Update on the CRISPR IP Saga and lessons to be learnt

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#healthcare #intellectualproperty

Background

In the **last 6 years** this field has generated:

- 600+ pending European patent applications
- 40+ granted European patents with “CRISPR” in the claims;
- 20+ oppositions in Europe;
- CRISPR market est. $10 billion by 2025
- $300 million in venture funding for gene-editing start ups,
- $3 billion+ est. combined value of publicly traded companies in this space (Citi GPS)

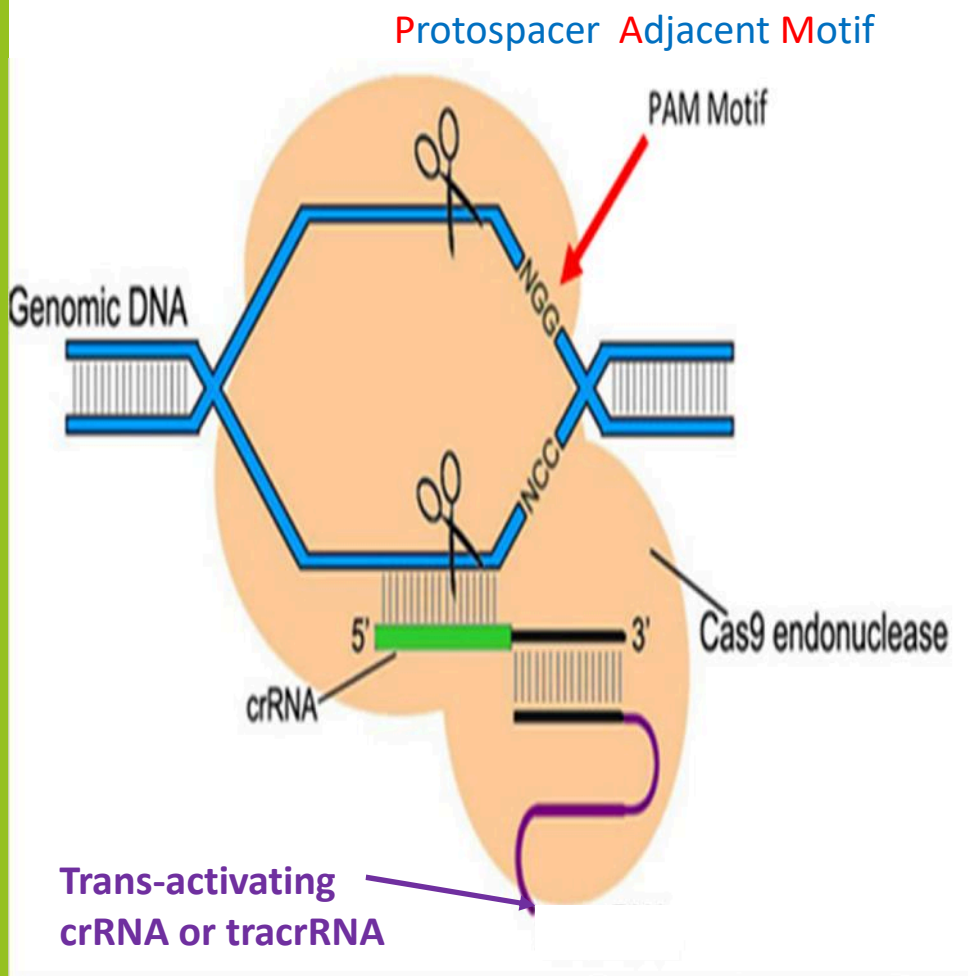
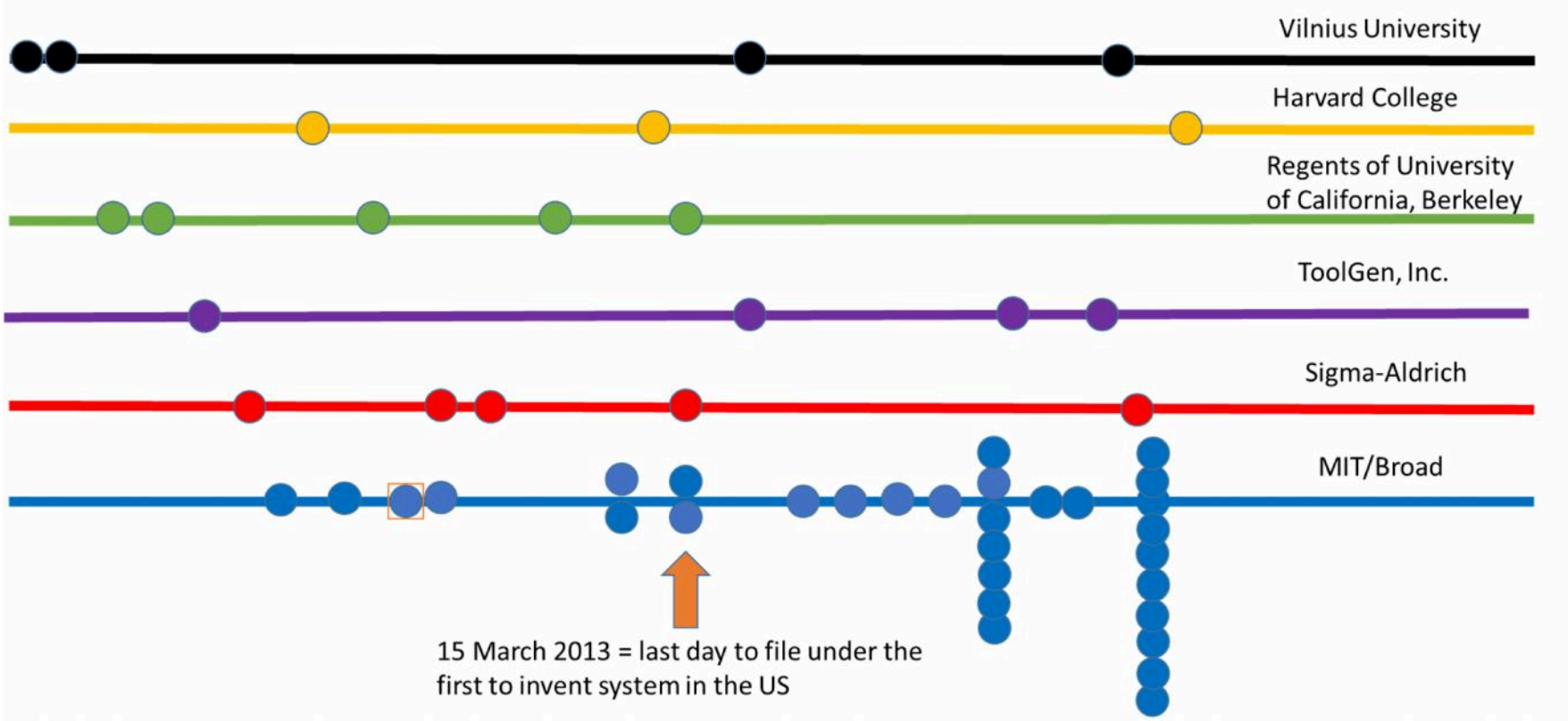


