

Article

Book Review of *The Code Breaker: Jennifer Doudna, Gene Editing, and The future of the Human Race*

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ABSTRACT

In this book review and accompanying commentary and Addendum, we focus on 5 principal topics/major themes that are of interest for our readership, with a focus on framing the translation of transformative technology into a platform business model in biopharma. We focus on: 1) the behavioral and personal side of the story of the academic scientist, in this case the principal “code breaker” – Jennifer Doudna; 2) the innovation/technology transfer models, including team building appropriate for successfully translating technology from the academic laboratory into the private sector; 3) the IP considerations needed for broad commercialization and dissemination of pivotal, platform inventions in biopharma; and, 4) framing the issues surrounding the ethical discussion related to use in patients associated with a transformative, gene editing technology like CRISPR. We also include an Addendum that covers, 5) Some pertinent, concluding comments on the importance of high-performance, diverse teams for founding, building, and growing successful biotechnology companies.

Journal of Commercial Biotechnology (2021) 26(2), 26–32. doi: 10.5912/jcb988

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INTRODUCTION

THIS ARTICLE IS intended to go beyond a traditional book review of the excellent book by Isaacson, who does his usual incredibly insightful and well documented job of writing on innovators like Steve Jobs and Leonardo da Vinci. This book focuses on the scientific creators of an emerging technology, and who also are engaged actively in the commercialization process. To those of us who have worked in technology management and transfer area in top-tier university programs, there is a saying that goes – “you don’t transfer the technology, you transfer the people”. Truth be told, both are most often ideal. Earlier in this volume, we highlighted a number of scientific innovators who exemplify this statement. The Isaacson book was released in mid-March 2021, and already at the time that this article has been written, several traditional book reviews quickly appeared, and they are cited herein. That speaks to the importance and timeliness of the topic, and also the challenges that remain ahead as the business model evolves over the next years (or decades) ahead. While Isaacson did cover the entire spectrum of academic scientists involved in the pursuit of CRISPR, he chose to focus on one of the innovators

(Dr. Jennifer Doudna, the principal code breaker) who were trying to unravel the science of gene editing. The book does a phenomenal job of following the story of Doudna, her academic career, an in-depth discussion on her pursuit of CRISPR with an array of US and international collaborators and competitors, and culminating in the award of a Nobel Prize along with her French partner Emmanuelle Charpentier. However, he also does a great job of bringing in the entire “cast” from around the US and the world who have played essential roles in advancing what was the mystery of the technology. Some have suggested that the title should have been the plural, code breakers, since most usual in the pursuit of science-driven innovation, there were a whole cast of others engaged as teams spread across the globe competed to publish first, but more importantly to patent their potentially breakthrough inventions (with freedom to operate). While good science and engineering is indeed a “team sport”, in this case Doudna is clearly the lead code breaker. The book tells this story in great detail and is a great read. And, the science is mostly understandable, even for physical scientists and engineers, as well as non-scientists. However, we note that the focus of J. Commercial Biotechnology readership is not on the transformative science itself (as interesting as that may

be). Therefore, we focus on the translation of that science from the lab into commercial practice – a principal focus of Jennifer Doudna who straddled the academic – private sector part of the commercialization process. Building and leading her team at UC Berkeley in that regard is certainly relevant to setting up the broader topic of commercialization and innovation – translation from lab to patient. We focus on those topics in this commentary.

DISCUSSION

We begin with examining the **traits and behaviors of academic scientists** who pursue transformative science and technology that is of Nobel Prize quality, while in parallel excelling at commercialization. The objective is challenging; and the result worthwhile, with the goal of **technology transfer from academia into the private sector**. Isaacson has many examples in both technology, and biotechnology that are covered nicely in the book as a contrast to the CRISPR story. In the last century, these have ranged from genes (DNA discovery and the Human Genome), and even into the physical sciences that deal with atoms/nuclear technology, and computer chips. Doudna does that very well, and there are lots of quotes that we extract for this article. Most of the others, including Charpentier are largely driven by the science. That is their role in the life cycle of discovery to invention to commercialization to breakthrough applications. In the book, we are also exposed to the Boston-based team at MIT/Harvard/Broad Institute, with Eric Lander, Tom Church, Feng Zhang, et al. who pursued not only prestigious publications, but patents (more on that later), and then to startup companies. The Boston team was well connected to the venture capital/business community. The Berkeley led team, not so much.

