

# Intellectual Property Protection of CRISPR Related Technologies

Zheng Miao, Dennis Fernandez

**Abstract**—CRISPR research has the potential to completely transform life science, agriculture, live-stock and the health care industry. The Intellectual Property derived from its research has raised significant attention in the academic as well as the biopharmaceutical industry culminating an urgent need for strategic IP protection. We review the rudimentary concepts and key competitors of CRISPR technologies as well as the paramount strategies for intellectual property protection. Further, we elaborate on prosecution issues related to CRISPR patents as well as possible solutions to various patent laws, interferences and litigation. Finally, we address how the bioinformatics of the CRISPR technology begs an inquiry into issues of privacy and a host of ethical concerns.

**Keywords**—Bioinformatics, CRISPR, biotechnology, intellectual property.

## I. INTRODUCTION

CLUSTERED regularly interspaced short palindromic repeats (CRISPR, pronounced *crisper*) are segments of prokaryotic DNA containing short, repetitive base sequences. CRISPR-associated system (Cas) is an enzyme for binding and cutting around the CRISPR sequences. The CRISPR/Cas system is a prokaryotic immune system defending against a virus infection [1]. CRISPR-Cas engraves bits of hereditary material as a memory of beforehand experienced infections of the virus [2]. Eukaryotic cells do not have an endogenous CRISPR system. Nevertheless, biologists harnessed this unique tool and modified it for prokaryotic as well as eukaryotic cell gene editing [1], [3], [4]. CRISPR/Cas technology comprises of two parts: a synthetic chimeric guide RNA (sgRNA or ChiRNA) and a CRISPR-associated system (Cas) enzyme or enzyme assembly [1], [3]. There are numerous Cas enzymes, for instance, Cas5, Cas6, Cas9 and Cpf1 [1], [3]. Under the direction of sgRNA, the Cas enzymes can site specifically bind to the protospacer adjacent motif (PAM) next to target gene and incise at a guided position. This technology can theoretically edit any DNA sequence by deleting and inserting either a whole gene or a single base within the gene [1]. There are a variety of Cas enzymes, which binds to various PAMs. Cas9 enzyme and its various mutations are currently the most extensively used in CRISPR/Cas technology. CRISPR/Cas is a prodigious tool for life science research to study and analyze specific gene functions. It is analogous to RNAi technology but with considerably

superior vigor. RNAi can decrease but not fully silence a gene and has caused an immense amount of misperception in the life science industry.

Two groups at Harvard University and Doudna's group at UC Berkeley have published efficacious applications in eukaryotic cells concurrently [4]-[6]. The CRISPR enzyme is a protein, therefore is unable to be delivered directly inside the cell membrane. A eukaryotic nucleus has a well-defined nuclear envelope and a highly-organized chromosome structure to protect foreign molecules infecting its genetic material. Thus, a large vector (plasmid) with a nuclear localization signals (NSLs) sequence encoding both the CRISPR enzyme and sgRNA is constructed for transfecting eukaryotic cells, which enables the CRISPR/Cas technology to overcome the barrier of extremely low transfection success rate and achieve a typical efficiency of above 50% with microfluidic chips [4], [7]. Similar delivery strategies have been developed by other gene-editing techniques like transcription activator-like effector nucleases (TALENs) and Zinc-finger nucleases (ZFN) technologies. However, CRISPR/Cas technology can calibrate the gRNA sequence to target different genes, while other gene-editing technology like TALENs and ZFN change the enzyme and the RNA for each target. CRISPR/Cas technology can target multiple genes synchronically by incorporating multiple gRNA in the same vector [4]. CRISPR has superior pliability and complaisance while keeping unprecedented precision leading to an exponential increase in research and patent publication.

## II. BASIC IP DEFINITIONS

### A. Patents

In the United States, a patent is a property right that protects inventions including "any process, machine, manufacture, or composition of matter, or any improvement thereof that are novel, useful, and non-obvious" [8]. There are three types of new patent application in the US: "utility, design, and plant patents", depending on which aspect of the invention to protect [9]. An assignee is the owner of a patent, who can give licenses to make or use the patented invention or transfer the patent ownership to a new assignee. In principle, patents and other intellectual properties can cultivate scholarly research and business development. The divulgence necessity guarantees the dispersal of advancement to people in general, and consequently the inventor/assignee is conceded lawful privileges of possession for a length of 17-20 years [10]. Albeit some contend that licenses are utilized for anticompetitive purposes that prompt restraining infrastructures, business analysts assert that licenses give

Dennis Fernandez is with the Fernandez and Associates LLP, Atherton, CA 94027 USA (corresponding author: phone: (650) 325-4999; fax: (650) 325-1203; e-mail: Dennis@iploft.com).

