ARRIGE
Association for Responsible Research and Innovation in Genome Editing
newsletter n°1

Editorial

Lluis Montoliu
ARRIGE President

Welcome to the ARRIGE Newsletter!

Dear members, colleagues and friends, welcome to this first issue of the ARRIGE newsletter. This is a new initiative to promote communication and exchange of ideas among members and other interested people, willing to share and discuss their thoughts about the responsible use, the different applications and the ethical issues of genome editing techniques.

We are currently living through difficult times. A simple coronavirus emerging from nature, SARS-CoV-2, has turned the world upside down and spread the COVID-19 disease, which has already killed hundreds of thousands of people. Most of us have been working from home since March and it is still unpredictable when we will return to work and recover a much desired normality. Consequently, this is a period to make use of all communication resources, devices and applications in order to remain in contact and united. We thought this would be an excellent opportunity to launch this newsletter and share reports, ideas and suggestions from all of you.

Genome editing was presented as the flagship of biotechnology. CRISPR genome editing tools have been presented as versatile and adaptable. Hence, society has the right to expect some reaction from the genome editing community regarding the current COVID-19 crisis. Two main applications have been reported, with CRISPR variants, to both diagnose and fight the coronavirus. The CRISPR techniques known as SHERLOCK and DETECTR, originating from Feng Zhang and Jennifer Doudna's laboratories, respectively, can be adapted to detect the RNA genome of coronaviruses in about or less than 1 hour, although about 10 times less sensitive than the current reference method, standard RT-PCR, requiring about 3-4 hours. Also, a new Cas variant, known as Cas13d or CasRx, able to cut RNA, has been proposed to target the coronavirus RNA genome and bring about its degradation. These are perhaps future applications and illustrate the power of genome editing in the COVID-19 scenario.

Medical doctors and researchers are currently under a lot of pressure to find more efficient diagnostic tests, a cure, a treatment or a vaccine to prevent COVID-19. There is increasing and escalating noise regarding the claims to relax, reduce, skip or avoid some of the usual steps or procedures which we all know well in biomedical research. We at ARRIGE believe that this is most dangerous. Shortcuts in research are unacceptable and can lead to unexpected consequences. There is a good reason why most biomedical laws and rules refer to the four bioethics principles (non-maleficence, beneficence, autonomy and justice), and why there is a clear path to convert a laboratory observation into a drug to treat patients. The required pre-clinical steps (cell culture experiments, laboratory animals) cannot be eliminated and should precede the eventual clinical trials, throughout all their phases. What is true for innovative gene therapy-oriented genome editing developments must also be true for COVID-19 treatments.

Let me finish by inviting you to participate in subsequent issues of this ARRIGE newsletter via: newsletter@arrige.org.

Also, I hope we will be able to meet again by mid-November this year, for another great ARRIGE meeting, which will have to hold online.

Thanks for your collaboration!

Latest News

Next ARRIGE Annual Meeting

The safety of ARRIGE community is our top priority. Due to the current COVID-19 outbreak, **the next ARRIGE General Assembly and Annual Meeting will go virtual**! We look forward to bringing together members and other interested participants to connect, exchange, debate and foresee a common future around the responsible use of genome editing technology through this new on-line format. You can already circle the date in your agendas: **Saturday November 14th, 2020 (2pm-5pm CET)**. More details to come.

ARRIGE Scientific Committee

Gaetan Burgio (Chair) and Tony Nolan (Vice-Chair)

The ARRIGE scientific committee was established in 2019 and is made up of 19 members who not only span a broad geographical range but also cover a broad suite of expertise in fields ranging from CRISPR basic biology and its use for genome editing in model organisms or for gene therapy, to bioethics, law and global governance. The primary role of the scientific committee (SC) is to provide independent advice to the ARRIGE board to inform and support their decision process and policies on gene editing related matters.

One of the first tasks of the committee was to establish its ethical governance, which it duly did, setting the voting procedures for electing chairs, dealing with conflict of interests and approving scientific recommendations and position statements of the committee. Dr Gaetan Burgio of the Australian National University and Dr Tony Nolan of the Liverpool School of Tropical Medicine were respectively elected Chair and Vice-Chair of the SC for a fixed term of 2 years.

The committee has collated all relevant areas of expertise covered by its members into a database in order to expedite queries arising in a timely fashion by establishing working groups with the relevant competencies. Further to this, we established an agreed route of communication between the Board, the Committee and the public.

