CRISPR – Editing your Genome

Who invented it and owns the patent?
MIT or the University of California

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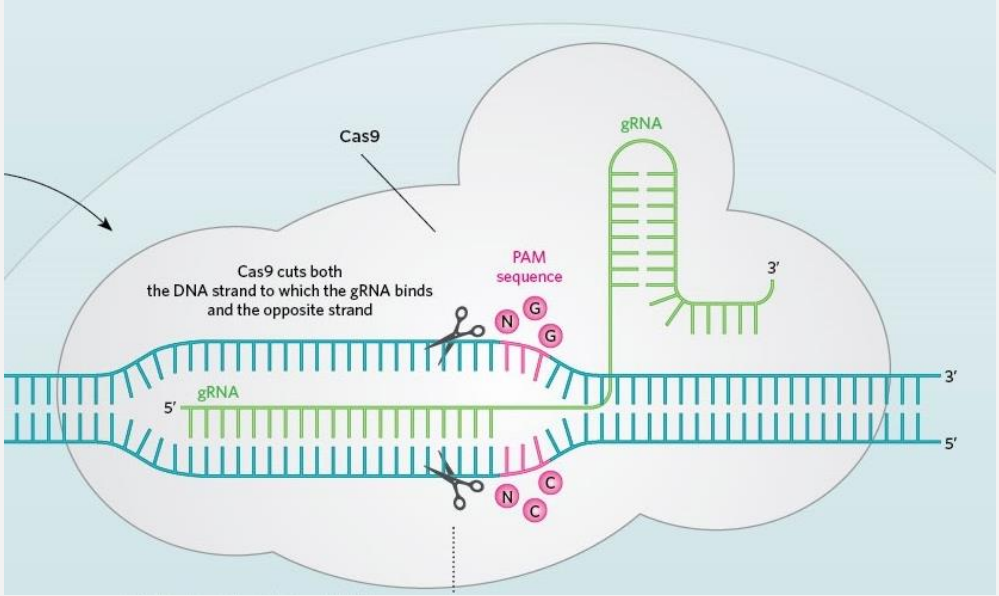
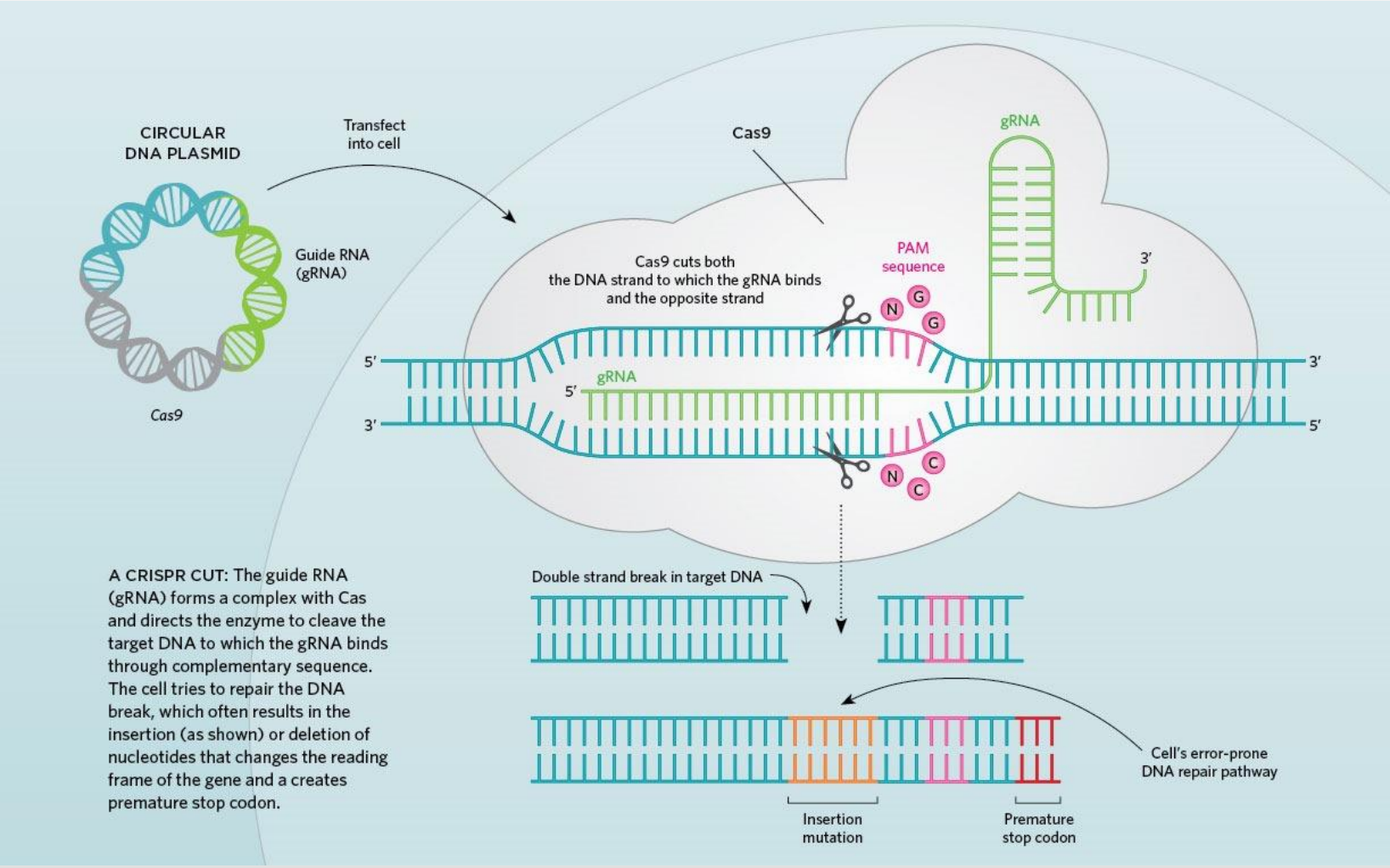


