

**Patenting foundational technologies:
Lessons from CRISPR and other core biotechnologies**

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Abstract

In 2012, a new and promising gene manipulation technique, CRISPR-Cas9, was announced which seems likely to be a foundational technique in healthcare and agriculture. However, patents have been granted. As with other technological developments, there are concerns of social justice regarding inequalities in access. Given the technologies' 'foundational' nature and societal impact, it is vital for such concerns to be translated into workable recommendations for policymakers and legislators. Colin Farrelly has proposed a moral justification for the use of patents to speed up the arrival of technology by encouraging innovation and investment. While sympathetic to his argument, this paper highlights a number of problems. By examining the role of patents in CRISPR and in two previous foundational technologies, we make some recommendations for realistic and workable guidelines for patenting and licensing.

Key words: CRISPR-Cas9, Patents, Social justice, licensing, foundational technologies.

Introduction

Imagine that a cure for all diseases is found that is only accessible to the wealthy or those in the industrialised countries, for twenty-odd years. Thomas Piketty (2014) suggests that such delay will allow the wealthy to solidify their hold on the distribution of the world's resources, perpetuating inequality and exacerbating the gap between the 'haves' and 'have-nots'. Thus, the arrival of any game-changing, foundational technology for which dramatic benefits are promised arouses concern as well as hope.

New technology requires investment, and, if seen as beneficial, we may agree to provide 'special' protection to encourage investment. We do this routinely by the allocation of time-limited 'Intellectual Property Rights' (IPRs), such as patents. In return for disclosing how an invention may be worked, the patentee is allowed to exclude others from performing it. This temporary monopoly does not necessarily delay access to the technology as the inventor, or her licensees, may supply the invention to those who can benefit from it at reasonable cost. However, as will be explained further below, patents can result in considerably reduced access. While this is not an issue for non-foundational inventions (e.g. improved shoe-laces), the moral justification of IPRs is on more shaky ground when delayed access can cause death, prolongation of serious disability, or exacerbation of an economic inequality.

Application of biotechnology in healthcare, agriculture and manufacturing is increasingly seen as a key driver of global productivity and economic growth

(European Commission 2012; OECD 2009). Biotechnology already accounts for a number of leading pharmaceutical (Philippidis 2017) and food (USDA 2017) products, and the focus of policy and resource allocation on the ‘bio-economy’ is only set to increase. Much of the explosion in the use of biotechnology in food and medicines has been facilitated by a small number of ground-breaking, ‘foundational’ developments, such as the ability to grow living cells and tissues outside the body, to establish the sequence of genetic material, to produce recombinant DNA (rDNA), and to multiply DNA sequences using the Polymerase Chain Reaction (PCR). (While rDNA is sometimes used to refer to DNA coding for ribosomal RNA, it is used here to refer only to recombinant DNA.)

Foundational techniques rarely yield direct societal benefit, but constitute important tools for further research, effectively underpinning important new products and services. Translating foundational discoveries into products with direct benefit can take considerable time, effort and capital. Indeed, accelerating such translational research is itself a significant feature of many nations’ life sciences policies (Morrison et al. 2016). Both rDNA and PCR were patented and their patenting played a significant part in the manner, extent and speed with which they were adopted, both in research and in commerce.

Recently, we have seen the development of another potentially ground-breaking, foundational technique – the CRISPR-Cas9 ‘gene-editing’ technique (Doudna and Sternberg 2017). CRISPR-Cas9 stands for Clustered Regularly Interspaced Short Palindromic Repeats – CRISPR-associated (nuclease

number) 9. Patents have been applied for CRISPR-Cas9 by Doudna et al. and many others. Some have been granted, some patent conflicts have arisen and some patent licences have been entered into. However, as explained below, the 'ownership' and control of the technique is not yet settled. The focus of this paper is on problems associated with such a foundational technique with profound social justice implications being subject to control by a patentee. Other foundational techniques have been patented in the past, for example the steam engine and the sewing machine (MacLeod 1988; Dutton 1984; Mossoff 2011), but they are not considered here as their appropriation was not threatening to life. We select rDNA and PCR because of their central importance to well-being and because their rapid uptake is mirrored by the explosion of interest in CRISPR (Sherkow 2017b).

Social justice concerns

A variety of political, ethical and social justice issues can arise from the patenting of technologies. These issues are especially significant if the technologies are 'foundational'.

Firstly, patenting itself is likely to raise the access costs of these technologies. This usually leads to less affordable treatments for end-users (patients), exacerbating ill-health or prolonging disability. As health is fundamental to equality of opportunities (Daniels 2008), knock-on inequalities reduce ability to compete for jobs thereby further cementing a social disadvantage. Globally, the

costs may affect entire countries, contributing to a continuation of dependence or delayed development.

Secondly, patents allow a small group of players to set the agenda for subsequent research through their licensing policies; both by deciding 'who' gets licences and 'for what purposes' and by setting the level of fees for a licence. Patents on foundational technologies risk being so broad that they effectively block 'downstream' research unless expensive licences are sought, while extensive IPR activity in an area can lead to a 'patent thicket' where progress is inhibited by multiple overlapping patents (Bubela et al. 2014). These limitations and delays have particularly severe consequences for the availability of medical treatments. Given the level of investment and hype involved, this has a number of consequences, such as reducing focus on and funding for alternatives as well as pressures on the balance between commercial imperatives and democratic oversight.

Finally, the CRISPR patent dispute itself (explained below), with two groups granting licences to others, may result in some licensees no longer having the rights previously assumed – a situation likely leading to further uncertainty, costly litigation, stifling of innovation and, once again, delays.

These problems are interconnected and the interconnections are not incidental but because the technology is foundational.

