ARK INVEST

CRISPR Genome-Editing

The Value of CRISPR's IP

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THE VALUE OF INTELLECTUAL PROPERTY

Intellectual property (IP) can be critical not only to commercial success but also to platform strategies upon which more innovation can take place. A strong patent portfolio might not guarantee success, but it can serve as a strategic asset, particularly in biotech. Patents provide a company with 20 years of exclusivity to advance innovations before others can compete. In the meantime, these companies receive licensing fees and/or royalty payments, but perhaps more importantly, attract talent seeking unfettered access to cutting edge technology.

Genentech is a prime example of the benefits of a strong IP position in the field of health care. In 1980, Genentech went public, largely on the strength of its IP in recombinant DNA technology.[1] Attracting some of biotech's brightest minds, it commercialized synthetic insulin two years later, four years before Roche took a majority interest. Genentech's stock scaled 11-fold at a 47% compound annual rate in the six years between its initial public offering (IPO) and Roche taking majority interest.

CRISPR'S IP LANDSCAPE

While Genentech benefited from a patent claim that was unambiguous, the CRISPR IP landscape is much more convoluted. In a high-profile patent battle between the University of California (UC), Berkeley and the Broad Institute, scientists are fighting for commercial claims to the "foundational" CRISPR IP. Jennifer Doudna, structural biologist, and Emmanuelle Charpentier, microbiologist, are fighting for the UC system and Feng Zhang, molecular biologist, for the Broad Institute.[2]

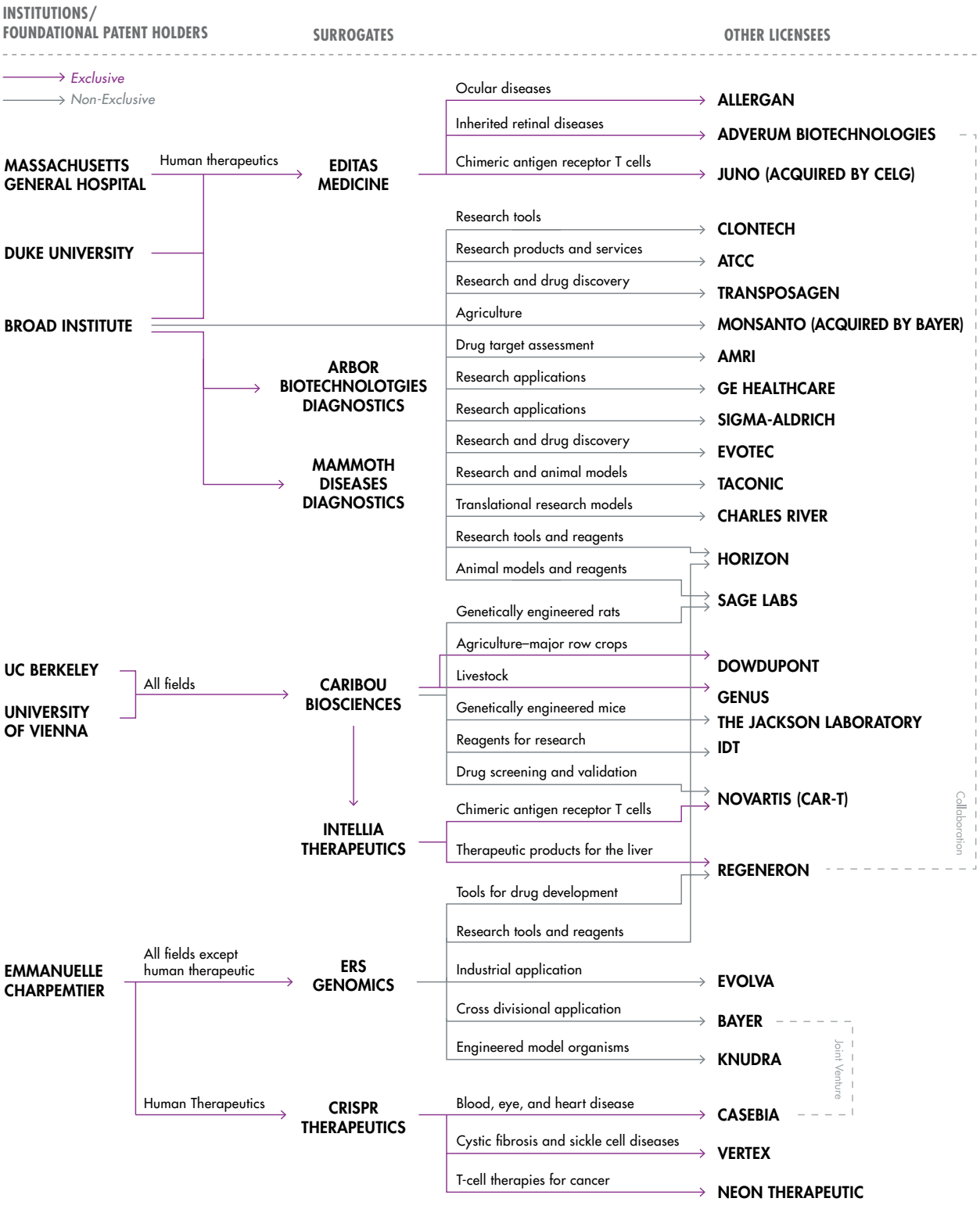
The foundational CRISPR IP focuses on the impact of the CRISPR-Cas9 system on DNA editing in a commercial setting. Three CRISPR companies, Editas Medicine (EDIT), Intellia Therapeutics (NTLA), and CRISPR Therapeutics (CRSP), have secured exclusive licenses for CRISPR-Cas9 in commercial therapeutic settings. Figure 1 summarizes the key CRISPR stakeholders and collaborations, including: i) licenses from the patent holders to the public and private CRISPR companies, ii) sublicenses from surrogates to collaborators, iii) areas of CRISPR research, and iv) exclusive vs. non-exclusive licenses — the IP landscape seems like a labyrinth.

