Questions about CRISPR

A huge industry will grow from its innovation, but the IP environment around CRISPR is far from established. **Marc Döring** and **Daniel Lim** investigate

The discovery of the potential of CRISPR and its first characterisation in the form of the CRISPR/Cas9 system represents a true revolution in the life sciences field. It is best known as a method that allows for the accurate and targeted cutting of DNA to enable editing of genes, but variants can accomplish a wide range of other extremely useful effects, including modulation of gene expression. The power and versatility of the system has opened the door to advances in a wide range of industries, including human therapeutics, animal health, agriculture and bioindustry. CRISPR has the potential to revolutionise any industry in which molecular biology and genetic technology play a part.

However, despite the clear potential of the technology, and leaving aside the significant amount of research and development still to be undertaken, question marks linger over the legal and regulatory position of CRISPR technology and CRISPR-based products.

Perhaps the most significant of these questions are:

- How to navigate and obtain freedom to operate in the current complex CRISPR IP licensing landscape;
- How the CRIPSR IP landscape may evolve by the time CRISPR-based products come to market;
- What sorts of CRISPR patents and products will come to be most commercially relevant in the long term; and
- How might regulatory and ethical issues impact on the development of CRISPR technology and products?

In this article, we will focus on the current and future CRISPR IP landscape, with particular reference to what we can learn from the public statements of the three principal CRISPR spin-out companies: Intellia Therapeutics (Intellia), CRISPR Therapeutics (CRISPR Tx) and Editas Medicine (Editas).

The complex CRISPR licensing landscape

The patents covering the fundamental components of the CRISPR/Cas9 system are held by three groups of institutions and individuals, who are currently embroiled in a global dispute as to who owns the foundational CRISPR/Cas9 IP. Each group features a pioneering CRISPR researcher who, together with their backing institution(s), has formed spin-out companies as vehicles to license and commercialise the CRISPR/Cas system for various applications.

One group comprises Intellia, Caribou Biosciences (Caribou), Caribou founder Jennifer Doudna and the University of California, Berkeley (UCB). That group is broadly aligned with CRISPR Tx, ERS Genomics and its founder Emmanuelle Charpentier, who collaborated with Doudna and co-owner of UCB's foundational CRISPR patents. On 16 December 2016, the Doudna and Charpentier camps formalised their alliance, signing a global cross-licensing and patent prosecution co-operation agreement.

Opposing them is Editas, its founder Feng Zhang and the Broad Institute of MIT and Harvard (the Broad), who hold a separate, competing portfolio of foundational CRISPR/Cas9 patents.

These spin-out companies have wasted no time in partnering variously with big pharma, venture capitalists and fellow disruptive biotech start-ups in a complex series of exclusive and non-exclusive licensing deals, joint ventures and strategic collaborations (see figure 1).

An analysis of the licensing activity of each of the groups reveals a clear division of the potential applications of CRISPR into four fields of general use, with distinctly different licensing policies applicable to each:

Basic non-commercial research: Non-commercial entities engaging in basic and other non-commercial research will likely be able to take advantage of non-exclusive licences to the technology, for example through plasmids made available on Addgene by both the Broad and UCB.

Development of tools to facilitate CRISPR-based research (eg kits, reagents, preclinical models and equipment): This is a field in which many non-exclusive licences have already been granted and more are likely to be available. The rationale behind this policy seems clear. The development of basic research tools encourages and facilitates further CRISPR-related development; in addition, increased participation in the CRISPR field will increase licensing revenue from the foundational IP.

Human therapeutics and diagnostics: This field is likely to be closely controlled by the spin-outs and subject to exclusive licences. It would appear that each of Intellia, CRISPR Tx, and Editas deals solely with human therapeutics – the commercialisation and rights to other fields

of use are left to other spin-outs retained by the proprietor institutions.

As probably the most commercially significant field, it is in the interests of these companies to sub-divide it as much as possible. The spin-outs will seek to attract investment from exclusive licensees and collaborators to develop CRISPR-based therapies for specific indications/research targets. At the same time, they will continue to pursue their own in-house research and development in respect of a number of lead targets.

Such in-house research has the dual purpose of showcasing their own technical expertise (and hence their attractiveness as a partner in a collaboration), as well as potentially leading to a viable future product.

Other fields (eg animal health, agriculture and bioindustry)

For fields outside of those identified above, a more diverse range of approaches seems to have been taken. Whereas Caribou has exclusively licensed the CRISPR/Cas9 system to Dupont for agricultural uses, the Broad has done the same for Monsanto but on a non-exclusive basis.