Diagram adapted from https://www.thebestgene.com/CRISPRInfoPage.do

Filing Pattern March 2012 to December 2013



EPO Oppositions

UC have earliest priority claim but accelerated prosecution strategy meant Broad achieved grant first

Broad/MIT/ Harvard ('Broad'):

Lead patent (EP2771468) revoked Jan 2018; appeal in progress;
10 oppositions pending; more applications

University of California et al. ('UC'):

2 patents in opposition, 1 due to grant April 2019 & new divisional
(NB also separate GB patents)

Sigma-Aldrich:

3 patents in opposition; additional applications

Toolgen:

1 patent in opposition; additional applications

Cellectis:

patent to preparing T-cells in opposition

Opposition Filing

With oppositions to the CRISPR EPs has crept in a new race strategy for those wishing to be Opponent no. 1 – file Notice as soon as possible (day of grant even) and complete opposition later within the 9 month term permitted.

Has been challenged but will the EPO stop? How little will do at start? Add in ability to file an opposition as a strawman and opportunity for abuse.

The US Interference No. 106,048

- Inevitable result of Broad's accelerated prosecution strategy

Broad/MIT/Harvard - Junior party
(Patents 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 & USSN 14/704,551)

v

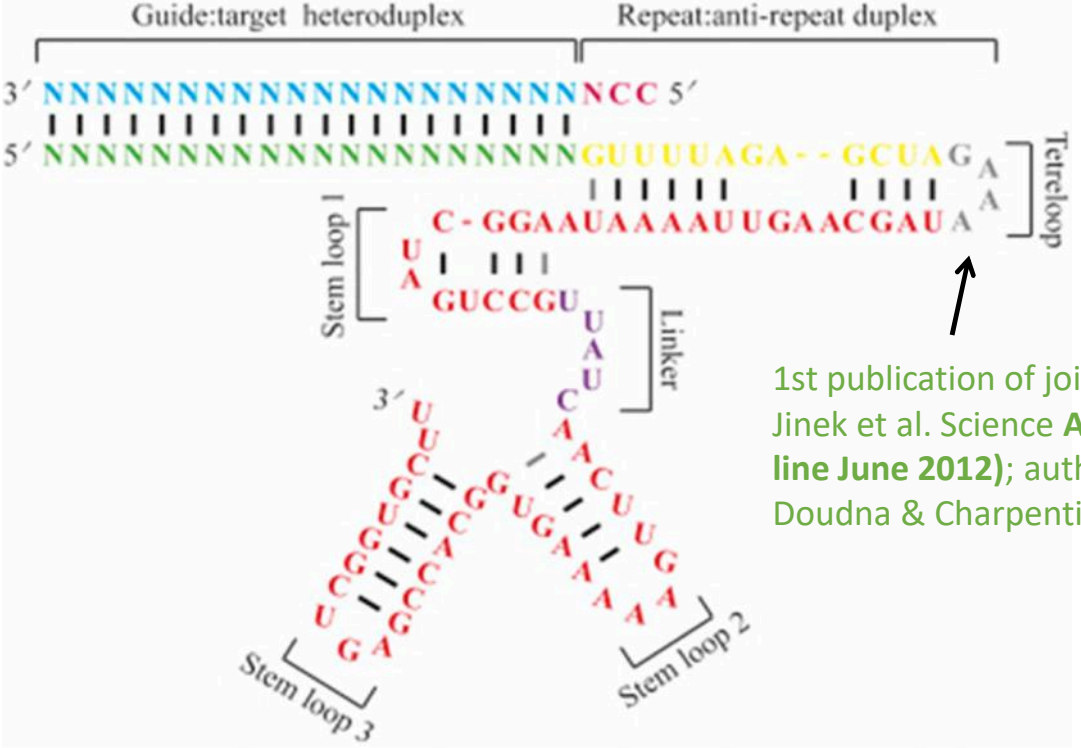
(USSN 13/842,859) **UC/ University of Vienna/ Emmanuelle Charpentier – Senior Party**

