ERA-DEFINING LIFE SCIENCES TECHNOLOGIES WEB CONFERENCE SERIES

Navigating the CRISPR Patent Landscape and Business Impact

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Speakers

Steve Maebius
Foley & Lardner LLP
- Partner, Chemical, Biotechnology & Pharmaceutical Practice
- Partner, Patent Office Trials Practice
- Former Chair, IP Department
- Editor, *PTAB Trial Insights* blog

Katherine Breedis, CFA, CMT
Stifel Nicolaus
- Managing Director and Senior Analyst – Major Pharmaceuticals & Biotechnology
- Previously at Pfizer, Eli Lilly and Company, Schroders, Goldman Sachs, and GE Capital

Simon Elliott, PhD
Foley & Lardner LLP
- Senior Counsel, Chemical, Biotechnology & Pharmaceutical Practice
- Co-Editor, *Pharma Patents* blog

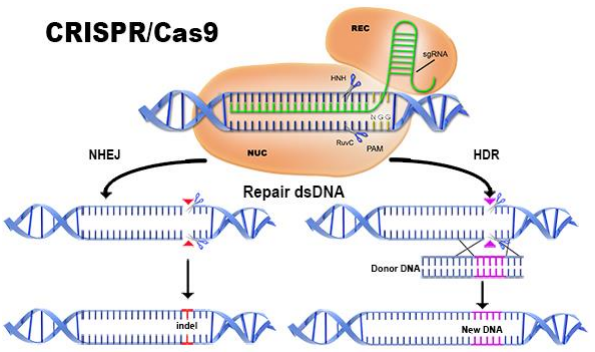
Tianran Yan
Foley & Lardner LLP
- Senior Counsel, Chemical, Biotechnology & Pharmaceutical Practice

Agenda

- What is CRISPR
- What is the market and investor viewpoint?
- What is the patent situation?
  - » Entities filing most patents
  - » Licenses
  - » Whitespace (or areas with fewer published applications)
  - » CRISPR prosecution and claim types
- Status of the CRISPR interference
- Strategies
  - » Licensing
  - » Safe harbor
  - » Enforcement

What is CRISPR?

- "Clustered Regularly Interspaced Short Palindromic Repeats"
- "Guide RNA" (sgRNA) targets a specific region for Cas9 to cut
- Cut DNA can:
  - Rejoin to delete DNA
  - Insert new DNA
- CRISPR is fast and specific
- CRISPR is a powerful tool with many applications



http://www.aati-us.com

Broad Market Opportunities

- R&D tool
  - CRISPR tools *per se* can be protected and monetized
  - CRISPR can produce cells/organisms useful for drug discovery
- Cell therapy
  - Cancer, HIV treatment (6/21: NIH approved clinical trial for CRISPR-modified cells for cancer)
  - Gene therapy
- Genetic modification of any species
  - Improved industrial fermentation
  - Crops
  - Non-browning mushrooms
  - Germline gene modification (e.g., designer babies)

Already on the Market: CRISPR-Edited Mushrooms

- Mushrooms resist browning–available now
  (see http://www.rsc.org/chemistryworld/2016/04/crispr-gene-editing-mushroom-dodges-gmo-regulation)
- How it got approved so fast?
  - » It contains no foreign DNA, so it is not classified as a genetically modified organism (GMO)
- But is it market acceptable?
- Demonstrates the promise and challenges of CRISPR
  - » Targeted market not averse to "GMO," e.g., farmers?

1st Proposed CRISPR Human Trial

- Objective is to use CRISPR to remove receptors in T cells targeting NY-ESO-1 that are expected to make them more persistent
- Designed to test whether CRISPR is safe for use in people, rather than whether it effectively treats cancer or not – approved by NIH Advisory Committee
- Funded by Sean Parker (Napster founder) institute

Publicly Announced Investments

- CRISPR Therapeutics
  - » Early VC from Versant
  - » Vertex $105M deal
  - » Bayer €325M investment in JV
- Editas
  - » $210M from several investors (Flagship, Polaris, Third Rock, Partners Innovation)
  - » $94M IPO
  - » collaboration with Juno
- Intellia
  - » VC's include Atlas Ventures, Orbimed, Novartis
  - » $108M IPO

Investor Viewpoint

- Which therapeutic areas of CRISPR are seeing a pipeline develop?
- Why is CRISPR/Cas9 perceived to be transformational for drug discovery, in vivo therapy and ex vivo therapy?
- How have the first 2 CRISPR companies to go public (Editas & Intellia) fared in terms of size, price, timing and performance since IPO?