A recent request from the Board for a viewpoint on the use of gene drives for population control will be the first test of the procedures we have put in place. Gene drives are genetic elements that can be re-designed to rapidly invade populations and spread desirable traits. They have great potential for the control of several pests and vectors of disease, however they are also controversial. A working group has been established with several gene drive experts from the committee, yet this will be chaired by an external chair, Professor Christian Siatka (University of Nimes), with no direct involvement in the technical development gene drive.

The committee hopes to present its position paper to the Board before the next newsletter.

Free Commentary

How Should We Regulate Heritable Genome Editing? A South African Human Rights Perspective

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Introduction

After the first democratic elections in 1994, South Africa has aspired to be a nation that could rise above its dark history of oppression, and become one in which freedom reigns. This marked a turning point in our legal system, which has also sought to rise above its complicity in the oppression of Black South Africans under the apartheid regime. With the promulgation of the Constitution of the Republic of South Africa in 1996, all South African law would henceforth be enjoined to conform to the aspiration embodied therein, to: "establish a society based on democratic values, social justice and fundamental human rights".

The commitment to fundamental human rights is reflected in how South Africa regulates assisted human reproduction. For instance, any woman has the right to make use of in vitro fertilisation without the requirement of a medical indication. Such a woman has the right to choose to use donor gametes, and to select the gamete donor based on a variety of characteristics, inter alia hair colour, eye colour, and level of educational qualification. These considerations colour what we suggest is a South African approach to heritable genome editing: An approach defined by considerations of freedom of choice and reproductive autonomy in the context of new reproductive technologies.

In this article, we first briefly describe the current South African legal and ethical position on heritable genome editing. This serves as a background to our discussion of the principle of procreative non-maleficence that emerged from recent South African case law – a principle that we suggest can be useful in policy decision-making regarding the regulation of heritable genome editing in a scenario where the safety and efficacy of heritable genome editing has been established.

Law and Ethics on Heritable Genome Editing in South Africa

The South African legal position relative to heritable genome editing is all but certain, but we suggest that approval for research on heritable genome editing, as well as clinical application of genome editing technologies judged safe and efficacious, is in principle possible in terms of South Africa's National Health Act [*Note to the reader: for those not interested in technical legal arguments, feel free to skip to the next paragraph*]. Nothing in the Act prohibits research on heritable genome editing, provided such research is approved by a health research ethics committee in terms of the Act, and the human biological material used for this research is collected and used in accordance with the Act and its regulations. Furthermore, nothing in the Act explicitly addresses heritable genome editing. However, section 57 of the Act does refer to the "genetic manipulation" of the human embryo. In terms of this provision, the "reproductive cloning" of a human being is prohibited, which is described as "the manipulation of genetic material in order to achieve the reproduction of a human being and includes nuclear transfer or embryo splitting for such a purpose". Does this reference to the manipulation of genetic material mean this prohibition extends to heritable genome editing? One might argue that it does, on the premise that the broadly-worded definition of reproductive cloning displays intent by the legislature to prohibit all forms of manipulation of

genetic material – and that heritable genome editing constitutes such "manipulation". Such an argument relies on the assumption that the legislature, when drafting this law, erroneously labelled all uses of genetic technologies in human reproduction as "reproductive cloning". However, even if this were the case, in South African law the interpretation of a provision in a statute does not turn on what the lawmakers intended, but on what they wrote, and the apparent purpose that these words reveal when read in the context of the statute. There are several indicators in section 57 that elucidate the apparent purpose of this section as being the regulation of human cloning, and not genetic manipulation in general: The explicit mention of the word "cloning" several times in section 57; the specific reference only to cloning techniques when defining "reproductive cloning" (i.e. nuclear transfer and embryo splitting), even though other techniques for genetic manipulation were known in 2003 when the law came into being; etc. As such, regardless of whether this is what the legislature intended, the principles of statutory interpretation favour the conclusion that heritable genome editing is not prohibited by section 57 of the National Health Act, and is thus legal in South Africa. That said, arguments of this nature are academic until either the legislature or the courts provide clarity on this issue.