PTAB: BROAD PARTY WIN - no interference in fact
Following publication of Jinek et al (2012),
"one of ordinary skill in the art would not have reasonably expected a CRISPR-Cas9 system to be successful in a eukaryotic environment"

CAFC: Upheld September 2018

UC Berkeley

- sgRNA – Jinek 2012
- PAM
- Missing essential technical features
- DNA binding proteins

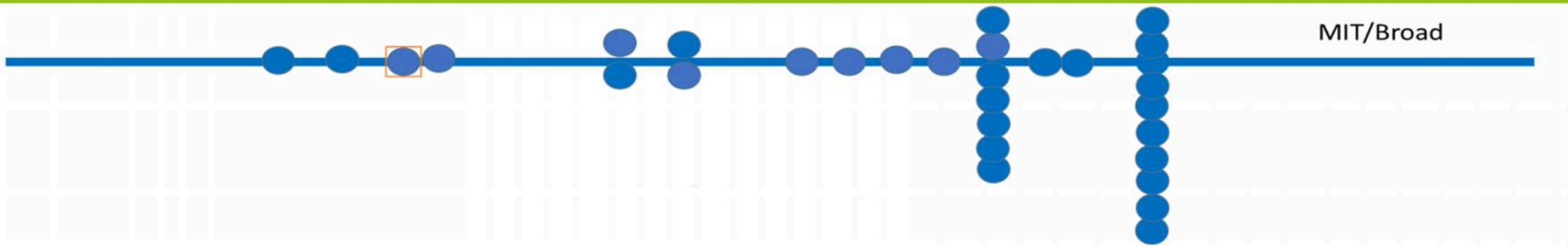


1st publication of joining linker in Jinek et al. Science **Aug 2012 (on-line June 2012)**; authors include Doudna & Charpentier

Diagram: Mei *et al*. Genetics and Genomics (2016) 43: 63-75 2016

Broad's Strategy

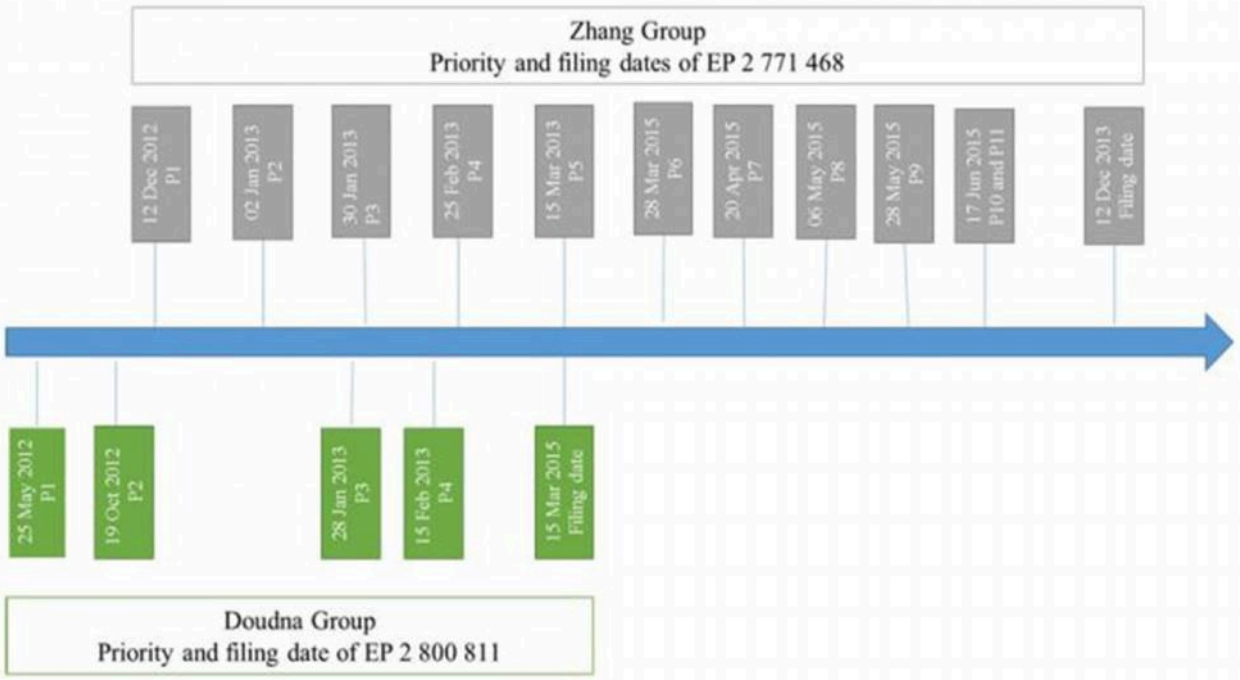
- Invest: number of priority filings a mixture of top-ups expanding on previous filings and ones having different focus
- Thicket and expedite to gain a dominant position
- Moving towards patent pools - do we want single cover all patent applications in emerging technologies?
- **ADVANTAGES**: early dominant position despite filing later
- **DISADVANTAGES**: costs, splitting out the inventions/ ownership consideration has led to priority issues