Zheng Miao is with Stanford University, Palo Alto, CA 94305 USA. (e-mail: miaozhengh@gmail.com).

critical impetuses to venture and exchange, both of which are crucial wellsprings of financial development [10].

Keeping in mind the end goal to acquire a patent, an inventor or an applicant must submit an application to a patent or intellectual property bureau like USPTO [10]. The process is lengthy and takes years to get a biotechnology patent. The average cost to prosecute a patent application is approximately \$15,000 [11].

#### B. Copyrights

Copyrights ensure the original expression of an idea but not the idea itself [12], [13]. Copyrights are automatically protected by the Federal law. For example, a draft of a novel is copyright protected so you don't need to enlist. However, it is savvy to enlist the work with the US Copyright office because, it will save one from proving money related harms from an infringement action [10], [13]. Unlike the registration process for patents, copyright registration is significantly proficient and less burdening on the inventor. Copyrights are usually valid for the author's lifetime plus 70 years or sometimes longer (75-100 years), if the work was created for hire.

#### C. Trademark

Trademarks protect the goodwill and branding of one's product and/or services. It alludes to the unmistakable mark check used to represent a company, product, service, name, or symbol [10]. A general registered mark costs less than \$5,000. It takes less than two years for approval. If not abandoned, it can be re-registered continuously every ten years [10], [14].

#### D. Trade Secrets

Trade secrets are any confidential technical or business knowledge that ensures a trading entity an edge over rivals [15]. Trade secrets cannot be protected by registration [14]. Organizations must endeavor to keep their precious knowledge through non-contend and non-disclosure agreements. Because of the absence of formal assurance, once the knowledge is freely dispersed, an outsider is not kept from copying and utilizing the knowledge [10], [14].

### III. KEY COMPETITORS AND RECENT DEVELOPMENT IN THE FIELD OF CRISPR TECHNOLOGY

CRISPR is an avant-garde revolutionary gene editing technology, where the power of gene editing has started to infiltrate all the various fields of life science research, bioinformatics, agriculture, live-stocks and healthcare. Recently, CRISPR technology patent application as well as its related technologies have exponentially increased and such a trend will probably continue to grow aggressively in next decade (Fig. 1). The genome altering industry sector (mostly eukaryotic genome) is anticipated to achieve USD 5.54 billion by 2021 from USD 2.84 billion in 2016, developing at a CAGR of 14.3% in the succeeding five years (2016 to 2021) [16]. A strategic path in charting a patent portfolio will be vital for a healthy development of a company as well as maintaining a competitive niche in the market.

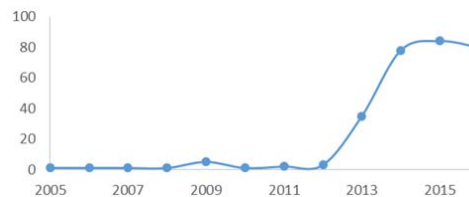


Fig. 1 The trend of CRISPR related patent applications

The Broad Institute at Harvard University and MIT are the leaders of CRISPR/Cas technologies. Of the 50 granted CRISPR or Cas9 patents, MIT and The Broad Institute are listed as the assignees on 13 patents (Fig. 2). They have 55 patents applications with claims related to CRISPR technologies still pending at the USPTO. Besides licensing the patents, the Broad Institute collaborated with AstraZeneca to evaluate a genome-wide CRISPR library against various cancer cell lines to identify novel therapeutic targets. In addition, CRISPR/Cas technology can be used for *in vitro* diagnosis. Recently, a Harvard University scientist has developed a low-cost, rapid paper-based diagnostic system for strain-specific detection of the Zika virus. CRISPR/Cas technology has a tremendous potential in the medical diagnostic field to speedily screen blood, urine, or saliva samples [17]. This proof-of-concept study showed the efficacy for the detection of the Zika virus and its conceivable adoption in detecting various other RNA viruses including Ebola, SARS, measles, influenza, hepatitis C, and West Nile fever. Its potential for applications in health and environmental screening, particularly in low resource areas, is enormous.