ARK believes that this legal battle will result in cross-licensing agreements and the proliferation of CRISPR technology globally. In filings with the U.S. Patent and Trademark Office, the UC system claims its patents cover the use of CRISPR in all types of cells, whereas the Broad Institute claims its cover the use in eukaryotes, which includes human therapeutics. As a result, companies focused on CRISPR therapeutics probably will have to license both patents.

1 Recombinant DNA is a legacy gene-modification technology

2 Kelly Servick "Broad Institute takes a hit in European CRISPR patent struggle" Science, Jan. 18, 2018; https://www.sciencemag.org/news/2018/01/broad-institute-takes-hit-european-crispr-patent-struggle

FIGURE 1
The CRISPR IP Patent-Landscape Overview — CRISPR-CAS9 licensing agreements



Source: Based on KEI, Knowledge Ecology International, 2017, https://www.keionline.org/sites/default/files/CRISPR-SecPrice-6Jan2017.pdf
Modified by ARK Investment Management LLC, 2018

While critics believe that an exclusive license for human therapeutics would limit CRISPR as a platform technology, others have offered three reasons why the impact would be marginal:

1. THE PATENT DISPUTE COVERS ONLY THE CAS9 NUCLEASE.
As discussed in ARK's white paper, "CRISPR Genome-Editing: Market Opportunity and Key Players", various nucleases enable different CRISPR use cases. Any company can discover and engineer a new nuclease, claiming patent rights to its source and its use.

2. A LICENSE TO USE CRISPR FOR ACADEMIC RESEARCH IS NOT REQUIRED.
Only if a company plans to use CRISPR-Cas9 for human therapeutic use in a commercial setting must it license the patent(s) from Editas, Intellia, and/or CRISPR Therapeutics. Agricultural licenses are easier to obtain from primary IP holders.

3. EXCLUSIVE LICENSES SIMPLY PROVIDE THE RIGHT OF FIRST REFUSAL.
If a company wants to commercialize a CRISPR therapeutic product, it will have to give first rights to the primary CRISPR patent holder. If it passes on the opportunity, the IP holder will no longer own claims to the product.