Farrelly's non-ideal response

Given the potential benefits, it is incumbent to assess the extent to which the current and future licensing strategies for CRISPR can be justifiable with regard to social justice concerns. It should be born in mind that many of the ethical arguments justifying patents are fraught with difficulties (Sterckx 2006) and that the search for a moral justification is not only to assess existing practices; it is to offer workable guidance as to the criteria that should be met. If this is too idealised –demanding too much of the actors (e.g. inventors, universities, and commercial entities) – it risks being little more than wishful thinking (Mason 2004).

John Dunn (1990) sees the purpose of political theory as being to diagnose practical predicaments and to show how best to confront them from the perspective of where we currently are. This 'non-ideal' approach has been gaining traction in normative social justice theory, especially with regard to environmental and migration issues. In the context of biotechnological developments, Farrelly has been the leading non-ideal normative theorist (Farrelly 2016).

Farrelly proposes encouraging technological developments to address social justice challenges, arguing for a social justice approach that offers a morally justifiable form of patenting that is reasonably achievable starting from the 'real-world' context. He advances a *prioritarian* justification for the use of patents to encourage private investment and innovation. Prioritarianism holds that

benefits to those who are worse off have a greater moral weight than benefits to those who are better off. Farrelly applies this approach to genetic interventions (Farrelly 2016), but it applies more broadly.

Farrelly's proposed framework has a 'conditional' moral presumption in favour of patents that satisfy a stringent 'utility' requirement, i.e. a presumption only if permitting the patent grant is actually efficient in speeding up the arrival of effective interventions, where 'efficacy' might include not just the outcome of individual uses but also the extent to which use is feasible for the disadvantaged. Although Farrelly refers to the utility requirement in US patent law, it seems that he means something more than this – otherwise all he is saying is that there should be a moral presumption in favour of granting patents, since the utility requirement (or its equivalent) is *already* present in most patent systems. To some extent, Farrelly does go beyond the stage of patent grant to consider post-grant effects by suggesting that, if a patent is found to have resulted in inefficiency, legislators should intervene to eliminate the inefficiencies (Farrelly 2016). Moreover, to speed up implementation of technological developments, he also notes the importance of 'march in' rights for governments to get technologies developed and commercialised.

Overall, he seeks to justify patents with a 'reasonable limitation.' However, he leaves this limitation unclear.

While sympathetic to Farrelly's argument, we see a number of problems that his approach faces *even if* patents speed up the arrival of new technology. We

need to specify what the 'reasonable limitation' would be in order to prevent his approach effectively falling back into simply justifying 'things as they are'.

Farrelly seems to accept 'patents as usual' – with wide-ranging ownership rights over a considerable period of time (20 plus years). If so, many of the potential problems of social justice are not addressed but seen as an acceptable cost for the future greater good. This could be acceptable if such costs were insignificant (e.g. lack of access to a new type of shoe-lace), but when they can range from raising monetary costs, restricting access, knock-on effects from healthcare inequalities, to an essentially permanent exacerbation of an economic inequality, it is clear that these costs are not minor – whatever the future promise might be.

Moreover, there seems a more fundamental problem with Farrelly's assumption that the current patent system has beneficial effects for innovation and development. To illustrate this, we will take a closer look first at the CRISPR story and subsequently at the lessons that can be learnt from the earlier rDNA and PCR foundational technologies.

The CRISPR story (so far)

Bacteria (and archaea, although we will refer here only to bacteria) have been locked in a life and death struggle with viruses for millions of years. The DNA of many bacteria contains segments (spacers) that are interspersed with

repeated palindromic sequences (i.e. sequences reading the same from either direction), with the spacers corresponding to sequences characteristic of viruses that have previously attacked the bacterium or its predecessors. In effect, these spacers are a memory of previous viral attacks. The DNA also contains sequences coding for nucleases (proteins such as Cas9) capable of cutting these viral sequences if brought into contact with them. Thus, viral attack triggers these nucleases to contact the viral DNA (or RNA) at the remembered sequences and cut it, so disabling the virus. CRISPR is thus a bacterial immune system.

From an understanding of this bacterial immune system, three questions arose: could the CRISPR system be used to cut *any* target DNA sequence rather than one already recorded in the spacers of a bacterial CRISPR array?; could this be done even in *eukaryotic* DNA (i.e. plant or animal DNA which, unlike bacterial DNA, is packaged and protected in the cell nucleus)?; and could the cut DNA be *changed*, e.g. to introduce a new, desired sequence at the cut? In this paper, we are particularly concerned with CRISPR transformation of eukaryote cells, perhaps the socially and commercially most important aspects of CRISPR.

In June 2012, Jennifer Doudna (University of California, Berkeley - UC) and Emmanuelle Charpentier (University of Umeå, Sweden) submitted a seminal paper to the journal *Science* (Jinek et al. 2012), confirming that *any* desired sequence in exposed DNA could be targeted by a CRISPR-Cas9 system, and not just the 'remembered' viral DNA segments. This paper was published on 28

June 2012 and its importance was rapidly understood. While it did not specifically disclose the concept of CRISPR-Cas gene-editing of eukaryotic DNA, it clearly invited readers to explore this possibility:

“the Cas9 endonuclease can be programmed ... to target and cleave any ... DNA sequence of interest. ... We propose ... [a] methodology based on ... Cas9 that could offer considerable potential for gene-targeting and genome-editing applications. ... M.J., K.C., J.A.D., and E.C. have filed a related patent.” (Jinek et al. 2012)

Although the paper and the corresponding US patent application filed in May 2012 were silent as to the possibility of CRISPR-Cas9 being used to edit eukaryotic DNA, they clearly suggested that it would be ‘obvious to try’ on eukaryotic cells. Hence, the key to the allowability of any subsequent patent application lies in the question of ‘non-obviousness’. To be patentable an invention must be non-obvious and one test of this is whether it would have been ‘obvious to try with a reasonable expectation of success’. Thus would a skilled person have considered that there was a ‘reasonable expectation of success’ for CRISPR gene editing of eukaryotes?