CRISPR/Cas9 Patents

- Patent *applications* do not publish for 18 months
- Untold numbers of unpublished applications in this area
- Highlights the importance of setting up patent "watches" (monitoring at regular intervals)
  - » For drafting of dominant claims to cover later filers
  - » Identifying cross-licensing/bundling opportunities to create more valuable portfolios
  - » Should track multiple jurisdictions (e.g., US, Europe, Japan, PCT)

CRISPR/Cas9 Patents

- New applications are publishing literally every week
- Number of published US applications with "CRISPR" and "maize" in claims: 7
- Number of published US applications with "CRISPR" and "cancer" in claims: 7
- Number of published US applications with "CRISPR" and "pancreas" in claims: 2

CRISPR & Maize in Claims

	PUB. APP. NO	Title
1	20160177327	METHOD FOR PROMOTING AN INCREASE IN PLANT BIOMASS, PRODUCTIVITY AND DROUGHT RESISTANCE
2	20160138041	IDENTIFICATION OF A XANTHOMONAS EUVESICATORIA RESISTANCE GENE FROM PEPPER (CAPSICUM ANNUUM) AND METHOD FOR GENERATING PLANTS WITH RESISTANCE
3	20150307889	HAPLOID MAIZE TRANSFORMATION
4	20150225734	GENE TARGETING IN PLANTS USING DNA VIRUSES
5	20150128309	Optimal Maize Loci
6	20140304853	METHODS AND COMPOSITIONS FOR INTEGRATION OF AN EXOGENOUS SEQUENCE WITHIN THE GENOME OF PLANTS
7	20130145497	Plants Having Enhanced Yield-Related Traits and a Method for Making the Same