Interwoven priorities

- Series of priority filings
- UCB – one patent of broad scope
  - expanding on the disclosure and data in each – series of top-ups
- Broad – thicket approach
  - mixture of top-ups and priority filings with different focus
  - Generating a number of overlapping patent applications

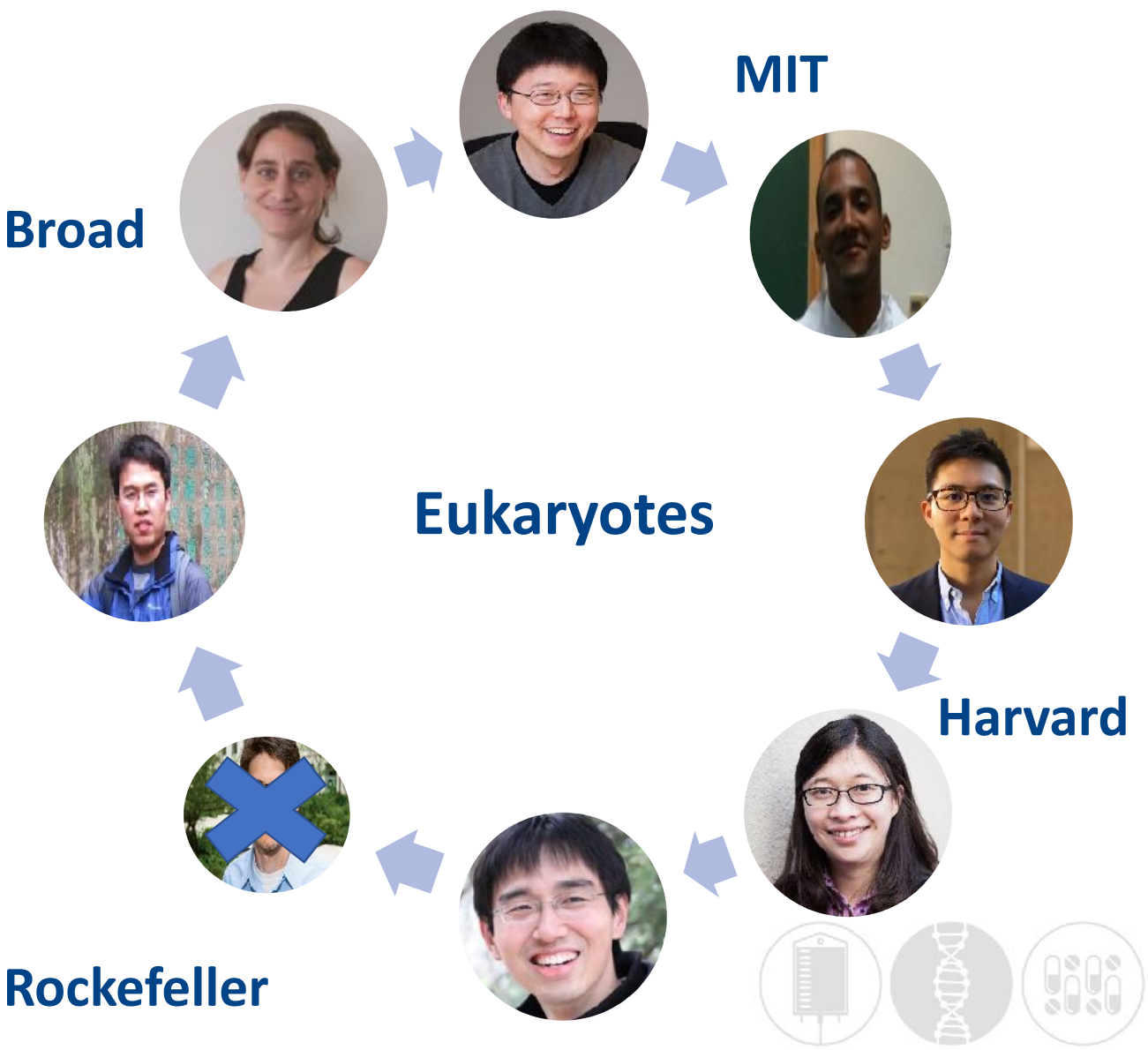
Figure 1: Timeline of filings by the Zhang and Doudna groups



Broad's priority issue

The Marraffini Issue:

- The main priority issue in the lead opposition to Broad's EP2771468
- Lack of consistency between inventors listed as applicants on 1st & 2nd priority filings and applicants for PCT filing as regards assignment of priority right



Keeping Priority

At the 12 month date from the priority filing, e.g. PCT filing date, Article 87(1) EPC applies

Article 87(1) EPC: Any person who has **duly filed**, in or for any state party to the Paris Convention…. **an application** …. or **his successor in title** shall enjoy, for the purpose of filing a European patent application in respect of the same invention, a right of priority during a twelve month period from the date of filing of the first patent application.