Feng Zhang and co-workers at MIT/Harvard/The Broad Institute successfully tried CRISPR on eukaryotic cells and submitted a paper for publication in October 2012 (Cong et al. 2013). Zhang et al. filed a US patent application in December 2012 and, unlike Doudna et al., requested its expedited examination thus leading to several granted US patents while Doudna et al.’s application was still pending.

Doudna et al.'s US patent application was eventually accepted and was put into interference with Zheng's patents, a procedure to determine which of the two groups actually invented the CRISPR-Cas9 procedure first and whether Zheng's process, operated on eukaryotic cells, was patentable even once use of CRISPR-Cas9 on bacterial or free DNA was known.

The Patent and Trademark Appeals Board decided that there was no interference – essentially that Zheng's application of CRISPR to eukaryotes was not something which was 'obvious to try with a reasonable expectation of success' – and that Doudna's patent could co-exist with Zheng's patents. The implication of that decision, however, was that the inventor of CRISPR-Cas9, as applied to eukaryotes, was Zheng rather than Doudna.

UC appealed the decision to the Court of Appeals for the Federal Circuit (the 'Federal Circuit'), and The Broad's response to the appeal was filed in October 2017. The Broad's defence is essentially that there was no 'reasonable expectation of success' that CRISPR-Cas9 was likely to work in eukaryotes.

If, as is likely given the importance of the case, the Federal Circuit decision (to be expected in 2018 or 2019) is appealed up to the US Supreme Court, we can expect the controversy not to be settled for some years yet. Key to the outcome, we believe, is the meaning of the word 'reasonable'. Is it absolute or context-specific? Is a tiny expectation of success 'reasonable' if the potential financial rewards attending success are immense? In the light of the popularity of lotteries, where, with a huge possible win, bets are laid with an astonishingly

low chance of success, we would suggest that in the case of CRISPR on eukaryotes the 'expectation of success' was indeed reasonable. It is, after all, open to the courts to refine this 'reasonableness' test.

In Europe, the patent dispute is following a different trajectory, based on different aspects of the law, and the eventual outcome is also likely to be different. In January 2018, the Opposition Division of the European Patent Office (EPO) decided to revoke one of The Broad's key patents on CRISPR. This decision has been appealed (appeal T-844/18), but since the appeal process seems likely to involve a reference to the Enlarged Board of Appeal, the EPO's highest instance, the final outcome is unlikely to be clear until the 2020s. The point at issue is somewhat formal, but most of The Broad's early European Patents on CRISPR are at risk – when filing a European patent application claiming the priority of an earlier patent application filed by others (here the US patent application filed by Zhang et al.), must the European applicant already have been assigned the right to claim priority by all those others? Since when priority is claimed, the earlier application will be published about 18 months after its filing, it does seem reasonable that *all* must have agreed. Thus The Broad's stance that the revocation will be overturned seems somewhat premature.

For its part, Doudna et al.'s application has led to the grant of two European Patents, but, although their claims recite the use of Cas9, where they relate to performance on eukaryotes the definition of Cas9 is quite narrow. Accordingly,

the power of these patents to dominate the CRISPR editing of eukaryotes, other than perhaps humans, may be in doubt.

The patent landscape regarding CRISPR gene editing is of course much more complex than simply the dispute between Doudna et al. and Zheng et al. with hundreds of patent applications having been filed by tens of individuals and groups. Indeed, one particularly early proposal for the use of CRISPR was patented by Šikšnys et al. (2017) but does not mention eukaryotes. Nonetheless, Doudna, Charpentier and Šikšnys (but not Zheng) have recently been awarded the USD 1M Kevli prize for ‘inventing’ CRISPR. While we are particularly concerned with the first inventors to combine CRISPR and eukaryotes, helpful overviews have been written by Egelie et al. (2016) and Sherkow (2018).

In any event, both sides to the Doudna/Zheng dispute have set up licensing strategies and have begun to license third parties. The licensing position, as of the end of 2016, is described by Contreras and Sherkow (2017). There are two licensing groups – those of The Broad and of UC. The Broad group includes Harvard, MIT, Duke University and Beam Therapeutics as well as The Broad itself. The UC group includes the University of Vienna, Charpentier and UC itself. The UC group brings together four sub-groups: Caribou Biosciences and Intellia Therapeutics deriving from UC and U Vienna; and ERS Genomics and CRISPR Therapeutics deriving from Charpentier. These four sub-groups announced a global agreement in December 2016. There is also an attempt to set up a patent pool of CRISPR patent holders in order to simplify licensing

procedures. The pool is to be overseen by MPEG LA and potential members currently include The Broad, MIT, Harvard, and Rockefeller University (Mika 2017). Some companies have licences from one of these groups, some from the other. Some may hedge their bets and take licences from both. If the use of Cas9 is critical, or if use on eukaryotes was obvious in the light of Jinek et al. (2012), then the patent licensing field is likely to be dominated by UC. It should be noted that if both UC and The Broad have granted exclusive licences for the same project to different parties then, when the patent situation becomes clear, it may be that one of these licences will be worthless and the investment of the 'failed' licensee would be wasted.

The Broad describes its licensing policy as follows:

"We license CRISPR IP non-exclusively to companies to use in their own commercial research.

We also license CRISPR IP non-exclusively to companies wishing to sell tools and reagents for genome editing.

For human therapeutics, we concluded that exclusivity is necessary to driving the level of investment needed to develop the technology...