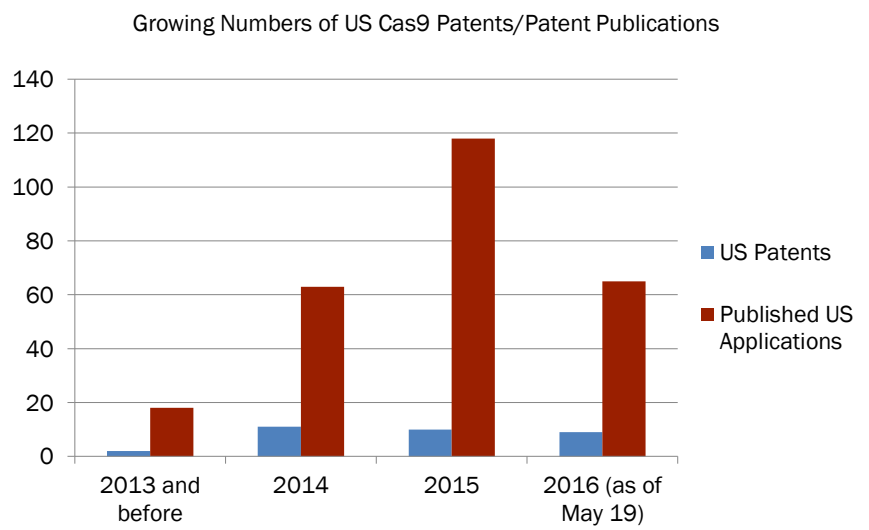
CRISPR & Cancer in Claims

	PUB. APP. NO	Title
1	20160168594	ONCOGENIC MODELS BASED ON DELIVERY AND USE OF THE CRISPR-CAS SYSTEMS, VECTORS AND COMPOSITIONS
2	20160168593	METHODS AND COMPOSITIONS FOR ENHANCING TARGETED TRANSGENE INTEGRATION
3	20160151491	CELLS PREPARED BY TRANSIENT TRANSFECTION AND METHODS OF USE THEREOF
4	20160138027	TREATMENT OF DISEASES AND CONDITIONS ASSOCIATED WITH DYSREGULATION OF MAMMALIAN TARGET OF RAPAMYCIN COMPLEX 1 (MTORC1)
5	20160120944	SYSTEMIC AND LOCAL EX VIVO GENE THERAPY OF THE SKELETON
6	20160022976	METHOD AND COMPOSITION FOR HYPERTHERMALLY TREATING CELLS
7	20150071946	TUMOR-SPECIFIC RETROTRANSPOSON INSERTIONS

CRISPR & Pancreas in Claims

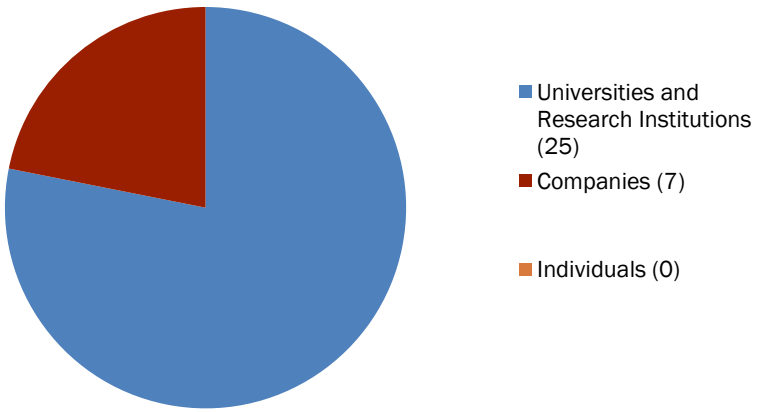
	PUB. APP. NO	Title
1	20160177273	STEM CELLS FOR MODELING TYPE 2 DIABETES
2	20150071946	TUMOR-SPECIFIC RETROTRANSPOSON INSERTIONS

CRISPR/Cas9 Patents



Who Holds CRISPR/Cas9 Patents?

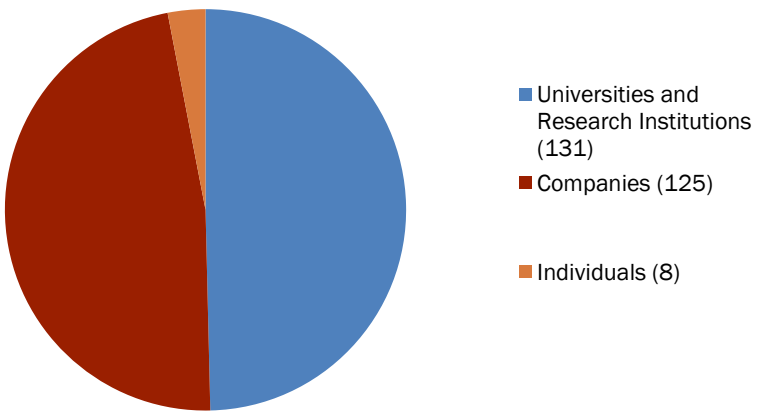
US Patents as of May 19, 2016



NOTE: Patent counts convey certain information about level of activity or investment towards obtaining protection, but scope and quality should also be considered.

Who Holds CRISPR/Cas9 Published Applications?

Published US Applications as of May 19, 2016



NOTE: Patent counts convey certain information about level of activity or investment towards obtaining protection, but scope and quality should also be considered.

Some University/Research Institution Filers

	US Patents	Published US Applications
Harvard	15	44
Broad Institute & MIT	13	35
U. Cal. & U. Vienna		8
Mass. General Hospital		7
Rockefeller U.		5
Vilnius		4
Stanford		4
U. Washington		4
U. Minnesota		3
U. Georgia	1	3

NOTE: does not cover unpublished or foreign patents; patent counts convey certain information about level of activity or investment towards obtaining protection, but scope and quality should also be considered.

