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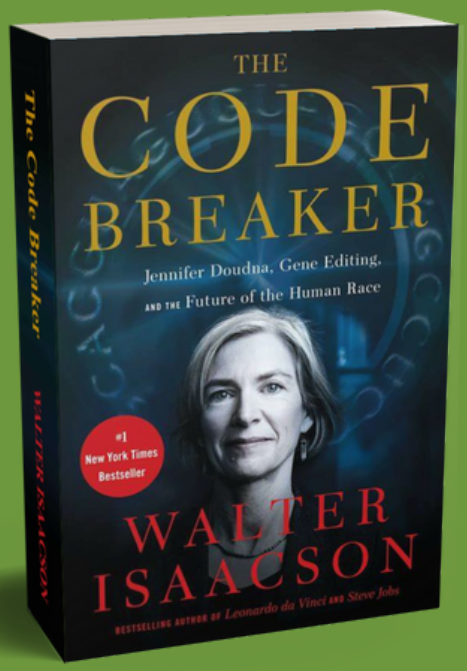
JENNIFER DOUDNA, GENE EDITING AND THE FUTURE OF HUMANITY

BY WALTER ISAACSON



In *The Innovators*, Walter Isaacson described the birth of the computer and the advent of the IT age. Now he walks us through the fascinating and somewhat scary landscape of biotechnology and genetic engineering. He does so in his fluid style, mixing accessible pedagogical explanations, riveting stories about individuals and events, surprising tales of selfless cooperation and bitter rivalry, and eye-opening glimpses behind the scenes of basic and applied research. It all makes for a mesmerizing trip into the future of mankind. Over the last hundred years humanity has experienced three major revolutions (the atom, the bit and now the gene). Each of these revolutions has raised major ethical questions; while they have the potential of massively improving our lives, they also carry the risk of escaping all controls and destroying humanity as we know it. As Stuart Russell puts in in his remarkable book about Artificial intelligence (*Human Compatible AI and the Problem of Control*), the question to ask is "*what if we succeed?*" Success could be the biggest event in human history and perhaps the last event in human history. The moral questions therefore loom large in Isaacson's book. Should everything which is feasible be done in reality? Is it ethical to 'play God' and set humanity on a path towards a brave new world (see Aldous Huxley's novel of 1932)? Is it ethical not to use available technology that can reduce the suffering of many people? Where is the dividing line? How to ensure both freedom of research and proper regulation? Who should decide in the end what is acceptable or not? The State and public authorities? The researchers, the citizens? I like the fact that Isaacson does not limit himself to theoretical considerations but looks at very concrete cases where the various questions arise. Once you do that, you quickly understand that there are no black and white answers nor simple solutions.

The book is structured in nine parts. The first three parts form one block in that they chart the course towards gene editing. It is the part I appreciated most because it gives you a (very) basic understanding of genetic research and at the same time it reads like a thriller describing the giddy and breathless race towards developing the tools needed to 'play God'. The next five parts are a bit of a mixed bag and lack the unity and purpose of the first overall block. I would have preferred a shorter and more coherent structure focusing on the moral issues, which are the dominant part here and crop up in the various parts. I am not sure that the

author's initiation into gene editing is indispensable here. Nor is the story of the descent into racist delirium of one of the key actors in the discovery of DNA (James Watson). The last part is about the Coronavirus crisis and the use of the new genetic technologies to fight the virus. It is self-containing and riveting. I will follow my structure in 3 parts below.

1) THE RACE TOWARDS GENE EDITING

The origins of life

Darwin and Mendel are two major precursors in the development of genetics. In the 1850s, Darwin publishes *The Origin of Species* where he exposes his theory of evolution and natural selection. Mendel a few years later (1866) discovers via the breeding of peas the role of genes (entities inside of living organisms that carry the code of heredity). In the 1940s, scientists discover that genes are carried by nucleic acids (the workhorses of heredity) in the shape of DNA (*deoxyribonucleic acid*); DNA is the repository of genetic information. Later, it appears that there is a less celebrated sibling of DNA in the shape of RNA (*ribonucleic acid*): a molecule that in a cell copy some of the instructions coded by the DNA and builds proteins. The structure of DNA and the way it codes genetic information then becomes the key focus of researchers such as James Watson and Francis Crick. Watson studies viruses (tiny packets of genetic material that are essentially lifeless but that, when they invade a living cell, hijack its machinery, and multiply themselves. The easiest to study are the viruses that attack bacteria (*bacteriophages or phages*). Together with Crick he studies the structure of DNA, using the tool of crystallography, with the assistance of Rosalind Franklin, an English biochemist and an expert in crystallography and x-ray diffraction. In 1953, they discover the double helix structure of DNA, with four bases, adenine (A) and thymine (T) that bond, and guanine (G) and cytosine (C) that also bond. They understand that the shape and structure of a chemical molecule determines what biological function it will play. Chemistry blends into biology. They do not yet know how this happens, but they do understand that the specific pairing of A,T,G,C suggests a possible copying mechanism for genetic material. After the discovery in the 1950s that all information can be encoded in binary digits (bits) opens the way for the digital revolution, we now have another major discovery opening the way for genetic coding: instructions for every cell in every form of life are encoded by the four-letter sequences of DNA. Watson, Crick, and Wilkins (not Franklin who had died meanwhile) receive the Nobel prize in 1962.