Appeal Decision T788/05

The principle of legal unity where an earlier application was filed by co-applicants

"the priority right belongs simultaneously and jointly to the two applicants, **who thus constitute a legal unity** unless one of them decides to transfer his right to the other applicant, who then becomes his successor in title **and this is before the filing date of the application**."

Priority Lesson

Make sure right to priority clearly with Applicant(s) at 12 month date for foreign fillings or PCT filing

- Get assignments properly executed from inventors within 12 month period;
- Should be signed on behalf of both parties

[English courts will consider legal principle of beneficial interest but best not to have to prove]

Appeal T725/14

Minutes February 2019 advise:

- The “or” in Article 87(1) EPC (in “or his successor in title”) is not an inclusive “or”
- Priority European application filed by Company A;
- A assigned to B before filing of PCT Application claiming priority;
- PCT application filed in name of A with subsequent recordal of B as applicant;
- No valid claim to priority of Applicant; carries through to divisional
- Priority application had been allowed to publish & Article 54(3) prior art for novelty assessment.

Priority Lesson 2:

- Be careful over inventorship
- Easy to add an inventor; more difficult to remove (except in the US! At EPO need agreement of inventor)
- Priority rights must be with the Applicant at the PCT FD, but ownership/ entitlement can be perfected later.
- Possible correction route for wrong applicant at PCT FD for UK entity – entitlement action at the UKIPO

Broad salvage claims Feb 2019

Information issued by EPO Feb 2019 on opposition oral proceedings for EP2896697

But narrow claims – restricted to very narrow guide RNA definitions

(1)

NNNNNNNNNNNNNNNNNNNNGTATTAGAGCTAGAAATAGCAAGTTAATATAAGGCTAGT

CCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTT

(2)

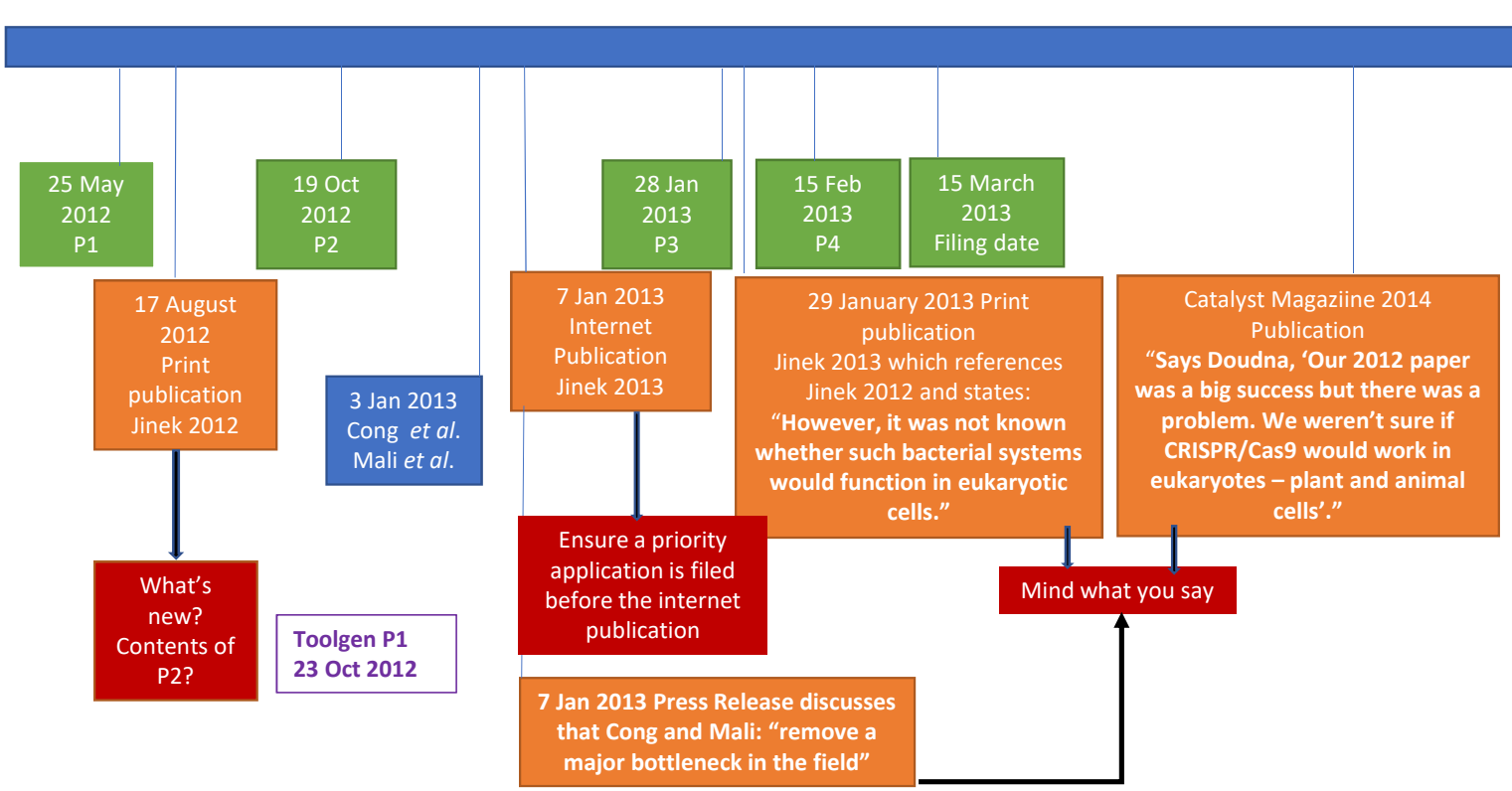
NNNNNNNNNNNNNNNNNNNNGTATTAGAGCTATGCTGTATTGGAAACAATACAGCATAG
CAAGTTAATATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTT
TTTT.