However the proprietors and the commercialisation arms divide these fields of use, there is a tension between the public interest in pursuing CRISPR research for as many uses and potential therapies as possible and the parties' interests in segmenting the market for their commercial benefit. Where there is an unmet need and whole therapeutic areas are left unexplored due to a lack of freedom to operate, there may be a possible role for the exercise of compulsory licensing or Crown use provisions to keep avenues of research open.

The Broad claims to address this concern via its "inclusive innovation" licensing model, under which Editas Medicine has a right to exclusively use the licensed technology to develop therapies for targets of its choosing. After an initial period, other companies may apply to license the IP for use against genes of interest not being pursued by Editas. Editas is then given a further first right of refusal, after which the Broad may grant a licence to the applicant. The actual effectiveness of this model in encouraging research has yet to be tested.

How might the IP landscape shift?

After the first few foundational patents, the CRISPR IP landscape will only become more complex – there are now hundreds, if not thousands, of CRISPR-related patent applications filed worldwide, by a wide array of companies. If even a fraction of these applications proceed to grant, we will be faced with an incredibly complex web of patent rights: many different owners holding patents of varying levels of strength and likely validity, with varying overlap and differing global coverage.

Unlike the telecommunications and technology industries, biotechnology does not lend itself so easily to the setting of formal centralised standards and patent pooling (although MPEG LA have announced they are exploring the pooling of patents to offer a one-stop licensing solution). Rather than the need to standardise protocols/techniques, in life sciences research there is benefit in a diversity of approaches and techniques and the constant adaptation/optimisation of techniques by individual laboratories for bespoke purposes is necessary to solve the many different challenges in the field.

That said, we may see a more organic consolidation of cross-licensing groups in respect of fundamental, platform-level CRISPR technology, possibly centred around the two already existing groups. As and when Intellia, CRISPR Tx and Editas start to find themselves needing to use new technology owned by other parties, such cross-licensing may become more attractive.

Freedom to operate

Companies seeking freedom to operate in the development of commercial applications of CRISPR/Cas9 technology may adopt one of several strategies.

One option is for a company to simply pick a side and seek a licence from the spin-out whose patent portfolio appears most likely to grant the necessary freedom to operate both now and in the future. For collaborations, the particular expertise and different technical capabilities of each spin-out will likely also be strong factors in this decision.

Alternatively, a company might wish to hedge its bets and seek licences from multiple parties. This seems to be the approach that (for example) Sage Labs and Horizon Discovery have taken, with licences from both the Broad and Caribou.

Given the different scope of the Broad and UCB's foundational patents, and the no interference-in-fact decision from the United States Patent and Trademark Office (USPTO),[1] there is a very real possibility that both the Broad and UCB will retain patents, and companies therefore need to license two sets of foundational patents to be sure of freedom to operate in the CRISPR/Cas9 field. This is particularly when one considers the global dimension, with a complex patchwork of different applications and granted patents for each party across the world.

The key CRISPR patents of the future

As research in the CRISPR field progresses and companies move closer to the development of CRISPR-based commercial products, the types of patents being filed and eventually enforced by companies will shift perceptibly.

