpentier!
- Fang Zhang and MIT were left out!
  - *“Conspicuously absent from the award was another researcher who has enjoyed the CRISPR spotlight, chemist Feng Zhang of the Broad Institute in Cambridge, Massachusetts.”*
- Apparently they sided with those who felt that Zhang’s work was an “obvious” extension.
- *“Doudna and Charpentier reported their findings in a landmark Science paper published online on 28 June 2012. But it took Šikšnys 5 months to publish his study; it was **rejected by Cell and Cell Reports**, and then moved slowly through editing at the Proceedings of the National Academy of Sciences (PNAS), which published it online on 25 September 2012.”*
- Asked if he has weighed in on the patent debate he replied: *“I’m following this, as many people do. It’s probably the field of lawyers and not scientists.”*

<https://www.sciencemag.org/news/2018/06/prestigious-prize-overshadowed-crispr-researcher-wins-spotlight>

# CRISPR –Bayh-Dole-First to Invent or File? Continued

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- Zhang claimed that he was the first to invent the use of CRISPR to edit the genes of living creatures. The patent office agreed.
  - The Doudna paper in January of 2009 showed how to edit genes in a test tube.
  - Zhang did the same for living creatures.
  - Now the UC Berkeley law suit claims that his extension to living creatures was “OBVIOUS.” MIT disagrees.
  - In fact MIT, claimed that the Doudna -Charpentier work was “obvious,” but the court refused to consider that claim.
- And now the dispute is in the courts.
- Who will win?
  - The latest: <http://www.statnews.com/2016/03/18/crispr-patent-dispute/>
- In December of 2016, the courts heard arguments from both sides. No definitive perspectives were expressed.
  - <http://www.sciencemag.org/news/2016/12/crispr-patent-hearing-produces-no-clear-winner-only-soft-signals>

# Easy to obtain, expensive to defend?

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- Patents are fairly easy to obtain, but can be very expensive to defend.

## **CRISPR patent fight: The legal bills are soaring**

Stat; August 12, 2016. (<https://www.statnews.com/2016/08/12/crispr-patent-fight-legal-bills-soaring/>)

- *“The meter is running like mad on the dispute over key patents on CRISPR genome editing. In its latest 10-Q filing with the Securities and Exchange Commission, Editas Medicine — which has licensed one of the patents in question — disclosed that it has spent \$10.9 million so far this year on legal fees incurred by the Broad Institute and Harvard, mostly to defend patents awarded for CRISPR inventions by the Broad’s Feng Zhang.”*  
*“That cost is on top of \$4.7 million spent in 2015. And the dispute has, in all likelihood, years to run.”*
- *“‘The thing about patent litigation is, no matter who wins, the lawyers always win,’ said Sherkow. ‘That’s not because the attorneys are doing anything improper, but because both sides are paying their attorneys to fight vigorously. Like any war of mercenaries, their employers can call off the fight if they wish. But when both sides are invested in victory, being a soldier of fortune is lucrative.’ And when someone else is footing the bill, there is little financial incentive to call off the war.”*

# A decision is rendered.

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- On February 15<sup>th</sup>, 2017, The Patent and Trademark Office Ruled in Favor of MIT.
  - <https://www.statnews.com/2017/02/16/crispr-patent-decision-six-takeaways/>
  - <https://www.theatlantic.com/science/archive/2017/02/crispr-patent-decision/516837/>
- The judges ruled that MIT's extension of CRISPR to eukaryotic cells was not an obvious extension of the UC work.
  - *"The patent board said in its decision that the achievement of the Broad's Feng Zhang in inventing a way to use CRISPR to edit the genomes of mouse and human cells "would not have been obvious" from the invention by Doudna and Charpentier "because one of ordinary skill in the art would not have reasonably expected a CRISPR-Cas9 system to be successful" in those higher-order cells."*
    - <https://www.statnews.com/2017/02/15/crispr-patent-ruling/>
- The University of California is not about to give up. They plan to press forward with their patent on CRISPR as an overarching patent that will encompass all living things. The patent on eukaryotic cells would then be a patent on an application of the UC patent (pending).
  - *"The patent judges' opinion offered UC reason to hope: An "earlier disclosure of a genus does not necessarily prevent patenting a species member of the genus," it wrote, suggesting that a larger category of something can be patented separately from a subset of it."*
    - <https://www.statnews.com/2017/02/16/crispr-patent-decision-six-takeaways/>



