CLEARING THE CRISPR PATENT LANDSCAPE: TOWARDS A SOLUTION FOR SOUTH AFRICA[*]

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Patenting activity regarding new CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) genome editing technology has mushroomed to create a vast and complex patent landscape. However, because of South Africa's current depository patent system, the South African CRISPR patent landscape contains foundational patents with overlapping claims, as highlighted by the ongoing litigation in the United States between the Broad Institute and the University of California. Both these parties were granted four patents in South Africa. Also, the South African landscape may contain multiple low-quality patents that have the potential to obstruct scientific research in South Africa. The solution in the South African context is threefold, but requires that the Intellectual Property Policy of South Africa: Phase I must first be operationalised to: (a) prioritise CRISPR patent applications for formal examination and substantive search and examination; (b) provide sufficient resources for extra-curial patent opposition proceedings regarding all CRISPR patent applications and granted patents; and (c) create certainty by developing an obviousness standard with well-defined parameters. Although CRISPR is not yet advanced enough to fall within the class of life-saving technologies in the short-term, CRISPR may become critical in the treatment and eradication of priority diseases such as HIV/AIDS and tuberculosis. Accordingly, prioritising CRISPR-related patent applications serves the public interest in access to healthcare. By using (a), (b) and (c) in tandem, a triple layer of mechanisms will counter the problems of overlapping claims and of low-quality patents, and hence remove these potential obstructions to CRISPR research in South Africa.

Access to healthcare – CRISPR – genome editing – patenting – public interest

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I INTRODUCTION

Genome editing has grown enormously, predominantly since the development of the CRISPR-Cas9 system, which thrust the field of biotechnology ('biotech') into the public view.[1] This revolutionary technology provides, in comparison to current research tools, a reasonably quick, easy, precise, and inexpensive method[2] of targeting and editing specific genetic sequences.[3] CRISPR-Cas9 has the potential to promote scientific research, enhance biotech, and aid in the diagnosis and treatment of human disease.[4] As such, CRISPR-Cas9 and its variants, generally referred to collectively as CRISPR, have been the subject of numerous patent applications, primarily in the United States ('US') and Europe, by various institutions.

The CRISPR patent landscape has, however, been dominated by ongoing litigation on the technology's foundational patents, which has left the global ownership and licensing position unclear. In this article, we demonstrate that contemporary patenting activity has created a complex

[1] Genome editing refers to 'the deliberate alteration of a selected DNA sequence in a living cell' in order to change a gene's function. Nuffield Council on Bioethics *Genome Editing and Human Reproduction: Social and Ethical Issues Short Guide* (2018) 3; Neil Kirby 'Gene editing and South African law' (2016) 16(3) *Without Prejudice* 17.

[2] Alternative gene editing techniques, such as zinc finger nucleases, have been found to cost approximately $5000 to order, and designing a single customised protein can cost over $1000. By contrast, CRISPR-Cas9 can cost as little as $30. Scientists can create an RNA template with free software and a DNA kit at a cost of about $65. Brian Wang 'Disruptive CRISPR gene therapy is 150 times cheaper than zinc fingers and CRISPR is faster and more precise' *Next Big Future* 9 June 2015, available at *http://nextbigfuture.com/2015/06/disruptive-crispr-gene-therapy-is-150.html*, accessed on 15 February 2021; Mark Shwartz 'Target, delete, repair: CRISPR is a revolutionary gene-editing tool, but it's not without risk' 2018 *Stanford Medicine*, available at *https://stanmed.stanford.edu/2018winter/CRISPR-for-gene-editing-is-revolutionary-but-it-comes-with-risks.html*, accessed on 15 February 2021.

[3] Catherine Jewell & Vijay Shankar Balakrishnan 'The battle to own the CRISPR-Cas9 gene-editing tool' *WIPO Magazine* April 2017, available at *https://www.wipo.int/wipo_magazine/en/2017/02/article_0005.html*, accessed on 10 September 2019.

[4] It is worth noting some of the potential therapeutic benefits of CRISPR technology. CRISPR can be, and has been, applied in numerous industries. The most significant of these are the medical and healthcare fields, where CRISPR can be utilised in the treatment and prevention of a variety of genetic and infectious diseases, including cystic fibrosis, Huntington's disease, muscular dystrophy, sickle cell anaemia, beta-thalassemia, blindness, certain cancers, and HIV/AIDS. Furthermore, CRISPR can be used in diagnostics for disease detection. Ibid; Clara Rodríguez Fernández '7 diseases CRISPR technology could cure' *Labiotech* 23 July 2019, available at *https://www.labiotech.eu/crispr/crispr-technology-cure-disease/*, accessed on 23 January 2020.

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landscape,[5] resulting in uncertainty as to how CRISPR technology can be utilised or researched further.[6] We also investigate some of the solutions posed by the Intellectual Property Policy of the Republic of South Africa: Phase I[7] ('IP Policy') and discuss how best to operationalise: (a) substantive search and examination (SSE) procedures; (b) heightened standards of patentability; and (c) patent opposition proceedings to combat the increasingly complex patent landscape — while taking into account the interests of various role players, and ensuring that the public health interests in this technology are served.

II THE CRISPR PATENT DISPUTE

(a) Background leading up to the dispute

The patenting of CRISPR has resulted in litigation in foreign jurisdictions, as two institutions have battled over sole rights to the technology.[8] This dispute has brought the perils associated with patents in health-based research and innovation to the fore. The key foundational patent holders for the CRISPR technology are Emmanuelle Charpentier from the University of Vienna, Jennifer Doudna from the University of California at Berkeley ('UC'), and Feng Zhang of the Broad Institute ('Broad').[9]

[5] As the number of patents that are granted increases, the patent claims outlining the scope of protection will narrow, decrease in value, and become more challenging to enforce. Timothé Cynober 'CRISPR: One patent to rule them all' *Labiotech* 11 February 2019, available at *https://labiotech.eu/features/crispr-patent-dispute-licensing/*, accessed on 10 September 2019.

[6] This may impact what the technology covers as well as the countries in which the patent applies. This is because patents are territorial and are required in each country where the invention is intended to be utilised. Joanne van Harmelen 'Intellectual property rights and genome editing: Navigating the patent thicket' *ENS Africa*, available at *http://biosafety.org.za/cms/modules/media/scripts/documents/document.handler.php?media_files_id=1201*, accessed on 15 September 2019; Jacob S Sherkow 'The CRISPR patent landscape: Past, present, and future' (2018) 1 *The CRISPR Journal* 2.

[7] Department of Trade and Industry 'Intellectual Property Policy of the Republic of South Africa: Phase 1' GN 518 *GG* 41870 of 31 August 2018, available at *https://www.gov.za/sites/default/files/gcis_document/201808/41870gen518_1.pdf*, accessed on 7 November 2020.

[8] Although CRISPR itself cannot be patented, Cas9 is an enzyme found in a natural bacterial process. What was sought to be patented were the methods, engineered elements, and structures modified from their natural state to be used for editing the genomes of living mammalian cells. Broad Communications 'For journalists: Statement and background on the CRISPR patent process' 16 January 2020, available at *https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-process*, accessed on 18 January 2020; AFP 'Broad Institute wins gene-editing patent case' *Yahoo News* 25 July 2014, available at *https://www.yahoo.com/news/broad-institute-wins-gene-editing-patent-case-015314896.html*, accessed on 14 December 2020.

[9] Jewell & Balakrishnan op cit note 3.

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CRISPR gained prominence in 2012 with the publication of a paper by Jinek et al.[10] This paper outlined how CRISPR, aided by an enzyme known as Cas9, could be converted into a tool for gene editing.[11] Doudna & Charpentier, who filed their original patent application (No 13/842,859) on 15 March 2013 with the US Patent and Trademark Office ('USPTO'),[12] but had a priority date of 25 May 2012, were the first to invent methods for using CRISPR-Cas9 beyond its natural environment. Their patent covered broad claims to the CRISPR-Cas9 technology in 'transgenic non-human multicellular organisms'.[13] This patent was accepted on 23 April 2019.

This is where the distinction between prokaryotes and eukaryotes is important. Prokaryotes include bacteria and archaea, and refer to organisms lacking a membrane-bound nucleus, mitochondria, and organelles.[14] By contrast, eukaryotes refer to living organisms with a nucleus and internal membranes, and may be multicellular. These include animals, plants and fungi.[15]

In 2012, Zhang, through the publication of a paper in *Science*,[16] reported the discovery of a method to use CRISPR-Cas9 to edit eukaryotic cells. This promoted interest in the technology's potential to produce new and

[10] Martin Jinek, Krzysztof Chylinski, Ines Fonfara et al 'A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity' (2012) 337(6096) *Science* 816.

[11] Although Doudna & Charpentier's paper attracted a great deal of interest for CRISPR, it had been discovered prior to 2012. CRISPR was initially recognised as a 'general purpose gene-editing tool' in a paper published by Erik Sontheimer & Luciano Marrafinni in 2008. A patent application was filed, but was rejected due to the scientists' inability to 'reduce it to any practical application'. Jewell & Balakrishnan op cit note 3.

[12] Joe Stanganelli 'Interference: A CRISPR patent dispute roadmap' *Bio IT World* 9 January 2017, available at *https://www.bio-itworld.com/news/2017/01/09/interference-a-crispr-patent-dispute-roadmap*, accessed on 15 February 2021.

[13] Jacob S Sherkow 'The CRISPR patent interference showdown is on: How did we get here and what comes next?' *SLS Blogs* 29 December 2015, available at *https://law.stanford.edu/2015/12/29/the-crispr-patent-interference-showdown-is-on-how-did-we-get-here-and-what-comes-next/*, accessed on 24 October 2019; AFP op cit note 8.

[14] The components within a cell such as proteins, DNA, and metabolites, exist together within the cell membrane, and not in separate cellular compartments. UC's patent applications are based on work in test tubes rather than cells, and therefore do not focus on eukaryotes. *Nature* 'Prokaryotes' available at *https://www.nature.com/subjects/prokaryote*, accessed on 2 January 2020; Broad Communications op cit note 8.

[15] *Nature* 'Eukaryotes' available at *https://www.nature.com/subjects/eukaryote*, accessed on 2 January 2020; Ulrich Storz 'CRISPR Cas9 — Licensing the unlicensable' (2018) 265 *Journal of Biotechnology* 86; Broad Communications op cit note 8.

[16] Le Cong et al 'Multiplex genome engineering using CRISPR/Cas systems' (2013) 339(6121) *Science* 819.

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more effective medical treatments, thus increasing its commercial value. Simply put, Doudna & Charpentier demonstrated a broad utilisation of the CRISPR-Cas9 system for gene editing in bacteria and cell-free systems (prokaryotes),[17] whereas Zhang showed the usage of this system in more complex organisms (eukaryotes).

Zhang filed his CRISPR patent application (No 14/054,414) with the USPTO for the use of the technology in eukaryotes on 15 October 2013, but received a priority date of 12 December 2012.[18] He simultaneously filed for an Accelerated Examination Request: a fast-track review process[19] which allows for a patent application to be expedited in exchange for a fee.[20] Zhang's expedited review was accepted,[21] resulting in the USPTO granting Zhang's patent in April 2014, with numerous other patents awarded to Broad thereafter.[22] Therefore, although it appeared that Doudna & Charpentier were the initial inventors of a workable CRISPR system, as well as the first to file a patent application encompassing it,[23] Zhang was triumphant regarding particular claims covering eukaryotic applications of CRISPR.[24] This ignited the current patent dispute between the two parties.[25]

An influential factor in the proceedings was the patent system used in the US at the time. Prior to 2013, the USPTO held that a patent would be awarded to the first inventor,[26] in line with the first-to-invent patent system.[27] When multiple inventors filed similar patent applications, it was held that the patent should be granted to the inventor who first formulated and reduced the concept to practice, even if they were not the initial

[17] UC's patent application covered essential elements of the CRISPR-Cas9 system to alter the DNA of bacteria, plant, animal and human cells. Storz op cit note 15 at 86.

[18] Sherkow op cit note 6; Sherkow op cit note 13.

[19] Jacob S Sherkow 'Patents in the time of CRISPR' 2016 *Genome Editing* 26.

[20] This procedure requests the USPTO to decide on an application provided that it is concise (a maximum of three independent claims), related to one invention, and on condition that the patentability of individual claims will not be contended during prosecution. The inventor must agree to an all-or-nothing decision on the application. Ibid at 26; Sherkow op cit note 13.

[21] Sherkow op cit note 13.

[22] AFP op cit note 8.

[23] Sherkow op cit note 19 at 26; Jacob S Sherkow 'What the CRISPR patent dispute is all about' *Scientific American* 12 December 2016, available at *https://blogs.scientificamerican.com/guest-blog/what-the-crispr-patent-dispute-is-all-about/*, accessed on 15 September 2019.

[24] Sherkow op cit note 13.

[25] Sherkow op cit note 6 at 2.

[26] Sherkow op cit note 19 at 27.

[27] Jewell & Balakrishnan op cit note 3.

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filers of an application.[28] However, this changed with the enactment of the Leahy-Smith America Invents Act,[29] which introduced the current first-to-file patent system.[30]

(b) Battle one: the first interference proceedings

(i) *Issues leading up to the proceedings in the Patent Trial and Appeal Board*

Due to the expedition of Zhang's patent application, UC requested the USPTO to launch a patent interference proceeding against the patents awarded to Broad because they interfered with UC's patent application.[31] This request also sought to determine if the inventions were identical, and who was the original inventor of CRISPR-Cas9.[32] As the filing of the patents in the CRISPR dispute occurred prior to March 2013, the first-to-invent system was still in place.[33] In terms of this system, an interference procedure was applicable, resulting in UC's request being granted by the USPTO's Patent Trial and Appeal Board ('PTAB').[34]

[28] Ibid; Leonid Kravets 'First-to-file patent law is imminent, but what will it mean?' *Tech Crunch* 17 February 2013, available at *https://techcrunch.com/2013/02/16/first-to-file-a-primer/*, accessed on 2 August 2019.