Because of the right of first refusal, royalty revenues from human therapeutic products can flow directly to universities instead of the exclusive licensees, Intellia, Editas, and CRISPR Therapeutics. For purposes of comparison, Genentech attracted the best talent in recombinant DNA, so it earned royalty rights in the absence of competition. Intellia, Editas, and CRISPR Therapeutics will have to earn their stripes by innovating around CRISPR functionality, developing strong product pipelines, executing on thoughtful business plans, and striking strong strategic partnerships.

While royalty rights have not been settled by the Patent Trial and Appeal Board yet, CRISPR will not be a zero-sum game in such a capacious field. Indeed, the combined market capitalization of the three public CRISPR stocks, Crispr Therapeutics (CRSP), Editas Medicine (EDIT), and Intellia Therapeutics (NTLA), is less than $5 billion[3], dwarfed by the size of the monogenic human therapeutic market that, on the basis of incidence, may deliver $75 billion in annual revenue and, on the basis of prevalence, represents an addressable market of more than $1 trillion.

Large pharmaceutical companies with indirect exposure to CRISPR technology, listed alphabetically, include: Allergan (AGN), Amgen (AMGN), AstraZeneca (AZN), Baxter (BAX), Biogen (BIIB), Celgene (CELG), DowDuPont (DD), Glaxo-Smith Kline (GSK), Johnson and Johnson (JNJ), Monsanto (MON), Novartis (NVS), Regeneron (REGN), and Vertex (VRTX). Though Genentech's experience suggests that companies with the strongest patent claims to breakthrough technologies will attract the best talent and access the most interesting opportunities, these companies provide larger cap exposure for more risk-averse or style-constrained investors.

3 Information as of 8/10/18

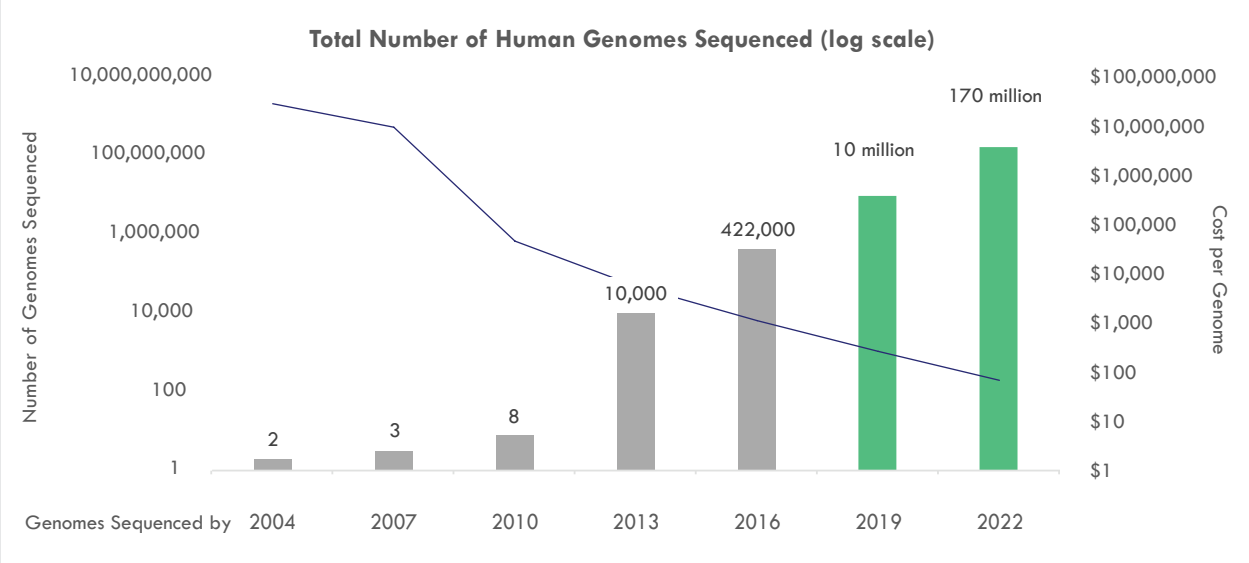
CRISPR TECHNOLOGY
THE DISRUPTORS AND THE DISRUPTED

Because it aims to cure disease, CRISPR will likely disrupt companies which treat chronic conditions and those with high-cost drug discovery, development, and manufacturing platforms. We believe its therapeutics will leapfrog current product development pipelines, particularly antibiotics, as CRISPR-based anti-microbials should be more targeted and effective. In the agriculture space, traditional seed companies relying on selective breeding techniques may be at risk.