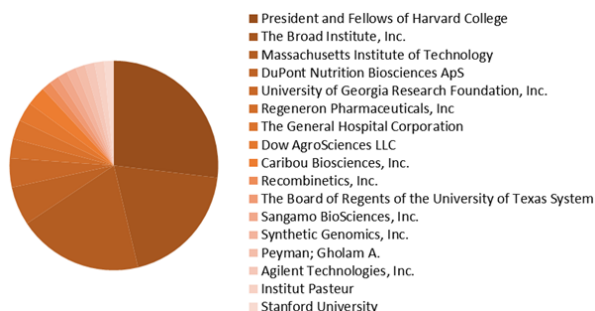


Fig. 2 Applicants/Assignees of CRISPR/Cas9 patents in US

Sangamo BioSciences (Sangamo Therapeutics), Inc. is a major competitor in the field of CRISPR therapeutics. The company has 19 CRISPR related patent applications (Fig. 3). It develops and markets gene-editing strategy using CRISPR and zinc finger DNA-binding (ZFN) technology for controlling gene expression and cell function. It currently has six therapeutic drug candidates under clinical trials including a HIV treatment.

Intellia Therapeutics/Caribou Biosciences, cofounded by Dr. Jennifer Doudna, are collaborating with a heavyweight pharmaceutical company Novartis AG for developing an innovative cancer treatment. One cancer patient may have hundreds of mutations concurrently. Thousands of genes related to cancer were screened by researchers at Novartis

Institutes for BioMedical Research (Cambridge, MA) and Novartis International AG (Basel, Switzerland) using the CRISPR technique generated models, to expeditiously and precisely investigate potential drug targets [18]. The effort would have been impossible without this genetic engineering technology.

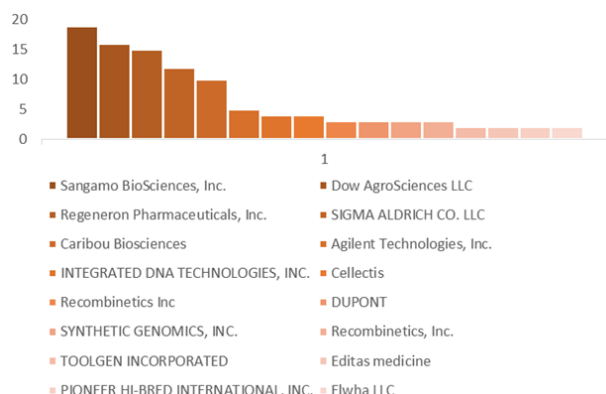


Fig. 3 CRISPR related patent applications of major competitors in US

Editas Medicine cofounded by Dr. Feng Zhang successfully applied the CRISPR/Cas9 mechanism for gene-editing in eukaryotic cells. The company launched exclusive collaboration with Juno therapeutics to create next-generation immune therapies. The alliance focused on creating chimeric antigen receptor (CAR T) and high-affinity T cell receptor (TCR) therapies to treat cancer. CAR T and TCR utilizes genetically engineered T cells that specifically binds to antigens expressed on cancer cell surfaces and subsequently triggers an immune response.

CRISPR Therapeutics, cofounded by Dr. Emmanuelle Charpentier who co-discovered the key CRISPR/Cas9 mechanism, is a leader of gene therapy *in vivo*. CRISPR Therapeutics has licensed Vertex for six CRISPR-Cas9-based treatments including cystic fibrosis. CRISPR Therapeutics entered a collaboration agreement with Bayer AG to develop therapeutics for blood disorders, blindness, and heart disease.

Toolgen Inc., of Seoul, South Korea, has two patent applications conceded by the Korea Intellectual Property Office (KIPO) with claims covering CRISPR genome editing technologies [19]. It has patent protection covering modifications for improved specificity of CRISPR/Cas9 nucleases. Currently, Toolgen has entered a licensing agreement with Thermo-Fisher Scientific for various *in vitro* applications and research kit development.

Dow AgroSciences LLC is the leader of CRISPR technology in the plant and agriculture field. Its business is focusing on pesticide and herbicide resistant crops. With versatile targeting and precise control, CRISPR techniques can help in engineering genetic modified crops (GMO) which are more environmentally friendly. However, some GMO crops such as, herbicide 2,4-D resistant soybean are still causing environmental concerns because of the herbicide toxicity and contamination to the soil.