Partial List of Corporate Filers

	US Patents	Published US Applications
Caribou	1	11
Regeneron	1	10
Agilent	1	9
Sangamo		15
Dow		12
DuPont	3	4
Recombinetics		6
Cellectis		4
Sigma Aldrich		4
Toolgen		4
Danisco		3

NOTE: does not cover unpublished or foreign patents; patent counts convey certain information about level of activity or investment towards obtaining protection, but scope and quality should also be considered.

Partial List of Inventors in CRISPR/Cas9

	US Patents	Published US Appl.
Feng Zhang (Broad/MIT)	13	35
David Liu (Harvard)	6	18
George Church (Harvard)	4	14
Jennifer Doudna (Berkeley)		17
Emmanuelle Charpentier (Max Planck)		8
Luciano Marraffini (Rockefeller)		7

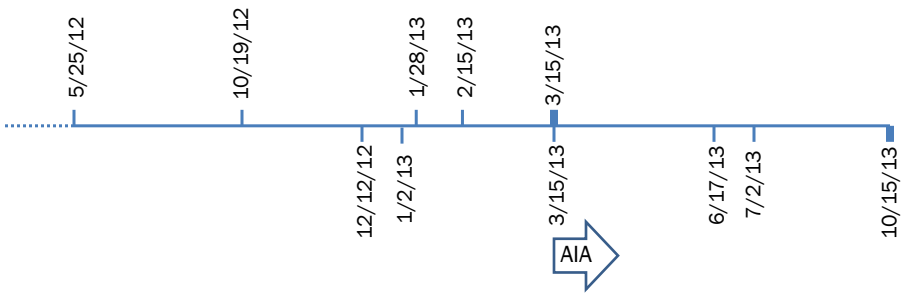
NOTE: does not cover unpublished or foreign patents; patent counts convey certain information about level of activity or investment towards obtaining protection, but scope and quality should also be considered.

Some Early CRISPR/ Cas9 Patents & Applications

		Comments
Broad Institute/Feng Zhang Patents	US Pat. Nos. 8697359, 8771945, 8795965, 8865406, 8871445, etc.	*Patent interference declared against Doudna/Charpentier patent applications
Doudna/Charpentier Patent Applications	US Pat. Appl. No. 13/842,859, etc.	*Patent interference declared against Broad's patents
Toolgen Patent Applications	US Pat. Appl. Nos. 14/438098, 14/685568 and 14/685510.	*Toolgen suggested for interference against Broad's patents in US 14/485568 and 14/685510 on April 13, 2015
Vilnius Univ. Patent Applications	US Pat. Appl. Nos. 14/385241, 14/385857, 14/683443 and 14/743764.	*Currently directed to CRISPR system assembled in vitro *The USPTO forwarded US 14/385241 to the BPAI for a potential interference on June 9, 2016

Interference

Doudna: 4 provisionals,
3/15/13 nonprovisional, all pre-AIA



Zhang: 3 provisionals, pre-AIA,
2 provisionals post AIA, 10/15/13 nonprovisional

The Current CRISPR Interference

- Senior Party – UC (US Ser. No. 13/842,859)
- Junior party – Broad Institute (US Pat. No. 8,697,359; 8,771,945; 8,795,965; 8,865,406; 8,871,445; 8,889,356; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; 8,999,641)

Scope of the Current CRISPR Interference

- Who was first to invent? (count 1):

A method, in a eukaryotic cell, of cleaving or editing a target DNA molecule or modulating transcription of at least one gene encoded thereon, the method comprising:

contacting, in a eukaryotic cell, a target DNA molecule having a target sequence with an engineered and/or non-naturally-occurring Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)- CRISPR associated (Cas) (CRISPR-Cas) system comprising:

a) a DNA-targeting RNA comprising

i) a targeter-RNA or guide sequence that hybridizes with the target sequence, and

ii) an activator-RNA or tracr sequence that hybridizes with the targeter-RNA to form a double-stranded RNA duplex of a protein-binding segment,

and

b) a Cas9 protein,

wherein the DNA-targeting RNA forms a complex with the Cas9

protein, thereby targeting the Cas9 protein to the target DNA molecule, whereby said target DNA molecule is cleaved or edited or transcription of at least one gene encoded by the target DNA molecule is modulated.

