WHO OWNS THE INTELLECTUAL PROPERTY? THE CRISPR-CAS9 DISPUTE

UTRF Tech Talks

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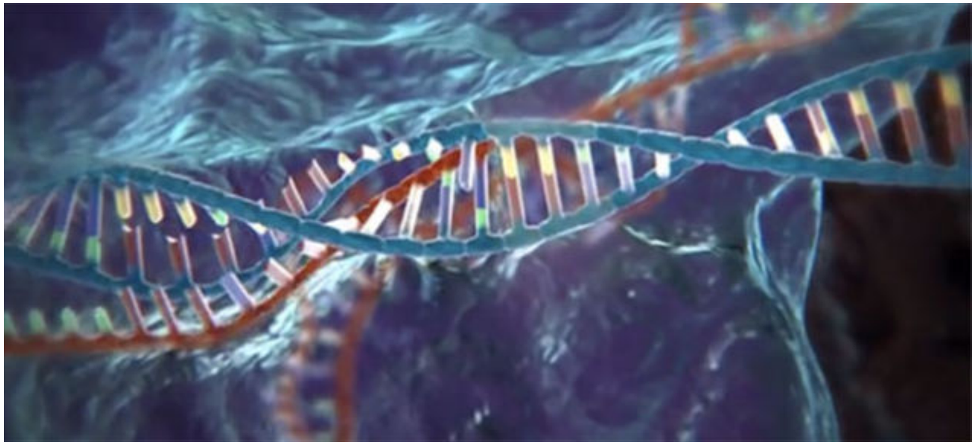
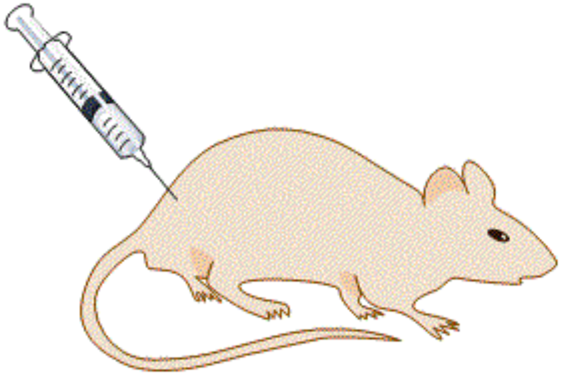
WHAT IS CRISPR-Cas9



- Clustered Regularly-Interspaced Short Palindromic Repeats/CRISPR associated proteins.
- Popular gene editing tool.
- Essential in adaptive immunity.
- Naturally occurring defense mechanism used by bacteria to protect from viral infection.
- Engineered by scientist to cut and paste other DNA sequences making it useful in genomics research.