CRISPR

An obscure researcher from Alicante, Francisco Mojica, discovers repeated DNA segments identical to each other and wonders what biological function this can have. He gives it the name of CRISPR (*clustered regularly interspersed short palindromic repeats*). They are flanked by genes that encode directions for making an enzyme. (*Cas* enzymes: CRISPR associated enzymes; enzymes are a type of proteins that act as catalysts for chemical reactions in the cells of living organisms; Cas can among others cut and splice DNA and RNA!). Between the repeated CRISPR segments there are spacer segments that match sequences that are in viruses attacking E. coli or other bacteria. It turns out that bacteria have an immune system that remembers past attacks by viruses. Bacteria with CRISPR spacer segments are immune to viruses with the same sequences. When attacked, they integrate some of the attacking virus's DNA, with the help of CRISPR associated enzymes! When she learns about this, Doudna and her team start examining how all of this happens. In this context, she concentrates on the roles of RNA, a 'star molecule' that catalyzes, folds into 3-D, structures and can carry information. As said above, the enzymes produced by the genes adjacent to the CRISPR sequences in a bacteria's DNR enable the system to cut and paste memories of viruses; they also create short segments of RNA called CRISPR RNA (*crRNA*), which can guide a scissors-like enzyme to a dangerous virus and cut up its genetic material. They discover that Cas1 has a distinct fold; it is a mechanism bacteria use to cleave a snippet of DNA from invading viruses and incorporate them into the CRISPR array. Doudna receives help form a Danish food company (DANISCO) and its fermentation specialists (Barrangou and Horvath); they have historical records of the DNA sequences of bacteria they have used for years in yoghurt and other foodstuffs. Doudna and the team then find out that they can themselves engineer immunity by devising and adding their own spacers. This gives a new boost to research and opens the way towards possible gene editing. At this stage enters Emmanuelle Charpentier who works on Cas9, the most promising of the CRISPR associated enzymes. To sum up: we now have three components at work:

- Cas9 enzymes,
- crRNAs (guiding Cas9 to attack viruses),
- tracerRNAs (facilitate the making of the crRNAs).

One question remains unclear: what happens to the tracerRNA when its work is done. In fact, it stays around and has a role in cleavage. Without the tracerRNA, the crRNA guide does not bind to the

Cas9 enzyme. The tracerRNA also serves as a handle to latch on to the invading virus so that the crRNA can target the right spot for the Cas9 enzyme to chop up the virus. This means that the crRNA can be modified to target any DNA sequence you may want to cut; it is programmable.

All of this opens the way towards a gene editing tool and the rewriting of the code of life. The team manages to make things even easier when it succeeds in engineering a single RNA tool molecule, combining the guide information on one end and the binding handle on the other (Single guide RNA or *sgRNA* = fusion of crRNA and tracerRNA).

Gene Editing

CRISPR, compared to the previous protein-based approach, is a huge step towards gene editing and engineering human genes. After the pathbreaking 2012 article by Doudna and Charpentier (which in 2020 will give them the Nobel prize), the race starts between Berkeley and the MIT/Harvard (Feng Zhang and George Church) to solve the problem of applying CRISPR to the editing of human genes. Feng Zhan engineers a longer version of the sgGNA, which makes it more efficient to work in human cells. There arises a controversy around this: is it, as Zhang claims, a fundamental new breakthrough, or is it an obvious further development. This leads to a protracted and bitter fight about patents between the two camps. The pioneers of CRISPR-Cas9 engineering end up in three different and competing companies: CRISPR Therapeutics (Charpentier and Novak)/ EDITAS Medicine (Zhang and Church (and, initially, Doudna who then dropped out and created her own company)/ INTELLIA Therapeutics (Doudna, Barragou and others).

2) THE MORAL ISSUES

As indicated above, the next 5 few parts are a bit all over the place and mix various themes. I focus only on the moral issues that crop all in most of the parts and which would have been better treated as one coherent chapter.