[29] 125 STAT 284. The 'first to invent' system was utilised in the US until March 2013, when it was replaced by the Leahy-Smith America Invents Act. Jewell & Balakrishnan op cit note 3.

[30] US patent law focuses on the first applicant for a patent, but this does not guarantee a patent to the inventor who files first. However, where similar inventions are filed, the initial filer will be entitled to pursue their patent. This system allows for more certainty and objectivity. Additionally, it brings the USPTO in line with other jurisdictions. USPTO 'First inventor to file is here: Learn how it works' *Inventors Eye* April 2013, available at *https://www.uspto.gov/learning-and-resources/newsletter/inventors-eye/first-inventor-file-here-learn-how-it-works*, accessed on 26 August 2019.

[31] Sherkow op cit note 13.

[32] This is a proceeding within the structures of the USPTO to determine the first inventor of a certain technology. Sherkow op cit note 19 at 26; Jewell & Balakrishnan op cit note 3; Van Harmelen op cit note 6.

[33] Doudna's original patent application was filed on 15 March 2013, one day before the first-to-file system was implemented. However, Doudna's invention was given a priority date of 25 May 2012. Zhang filed his patent application on 15 October 2013, after the first-to-file system was implemented. However, Zhang claimed a priority date of 12 December 2012, which meant that his patent application fell under the preceding first-to-invent system. Sherkow op cit note 13; Jewell & Balakrishnan op cit note 3.

[34] The interference proceeding operates as a trial within the USPTO to determine the initial inventor of the subject in dispute and to decide the scope and importance of the conflicting patent applications. This proceeding is utilised in order to determine who invented what, by comparing the claims of both parties. A two-way test, taken from the case of *Eli Lilly and Company v Human Genome Sciences Inc* [2011] UKSC 51, was used to compare the involved claims. The test revolves around the finding of obviousness and asks whether the claims of one party, if taken to be prior art, would render the claims of the opposing

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The dispute centred on whether UC's initial patent application contained sufficient information to allow an ordinary molecular biologist to utilise the CRISPR technology in eukaryotes. If this was the case, UC would be entitled to CRISPR patents in any cell system. However, if the application failed to reveal adequate information regarding use in eukaryotes, Zhang would be granted multiple CRISPR patents.[35] What the issue came down to was whether there was interference between the patents issued to Broad and UC's foundational patent application and, if so, who was the first to invent a single guide RNA (sgRNA)-mediated CRISPR-Cas9 gene editing system in a eukaryotic cell.

(ii) *The decision in the Patent Trial and Appeal Board*

The issue in the PTAB, which was decided under 35 USC § 102(g),[36] required an examination into whether both parties had patently indistinct subject matter.[37] Broad argued that there was no interference-in-fact

party obvious (and vice versa). A three-judge panel hears evidence on the work undertaken by each party, what was disclosed in their original patent applications, and how 'an average molecular biologist would have viewed this information as the technology progressed through 2012'. The panel then determines which aspects of the disputed patents, if any, overlap. To assist in this process, the panel drafts a 'count', which is a hypothetical patent that covers both sets of technologies. The scientists' attorneys file several sets of motions arguing that the count does or does not cover the technology in dispute, or that the count needs to be rewritten or divided in order to cover the contested inventions. Sherkow op cit note 6 at 2; Sherkow op cit note 19 at 27–8; Sherkow op cit note 13; Jewell & Balakrishnan op cit note 3; see *Regents of University of California v Broad Institute Inc* 903 F 3d 1286 (2018) para 8.

[35] Sherkow op cit note 23.

[36] This section of the United States Code reads: 'A person shall be entitled to patent unless … (g)(1) during the course of an interference … another inventor involved therein establishes … that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed.'

[37] *Regents of University of California v Broad Institute Inc* supra note 34 para 8. UC argued that there was interference because, without their work on CRISPR, Broad's research would not have occurred. If that was found to be the case, an interference would be established, resulting in the patent being awarded to the first inventor. During the initial interlocutory stage of the interference proceedings, the parties have the opportunity to present initial briefs which consist of substantive statements regarding the patentability of the disputed invention, whether there is interference-in-fact, or whether the PTAB should specify the interference's ambit. Moreover, the PTAB may examine motions regarding why the parties qualify for particular priority dates — the decisive factor in the granting of patents if an interference-in-fact exists. Following the interlocutory phase, the three-judge panel determines unresolved motions. Ultimately, the panel will determine interference and award the relevant patents to one or none of the parties. Sherkow op cit note 13; Alessandra Potenza 'Who owns CRISPR — One of the most important genetic inventions of our time?' *The Verge* 6 December 2016, available

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as their patents were inventive over UC's application,[38] and were thus separately patentable.[39]

The PTAB focused on whether Broad's work was original or whether it was 'the next obvious step to take, and/or fundamentally based on prior art'.[40] UC argued that Broad's process for editing eukaryotic cell genes was a clear extension of its work on cutting purified DNA in test tubes, and hence unpatentable. Furthermore, UC contended that the decision should not turn on distinguishing between prokaryotes and eukaryotes, but rather the sgRNA utilised in any cell system. This was because transferring UC's invention from bacteria to eukaryotes was straightforward and could be accomplished by an ordinary molecular biologist.[41] However, the judges were not convinced about the simplicity of translating CRISPR to eukaryotes.[42]

In examining the claims of Broad's patent and UC's application,[43] the PTAB found that none of UC's claims were limited to a particular environment, whereas Broad's claims were eukaryote-specific.[44] The PTAB inquired whether one of ordinary skill, in light of the prior art, would see the claim as having 'a reasonable likelihood of success'.[45] In 2017, the PTAB decided that the patents awarded to Broad for the

at *https://www.theverge.com/2016/12/6/13857674/crispr-gene-editing-patent-dispute-berkeley-broad-mit-jennifer-doudna-feng-zhang*, accessed on 3 September 2019.

[38] Broad argued that there should not be an interference as Zhang had done something different and was therefore entitled to his own patents. NYU School of Law video presentation 'The CRISPR patent battle: Implications for downstream innovation in gene editing' 21 March 2017, available at *https://www.youtube.com/watch?v=UHNNBX6e8dE*.

[39] This would mean that Broad would hold various patents involving CRISPR in eukaryotes, including human gene editing, while UC would only be allowed to use CRISPR in bacteria, which is less profitable. Sherkow op cit note 23.

[40] Jewell & Balakrishnan op cit note 3.

[41] If this argument were successful, UC would be granted a broad patent covering the majority of uses of CRISPR, while Broad would lose its patents. Sherkow op cit note 23.

[42] This was because other systems, not just CRISPR, experienced difficulties in moving the process to eukaryotic cells. Moreover, simultaneous experiments did not mean that scientists were certain that CRISPR could be successfully or easily applied in eukaryotes. Ibid.

[43] *Regents of University of California v Broad Institute Inc* supra note 34 para 8.

[44] Ibid para 11.

[45] The rationale for this decision was the limitation present in Broad's patents, being the eukaryotic system. The PTAB then found that should UC's claims be treated as prior art, it would not render Broad's claims obvious as the skilled artisan would not have had a reasonable expectation of success. What led the PTAB to this conclusion was evidence based on statements made by persons skilled in the art, information in the 2012 paper by Jinek et al (which did not list that the results of the experiment would work in eukaryotes), and statements made by Doudna in the media regarding her uncertainty about the success of her system in eukaryotes. Ibid para 12; Jinek et al op cit note 10.

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use of CRISPR-Cas9 in eukaryotic cells involved dissimilar inventions and did not overlap or inhibit those of UC[46] for the use of CRISPR-Cas9 in any environment.[47] Therefore, the inventions were separately patentable.[48] While the PTAB did not determine who the first inventor of the CRISPR-Cas9 system in eukaryotes was,[49] it did leave both Broad and UC in control of key areas such as gene therapy, drug discovery and development, and also other human therapeutic applications.[50]

This outcome means that should a prospective licensee wish to commercialise a human therapeutic application of CRISPR entailing eukaryotic usage, a licence would be required from both Broad and UC.[51] However, those wishing to utilise the CRISPR-Cas9 technology in other cell systems would only need a licence from UC. As Doudna explained, '[Broad] will have a patent on green tennis balls … [UC] will get a patent on all tennis balls'.[52]

(c) Battle two: the appeal

Following the decision of the PTAB, UC appealed to the US Court of Appeals for the Federal Circuit.[53] The court was required to consider whether there was substantial evidence to support the PTAB's finding. The purpose of the appeal was not to hear the matter afresh, but rather to evaluate whether the decision of the PTAB was reasonable.

[46] Jewell & Balakrishnan op cit note 3.

[47] Ibid.

[48] Sherkow op cit note 6 at 2.

[49] There was no reason for the PTAB to determine who the first inventor of the CRISPR system in eukaryotes was, because the inventions were separately patentable. Because there was no interference, the patents were separate and there was no argument over the initial inventor, as each party was deemed to be the initial inventor of the claims in their respective patents. Allie Nawrat 'USPTO reverses decision regarding interfering CRISPR patents' *Pharmaceutical Technology* 26 June 2019, available at *https://www.pharmaceutical-technology.com/news/uspto-reverses-decision-interfering-crispr-patents/*, accessed on 5 January 2020.

[50] 'Federal Court hands Broad Institute victory in CRISPR patent fight against UC Berkeley' *GenomeWeb* 10 September 2018, available at *https://www.genomeweb.com/business-news/federal-court-hands-broad-institute-victory-crispr-patent-fight-against-uc-berkeley#.XkLadVUzbIU*, accessed on 3 January 2020.

[51] This is because, while Broad holds patents for the use of CRISPR-Cas9 in eukaryotes, UC's patents relate to CRISPR-Cas9 in any cell.

[52] Aaron Dy 'Reactions to CRISPR patent decision' *PLOS Blog* 17 February 2017, available at *https://theplosblog.plos.org/2017/02/reactions-to-crispr-patent-decision/*, accessed on 13 December 2020, who also notes that an invention in a certain category may be patented (tennis balls), and this does not prevent a new aspect of that category from being eligible for patent protection (green tennis balls). However, if the initial patent was for green tennis balls, one cannot then patent all tennis balls, as it forms part of the prior art.

[53] *Regents of the University of California v Broad Institute* No 2017-1907 (Fed Cir Sep 10 2018).

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UC attempted to convince the judges of its view that a skilled person would have had a reasonable expectation of success in utilising CRISPR-Cas9 in eukaryotes. However, the court held that although there is evidence 'that could support this position … [w]e do not reweigh the evidence. It is not our role to ask whether substantial evidence supports fact-findings not made by the [PTAB], but instead whether such evidence supports the findings that were in fact made'.[54]

In 2018, the court confirmed and upheld the PTAB's ruling of no interference-in-fact. It held that the PTAB analysed the evidence and

> 'considered a variety of statements by experts for both parties and the inventors, past failures and successes in the field, evidence of simultaneous invention, and the extent to which the art provided instructions for applying the CRISPR-Cas9 technology in a new environment'.[55]

As a result, the court held that Broad's patents were sufficiently inventive over UC's.[56]

(d) Battle three: the new interference proceedings

On 24 June 2019 the PTAB, of its own accord, declared a new interference proceeding that challenged the validity of UC's eukaryotic claims.[57] The declaration of an interference means that the USPTO has found that more than one patent application defines an invention that is considerably similar to existing patented inventions.[58] Broad's patents from the previous

[54] Ibid at 12.

[55] Ibid at 16.

[56] The court found that Broad's patent utilising CRISPR-Cas9 in plant and animal cells was separately patentable from UC's use in any environment. Therefore, the patent claims involved diverse subject matter that did not interfere with one another. Jacob S Sherkow 'CRISPR patent decision didn't get the science right, but the ruling was fair' *STAT News* 11 September 2018, available at *https://www.statnews.com/2018/09/11/crispr-patent-decision-science/*, accessed on 25 August 2019; *Genome Web* op cit note 50.

[57] Patent Interference No. 106,115 (DK) Declaration — 37 CFR § 41.203(b). This was decided under 35 SC § 135(a), which deals with derivation proceedings. The decision by the PTAB is expected within the next two years, with parties currently submitting their respective motions. All documents including motions, oppositions, notices, and orders can be accessed through the USPTO at *https://acts.uspto.gov/ifiling/ PublicView.jsp?identifier=106115&identifier2=null&tabSel=4&action=filecontent&replyTo=PublicView.jsp*, accessed on 2 January 2020. USPTO '2301 Interference proceedings [R-08.2017]', available at *https://www.uspto.gov/web/offices/pac/mpep/s2301.html#d0e238030*, accessed on 22 September 2019.