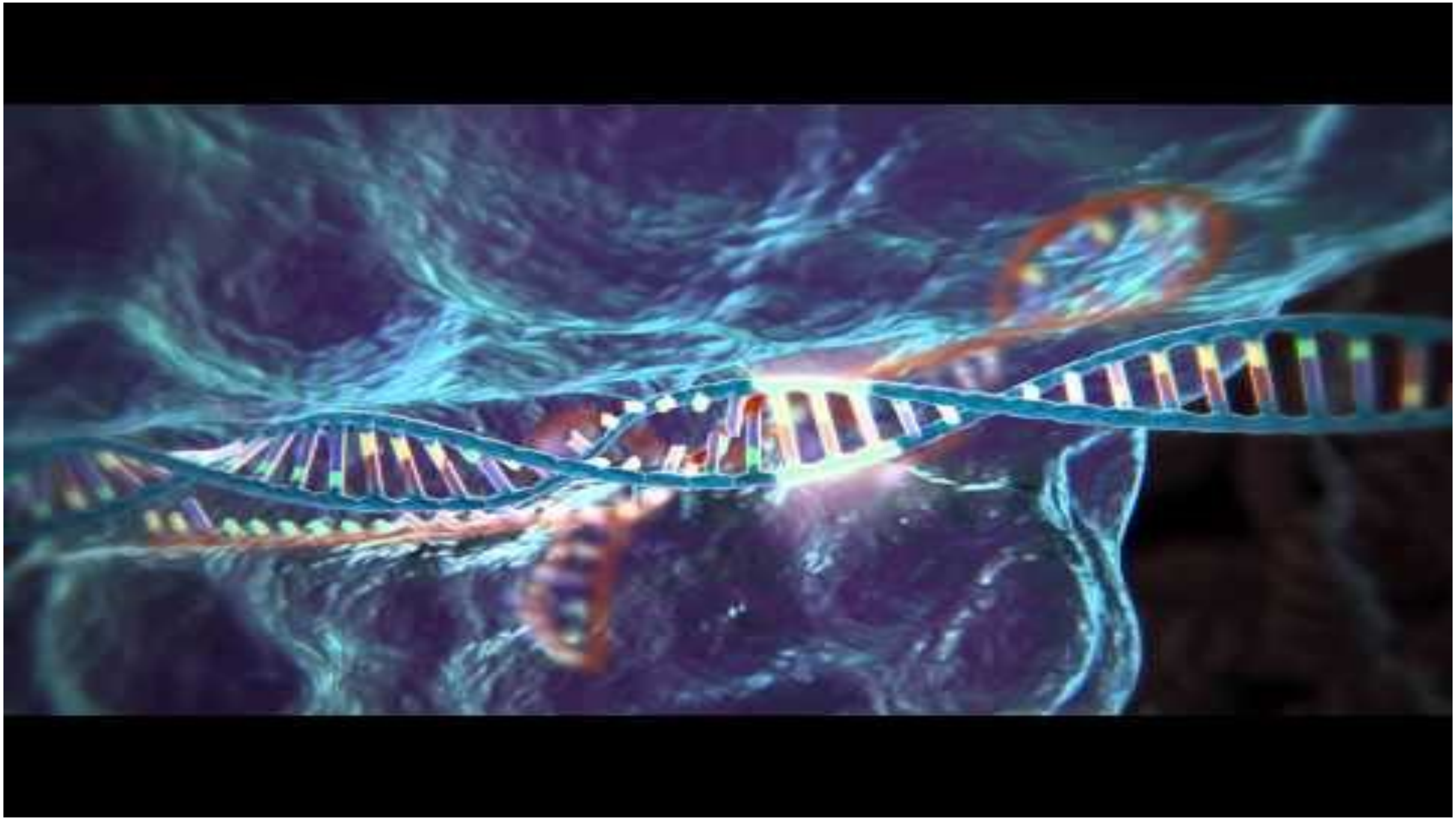
SIGNIFICANCE OF CRISPR

- Can create mouse models of human diseases **much more quickly** than before.
- Study individual genes **much faster**, and easily change multiple genes in cells **at once** to study their interactions.
- Could potentially lead to new types of treatments and **even cures** for diseases.



RESEARCH FOUNDATION

CRISPR-Cas9

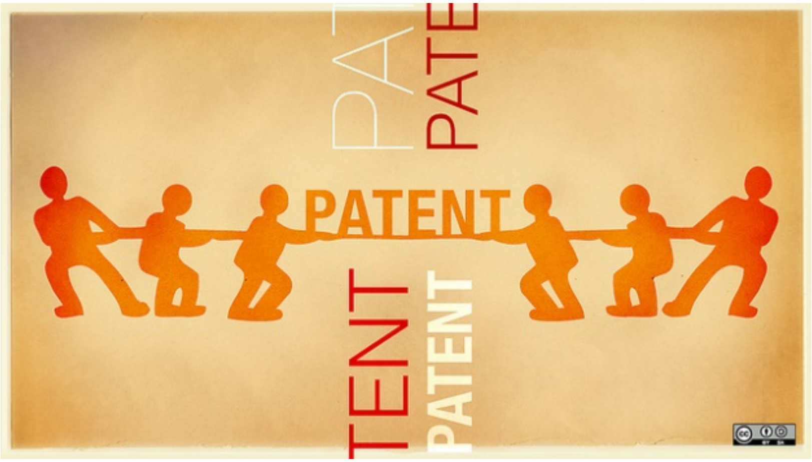


BASICS OF U.S. PATENT LAW

- A patent is granted to an inventor (one who conceives of the invention).
- Invention should be reduced to practice.

Patent Requirements

- Patentable subject matter
- Utility
- Novelty
- **Non-obviousness**
- **Enablement**
- **Claims**



- U.S. is now a **first-to-file** jurisdiction, as of March 16, 2013 (previously **first-to-invent**)
- Interference

WHO OWNS CRISPR?