Broad ... therefore developed ... an "inclusive innovation" model. Under this model, Broad ... have licensed their CRISPR technology to a primary licensee, Editas Medicine, Inc. (Editas). Editas has a right to exclusively use the technology on targets of its choosing for the development of genomic medicines. However, after an initial period, other companies may apply to license certain CRISPR IP for use against genes of interest not being pursued by Editas. Specifically:

- (i) a third party interested in an individual gene target would provide a *bona fide* development plan,
- (ii) Editas then has a pre-defined period to decide whether it intends to pursue the gene of interest and to commit funding and launch a program, and;
- (iii) if Editas is not already working on the gene of interest and chooses not to launch a new program of its own within this period, the IP may be available for licensing ... to the third party." (Broad Institute 2017)

This policy statement highlights the best-case scenario with regard to The Broad's intentions on encouraging the development of the CRISPR technique. However, there is cause for concern regarding the exclusivity for human therapeutics since there is a significant risk of delay where exclusivity prevents wider use of a technology. The Broad's 'inclusive innovation model' suggests it recognizes this problem but the model is still highly susceptible to some problems. While another company can apply to license a use which neither is being pursued by Editas nor is an attractive prospect for Editas, it will have to wait an undefined period for a decision by Editas. Moreover, if one was to be legitimately skeptical, it seems a big ask for an applicant to give over a *bona fide* development plan to Editas – especially as the applicant seems to have no protection against Editas simply appropriating it. There is, at the very least, a significant moral hazard.

It should be noted that, while speaking of the presence of such moral hazards, there is no attempt here to impugn anyone's motivations. Indeed, Editas can be seen to pursue a socially responsible approach by the terms of its licence agreements, for instance, forbidding use in tobacco or in generating new forms of terminator seeds, as well as a clause allowing licences to be revoked the licence in case of negative unforeseen events. In a time where state and political actors can be seen to act irresponsibly, we are not arguing that private actors cannot act in socially responsible ways and would suggest that such socially responsible actions be prompted and fostered. The issue is with the voluntariness of this action by the patent holder, which cannot be guaranteed.

As Guerrini et al (2017b) note, one challenge to this voluntary socially responsible approach is that it may not be adopted by those seeking to maximize more financially lucrative arrangements. Laws and regulations are important – albeit slow – efforts in responsible governance of new technologies but adopting a private governance model is not an entirely satisfactory alternative. Nevertheless, a mixed approach may be viable (Guerrini et al. 2017b; Sherkow 2017a).

In contrast to The Broad’s ‘inclusive innovation model’, UC has been more willing to grant exclusive licences (see Contreras and Sherkow 2017). Hence, for therapeutic applications at least, the current situation appears to be that third parties can be granted exclusive licences, and that they will be able to charge end users the highest prices that the market will allow.

Licensing of foundational technologies: Lessons from the rDNA and PCR stories

To shed some light onto the question of the patenting of ‘foundational’ technologies, we believe it is instructive to compare the CRISPR story above with two earlier instances where foundational biotechnological techniques were developed and patented – recombinant DNA (rDNA) and the Polymerase Chain Reaction (PCR).

The rDNA story

Our first example, rDNA, predates the mushrooming of the biotechnology industry, which followed the ground-breaking decision by the US Supreme Court as to the limits of what biotechnologies might be patentable (*Diamond v. Chakrabarty*, 1980), and the introduction in the US of the Bayh-Dole Act (1980), a change in law that was intended to foster technology transfer from university to industry. In many other countries, where inventions made by academics had previously been considered to belong to the inventors, laws were changed to give the university employers ownership rights. This caused a flurry of technology transfer office creation by universities and a drive to 'valorize' the products of university research which continues to this day.

The rDNA concept was apparently thought up in 1973/4 by Stanley Cohen of Stanford University and Herbert Boyer of UC San Francisco (although some consider that the idea came from graduate student Peter Lobban (see Lear 1978)), and in 1974 Stanford applied for patents (Hughes 2001). The major US patents were granted between 1980 and 1988 and had expired by the end of 1998.

Cohen and Boyer's invention was to use nucleases (see above) to cut the plasmid (circular DNA) of a bacterium and to introduce a new DNA sequence. The modified plasmid can then be inserted into a cell from a bacterium, plant or animal where it will serve to produce the protein coded for by the inserted

sequence. Thus, bacterial or animal cells can be engineered to produce a medically or commercially valuable protein.

The licensing programme pursued by Stanford has been hailed as one of the most successful university licensing strategies (Feldman et al. 2007). A key reason behind Stanford's decision to patent and license was to act as a spur for innovation and be a source of university income (Cook-Deegan and Heaney 2010). This licensing strategy resulted in an income for Stanford of USD 254M and, for the biotechnology sector, the generation of over USD 35B from the resulting products (Feldman et al. 2007).

Feldman et al. (2007) note four goals guiding Stanford's strategy: (1) to be consistent with the university's goals of public service; (2) to provide incentives for technology to be commercialized for public benefit in an adequate and timely manner; (3) to minimize the potential for biohazards; and (4) to provide income for educational and research purposes. In short, profit was not Stanford's *primary* motive.

Moreover, Stanford offered *non-exclusive* licences to the rDNA technique. For industry, there were relatively small initial up-front and annual fees, and a larger royalty payable as a percentage of the income on the sales of the resulting products (Feldman et al. 2007). For non-profit organisations, permission was given to use the method non-exclusively and royalty-free (Feldman et al. 2007).

In sum, Stanford's licensing strategy was to grant royalty-carrying non-exclusive licences to industry; implicitly grant royalty-free non-exclusive licences to non-profit organisations; and require the commercial products of non-profit research to be covered by royalty-bearing non-exclusive licences.

The PCR story

Our second example from which to seek to draw lessons is the Polymerase Chain Reaction (PCR). The development of PCR in 1983 is attributed to Nobel Prize winner Kary Mullis, then with the company Cetus. As with CRISPR and rDNA, some consider that there was a different inventor behind PCR, namely Kleppe et al. (1971).