[58] According to Eldora L Ellison, a lead patent strategist on CRISPR matters for UC, 'the initiation of this interference proceeding highlights that previous decisions involving Broad did not determine who was the first to invent this technology, and it lays out a pathway for resolving this important issue'. 'Patent office renews dispute over patent rights to CRISPR-Cas9' *Berkeley News* 25 June 2019, available at *https://news.berkeley.edu/2019/06/25/patent-office-renews-*

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interference[59] and UC's later patent applications were evaluated[60] — all of which related to the usage of CRISPR-Cas9 in eukaryotic systems. Through this second interference proceeding, the PTAB determined who was the first inventor of CRISPR-Cas9 in eukaryotes.[61] In the new interference proceedings, the USPTO named Broad as the senior party and UC as the junior party. The senior party is listed as the party who filed at the earlier date and is assumed to be the initial inventor, while the junior party carries the burden of proof to show otherwise. UC was required to prove that Broad did not invent the CRISPR-Cas9 system in eukaryotes, which made its case challenging.[62]

On 10 September 2020, the PTAB decided key motions in this second interference proceeding. The PTAB rejected UC's arguments and assigned it a filing date of 28 January 2013, whilst Broad was given an earlier filing date of 12 December 2012. The implication of this decision means that Broad has priority in using CRISPR-Cas9 in plant and animal cells, while UC has priority for CRISPR-Cas9 usage in other cells, such as bacterial cells.[63]

dispute-over-patent-rights-to-crispr-cas9/, accessed on 22 January 2020; Sharon Begley 'Patent office reopens major CRISPR battle between Broad Institute and Univ. of California' *STAT News* 25 June 2019, available at *https://www.statnews.com/2019/06/25/crispr-patents-interference/*, accessed on 11 September 2019.

[59] Broad patents 8,697,359; 8,771,945; 8,865,406; 8,871,445; 8,889,356; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; 8,999,641; 9,840,713 and application 14/704,551. UC Berkeley op cit note 56.

[60] UC applications 15/947,680; 15/947,700; 15/947,718; 15/981,807; 15/981,808; 15/981,809; 16/136,159; 16/136,165; 16/136,168 and 16/136,175.

[61] This new interference proceeding relates only to a sgRNA CRISPR-Cas9 system. Eric Rhodes 'Interference declared over CRISPR-Cas9 for eukaryotic cells, reigniting patent war' *GEN* 28 June 2019, available at *https://www.genengnews.com/news/interference-declared-over-crispr-cas9-for-eukaryotic-cells-reigniting-patent-war/*, accessed on 27 August 2019; Drug Target Review 'Dispute over patent rights to CRISPR-Cas9 renewed by patent office', available at *https://www.drugtargetreview.com/news/45670/patent-rights-crispr-cas9-patent-office/*, accessed on 11 September 2019.

[62] However, UC has requested, in its Motions List, that the USPTO reverse its designation and assign UC as the senior party instead of Broad. 'Broad Institute, UC file motions lists in latest CRISPR interference proceeding' *GEN* 1 August 2019, available at *https://www.genengnews.com/news/broad-institute-uc-file-motions-lists-in-latest-crispr-interference-proceeding/*, accessed on 28 December 2019; Donna Young 'US patent office triggers new CRISPR gene-editing fight' *S&P Global* 25 June 2019, available at *https://www.spglobal.com/marketintelligence/en/news-insights/latest-news-headlines/52561540*, accessed on 4 January 2020; Rhodes op cit note 61.

[63] Vincent M de Grandpré & Felicia Lozon 'Making sense of the battle for the CRISPR-Cas9 patent rights' *Osler* 15 March 2021, available at *https://www.osler.com/en/resources/critical-situations/2021/making-sense-of-the-battle-for-the-crispr-cas9-patent-rights*, accessed on 16 June 2021.

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(i) *Did the patent dispute spill over to Europe?*

In Europe, the legitimacy of Broad's patents was disputed at the European Patent Office ('EPO').[64] The EPO Boards of Appeal, upholding a first instance decision by the Opposition Division ('OD'), withdrew Broad's foundational patent (EP 2771468) for eukaryotic applications of CRISPR.[65] In addition to this defeat, the OD rejected Broad's divisional patent application (EP 2784162) in 2019.[66]

The reasons for the removal of Broad's foundational patent were initially withheld,[67] but the EPO has since released its reasons, noting that the patent was revoked for a 'lack of novelty in view of intermediate prior art'.[68] Furthermore, the EPO observed that the Patent Cooperation Treaty ('PCT') application,[69] on which the EPO patent is based, did not disclose all the relevant inventors as per the US patent application, thus rendering the priority claim invalid.[70]

[64] Christopher Wilkins 'European Union: CRISPR patent portfolio edited: The Broad Institute has lost its appeal on a key CRISPR patent in Europe' *Mondaq* 20 January 2020, available at *https://www.mondaq.com/uk/Intellectual-Property/885192/CRISPR-Patent-Portfolio-Edited-The-Broad-Institute-Has-Lost-Its-Appeal-On-A-Key-CRISPR-Patent-In-Europe*, accessed on 23 January 2020.

[65] Revocation of the parent patent will not necessarily hamper Broad as it has numerous pending European patent applications, as well as a variety of granted European patents based on CRISPR technology. The patent family comprises four other patents; a second divisional patent application for patent EP 289669 was upheld to a limited extent. Appeals for both patents are pending. Two other patents (EP 2940140 and EP 2921557) were opposed, and one (EP 3144390) has not yet been granted. Amy Sandys 'EPO revokes Broad Institute patent — But it's just the beginning for CRISPR-Cas' *JUVE Patent* 17 January 2020, available at *https://www.juve-patent.com/news-and-stories/cases/epo-revokes-broad-institute-patent-but-its-just-the-beginning-for-crispr-cas/*, accessed on 20 January 2020.

[66] Wilkins op cit note 64.

[67] 'Decision in case T 844/18 on the CRISPR gene editing technology' *EPO* 17 January 2020, available at *https://www.epo.org/law-practice/case-law-appeals/communications/2020/20200117.html*, accessed on 22 January 2020.

[68] Ibid.

[69] 1970, 28 UFT 7647. The PCT is an international treaty that is managed by the World Intellectual Property Organisation ('WIPO'), and allows patent protection to be sought contemporaneously in numerous countries through the filing of a single, international patent application which replaces the separate, foreign applications usually necessary for protection abroad. Gene Quinn 'PCT basics: Obtaining patent rights around the world' *IP Watchdog* 26 December 2015, available at *https://www.ipwatchdog.com/2015/12/26/pct-basics-patent-rights-around-the-world/id=64141/*, accessed on 13 December 2019.

[70] It was held that the priority of Broad's foundational patent was void due to a lack of entitlement and because the patent claim lacked novelty over prior art published in the priority year. A PCT application founds a sole filing date in all member states. A priority claim is a reference in a later filed patent application to a previous application. A priority claim allows the later patent application to use the filing date of the earlier patent application as a priority date. In the case of Broad, the prior art was relevant as the OD failed to acknowledge

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Many other patent claims involving CRISPR-Cas9 have been heard in Europe.[71] Oral argument in the opposition proceedings against UC's primary European patent (EP 2800811) commenced in February 2020, with the EPO affirming UC's patent encompassing the single-guide CRISPR-Cas9 system and dismissing opposing arguments filed by Broad.[72] In August 2019, the OD found in favour of UC. Therefore, it is possible that UC may control eukaryotic applications of CRISPR in Europe[73] — in contrast to the current situation in the US.[74]

Broad's 'claim to priority from a US provisional application naming more applicants than the subsequent PCT application from which [the foundational patent] is derived'. Since the omitted applicant had not transferred his rights to the PCT application, the priority claim was deemed invalid. Broad noted that the naming issue would affect up to nine of the 21 European patents, including vital patents. *EPO* op cit note 67; James Yang 'Claim of priority to an earlier filed patent application' *OC Patent Lawyer* 25 April 2018, available at *https://ocpatentlawyer.com/priority-claim-patent-application/*, accessed on 5 January 2020; European Patent Academy 'Priority' *Patent Litigation Block 1* 4; 'Revocation of Broad Institute CRISPR patent upheld in Europe' *GenomeWeb* 17 January 2020, available at *https://www.genomeweb.com/business-news/revocation-broad-institute-crispr-patent-upheld-europe#.XlBLJZUzbIV*, accessed on 22 January 2020.

[71] Two other cases are pending before the Boards of Appeal, both involving the same issues of priority. Sandys op cit note 65.

[72] Alex Philippidis 'Rejecting Broad Institute opposition, EPO affirms CRISPR patent issued to Charpentier, UC, and U Vienna' *GEN* 20 February 2020, available at *https://www.genengnews.com/news/rejecting-broad-institute-opposition-epo-affirms-crispr-patent-issued-to-charpentier-uc-and-u-vienna/*, accessed on 2 January 2021.

[73] The central issue in this matter is whether the priority from UC's first provisional US application for the protospacer adjacent motif ('PAM') is valid. The PAM is a short DNA sequence that follows the DNA region targeted for cleavage (cutting) by the CRISPR system. If the priority is not valid, the patent's effective date would fall after the publication of UC's CRISPR-Cas9 paper in *Science*, thus affecting the patentability of certain claims. However, during examination before the EPO and in other litigation, UC was successful in arguing that the PAM formed part of common general knowledge. According to European practice, claiming priority of 'the same invention' in terms of art 87(1) of the European Patent Convention ('EPC') means that priority can only be acknowledged if a skilled person can derive the subject matter directly and unambiguously, using common general knowledge, from the previous application as a whole. The OD's acceptance that the PAM was part of the common general knowledge when the patent was filed means that it tentatively determined that the disclosure of the patent is enabling over the entire claim scope, including eukaryotic applications. The OD also argued that the claims meet the requirements of novelty and inventiveness. The invention's capabilities offer greater versatility in gene editing. Furthermore, the examples provided in UC's patent show that the invention achieves, or is likely to achieve, this result. Ibid; Synthego 'Importance of the PAM sequence in CRISPR experiments' available at *https://www.synthego.com/guide/how-to-use-crispr/pam-sequence*, accessed on 19 December 2019; Joanna Applequist 'The Crispr-Cas9 patent tussle continues: The case of UC Berkeley at the EPO' *Lexology* 15 November 2019, available at *https://www.lexology.com/library/detail.aspx?g=01e7cd32-be9e-41ba-99f6-a6cff718c0f6*, accessed on 6 December 2019.

[74] The differences between US and European law have led to contrasting outcomes concerning patents on CRISPR. While the basic principles of patent

(e) The impact of the CRISPR patent dispute

CRISPR-Cas9 and its derivatives are being used in almost all genetics and microbiology laboratories worldwide. While both UC and Broad presently allow non-commercial research uses of CRISPR technologies without the need to obtain a written licence, this leaves those who wish to perform commercial research, such as biotech start-ups, in a difficult position. Currently, depending on the jurisdiction in which the commercial research is to be undertaken, and who is judged to be the holder of the foundational patents, companies may see fit to obtain licences from both entities — therefore paying double in terms of licensing fees. From a South African perspective, if the country wishes to grow its nascent biotech sector,[75] this is clearly not an ideal situation.

Should the final decision in the US CRISPR patent dispute favour UC, it would mean that UC's US patents are valid, while Broad's would be invalidated.[76] If Broad were unsuccessful in the patent dispute, it is unclear what would happen to its spin-out companies ('spin-outs'),[77] such

law are similar in the US and Europe, certain differences do exist, specifically in the fields of pharmaceuticals and biotech. The primary distinction between the patent laws of the US and Europe, and the reason why certain CRISPR decisions have had different outcomes, is the fact that the first interference proceedings in the US CRISPR patent dispute were decided based on the old first-to-invent system. Although this practice has now changed and is in line with the European approach, this system had an impact on the patent laws and CRISPR decisions. 'Take a look at the key differences between US and European patent law and examine the patent issues relating to the biopharmaceutical industry' *BusinessWire* 31 March 2006, available at *https://www.businesswire.com/news/home/20060331005205/en/Key-Differences-European-Patent-Law-Examine-Patent*, accessed on 6 January 2020.

[75] South Africa's 2013 Bio-Economy Strategy envisions that the country's bio-economy will contribute to economic growth through the formation and development of novel industries. To be more responsive and have a positive impact on all South Africans, the Bio-Economy Strategy offers a framework to guide biosciences research and innovation investments. The Bio-Economy Strategy aims to build an enabling environment for various role players, including 'government departments, established industry, venture capital and the broader public; and on interacting with life-science role players, academics, researchers and private sector entrepreneurs to create value'. It focuses on recognising areas where public policy can 'encourage innovation and improve cooperation between stakeholders'. Three key sectors — agriculture, health, and industry — have been identified as vital in implementing the Bio-Economy Strategy. South Africa Department of Science and Technology *The Bio-Economy Strategy* (2013) 3.

[76] This would leave Broad in a difficult position as many of its patents relate to eukaryotic applications. Furthermore, the vast amounts of public money that Broad and UC spent funding the litigation could have been used elsewhere in furthering scientific innovation.

[77] A spin-out is formed through separation from the main company in order to form a new and independent corporation. Caribou Biosciences and Intellia Therapeutics (Intellia) are associated with UC, while Editas is linked to Broad.

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as Editas Medicine ('Editas'), as well as the licensing agreements relating to the invalidated patents. Companies such as Editas have granted licences to large pharmaceutical companies in multimillion-dollar deals. Large portions of this money have already been used in clinical trials and other costs associated with commercialisation.[78] If Broad's patents were to be revoked, it would have dire consequences for licensees as commercialising CRISPR applications through Broad's rescinded licences would then infringe on the patents of UC. Alternatively, Broad could attempt to obtain licences for UC's patents, but this may be unsuccessful for two reasons: (1) Broad is not entitled to a licence and, therefore, UC could reject the licence request for market-based reasons;[79] and

Allen & Overy 'Key players in CRISPR' available at *https://www.allenovery.com/en-gb/global/news-and-insights/crispr/key-players-in-crispr*, accessed on 18 October 2019.

