ARRIGE
Association for Responsible Research and Innovation in Genome Editing

Gene drive technology: State of the question on science and ethics

The development of gene editing technologies over the last few years has considerably improved our understanding of biological processes by being able to change the genetic material of many organisms with versatility and ease and examine the effects of these changes. This understanding improves our prospects for the control of disease - either directly, by introducing genetic modifications that prevent and treat disease, or indirectly, by understanding the genetic causes of disease and allowing targeted therapies that specifically affect these processes. They also have a scientific and cultural impact on our representations of what is human and modify the extent of our ethical responsibilities and require a dialogue between social sciences and STEM disciplines.

Gene drive: a powerful technology to potentially control pests or vector borne diseases

'Gene drive' refers to a phenomenon that occurs in nature but can also be synthetically generated. It describes the behaviour of genetic elements - also referred to as gene drive elements - that are able to bias their own inheritance when a sexually reproducing organism produces its gametes (sperm or eggs). Ordinarily, one copy of a gene has a 50% chance of being included in any gamete but gene drives can be present in a higher fraction of gametes because they either make extra copies of themselves prior to gamete formation, or because they outcompete gametes that do not contain them. Individuals containing a gene drive therefore produce a much higher proportion of the offspring in each generation up to 100% versus 50% for classical genetic inheritance. Because of this behaviour, gene drives can spread rapidly in a given population, transforming it such that potentially all individuals contain the gene drive. It is theoretically possible to design an engineered gene drive to spread a genetic modification of choice into a population in order to change it. The new genome editing technologies, including CRISPR-Cas, make this more feasible and designs have been inspired by existing natural versions of gene drive.

Synthetic gene drives are particularly suited to organisms that have short generation times and they have the advantage of being both species-specific and self-sustaining: the release of a relatively low number of individuals containing the gene drive can be sufficient to seek out and mate with the local population, spreading the gene drive as they do so. Depending on the specific gene drive design, it is possible to moderate both the strength of its ability to invade a population and the threshold number of organisms that needs to be released.

A lot of recent research has looked at developing gene drives for the control of invasive rodent pests and insects that transmit disease. This follows decades of research in controlling vector borne diseases or invasive species using conventional methods such as insecticides, rodenticides; artificial habitat clearing; introduction of predators etc… that have not yet been applied in every needed environment. To date, most success in the laboratory has centred on the development of gene drives in mosquito species that transmit a range of pathogens, including malaria parasites, dengue and yellow fever viruses. By contrast this same type of gene drive has not proven successful in rodents to date, highlighting some of the unknowns in the general applicability of gene drive. Two approaches are being followed: spread a gene drive that also contains an engineered genetic construct that modifies the mosquito's ability to harbour the pathogen; spread a gene drive that negatively affects the ability of female mosquitoes to reproduce, thereby debilitating the population as it spreads. Both types of gene drive have shown promise and spread rapidly when released into laboratory populations. These successes notwithstanding, there remain a number of technical issues to be resolved, not least the possibility of genetic resistance arising in the population.

Regulating gene drive release:

At a regulation level, there are considerable efforts to establish local and international guidelines for the use of gene drive from the WHO, the African Union, the CDC - Africa, the European Union, NASEM in the USA or the Royal Society of New Zealand, and different governments across the endemic areas for vector borne diseases and invasive pests control. While there is still a need for improvement to implement a regulation on gene drive in many countries, an important issue with the gene drive approach is the potential for crossing the boundaries of multiple countries.
A regional implementation of the regulation will enable to better manage the release of the gene drive organisms and to minimise the risks such as trans-boundaries movements of the gene drive organism. As scientists, our role is to inform and discuss with regulatory agencies and stakeholders the benefits and the risks of the technology, in order to help develop ethical guidelines and regulations for its implementation and to coordinate a safe risk management of the gene drive approach that is consistent with the Cartagena protocol on biosafety.

Ethical concerns regarding the use of gene drive:

The idea that gene drives could modify evolutionary trajectory and cause the extinction of certain species, be it mosquitoes or pest, is a disruptive idea in the public. It confronts us with the fact that the Anthropocene is not just an idea but is a possibility and a responsibility of humans to replace a defective "natural gene" with a synthetic one in organisms targeted for gene drive Moreover, it cannot perfectly control the implied outcomes of these experiments and cannot therefore establish a governance of shared anticipated risks. When gene drive is viewed as continuity rather than a rupture with nature, gene drive can be described as a form of enhancement of existing gene drive functions found in Nature itself.

The discourse of promise and hype is often advanced but cannot be verified. For instance, it claims that we could suppress nuisance species such as malaria causing mosquitoes, but researchers in the field are still working hard to determine the broader ecological and environmental impacts of using gene drive, which strongly suggests the need to evaluate its consequences, beyond the risk/benefit utilitarian model. In terms of responsible science, it requires to clearly describe the shared risks and to anticipate and determine the supposed benefits for whom and what.

Would the application of this technology in a given circumstance be accessible, in terms of distributive justice or access to health, facilitating compliance from the most exposed populations? At stake is the social contract of science, to share a responsibility to alter the polysemic cultural concept of "Nature" across cultures, to avoid conflict of interpretations and thus conflicts of interests.