#### IV. PATENTING STRATEGIES FOR CRISPR RELATED TECHNOLOGIES.

##### A. Patent Portfolio Development by Start-Up Companies

The beginning stage in protected innovation for organizations is an assessment of the present condition of the licensed innovation possessed or authorized by the organization [20]. Does the scope of current intellectual property portfolio include the CRISPR technology? Who are important competitors in the field of CRISPR/Cas technologies? Does the CRISPR technology form the core of the product line of a company to maintain a companies' competitiveness? Do CRISPR technology inventions provide a short-term or a long-term value? Through answering these questions, a strategically developed patent portfolio may have a greater chance to be industrialized. CRISPR related patents are closely related to various gene editing technologies. Many biotech and biopharmaceutical companies already have products manufactured with other gene editing technologies.

Vertex Pharmaceuticals have obtained licenses from CRISPR Therapeutics and collaborated on developing CRISPR/Cas9 technology for *ex vivo* treatment. The company has a strong patent portfolio in TALENS technology. Vertex Pharmaceuticals' next venture is to develop new products as well as expand and protect existing patents for gene editing in CAR-T cell therapies against competitors, like Collectis and Intellia Therapeutics. In a short-term, CRISPR/Cas9 technology will provide more value in *ex vivo* therapeutics including, cystic fibrosis and sickle cell disease. In a long-term, Vertex Pharmaceuticals/ will have an imperative need to develop their own CRISPR related strategic patent portfolio to maintain competitiveness, especially when the current limit of six-drugs quota for treatment developments with CRISPR technology is reached. In contrast, Intellia Therapeutics/ Caribou Biosciences are the pioneers of CRISPR/Cas9 gene editing in CAR-T cells. Intellia Therapeutics/Caribou Biosciences have a solid patent portfolio of CRISPR/Cas technology, but fail to hold competitiveness in other gene editing technologies. With collaboration and a joint venture with Novartis AG, they are launching a product line which will implement CRISPR/Cas9 technology to treat blood cancers, as well as inherited disorders such as sickle cell anemia and beta thalassemia. CRISPR/Cas9 technologies for gene editing *ex vivo* will provide an increased short-term value than a long-term gain. Drug delivery related technology for CRISPR gene-edited hematopoietic stem cells are important in the long-term. Stem cell gene-editing can be achieved with viral and/or non-viral delivery systems, for example by incorporating cell penetrating peptides to construct a fusion protein to increase cell uptake (Patent Number #9,526,784).

##### B. Patent Portfolio Development in Academic and Charitable Foundations

Portfolio development can be carried out by acquiring or licensing patents or applications from universities. Numerous biotechnology new businesses deliberately construct and fortify their patent portfolios by negotiating with research institutions for licensing their innovations [19]. The Bayh-

Dole Act in 1980 enables universities to transfer their patented technology to businesses in the industry. In this model, the universities benefit from the revenue generated from patent licensing. The utmost advantage for CRISPR based businesses and industries will be to attract high-risk capital investors emphasizing investment in downstream development. The licensing fee obtained from the industry can help the universities to focus on innovative research and the free exchange of ideas [19]. Additionally, a successful licensing deal can accelerate the clinical research at academic and research institutions, thus, improving healthcare. Large companies like DuPont attained exclusive licensing rights from Vilnius University in Lithuania for human and animal therapeutics, diagnostics, industrial biotechnology, research tools, and various other agriculture sectors. Start-up companies like Editas Medicine were successful in obtaining exclusive patent rights of CRISPR/Cas9 technology for eukaryotic cell gene editing from The Broad Institute (IP pragmatics gene editing). Gaining the exclusivity on the technology, Editas Medicine developed CRISPR/Cas technology for treatment of Cystic Fibrosis as well as various other human diseases and licensed it to Massachusetts General Hospital of Harvard University (IP pragmatics gene editing). University of Pennsylvania is planning to conduct the first clinical study of T cell cancer therapy in the US with CRISPR/Cas technology. This will also be the first clinical study funded by Billionaire Sean Parker's charitable foundation.

