The Ethical Debate

Genome editing scrutinised around the globe

There will always be ethical debate when scientific researchers start tinkering with genes and human embryos, even if the intention is to treat or even eradicate certain diseases. Human embryonic stem cell research and genetic engineering practices such as mitochondrial DNA transfer have been in the firing line for a while now, and indeed they are still the subject of much discussion. At the moment, however, promising new genome editing techniques that may hold the key to treating diseases ranging from cystic fibrosis to cancer seem to be the subject of the most intense scrutiny.

The Hinxton Group, an international consortium of researchers, bioethicists and policy experts interested in ethical and well-regulated science, released a paper in September 2015 that bears witness to this.[1] Though it notes that the ethical wrangling is nothing new – it happens every time there is an incremental step towards the ability to create germline changes in the human genome – the context has changed because the science has advanced dramatically and it encompasses more people from varying cultures and regulatory environments.

This has led to many conversations taking place simultaneously around the world. As such, the group aims to inform ongoing debates and provide guidance to decision-makers on the use of these technologies in humans, particularly their use to intervene in the human germline. Before going into more detail about the Hinxton Group's paper and other stakeholders' views, a brief overview of the technology is necessary.

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>
> *Nessan Bermingham*

The technology in a nutshell

Genome editing is a type of genetic engineering that has been likened to a pair of 'molecular scissors' because it is a tool that makes it possible to insert, replace or remove DNA from a genome. For example, a patient's immune cells could be 'edited' to make him/her resistant to viruses such as HIV. The technology has been around for years but the most recent methods are extremely precise, inexpensive, relatively easy and very efficient. They could lead to therapeutic indications that have previously been unachievable with traditional gene therapy, gene knock-down or other genome modification techniques. In other words, they have the potential to transform modern medicine.

The newer approaches that have drawn the most attention are zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and clustered regularly interspaced short palindromic repeats (CRISPRs). They work by guiding a DNA-cutting enzyme (the Fok1 nuclease for the first two and Cas9 for the third) to specific DNA sequences. While ZFs and TALEs are DNA-binding proteins, CRISPR methods make use of RNA.

All three approaches rely on the processes of DNA repair that occur naturally within cells, but the CRISPR/Cas9 system is in a different league in terms of the potential for clinical application. It is "so much simpler and easier because it makes use of an RNA, which is then translated into a protein. RNAs can be made complimentary to a DNA sequence and they are able to interact with that DNA. So the CRISPR/Cas9 mechanism relies on what we refer to as a 'guide RNA' to find the right DNA you want to alter", explained Robin Lovell-Badge, head of the Division of Stem Cell Biology and Developmental Genetics at the Francis Crick Institute in London. The Cas9 protein cuts the DNA to generate a double-stranded break at the exact location in the genome where there are disease-causing mutations. In doing so, it harnesses the human body's own cellular repair process to replace the mutation with the correct gene sequence, insert a replacement gene or inactivate the gene.

The technology is considered to be so revolutionary that Jennifer Doudna and Emmanuelle Charpentier, the scientists credited with co-discovering CRISPR/Cas9, were awarded the prestigious $3 million Breakthrough Prize in Life Sciences for it. This is notwithstanding an ongoing patent dispute between the two scientists and Massachusetts Institute of Technology's Feng Zhang, who has been awarded the key patent for CRISPR/Cas9 by the US Patent and Trademark Office.[2]

Regardless of who is responsible for discovering CRISPR/Cas9, the three-year-old technology is already being used in drug discovery – but only with human somatic (i.e. non-germline) cells. For example, Intellia Therapeutics, founded by Dr Doudna, among others, is focusing on developing *ex vivo* and *in vivo* therapies for diseases of the liver and blood, and for the treatment of cancer. Another major player is Switzerland-based Crispr Therapeutics, which is exploring diseases that can be treated *ex vivo* (please see article on pages 8 and 9). Dr Charpentier is one of its founders. Editas Medicine, for which Dr Zhang is a scientific advisor as well as a founder, is looking into therapies based on both CRISPR/Cas9 and TALENs technologies. Dr Doudna is also an Editas founder.