Sociologically, this matter requires a certain amount of scientific knowledge, not equally distributed on the planet and still a privilege of affluent countries, but it is also a cultural model *per se*, that cannot be considered universal *a priori*. It challenges the classical Darwinian model of evolution, as a tree of life at the very moment its mutation, becoming more complex than simply leading to evolution or extinction. Moreover, some countries or traditional cultures are still thinking in a fixist creationist frame, which cannot accept the idea of human acting on gene alteration or construction of a synthetic organism that has an impact on natural process. Some defend a teleological idea of nature that is preeminent to culture and requires a difference between instrumental and intrinsic values of living organisms. This divide exists also in the so-called "Northern countries" and creates ideological tensions around the design of a common reference frame of ethical responsibility that could be pluralistic without falling into cultural relativism. It requires to rethink the necessity raised by gene drive technology and any human intervention to differentiate between nature values and human interests. This cultural divide confronts lay persons with representation dilemmas that cannot be reduced to ignorance and rely on cultural representations that evolve in a very different time frame. The idea that living organisms can be artifacts, tailored to human design, not only does something to how we value nonhuman nature but risks having knock-on effects upon the way we value human life according to environmentalists, since it blurs the distinction between animal and machine that is the core of Cartesian discourse.

We are facing a change of paradigm that must lead us to be responsible for altered inheritance and the hybridization between artefacts, considered as natural or artificial, at the very moment when this division itself is blurred by the engineering capacity to act on mutations, without knowing in advance the possibly adverse, short or long term, side effects, on the manipulated and other connected species. It raises the following questions. Would the technology affect the environment such as protected species in the ecosystem, do the animals deserve the right to be protected? Are native species, close to the invading ones, valued by the local community? We have to be clear on the definition of artefacts synthetic biology creates. Synthetic biologists create artificial organisms but they do not create an alternative "Nature". It will require public involvement in finding a *lingua franca* between evolving scientific discourse and cultural representation adaptations without presupposing enhancement, which is still associated with some forms of eugenism.

Engaging with the community and stakeholders:

Regarding issues in vector borne diseases and invasive pests control, it is important to take into consideration, the community's point of view and a clear engagement after being well informed and consent to the risks and benefits of the use of gene drive technology. The community living in the areas where there is an important need are particularly vulnerable and prone to suffer from misconduct or mis-implementation of the new technology even though it's for their own interest.

Governments in many countries may need further assistance from stakeholders, to allow the implementation of a gene drive in their communities, considering the global environmental impact and consequences on individuals. Existing data based on this technology is limited to laboratory-based settings. There is no community-based data on safety nor a long-term effect of the gene drive. Therefore, while much progress has been made, it will be more than crucial to develop a model in the Western community with evidence-based safety data before moving to the endemic developing countries, for example with vector borne diseases where there is a need. A legal framework for capturing these concerns on community acceptance has been developed for implementation following four principles. Firstly, do existing research ethics guidance frameworks such as the Helsinki declaration apply to gene drive research? Is it necessary to obtain individual informed consent for field release of GM vectors? Is there a precedent in other research fields for not soliciting individual informed consent? Is there a precedent for community engagement approaches that would be appropriate for gene drive? The development of a local community program where anyone can be involved and informed regarding the benefits and potential risks of this technology is a must. This program should include the participation of local community, researchers, regulatory agencies and the Ministries of Health, Environment and Livestock and Agriculture in the case of pest control. A deep discussion would help to engage all the actors and have success in the implementation of gene drive technology. Also, the possibility to repopulate a given population if drastic changes arouses due to its eradication should exist, in the form of frozen germplasm material that can be resurrected and released again. This can help to give peace of mind to the general public and have a backup plan in such a case. Anyhow, it is expected that benefits in terms of public health and economic gain are considerably higher than the potential risks.

How ARRIGE could play a role on gene drives?

The role of ARRIGE, beyond the explanation of concepts and a form of democratization of knowledge, must also be to promote confidence in some controlled mode of genetic engineering, while taking seriously into account the social and cultural aspects of persons or indigenous groups possibly impacted by the effects of this new engineering technique and its effect on the environment.

Some concrete examples

We consider the capability to share knowledge as the condition of democratic science at the service of human life.

Gene drives concern mostly the mutations in animal species for the moment. We will concentrate on what exists and speak of vector-borne disease and pest control.

In Nantucket (Massachusetts, USA), local councils accepted transgenic mice as a capacitating tool to fight tick-borne Lyme disease. It stages for us the capacity of a plurality of populations to re-appropriate new technologies, beyond the discourse of dual use, through a hierarchisation of values and interests.

In New Zealand, an attempt to use genome editing to eradicate rats has been proposed to local populations, which refused. We will have to analyze there the dominating science narrative.

In Burkina Faso, the experiment on genetically modified mosquitoes, to eradicate malaria, led to acquitting new skills or exploring new local resources, which raised the question of scientific knowledge, financial and logistic capabilities of local vulnerable populations facing the transfer of gene editing technology.

Acceptance of a potentially feared technology, and eventual transfer/adoption of the technology depends on a good communication and participative and relational ethics. The lack of information leads some to perceive innovative technologies as a new form of cultural domination and eradication of local cultures. This dismissal should be taken seriously and resolved in terms of convergence of interests.

Future perspectives

The ethical issues for ARRIGE will be to develop a shared hierarchy of values to analyze the impact of technology transfer as enhancement or destruction of species, both in the South and the North. The ethical justification of gene drive must be addressed in terms of limiting vulnerabilities and enhancing capabilities in a bottom up approach, taking seriously into account plural representations. Confidence in scientific advances depends upon science's constant will to be at the service of humanity while considering its interdependence with living beings at large. In addition to the wider ethical concerns regarding their use, a number of technical questions remain and are the subject of ongoing research. These include questions such as how to counter the development of potential arising genetic resistance and how to predict the dynamics of spread and the resulting effects of the population control.

Statement promoted by the ARRIGE Scientific Committee and endorsed by ARRIGE

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