#### *C. Due Diligence on Patent Applications and Patent Interference/Litigation*

Applying due diligence on patent applications and widely scanning for a potential violation of issued licenses are constantly essential in patent "negative right" protection. When patent applicants pursue patents for their inventions, they need to fine tune their claims to carefully avoid infringement, but it is imperative to cover the broadest possible claim cover, so that it is not easily bypassed by the competitors [20]. The main issues of patent claims include "obviousness", "non-enabling" and "reasonable expectation of success". Resolving these issues early could save an interference or litigation in the future. If an invention is prime facie obvious to the person of ordinary art in light of specifications of prior patents, it can be rejected on "obviousness" basis. Because it is simply a discovery of "inherent" property or obvious improvement of a prior art with a predictable success. In contrast, if a competitor's patent application is "non-enabling" or has no "reasonable expectation of success", a non-obvious improvement to the current technology will worth a patent. A biotechnology-related patent prosecution requires an average cost of about \$15,000 plus amendment fees and takes three to four years, therefore before submitting patent applications to build up a patent portfolio, potential litigation and interference should be altogether researched [13], [21].

There is an advantage to draft a narrow claim in a very competitive field to avoid an "enablement" issue. In the

interference trial between UC Berkeley and The Broad Institute, the PATENT TRIAL AND APPEAL BOARD (PTAB, Board) decided that the more general claims by UC Berkeley patent applications does not interfere with the narrower claims by The Broad Institute. Specifically, the application of CRISPR/Cas9 in eukaryotic cells is not an obvious thing from the results in prokaryotic cells and test tubes [22]. Therefore, The Board concluded that it is a novel invention and deserves a patent.

Record-keeping of all innovation by the inventors is considered to be of utmost importance. Further, all inventor scratch paper, verbal and written disclosure, patent recommendations and writing must unveil developments as classified. All inventors who have made a contribution in the conception of an invention have a right to inventorship on the patent [20]. For example, in the case of *Ethicon Inc. v. U.S. Surgical Corp.*, U.S. Surgical discovered that Young Jae Choi contributed to two claims in the patent involving litigation, but Choi is not listed as an inventor. Choi was later granted co-inventorship by the court and the lawsuit was dismissed (*ETHICON, INC. vs U.S. SURGICAL CORPORATION*) [23]. The AIA reform changed the US patent system from first-to-invent to first-to-file system effective March 16<sup>th</sup>, 2013. Patent applications with a priority date earlier than March 16<sup>th</sup>, 2013 still follow a first-to-invent rule. On March 15<sup>th</sup>, 2013, a patent application by UC Berkeley related to CRISPR was submitted to USPTO. After "conception" of an invention, "reasonable diligence" is critical until "reduction to practice". *Hull v. Davenport*, 90 F.2d 103, 105, 33 USPQ 506, 508 (CCPA 1937). All evidence before the entry time of the other players demonstrating that the CRISPR/Cas9 technology could work in eukaryotic cells can be used in later litigation to claim contribution as the first inventor or co-inventor. In the first-to-file system, the constructive "reduction to practice" happens at the time of patent filing, thus the inventor will be the sole party to obtain a patent.

#### *D. Maximizing Marketing Value from CRISPR Patent Portfolios*

A patentee may intentionally choose not to permit protected core innovative technologies to safeguard its leading position in the market [20]. In any case, to amplify the estimations of an arrangement of licenses, patentees may consider: (I) authorizing out-licenses that will not be used or will not be used in light of the fact that the licenses don't meet the organization's business objective; (II) initiate lawsuits against contenders to get monetary compensation and reinforce the patentees position in the commercial center; or (III) cross-permit with contenders for pioneering innovation to accelerate growth of immature market [20]. As of Feb 18<sup>th</sup>, 2017, 473 patent publications available for download at the USPTO website made some reference of CRISPR or Cas9 in their claims, many of which were highly relevant and are made in earnest. Further yet, 50 issued patents include the term in the claims. Most of the issued patents have been assigned and/or licensed. MIT and The Broad Institute are listed as the shared assignees on 13 issued patents, while President and Fellows of

Harvard College have 18 patents (Fig. 2). However, the area still appears open in terms of ownership; opportunities to form alliances in the event of significant commercialization of CRISPRs are still thriving. As of the same date, 1009 of the not-yet-issued patent applications on USPTO website mentioned CRISPR in the specifications. Majority of these are likely to be irrelevant to individual patent applications, but it is still critical that they be considered carefully to ensure confidence in a patent.