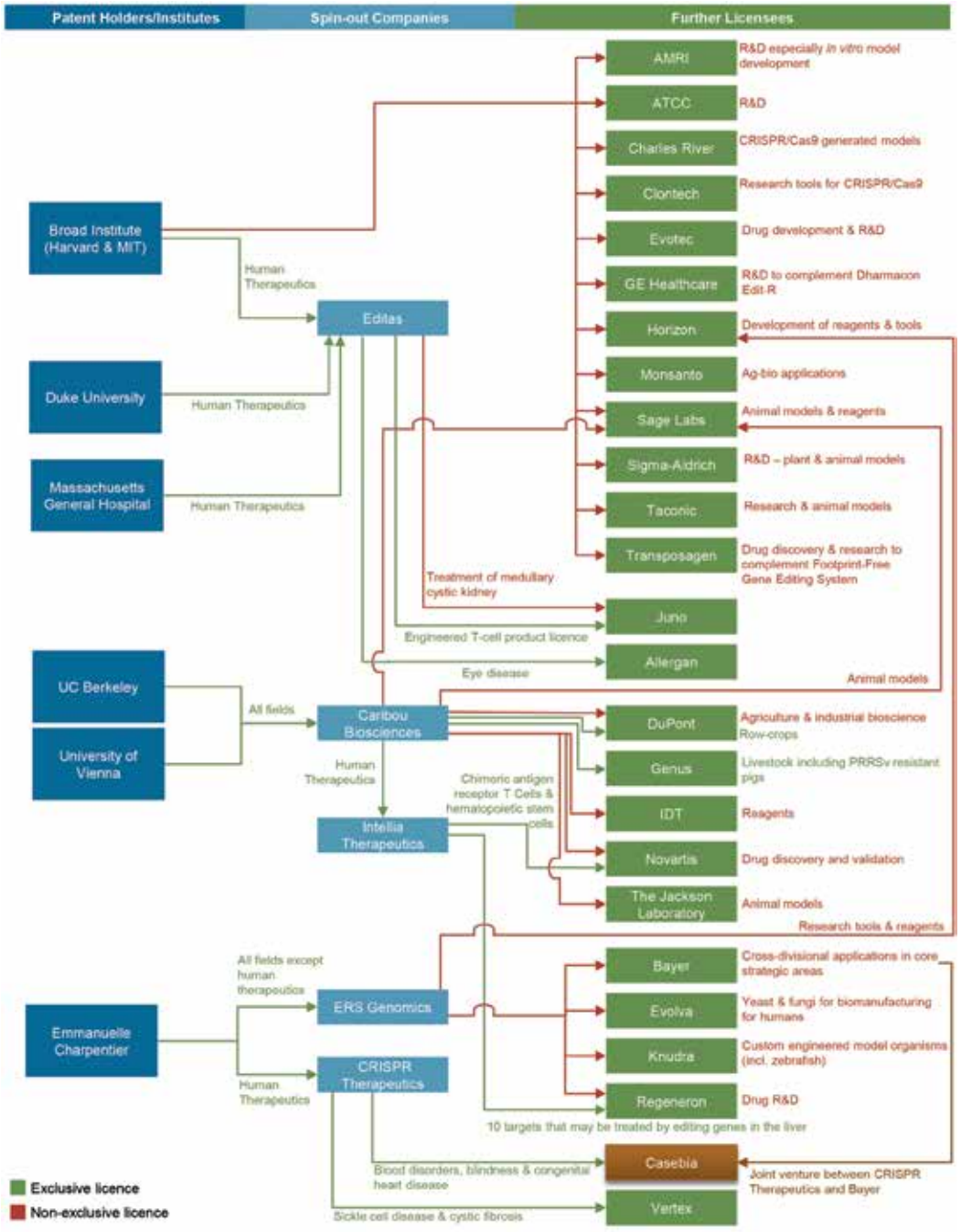
Most current CRISPR patents are more platform-level in nature and directed towards fundamental components of the CRISPR system, ie components such as the Cas protein itself, delivery vectors, guide RNA and general protocols. These will remain important and may come to define the preferred platform(s), product offering and particular expertise of the different groups – eg Editas is the exclusive licensee of the foundational patents over the newer CRISPR/Cpf1 system, which could come to be a competing system to CRISPR/Cas9. Whether these core and supporting platform technologies are deployed as blocking patents to be strongly enforced or as a source of revenue to be broadly licensed remains to be seen (and of course different companies may take very different approaches).

That said, it is probable that, when CRISPR-based products come to market, the most commercially relevant IP protection for those products, relied on to provide exclusivity and significant revenue streams, will be product specific patents. These patents can be expected to cover inventions such as final product compositions, cell treatment processes, specific editing strategies, administration/delivery systems targeting particular cells, new guide RNA designs, particular product specific gene editing processes, guide RNA and template DNA, and use of the product to treat particular indications. It is well recognised by the spin-outs that the foundational IP currently in dispute may expire before products come to market and, in the case of Intellia and CRISPR Tx, do not provide absolute exclusivity at any rate.

This was a point emphasised in the conference call held by the leadership of Intellia shortly after the USPTO decision, in which the long term importance of the foundational CRISPR/Cas9 IP to protect future revenue streams was downplayed and the importance of product specific patents highlighted. Similarly, the corporate presentations prepared by each of Intellia, CRISPR Tx and Editas ahead of the March healthcare conferences emphasise the importance of patent protection over product specific inventions.

In those presentations, Editas understandably emphasises its currently strong position on a broad platform of CRISPR patents (with over 500 pending applications between Editas and its licensors) including patents over the CRISPR/Cpf1 system. Intellia and CRISPR Tx's presentations reflect an awareness that they need to catch up and each outline a strategy to product specific IP and increase their patent filings.

Figure 1: Flowchart of spin-out companies partnering with big pharma in the application of the CRISPR system



Summary

The legal position of many pending CRISPR patents will remain uncertain for a long time as prosecution and opposition proceedings play out in the patent offices. Some patents will be weeded out, but many more will be granted and will not truly be tested until a dispute arises which will bring the question of the patent's validity before the courts. In such a complex and uncertain landscape, good freedom to operate searches and assessment of validity will be essential, particularly given the high cost to develop any CRISPR-based product. Unfortunately, unless a mass patent pooling solution emerges (which seems unlikely given the level of investment in each of the spin-outs from big pharma), the CRISPR question marks of today seem destined to also be those of tomorrow.

Footnote

1. See USPTO Decision on Motions dated 15 February 2017

Authors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