We discuss how Dr. Doudna identified doctoral students and post-docs for her lab not only for their scientific **skill**, but for their **will** and **fit** into the culture that she nurtured. Early in her career, she recognized that she really liked pursuing the commercial implications of their collaborative work thru startup companies and has done a few as part of her pursuit to understand and commercialize CRISPR (we discuss them below). So, she stands out as one who learned how to straddle the gap between academia and commercialization. And as usual here, all of us who have gone thru this process “learn from our mistakes” and pivot the next time through the process. There is great material in the book that identifies her as an individual who excels at science, but who definitely keeps her eye on the outside work to take invention from “lab or bench top” to patients. As we discuss later in the article, perhaps she would have benefitted

from a more experienced technology transfer/business school partnership along the way. But, we all learn from our experiences, and the book points out many “lessons learned” by Dr. Doudna.

The **topic of innovation** itself is worth discussing, and we have covered the promise of transformative technologies and their business model challenges, c. f., J. Commercial Biotechnology, Vol. 25, No.4 (2020). We refer the interested reader to that volume. Also, consider our “Boot Camp 2.0 volume, that covers all of the topics needed from translation of science into business in a two-day boot camp offered annually in partnership with BIO (the Biotechnology Innovation Organization); J. Commercial Biotechnology, Vol. 24, No.4 (2019). In the case of CRISPR, the technologies are indeed major breakthroughs, and Isaacson likens them by analogy to the 3 great scientific revolutions of our times, e. g. **atoms, bits, and genes** and how the academic and commercial institutions and their leaders participated in those races. And, as a subset, what are the characteristics and behavioral traits of innovators vs ‘inventors/professors’. Her “epiphany” upon leaving a tenured position at the University of California, Berkeley for Genentech, and then quickly returning is worthy of note, and we also cover that below.

We believe that innovation is inherently a “team sport”, including those innovations originating in academic institutions where the process starts in the university lab. The technology (and the IP) is then “transferred” for commercialization in a NewCo (or licensed directly to larger, established organizations), and then progresses thru the regulatory/reimbursement process, and ends up accessing the market via channels controlled by larger partners in biotech and biopharma. These transitions are discussed in the Isaacson “Code Breaker” book. We believe that for successful commercialization, a strong intellectual property (IP) foundation is required to build a competitive, commercial platform. While we cannot and do not go into great depth, we do cover some of the fundamental concepts below.

Intellectual property (IP) and its issues is of course, is always a critical factor in building any successful tech/biotech based business – especially for a transformative, platform technology like CRISPR. And, that leads to the topic of patents (one form of intellectual property that is essential for commercial practice; vs. trade secrets). Simply put, a **patent** is a title that gives its owner the legal right to exclude others from making, using, or selling an invention for a limited period of years in exchange for publishing an enabling public disclosure of the invention – so it is necessary to be first to invent. In simple terms, the invention must be **new, useful, and non-obvious** (to one skilled in the art). That last caveat is always worthy of discussion, and turns out to have been critical here as is

pointed out in the Isaacson book. We refer the interested reader to 3 articles on IP written by : Kathryn Doyle (pp 32-37), Raymond Miller (pp 38-41), who are two excellent IP attorneys who talk about this material in our Entrepreneurship Boot Camp at each international BIO meeting since 2005. We also recommend the more recent article by James Jordan (pp 42-47). All of these articles are published in our previous special edition; “Boot Camp 2.0”, c. f., J. Commercial Biotechnology, Vol. 24, No.4 (2019). The Jordan article goes beyond IP per se to articulate an IP Pyramid strategy that builds on patents, but also incorporates other factors to build “an impermeable competitive advantage” beyond IP, e. g. proprietary relationships, and proprietary knowledge (these are largely team and partner related). These later factors will become obvious in the discussions on patents and competitive advantage that appear in the Isaacson book.