Mind What You Say

Even after a priority filing

- **In the US interference both the PTAB and CAFC gave more weight to contemporaneous statements** at the time CRISPR-Cas9 was first announced to work in eukaryotic cells and soon after
- Included Berkeley News website announcement on 7 January 2013 of the Jinek et al 2013 eLife paper **with link to unpublished paper**

PTAB: "if the inventors themselves were uncertain, it seems that ordinary skilled artisans would have been even more uncertain"



Timeline showing the priority and patent application dates of EP2800811A (UC Berkeley) in green, publications by the inventors in orange, third party publications in blue and considerations in red.

First published LSIPR 29-10-2015 "CRISPR: careless talk costs patents" C. Coombes, HGF Limited. Box added to show timing of Toolgen P1

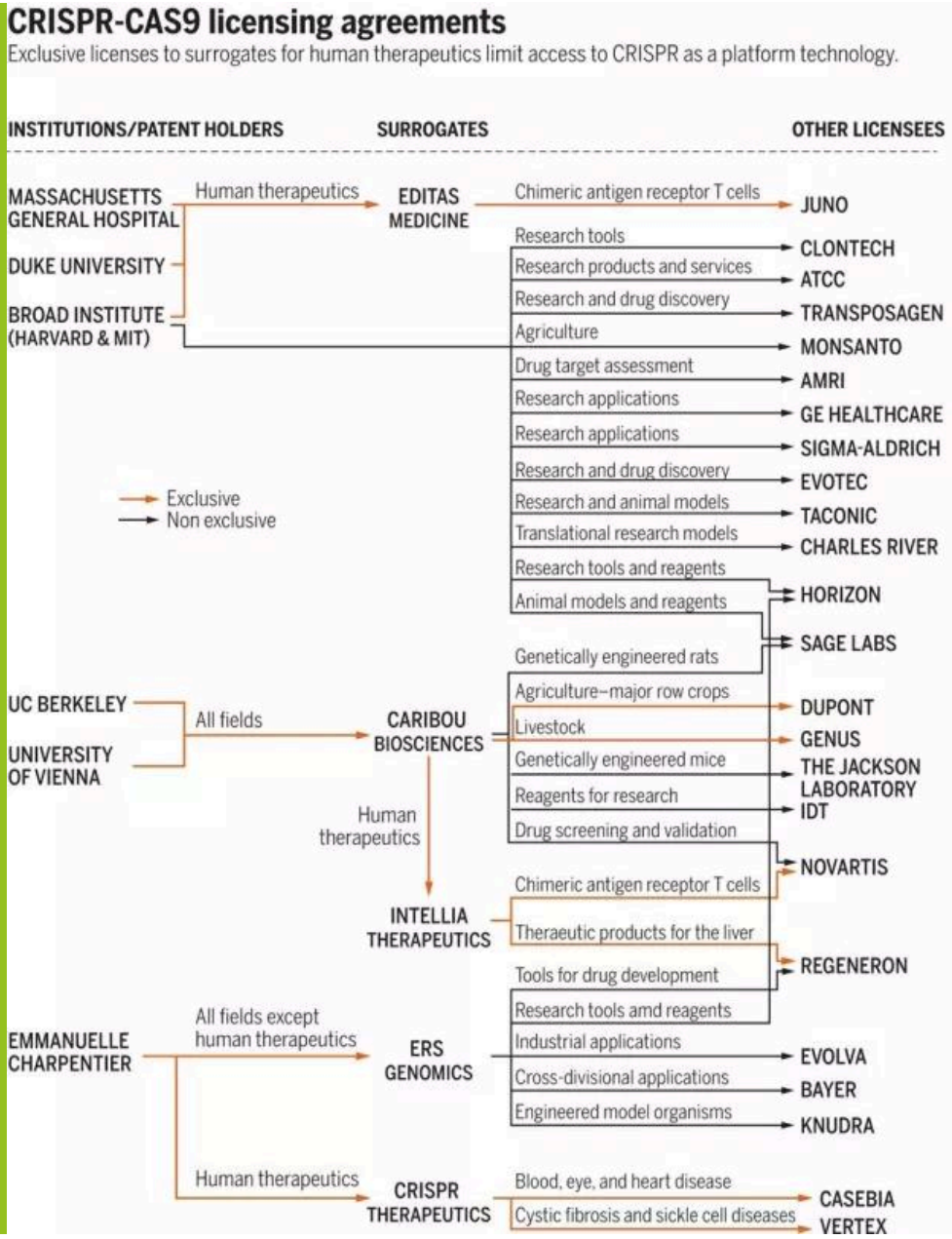
Landscape

- 2000+ patent families;
- Overlapping rights;
- Key components for therapeutics still unknown.
- What improvements will become essential?
- More than CRISPR/cas9

Image from CRISPR Therapeutics 2015 website

The FTO Minefield

- Basic research no FTO needed but number of reach through licences available;
