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Editorial

Looking for an effective, affordable and sustainable approach to control pest species: the case of screwworm

En busca de un enfoque eficaz, asequible y sostenible para el control de especies de plagas: el caso del gusano barrenador

Em busca de uma abordagem eficaz, acessível e sustentável para o controle de espécies de pragas: o caso da bicheira

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Certain animal species become pests or turn invasive, conspiring against other species, the environment, biodiversity, food production and public health. Throughout history, humans have developed different strategies to control or eradicate these problems. Through more effective and affordable tools, and more respectful to the environment and harmless to other species, it will be possible to control more appropriately this kind of threat. CRISPR-based technologies can be applied to achieve this goal by controlling pests that threaten food supply in a growing world population, or preserving ecosystems affected by invasive species in islands and other particular environments. And most importantly, without adversely affecting - and even improving - the global effort focused on the One Health approach.

Altering key genes that control sex determination, fertility or fitness, can be used to control the number or gender of the progeny resulting in a novel, environmentally friendly, and low-cost method to control harmful species. Indeed, other conventional

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strategies such as hunting and poisoning animals that generates associated problems regarding ethics and animal welfare, or the use of pesticides in invertebrates that generates environmental or food safety problems can be avoided. These kind of CRISPR-based approaches are being developed in Uruguay to control screwworm, a problem that produces 3 billion dollars losses in South America every year. This editorial note is an opinion piece focused on the case of screwworm, and the development of novel ideas to improve our intervention in nature without affecting beyond what we intend.

The case of screwworm

Bichera is the term used in South America to refer to the myiasis caused by the New World screwworm, the larval stage of the fly known as *Cochliomya hominivorax.* The fly lays its eggs in a pre-existing wound of live animals, including humans, which quickly transform into larvae and get into the meat, feeding and growing as they devour the tissues of the host. The initial wound then becomes a large injury that begins to affect not only the superficial tissues, but also the deeper tissues such as muscles entering other cavities and causing death. Usually death occurs due to the animal's own weakening and suffering, or another disease appearing in consequence. This parasitic phase is a serious problem on animal welfare and health, and in humans is considered a neglected public health issue; in livestock is responsible for important losses in food production and causes significant economic losses.

Conventional control strategy is based on local use of insecticides on the myiasis, contributing with another problem associated with the excessive use of pesticides in agriculture and livestock. Although is an effective method, in many cases the animals suffer permanent sequelae that require the sacrifice or slaughter, and as with any other chemical, the possibility of resistance should not be ruled out. The alternative method available by several decades is the use of sterile insect technique (SIT). This strategy uses radiation to produce genetic mutations or chromosomal breaks to generate sterile adult insects, which are released in nature with the aim that sterile males compete with their fertile wild counterparts to suppress reproduction. This method allowed eradication of this insect in North and Central America, and its implementation in some South American countries has been proposed in several occasions. However, it requires a significant investment to achieve a real impact on the fly population, and a significant cost to maintain a barrier by permanently releasing sterile males. Moreover, an eventual lack of sterile insect release will allow the flies to re-enter the territory from countries or regions not controlling it. On the other hand, a control plan for the entire continent would imply collaboration, agreement and investment from all countries, which for various reasons seems unlikely.

CRISPR-based technologies

CRISPR-Cas system is a molecular genetic engineering tool to edit the genome of any species in a precise, efficient, non-expensive, and relatively simply approach. This technology has been applied in livestock to improve productive traits, to generate resistance to infectious diseases, to improve resilience and animal welfare, and to control pest or harmful species. Through the use of CRISPR it is possible to generate a system of directed inheritance known as gene drive that has the potential to perpetuate a trait much more efficiently than Mendelian inheritance. When an individual carrying the gene drive system is breeding with the wild population, all the offspring express the desired trait and transmit it again to all their offspring. This system is ideal for application in wild species where it is not possible to implement a breeding and selection system such as those implemented in farm animals to fix a particular trait. The possibility of using gene drive to control a wild population has been raised in different areas and has begun to be tested in some animal models, however, its implementation is still a challenge in some aspects.

Pending issues

The implementation of this tool requires overcoming some issues that go beyond technical limitations and that implies the political decision to apply it or not. The first question is about differences between transgenesis and CRISPR-based techniques. The CRISPR-based methods should not be considered a conventional transgenesis technique, even when individuals express new DNA. Transgenesis techniques involve the random introduction of exogenous DNA into the genome, while the use of CRISPR is different. First, the genome can be edited without the need to introduce exogenous DNA, and then these animals are not transgenic by any means. Although a gene drive system is more complex than genome editing and requires components that involve the introduction of DNA, when use CRISPR the strategy is much more precise than

transgenesis methods and never random. Furthermore, in a gene drive CRISPR-based system it can be demonstrated with certainty that the introduced DNA is present only at the targeted site. When compared with other strategies like SIT, CRISPR-based system is even safer. In practice, when SIT flies are released in millions every week do not undergo an evaluation of their genome, and potential mutations induced during the radiation procedure cannot be ensured.

Other concern is regarding the environmental impact of suppressing or controlling a species that already exist in nature long before all the species introduced after European colonization. The impact that the introduction or control of a species can generate on the environment has not always been considered. In fact, the screwworm fly was eradicated from North and Central America and there are no known environmental impact studies conducted before the beginning of this program. On the other hand, it must also be recognized that after having eradicated this species from a large part of the continent, no evidence of a significant environmental impact has been reported. With the SIT in mind, Uruguay has made progress to evaluate the environmental impact of eradicate or control screwworm, and part of the results are shown in this volume of the journal.

Finally, to apply a biological control program, an appropriate regulatory system is required. For that, it is pertinent to consider the global context and the need to produce more food while affecting as little as possible the rest of the environment. Countries such as Argentina, Brazil, USA, Israel, Japan, among others, have developed specific regulatory systems for CRISPR-based technologies, which are different from those regulatory systems involving transgenesis. Conversely, the European Union maintains a more conservative position and currently it is not possible to release or apply a CRISPR-based system in livestock or agriculture, applying the same regulation as for transgenics. Uruguay is currently discussing its position and developing its regulatory system. The path that the aforementioned countries have already taken allows them to develop novel opportunities with different companies starting several initiatives. This progress associated with appropriate intellectual and industrial property systems opens up new opportunities for these countries.

In summary, novel technologies can be implemented to control pest species in an effective, affordable and sustainable approach. The case of the screwworm control in South America is a good example and serve as a proof of concept by solving local problems with global perspective.