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Riding the wave into a crisper future?

A Crack in Creation: The New Power to Control Evolution, Jennifer Doudna, Samuel Sternberg. Bodley Head, London (2017). 304 pp., Price £20 hardcover, ISBN: 9781847923813

CRISPR-Cas9 is a molecular tool that – even though still in its infancy – is already recognised as one of the biggest game-changers in the life sciences in recent decades. Often referred to as 'molecular scissors', the CRISPR-Cas9 system (or 'CRISPR' for short) can be used to cut the genomic DNA of virtually any living being in a highly precise manner. This allows researchers to remove whole chunks of genomic DNA, to insert new sequences that are normally not present or to re-write the existing code.

What makes CRISPR a revolutionary tool, however, is not so much what it can do – researchers have been able to edit genomic DNA for more than a decade using other molecular tools – but how it does it: CRISPR's success lies in its simplicity and ease of use. Because of its simplicity, the system enables researchers to perform experiments that were unthinkable only a few years ago. It is little surprise, then, that the technology has spread like wildfire through the world's laboratories (and the biomedical industry) in the five years since its inception in the laboratories of Jennifer Doudna and Emmanuelle Charpentier (Jinek et al., 2012).

'A Crack in Creation' – written by Doudna and her former graduate student Samuel Sternberg (but narrated exclusively in Doudna's voice) – tells the story of the CRISPR-Cas9 system from the perspective of one of its key developers. Apart from describing Doudna's own path into CRISPR research, the book also provides an introduction to the science behind the technology and the ethical and social issues it raises. Almost in passing, 'A Crack in Creation' also gives a helpful overview of the different uses to which the system has already been put, be it the creation of mushrooms that resist browning[1] or the modification of human T cells to turn them into weapons against particular types of cancer (Cyranoski, 2016).

The book has received contrasting reviews. The historian of science Nathaniel Comfort – writing in *Nature* – claims that the book presents a polished counter-narrative to the controversial 'Heroes of CRISPR' article by Eric Lander (more on this below) and that 'A Crack in Creation' simply aims to show that Doudna is the real hero of the CRISPR story (Comfort, 2017). Mathew Cobb, a professor of zoology at University of Manchester, calls the book a "guidebook to the CRISPR revolution" that is "required reading for every concerned citizen" (Cobb, 2017). Philip Kitcher thinks the book provides a "thoughtful and sensitive" discussion of the ethical issues the technology raises (Kitcher, 2017). Henry Greely, a professor of law at Stanford University, agrees with Cobb's assessment but disagrees with Kitcher, as he thinks that the book does not provide a deep analysis of the ethical issues surrounding CRISPR (Greely, 2017).

Here I want to pick up an aspect of the book that so far has not been addressed by its reviewers, namely the wave metaphor that Doudna and Sternberg use to characterise the technology and its development. This metaphor might seem innocuous at first but it is fundamental to understanding the book and the story it presents.

1. The power of CRISPR

There is something very powerful but also over-powering about CRISPR. Once unleashed in 2012, the technology has kept on moving and this forward movement is at once full of promise but also potential danger. Altering an organism's DNA has great potential for both research and clinical uses. But it can also have unintended consequences both for the individual modified and for future generations (if the modification happens in germline cells, i.e. those cells whose genetic material is passed on to an organism's offspring). Equally problematic are the *intended* consequences, as ideas such as 'designer babies' and human enhancement are on the table again.

Doudna is aware of the issues the new technology raises and she and her co-author discuss them at length in the second part of the book. Their stance on the ethics of CRISPR is largely undecided. Halfway through the book they state (in Doudna's voice): "I pose these questions [about what to do with CRISPR] because I, too, am searching for answers. The stakes are high enough to make these some of the most pressing scientific issues facing us today. It is vital that we all weigh in on how this new biotechnology should be used in the plant and animal worlds" (Doudna & Sternberg, 2017, p. 153).

The approach the authors choose to deal with the questions and the uncertainty that surround CRISPR is to be open and inclusive: they think that the question of how the technology should be used is not something that scientists can or should answer on their own; it has to be addressed by a more inclusive group that also includes members of the public and other stakeholders. In this they follow researchers such as Sheila Jasanoff or Daniel Sarewitz who pointed out the need for an inclusive deliberation on the uses of the new technology (Jasanoff, Hurlbut, & Saha, 2015; Sarewitz, 2015).

This openness to involving the public is certainly a good thing and something that is still not common within the scientific community. But

[1] https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-321-01_air_inquiry.pdf.

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Doudna and Sternberg's approach to public involvement is also limited as they seem to have a very narrow role for the public in mind: in their framework there is no deeper role the public could play, for instance by affecting the ongoing development of the technology. All that is open to lay people is to join the discussion on how to use the existing technology. This means that non-scientists are only brought into the fold once the scene has been set.[2] Furthermore, the scientists themselves seem to have a very limited set of responsibilities when it comes to the complex issues the technology raises: the main role Doudna and Sternberg see for scientists is to inform the public about the technology and its workings. This is a one-way communication scheme that authors such as Sarewitz already criticised more than 20 years ago (Sarewitz, 1996).

Whether such a narrow view of the role of the public and scientists is warranted is a complex question that cannot be dealt with in the context of this book review and which other authors have written about at length. But what is interesting here is that even if we buy into the one-way communication scheme promoted by Doudna and Sternberg the book itself does not live up to its own recommendations. As a number of reviewers of the book already pointed out, several key developments in the CRISPR field are deliberately left out of the narrative presented (Comfort, 2017; Greely, 2017). And as I will show in the next two sections, the wave metaphor the authors mobilise has a key role to play in all of this.