The pace of science is advancing so rapidly that there is no telling whether CRISPR/Cas9 will remain the main focus of genome editing R&D going forward. In fact, as *MedNous* was going to press, a team of researchers (including Dr Zhang) at the Broad Institute of MIT and Harvard announced the identification of another CRISPR system, CRISPR/Cpf1, which

cuts DNA in a different manner than the Cas9 and, they say, is even more precise and flexible than CRISPR/Cas9.[3]

Somatic vs. germline cells

At the root of the current ethical debate is the distinction between genome editing in somatic cells and in germline cells. The latter requires the use of human embryos, and the scientific community and other stakeholders are divided over whether this type of research is morally acceptable. Of course there are fears about safety, too, particularly in light of reports that there are some clinics offering unproven stem cell-based treatments.

Governments and policymakers also have diverging views. The US government refuses to fund research using human embryos, but that still leaves the door open to privately-funded studies in the states that allow it. In May 2015, following the publication of a Chinese genome editing study in *Nature*, the White House issued a statement on the use of human embryos in this research, stating that it raised serious and urgent questions about the potential implications for clinical applications that could lead to genetically altered humans. In Europe, the laws governing human embryonic research vary from country to country. The rules are sketchy in other places such as China, Russia and South America.

The Hinxton Group paper mentions concerns that genome editing technologies could be used in reproductive contexts such as *in vitro* fertilisation (IVF) "long before there are data sufficient to support such use, and before the international community has had the opportunity to weigh the benefits and harms of moving forward". Given the unpredictable effect this could have on future generations, stakeholders including the Alliance for Regenerative Medicine (ARM) in the US are calling for a moratorium on genome editing using germline cells until a consensus is reached on how, and for what purposes, such research should be carried out – if at all.[4]

In addition to apprehension about safety, those opposed to the use of germline cells in research warn that it could be exploited for non-therapeutic genetic enhancement (e.g. creating 'designer' babies). They argue that there is a risk of public outcry, which could then hinder all types of genome editing and its potential to treat many human diseases including HIV/AIDS, haemophilia, sickle-cell anaemia and various forms of cancer.

In comments to *MedNous*, ARM's chief executive officer Edward Lanphier, who is also the chief executive officer of Sangamo BioSciences, acknowledged that there is "undoubtedly new information that can be generated from continued research in this field" but added that "effective methods to prevent human inherited diseases without the direct modification of DNA are available or are being developed, without crossing safety and ethical boundaries by making edits to the human germline".

In agreement is Intellia's chief executive officer, Nessan Bermingham, who emphasised to *MedNous* that this is the general consensus in the US. "There needs to be discussion to understand the technology's applications, and frankly, its limitations. One thing that people are forgetting is that there's much more opportunity to explore and learn about the technology," he said. The company published a clear position statement in August 2015 stating that it would not pursue germline editing until scientists and society agreed that it was safe and ethical to do so.

Others, including the Hinxton Group and Dr Lovell-Badge, who sits on its steering committee, believe that human genome editing has tremendous value as a tool to address fundamental questions of human and non-human animal biology, and their similarities and differences. To this end, the Hinxton paper says that "even if one opposes human genome editing for clinical reproductive purposes, there is important research to be done that does not serve that end". As such, it advises policymakers to "refrain from constraining scientific inquiry unless there is a substantial justification for doing so that reaches beyond disagreements based solely on divergent moral convictions".

Dr Lovell-Badge told *MedNous* that there was a "moral imperative to do those experiments", pointing to the Francis Crick Institute's recent application to the UK Human Fertilisation and Embryology Authority (HFEA) for a genome editing project that would be "critical to understanding more about early development of the human embryo".

In his opinion, a moratorium would not serve much purpose because countries that do not follow regulations anyway would not be deterred. He suggested that a moratorium "may also give a false sense of security that things are being regulated and not allowed when that's not the case. It's much better to have a really open dialogue about all of this. That would hopefully deter rogue clinics offering treatments that are unethical and unsafe, as occurs with the use of stem cells for regenerative medicine, and it would deter patients going to use such services."

Dr Lovell-Badge is on the planning committee for an international summit that is being organised by the US National Academy of Science and the National Academy of Medicine, which will provide a forum for global experts to discuss the scientific, ethical and governance issues associated with human genome editing research. The Chinese Academy of Sciences and the UK's Royal Society will also participate in the December 2015 meeting. In addition, an international multidisciplinary committee will conduct a comprehensive study of the scientific underpinnings and clinical, ethical, legal and social implications of human genome editing. It is expected to issue a report with findings and recommendations in 2016.

References:

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