[78] Editas's leading drug candidate is a therapy, EDIT-101, which uses CRISPR to treat an uncommon genetic infant blindness known as Leber congenital amaurosis type 10 (LCA10). There is a significant need for successful therapies as the sole treatment that presently exists cannot cure all types of LCA. Editas is developing EDIT-101 in partnership with Allergan, who may in-license up to five eye therapies, including EDIT-101. However, Editas is entitled to receive potential profits and royalties therefrom. Additionally, Editas is developing potential CRISPR treatments for other eye diseases, including Usher Syndrome type 2A (USH2A) and ocular Herpes Simplex Virus type 1 (HSV-1). Editas's second major drug candidate is EDIT-301, a gene therapy that aims to treat sickle cell disease and beta-thalassemia. However, CRISPR Therapeutics is also developing its own sickle cell treatment, CTX001. CRISPR Therapeutics has partnered with Vertex Pharmaceuticals ('Vertex') in order to jointly develop, and profit from, CTX001. Vertex holds exclusive rights to license up to five other CRISPR-based therapies that arise from the partnership. Editas has collaborations with large pharmaceutical companies regarding its technology, which provide research support and funds to assist in the development of human therapeutic applications of CRISPR. As Editas currently lacks a product portfolio, it is reliant on its partners for revenue. Editas has a collaboration and licensing agreement with Juno Therapeutics ('Juno'). Editas granted Juno an exclusive licence to utilise gene editing methods, including CRISPR-Cas9, for cancer treatments. Editas also has a research and cross-licensing agreement with BlueRock Therapeutics to amalgamate gene editing technologies that would assist in the development of novel engineered cell medicines. In 2019, Editas entered into collaboration with AskBio to develop in vivo CRISPR medicines to treat neurological diseases. Mark Prvulovic 'Is Editas Medicine a buy?' *The Motley Fool* 18 December 2019, available at *https://www.fool.com/investing/2019/12/18/is-editas-medicine-a-buy.aspx*, accessed on 12 January 2020; 'Editas (EDIT) focuses on developing eye candidate EDIT-101' *Nasdaq* 6 January 2020, available at *https://www.nasdaq.com/articles/editas-edit-focuses-on-developing-eye-candidate-edit-101-2020-01-06*, accessed on 15 January 2020; Keith Speights 'Better buy: Editas Medicine vs CRISPR Therapeutics' *The Motley Fool* 27 April 2019, available at *https://finance.yahoo.com/news/better-buy-editas-medicine-vs-170000299.html*, accessed on 9 January 2020; Cynober op cit note 5.

[79] UC could be motivated to reject the applications as they would want to control markets and retain a monopoly over human therapeutics. This would result in higher profits for UC, and all involved.

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(2) UC exclusively licensed its patents to spin-outs, thus preventing licensing to Broad, as exclusive licences lack a grant-back clause.[80] The spin-outs to whom UC has granted licences have already licensed exclusively to other private companies,[81] which would preclude them from licensing to Broad.

If Broad were to win the US patent dispute, the status quo would remain, and entities interested in pursuing CRISPR technologies would have to obtain licences from both Broad and UC for human therapeutic applications.[82] Broad would have to acquire a licence from UC, as UC holds the foundational patent on CRISPR, and UC would require a licence from Broad, whose patents are eukaryote-specific. The costs of cross-licensing will likely be reflected in the prices of the resulting CRISPR-related products which, in turn, would mean that the public would have to pay increased costs.

Seeing an opportunity, MPEG LA announced in 2016 its intention to create a CRISPR-Cas9 patent pool to make the technology accessible.[83] Patent pools involve agreements between multiple patent owners to combine patents and license them to each other or to third parties.[84] They grant numerous companies, in exchange for payment, access to, and use of, several patents. Patent pools are often used to create bundle licences for complex technologies, and where patent thickets are present,

[80] A patentee (licensor) is granted monopoly rights over an invention. However, this exclusive right may be undermined by improvements to, or substitutes for, the patented invention. Grant-backs are often used to control new developments (improvement patents). Therefore, the patentee requires the potential licensee to agree to grant back rights to improvement patents to the patentee. These are improvements developed by the licensee which relate to the initial patent. Richard Schmalbeck 'The validity of grant-back clauses in patent licensing agreements' (1975) 42 *University of Chicago LR* 733.

[81] Such as Intellia licensing human therapeutic applications of CRISPR to Novartis and Regeneron. Cynober op cit note 5.

[82] This means that Broad and UC, through their surrogate companies, would have to cross-license for human therapeutic applications of CRISPR. Cross-licensing involves an agreement between parties to grant mutual rights to one another's intellectual property, meaning that parties license from each another. Shai Jalfin 'The good, bad and ugly of cross-licensing your technology patents' *IP Watchdog* 15 December 2017, available at *https://www.ipwatchdog.com/2017/12/15/good-bad-ugly-cross-licensing-technology-patents/id=90954/*, accessed on 29 December 2019.

[83] MPEG LA 'CRISPR', available at *https://www.mpegla.com/crispr/initiative/*, accessed on 25 January 2020.

[84] The pooled patents are available to the members of the pool and to non-members via a licence. All the pooled patents will be available to prospective licensees under one single licence agreement at a single fee, with a set royalty rate. The patent pool will usually divide the licensing fees collected according to the value of the patents supplied.

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they form the basis of an industry standard.[85] Patent pools hold the potential to advance reciprocal technology transfer and lessen transaction costs by alleviating patent thickets.[86] Companies with similar technologies combine their standard, essential patents into a pool in order to establish a clearinghouse for patent rights.

A patent pool comprising complementary CRISPR patents can create an enabling environment for innovation, therefore increasing efficiency.[87] The 'one-stop licence' is cheaper and more convenient for potential licensees to acquire as opposed to negotiating with numerous patent holders, and paying multiplicities of fees and royalty stacking.[88] It can also eliminate the need for litigation, thus saving money for licensees. If the patent pool consists of complementary patents,[89] it will also have the effect of clearing blocking patents.[90]

[85] Patent thickets are upstream, overlapping patents controlled by different entities which, in turn, would require a prospective innovator to obtain licences from various sources. This will be a very costly exercise for the innovator and could therefore deter innovation and investment. Currently, with the numerous CRISPR patents, it is very difficult for potential innovators to determine which patents are necessary for them to obtain, for this very reason. Sirpa Soini et al 'Patenting and licensing in genetic testing: Ethical, legal and social issues' (2008) 16 *Eur J Hum Genet* 29.

[86] The UNITAID-supported Medicines Patent Pool ('MPP') has made life-saving HIV/AIDS, tuberculosis ('TB') and Hepatitis C medicines accessible and affordable in developing countries. Although patents aim to reward innovation, they can affect access to safe, effective and affordable medicines and technologies. The MPP has been essential in increasing the affordability and availability of quality medicines for HIV and Hepatitis C by arranging voluntary licences with patent holders. These licences allow other pharmaceutical manufacturers to create generics of patented medicines for low-income countries. Based on its success, the MPP has broadened its scope to encompass long-acting technologies and patented medicines that are included in the World Health Organisation's ('WHO') Essential Medicines List. Unitaid 'The medicines patent pool' available at *https://unitaid.org/project/medicines-patent-pool/#en*, accessed on 16 February 2021.

[87] WIPO 'Patent pools and antitrust — A comparative analysis' prepared by the Secretariat (March 2014), available at *https://www.wipo.int/export/sites/www/ip-competition/en/studies/patent_pools_report.pdf*, accessed on 15 July 2021.

[88] Royalty stacking is a circumstance whereby the utilisation of an invention calls for numerous licences from a variety of patent holders, thus raising the cost of end products. Ibid; Soini et al op cit note 85 at 24.

[89] Complementary patents are patents on technologies which are not substitutes for one another, but also rely on one another to bring the invention to life. WIPO op cit note 87 at 4.

[90] A blocking patent prohibits a third party from utilising or commercialising a modified version of a patented invention. When a patent prevents another invention from being developed, as it would result in infringement, this is referred to as a blocking patent. Amir Adibi 'Blocking patents explained' 26 March 2017, available at *https://www.patentlawyer.io/what-is-a-blocking-patent/*, accessed on 6 January 2020.

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MPEG LA is an independent[91] and neutral[92] administrator with the necessary infrastructure and experience to make the patent pool a reality. As it stands, at the time of writing, Broad is the only notable patent holder to have joined the CRISPR patent pool. Perhaps a true CRISPR patent pool is unattainable.[93]

Finally, the CRISPR patent dispute may become redundant, as it revolves around the Cas9 enzyme. Since 2012, numerous other enzymes have been found to be more effective than Cas9, such as Cas12a or CasX.[94] It is likely that the CRISPR patent dispute has centred on, and is being tirelessly fought over, an aspect of the technology that is slowly becoming irrelevant.[95] This appears to be the case unless it can be shown that the new systems depend on the previous, patented CRISPR-Cas9 systems or that the issues raised in the CRISPR-Cas9 dispute are still relevant to future patent disputes.

Although new technological developments may eventually render the ongoing CRISPR patent dispute irrelevant, this is speculative. Presently the patent dispute is clearly causing uncertainty in the CRISPR patent landscape and is standing in the way of potential collaboration, such as patent pooling, which would greatly simplify licensing transactions for researcher-licensees.

[91] They are not aligned with any particular shareholder, eliminating the possibility of bias towards a certain group. Tom O'Reilly 'MPEG LA issues statement regarding CRISPR patent licensing' *Business Wire* 25 July 2019, available at *https://www.businesswire.com/news/home/20190725005951/en/MPEG-LA-Issues-Statement-CRISPR-Patent-Licensing*, accessed on 25 January 2020.

[92] This is important to ensure that the patent pool is pro-competitive. Ibid.

[93] Note that patent pools are not a panacea. See, for example, Jorge L Contreras & Jacob S Sherkow 'Patent pools for CRISPR technology — Response' (2017) 355(6331) *Science* 1274–5.

[94] In 2015, Zhang discovered Cpf1, which was simpler and less error-prone than Cas9. UC recently discovered CasX and CasY, which are smaller and may prove to be more useful than Cas9. Researchers have also discovered a new CRISPR system, C2c2, which has the potential to allow the editing of RNA as opposed to DNA. CRISPR-Cas9 enables the editing of DNA, thus permanently altering a cell's genome. However, C2c2 will allow researchers to target RNA and make provisional alterations to the genome of a cell. Deborah Ku 'The patentability of the CRISPR-Cas9 genome editing tool' (2017) 16 *Chicago-Kent Journal of Intellectual Property* 414 and 439.

[95] However, the ultimate decision in the CRISPR patent dispute may influence the scope of patent protection applicable to alternate genome editing tools and enzymes, and could serve to guide researchers and their institutions in approaching similar matters in the future, so as to avoid a repeat of the dispute involving CRISPR-Cas9. Ibid at 439.

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(f) Relevance of the CRISPR patent dispute to South Africa

Because patents are territorial in nature, the various decisions regarding CRISPR patents apply only in the countries in which they were made. If a patent is invalidated in the US or Europe, it does not mean that the patent, via the PCT,[96] would be invalidated in South Africa. A patent involves a right to exclude others from using an invention without the permission of the patent holder.[97] However, if a patent is invalidated, this restriction would no longer apply.[98] As the validity of a patent is dependent on the particular laws of a country, a patent on a CRISPR process may be deemed invalid in the US, but may still be granted in South Africa.

[96] The PCT provides a simpler way of obtaining patents in other jurisdictions. A PCT application has the same effect as if a national patent application had been filed with the patent office in PCT member states. As patents are granted within a country in terms of individual patent laws, an international patent application must evolve into a national patent application. The PCT procedure involves two phases: the International Phase and the National Phase. The International Phase is a convenient way for applicants to acquire patent protection in multiple jurisdictions without having to file patent applications separately for each country. The ensuing National Phase results in the PCT application being adapted into various independent patent applications in specific countries. This is the stage at which the costs can increase as national fees are required to be paid to each country where patent protection is sought, as well as the translation of patent applications where necessary. The authority to grant patents rests with national patent offices in countries in which patent protection is requested. These requirements differ between countries, and when the PCT application enters into this phase, it is assessed in terms of national patent laws. Quinn op cit note 69; Mewburn Ellis 'International (PCT) patent applications — The basics' available at *https://www.mewburn.com/law-practice-library/international-pct-patent-applications-the-basics*, accessed on 10 December 2019; Adrian Hocking 'Knocking-out a patent' *Albright IP* 16 May 2013, available at *https://www.albright-ip.co.uk/2013/05/knocking-out-a-patent/*, accessed on 30 December 2019; WIPO 'Summary of the Patent Cooperation Treaty (PCT) (1970)', available at *https://www.wipo.int/treaties/en/registration/pct/summary_pct.html*, accessed on 28 August 2019; Dietmar Harhoff et al 'The strategic use of patents and its implications for enterprise and competition policies, Report ENTR/05/82 for DG Enterprise, European Commission' 2014 *Innovation and Entrepreneurship Research* 17; WIPO 'PCT — The international patent system' available at *https://www.wipo.int/pct/en/*, accessed on 27 August 2019; United Nations 'WIPO Patent Cooperation Treaty (PCT)' available at *https://www.un.org/ldcportal/wipo-patent-cooperation-treaty-pct/*, accessed on 30 August 2019.

[97] Sherkow op cit note 23.