- Parties working on the CRISPR-Cas Systems
  - University of California Berkley, Helmholtz Center for Infection Research, University of Vienna(Jennifer Doudna and Emmanuelle Charpentier)
  - The Broad Institute (Feng Zhang)

THE DISCOVERIES AND THE DISPUTE

- Doudna (UC) was the first to demonstrate CRISPR/Cas system's ability to target and cut DNA in prokaryotic (e.g. bacteria) cells.
- Zhang (Broad) demonstrated that this technology can be used for genetic editing in eukaryotic (e.g. plant and animal) cells.
- UC's patent application makes broader claims over using CRISPR in any organism.
- In 2012, when UC patent was filed, gene editing only demonstrated in prokaryotes. Later applied technique to eukaryotes. (Reduction to practice).
- Broad's patent claims are limited to using CRISPR/Cas9 in eukaryotes.

Did the parties claim patently distinct subject matter or does UC's application cover the entire CRISPR-Cas landscape?

HOW CAN CRISPR-CAS9 BE PATENTED?

- This naturally-occurring bacterial process cannot be patented; even if isolated.
- The parties have created **methods**, **components** and **compositions** that are **adaptations** of the naturally occurring system and made them useful in methods for editing genomes. These are all patentable.
- This naturally occurring system was repurposed.

PATENT CLAIMS

Representative UC claim (Application No. 13/842,859)

•A **method** of cleaving a nucleic acid comprising **contacting a target DNA molecule having a target sequence** with an engineered and/or **non-naturally-occurring** ….(CRISPR)— CRISPR associated (Cas) (CRISPR-Cas) system comprising a) a Cas9 protein; and b) **a single molecule DNA-targeting RNA comprising** ………… whereby….and the Cas9 protein **cleaves the target DNA molecule**.

Representative Broad claim (Patent No. 8,697,359)

•A **method** of altering expression…..comprising introducing into a **eukaryotic cell** containing and expressing a DNA molecule having a **target sequence** and encoding the gene product an engineered, **non-naturally occurring** …. (CRISPR)--CRISPR associated (Cas) (CRISPR-Cas) system comprising one or more vectors comprising: a) a first regulatory element operable in a **eukaryotic cell** ………whereby the **guide RNA targets** the target sequence and the Cas9 protein cleaves the DNA molecule, …….

TIMELINE OF EVENTS

2012

May 25, 2012, UC files provisional, CRISPR technique for use in targeting and cutting DNA (in vitro)

June 28, 2012, UC publishes *Science* paper, a new method of precisely targeting and cutting DNA

December 12, 2012 Broad files provisional application for use of technique in eukaryotic cells

January 3, 2013, Broad publishes Science Paper, CRISPR-Cas9 used for mammalian genomic editing

April 16, 2013 Caribou founded by UC inventors

April 15, 2014, Broad's patent issues (fast track). First US patent for CRISPR/Cas gene editing.

Nov 2014, CRISPR founded by Helmholtz inventor; Dec 2014, Editas founded by UC and Broad inventors.

April 13, 2015 UC filed Suggestion for interference

January 11, 2016, Patent office declares interference

2016

PATENT INTERFERENCE

- A process under the old first-to-invent patent system to resolve 2 patent applications claiming overlapping inventions.
- Applicable in this case because both applications were filed before March 16, 2013.
- Patent office (Patent Trial and Appeals Board-PTAB) considers and compares documentary evidence from the applicants concerning invention dates.
- Which applicant was the first to invent by reducing the concept to practice?

UC is alleging that Broad's patent claims what UC first invented and claimed in their patent application.

THE ARGUMENTS

Broad

- We demonstrated this system in a eukaryotic environment.
- Doudna only showed targeting and cutting of DNA. No cells, no genome, no editing.

UC

- Our application has claims that this can be done in all cells.
- Broad's patent should not be allowed because our patent claims use of the system in any organism.

THE ARGUMENTS

Broad

- UC's provisional priority application did not enable doing this in all cell types.
- There was no reasonable expectation of success that system would work in eukaryotic cells.

UC

- Using the CRISPR-Cas9 system in eukaryotic cells is not separately patentable from using the system in other cell types
- Statement in our paper and statements by experts indicate that there could be success in eukaryotic systems.
- We would not have pursued this work if we had no reasonable expectation of success

ISSUES TO SETTLE

Was Zhang's (**Broad**) work novel or was it the next obvious step to take?

