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Patent Protection for Microbial Technologies

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Commentary

COMMENTARY – Professional Development

Patent protection for microbial technologies

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One sentence summary: The development of microbial technologies depends, in part, on how they can and cannot be patented.

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ABSTRACT

Microbial technologies often serve as the basis of fundamental research tools in molecular biology. These present a variety of ethical, legal and social issues concerning their patenting. This commentary presents several case studies of these issues across three major microbiological tools: CRISPR, viral vectors and antimicrobial resistance drugs. It concludes that the development of these technologies—both scientifically and commercially—depend, in part, on the patent regime available for each, and researchers' willingness to enforce those patents against others.

Keywords: patents; CRISPR; virus; AMR; incentives

INTRODUCTION

Microbiology has long served as both the source of and inspiration for fundamental research tools in molecular biology. Viral vectors, antimicrobial drugs and, of course, CRISPR-Cas9 are all, today, workhorses of molecular biology derived from microorganisms. But these tools also straddle the line between basic and applied research; between instruments of scientific inquiry and commercial commodities. Consequently, researchers have long been patenting these tools and their derivatives. This commentary reviews the historical landscape of patent protection for microbial biotechnology, along with several ethical, legal and social issues surrounding patent protection for microbiology. In short, patents covering microbial technology both encourage the development of research tools and contribute to excesses of enforcement.

CRISPR

CRISPR (clustered regularly interspace short palindromic repeats) is a revolutionary genetic editing technology first discovered in *Streptococcus pyogenes* in 2012 (Jinek *et al*. 2012; Gasiunas *et al*. 2012). Precise, easy, cheap and flexible, most engineered forms of CRISPR require only two components: a CRISPR nuclease, such as the archetype Cas9, and a single guide RNA (sgRNA) complementary to the genomic target. The technology has been so widely hailed by scientists that it is now cliché to refer to it, as Giedrius Gasiunas and Virginijus Siksnys did in 2013, as the 'Holy Grail' of molecular biology (Gasiunas and Siksnys 2013). The technology is also the subject of a contentious patent dispute between the University of California, Berkeley (USA) and the Broad Institute (USA) (Sherkow 2017).

CRISPR patents cover basic forms of the technology, including any genome-editing system using a prepackaged Cas9:sgRNA ribonucleoprotein complex (U.S. Patent No. 9,637,739). Some more recently issued CRISPR patents cover specific applications of the technology, such as Cellectis's patent claiming the use of endogenously expressed CRISPR components for chimeric antigen receptor T-cell immunotherapy (European Patent No. 3,004,337). Legal scholars have accordingly questioned whether these fundamental patents are drawn narrowly enough to permit sufficient experimentation and development (Contreras and Sherkow 2017).

Fortunately, academic research has not been hampered by the explosion of CRISPR patents—as demonstrated by the thousands of CRISPR research papers since 2012. Europe provides robust immunity from patent infringement for basic academic

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research (van Overwalle 2011). And while the United States does not have such an exception, many American researchers obtain plasmid constructs of CRISPR components through AddGene, a nonprofit organization that provides reagents and academic patent licenses to research institutions. AddGene has depository agreements, too, with many European academic institutions—268 as of this writing (AddGene). Lastly, the Broad Institute has submitted some of its patents to a 'patent pool,' a group of patents that can be fairly and collectively licensed by those interested in developing the technology, although the success of this project remains uncertain (Mika 2017).

At the same time, patent issues surrounding CRISPR make commercial research more difficult. Patent disputes have likely given some developers pause (Kolker 2016). For-profit surrogate companies, like the Broad Institute's Editas Medicine, simultaneously compete in the therapeutic development market and control a large swath of commercial patent licenses (Contreras and Sherkow 2017). Microbiologists have the unenviable task of navigating these patent licenses should they wish to develop CRISPR for therapeutic products.

VIRAL VECTORS

Microbiologists have also relied on viruses as basic tools of research (Flint *et al.* 2015). And viruses are, too, objects of study themselves. Since the cloning of the first viral particle—a poliovirus plasmid in 1981—viruses have become an indispensable tool for molecular biologists (Flint *et al.* 2015). But the nature of viruses—as defined by the sequence of their genome—has raised, and continues to raise, significant issues concerning patents' availability for and their enforcement in vaccine development.

Researchers have been patenting viruses for decades (Sherkow and Greely 2015). Perhaps the most famous example concerns Stephen E. Wright's patents covering variants of Prague Avian Sarcoma Virus (PrASV) (Canady 1994). Wright waged a multiyear, partially successful effort to patent both the native form of PrASV, as well as processes of using it to provoke immune responses (In re Wright 1993). Wright's case stands as an exemplar of both the difficulties in patenting viruses and inventor overreach (Lang 2003). More recently, Monsanto Co. has obtained patents on several forms of baculoviruses for plant transfection (Rogers 2013), while lentiviral transfection systems are now subject to hundreds of patents across the globe (Picanço-Castro, de Sousa Russo-Carbolante and Covas 2012).

