CRISPR-Cas9 Germline Editing: Full Steam Ahead to Revolutionary Profit or Revolutionary Public Medicine?

Yuka Sai

University of Ottawa, Faculty of Law, Ontario, Canada

ABSTRACT

The CRISPR-Cas9 system uses precise germline genome editing, which enables the mutagenesis of disease sequences in embryonic DNA, thus enabling the birth of healthy individuals who would otherwise inherit genetic diseases. In 2012, the scientific community rushed to claim intellectual property in anticipation of CRISPR's future economic potential. As the war for commercial territory forges ahead, the question of public accessibility and affordability has largely gone unaddressed. The current drive towards total CRISPR-Cas9 commercialization will lead to exorbitant costs of accessing life-giving treatment, especially in regulatory frameworks that prohibit federal funding of germline editing research.

RÉSUMÉ

Le système CRIPSPR-Cas9 utilise l'édition génique de la lignée germinale qui permet la mutagenèse des séquences malades de l'ADN embryonnaire, permettant ainsi de naître un individu en santé qui aurait autrement hérité des maladies génétiques. En 2012, la communauté scientifique se pressait pour le droit à la propriété intellectuelle, en anticipant le potentiel économique de CRISPR au futur. Face à la guerre pour le territoire commercial, la question de caractère abordable et d'accès pour le grand public n'a pas été abordée en gros. Le mouvement courant vers la commercialisation totale de CRISPR-Cas9 mènera à des coûts exorbitants pour l'accès à un traitement vivifiant, notamment avec des cadres régulatrices qui prohibassent le financement fédéral de recherche dans l'édition de la lignée germinale.

In the modern era of medical research, CRISPR-Cas9 gene editing is one of the most promising therapeutic technologies for the advancement of human health through disease prevention. Although CRISPR-Cas9 gene editing research has not yet progressed to human clinical trials in earnest, scientists are cautiously beginning to study the technology in more complex animal models. For example, CRISPR-Cas9 was recently used to successfully restore an essential muscle protein called dystrophin in a canine model of Duchenne Muscular Dystrophy (1). However, the current battle over the intellectual property rights to CRISPR raises the question of whether this potentially life-saving technology will be accessible to everyone when the dust has settled. While scientists continue to refine the efficacy and safety of the technology for human therapeutics, there has already been considerable movement among research institutions to pre-emptively establish territory for commercialization. However, in this rush to claim commercial rights, meaningful ethical discourse has fallen to the wayside, particularly regarding the implications for global health and accessibility. The unfortunate reality may be that while CRISPR picks up momentum in labs and in the media, scientists are becoming increasingly fixed upon a path that will lead to financial payoff at the high cost of equitable public access to revolutionary medical technology.

The rise of CRISPR-Cas9 in the biomedical research community has been meteoric, and for good reason. "CRISPR" stands for Clustered Regularly Interspaced Short Palindromic Repeats, which is a mechanism of genome cutting found initially in bacteria (2). Specifically, bacteria recognize and copy the DNA sequences of invading viruses, thus creating CRISPR arrays which match up to and target viral DNA if similar viral strains invade again. The Cas9 enzyme then deactivates the virus by cutting apart the virus' DNA. Researchers have exploited this mechanism by creating their own targeting sequences, which binds to a known segment of a genome and then uses the Cas9 enzyme to mutate the targeted segment (2). The unlimited application to genetic modification comes into play when the mutated segment is replaced by a customized DNA sequence.

THE PATENT BATTLE

This powerful technique and its wide application were first described by Jennifer Doudna from the University of California (UC), Berkeley, and Emmanuelle Charpentier from

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the Helmholtz Centre for Infection Research in Germany in a landmark 2012 study in Science (3). Another high-profile leader in the CRISPR field is the Broad Institute's Feng Zhang, who has gone toe-to-toe with UC Berkeley since the technology first came to attention in 2012. Although Doudna first demonstrated in publication that the CRISPR-Cas9 system works to cut DNA in a test tube, Zhang published an article six months later showing that the system could be applied to human cells, thus staking for Zhang a major intellectual landmark for the application of CRISPR-Cas9 in humans (4). Zhang and the Broad Institute of Harvard and MIT were the first to win a patent in 2014 for their application of CRISPR-Cas9 in human cells (5).