The CRISPR Interference: Preliminary Motions

- Parties dispute scope
  - » Before deciding who was *first* to invent, PTO must decide *what* the dispute is over
  - » UC argues that the count should not require *eukaryotes*
- Parties disagree on whether an interference is possible
  - » UC asserts Broad filed its applications under the AIA and therefore cannot participate in interference.
- Preliminary motions may be decided Nov. 17th at hearing
- If not dispositive, then priority phase would begin to determine who invented first

Resolution of Past Biotech Interferences

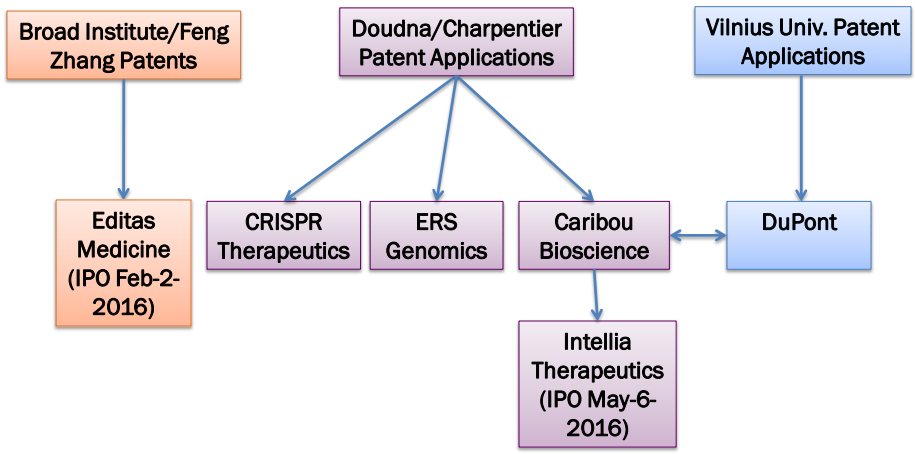
- **HPV vaccine interference timeline**

July 19, 1991	Frazer *et al*. (Queensland) file international patent application in Australia
June 25, 1992	Schlegel *et al*. (Georgetown) file patent application in US
September 3, 1992	Schiller and Lowy *et al*. (NCI, NIH) file patent application in US
March 9, 1993	Rose *et al*. (Rochester) file patent application in US
February 1995	Queensland's commercial arm UniQuest licenses HPV vaccine technology to CSL (Melbourne)
October 5, 1995	MedImmune acquires exclusive license to HPV vaccine technology from University of Rochester
1995	Merck licenses HPV vaccine technology from CSL
June 26, 1996	MedImmune in-licenses key HPV IP from German Cancer Research Center
January 7, 1997	NCI non-exclusively licenses HPV vaccine technology to MedImmune
June 24, 1997	USPTO declares initial interference
December 1997	NCI nonexclusively licenses HPV vaccine technology to Merck
December 11, 1997	MedImmune and SmithKline Beecham form worldwide HPV vaccine alliance
January 16, 1998	MedImmune finalizes vaccine agreement with SmithKline Beecham
October 24, 2001	USPTO declares **6 patent interferences** between different combinations of parties
February 2005	Merck and GSK enter cross-license agreement for HPV patents
May 2005	NCI's nonexclusive licenses convert to co-exclusive licenses
September 20, 2005	USPTO Board of Interference awards priority to Schlegel *et al*.
December 29, 2005	Frazer *et al*. appeal USPTO decision, case docketed in CAFC
August 20, 2007	CAFC reverses USPTO decision and awards priority to Frazer *et al*.