2. Fighting over patents and Nobel prices

When Doudna and Charpentier published their findings on CRISPR-Cas9 in 2012 their paper was quickly followed by two separate publications from the laboratories of Feng Zhang at the Broad Institute (Cong et al., 2013) and George Church at Harvard (Mali et al., 2013). Both of these papers showed how the CRISPR-Cas9 system has to be modified so it can be used to edit the genomes of eukaryotic cells (which, importantly, include human cells). The original publication by Doudna and Charpentier did not look at (or directly comment on) this possibility as it focused exclusively on how to use CRISPR on isolated DNA molecules in a test tube. The Doudna laboratory eventually followed up their earlier work with a paper showing that CRISPR-Cas9 can also work in eukaryotic cells (Jinek et al., 2013), but this paper was published in late January 2013, a few weeks after the publications by the Zhang and the Church laboratories.

All these details regarding publication dates matter because, as is so often the case these days, the researchers filed patent applications for their developments, a practise that was made possible in the US in 1980 through the Bayh-Dole act. Under this act, scientists and universities are allowed to hold patents and, most importantly, grant exclusive licenses on innovations they made through publicly-funded research.

The story of how the CRISPR patents were awarded is complicated but in the end the Broad Institute – closely affiliated with MIT and Harvard – ended up getting the US patent for the use of CRISPR in eukaryotic cells (Ledford, 2017; Reardon, 2016). This was an important decision as it means that companies who want to use the technology in humans will have to pay significant licensing fees to the patent holder.

The Berkeley team (which includes the University of Vienna, where Charpentier was based at the time) contested this decision, claiming that the patents of the Broad Institute interfered with their own patent application. But in February 2017 the US Patent and Trademark office sided with the Broad Institute and upheld their patents. Inevitably, given how much money is at stake, the UCB has appealed this decision. The battle therefore continues.

The idea behind the Bayh-Dole act, which has been controversial since its inception (Boettiger & Bennett, 2006), was to enable and encourage a more efficient technology transfer out of universities and into industry. This now often happens through so-called ‘surrogate licensing’, a practice that has also been hugely popular in the case of CRISPR (Contreras & Sherkow, 2017).

In the surrogate licensing model the patent-holding universities grant broad exclusive licenses to surrogate companies that then act as de-facto patent holder and that grant individual licenses to other companies or research institutions. The university and the investigators involved usually hold significant equity in these companies and profit from interest and royalties. Importantly, in the case of CRISPR all of this licensing and sub-licensing activity has started before the patent situation has been resolved. UC Berkeley, for instance, has granted an exclusive license to its surrogate Caribou Biosciences, which has sub-licensed the technology to other companies such as DuPont or Novartis (Contreras & Sherkow, 2017). This matters because all of these arrangements intimately shape where the development of CRISPR is going, i.e. what the technology becomes and who is in charge of it. What was initially a largely publicly-funded enterprise is now in large part steered by companies and their commercial interests.

What is interesting about all of this in the context of ‘A Crack in Creation’ is that the fierce patent dispute and the complex licensing landscape don't feature in the book – the dispute, for instance, is only briefly mentioned once, more as an aside than anything else. This led Greely to suspect that lawyers put shackles on Doudna and Sternberg and kept them from telling the whole story of CRISPR-Cas9 (Greely, 2017).

Whether or not that is the case, what matters here is that key factors that shape the technology and its future development are simply not present and the naïve reader (i.e. someone who has not already followed the development of the field) will not be informed about these aspects of the field by reading ‘A Crack in Creation’.

There is also a second elephant in the room, namely the looming Nobel Prize. It is clear to everyone in the field that a development of such magnitude as the CRISPR-Cas9 system will eventually earn someone the prize. The big question, of course, is whom it should be awarded to.

The debate about this issue has been set on fire by Eric Lander's article ‘The Heroes of CRISPR’ (Lander, 2016). In this article, published in the prestigious journal *Cell*, Lander takes a look at the ecosystem of researchers that was involved in the discovery and development of the CRISPR system (something that Doudna and Sternberg also do in their book). He emphasises in particular how researchers from unexpected and often overlooked areas of research (be it small research groups from lesser-known universities or corporate researchers at dairy companies) have played crucial roles in bringing CRISPR-Cas9 into existence.

Surely, giving credit to all those involved is what you would expect of honest research. But Lander's article also had a certain edge to it, as it did not put much emphasis on Doudna and Charpentier's work and put a much larger emphasis on Zhang's. Such a shift in emphasis might not be too dramatic in itself, but it becomes explosive once we take into account that Lander is the head of the Broad Institute, where Zhang is employed; clearly, there is a conflict of interest here but nowhere in the article is this discussed.

The research community quickly picked up on this and after a short Twitterstorm, a series of blog articles attacked Lander (and *Cell*) for what was seen as outlandish behaviour.[3] The charge was that he was trying to downplay Doudna and Charpentier's achievements whilst propping up Zhang's role in an attempt to lobby for a potential Nobel Prize for an employee of his own research institute. Interestingly, in ‘A Crack in Creation’ none of these battles are mentioned. The Lander article and the controversy that surrounded it are completely ignored. This might be surprising given how

[2] The idea of ‘upstream engagement’ of the public immediately comes to mind here, see for instance (Willis & Wilsdon, 2004) but also (Wynne, 2006) or (Tait, 2009).

[3] See for instance here http://www.michaeleisen.org/blog/?p=1825 or here https://jezebel.com/how-one-man-tried-to-write-women-out-of-crispr-the-big-1753996281.