#### V. ETHICAL CONCERNS AND BIOINFORMATICS RELATED TO CRISPR TECHNOLOGY

USPTO does not allow any organs of humans to be patented. However, the USPTO considers non-human cloning-related developments patentable topic and seldom rejects applications in view of open strategy and ethical quality grounds, so long as the invention meets the criteria of novelty, utility and nonobviousness [20]. For instance, the Jackson Laboratory has obtained licenses from both The Broad Institute and Caribou Bioscience for CRISPR techniques which generate gene-knock out mice with simplified cloning procedure. Recently, scientists created human-pig chimeric embryos. The pig blastocysts were edited by CRISPR/Cas technology to remove the genes for certain organ formation to be replaced by human adult stem cells injected into pig blastocysts. Currently, the technology is far from applicable because of the extremely low success rate. Researchers say that this work could eventually provide life-saving organs for those waiting on donor lists, even though it raised the ethical concerns related to the CRISPR technology [24]. Extreme caution should be raised when dealing with heritable human traits. "These are important issues, but I do not think right at this second we should be overly concerned about it. It is too far off," Zhang says (South China morning Post). Similarly, in many other developing countries like Mexico and P. R. China, the patent law also prohibits patenting any human body parts.

The bioinformatics of the CRISPR technology begs an inquiry into issues of privacy. CRISPR is a very powerful tool to build large biological databases. The combination of CRISPR-related technology along with bioinformatics will transform precision medicine. CRISPR technology "democratized" the gene-editing technology. Millions of CRISPR reagents and kits are available in the market. Over 5,000 publications related to CRISPR were published in span of a few years. Bioinformatics software will not only provide tool to design genome wide sgRNA to CRISPR, but also provide guidance for diagnosis and treatment response simulation/monitoring. In the long term, CRISPR technology may be used *in vivo* by programmable/active delivery of bioactive compounds and/or bioactive molecules, a real-time delivery system armed with bioinformatics software may also be connected to the internet to provide useful diagnosis and treatment information. Pooled library screen analysis using CRISPR-Cas technologies hold great promise to genome-wide functional studies [25]. The bioinformatics tool can help with mapping, data QC, library QC, statistical analysis and visualization in genome-wide pooled screens, dissecting

regulatory networks and pathway identification [25], [26]. Thus, the genomics and other systems biology studies combined with CRISPR technology will give enormous opportunities for developing various bioinformatic tools to deal with biological data. In *Alice Corporation v. CLS Bank International*, the Supreme Court ruled that a patent application describing generic computer implementation of an abstract idea is not patentable [27]. It will have long and lasting impact for bioinformatics patents as nearly all of these patents could be drawn down to an abstract idea implemented by a generic computer.

#### ACKNOWLEDGMENTS

We would like to thank Unisha Patel at Fernandez & Associates LLP for helpful suggestions with writing of this article.