DNA is made up of paired strands of bases (nucleic acids denoted by the letters C, A, G and T) where each base pairs with one other, T binding to A, and G to C, linking the two strands in the famous double helix structure. If natural DNA is chopped up with nucleases, and if short DNA sequences (primers) are added to the mixture, then one has a mixture containing cut fragments bound to the added primers. Adding nucleic acids and an enzyme (DNA polymerase), which causes the ragged ends of these bound fragments to be extended with the appropriate nucleic acids to become blunt-ended, yields a mixture of short, paired DNA molecules. Repeatedly separating and regrowing the paired sections yields multiple copies of the short paired molecules: starting with one combination of GGAGCTTAG bound to its complementary sequence CCTCGAATC yields two versions of each in the first replication, four in the

second, and so on. The increase of copies is exponential and, by analogy with nuclear fission in a reactor or bomb, is called a chain reaction – the ‘Polymerase Chain Reaction’ or PCR. In this way, enough copies of the short paired molecules can be produced relatively cheaply and quickly as to enable detection and characterisation.

While PCR was conceived in 1983, the first patent application was filed in 1985, with the most important US patents being granted in 1987 and expiring in 2004. Unlike the rDNA technique, PCR was developed and patented by a commercial entity, the company Cetus, which at first sought to profit from it by licensing, requiring an up-front payment and royalties on resulting products from both commercial and academic licensees.

Cetus later sold its rights to the pharmaceutical giant Hoffmann-La Roche which adopted a different licensing strategy intended to increase the uptake of PCR while still deriving financial benefit. Roche granted non-exclusive licences with royalties payable on sales of PCR-related products, and eliminated the up-front fee and derived profits on research and development use of PCR by selling equipment and reagents for use in the process (Fore et al. 2006; Cook-Deegan and Heaney 2010). PCR generated approximately USD 2B revenue for its rights holders before the patents began to expire.

Lessons for the licensing of foundational technologies

For both rDNA and PCR, the uptake in research and development was considerable and was strongly facilitated by Roche's and Stanford's licensing strategies. Given the relative cheapness of these techniques to develop, the grant of patents on the techniques would not seem to be supported by Farrelly's argument. However, for expensive-to-develop products arising from the techniques, a granting of exclusive licences would seem aligned with Farrelly's goal of providing reassurance to private investors.

Nevertheless, it must be noted that the rDNA and PCR patents did not *of themselves* provide reassurance to the licensees that their investments might be recouped. Instead, the strategy of both Stanford and Roche, unlike that of Cetus, sought to facilitate research and development, with the bulk of the 'licensing' income coming either from royalties on the sale of the resulting products or from the sale of products for use in the patented process.

With regard to the argument of Editas for licences to cover the level of investment needed to develop the technology, one could ask why 'exclusive' licences might be required in the context of CRISPR while non-exclusive licences seemed sufficient for rDNA and PCR. It is, at least, arguable that exclusive licensing of a foundational technique should not be treated as the default approach. One must, of course, balance the argument for increased investment with the argument to avoid 'bottle-necking' factors, but it is not clear why this would necessarily tip the balance in favor of exclusivity in the case of

CRISPR, especially given the cases of the previous two comparable foundational techniques. This doubt is strengthened when one considers that it is a relatively cheap and easy foundational technology and while significant investment may be required when using it for specific purposes ‘downstream’, exclusive control over the use of the underlying technique so far ‘upstream’ seems more problematic to justify. Recalling the more collaborative nature of the Stanford approach above, there is a danger that such collaborations between institutions and researchers are being diminished due to increasing patent disputes (Sherkow 2017a).

Even if excluding patents from being granted would not be a realistic option, it seems that non-exclusive licences could still be seen as more justifiable than exclusive ones. In short, they would seem capable of approximating a (more) reasonable balance between incentivizing innovation and encouraging diffusion. We do, however, accept that there may be pressing reasons to grant at least temporarily exclusive licences, e.g. to draw forth the investment necessary to bring a technique from the laboratory bench to the market.

In this respect, Farrelly’s approach would need to be revised to account for different licensing regimes and also move away from treating ‘patents’ as a fully pre-defined entity. Viewing the consequences of the approaches to patents in the cases of rDNA and PCR, suggests some empirical basis for the viability of non-exclusive licensing and thereby highlights how such a requirement would be a realistic possibility for a non-ideal social justice approach, such as could be incorporated in a revised version of Farrelly’s argument.

While our paper focuses on Farrelly's approach due to his explicit social justice focus on the role of patents in the context of new biotechnologies, there are similarities between Farrelly's approach and that of Edmund Kitch's prospect theory (1977) insofar as both seek to incentivize innovation via patent protection. Kitch seeks this by awarding patent rights for new inventions to encourage the necessary investment to turn such 'prospects' into realities (Kitch 1977). Nevertheless, while this is a broader justification of patents than Farrelly seeks, similar issues arise. For instance, Kitch seems strongly in favour of granting broad patents upstream in the development process and to having a "preference for single-firm domination of a technological prospect" (Merges and Nelson 1990). Kitch's approach would fall foul of the same issues as Farrelly - insofar as patents preclude competition, caused bottle-necks and so on – but to a worse degree. While Farrelly is less defined and so leaves open such negative possibilities, Kitch's degree of specification gives him far less room to manoeuvre. In this respect, Farrelly would seem a more moderate position to take and insofar as this approach is found to be problematic by this paper, then this would apply to Kitch too.

Propertisation of foundational technologies

Where a novel technology carries the prospect of providing fundamental and extensive social benefits, we can envisage it as being unowned, state-owned or privately owned, in the latter case with or without constraints on the owner's

powers of control. Farrelly proposes that the grant of patents (with appropriate unspecified constraints) is the pragmatic way to ensure the eventual public availability of the technology's benefits.