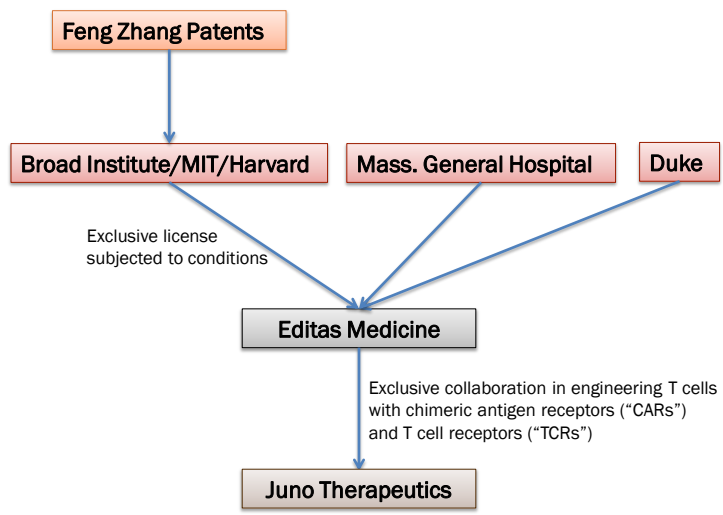
Resolution of Past Biotech Interferences

- In HPV vaccine case, parties settled before interference decided but interference continued to enable determination of first inventor(s)
- Parties may settle pending outcome of interference or parties could settle and terminate interference before final decision
- Interference started 10 year after first filed application, issues were not settled until 6 years later

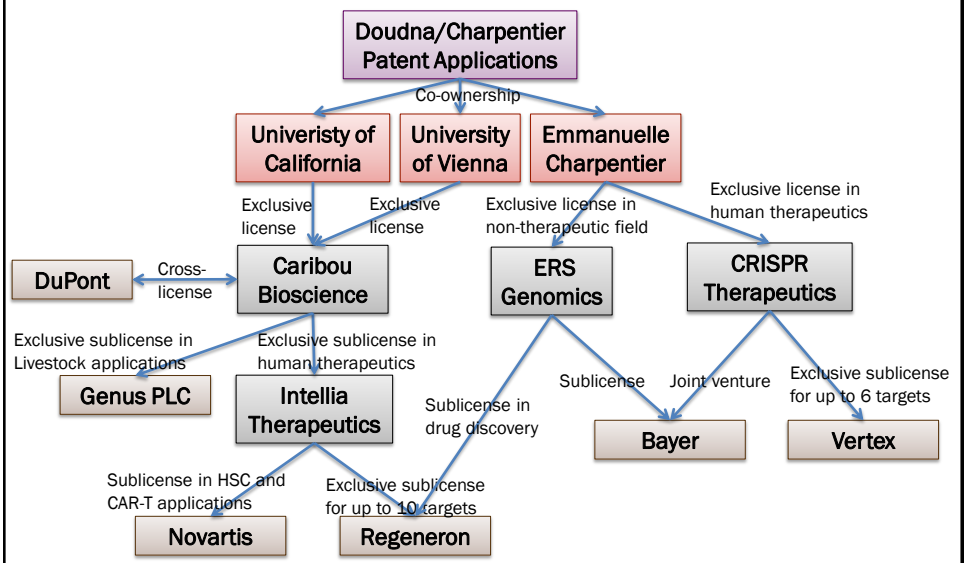
Publicly Announced Licenses to Early CRISPR/Cas9 Patents



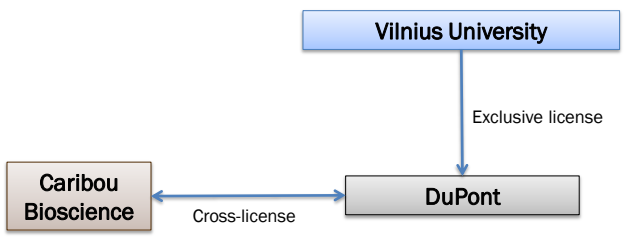
Publicly Announced Licensing Relating to Broad/Zhang Patents



Publicly Announced Licensing Relating to Doudna/Charpentier



Publicly Announced Licensing of Vilnius Applications



What is Being Claimed in CRISPR/ Cas9 Patents & Applications?