Zhang's claim was contested by UC Berkeley, who argued that they were the first to show that the CRISPR-Cas9 system can be harnessed to edit genes in all cell types, and that their discoveries are separately patentable. Indeed, the USPTO's Patient Trial and Appeal Board (PTAB) ruled that UC Berkeley's claim to CRISPR-Cas9's application in any setting does not directly compete with the Broad Institute's specific application of CRISPR-Cas9 in mammalian cells, even though the board has yet to grant UC Berkeley's patent (6).

As the patent battle between UC Berkeley and the Broad Institute rages on, other research institutions have not lain idle. As of August 2018, the USPTO has granted more than 90 patents that advance, vary or use the CRISPR-Cas9 technique (7). As CRISPR-Cas9 is refined, modified, and adapted for different applications, more patents will be granted, thus necessitating the purchase of multiple licenses to fully use the latest versions of the technique. Biotech companies will have to pay licensing and sub-licensing fees to a multitude of institutions. The barrier to access the complete toolbox of CRISPR-Cas9 could become prohibitively high for anyone except the most financially flush biotech companies.

IMPLICATIONS FOR AFFORDABILITY

The field of CRISPR research is undoubtedly exciting because of its potential to widely and drastically revolutionize medicine, but evidently researchers are as much driven by the promise of a massive financial payoff for those who can lay claim to bigger pieces of the intellectual property pie. If all patent holders demand licenses to allow others to use their technological variations, only a handful of commercial enterprises will be able to afford to harness and commercialize the technology. However, this problem has not gone completely ignored. In April 2017, the patent packaging company MPEG LA invited CRISPR patent holders to submit their patented technology into a pool that users could buy into as part of a non-exclusive licensing agreement with the patent owners (8). The goal is to help smaller companies more quickly and affordably obtain more pieces of the CRISPR technology in one package, rather than buying the individual licenses in a piecemeal manner. As of October 2017, 22 patents from the Broad Institute, Rockefeller University, Harvard, and MIT have been submitted for consideration into the pool, though UC Berkeley has been silent on their intention to participate (8). Given that the drive behind commercial investment in any developing human therapeutic is the promise of market monopoly through exclusive licenses, these proposed patent pools are perhaps too idealistic. Clinical trials are extremely expensive, so for biotech companies to take on the immense cost of developing human therapeutics, they must have the incentive of a future larger market share. All of the major academic institutions and their leading researchers have created their own start-ups to field exclusive licences coming out of their academic labs. UC Berkeley established Caribou Biosciences, Intellia Therapeutics, and CRISPR Therapeutics, while the Broad Institute established Editas, all of which already have exclusive rights to their respective institutes' CRISPR technologies, enabling these enterprises to sub-license out their foundational techniques to other entities. The rush to claim licensing territory has defined the impetus behind CRISPR development as one of commercial profit rather than public benefit. Lisa Larrimore Ouellette, a law professor at Stanford University, expressed this concern by stating "[t]here is not enough attention being paid to whether research from public institutions, funded by public money, is licensed in a manner that serves public interest." (8)

All signs point to the future birth of the first clinically-proven germline editing therapies in the handful of commercial labs who were able to afford exclusive licenses. These labs could therefore command large portions of the therapeutic market by demanding exorbitant prices to access literally life-changing treatments. Since these biotech enterprises would likely be the scant few able to advance the technology, they would also be the few who would hold most patent rights on more advanced CRISPR tech down the line. To complicate the picture even more, major institutions currently have varying IP footholds in other jurisdictions. China's State Intellectual Property Office (SIPO) and the European Patent Office (EPO) have both granted UC Berkeley its original patent for general CRISPR application, whereas the USPTO still has not. These regional variations would subject biotech companies around the world to different

licensing costs, depending on who owns the patent rights under a particular framework.