Without further appropriate constraints, however, granting a patent for the technology risks its under-development, at least in the short term, since the patentee may focus her resources on few of the possible applications (e.g. those promising the greatest likelihood of profit and possibly ones offering little public benefit). These applications may, at least initially, receive little deployment, e.g. due to cost or the patentee's choice of market location. Furthermore, where practical application of the technology is covered by patents held by two or more parties, deployment may be blocked unless all agree and unless the total royalties still allow for a commercially viable product.

Patents, moreover, may block the development of still further technological advances by hindering research or by making research unattractive in view of the impossibility of recouping costs by sales in the near future. Put simply, therefore, granting patents without constraints may not be enough to achieve sufficiently rapid and extensive uptake of technology which promises social benefits, including for the worst off.

Where patents are granted, the licensing strategy adopted by the patentee may promote or hinder uptake. As Farrelly suggests, and as The Broad has realised, the availability of exclusive rights for expensive-to-develop products may promote their development. However, it is insufficient to promote their rapid and

widespread deployment – for that, some limitations on the patentee’s rights are required. For cheap-to-develop applications of foundational technology, all three of our case studies in this paper show that *non-exclusive licensing* and *minimal restriction of pre-commercial research* provide a reasonable likelihood of development and widespread deployment.

A better way forward

A realistic, pragmatic, ‘non-ideal’ solution requires clarity for the players involved, particularly governments, companies, inventors, and non-profit organisations. This realistic approach would not make a simple demand to get rid of patents. That is precluded by global regulation, most importantly the 1994 Agreement on Trade Related aspects of Intellectual Property Rights of the World Trade Organisation (TRIPS 1994). The TRIPS Agreement guarantees the grant of patents by WTO Member States (i.e. almost all countries in the world) for almost all technologies. The question is thus which constraints on patents for foundational technologies are necessary and at the same time feasible given the binding nature of the TRIPS Agreement.

The constraints, some of which would require changes to statute law, can be before or after patent grant and we will look to pre-grant measures first. We must, however, stress that some of the points we make have already been made by others.

Pre-grant constraints

Two options are available – to declare the subject matter not patent-eligible or to restrict the scope of the patent claims before the patent grant. Again, we will consider patent-eligibility first.

Patent-eligibility

Eligibility for patenting can be constrained in two ways, by stating that: ‘this sort of thing’ should not be patented; or it is not an invention, and therefore not patent-eligible. The first option was traditionally popular; patent laws routinely excluded from patent-eligibility subject matter such as drugs, chemicals, foodstuffs, methods of medical treatment, etc. However, TRIPS put an end to that. Exclusion is now limited to the subject matter recited in Art. 53 of the European Patent Convention (EPC), e.g. plant and animal varieties, methods of medical treatment, and inventions which would be immoral to commercialise. This route thus offers no general constraint on the patenting of foundational technologies.

The second option, to declare that subject matter of a particular form is not an invention (or not patent-eligible), is widely in place, although its form and its effectiveness vary between countries. Three forms are prevalent. The first is the European approach in which the statute law simply states that X is not an invention. The second derives from seventeenth century English law – to be patent-eligible the subject must be a ‘manner of manufacture’. The third is the

US approach, to apply Section 101 of the US Patent law (i.e. 35 USC 101). The second and third constrain patent-eligibility on the basis of case law, i.e. court decisions and in both cases bend the words of the law to achieve the socio-political goal of excluding subject matter the pre-emption of which by patents would be undesirable.

For our purposes here, the relevant exclusion in European law is the statement in Art. 52 EPC that discoveries are not inventions. However, the law restricts the exclusion to discoveries ‘as such’ and the case law (mostly deriving from computer-related cases) has developed to the stage that X is *not* X ‘as such’ if it has a technical effect (Sterckx and Cockbain 2012). The seventeenth century approach, most recently evidenced in the Australian High Court decision in *D’Arcy v. Myriad* (2015), is effectively to state that the natural, and anything obvious over the natural, is not a manner of manufacture and hence is not patent-eligible. Thus, in *D’Arcy*, naturally occurring DNA sequences, molecules corresponding to a part of such a sequence, and molecules (i.e. cDNA) corresponding to such a sequence with the ‘noise’, the non-coding regions, deleted, were not a manner of new manufacture.

In the US, the Supreme Court, in a series of recent cases, most recently *Alice v CLS* (2014), has sought to exclude from patent-eligibility the natural and things obvious over the natural in order to prevent patents from pre-empting the use of the building blocks of science to advance knowledge. In one of these cases, the US equivalent of Australia’s *D’Arcy*, naturally occurring DNA sequences and molecules corresponding to fragments of such sequences were

found not-patent-eligible. The most coherent submissions made during this case, *AMP v Myriad* (2013), were by the US Justice Department, and since the Justice Department accepted that cDNA should be patent-eligible, the Supreme Court also, to our mind surprisingly, agreed. As many readers may dispute our interpretation of the *Alice* series of cases, we would point to the Court's repeated requirement for patent claims to include an 'inventive concept', something 'of significance' beyond the non-patent-eligible natural law or abstract idea, something which is not a purely conventional or 'obvious' feature (see *Alice Corporation v CLS Bank International* (2014) and the passages from *Mayo Collaborative Services v Prometheus Laboratories* (2012) quoted therein).

In any event, while laudable, the exclusion of discoveries (as such), or of obvious applications of the natural, does not solve the problem of the patenting of foundational technologies. PCR clearly would not be excluded and CRISPR's eligibility depends on the 'reasonableness' test discussed above. Interestingly though, at least one author has argued that the basic patents to CRISPR would be non-eligible for patenting under the rationale set out in the *Alice* series of cases (Tuttle 2016).