In human therapeutics, CAR-T therapy will challenge traditional cancer care including chemotherapy. While still early stage and available primarily to patients who have failed multiple lines of therapy, CAR-T is helping patients unleash their own immune systems against cancer, leading to seemingly miraculous results. Future CAR-T companies will be empowered through CRISPR technology.

CRISPR also could pose a threat to RNA interference (RNAi) therapy. RNAi targets only liver-based diseases today while, in contrast, CRISPR-mediated RNA interference may be able to tackle a broad-based range of diseases. With IP generated in 2014 from UC's Doudna lab, Locana has developed therapeutics aimed at neurodegenerative diseases such as ALS and Huntington's Disease.[4] Separately, the Broad Institute released a paper in Nature which described CRISPR-Cas13a as equally effective as RNAi technology but with higher rates of specificity.[5]

FIGURE 2
Cost Decline of Genomic Sequencing



Source: ARK Investment Management LLC, 2018

4 Yarris, Lynn. "RCas9: A Programmable RNA Editing Tool." Berkeley Lab, 3 Oct. 2014, newscenter.lbl.gov/2014/10/03/rcas9/.

5 Abudayyeh, Omar O., et al. "RNA Targeting with CRISPR–Cas13." Nature, 4 Oct. 2017, www.nature.com/articles/nature24049.

CRISPR technology will increase the value of companies other than the primary patent holders, particularly those focused on genomics data and molecular diagnostic tests. Based on ARK's research, DNA sequencing costs are dropping by 37% per year but the data's value has been limited because most mutations cannot be treated today, a weak link that CRISPR technology should help change. Accounting for roughly 95% of all base pairs of DNA sequenced in the world today, Illumina (ILMN) could drive sequencing costs down from roughly $1,000 today to less than $100 during the next four to five years, potentially making sequencing DNA an important part of an individual's annual physical exam to identify mutations. Soon, the mutations, or programming errors, in an individual's DNA will be corrected or reprogrammed by CRISPR technology. As a result, the number of whole human genome sequences should scale more than 100-fold from 1.5 million in 2017 to 170 million in 2021, as shown before in Figure 2.

Other sequencing and software companies also stand to benefit, particularly given the explosion of computing power that will be necessary to sequence, store, and analyze genomic data. Semiconductor chip companies such as Nvidia (NVDA) and cloud storage companies like Google (GOOG) and Amazon (AMZN) could see increased demand for their services thanks to CRISPR. As the cost of benchtop sequencers drops, academic and other research centers should adopt more sequencing technologies, such as Nanostring's (NSTG) 3D protein analysis assays as well as PacBio's (PACB) and Oxford Nanopore's long read length sequencers, the latter necessary for agricultural markets.

Finally, diagnostics companies such as Foundation Medicine (FMI), a Roche Company, Invitae (NVTA), Veracyte (VCYT), and Accelerate Diagnostics (AXDX) should benefit from favorable reimbursement decisions, as the value of early and more accurate diagnoses could save the health care system significant costs over the long term. We are already seeing health systems such as Geisinger release pilot programs for patients under coverage to cover sequencing tests for routine care.[6]

CONCLUSION

As the history of the health care market has shown, those with significant IP advantages have succeeded in capturing the lion's share of profits in this winner-take-most environment by attracting top talent and continuing to lead in IP generation. In this IP dependent market, the heated battle for CRISPR's foundational IP rights is not surprising. While the resolution might be years to come, the benefits of CRISPR are already tangible.

6 Geisinger Caring, DNA sequencing to become part of Geisinger's routine clinical care, 7 May 2018, https://www.geisinger.org/about-geisinger/news-and-media/news-releases/2018/05/07/12/18/dna-sequencing-to-become-part-of-geisingers-routine-clinical-care

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