Ownership rights…

The extent of ownership determines the rights that can be licensed. (not just about academics)

PTAB DECISION

- February 15, 2017-Broad's patents do not interfere.
- Patents are sufficiently different. Claims are not identical.
- "…one of ordinary skill in the art would not have reasonably expected a CRISPR-Cas9 system to be successful" in eukaryotic cells.
- Evidence that others were able to use the system in eukaryotic cells after the paper was not an expectation of success.

WHY THIS RESULT

- At the time of the patent application in 2012, UC had not demonstrated use in a eukaryotic environment. Not reduced to practice.

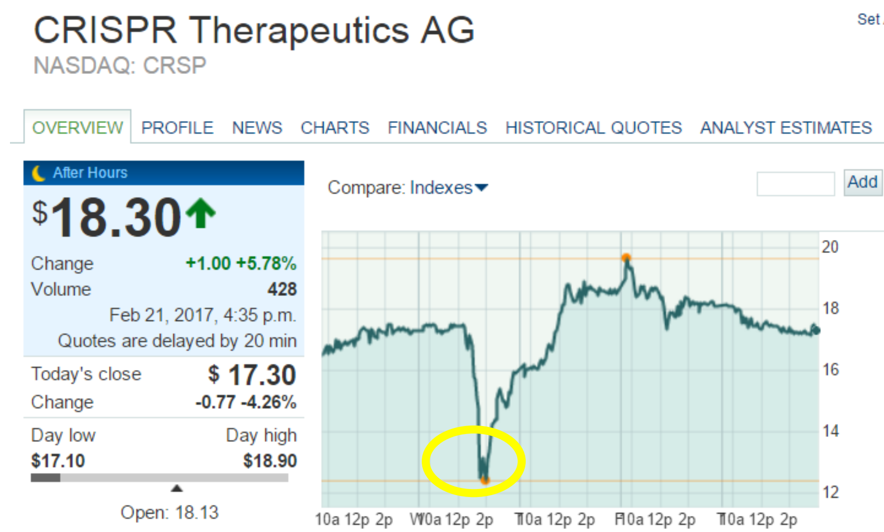
- Initial application contained broad claims.

- Claims must be supported by description in the application (experimental work).

WHAT THE DECISION MEANS

- Broad owns its patent(s). Can continue to move forward with licensing (eukaryotic).
- UC can continue with patent prosecution at the patent office. It has no issued patent yet.
- If UC's patent is ultimately granted, it would likely be limited to use in prokaryotic environments.
- Companies seeking to license IP for use in all environments would likely have to obtain licenses from both.

IMPACT OF THE DECISION



CRISPR-CAS9 PATENT LANDSCAPE

- As of November 2016, 42 patents with claims to CRISPR and/or Cas9
- 13 CRISPR patents to the Broad Institute directed to mammalian genome editing methods
- 10 additional CRISPR patents to Harvard University.
- 3 CRISPR patents to DuPont; 1 to Agilent Technologies; 1 to University of Georgia Research Foundation; 1 to Institut Pasteur, and 1 to Caribou Biosciences.
- European Patent Office (EPO) has granted six of Broad's patent applications as of February 2016.

WHY DOES IT MATTER

Companies (licensees) investing money; generating drug pipelines and developing therapeutic programs.

Broad

Editas Medicine

- Gene editing in T cells to treat cancer
- Genetic diseases of the eye
- Sickle cell
- Cystic fibrosis

UC

Caribou Biosciences

- Blood disorders and cancers
- Resistant crops

•CRISPR Therapeutics

- Sickle cell
- Cystic fibrosis
- Immuno-oncology
- Hemophilia
- Partnership with Verte

OTHER LICENSEES (RESEARCH TOOLS)

- Taconic Biosciences, Inc. (constitutive knockout and point-mutation knock-in mice).
- Horizon Discovery (makes genome edited cell lines and animals)
- Addgene-since February 2013, has shared more than 37,000 CRISPR plasmids and reagents with more than 2,000 institutions across 59 countries

TAKEAWAYS

- Keep good notebook records to prove invention and invention dates.
- Try to demonstrate every aspect of what you are claiming as your invention.
- Universities could have tried to work on settlement on the IP. As of summer 2016, the amount spent on legal fees:
  - $15+ million (Broad's licensee)
  - $5+ million (UC licensee)

QUESTIONS?

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