Patent claim scope

Some commentators (e.g. Rai and Cook-Deegan 2017) argue that patents should become narrower (i.e. that the breadth of the patent claims should be reduced). However, this may also face some problems in terms of efficacy and

fairness. To limit the patent applicant to patent claims of a scope that mirrors, rather than is commensurate with, the disclosure in the patent application may have been, and has sometimes seen to be, reasonable in a country trying to establish a modern industry (e.g. post-war Japan). Narrow claims, however, are easily circumvented (Guerrini et al. 2017a) thereby reducing the investor's incentive to invest, and in any event such a strategy guarantees a greater chance of a strong patent to those companies with the financial muscle to provide broader exemplification, and not least to those companies with more skillful patent attorneys.

Since feasible pre-grant measures are insufficient, we must look to post-grant measures.

Post-grant

Post-grant measures involve limiting the ability of the patentee to exclude others from practising her patented invention. Three approaches are available: (1) restricting the technological field in which rights may be exercised; (2) restricting the types of activity which can be constrained, e.g. research might be excluded; and (3) restricting the period for which the patentee can impose exclusivity. We will consider these in turn.

Limitations regarding technological field

As far as field of use is concerned, for our purposes this concerns fields where social justice concerns demand quicker or more extensive access to the fruits of the technology. These will tend to be fields relating to the environment or health, e.g. treating an epidemic or combatting climate change. One possible at least partial solution here might be drawn from the electronics world where equipment needs to conform to certain standards in order to be interoperable. Since compliance with a standard can cause the product to fall within an existing patent, a system has been developed under which non-exclusive licences under such patents are automatically available on 'fair, reasonable, and non-discriminatory' (FRAND) terms. Although this system has not been without difficulties (Cotter 2014), it might conceivably be applied to foundational technologies. Indeed, although in relation to *necessary* rather than *foundational* technology, an interesting proposal has been made to treat US patents protecting some genetically modified seeds in a way which implies a FRAND licence (Cole et al. 2014).

Such an approach, however, is complicated because of the constraints on compulsory licensing set down in Article 31 of the TRIPS Agreement and because they discriminate between technological fields, which is forbidden by Art. 27 TRIPS. They also suffer from a lack of clarity – at the time an investor must decide whether or not to invest, it may not be clear whether or not such licences might later be imposed. Nonetheless, if the patented technology is foundational and its use is to address a serious unmet or urgent medical need,

the flexibilities of the TRIPS Agreement (Zhuang 2017) might in some circumstances be sufficient to allow such licences. If governments declaring such fields to exist were also required to compensate the patentees, a FRAND-like licensing system might be viable and acceptable. However, the issue of identifying particular cases to which the TRIPS flexibilities would apply, is hugely complicated.

Importantly, what we are concerned with here does not correspond to traditional government use of patented technologies (28 USC 1498) or march-in rights (limited to patents that result from government funding, when a patented invention is not made ‘available to the public on reasonable terms’ (35 USC 201(f))). Besides the fact that these mechanisms have only rarely been used (Treasure et al. 2015; Brennan et al. 2016; Kapczynski and Kesselheim 2016), rights for other, non-governmental, actors to ‘march-in’ might better correspond to the reality of the patent landscape for foundational technologies such as CRISPR (Feldman 2016).

Our suggestion, that governments declare certain technologies to be essential to perform, and so subject to FRAND licensing, thus aims to minimize licensing abuses in an environment where numerous private actors interact and bargain, a context in which it is difficult to predict whether a licensing strategy of a patentee might unnecessarily delay development of sequential innovations or unduly increase prices for end-users. However, the existence of some limitations on the exclusivity rights of patentees may encourage the creation of

a level playing field in which non-exclusive licensing of foundational technologies is stimulated.

The FRAND solution, however, is more appropriate to a developing technology rather than an old or new/foundational one. As a new technology develops towards the market place, and in its early years on the market place, multiple players make inventions which address one aspect or other that a product must have in order to be sufficiently safe, effective, attractive, cheap, etc. enough in order to be able to compete on the market – an automobile needs brakes, suspension, windshield, The result is that to reach the market, a company needs licences under many patents – there is a patent thicket surrounding the technology. The original inventor of a foundational technology with a patent still covering all possible embodiments is in a unique position to leverage access to all necessary patents by offering access to the ‘master patent’. For the others, a tried and tested approach has been the patent pool as well described by Barnett (2017). However, unless a foundational technology is simultaneously invented by large numbers of people (which casts its inventiveness into doubt), the patent thicket is a problem at a stage later than the one we are focused on – the stage where the originator of the foundational technology can obtain a patent which pre-empts its uptake.

Limitations regarding type of use

Important discoveries in the life sciences are often hailed as ‘revolutionary’, but studies have shown that development of products with human benefit is often

slow and incremental (Hopkins et al. 2007; Nightingale and Martin 2004). The translational ‘path’ between discovery of a foundational technology and its deployment in new medicines or foodstuffs is often time-consuming and complex. Indeed, for complex areas of biology like genomics and stem cell science, the ability to leverage foundational knowledge of biological processes into new products and services is increasingly recognised to lie beyond the capacity of any single institution or company.

This has resulted in the idea of a necessary ‘pre-competitive’ space where collaboration between scientists in public and/or private bodies is needed to advance the technology to a state where subsequent competitive development of new products is possible (Altshuler et al. 2010; Bubela et al. 2014). Such pre-competitive space is indeed perhaps the norm in the history of technical development. We would therefore strongly recommend that countries expand the definitions of non-actionable patent infringements to include activities performed in a non-commercial context, the pre-competitive phase, with the production, sale or use of the resulting products being actionable.