Most Common

- **Methods of using CRISPR**
  - Methods for genome editing in eukaryotic cells
  - Methods for cleaving a target DNA
  - Methods for inserting a replacement DNA for homologous recombination
  - Methods for activate or repress target DNA transcription using mutated Cas9
  - Methods for treating a disease by correcting mutations
- **Compositions/components of CRISPR**
  - Mutated Cas9 protein
  - Cas9 fusion protein (e.g., Cas9-FokI fusion)
  - Cas9-guide RNA complex assembled in vitro
  - Single guide RNA (sgRNA)
  - System comprising Cas9 and guide RNA
  - Vector encoding Cas9 and guide RNA
  - Switchable CRISPR system
- **Genetically-engineered cells/organisms obtained by CRISPR**

Patent Prosecution Lessons for Handling CRISPR Cases

- **Eligibility**
  - Some subject matter is difficult to claim in different jurisdictions
    - Human treatment
    - Cloned animals
    - DNA sequences
    - Natural processes
- **Reach-through claims**
  - Can a patent on a basic invention reach through to a valuable end product?
  - May depend on quality and number of examples
- **Prior art**
- **Double patenting**

New CRISPR Areas

- CRISPR system that does not use Cas9 enzyme, e.g., CRISPR/Cpf1
  - » Analogies to PCR and *Taq*
- CRISPR-like systems, e.g. NgAgo
- Investment issues
  - » How will these perform relative to CRISPR/Cas9?
  - » Overlapping claim scope and improvement claims

New CRISPR Areas, *cont.*

- Specific CRISPR applications in human therapeutics
- New species created by CRISPR
  - » DuPont-Pioneer's CRISPR/Cas9-edited waxy corn
  - » Penn State's CRISPR/Cas9-edited white button mushroom (announced filing of provisional patent application, but not yet published)
- Gene drives that spread CRISPR editing of a gene through a population, such as mosquitoes bred to be resistant to malaria

Licensing Strategies

- Some have pointed to Cohen-Boyer patent on original genetic engineering methods
  - » Low cost and widely licensed on a non-exclusive basis
  - » *"Stanford was trying to license an invention for which products had never been sold and which would apply to many diverse, established industries, in addition to the newly emerging biotechnology industry."* Ku, 1983 (LES meeting)
- Some commentators fear that CRISPR will be owned by a single entity, but so far there have been many collaborations/licenses and research programs announced, as well as one ag product already on the market

Licensing Strategies

- How to license in the face of uncertainty and potentially overlapping patent positions?
- Anti-royalty stacking (offsetting payments based on future licenses that may be required)
- Contingent payments (contingent on issuance of future claims covering actually developed products)
- Indemnification (requiring licensor to address need for future licenses)
- Narrow fields of use; research v. commercial

Enforcement Challenges

- What kinds of products will be made?
- Can use of CRISPR be detected in the end product?
- §271(e) Safe Harbor in the US and research use exemptions abroad
- *Bayer v. Housey* § 271(g) loophole – importing information (chemical structure) does not infringe a US method patent if steps performed in a country where it is not patented

Conclusions

- Some areas offer quick commercialization pathways (e.g., agbio – CRISPR mushroom)
- Claim strategy should consider who is performing various steps, how components and intermediates are used, and ultimate commercial end products
- Moving quickly to identify end products will allow further patent applications to be filed
- Monitoring competitor applications through regular systematic key word searching of both US and foreign patent applications to assess filing dominant claims
- Creative licensing strategies may be needed to address current uncertainties (anti-stacking, cross-licensing/ bundling)

Thank You

FOR MORE INFORMATION:

Foley proudly presents Era-Defining Life Sciences Technologies, a web conference series that addresses the key intellectual property issues and business challenges of technology innovations – including those contributing to the discovery, development, and commercialization of regenerative and personalized medicines – that are disrupting the life sciences industry and creating new and uncertain opportunities.

Future series topics will include chimeric antigen receptor (CAR) T-cell immunotherapies and induced pluripotent stem cells (iPSCs).