There is extensive discussion in the Isaacson book on the topic of “the race to invent first” between the Doudna (UC Berkeley) and Zhang (MIT/Harvard/Broad Institute) groups that are still being resolved. While Doudna was beaten in the “first to file race” by a few weeks by Zhang and Church, Zhang contends in the book that was not obvious that getting the “trifecta” to work in human cells (that lab had extensive expertise in working with human cells). Doudna contends that it was obvious to her (one skilled in the art), but the expertise in her lab at the time was not primarily in studies associated with human cells. There were extensive discussions among all of the parties, who clearly recognized the fact that for successful commercialization, unification and consolidation of the UC Berkeley, Broad/Harvard patents, it would be strategically necessary to exploit the full potential of the “CRISPR platform”. And we add parenthetically how other industries have handled this issue with broad, cross licensing; e. g. with computer chips, or with non-exclusive licensing. In the post Bayh-Dole era (where universities were granted ownership of government-funded research – licensing proceeds are to be shared with the inventors). Apparently, human behavior got in the way, and Doudna had qualms – “I just did not get a good feeling from Zhang” (there is our previous reference to “trust” as an essential element of an effective team). And, according to Isaacson, the feeling was mutual. While the university made the decision, the principal inventor decided to give an exclusive license of the Berkeley technology to Caribou a startup company that she started with Rachel Haurwitz at the helm. While Haurwitz did have some background in business, Zhang argued that “someone more “seasoned” would be required to move the technology forward. (We would agree that advancing the technology in parallel with advancing the business model is essential for ultimate success; c. f. our discussion on teams at the end

of this article). Doudna did quote in the Isaacson book that “if I had to do it over again, I would have licensed it differently”. “When you have a platform technology like CRISPR, it is probably a better idea to license in a way that offers it as broadly as possible”; since, neither she, nor the university had experience with licensing a broad, transformative technology. There is a telling quote from Doudna in the Isaacson book. “A couple of people that I trusted at Berkeley were telling me to definitely work with the people in Boston, since they were better at business”.

Several other points regarding patenting and IP are worth noting. For those not familiar with licensing of pivotal patents, the Isaacson book points out that Stanford “made \$25 million in 25 years for non-exclusive licensing of the Cohen and Boyer patents for recombinant DNA”. Indeed, the Association of University Technology Managers (AUTM) was developed to establish and share best practices amongst universities so that the benefits of commercializing government sponsored research and the Bayh Dole Act could be optimized.

One further point relates to a fact that reflects on the astuteness of the Broad Institute with regard to the commercial implications of these fundamental, foundational patents. They chose to take advantage of a provision in patent law to request an expedited review. Isaacson states that “it did not occur to them (at Berkeley) to spend a little extra (money) to have the application expedited”. “The US PTO granted the Zhang patent on April 15, 2015, even while the Doudna patent was still being considered”. Under US law, when this situation exists, the person whose application is still under review has a right to file for an interference hearing. These battle line were initiated in April 2015, and continued thru lengthy and expensive legal hearings. Isaacson correctly points out that it might have been more expeditious for the Berkeley and Broad teams to work out an arrangement to cross license their respective patents and to share the proceeds. Also keep in mind that in 2013, the USPTO adopted a first to file provision. Isaacson provides a very succinct analogy taken from the cross-licensing agreement between Texas Instruments and Intel, and ends with a quote “don’t fight over divvying up the proceeds until you finish robbing the stagecoach”.

And last, but not least, there are significant **ethical issues** involved, and they too go unresolved. We anticipate that this debate will go on for years as commercialization of CRISPR proceeds. There are many who advise a cautious approach with a concern about the technology racing ahead of the bioethics legal issues and a full assessment of the long term consequences. Most of the first generation use of CRISPR Cas9 is targeted at diseases that edit some of the body (somatic) cells and make changes that are not inherited. This can be done by ex

vivo or in vivo modalities. In 2019, sickle cell disease was done with an ex vivo treatment in Nashville, under the auspices of CRISPR Therapeutics (that company affiliated with Emmanuelle Charpentier). In the book, Isaacson covers in detail why the ex vivo use of CRISPR is a perfect example for, in our words “a market entry point, for CRISPR”. And, it worked!