[98] Because a PCT application will never become a patent, it is important to consider the implications of this. A patent may be withdrawn or deemed invalid after the International Phase, in which case the patent may be abandoned. The decision to grant a patent is controlled by national offices during the National Phase. WIPO op cit note 96; CIPC 'Patents', available at *http://www.cipc.co.za/index.php/trade-marks-patents-designs-copyright/patents/*, accessed on 28 December 2019.

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If a patent such as Broad's has been invalidated in the US interference proceedings, in addition to the revocation of its European patent, one would question whether the South African counterpart would be maintained or withdrawn. Withdrawal of a patent would depend on whether maintaining the patent in South Africa was viewed as commercially viable, as it requires the payment of maintenance fees. Commercial importance is contingent on whether there exists an intention to use, license, manufacture, sell, or import any products using the CRISPR patent in South Africa. However, as mentioned, the PTAB has effectively granted Broad the priority over UC. Generally speaking, the maintaining of a patent in South Africa which has been invalidated in other jurisdictions could invite litigation where the applicant can base its case on the rationale of the foreign jurisdiction's invalidity declaration.

III THE CRISPR PATENT LANDSCAPE IN SOUTH AFRICA

Ascertaining the current CRISPR patent landscape, both in South Africa and globally, is important to gain an understanding of the patenting activity of foreign and local entities. A patent search allows us to highlight directly some of the challenges that South African researchers may face in using CRISPR technology.

(a) Purpose

We undertook a patent search in order to provide a brief overview of the current CRISPR patent landscape in South Africa and internationally.[99] Such patent landscaping is essential in freedom-to-operate ('FTO') analyses, as well as for potential South African inventors (researchers and developers). This is because it will denote what CRISPR-related technologies have been patented in South Africa (the foundational patents that have been applied for and those which have been granted), by whom (who the controlling party is in South Africa), what potential opportunities there are for exploitation, and the parties from which licences would be required. Importantly, by accessing the available information in a patent search and completing this process first-hand, we were able to place ourselves in the shoes of a potential developer and expose any potential

[99] A patent search is a research process that provides an overview of the patent situation relating to a particular technology, either within a specific country or internationally. This search ascertains pending and granted patents in a certain field. It involves an electronic search of the applicable technology in patent databases, followed by an analysis of the information available. WIPO 'Patent landscape reports' available at *https://www.wipo.int/patentscope/en/programs/patent_landscapes/*, accessed on 10 January 2020; Joanne van Harmelen 'South Africa: Patent landscaping: The road to success' *ENSafrica* 11 October 2018, available at *https://www.mondaq.com/southafrica/Intellectual-Property/744754/Patent-Landscaping-The-Road-To-Success*, accessed on 10 January 2020.

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hurdles — both in patent searches and the current CRISPR patent landscape — which inventors and researchers alike may face in practice.

(b) Aim

The idea behind the patent searches was to gain an insight into issues regarding CRISPR technologies. However, due to search restrictions and the unreliability of the national patent database,[100] this was not achievable. As the national search was unavailable, a request containing questions relevant to the aim of the search was sent to the Companies Intellectual Properties Commission ('CIPC') on 12 December 2019.[101]

The initial objective of the patent search was to establish which CRISPR patent applications have been filed via the PCT,[102] and granted, in South Africa. This provides a surface-level understanding of the patent landscape in South Africa regarding CRISPR and can serve as a starting point for a more substantive examination in the future. However, given the challenges noted above, the search had to be restricted simply to determining what the current landscape is, both globally and in South Africa. Establishing which CRISPR patents have been granted in South Africa would be difficult without the assistance of the national database and would require one to physically approach the CIPC headquarters and sift through the relevant documents in person.

(c) Justification for choice of search database

For practical reasons, Patentscope was chosen as the website for the patent search over Google Patents, the South African CIPC, and other free search databases.[103] Patentscope is the most comprehensive free patent

[100] This is because it is in a constant state of flux. CIPC 'Log in — CIPC intellectual property online' available at *https://iponline.cipc.co.za/Account/Login.aspx?pb=aVMvEDtYJoBv4STTqmvCTpb7MWDx2eY0ESHMO1dLY8+DkrV5ADDUPw==*, accessed on 24 November 2019.

[101] The functions of the CIPC are inter alia to register and maintain intellectual property and ensure compliance with relevant legislation. National Government of South Africa 'Companies and Intellectual Property Commission (CIPC)', available at *https://nationalgovernment.co.za/units/view/84/companies-and-intellectual-property-commission-cipc*, accessed on 5 January 2020. A response was received on 10 September 2020 indicating that a ticket had been created and required our acceptance. Despite the acceptance of the ticket, a further email noted the ticket was awaiting acceptance (or rejection) and had been automatically closed. This, of course, raised a challenge and thus an alternative search engine was required.

[102] The PCT allows for the filing of patent applications in multiple contracting states simultaneously via a single application. This allows one possibly to gain protection in more than one country, without needing to visit each national patent office. One must file in a desired country within one year of filing the initial patent application. More information regarding the PCT and the process can be obtained from WIPO op cit note 96.

[103] Such as Lens, available at *https://www.lens.org/*, accessed on 13 November 2019.

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database and contains more parameters for refining searches.[104] Google Patents and other free patent search databases are not as accurate and lack search variability.

The keyword 'CRISPR' was chosen for the patent search in order to obtain a conclusive result on all CRISPR-centred patents or applications. 'CRISPR-Cas9' was also considered as a search term, but there have been many more Cas systems developed since the Cas9 system, and it would be inaccurate to exclude these.

(d) Methodology

1. An advanced search was conducted on the Patentscope website on 9 November 2020.
2. We extracted the global totals for CRISPR patents in two parts. Part (a) sought to obtain the global general patent totals that had 'CRISPR' contained anywhere in the application. In order to do this, we searched the phrase, 'EN_ALLTXT: CRISPR' while selecting 'All offices'. This code searches every word of every PCT application for the term 'CRISPR', hence maximising the results of the data. Once this total was acquired, part (b) attempted to only capture global patents with CRISPR as the core technology of the patent — rather than being an ancillary technology contained therein. To achieve this, a front-page search was undertaken by searching, 'FP:(CRISPR)', with 'All offices' being selected once more. A front-page search displays results that have the word 'CRISPR' on the front page, including in the title or the abstract of a patent. This maximises relevance, as the resulting patents would likely utilise CRISPR as a core technology central to the application.
3. The second phase of the search consisted of determining which PCT applications relating to CRISPR technology selected South Africa as a designated state. This also followed a two-part approach. Part (a) sought to obtain the total number of PCT applications that selected South Africa as a designated state, with 'CRISPR' contained anywhere in the application. In order to do this, we searched the phrase, 'EN_ALLTXT: CRISPR AND DS:(ZA)', while selecting 'PCT'. Once this total was acquired, part (b) attempted to capture PCT applications that selected South Africa as a designated state, but which contained CRISPR as the core technology of the patent, and not simply an ancillary technology. In order to do so, a front-page search was conducted by searching, 'FP:(CRISPR) AND DS:(ZA)', with 'PCT' being selected.

[104] Patentscope 'WIPO — Search international and national patent collections' available at *https://patentscope.wipo.int/search/en/result.jsf?vid=P10-K5SAFW-49155*, accessed on 24 November 2019.

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(e) Limitations

Due to limitations in the search functionality of free patent databases and the large volume of results, a duplication of findings and irrelevant data are possible. Multiple database searches would be ideal for companies considering investing in CRISPR. The other free patent search sites have limited databases or field searches, and are not accurate or up to date. Additionally, several sites do not include South Africa as an option when filtering results.

Searches generally contain inaccuracies and imprecise results and may not indicate the true number of existing patent applications, because there may be delays before publications reflect. In recent months, changes to Patentscope have resulted in data not always being linked correctly, meaning that an identical search done at different times may produce disparate results.

(f) Results

The results for the search reflected the following: the general CRISPR search in South Africa on all texts reflected 9171 results, while the front-page search reflected 983 results. Comparatively, a general search on CRISPR in all patent offices worldwide reflected 34 692 results, and a front-page search reflected 5430 results.

(g) Discussion

Since Pillay & Thaldar published their article in 2018,[105] the CRISPR patent landscape has grown considerably. The global general search result is enormous, which shows that, despite the US patent dispute, the CRISPR market continues to increase. However, the outcome of the search cannot be relied upon until a manual clean-up is conducted to remove any irrelevant results. After a brief examination of the various pages of results, it was clear that CRISPR was not the core technology in many patents. Rather, CRISPR was merely utilised or mentioned therein — perhaps to extend the scope of the patent.[106] However, this could also occur if the patent revolves around an accessory technology such as viral vectors.[107]

[105] S Pillay & D W Thaldar 'CRISPR: Challenges to South African biotechnology law' (2018) 11 *SA Journal of Bioethics and Law* 92.

[106] Jacqueline Martin-Laffon, Marcel Kuntz & Anges E Ricroch 'Worldwide CRISPR patent landscape shows strong geographical biases' (2019) 37 *Nature Biotechnology* 614.

[107] Vectors act as a vessel providing a means for enzymes to enter a cell, with viral vectors being most commonly used. Jacob S Sherkow & Christopher Thomas Scott 'The pick-and-shovel play: Bioethics for gene-editing vector patents' (2019) 97 *North Carolina LR* 1503.

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The front-page search yielded a more accurate view of the number of patents containing CRISPR as a core technology — far fewer than the full-text results. However, a simple front-page search is also inaccurate, and a manual clean-up will be required to further evaluate which patents are foundational and which are merely technology improvement patents.

Examining the CRISPR patent landscape in South Africa alone is a difficult task due to the limitations of online search systems. The CIPC database is the only free database that contains up-to-date information on South African patents, but the site is largely inoperative and when it is active the search functionality is temperamental and contains restricted parameters, rendering it unhelpful. The CIPC search fields are limited to simple searches such as the title, inventors and applicants, and do not pick up information unless the search phrase is exact.[108] Furthermore, the CIPC database contains no proximity functions.[109] These are simple infrastructure issues that will require rectification if the changes, such as SSE procedures that the IP Policy intends to implement, are to be effective.[110] If weaknesses in the system prevent inventors from establishing what has been patented in South Africa, the IP Policy mechanisms (to be discussed below) will be futile and a tremendous waste of resources.

In order to gain a full understanding of the current patent landscape in South Africa, one would need to conduct refined searches and patent family searches for accuracy. Issues in patent searches will present difficulties for biotech entrepreneurs and the like when attempting to conduct searches on their own, and a patent attorney with access to a formidable, up-to-date database will be required.[111] However, employing the services of a patent attorney is costly, which may preclude smaller inventors from ascertaining the information that they need. Furthermore, it is good practice for inventors and researchers to undertake a basic patent search themselves in the early stages of their work to enable them to determine what is out there and what gaps exist. The current patent search system fails to assist inventors, researchers and the general science and innovation community in South Africa.

[108] For example, if one searched 'Broad Institute', no results would be found as the exact name, 'Broad Institute of Massachusetts Institute of Technology and Harvard', is required.

[109] This can make things difficult as sometimes searching by inventor is the only option. Even simply not adding in a space, or adding in a space where there should be one when searching using patent application numbers, returns no results.

[110] T Schonwetter, Y A Vawda et al 'Comments at the Draft National Policy on Intellectual Property (IP) of South Africa', available at *http://www.dpru.uct.ac.za/sites/default/files/image_tool/images/317/News/Archive/DTI_plans_conference/IP-Policy-Academics-Submission_final17101*, accessed on 16 July 2021.

[111] One such example is Orbit Intelligence. See 'Orbit Intelligence' available at *https://www.orbit.com/*, accessed on 15 December 2019.

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The last documented patent search in South Africa reflected that four CRISPR patents had been granted to UC and four to Broad,[112] showing that South Africa is a target area for CRISPR-related inventions. As South Africa currently employs a depository patent system,[113] all patent applications which pass a formal examination will be granted. Therefore, it is likely that a large percentage of those 9171 CRISPR patent applications will be successful. Importantly, some foundational patents, such as Broad's PCT application, which is the foundational patent for eukaryotic applications of CRISPR-Cas9, lists South Africa as a designated state.[114]

How are South African researchers to function in a CRISPR patent landscape that is complex and expanding at a seemingly exponential rate? Also, even if the CRISPR patent dispute is eventually judged in one party's favour in the US and in Europe, it does not mean that the outcome is applicable in South Africa. The losing party in the US CRISPR patent dispute is entitled to maintain its patents in South Africa — subject only to litigation in the South African courts. The CRISPR patent landscape in South Africa confronts researchers with overlapping foundational patents held by different foreign entities as well as numerous complementary patents with claims that might be overblown and which are of low-quality.[115] Clearly, this has the potential to stifle CRISPR research in South Africa. But the question remains: is there a solution?

IV CLEARING THE SOUTH AFRICAN CRISPR PATENT LANDSCAPE

As mentioned above, we look to the IP Policy for potential solutions. In the following subparts, we explore how the provisions of the IP Policy

[112] Note that these numbers have probably since increased. Van Harmelen op cit note 6.

[113] This means that patents are only examined for compliance with formal requirements. Catherine Tomlinson, John Ashmore, Anele Yawa et al 'Reforming South Africa's procedures for granting patents to improve medicine access' (2015) 105 *SAMJ* 741.

[114] However, according to Patentscope, this application has not yet been granted or published in the PCT National Phase in South Africa. Furthermore, the requisite PCT application for UC's foundational patent could not be found.