# But wait! There's more!!!!

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- **“Federal appeals court hears CRISPR patent dispute;”** Science Mag.; Jon Cohen; Apr. 30, 2018.
  - <https://www.sciencemag.org/news/2018/04/federal-appeals-court-hears-crispr-patent-dispute>
  - *After the hearing, Broad issued a statement that said, “We are even more confident the federal circuit will affirm the PTAB’s judgment.”*
  - *Charles Robinson, UC general counsel and vice president of legal affairs, also expressed confidence in a statement: “We presented compelling arguments today that the PTAB committed several legal errors, including disregarding Supreme Court and federal circuit precedent. Based on the questioning today, we are optimistic that the court has serious doubts about several aspects of the PTAB’s decision.”*
- And then: **Appeals court upholds CRISPR patents awarded to the Broad Institute;** Sharon Begley @sxbegle September 10, 2018 .
- And then: **“New patent win for University of California upends CRISPR legal battle;”** Science Mag.; Jon Cohen Feb 8th, 2019.
  - *The fight over who invented CRISPR has raged for several years, and many scientists predict its creation will lead to a Nobel Prize. UC earlier lost a high-profile fight over a CRISPR patent issued to a team led by the Broad Institute in Cambridge, Massachusetts. Various companies have licensed the CRISPR-related intellectual property of Broad and UC, even as the patents have been in dispute.*
  - *The University of California (UC) has received good news on a patent for the invention of the genome editor known as CRISPR—and it likely moves a fierce legal war over who owns the valuable intellectual property for this powerful tool closer to a peace treaty.*

# Is a Settlement Possible?

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- Many expensive lawsuits are settled through negotiations rather than through protracted and expensive litigation.
  - Litigation can delay investments in the technology since companies cannot rely upon their investments being protected until they know who owns the patents.
  - Legal fees add additional expenses which may never be recovered.
- Long ago experts suggested that they should have done a deal
  - *The Broad and UC “should have done a cross-licensing deal,” said Cook-Deegan. “Everyone could have kept more money in their pockets with much [less] scientific rivalry and animus, and they could still have divvied up the rewards.” The result “really is too bad,” he added, “because UC could use the money a whole lot more than the Broad.”*
  - Dr. Robert Cook-Deegan, Arizona State University,
    - an expert on legal and ethical issues surrounding biotechnology.
  - <https://www.statnews.com/2017/02/16/crispr-patent-decision-six-takeaways/>

# Does this mean a move toward peace or further contention?

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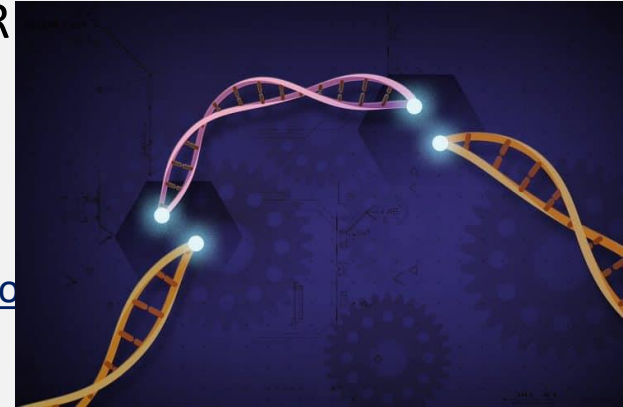
- University of California to be granted long-sought CRISPR patent, possibly reviving dispute with the Broad Institute; STAT; Sharon Begley @sxbegley; February 8, 2019.
  - *Assuming UC's patent stands, however, then attention will turn to the two patent holders' licensees, especially Editas and Caribou. Editas, of Cambridge, Mass., has an exclusive license (for use in human therapeutics) on the patents issued to the Broad Institute. Caribou licensed UC's intellectual property (and was co-founded by Doudna).*
  - *"It seems to me the companies [using CRISPR-Cas9] have to make a deal," said patent attorney Kevin Noonan, a partner in Chicago-based McDonnell Boehnen Hulbert & Berghoff. "If you want to edit genomes [for profit], you need two licenses, from both the Broad and UC" since the two institutions' patents cover such similar terrain. "Otherwise, they'll sue for infringement whoever hasn't licensed their patent."*
  - *He doubts that will happen, however, since a rational solution such as cross-licensing is available. For that, Editas would license UC's patent and Caribou would license the Broad's. That would require renegotiating the exclusive deals that the companies now have with the patent holders. "That might be in the cards, especially if they're tired of fighting over this," Ouellette said. Or as Noonan said, "**Come on, guys, you should be able to work this out.**"*