The next issue is a big one – cost. Since treatments are in excess of \$1M, can the healthcare system afford it? And this is a factor that impacts virtually all of the breakthrough, transformative technology biotechnology products. And, kudos to Doudna for the formation of the Innovative Genomics Institute with funding from the Gates Foundation and the NIH. Their first focus was on sickle cell disease. The Chinese have moved on to focus on cancer that is also a significant disease with high treatment costs for emerging technologies. CRISPR is also being used for diagnosis of cancer via a Doudna spinoff company, Mammoth Biosciences. And for treatment of congenital blindness via an in vivo treatment in clinical trials run by Editas (a Zhang et al company).

These early trials are promising, even with the cost issue looming. But, then we have already seen some of the longer-term issues emerge, including the “designer babies” episode in China in 2018 that has initiated ethical discussion that will continue to be debated going forward. As a current resident of Napa, CA, I was surprised to see in Isaacson’s book reference to an “Asilomar like” conference organized to discuss the then emerging field of recombinant DNA. This conference was organized by Doudna who invited 18 experts in the emerging field, to discuss the ethical implications of CRISPR – like creating designer/babies.

These will surely take a generation or two as the technology evolves, and the community learns and adapts to this truly transformative technology. We have highlighted some of these from the Isaacson book, but we also refer the interested reader to the following two recent book reviews of the Isaacson book that recently appeared in Foreign Policy and the New York Times.

FROM: FOREIGN POLICY ARTICLE BY MICHAEL HIRSH

<https://foreignpolicy.com/2021/04/02/what-is-it-to-be-human-anymore/>

In this Foreign Policy article, Michael Hirsh writes that “in the beginning, Doudna was frightened by the implications of what she had created, waking from a nightmare in which she dreamed she had met Adolf Hitler, who pressed her for answers about her technology”. “Have we created a toolbox for future Frankensteins?”

Hirsh then writes, “these may be the hardest ethical questions of our time, but they require a book more profound than Isaacson’s to address them. Will children, as they age feel that they are becoming obsolete?” Isaacson writes. “Fortunately, these are questions we can ask for amusement, but not for an answer. It will be up to our grandchildren to figure these out.”

“In the end, just what Doudna and her colleagues have let out of the lab remains to be seen, and the answers to all these questions might, as Isaacson (and we) says, await another generation or two. They certainly will require another book than this one, as impressive an accomplishment as it is”.

FROM: NYT INTERVIEW WITH EZRA KLEIN.

<https://www.nytimes.com/2021/04/02/podcasts/ezra-klein-podcast-walter-isaacson-transcript.html?smid=em-share>

This very well done and thoughtful interview, and goes well beyond the scope of this article. We highly recommend it for our audience, and include a few key quotes as excerpts below:

EZRA KLEIN

“So, it sounds to me there’s almost a ladder of programming complexity here. There’s, as you say, a set of conditions that we understand. There is a mistake in the code, and we can look at it. We can look at normal code. We can look at code that has this error in it, and then you say, OK, we’re going to just change that little mistake”.

“Then there are things where we pretty well understand how it works, like, say, muscle mass. We know there are certain things we can turn on and off because we’ve watched it happen in people. Then there are things we know people currently have like bipolar disorder or schizophrenia or high IQ, but we don’t really know how it works”.

“And then I assume there are things that people don’t currently have. You bring this up in the book. Like one can imagine in the future us understanding how to give people capabilities they don’t currently have through genomic editing. But because we can’t currently look at people and see that, we don’t know how to do that, that coding. Is that a reasonable way of framing the ladder?”

WALTER ISAACSON

“Absolutely, and the interesting thing about the ladder is we could create new things for human capabilities, maybe even to hear different frequencies or be able to see colors that are off the normal visible spectrum. But the important thing you put your finger on is we say it’s not in the wild. In other words, nobody really has it. And so it’s far safer to edit the human genome to create a genome that already exists in other people in the wild form. But if you’re going to edit something that’s never existed before, I think we’ve got a few decades before we’re going to try to cross that line”.