- Licences required for CRISPR/cas9 for carrying out ds breaks, modulating DNA, amplifying DNA, using sgRNA
- Do not appear to be enforcing rights currently
- For agriculture, collaboration in place
- Discussion of a patent pool



New uses & IVS

For new application of CRISPR need to establish **not obvious one-way street** scenario; **advantages** must be **more than mere bonus effect** of obvious route

Example of prosecution problem: Exam report 2017 for EP3019595A (Harvard et al.) re use of CRISPR/cas9 to correct sickle cell disease

Reply since filed restricting to primary human cells and prosecution on-going

EP2931897 (Broad et al) Article 54(3) prior art re CRISPR/Cas9 for therapy- under opposition

"Of course the applicant will try to argue that it was not a one-way street situation because he could have chosen other options… **However, where one option is akin to a motorway while the other is winding unpaved roads, the applicant is presented with a clear one-way street situation**."

Definitions

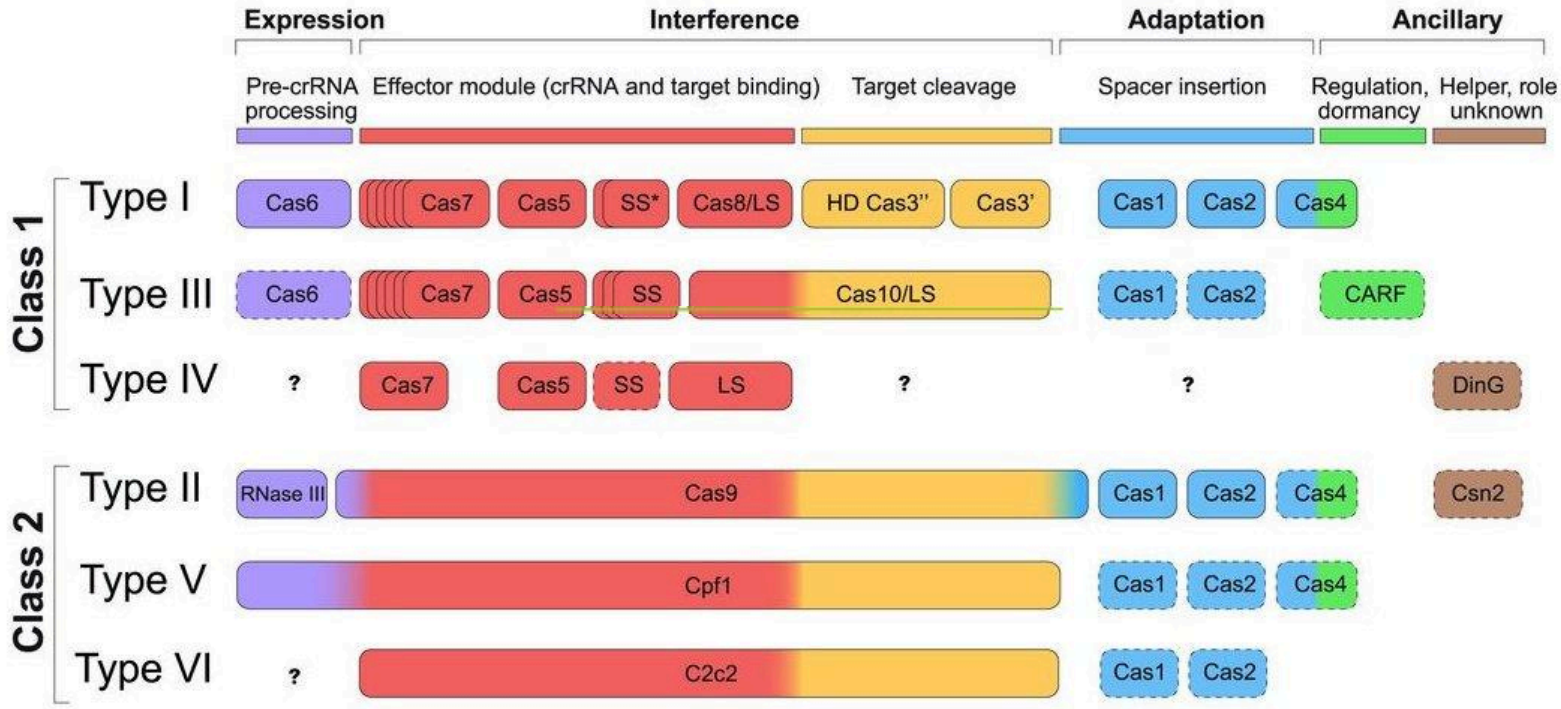
- Beware of 'boilerplate language' which simply adds pages you pay for, but also beware need for a term to extend beyond conventional use

