Genome Editing for Human Benefit: Ethics, Engagement and Governance

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Guidance and policy paper: Readiness level of the Brazilian regulatory framework: Can we face genome editing?

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Brief description of the context

Technological advances are leading to unprecedented access to genetic modification methods, However, intentional genetic modification of organisms is not a new idea in science. Over 60 years ago, the notorious case involving accidental release of African honey bees (*Apis mellifera scutellata*) from a research lab in Brazil led to genetic changes in bees across the continent and increased morbi-mortality due to human-bee interaction. This was a warning call on the unanticipated consequences of transitioning genetic modification techniques from laboratory settings to field applications. In many instances, lessons were learnt and regulation was set in place to deal with these known risks. However, in all cases the full extent of the impacts was unknown *a priori*. This will probably be the case with the eventual release of genetically modified disease vectors. Introduction of Genetically Modified Organisms (GMO) such as crop seeds triggered discussion on GMO regulations in Brazil, resulting in the approval of the National Biosecurity Law in 2005 and the establishment of a federal and local network of councils/committees, headed by the National Biosecurity Council (CNBS) and the National Technical Biosecurity Commission (CTNBio). An ongoing debate is in course on whether CRISPR-mediated gene editing should be classified together with other recombinant DNA technologies. This has important implications for the oversight of research and eventually the release of gene edited "products" such as vectors and human therapies derived from these technologies.

Here we examine the current Brazilian regulatory framework on research and eventual application of human germline genome editing and gene drives, and discuss their strengths and weaknesses, in order to determine if this framework is robust to foster responsible research.

Regulation of genome editing in human germline cells

GMOs research and commercial release are regulated by the National Biosecurity Council (CNBS) and the National Technical Biosecurity Commission (CTNBio). The 2005 National Biosecurity Law defines GMOs as any organism whose DNA/RNA has been modified by genetic engineering, defined as the activity of producing and manipulating recombinant DNA/RNA. In its turn, recombinant DNA/RNA is defined as those nucleic acids manipulated outside living cells, with the ability to replicate inside a living cell, and the molecules resulting from this replication; synthetic DNA/RNA equivalent to the natural nucleic acids also falls into this category. Genome editing technologies may not fall into this classification because in some cases the foreign material (eg., Cas9 DNA in an expression vector or as free protein) is not integrated into the host genome or does not remain active in the host cell after effecting its function. In order to address this challenge, the CTNBio issued a Resolution determining that any use of a list of technologies - including CRISPR-Cas9 - should be preceded by consultation with the Commission, which will classify the project as involving GMOs (requiring comprehensive analysis by CTNBio) or non-GMOs (exempting the project from submission to CTNBio). Therefore, if the applicant wants to be exempt from CTNBio analysis, the proposed technique has to be proven not to lead to residual recombinant nucleic acids (irrespective of the ability to self-replicate) in the target cell/organism. In the case of human germline editing, the National Biosecurity Law imposes another barrier by strictly prohibiting genetic engineering in human germline cells up to the embryo stage.

Experimental and therapeutic gene editing in both human somatic and germline cells (depending on the method used) even if deemed exempt from analysis by the CTNBio, are subject to the regulatory framework of the National Commission on Ethics in Research (CONEP), which evaluates genetics/genomics research protocols with human subjects, as well as clinical study protocols prior to submission to the Brazilian Regulatory Agency (ANVISA).

Regulation on research on gene drive and release of gene drive modified mosquitoes

Due to the huge economical and social impact of mosquito-borne viral diseases in Brazil, such as Dengue, Chikungunya and Zika, with more viruses unfortunately on their way, Brazil is an obvious testing ground for new mosquito control technologies. The use of the GMO *Aedes aegypti* OX513A strain as vector control is subject to legal dispute after CTNBio authorized its commercial release in 2014. ANVISA ruled that the strain needed approval in terms of safety for human populations in 2016, but in 2018 a preliminary court decision favouring Oxitec ruled that CTNBio was the legally competent agency to review the safety of GMOs. The case may not be over yet, highlighting gray areas for regulation in the future, including the establishment of boundaries for responsibilities of the Environmental, Health, Agriculture and Ethics government regulatory bodies. As for today, release of the OX513A mosquitoes is underway in a few Brazilian cities.

A recent study has found introgression of the OX513A genome into the natural mosquito population in a Northeastern Brazil city where experimental releases took place[1], but a press release by Oxitec[2] challenges most of the paper's conclusions. CTNBio issued a Note stating that it is following the case and that preliminary analysis of the paper results does not indicate potential harm to humans or the environment.

Community engagement

1. The CTNBio regulations have no provisions for mandatory community engagement actions but this was carried out during trial releases of Oxitec GM mosquitoes.
2. Likewise, CONEP does not require community engagement by the applicants of genetics/genomics/gene editing research projects involving human subjects.
3. Social acceptability of human germline editing has been addressed in a recent survey by the Catholic University of the State of Paraná with approximately 600 people. Considering respondents who had an opinion on the prohibition of human germline editing (360 out of 449), a majority were in favor of partial flexibilization. Preliminary analysis suggests that opinions in favor or against more flexible rules for germline genome editing research are not substantially associated with education levels.

Commentary

The Brazilian regulatory framework for research and clinical studies using novel gene editing technologies in somatic cells seems appropriate, in particular for applications targeting rare and life-threatening diseases using somatic cell editing. On the other hand, human germline research is in essence forbidden in Brazil.

The recent event with GM mosquitoes will be a stress test for the regulatory agencies and its outcome may have an important impact in future regulations and also on social acceptability, especially with the advent of gene drives, whose consequences are even more unpredictable than "traditional" GMOs. Proper and timely communication will be key to address this issue.

The challenges posed by the new human germline and disease vector genome editing technologies are far reaching, and may not have been thoroughly addressed by the current Brazilian regulatory framework, because they did not exist when the National Biosecurity Law was passed.

A challenge still remains in terms of a comprehensive communication with the various sectors of society so that risks and benefits (in particular for future generations) are understood, fears and opinions are heard, and informed decisions are taken. These settings might include forums and workshops with religious group leaders, patient advocacy groups, scientists and policymakers.

Recommendations

Public support for more flexibility in germline editing research should be addressed by additional surveys and, if confirmed, should spark public debate for reviewing the current prohibition.

Coordination should be pursued by Brazilian Government bodies to define which of them has the authority for solving genome editing issues.

References

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2. Oxitec's response to the paper by Evans et al. (2019): https://www.oxitec.com/news/oxitec-response-scientific-reports-article