EZRA KLEIN

“So, as you gesture towards, we’ve had the capacity to do some level of genetic editing or changing for some decades now. What did CRISPR add to our capabilities here? What made CRISPR different?”

WALTER ISAACSON

“What made CRISPR different is it’s not just recombining DNA or even using the old, clunky tools we used to have that could try to cut DNA and make an edit known as ZFNs or TALENs and things like that. What made it different is that it’s easily reprogrammed. You can say, OK, I want to do it right here at this sequence. And so you have this guide RNA, and the guide RNA can just be much more precise, and it can be done much more quickly”.

EZRA KLEIN

“Let’s say you had unlimited money and few ethical strictures. What could CRISPR actually probably do right now?”

WALTER ISAACSON

“Right now, it’s best at single-gene mutations. But if you really had a doctor in a clinic somewhere with no ethical guidelines, certainly there are things that clearly predispose height, for example, or muscle mass, as we talked about with our friend the biohacker. That’s just a myostatin regulator”.

“And certainly, by the way, if we can make cells so that they aren’t sickled in the blood and carry more oxygen, that might make muscle mass or blood or endurance much better. And then obviously, the type of diseases we

have — Tay Sachs, muscular dystrophy — you’d edit those out of your children if you wanted to”.

SO, WHAT’S COMING NEXT FROM THE DOUDNA LAB?

As a result of the lack of trust between the early, academic pioneers who developed CRISPR and the patents that came out of that, Isaacson discusses the split that occurred when Doudna lost trust and respect for what she refers to as the “gang of men who dominated the biotech and finance world in Boston”. She resigned from Editas and went on to found other companies with those whom she respected and trusted. “They were people who do good science, but are more importantly, honorable straight-shooters”. As a result, the CRISPR – Cas 9 pioneers ended up in three companies (CRISPR Therapeutics, Editas Medicine, and Intellia Therapeutics).

These have been highlighted in a previous section of this issue of JCB. Herein we highlight that the Doudna team has three additional early stage companies in development pursuing commercialization of the CRISPR technology. They have all closed recent rounds of financing and also entered into key partnerships. They are **Scribe Therapeutics, Caribou, Mammoth BioSciences, and Intellia Therapeutics**.

San Francisco-based **Scribe Therapeutics** is using the CRISPR technology with its next-generation platform for gene editing. The company recently announced a collaboration with Biogen to develop CRISPR-based genetic medicines for neurological diseases, including Amyotrophic Lateral Sclerosis (ALS). The company also recently closed a \$20M funding round.

Caribou Biosciences, Inc., a leading clinical-stage CRISPR genome editing biotechnology company, announced today the successful completion of an oversubscribed \$115 million Series C financing. Proceeds from the financing will be used to further develop the Company’s proprietary, next-generation CRISPR technology platform and to advance the Company’s pipeline of wholly-owned allogeneic immune cell therapies for oncology with best-in-class potential. Business Wire reported that Caribou has developed a next-generation CRISPR technology platform with substantial advantages in genome editing specificity and efficiency. The Company’s technology platform has fueled a pipeline of allogeneic cell therapies for oncology with best-in-class potential including enhanced persistence of its off-the-shelf cell therapies that is expected to drive the clinical durability of effect in multiple malignancies. Rachel Haurwitz,

former Doudna protégé is President and CEO of the company.

Mammoth Biosciences, a company that uses gene-editing technology Crispr for disease testing, said Thursday that it had raised \$45 million in Series B funding to expand into treatments. The round, led by Decheng Capital and including new investor Verily, brings total funding to over \$70 million. <https://www.forbes.com/sites/leahrosenbaum/2020/01/30/mammoth-biosciences-raises-45-million-to-create-crispr-diagnostic-tests-and-its-tech-is-already-being-used-against-coronavirus/?sh=6be915cf56c9>

The South San Francisco-based company, founded in 2017 by *Forbes Under 30* honorees Trevor Martin, Janice Chen, Lucas Harrington and CRISPR pioneer Jennifer Doudna, uses CRISPR as a genetic “search engine” to find disease markers and alert researchers of their presence. They’ve already partnered with others, such as gene-editing company Horizon Discovery and a UC San Francisco researcher who is creating a rapid diagnostic test to identify people infected with the new coronavirus.