#### REFERENCES

- [1] M. Jinek, K. Chylinski, I. Fonfara, et al. "Programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity." *Science*, vol. 337, Aug. 2012, pp. 816-821.
- [2] K. Chylinski, K. S. Makarova, E. Charpentier, and E. V. Koonin, "Classification and evolution of type II CRISPR-Cas systems." *Nucleic Acids Res.*, vol. 42, Jun. 2014, pp. 6091-6105.
- [3] I. Fonfara, H. Richter, M. Bratovič, A. Le Rhun, E. Charpentier, "The CRISPR-associated DNA-cleaving enzyme Cpf1 also processes precursor CRISPR RNA." *Nature*, vol. 532, Apr. 2016, pp. 517-521.
- [4] L. Cong, F. A. Ran, Cox, D., et al. "Multiplex genome engineering using CRISPR/Cas systems." *Science*, vol. 339, Feb. 2013, pp. 819-823.
- [5] P. Mali, L. Yang, K. M. Esvelt, et al. "RNA-guided human genome engineering via Cas9." *Science*, vol. 339, Feb. 2013, pp. 823-826.
- [6] M. Jinek, A. East, A. Cheng, et al. "RNA-programmed genome editing in human cells." *Elife*, Jan. 2013, e00471. doi: 10.7554/eLife.00471.
- [7] X. Han, Z. Liu, M. C. Jo, et al. "CRISPR-Cas9 delivery to hard-to-transfect cells via membrane deformation." *Sci Adv.*, vol. 1, Aug. 2015, e1500454. doi: 10.1126/sciadv.1500454.
- [8] Leahy-Smith America Invents Act. United States Code Title 35. §§ 101-103. USPTO MPEP Appendix L - Patent Laws CHAPTER 10. "Patentability of inventions", Sept. 2011.
- [9] U.S. PATENT AND TRADEMARK OFFICE. Types of Patents. [www.uspto.gov/web/offices/ac/ido/ocip/taf/patdesc.htm](http://www.uspto.gov/web/offices/ac/ido/ocip/taf/patdesc.htm). Accessed on 16/03/2017.
- [10] D. Fernandez, C. Chun, "Intellectual property protection in the EDA industry". *International journal of novel research in marketing management and economics*, vol. 2, 2015, pp. 55-63.
- [11] Richards Patent Law, How much does a patent cost? <http://www.richardspatentlaw.com/faq/have-an-idea/how-much-does-a-patent-cost/>, 2012. Accessed on 16/03/2017.
- [12] S. Halpern, Copyright Law: Protection of original expression (Carolina Academic Press, 2002).
- [13] K. Chan, D. S. Fernandez, "Patent Prosecution in Proteomics." *Computer & high technology law journal*, vol. 19, 2003, pp. 458-470.
- [14] D. Fernandez, A. Maninang, S. Kobayashi, et al. "Intellectual Property Protection for Bioinformatics and Computational Biology." *IWBBIO*, 2015, Part I, LNCS 9043, pp. 85-95.
- [15] H. C. Anawalt, E. E. Powers, IP Strategy – Complete intellectual property planning, access, and protection, West Group, §1.01, at 1-3, 2001.
- [16] Genome editing/genome engineering market by technology (CRISPR, TALEN, ZFN), Applications (Cell Line Engineering, Animal Genetic Engineering, Plant Genetic Engineering), End User (Biotechnology & Pharmaceutical Companies, CROs - Global Forecast to 2021. Published in Oct. 2016.
- [17] K. Pardee, A. A. Green, M. K. Takahashi et al. "Rapid, low-cost detection of Zika virus using programmable biomolecular components." *Cell*, vol. 165, May 2016, pp. 1255-1266. doi: 10.1016/j.cell.2016.04.059.
- [18] M. K. Kiessling, S. Schuierer, S. Stertz, et al. "Identification of

- oncogenic driver mutations by genome-wide CRISPR-Cas9 dropout screening.” *BMC Genomics*, vol. 17, Sept. 2016, pp. 723. doi: 10.1186/s12864-016-3042-2.
- [19] S. Ellis, Toolgen wins critical CRISPR patent in Korea. <http://www.bioworld.com/content/toolgen-wins-critical-crispr-patent-korea-0>. Accessed on 16/03/2017.
- [20] J. J. Yeh, D. Fernandez, N. Hansen, “Patent prosecution strategies for stem cell-related applications.” *APBN*, vol. 9, 2005, pp. 1212-1219.
- [21] R. Kumar, J. J. Yeh, D. Fernandez, N. Hansen, Patent prosecution strategies for stem cell-related applications. *Journal of Biomolecular Screening*, vol. 12, 2007, pp. 769-774. doi: 10.1177/1087057107305828.
- [22] <https://acts.uspto.gov/efiling/PublicView.jsp?identifier=106048&identifier2=null&tabSel=1&action=filewrapper&replyTo=PublicView.jsp>. Accessed on 16/03/2017.
- [23] *Ethicon, INC. vs U.S. Surgical Corporation*, Fed. Cir., 1998 (135 F.3d 145645 U.S.P.Q.2d 1545, 48 Fed. R. Evid. Serv. 1226).
- [24] J. Wu, A. Platero-Luengo, M. Sakurai, et al. “Interspecies chimerism with mammalian pluripotent stem cells.” *Cell*, vol. 168, 2017, pp. 473. doi: 10.1016/j.cell.2016.12.036
- [25] J. Mun, D. U. Kim, K. L. Hoe, S. Y. Kim, “Genome-wide functional analysis using the barcode sequence alignment and statistical analysis (Barcas) tool.” *BMC Bioinformatics*. Vol. 17(Suppl 17), Dec. 2016 , pp. 475.
- [26] O. Parnas, M. Jovanovic, T. M. Eisenhaure, et al. “A Genome-wide CRISPR screen in primary immune cells to dissect regulatory networks.” *Cell*, vol. 162, July 2015, pp. 675-686. doi: 10.1016/j.cell.2015.06.059.
- [27] *Alice Corporation v. CLS Bank International*, 573 U.S. \_\_\_\_ (2014) (June 2014).