# The story continues to ebb and flow!

- 2019 brought hope to UC: “In case you needed more convincing that the IP landscape is hard to navigate, the protracted CRISPR yet another turn when the USPTO issued a “notice of allowance” to UC Berkeley last month. Who owns CRISPR now?” (March 19, 2019)

Image source: Ernesto del Aguila III, National Human Genome Research Institute, NIH

- <https://synbiobeta.com/with-the-recent-patent-news-who>



- In September 2020 things continued to be murky but leaned back toward MIT.
  - The Patent Trial and Appeal Board (PTAB) ruled on 10 September that a group led by the Broad Institute has “priority” in its already granted patents for uses of the original CRISPR system in eukaryotic cells, which covers potentially lucrative applications in lab-grown human cells or in people directly. But the ruling also gives the UC group, which the court refers to as CVC because it includes the University of Vienna and scientist Emmanuelle Charpentier, a leg up on the invention of one critical component of the CRISPR tool kit. -
  - <https://www.sciencemag.org/news/2020/09/latest-round-crispr-patent-battle-has-apparent-victor-fight-continues>

## But in 2022, the Patent & Trademark Office ruled for MIT

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- *“Ending the latest chapter in a years-long legal battle over who invented CRISPR, the U.S. Patent and Trademark Office ruled on Monday that the revolutionary genome editing technology belongs to the Broad Institute of Harvard and MIT.”*
  - <https://www.statnews.com/2022/02/28/uc-berkeley-loses-crispr-patent-case-invalidating-licenses-it-granted-gene-editing-companies/>
- The different perspectives of the scientific community versus the legal community are brought into stark relief here. The Nobel Prize to Doudna and Charpentier represent the scientific viewpoint, but the February 2022 decision by the PTO came down firmly in the side of MIT.
- Here is how one observer described it in the article cited: *“What the evidence shows is that the CVC team are like the Wright Brothers and Broad is like Boeing or Airbus,” said Sherkow. “And generally speaking, patent law awards patents to the Wright Brothers. But this decision is kind of saying that the inventor of the airplane was the first person to fly a plane across the country rather than the ones who got a plane aloft for 60 seconds at Kitty Hawk.”*

# Potential scientific misconduct?

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- *“In a departure from earlier proceedings, the University of California side focused on new evidence its lawyers filed in March 2021, which they claim showed that Zhang’s first success in editing eukaryotic cells relied on information inappropriately obtained from Doudna and Charpentier’s then-unpublished work on CRISPR’s guide RNA.”*

*“According to court filings, Luciano Marraffini, a Rockefeller University microbiologist and collaborator of Zhang’s, received a confidential copy of the now-infamous Science paper in early June, in order to review it for the journal. He also attended a public conference at UC Berkeley in which the results were discussed a week before the paper appeared online. According to emails, Marraffini conveyed details of the guide RNA structure, including a figure from Doudna and Charpentier’s manuscript, to Zhang two days prior to its publication. CVC’s attorneys argued this insight was key to Zhang ultimately succeeding in applying the technology to mouse and human cells. “*