Even as CRISPR-based human therapeutics advances at breakneck speed, there still exists a strong ethical stance against germline editing, generally at the international level, and in varying degrees between nations (9). Even now, as investors funnel huge amounts of money into biotech in anticipation of a future CRISPR therapeutics boom, ethical opposition from the public and within legal frameworks is still a limiting factor against advancement and may increasingly bias the development of CRISPR research within the private sector. For example, in the US, the transition of CRISPR research into human embryos is impeded by the fact that studies using gene-editing on human embryos are ineligible for federal funding from the NIH, a prohibition passed down from Congress based on public aversion against the use of taxpayer money to fund embryo-destroying research (9). The direct effect of this federal funding ban is a heavy reliance on private sector funding, which further pressures US researchers to develop CRISPR technology for commercial benefit instead of public benefit.

THE REGULATORY LANDSCAPE

Even if CRISPR germline editing technology were to become available as a safe human therapeutic today, there would still be international and national regulatory instruments that would make universal accessibility extremely difficult. UNESCO's Universal Declaration on the Human Genome and Human Rights characterizes germline editing as a human rights issue, specifically that germline interventions are "contrary to human dignity" (10). Although UN Declarations are not legally binding, they still express "political commitment on matters of global significance" from the states that vote in favour of the Declaration (11). This supposed universal sentiment of caution and moral opposition toward germline editing has largely been overridden by the current push in significant swaths of the scientific community to develop germline interventions through CRISPR technology, especially in the US. There are two possible, interrelated explanations for this disconnect: one is simply that the Declaration is outdated, because it was adopted at a time when safe and accurate germline editing was not yet scientifically possible. Another possible explanation is that commercial incentives encourage nations to flout unenforceable "soft laws" like the Universal Declaration on the Human Genome and Human Rights.

Currently, the research community seems to have mired itself in a short-sighted approach that fails to truly take into account public interest on a national and international level. The unpopular question must be asked whether CRISPR should be patented at all if such technology potentially confers a huge global health benefit. A mindset against CRISPR patents and commercialization exists within the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), whose objective is to harmonize global IP rights. TRIPS protects patent rights for inventions in all fields of technology, but allows World Trade Organization member states to block the commercial exploitation of inventions necessary to protect human life or health (12). This broad goal could be connected to the more specific statement in the 1998 Directive of the European Parliament on the legal protection of biotechnological inventions: "...whereas it is therefore important to exclude unequivocally from patentability processes for modifying the germ line genetic identity of human beings..." (13). Despite these long-standing international expressions against the patentability of human germline editing, they have largely been ignored as patent offices continue to grant patents for CRISPR technology. The current trajectory of CRISPR development is undoubtedly driven by commercial incentive, which spells trouble for the affordability of future therapeutics. A CRISPR revolution with a high price tag would likely keep the revolutionary medical advancement out of reach to everyone but the wealthiest, thus widening the socioeconomic gap as the poor remain handicapped by preventable and curable genetic diseases.

FUTURE APPROACHES

The advent of CRISPR-Cas9 germline therapeutics should be accompanied by a concerted effort on the part of governments, regulatory bodies, research institutions and scientists to ensure such revolutionary medicine is available and affordable for everyone. For instance, a more serious commitment to negotiating and building patent pools could help reduce the development costs for more biotech companies, thus increasing competition and reducing the price of the final product. Public and non-profit health sectors could also intervene by buying CRISPR-Cas9 therapeutics in bulk as part of special contracts called advance market commitments. These advance agreements enable care providers to negotiate for lower prices by guaranteeing a viable market to manufacturers. This approach was used by UNICEF to secure pneumococcal vaccines for developing countries, ultimately saving almost $800 million since 2011 (14). Through multiple strategies to mitigate the development and market costs of CRISPR-Cas9 therapeutics, the private and public sectors could share the future triumph over genetic diseases

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