The issue of human invention getting out of control is an old 19th century theme; just remember Mary Shelley's *Frankenstein* (1818) or H.G. Wells' *The Time Machine* (1895), and a few decades later, Aldous Huxley's *Brave New World* (1932). In the debate around the genetic revolution starting in the 1960s, enthusiasts (or utopians?) seeing the potential good that can come out of this are opposed by bio-conservatives who warn against the calamitous consequences that could arise from tinkering with genes. 'Is it moral to forsake the possibility of eradicating crippling diseases like Huntington's disease or sickle cell disease or blindness or AIDS?', ask the former. Is it ethically responsible to try and 'play God without knowing what the long term effects will be in terms of the nature of humankind or in generating new inequalities?', reply to the latter. Most of the involved researchers are looking for a middle ground. Under the leadership of the American researchers, they call conferences and work out agreed statements and guidelines trying to avoid blocking all further research while setting safeguards and red lines. Somatic editing is not controversial, but there is a lot of resistance to germ-line gene editing changing the human DNA for all future descendants. That is why the editing of the HIV virus in human embryos before implanting them into the mother's womb done by a young and ambitious Chinese scientist (He Jiankui) in 2018 is seen as an unacceptable transgression, even though some voices claim that eradicating for good the HIV virus would not be such a bad idea. Overall, genetic editing for treatment is seen as legitimate, while efforts at enhancing humans are much more problematic. It is too early to say how things will develop. Some things that now seem beyond limits may well be acceptable in ten or twenty years.

One of the key questions that arises is *who* decides in the end what is licit or illicit. The Chinese way of having an all-powerful State (and a very autocratic one to boot) pulling all the strings is certainly not very appealing from our European perspective, the less so since we have seen in the AI debate how the Chinese State misuses some of its achievements for increasing control on the individuals. At the same time, there is a fear that just relying on the ethical behaviour of researchers, and on codes of behaviour, will not be enough in view of the magnitude of the potential effects. Isn't there a risk that if the American model wins the day and dictates developments, that the balance will tilt too far in the direction of the individual choice (often based on personal ambition and greed), to the detriment of society, with huge risks of creating an even worse form of inequality than the one we now know? It seems to me that the EU maybe has a major role to play here in helping to find the right balance in setting up adequate regulation and framing the debate in the interest of society. This is after all what the EU is already trying to do in the digital area including the development of AI.

3) GENETICS AND THE CORONAVIRUS

The last part of the book looks at the coronavirus pandemic and the use of the new genetic instruments. It is self-contained and highly

interesting. The good news is that in this instance the old habits of fighting aver status and patents and money are cast out of the window and that researchers particularly in the West cooperate in developing tests and vaccines.

Testing

Developing tests was of key importance. In the US, the Trump administration was very slow off the start and bungled the response. It was only when universities and research institutes just took matters into their hands that the situation improved, and the administration rallied around private initiative. It soon appeared that the most promising testing was linked to using the CRISPR technology to directly detect the RNA of the virus and target it. This was more efficient and quicker than the traditional method of amplifying the genetic material of the virus by swabs using a PCR reaction (polymerase chain reaction). Antigen tests detecting the presence of proteins existing on the surface of a virus were also used; they work well when the patient has become highly infectious to others but not before.

Vaccines

The traditional vaccine consists of de-activated components of the targeted virus that are injected to stimulate a person's immune system. Pfizer and BioNTech as well as Moderna developed a genetic RNA-based vaccine (injection of snippets of RNA to make the cells produce on their own components of the virus). (There were also DNA based vaccines). This certainly is a breakthrough with wide-ranging consequences.

4) CONCLUDING WORDS

All in all, a fascinating read, and a thought-provoking narrative. Decision-makers across the globe and their advisors should read books of this type. It is vital to have a minimal knowledge of scientific progress and the questions it raises. As the EU gears up for a new institutional cycle starting in 2024, this is a good moment to launch an informed debate about issues such as AI and genetics and other major advances in research and development.

I will conclude with a quote by Carl Sagan dating back to 1995 (in *The Demon-haunted World: Science as a Candle in the Dark*) and which should make us think:

"Science is more than a body of knowledge. It is a way of thinking. I have a foreboding of an America in my children's or grandchildren's time when the United States as a service and information economy, when nearly all the key manufacturing industries have slipped away to other countries, when awesome technological powers are in the hands of a very few, and no one representing the public interest can even grasp the issues. When the people have lost the ability to set their own agendas or knowledgeably question those in authority, when, clutching our crystals and nervously consulting our horoscopes, our critical faculties in decline, unable to distinguish between what feels good and what's true, we slide, almost without noticing, back into superstition and darkness."

Jim Cloos, TEPSA Secretary-General