- <https://www.statnews.com/2022/02/28/uc-berkeley-loses-crispr-patent-case-invalidating-licenses-it-granted-gene-editing-companies/>

# Wright brothers or Boeing!

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- The February 2022 decision by the PTO highlighted some key facets of the case. They agreed that the CVC group (U California, U Vienna, Charpentier) had originated the work in a test tube, but they did not develop an efficient and effective mechanism to edit eukaryotic cells. But Zhang at MIT developed an efficient and effective mechanism to do the editing in cells.  
Thus the analogy to Boeing that perfected the airplane versus the Wright brothers who demonstrated only a short and not terribly useful flight.
- The University of California (CVC) group has vowed to appeal this further, but the path forward is getting more difficult.

# Questions (posed before February 15<sup>th</sup>, 2017)

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- Based upon the facts presented who do you think should have received the patent? Explain why.
- Each side claimed that the others work as “obvious.” Why did they do that? Do you find either claim credible?
- If the dates in this case were all one year later, with filings in 2014 instead of prior to August 15, 2013, would this change the course of this case?



# Questions (posed after February 15<sup>th</sup>, 2017)

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- Do you agree with the February 2017 decision by the Patent and Trademark Court? Explain why.
- Would you expect the Patent Office to grant the patent to UC, based upon the comments of the judges in 2017?
- Do you agree with the February 2022 decision by the Patent and Trademark Office? Explain why.
- Each side claimed that the others work as “obvious.” Why did they do that? Do you find either claim credible?
- If the dates in this case were all one year later, with filings in 2014 instead of prior to August 15, 2013, would that have changed the course of this case?
- If you were leading the MIT or UC legal teams, would you try for some kind of a settlement –or just try too win it all?

# Addendum: ASEE Report August 3, 2017

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- Scientists Repair Disease-Causing Genetic Mutation In Dozens Of Embryos Using CRISPR.
- The *CBS Evening News* (8/2, story 11, 1:20, Mason) reported, “Researchers say they’ve made a major breakthrough in gene editing. For the first time, they successfully repaired a genetic mutation in human embryos.”
- The *New York Times* (8/2, A1, Belluck, Subscription Publication) reports that for the first time, scientists “successfully edited genes in human embryos to repair a” disease-causing mutation, according to a study published in *Nature*. The study “marks a major milestone and...raises the prospect that gene editing may one day protect babies from a variety of hereditary conditions,” but also raises ethical concerns about human genetic engineering.
- The *Washington Post* (8/2, A1, Cha) reports in “To Your Health” that researchers injected sperm carrying a mutation that causes hypertrophic cardiomyopathy into eggs without the mutation, and then used CRISPR to remove the mutation from the resulting embryos. The researchers found that the mutation was absent from around 72% of the embryos, and the process did not cause any other changes to the cells’ DNA.
- *USA Today* (8/2, Painter) reports that the research raises the prospect that the single mutations that cause many genetic diseases could be repaired in embryos thereby preventing them from being passed on to future generations. The article points out, however, that the US and many other countries currently prohibit genetic research that could alter germ lines, because of safety and ethical concerns.
- On its website, the *NPR* (8/2, Stein) “Shots” blog reports that the Food and Drug Administration is prohibited “from considering any experiments that involve genetically modified human embryos,” and “the National Institutes of Health will not fund any research involving human embryos.”
- *CNN* (8/2, Howard) reports on its website that some critics of CRISPR research “have argued that gene editing may give way to eugenics and to allowing embryos to be edited with certain features in order to develop so-called designer babies.”
- *STAT* (8/2, Begley) reports, however, that the researchers found the embryos used the egg’s copy of the gene without the mutation to repair themselves, rather than the genetic material that the investigators provided through CRISPR. The study’s lead researcher Shoukhrat Mitalipov said that finding should help alleviate fears that the process could be used to create “designer babies.”
  - <https://www.statnews.com/2017/08/02/crispr-designer-babies/>