[115] Patent quality is determined by a patent's ability to meet the legal requirements for patentability — novelty, inventiveness, and industrial application. Therefore, a low-quality patent is one that is granted for an invention which does not meet these criteria. Low-quality patents affect the ability of those working in the field and restrict their operations unless they obtain costly licences, often for inventions that are undeserving of patent protection. A further concern with low-quality patents is that they undermine the patent system, thus impacting researchers, patent holders and the public. R Polk Wagner 'Understanding patent-quality mechanisms' (2009) 157 *University of Pennsylvania LR* 2138; Christi J Guerrini 'Defining patent quality' (2014) 82 *Fordham LR* 3092.

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can be used metaphorically to clear the South African CRISPR patent landscape, and why it is in the public interest to do so.

(a) Substantive search and examination procedures

Unlike the US, South Africa is currently a depository patent system,[116] meaning that patent applications filed at the South African Patent Office ('SAPO') are only subject to a formality examination.[117] There is no SSE procedure that evaluates the actual substance (such as the inventiveness) of a patent.[118] As Vawda argues, the drawback of this system is that the requirements for patent eligibility are not tested in the application process — ultimately leading to patents being granted that would otherwise not meet the standards for patentability. The IP Policy regards the granting of these low-quality patents as detrimental to the innovation ecosystem and the public,[119] and aims to change this by introducing SSE procedures at the SAPO.[120] The SSE mechanism does not operate in a vacuum. For it to be successful, other issues must also be dealt with, such as human resource development and retention. SSE procedures might be a hindrance to innovation if the SAPO cannot cope with the volume of patent applications received. If this is the case, as it is in India and Brazil, the granting of a patent could take years, which would stifle innovation.

From a logistics point of view, there must be a synergy between the examination procedure and the formal requirements. While the CIPC is currently upgrading to online databases, allowing formal applications to be filed electronically (and hence creating fewer hurdles to the examination process), the patent process does not end with filing an application. Currently, every motion after filing, such as filing amendments or contracts of assignment, needs to be done in hard copy format. Under this

[116] Ramon Pereira & Gizela Lombard 'Phase 1 of South Africa's IP policy: What you need to know' available at *https://www.adams.africa/insights/phase-1-south-africas-ip-policy-need-know/*, accessed on 4 November 2019.

[117] This simply looks at compliance with formal requirements such as fee payments and whether the requisite forms are completed.

[118] This only occurs through revocation or infringement proceedings which dispute a patent's validity. Typically, this involves a costly and lengthy application before the Commissioner of Patents, a judge of the high court with jurisdiction. See ss 25, 61–71 of the Patents Act 57 of 1978; Yousuf A Vawda 'Compulsory licensing jurisprudence in South Africa: Do we have our priorities right?' (2018) Research Paper 90 *South Centre* 3.

[119] Polk Wagner op cit note 115 at 2138; Guerrini op cit note 115 at 3092–3.

[120] However, according to Baker & Vawda in their 2017 submissions on the IP Policy, regs 40 and 41 of Patent Regulations, 1978 do not currently provide for SSE and would require amendment. Brook K Baker & Yousuf Vawda 'Submission by University of KwaZulu-Natal-affiliated academics on the Draft Intellectual Property Policy of the Republic of South Africa Phase 1 2017' (2017) 5; Pereira & Lombard op cit note 116.

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current system, it is not uncommon for records to go missing, and the issuing of important documents, such as patent certificates, can be delayed for years. While in principle SSE is the primary mechanism for avoiding a situation where low-quality patents 'overgrow' the patent landscape, in order for SSE procedures to be effective and not simply add another layer of logistical nightmares, the infrastructure issues need to be addressed. Such procedures require both resources and management. Infrastructure, such as the systems that oversee the receiving of patent applications, needs to be maintained and upgraded. The CIPC is currently improving its systems and should soon allow for the electronic filing of patent applications. Despite the ability to file electronically, subsequent processes — such as amendments and assignments of patents — are still done manually via hard copy. Even the current formal examination proceedings are problematic due to delays — for example, delays in certificates of granting being sent to the grantee. It must be noted that SSE procedures add an extra layer of administration. Thus, SSE procedures cannot be successful if formal examination is not optimised.[121]

As noted in the IP Policy, the SAPO has limited resources.[122] Therefore, the IP Policy is to follow the World Intellectual Property Organisation ('WIPO') recommendations set out in its *Alternatives in Patent Search and Examination*,[123] whereby SSE procedures will be limited to selected sectors until capacity constraints lessen and other fields can be incorporated.[124] The chosen sectors will be based on *public interest* considerations[125]

[121] Additional issues include ensuring that South Africa has sufficient resources for implementing SSE procedures; the means to attract, hire, or train qualified patent examiners; and the funds and capacities necessary to update the patent database and bring it in line with the current intellectual property landscape. Sadulla Karjiker & Madelein Kleyn 'Commentary: Draft Intellectual Property Policy Phase 1 2017' *CIP* 8 November 2019, available at *https://blogs.sun.ac.za/iplaw/2017/11/08/commentary-draft-intellectual-property-policy-phase-1-2017/*, accessed on 4 October 2019; Tomlinson et al op cit note 113 at 742; Lonias Ndlovu 'Why South Africa should introduce patent searches and substantive examinations to improve access to essential medicines' (2015) *WIPO-WTO Colloquium Papers* 79.

[122] IP Policy op cit note 7 at 17–18.

[123] WIPO *Alternatives in Patent Search and Examination* (2014).

[124] This may not be a full examination as per WIPO's guidelines. Ibid; Pereira & Lombard op cit note 116.

[125] Although the qualifications of patent examiners are diverse, they predominantly fall within the life sciences, focusing on chemistry, biochemistry, and medicinal chemistry. Secondary fields of qualification include electrical and electronic engineering and pure physics. Therefore, it is likely that patent applications relating to pharmaceuticals and other chemistry-based fields will be examined initially. Von Seidels 'South Africa prepares for a thorough examination' available at *https://www.vonseidels.com/south-africa-prepares-for-a-thorough-examination/*, accessed on 3 November 2019.

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and given the aims and the wording of the IP Policy,[126] it is likely that initial examination will include the health sector.[127] Seemingly, pharmaceuticals may be the immediate focus due to their direct impact on human health and the high costs of many life-saving drugs.[128] We suggest that CRISPR-related patent applications *in general* should also be prioritised for full SSE.[129] Although CRISPR technology is not solely focused on human health, the technology in general has the potential to dramatically impact on human health in the future. To substantiate our point, we consider two uses of the technology, namely: (1) somatic uses; and (2) germline uses.

Somatic uses encompass a private-interest dimension as well as a public-interest dimension.[130] The private-interest dimension is that an

[126] The IP Policy op cit note 7 at 18 states that 'concerns expressed by some stakeholders that patent applications in only one field of technology (namely pharmaceuticals) will be subject to full substantive examination are misplaced. The intention is to identify a range of strategic sectors for full SSE, including and beyond the health sphere, based on capacity within government, as well as development and public interest considerations'. The IP Policy op cit note 7 at 5 states that '[i]mportantly, SSE will not only apply in the health sphere; it will eventually have much broader application. However, with due regard to capacity constraints and resources, the IMCIP — in consultation with diverse stakeholders — will determine the initial fields in which full SSE will occur.'

[127] The IP Policy ibid states that 'SSE will not *only* apply in the health sphere' and that the 'intention is to identify a range of strategic sectors for full SSE, including and beyond the health sphere' (emphasis supplied). This means that the health sector is an area of focus, but not the only area. Schonwetter & Vawda op cit note 110 at 18 have supported the idea that SSE be implemented for health technologies. See also Pereira & Lombard op cit note 116.

[128] The Industrial Policy Action Plan ('IPAP') recognised the pharmaceutical industry as a significant sector. Although the local pharmaceutical market is the largest in sub-Saharan Africa, this sector does not have a large global impact. The pharmaceutical industry has the potential to develop and contribute to the economy as well as to ensure the availability and accessibility of vital drugs. While the importing of medicines is essential, an increase in domestic capacity will ensure security in supply, especially given South Africa's disease rate. Additionally, a dynamic pharmaceutical sector is essential in the development of science and technology. IP Policy op cit note 7 at 16.

[129] Not all CRISPR applications are in the health space. Non-health-related applications of CRISPR include areas such as (i) agriculture, where foods are genetically modified to contain more nutrients and have an increased shelf-life in order to combat the global food crisis; and (ii) the environment, where CRISPR can be used to modify bacteria in order to produce biofuels. Vivian S Vigliotti & Isabel Martinez 'Public health applications of CRISPR: How children's health can benefit' (2018) 42 *Semin Perinatol* 531; Meenakshi Prabhune 'CRISPR applications: Agriculture, medicine, bioenergy, & the future' *Synthego* 8 May 2019, available at *https://www.synthego.com/blog/crispr-applications*, accessed on 16 February 2021.

[130] Somatic cells refer to any cell in the body that does not constitute gametes, germ cells, or stem cells. Somatic gene editing endeavours to alter the DNA

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individual is, independently or in combination, cured, treated to reduce symptoms or the length of an ailment, or prevented from developing a certain condition. This alteration is not passed down through generations, as somatic uses only affect that specific individual. Germline uses refer to gamete or embryonic edits,[131] which result in a genetic alteration being passed on to descendants.[132] This has a 'heritability' effect, in that the genetic alteration could be expressed vertically in many generations down the line from the initial edit.

While germline applications of CRISPR technologies currently remain purely academic (apart from a rogue actor who prematurely experimented with germline editing[133]), somatic applications have been successfully applied in the clinical context. As CRISPR technology advances and shows even greater potential in alleviating certain conditions,[134] it is clear that this technology will likely become a therapeutic technology unlike any other — possibly eclipsing the efficacy, impact, and necessity of essential drugs[135] or scarce treatments.[136] Due to the site-specific nature of gene editing technologies such as CRISPR — through both somatic and germline edits — it is possible that essential drugs may become redundant or, at the very least, they may not be needed to the same degree in South Africa.

As germline edits can lead to permanent multigenerational consequences, health benefits can be multigenerational. An example is a germline edit that makes one resistant to HIV. This benefits not only the individual,

within multiple target cells, typically through a virus or vector. *Biology Dictionary* s v 'somatic cells' available at *https://biologydictionary.net/somatic-cells/*, accessed on 10 November 2019; Francis Fukuyama *Our Posthuman Future: Consequences of the Biotechnology Revolution* (2002) 76.

[131] A germ cell is a reproductive cell, either an egg or sperm cell. Medicine Net 'Medical definition of germ cell' available at *https://www.medicinenet.com/script/main/art.asp?articlekey=8591*, accessed on 10 November 2019.

[132] Germline alterations are duplicated in each cell of the embryo, meaning that edits would be transferred to all progeny cells and passed on to descendants. Joanne van Harmelen 'Human genome editing with CRISPR-Cas9: South African legal perspective' *International Law Office* 17 May 2017, available at *https://www.internationallawoffice.com/Newsletters/Healthcare-Life-Sciences/South-Africa/ENSafrica/Human-genome-editing-with-CRISPR-Cas9-South-African-legal-perspective?redir=1*, accessed on 30 August 2019.

[133] See Donrich Thaldar, Marietjie Botes, Bonginkosi Shozi et al 'Human germline editing: Legal-ethical guidelines for South Africa' (2020) 116(9/10) *SA J of Science* 1–7.

[134] This is in terms of more effective screening, testing, and therapeutics. A current example is the SARS-CoV-2 pandemic.

[135] For example, antiretroviral drugs used to control HIV.

[136] Such as dialysis machines and the requisite staff needed for patients with kidney failure.

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but also the individual's family,[137] spouse,[138] the state,[139] and global populations.[140] In this way, certain ailments can be eliminated entirely from families, communities, ethnicities and countries. The results of germline editing are not linear but asymmetric and, as a result, have the potential to exponentially impact on the genetic makeup of the global population over many generations.[141] The HIV/AIDS epidemic provides a snapshot of a single challenge facing South Africa.[142] In 2018, there were almost 250 000 new HIV infections, suggesting substantial growth of the virus, despite the implementation of state-wide measures. South Africa has spent a very substantial sum of money, comprising mostly its own funds, for the antiretroviral ('ARV') treatment programme.[143] CRISPR potentially poses a cheaper and more effective multigenerational, global-scale solution.[144]

Groups, organisations and political leaders have called for a ban on germline editing because of safety and ethical concerns. Such concerns seem to be shared by the patent-holding institutions themselves, namely Broad and UC, which have incorporated restrictions in their licence

[137] This is due to a reduced social and economic burden. Offspring may also be positively affected, and their offspring … and so on.

[138] By reducing the risk of transmission to the partner and offspring.

[139] By reducing the burden on the state in terms of social welfare, such as medical and pharmaceutical claims.

[140] By reducing the number of infections which, on a larger scale of implementation, can also reduce the risk of contracting HIV, hence possibly removing the virus from communities all over the world.

[141] This is due to widespread travel between states, reproduction, and the heritability factor associated with germline editing.

[142] Currently, the country has the largest HIV epidemic in the world, with close to eight million positive cases. In 2018, there were over 70 000 HIV-related deaths. Avert 'HIV and AIDS in South Africa' 15 April 2020, available at *https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/south-africa*, accessed on 9 January 2020.

[143] South Africa has the world's biggest antiretroviral treatment ('ART') programme. The money spent on the ART programme is equivalent to over $1.5 billion per year. Gesine Meyer-Rath, Leigh F Johnson, Yogan Pillay et al 'Changing the South African national antiretroviral therapy guidelines: The role of cost modelling' (2017) 12(10) *PLoS ONE* 2.