The position in relation to the ethics of research on heritable genome editing is similarly unclear, but we suggest human rights considerations support research on heritable genome editing as being, in principle, permissible. The procedures for ethical approval of research in South Africa are governed by a number of ethics guidelines, including the ethics guidelines of the Department of Health (DoH), the Health Professions Council of South Africa (HPCSA), and the Medical Research Council (MRC). The latter two ethics guidelines prohibit research on heritable genome editing – but in the case of the HPCSA only insofar as it has a therapeutic purpose. Yet, we suggest that the prohibition in these ethics guidelines is unlikely to survive constitutional scrutiny. Indeed, in South Africa the right to freedom of scientific research is a constitutionally protected human right. Accordingly, there is an onus on anyone who limits this right to show that such limitation is justifiable in an open and democratic society based on dignity, equality and freedom. Dignity is interpreted by South African courts as referring to an individual's self-worth, self-actualisation and personal moral autonomy – in other words, the opposite of a society enforcing its morality on the individual. Accordingly, we suggest that a determined scientist whose aim is set on doing heritable genome editing research – and who is not afraid of litigation to clear possible obstacles out of the way – will, in all probability, be able to succeed in gaining official approval.

The Principle of Procreative Non-Maleficence

One of the main reasons why many States have taken the route of prohibiting heritable genome editing has been concerns about the safety of nascent genome editing technologies like CRISPR-Cas9. However, these technologies are developing at a rapid pace, and it seems that many of the risks associated with early versions of the technology, like off-site edits and mosaicism, can and will be overcome in the foreseeable future. As this future approaches, one of the biggest questions facing, not only South African policymakers, but many countries around the world is this: If the safety and efficacy issues relating to heritable genome editing can be resolved, how should liberal democratic societies regulate the use of this technology by prospective parents who wish to carry out edits to the genomes of their prospective children?

In an article recently published in the CRISPR Journal (https://doi.org/10.1089/crispr.2019.0036), we argue that South Africa and other liberal democracies should make decisions about the regulation of heritable genome editing in a manner that is mindful of human rights that underline its clinical application.

Furthermore, an often overlooked right in debates about controversial assisted reproductive technologies is the freedom of prospective parents to have access to and use these technologies. In South Africa, this freedom is protected under the right to reproductive autonomy contained in section 12(2)(a) of the Constitution. However, the freedoms of prospective parents must also be balanced against another important consideration, which is recognised in both international law and national legislation around the world: the principle of the "best interests of the child". In South Africa, this principle finds its expression in section 28 of the Constitution, which provides that: "A child's best interests are of paramount importance in every matter concerning the child".

Even if safety and efficacy considerations have been limited as far as possible through research and clinical trials, certain applications of heritable genome editing technology may arguably be contrary to the best interests of the prospective child – such as when prospective parents intentionally have an embryo genetically modified to ensure that a child not be born with a serious genetic disorder. Is it possible, then, to balance the rights of prospective parents with the imperative of protecting the best interests of the prospective child? We suggest that it is, through a principle which was developed in the South African Constitutional Court case of *AB v Minister of Social Development* 2017 (3) SA 570 (CC). This principle can be formulated as follows: The scope of possible reproductive decisions that prospective parents may take, at least in the context of artificial reproduction, should be legally limited to exclude decisions that will cause harm to the prospective child. This principle, we suggest, presents a mechanism for giving effect to the constitutionally protected rights of prospective parents in choosing to use heritable genome editing technologies in reproduction, while equitably balancing them against the interests of prospective children, *i.e.* not being subjected to harm.

It is important, however, to distinguish the prospective child from the embryo. Embryos in South Africa are not recognised as having legal personhood, and as the Johannesburg High Court elucidated in Ex Parte KAF 2019 (2) SA 510 (GJ), for the purposes of the "best interests of the child", no individual embryo can be equated with a prospective child. Rather, what the principle of procreative non-malificence requires is that the child, who is eventually born as a result of the use of assisted reproductive technologies, must be protected from a prospective parent knowingly and intentionally making a decision (sometime before birth) that would harm the child (once he or she is born).

Conclusion

A powerful idea in South African human rights jurisprudence is that the application of fundamental rights evolves along with societal advances. The Constitutional Court held as follows in *Minister of Home Affairs v Fourie* 2006 (1) SA 524 (CC):

"Indeed, rights by their nature will atrophy if they are frozen. As the conditions of humanity alter and as ideas of justice and equity evolve, so do concepts of rights take on new texture and meaning. The horizon of rights is as limitless as the hopes and expectations of humanity."

In this light, we suggest that the right to reproductive autonomy will not remain confined to present artificial reproductive technologies like IVF and gamete donor selection, but will, once the technology is safe and effective, include the right to use heritable genome editing. This will be balanced by a legal principle that has already emerged in the context of artificial reproduction in South African law – namely the principle of procreative non-maleficence.

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