At the same time, the genetic nature of viruses continues to present challenges. The United States recently eliminated the patenting of 'isolated and purified' genetic products in a widely watched Supreme Court case. Europe, however, continues to allow the patenting of genetic isolates, including viruses. Rule 27 of Article 52 of the European Patent Convention (EPC) permits patenting of 'biological material which is isolated from its natural environment… even if it previously occurred in nature,' including 'a microbiological or other technical process' (European Patent Convention 2016). Nonetheless, a 2015 empirical study of patenting in this area showed its practical effects to be modest (Liddicoat, Whitton and Nicol 2015).

More controversially, virologists have also begun to patent genetic sequences to recently discovered pathogenic viruses, valuable to vaccine development. Peter K. Yu has documented competing patent claims to the sequence of SARS-CoV in the early 2000s (Yu 2013). Researchers have also attempted to patent the sequence of MERS-CoV (Bollinger 2015). And recent work by Ana Santos Rutschman has shown that patents are at least partially to blame for the delay in the introduction of Ebola and Zika virus vaccines (Rutschman 2018). This work and others demonstrate patents' importance, and drawbacks, as tools for research and development of viruses.

ANTIMICROBIAL DRUGS

Antimicrobials—chemicals that destroy or inhibit the growth of microbiological agents—serve as both research tools and human therapies. They can provide selective pressure on recombinant bacteria and halt viral reproduction. Their overuse, however, has contributed to the global phenomenon of antimicrobial resistance (AMR), the immunity of pathogenic agents to once-useful therapies (O'Neill 2016). AMR will arguably be the most difficult public health problem of the twenty-first century, what the World Health Organization calls an 'apocalyptic fantasy' (WHO 2014).

To that end, public policy has widely encouraged the development of new anti-AMR technologies. Rule 27(c) of Article 52 of the EPC specifically contemplates the patentability of products of microbial processes (EPC 2016). And the U.S. Patent and Trademark Office has issued guidelines explicitly permitting patents covering structural variants of naturally occurring compounds (USPTO 2014).

And yet, patent incentives appear to be doing a poor job of encouraging the development of AMR technologies. Only two new classes of antibacterials—daptomycin, a lipopeptide, and linezolid, an oxazolidinone—have been approved by regulatory agencies since 1998 (Spellberg *et al.* 2004). And while there is a slate of antimicrobial drugs currently being developed, AMR technologies experienced a research desert for at least a decade, in the 1990s (Spellberg *et al.* 2004).

It is unclear whether this lack of success is rooted in policy or the science of AMR. Disconcertingly, the 2016 O'Neill Report on AMR—commissioned by the Wellcome Trust and the United Kingdom Department of Health—suggested the latter. Among many causes for the lack of development, the Report concluded that the "low-hanging fruit' of easily-isolated natural antibiotic products is gone and early genomic screening techniques… failed to deliver on their promise of a revolution in antibiotic discovery' (O'Neill 2016). Nonetheless, the Report also ignited some hope that new regulatory and legal incentive policies—including modifications to the patent regime—could rekindle private interest in anti-AMR development.

Thus far, governments have bet on hope. Europe has placed significant resources toward a worldwide AMR surveillance network (Morrissey *et al.* 2013). Further, the European Academies Science Advisory Council and the Federation of European Academies of Medicine have proposed both Europe-wide and domestic policies to combat AMR (van der Meer and Charpentier 2016). The United States, meanwhile, recently enacted the Generating Antibiotic Incentives Now Act, providing extended regulatory exclusivity periods for new classes of antibiotics (Brown 2013). In addition, CARB-X, a $350 million USD project directed by Boston University professor Kevin Outterson, has recently been created to establish public-private partnerships and research grants focused on creating first-in-class antibacterials (Outterson *et al.* 2016). Time will tell whether these economic incentives are successful to spur development of new AMR technologies.

OUTLOOK

Microbial technologies are diverse, and so are issues concerning their patenting. The outlook for new microbial technologies depends as much on the consistency of patent protection as the underlying science. CRISPR, for example, enjoys enormous popularity among scientists and industry researchers alike—so much so, that its development rapidly continues despite serious concerns over patent ownership and licensing (Contreras and Sherkow 2017). Patents complicate the development of viral vectors, on the other hand, bringing significant uncertainty to their development and, in some cases, social condemnation (Rutschman 2018). And yet, patents alone do not appear to be doing enough to encourage development of new AMR technologies (Outterson *et al*. 2016). These differences suggest that the development of future microbial technologies will depend on human laws as much as Nature's.

Conflicts of interest. None declared.

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