[144] HIV attacks the immune system by targeting CD4 immune cells. HIV-1 enters host cells by fusing with the CD4 receptor and CCR5 co-receptors. A homozygous 32-bp deletion in the CCR5 gene (CCR5Δ32) can cause resistance to HIV-1 infection. CCR5Δ32 is a genetic mutation which disables the CCR5 receptor on white blood cells, thus preventing HIV from penetrating the cells of the immune system. CRISPR-Cas9 has the ability to produce deletion variations of CCR5 that mirror the CCR5Δ32 mutation and prevent the virus from entering the cell. Qiaoqiao Xiao et al 'Application of CRISPR/Cas9-based gene editing in HIV-1/AIDS therapy' (2019) 9(69) *Front Cell Infect Microbiol* 6; Sheena Saayman et al 'The therapeutic application of CRISPR/Cas9 technologies for HIV' (2015) 15(6) *Expert Opin Biol Ther* 6; Martha Kempner 'The genetic mutation behind the only apparent cure for HIV' *The Body Pro* 14 March 2019, available at *https://www.thebodypro.com/article/genetic-mutation-behind-hiv-cure*, accessed on 14 December 2020.

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agreements that prohibit germline editing. We suggest that this is an over-reaction, and agree with Thaldar et al that research into germline editing in South Africa should proceed in a responsible, constitutionally aligned manner.[145] In the event that a South African research institution intends to conduct research into germline editing using CRISPR, instead of approaching the court for a compulsory licence from Broad and UC — as this would not fit into the rather narrow grounds for compulsory licensing that the Patents Act 57 of 1978 allows[146] — we suggest that the proposed research and experimental exception indicated in the IP Policy should be actioned.[147]

As our patent landscaping search has shown, there are currently numerous pending CRISPR patent applications in South Africa.[148] CRISPR holds great potential in the treatment of various disorders over previous gene-editing methods, and the technology is ever-developing.[149] However, it is arguable that CRISPR has not yet advanced into the class of life-saving technologies and perhaps would not fall into a strategic sector, as determined by the IP Policy, for examination. However, CRISPR's future potential must not be underestimated. Thus, we suggest that it would be in the interests of public health to consider CRISPR as critical in achieving goals relating to the treatment and eradication of priority diseases such as HIV/AIDS and TB. Therefore, it is vital that patent applications utilising CRISPR technology are examined to ensure that they are valid, beneficial, and of a certain standard, as low-quality CRISPR patents can impede the progress of this technology. The granting of low-quality patents links to apprehension that patents are being awarded for inventions undeserving of patent protection.[150]

[145] Thaldar et al op cit note 133 at 5.

[146] Sections 55 and 56 of the Patents Act deal with compulsory licensing and require that an application for a licence be made to the Commissioner of Patents, who is a judge of the high court with jurisdiction.

[147] The IP Policy aims to establish exceptions for research and experimental activities. IP Policy op cit note 7 at 26.

[148] These will be granted, subject to meeting the formal patent requirements of the SAPO.

[149] Ku op cit note 94 at 439.

[150] The granting of low-quality patents may be occurring in two ways. The first is that patent offices may apply too lenient a standard. The second relates to mistakes — granting patents that fail to meet a certain standard. There is concern that patent offices award too many patents for questionable inventions that would not pass a thorough review. Although criteria for patentability exist, subjective factors impact on the uniformity of decisions. The decision to grant a patent depends on a person's (or team's) comparison of the inventive merit of the application, the level of disclosure, and the standards for patentability. Therefore, cohesion of decisions among examiners seems improbable. Gaétan de Rassenfosse, William E Griffiths, Adam B Jaffe et al 'Low-quality patents in the eye of the beholder: Evidence from multiple examiners' (2019) *NBER Working Paper Series* Working Paper 2244 at 2.

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We should aim to avoid a situation where a future application of CRISPR becomes as effective as a key drug, but where a saturated patent landscape acts as a deterrent to research, development or commercialisation. Saturation or patent thickets (especially of low-quality patents) may require entities to obtain numerous licences, for which the combined costs are too high. Such thickets present a major obstacle to the efficient commercialisation of innovation — mostly affecting small biotech companies by increasing the risk of litigation and licensing costs. From the perspective of universities, it is true that patents rarely have a direct impact on academic research as they tend to be overlooked by researchers, who often avoid being sued for infringement.[151] Yet, patents do affect access to materials,[152] as well as scientific standards and procedures.[153] Commercialisation is, however, necessary in securing tangible benefits for the public by bringing products to market.[154] If patent offices are lenient in their granting of low-quality patents, this may hinder research and development, investment, and commercialisation processes — either due to uncertainty regarding FTO or because of possible litigation.[155] Ultimately, we suggest that CRISPR-related patent applications with a therapeutic focus should be prioritised for formal examination and full SSE, as this is directly in the public interest and may serve to advance public health.

(b) Patentability criteria

The IP Policy reiterates that the Agreement on Trade-Related Aspects of Intellectual Property Rights ('TRIPS') allows nations to interpret and implement the patentability requirements according to their own

[151] Many countries, including Germany, the United Kingdom ('UK'), Japan, and Korea, have experimental-use exemptions from patent infringement. This protects those who utilise patents for basic research from being sued for infringement. Scientists generally believe that they will not be sued despite an infringement, as they are conducting research for the benefit of the public. As scientists tend to overlook patents and are seldom sued, an experimental-use exemption is unlikely to be effective (in the US context where there is no experimental-use exemption). Ian Ayres & Lisa Larrimore Ouellette 'A market test for Bayh-Dole patents' (2017) 102 *Cornell LR* 281; Lisa Larrimore Ouellette 'Note: Access to bio-knowledge: From gene patents to biomedical materials' (2010) *Stan Tech L Rev* N1.

[152] Such as cell lines.

[153] Ayres & Ouellette op cit note 151 at 282.

[154] Productisation refers to the process of transforming a development into a product for market. It encompasses a variety of elements, from the early stages of designing a product to the commercial aspects of sale and distribution. Peter Artz, Inge van de Weerd & Sjaak Brinkkemper 'Productization: The process of transforming from customer-specific software development to product software development' 2010 *Department of Information and Computing Sciences Technical Report* 7.

[155] De Rassenfosse et al op cit note 150 at 2.

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needs,[156] and should therefore be exploited as a means to promote and address South Africa's public health concerns. Article 27.1,[157] read with art 1.1 of TRIPS,[158] sets out the criteria for patent eligibility (novel, inventive and capable of industrial application). However, member states are free to define each of these criteria. South Africa thus has the freedom within TRIPS to determine the content of each of these requirements and can set high standards for patentability, thereby reducing the influx of weaker patents and increasing the quality of the patents that are granted.[159]

Scholars have discussed the possible introduction of higher standards for novelty[160] and the person skilled in the art.[161] However, we focus on a solution that centres on the non-obviousness criterion for inventiveness. We recommend that the development of South African public policy, including a patent manual for examiners, should take into account the following considerations.

(i) *Inventiveness*

Section 25 of the Patents Act stipulates that an invention must contain an inventive step. Section 25(10) of the Patents Act further provides that an inventive step is present where the step is not obvious to one who is skilled in the art.[162] The question then becomes: what is obvious?

[156] Agreement on Trade-Related Aspects of Intellectual Property Rights, 15 April 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, 1869 UNTS 299 (1994).

[157] Article 27.1 of TRIPS states: 'Subject to the provisions of paragraphs 2 and 3, patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. Subject to paragraph 4 of article 65, paragraph 8 of article 70 and paragraph 3 of this article, patents shall be available and patent rights enjoyable without discrimination as to the place of invention, the field of technology and whether products are imported or locally produced.'

[158] Article 1.1 of TRIPS states: 'Members shall give effect to the provisions of this Agreement. Members may, but shall not be obliged to, implement in their law more extensive protection than is required by this Agreement, provided that such protection does not contravene the provisions of this Agreement. Members shall be free to determine the appropriate method of implementing the provisions of this Agreement within their own legal system and practice.'

[159] Baker & Vawda op cit note 120 at 20.

[160] Ibid at 21–2; Chan Park, Achal Prabhala & Jonathan Berger 'Using law to accelerate treatment access in South Africa: An analysis of patent, competition and medicines law' 2013 *United Nations Development Programme* 26; UCT IP Unit 'Draft Intellectual Property Policy of the Republic of South Africa Phase I 2017 comments' November 2017 at 18, available at *http://ip-unit.org/wp-content/uploads/2017/11/Submission_IPUnit_IPPolicyI102017_FINAL.pdf*.

[161] Baker & Vawda op cit note 120 at 25–6. One suggestion by the authors is to make the hypothetical person highly skilled in the art, compared to the current requirement of ordinary skill.

[162] Section 25(10) of the Patents Act states: 'Subject to the provisions of section 39(6), an invention shall be deemed to involve an inventive step if it is

(ii) *Obviousness*

Currently, obviousness serves as a ground to challenge a patent for revocation in court. This is hence a post-grant challenge to the patent. However, with the introduction of SSE procedures,[163] a patent will only be granted if it meets the legal criteria for patentability (pre-grant) — including non-obviousness. Simply put, instead of obviousness being a ground for challenging an already granted patent, a prospective patent application will now need to meet the criterion of non-obviousness — which is to be judged by patent examiners. Currently, South Africa does not have a patent manual that sets out criteria and how obviousness is to be judged by patent examiners (in the absence of SSE, there was previously no need for one). South Africa may end up following the European approach in terms of SSE procedures,[164] due to similarities between the patent laws. While the IP Policy does not explicitly state this, it does however make reference to a CIPC-EPO Memorandum of Understanding ('MoU') for the training of patent examiners. It remains to be seen how the requirement of non-obviousness will unfold, with some commentators such as Vawda and Baker expressing a preference for standards that are similar to those of s 3*(d)* of the Indian Patent Act of 1970[165] and the guidelines for examiners developed by the Argentinian Patent Office.[166] This is relevant as the

not obvious to a person skilled in the art, having regard to any matter which forms, immediately before the priority date of any claim to the invention, part of the state of the art by virtue only of subsection (6) (and disregarding subsections (7) and (8))'. *Ensign Bickford (South Africa) (Pty) Ltd v AECI Explosives and Chemicals Ltd* 1999 (1) SA 70 (SCA) introduced into our law the following four-step inquiry for an inventive step: 1. What is the inventive step said to be involved in the patent in suit? 2. What was, at the priority date, the state of the art (as statutorily defined) relevant to that step? 3. In what respect does the step go beyond or differ from that state of the art? 4. Having regard to such development or difference, would the taking of the step be obvious to the skilled person?

[163] IP Policy op cit note 7 at 17–18.

[164] The European perspective is based on the problem-solution approach. This approach involves examining the problem, looking at the steps taken by the inventor to solve the problem, what others have done to solve the problem, comparing the different approaches, and then determining if it was an obvious step to take. European Patent Office 'Case law of the Boards of Appeal' available at *https://www.epo.org/law-practice/case-law-appeals/case-law.html*, accessed on 14 December 2020.

[165] Section 3*(d)* of the Indian Patent Act states that 'the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant' is not patentable. A 'new form' of an existing substance cannot be patented unless it shows greater efficacy.

[166] Joint Resolution No 118/2012, 546/2012 and 107/2012 of May 2, 2012, of the Ministry of Industry, Ministry of Health and the National Industrial

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training and technical expertise of the patent examiners will play a role in determining the meaning of obviousness.[167]

When one considers the sui generis nature of biotech, there is a need for legal certainty about what constitutes (non-)obviousness and how it will be established in practice by patent examiners. CRISPR raises a few nuanced issues, such as what Sherkow terms the 'classic disconnect between the legal standards of patent law and the realities of scientific research',[168] as evidenced by the US CRISPR patent dispute. The finding of non-obviousness by the USPTO perplexed scientists, who argued that there were readily available solutions to the issues that gave rise to the finding.[169] Initially, the dispute centred around a single nucleus, but since then, new nuclei and enzymes have been discovered. Currently, it is established practice that new nuclei can work, and sometimes work better than the original Cas9 enzyme, making it unclear whether that would then render the use of all different nuclei obvious and hence unpatentable.[170] The CRISPR technology itself in 2021 (compared to 2012) is firmly established; when dealing with any genetic alteration, CRISPR would be the go-to technology — it is essentially 'obvious to try'.

In South African jurisprudence, different obviousness tests have been formulated by the courts, which can lead to different outcomes when applied to biotech inventions. Currently, the problem-solution approach is the principal test when determining questions of obviousness. This test requires the court to ask: what problem facing an industry does the invention solve?[171] Put differently, the problem-solution approach asks

Property Institute, approving the Guidelines for the Examination of Patent Applications of Pharmaceutical and Chemical Inventions, Date of Entry into Force: 16 May 2012, available at *http:// www.wipo.int/wipolex/en/details.jsp?id=13007*, accessed on 14 December 2020.

[167] The SAPO has completed the task of selecting examiners. The CIPC has already recruited twenty examiners with a variety of technical backgrounds. The South African trainee patent examiners are required to undergo an extensive training programme for two years before they are able to formally examine new patent applications. Von Seidels op cit note 125.

[168] Sherkow op cit note 56; Bheki Zulu, Maanda Phosiwa & Mehluli Ncube et al 'CIPC to introduce substantive search and examination' (2018) January *De Rebus*, available at *http://www.derebus.org.za/cipc-introduce-substantive-search-examination/*, accessed on 14 October 2019.

[169] Jacob S Sherkow 'Inventive steps: The CRISPR patent dispute and scientific progress' (2017) 18 *EMBO Rep* 1047.

[170] Ibid at 1050.