- Drafting now needs to take account of other Class 2 CRISPR systems

What makes a polypeptide a Cas9 polypeptide when departing from naturally occurring proteins? If only interested in DNA cleavage can rely on maintenance of function, but if invention encompasses the use of dead Cas9?

Post-grant: How broad could "Cas9 polypeptide" be if apply infringement analysis of UKSC in Actavis v Eli Lilly?

Some of the complexity



The 3 questions:

i) Notwithstanding that it is not within the literal meaning of the relevant claim(s) of the patent, does the variant achieve **substantially the same result in substantially the same way as the invention**, i.e. the inventive concept revealed by the patent?

ii) Would it be obvious to the person skilled in the art, reading the patent at the priority date, but knowing that the variant achieves substantially the same result as the invention, that it does so in substantially the same way as the invention?

iii) Would such a reader of the patent have concluded that the patentee nonetheless intended that strict compliance with the literal meaning of the relevant claim(s) of the patent was an essential requirement of the invention?

Can Cas 9 = another Class 2?

Also need to consider definition of RNA = “DNA-targeting RNA” in UC’s divisionals

Put in effort at the start

- **The ToolGen problem**; beware the quick US filing

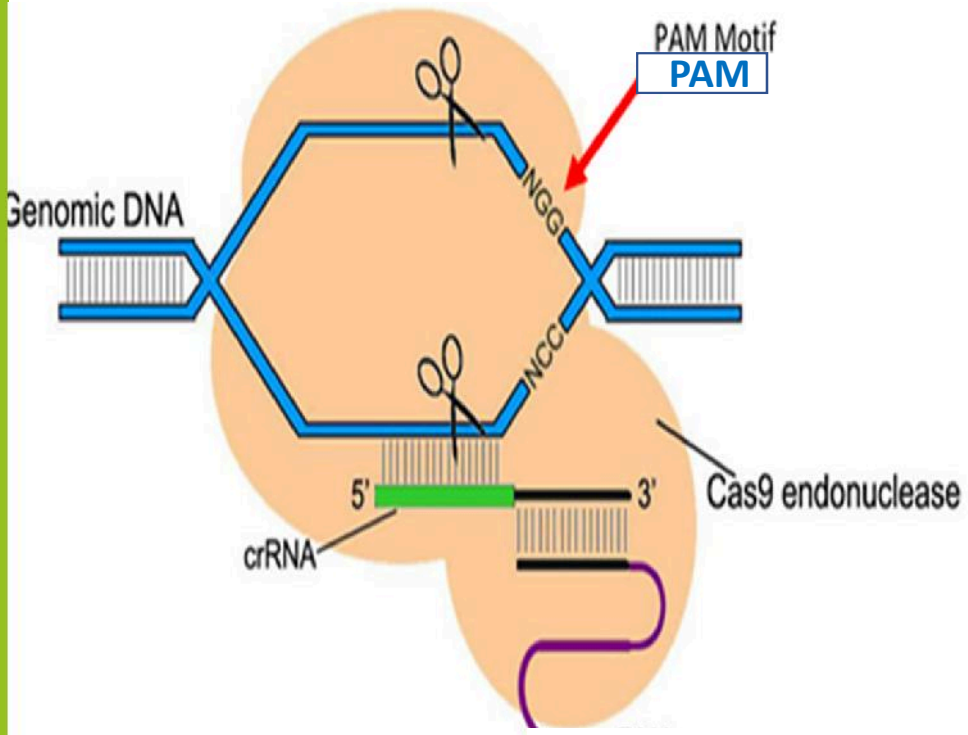
- First to file US provisional on use of CRISPR/Cas9 cleavage in eukaryotic cells, but little more then a draft of a journal paper meaning added subject matter and inventive step attacks at the EPO

EP2912175B specifies Cas9 with one NLS at the C-terminus + sgRNA; under opposition

Korean patent issued; licensed by Thermofisher

Put in effort at the start-2

- Main issue at EPO for UC remains the missing essential feature
- Overcame before the UKIPO for corresponding GB patents
- Common general knowledge argument, but context of CGK raised in opposition
- GB patents free of opposition & ready to be enforced in the English courts



Breadth of UC's claims

- If the PAM issue is overcome, then this will not be the end of the priority issues argued by the opponents
- 2nd Divisional EP3401400A due to be granted 3rd April with method claims referring to target DNA cleavage in a single-cell eukaryotic organism, **an animal cell or plant cell**.
- Expect early opposition

Think from the start about plausibility of extrapolation from the exemplification

Thank you

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