CRISPR

- **C**lustered **R**egularly **I**nterspersed **S**hort **P**alindromic **R**epeats Array



CRISPR – a way to edit the genome of living creatures

- 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 must 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.

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

- 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?
  - The latest: http://www.statnews.com/2016/03/18/crispr-patent-dispute/
  - The most recent answer: https://www.statnews.com/2017/02/16/crispr-patent-decision-six-takeaways/

Patents

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

- 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

- 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

- 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?

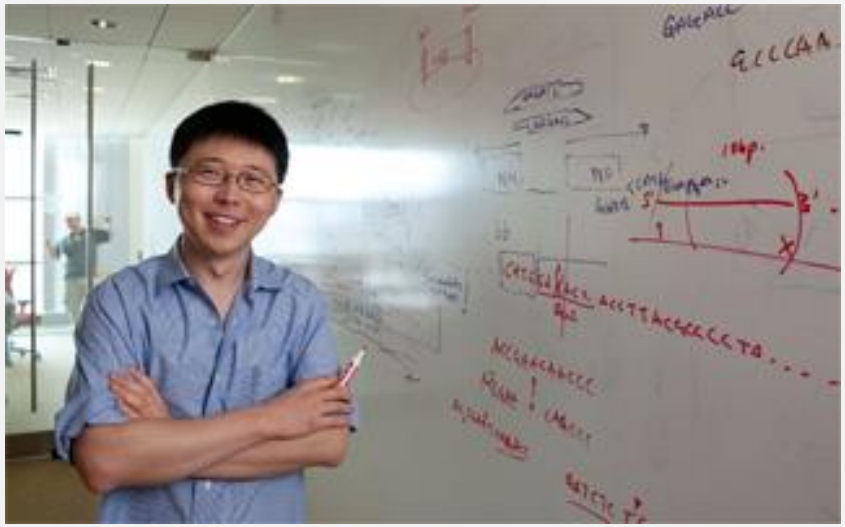
- In 2016 we were seeing one of the titanic fights over intellectual property. The potential monetary implications were huge!
  - http://www.statnews.com/2016/03/08/crispr-patent-fight/
- As we saw earlier there are two claims to be the inventor of CRISPR?
  - MIT: Feng Zhang of MIT's Broad Institute 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

"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



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

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.

"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

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

- 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?

- 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.

- On February 15th, 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/

Is a Settlement Possible?

- 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.

- *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/

Questions (posed before February 15th, 2017)

- 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 15th, 2017)

- Do you agree with the February decision by the Patent and Trademark Court? 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?
- Would you expect the Patent Office to grant the patent to UC, based upon the comments of the judges?
- 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?