“The company has been one of the most prolific innovators in the overall CRISPR ecosystem,” says Ursheet Parikh, an investor at the Mayfield Fund, which also participated in the round. As noted, the technology is already in use for Covid-19 applications. Mammoth has also moved into new lab space on the South San Francisco campus of Verily, Alphabet’s life sciences company.

Intellia Therapeutics is a biotechnology company developing biopharmaceuticals using a CRISPR gene-editing system invented by Jennifer Doudna and Virginijus Sikšnys. The company has partnerships with Novartis and Regeneron. Wikipedia.

In closing, it is very clear that CRISPR is being commercialized rapidly in response to ongoing need in the community. Additionally, the impact of Doudna’s work is not only advancing the science and technology, but is rapidly leaving the lab to be used for improving the lives and health of patients worldwide.

ADDENDUM – SOME PERTINENT, CONCLUDING COMMENTS ON THE IMPORTANCE OF HIGH –PERFORMANCE TEAMS FOR FOUNDING, BUILDING, AND GROWING SUCCESSFUL BIOTECHNOLOGY COMPANIES

Building teams for advancement of the science and technology is essential for any academic scientist who has

aspirations to create new entrepreneur. However, when it is apparent that there is commercial potential, especially of a transformative magnitude any spinoff company has to be started as an independent organization and one with a team formed to advance that technology to several important downstream milestones. While this topic is discussed in the Isaacson book, we believe that it is important to include this Addendum to discuss the topic further.

Our top 10 takeaways on building high-performance teams:

1. While the startup team is small (perhaps two or three people), it needs to include credible technology and business expertise along with a few key advisors and coaches from day one.
2. Build diversity into the team from day one.
3. Note that teams include: Founders with technology and business experience; Advisors/coaches for technology, business, and legal (IP, reimbursement); Directors who bring independent perspective, and also who have fiduciary responsibility.
4. What is required from the team includes: access to people, capital/investors, partners, legal counsel for IP and transactions, experienced advisors/mentors/coaches. (Note that a great team attracts great people, partners, etc.)
5. Team members require competence, commitment, and a common goal or vision – look for skill, will, and fit.
6. Strive to add value and reduce risk incrementally by building and scaling a team across the product life cycle from startup; to development stage; to and through clinical stage; to market entry and growth.
7. As you go through these stages evolve your team thru the “evolution and revolution” that could occur at each transition.
8. Remember that “a startup is a “temporary organization” in search of a scalable, repeatable, profitable business model” – think lean startup.
9. Adopt the Innovator’s DNA perspective of questioning, observing, networking, experimenting/testing hypotheses, and use recognize the diverse teams are better suited to use associative thinking that provides ‘out of the box’ perspective from different disciplines and backgrounds.
10. Failure does occur, but the most likely failure is caused by lack of performance of the team, followed by market/competitive factors, and then the technology itself does is bypassed

by alternatives with alternative performance metrics.

We refer the interested reader to several of our previous publications for a more detailed discussion of the fundamentals of building and leading teams.

1. Boni, Arthur A., Laurie Weingart, and Gergana Todorova, Chapter 7 in “Building, Managing, and Motivating Great Teams”, in “Biotechnology Entrepreneurship, Starting, Managing, and Leading Biotech Companies”, Academic Press (2020), 2nd Edition (Craig Shimasaki).
2. Boni, Arthur A. “Leading and Managing Teams in Entrepreneurial Organizations, an Experiential Perspective”, J. Commercial

Biotechnology, Vol. 24, No 4, pp 74–80, (2019).

3. Todorova, Gergana, “Building and Managing Great Teams: An Evidence-Based Approach, J. Commercial Biotechnology, Vol. 24, No. 4, pp 81–85 (2019).