This approach addresses undesirable post-patent-grant effects concerning not the field but instead the *type* of use. More specifically, we should like to refer here to the debates on the patenting of ‘research tools’ and on the (non)desirability of exempting research uses of patented inventions from patent infringement (so-called ‘research use exemptions’ or ‘experimental use exemptions’).

An increasing number of patents, including academic patents, are being applied for and obtained for procedures of 'upstream' research – sometimes referred to as patenting of 'research tools', particularly in biomedical fields (National Research Council 2004; Lemley 2005; Geiger and Sa 2008). Such patents pose particular problems (Heller and Eisenberg 1998; Rai 1999; Eisenberg 2001; Nelson 2001). A proliferation of intellectual property rights on results of 'upstream' research may stifle 'downstream' research and development, for the greater the number of people whose agreement needs to be obtained in order to allow a project to proceed, the higher the risk that bargaining will fail or that transaction costs will become too high. Just as too *few* property rights can lead to *overuse* of resources in a 'tragedy of the commons', too *many* property rights can cause *underuse* of resources in a 'tragedy of the anticommons' where many owners can block each other. Hence, future research can be stalled since:

Each upstream patent allows its owner to set up another tollbooth on the road to product development, adding to the cost and slowing the pace of downstream ... innovation. (Heller and Eisenberg 1998, 698)

'Upstream patenting' may also reduce the number of players in the research field. Unlike traditional patents to commercial end products, which are rarely infringed by university researchers, 'research tool' patents cover almost by definition the type of research carried out by academics. While academics may believe that their research cannot infringe patents, unlicensed use of patented research tools by university researchers in the US and much of Europe may constitute patent infringement. Thus, research tool patents act not only to

exclude commercial research players but also academic ones. Indeed, universities risk being sued for patent infringement in countries that do not have a sufficiently broad 'research exemption' in their patent law. National patent laws differ as to whether they include a research exemption or not, and how narrow or broad it is (Cook 2006; Dent et al. 2006).

As explained by Dent et al. (2006), if research is considered to be a public good then research use may need to be excluded from the infringement provisions of patent law, for example: by limiting the rights that attach to a patent to specific classes of action rather than the usual broad formulations as rights to "use" or "exploit"; by defining 'infringement' so that research falls outside the category of infringing behaviour; by introducing a 'compulsory research licence'; or by adding a statutory research use exemption to the patent law (Cooper Dreyfuss 2017). The TRIPS Agreement does not preclude the adoption of research use exemptions (cf. Art. 30 TRIPS) provided that the exemption is limited, does not detract significantly from the economic benefits arising from the patent, and is justified in the sense of being supported by a legitimate public policy purpose.

We would propose that the performance of a process in research should be considered to be a non-infringing act, whoever performs it. Since a process works on a 'starting product' to generate an 'end product', these products (e.g. materials, apparatus or information) too must be immune to at least a minimal extent. Thus the production, keeping and use by the process performer (in or for the exempt process) of the starting products should be exempt and likewise the production and keeping of the end product in or from the process should be

exempt. The giving of the end product to performers of further such processes should be exempt, but its sale or its use in commercial applications or its gift by a for-profit company to potential customers need not. This suggestion, to a large extent, is in line with the licensing policy adopted by Stanford in relation to rDNA, but that adoption was voluntary rather than required.

However, while the previous proposal addresses the problem of *development* of foundational technology being delayed, it does nothing to address the problem of *access* to the fruits of that technology. Hence, we believe that a third proposal should also be considered. We therefore turn to the third post-grant option.

Time-limitation of exclusivity

This option involves a reduction of the period of *exclusivity* granted by patents, although without any reduction to the period during which the patentee can legitimately claim rents. Perhaps any patent holder should be required to grant *non-exclusive* licences 8 years post first sale *anywhere* (this would still generate royalty income for the patent holder), or more minimally such *non-exclusive* licences for anything that requires marketing approval. Here, while noting the pharmaceutical industry's claim that bringing a new drug to the market costs in the region of USD 1-2B (including the costs of failures), we also note the controversy surrounding these figures (Prasad and Mailankody 2017) and the fact that it is not unusual for such products to generate sales of a similar order each year after introduction.

While this paper has been written with foundational improvements in healthcare in mind, it will be appreciated that these recommendations apply equally to other social justice related technologies, including food production and climate change mitigation.

Concluding remarks

Foundational technologies, the ‘building blocks’ of science and of technological development, hold out the promise of socially beneficial products. However, as the law stands, many such technologies can be patented raising the risk that their widespread adoption is unnecessarily delayed. In the real, non-ideal, world, denying patentability is not an available solution and relying on the altruism of the patentee is not enough. This paper therefore proposes that the constraints on patenting mentioned, but not specified, by Farrelly should be restrictions on the exclusivity that the patentee is granted.

The examples of rDNA, PCR and, to some extent, CRISPR, as well as existing pre-commercial ‘sharing’ schemes, show that, in the end, for *cheap*-to-develop foundational technologies, one can possibly rely on the patentee’s self-interest to grant non-exclusive licences. However, *voluntary* pre-commercial sharing schemes *cannot* be relied upon. Small or medium-sized companies simply cannot afford to give away their ‘family jewels’ (cf. Cetus’ failure to make much

of PCR). Hence, even though pre-commercial sharing can be beneficial, voluntary schemes will be technology-specific and at the whim of industry.

Thus the solution seems to lie in imposing limits on the extent to which patentees may enjoy exclusivity. This could take three possible forms, limiting: the fields in which the patentee may exclude others from operating in; the type of use patentees may block or charge rent for; and the duration for which the patentee has exclusivity, even though she may still extract rents from others. The proposals made satisfy Farrelly's argument that investors need an incentive to invest in expensive-to-develop technology, while at the same time offering the constraints necessary to satisfy Farrelly's concerns on social justice.

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