[171] In *Gentiruco AG v Firestone SA (Pty) Ltd* 1972 (1) SA 589 (A) ('*Gentiruco*'), non-obviousness was elucidated upon. Trollip JA noted at 664G that 'there are some positive indications that it was inventive. It did successfully solve the problem that existed ... a solution for which … the industry had sought but had not previously found; it must have taken the inventors much time, energy and effort to discover it'.

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what technical solution or modification the closest prior art would need to undergo in order to arrive at the invention in question. There are, however, challenges in applying this approach (or the now antiquated 'obvious to try' approach) when it comes to inventions involving technology with a biological application — such as reproducibility and predictability difficulties.[172]

Due to the unpredictability inherent in biotech inventiveness, such inventions are often challenging to replicate and translate into other mediums. In any invention that involves biological material, a problem may have a variety of theoretical solutions which are obvious to try.[173] However, the expectation of success and difficulty associated with getting the solution to work clinically is not that simple. Often in this field, theoretical solutions do not work, and require improvised tinkering. These difficulties may very well lead a court (or examiner) to the decision that the invention is non-obvious.[174] Hence, in any biotech invention the kind of obviousness standard being applied can determine whether many, or very few, patents are granted.

Based on the issues of reproducibility and the difficulties associated with creating an effective biotech therapeutic application, a wider construction[175] of the problem-solution approach will lead to more non-obvious findings, thus rendering many biotech applications patentable. We suggest that South African patent law should be strengthened by the development of a patent manual which should contain a well-defined obviousness test, to avoid these issues. By adding further considerations, the SAPO could outline and reduce the scope of non-obviousness, thereby ensuring that only higher quality patents are granted. We suggest that the adoption of guidelines that can be contained in a patent manual for examiners (and court guidance) would greatly aid in this regard.

[172] ATCC 'Six factors affecting reproducibility in life science research and how to handle them' *Nature Research* available at *https://www.nature.com/articles/d42473-019-00004-y*, accessed on 25 November 2020.

[173] Sherkow op cit note 169.

[174] Ibid at 1049.

[175] In *Marine Construction & Design Co v Hansen's Marine Equipment (Pty) Ltd* 1972 (2) SA 181 (A) at 193, Botha JA, applying *Veasey v Denver Rock Drill and Machinery* 1930 AD 243 and *Gentiruco* supra note 171, said that 'an application of the test therefore involves an inquiry into (1) the ambit of the relevant art or, into what amounts to more or less the same thing, the identity of the persons who would have been faced with the problem solved by the invention; (2) the extent of the common knowledge in the art at the time; and (3) whether such persons could, having regard to such common knowledge, easily have solved that problem'. Step (3) creates a wider approach to obviousness, which can render many undesirable inventions patentable. A problem can be moderately difficult (as opposed to easy) to solve — and still be obvious. Difficulty (or ease) is not the only important consideration when determining obviousness.

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Assistance can be sought from the United Kingdom ('UK') Supreme Court judgment of *Actavis Group PTC EHF v ICOS Corporation* ('*Actavis Group*'),[176] which formulated a nine-step enquiry for ascertaining what renders something obvious.[177] These steps are: (1) whether something was obvious to try at the priority date;[178] (2) whether the nature of the research was routine;[179] (3) the difficulty and costs associated with the research; (4) the urgency and nature of any value judgments taken in the course of development of the subject matter; (5) whether there were alternative paths of research;[180] (6) whether there was a motive/the nature of the motive behind the skilled person;[181] (7) whether the results of the research were unexpected or surprising to the researcher;[182] (8) whether hindsight is used in evaluating obviousness;[183] and (9) whether the feature of the claimed invention is an added benefit in which the claimed invention is obvious for another purpose.

While step (1) has been discussed, challenges are evident from step (2) onwards. Routine research would indicate whether a method or process would be the natural next step for researchers in their investigation. But while something may be the next natural step, this does not necessarily indicate that something is obvious. It will then be the responsibility of the South African courts to determine and assign value to each of the steps mentioned above. The adoption of these steps will result in clarity

[176] [2019] UKSC 15.

[177] Ibid paras 64–73.

[178] The court, ibid para 65, noted that this is based on whether undertaking a specific form of research was obvious to try as there was a reasonable or fair prospect of success. The court noted that likelihood is an indicator of success for obviousness. However, in some circumstances, a test result can be entirely unpredictable, but still obvious to try. Thus, the obvious to try test is to be balanced against other considerations in light of the facts.

[179] The court, ibid para 66, noted that established practices are a relevant consideration that must be weighed against whether it was 'obvious to try' or not to try.

[180] The court, ibid para 69, noted that the existence of alternative paths indicates that the invention or claims therein were not obvious. A single path conversely indicates that the invention was obvious. However, these must be evaluated in light of the facts, as multiple paths may be known that can produce the invention — each of which can be obvious.

[181] The absence of a motive indicates that the inventive step is not obvious. The court, ibid para 70, noted that a skilled person is assumed to have a technical effect in mind when acting, and this must be evaluated in light of the state of the art. The court also noted that this importantly informs the problem-solution approach that is adopted by the EPO.

[182] If the researcher is surprised or faced with unexpected results, the court noted, ibid para 71, that this is an indicator of non-obviousness as seemingly the inventive concept was not obvious to try.

[183] The court, ibid para 72, cautioned against using hindsight to evaluate obviousness.

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as to how biotech patent applications should be evaluated where there is uncertainty, and can also help to ensure that patents of a higher standard are eventually published.

(c) Patent opposition proceedings

Currently, the Patents Act does not contain any provisions that relate to pre- or post-grant opposition procedures. Parties who wish to challenge patents are restricted to doing so through the courts. The IP Policy recognises this issue, and makes provision for the realization of:

- third-party observations, which enables third parties to submit information pertinent to the consideration of a patent application;[184]
- pre-grant patent opposition proceedings, which allow third parties to oppose the granting of a patent any time between the submission of the application and the decision;[185] and
- post-grant patent opposition proceedings,[186] which permit third parties to review or appeal the granting of a patent within a specific time period.[187]

With the introduction of these procedures, in addition to SSE, entities wishing to patent CRISPR-related inventions in South Africa need to ensure that their patents meet both the formal and substantive requirements.[188] This allows interested parties to launch relatively inexpensive challenges outside of court.[189]

[184] The IP Policy op cit note 7 at 19–20 aims to provide for self-identified parties to oppose the granting of a patent through written submissions.

[185] The IP Policy ibid recognises that pre-grant opposition proceedings should be allowed once the SSE system has adequate capacity.

[186] Post-grant procedures would require the development and promulgation of regulations. IP Policy ibid at 20.

[187] The IP Policy ibid aims to introduce pre-grant, post-grant, and third-party opposition procedures. These kinds of procedures will have the effect of acting as further preventative and remedial safeguards for the quality of the patents that are granted in South Africa. They allow for public intervention in the application proceedings or after the granting of a patent. This allows third parties either to submit relevant information for consideration by the examiners or actively to oppose the application for the granting of a patent.

[188] The introduction of SSE procedures is not a solution in itself. From a logistics point of view, important issues are resources and infrastructure management. Karjiker & Kleyn op cit note 121.

[189] Extra-curial procedures have an advantage over court proceedings, which have typically proven to be time-consuming and too costly for smaller inventors. Challenging a patent requires going to the high court as the court of the Commissioner of Patents is the high court. Brook K Baker 'International collaboration on IP/access to medicines: Birth of South Africa's fix the patent laws campaign' (2015/16) 60 *NY Law School LR* 319.

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There is, however, an urgent need to create the infrastructure required to set up these systems.[190] In order for these systems to be successful, the immediate digital publication of a patent or patent application is necessary in an interactive,[191] simple, and freely accessible-to-all resource. A further suggestion we find useful would be to ensure that this system can differentiate between classifications of patents. This will allow for simpler discernment between the fields of technology contained in patents, and hence allow for the immediate retrieval of any patents that relate to CRISPR (or health-related) technologies. This ability to oppose must however be restricted to fair and reasonable time limits and must require the opposing parties to file digital motions with full reasons for opposition. To ensure fairness, the opposition proceedings must allow for the (prospective) patentee to make representations in defence of their patent. The challenging of a (prospective) patent should be limited to specific criteria, taking into account the obviousness criteria mentioned above.

As third-party systems[192] are the least resource-intensive[193] and serve as a workable safeguard while the other procedures are being developed, we recommend that third-party proceedings be implemented immediately. In order for this to be effective, the digital publication of patent applications should be freely accessible to, and searchable by, all on a system that allows for the submission of public comments, and which should be readily accessible by patent examiners. This procedure can be further strengthened by requiring the examiners to consider these comments and to provide reasons for their decisions in relation to the comments.

In the case of pre-grant opposition proceedings, which are more resource-intensive than third-party systems,[194] we recommend that the website or medium of digital publication for pre-grant applications should directly notify the SAPO examiners, who should then consider the opposing submissions when determining patentability. We suggest

[190] Schonwetter & Vawda op cit note 110 at 16–17.

[191] The interactive function must allow for speedy commentary and opposition challenges to be launched by interested parties. Parties should be able to view other information such as the progress of the application, whether it is currently being challenged, and commentary from other parties.

[192] Opposition procedures being open to competitors and other parties could result in information and arguments regarding the prior art and standards of patentability, which could result in higher quality patents. Baker op cit note 189 at 319.

[193] The IP Policy op cit note 7 at 19–29 recognises that the third-party observation mechanism is the least resource-intensive, as it does not activate a particular procedure involving the third party following the submission of the necessary information.

[194] IP Policy ibid. Pre-grant opposition proceedings require more resources as the state must implement an administrative process that allows applicants and third parties to participate.

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that pre-grant proceedings should also require examiners to consider comments and provide feedback to involved parties.

V CONCLUSION

As we have discussed throughout this article, CRISPR technologies hold great potential in the prevention and treatment of priority diseases such as HIV/AIDS, thus showing promise in alleviating the disease burden facing South Africa. However, a primary concern which has been highlighted and that our patent landscaping search has demonstrated, is that the CRISPR patent landscape is increasingly complex and saturated, requiring careful consideration when undertaking any genome editing research that may have a commercially viable result. This situation poses a challenge for CRISPR researchers and developers in South Africa.

(a) Recommendations

(i) *General recommendations*

Although various solutions and recommendations can be proposed for improving the CRISPR patent landscape in South Africa, these are futile without having a robust foundation upon which to operate. While South Africa is currently in the process of upgrading and digitising the patent system, other infrastructure issues affecting the online databases also block the flow of research. Therefore, we recommend that the CIPC further develop the online search functionalities of the national database, which should allow for variable and broader search functions, inclusive of proximity searches. Other upgrades that are required include the digital submissions platform, which should allow for amendments and transfers of patents to be done online, and for the creation of an online system that allows for commentary by opposition or third parties. These comments should be easily ascertainable by the patent examiners, who should then also be able to provide feedback on the same system.

As a matter of priority, policy-makers should ensure that there is greater investment in an accessible, operational, accurate, and up-to-date patent database in South Africa. Sufficient resources will also need to be directed towards ensuring that patent examiners are attracted, hired and do not leave the country, taking with them their valuable training and skills.

(ii) *Recommendation 1*

Given CRISPR's potential in the prevention and treatment of disease, which aims to serve the public interest in access to healthcare, we suggest that policy-makers and the SAPO consider the importance and potential of CRISPR as a health technology. In order to combat an already saturated patent landscape, we suggest that patent applications that utilise CRISPR technology in general should be considered as a priority for examination.

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Although CRISPR may not fall into one of the sectors identified by the IP Policy for examination, we suggest that it is in the long-term interests of public health to recognise the potential that CRISPR holds in treating and possibly eradicating priority diseases such as HIV/AIDS and TB. Thus, examining patent applications utilising CRISPR technology to ensure their validity, benefit and quality will help to ensure that the public health interests in this technology are served.

(iii) *Recommendation 2*

Given the pending introduction of SSE procedures in South Africa, we recommend that policy-makers create guidelines for patent examiners, which could be contained within a patent manual. These guidelines should set out the processes and considerations for examiners when evaluating patents. In addition, we recommend that policy-makers clarify and develop an obviousness standard to ensure that there is certainty regarding the patent eligibility of complex biotechnologies such as CRISPR. We suggest that using the UK judgment of *Actavis Group*[195] — which established a nine-step enquiry for obviousness — as a foundation, can provide clarity in this regard.

(iv) *Recommendation 3*

It is important that mechanisms allowing parties to challenge patents are established. As third-party systems require the fewest resources, and can be employed while other procedures are developed, we support the urgent implementation of a more meaningful third-party observation procedure. For this to be successful, the digital publication of patent applications should be publicly accessible and should allow for the submission of public comments that are available to patent examiners. With regard to pre-grant opposition proceedings, we recommend that the platform for digital publication of pre-grant applications directly notify the SAPO patent examiners, who should then consider opposing submissions when determining patentability. We further suggest that policy-makers make it peremptory that these comments are considered by examiners when making a decision, and are addressed by way of responses and reasons for decisions for all three types of opposition proceedings (pre-grant, post-grant and third-party opposition proceedings).

The saturated CRISPR patent landscape in South Africa might hinder research. However, there is a solution to clearing this patent landscape. It lies in considering patent applications utilising CRISPR technologies for examination, guidelines contained in a patent manual for examiners, a well-defined obviousness standard, working and meaningful opposition

[195] *Actavis Group* supra note 176.

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mechanisms, stricter disclosure requirements for patentability, an effective and efficient SSE procedure, and the optimisation of infrastructure and patent databases. These mechanisms act as pre-emptive and post-operative safeguards to ensure that a higher quality of patents is produced as output — thereby creating a more enabling environment.

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