

# ARRIGE Kick-off meeting Paris 23 march 2018

**Fostering responsible research and innovation with genome  
editing technologies:  
the need for a permanent forum  
The main goals of ARRIGE**

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## Declaration of links of interest

**President Inserm Ethic Committee (France)  
Member International Bioethic Committee (UNESCO)**

**Head Neuroscience Paris Seine (CNRS INSERM Sorbonne  
Université)**

**I declare that I have no conflict of interest with the data presented  
thereafter**

## A short history of ELSA concerns in the field of genome editing

- **Jan 2015** some « happy fews » meet in Napa Valley USA
- **Apr 2015** first chinese publication using 3PN human embryos
- **May 2015** HIROs' Meeting Canada and « saisine » from Pr Yves Levy, Inserm CEO, 17 june
- **Sept 2015** « The opportunities and limits of genome editing » National Academy of Science Leopoldina/DFG/Union of German academies. Up-dated mars 2017 « Genome editing in human cells ».
- **Dec 2015** Note du Comité d'éthique Inserm
- **Dec 2015** Washington meeting NAS/Acad. Sci. China/ Royal Academy and « Human genome editing: Science, Ethics and Governance » oct 2017.
- **Mar 2016** Paris European meeting

## Forstoring an international and inclusive debate

- Short Note **Nature** 6 Jan 2017 and White paper in **TRAG** june 2017: « Fostering Responsible Research with Genome Editing Technologies: a European Perspective »
- **Vienna** 07/09/16 organized by Christiane Druml “Fighting Malaria with CRISPR/Cas9: Ethical implications”
- **Buenos-Aires** 01/11/16 partnership IEC/Wellcome Trust as a satellite symposium of GFBR 2017
- Contribution to HIROs paper “Principles for Sponsors and Supporters of Gene Drive Research” **Science** 2017
- **New Dehli** 27-28/04/2017 IEC/Wellcome Trust, ICMR and DBT Fostering global responsible research with Crispr/Cas9
- **Geneva** 30/05/2017 partnership Swiss National Ethic Commission
- **Berlin** 6-7/07/2017 OECD Regulating GE for human cell uses
- **Brazzaville** 20/02/2018 organized by Francine Ntoumi partnership IEC/Fond. Congolaise Rech Med.

- **Convergence of scientific advances and technical breaks in genomics and embryology :**
- **CRISPR-Cas9 but also other Cas family members and more (C2c2 ...)**
- **The human genome for less than \$1000 (exome for less than 400\$)**
- **In vitro human embryos till day 13 post-fertilization**
- **Need to consider other genetic interventions: NIPD, mitochondrial transfer..**
  
- **What kind of new interventions this may allow on our body (including human embryos and human brain) or on our environment?**
- **The debate is not new but genome editing is now precise, efficient, rapid and not expensive**



# Ethical questions

- **Human** applications versus **animal** versus **plants**
- **Research** versus **medical** and/or **commercial** use
- Transmission/dissemination/heritability
- Precautionary principle
- 1- Application of this technology to **humans** essentially raises the question of changes in the **germ line and the zygote**;
- 2- Application of this technology to **animals**, especially to “harmful” species, raises the question of a possible lateral gene transfer and the emergence of irreversible damage to biodiversity; additional: ethic of animal enhancement (muscle lamb, muscle veal, muscle dogs, mini-pigs..)
- 3- Risk of damage to the **environment**.
- 4- **Genetic Engineering**: what is a GMO vs Micro Organism Genetically Engineered (MOGE)



## Common Technical risks

- **On-target:** uncontrolled repair, create a mutation instead of a disruption
- **Off-target:** mutation in an untargeted place
- cleavage of a single DNA strand, which could become uncontrolled and may induce **mosaicism** or chimerism in the progeny of the modified cell.
- the targeted mutation is **counterbalanced** by other adaptations of genome expression, and that its correction results in a new balance with unknown effects.
- **long-term consequences** of the correction on genome stability must be assessed.

## Proposals (Hirsch et al. Nature 2017, Chneiweiss et al. TRAG 2017)

- **A moratorium seems implausible** because the idea does not seem to be benefitting from the same international consensus as the 1975 Asilomar conference did.
- At the level of our research institutions there are **no bio-security issues** here that have not already been considered by previous technologies.
- But, it is not because the technic is easy that it should not go through a **rigorous benefit/risk evaluation**
- Call for a responsible use of the technic. We need **to take care of public expectation** and of the present stage of knowledge : a lot remains to be proven.
- **DIY movement might** need another consideration and scientists should engage discussions with these groups to increase their understanding of potential harms associated with DNA manipulation.

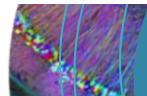
## Foster research to assess the feasibility, the efficacy and the safety of GE technology in experimental models

setting-up of a **European Steering Committee** (ESC) gathering together experts in different disciplines as diverse as molecular biology, ecology and a variety of social sciences, to determine the methods, standards and references.

These methods and standards to evaluate:

- ☐ ?acceptable levels and types of off-target effects,
- ☐ ?acceptable levels of mosaicism,
- ☐ ?acceptable levels of epigenetic effects.

**ARRIGE** should create now an International Steering Committee that should rely on stakeholders for an open and transparent process. These stakeholders will include patient organizations, and representatives of ethics committees and of the economic sector.

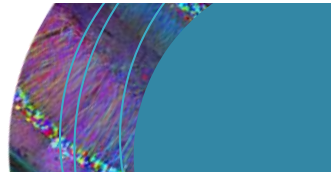


## Adapt the ban on all modifications of the germ line nuclear genome for clinical application in human reproduction.

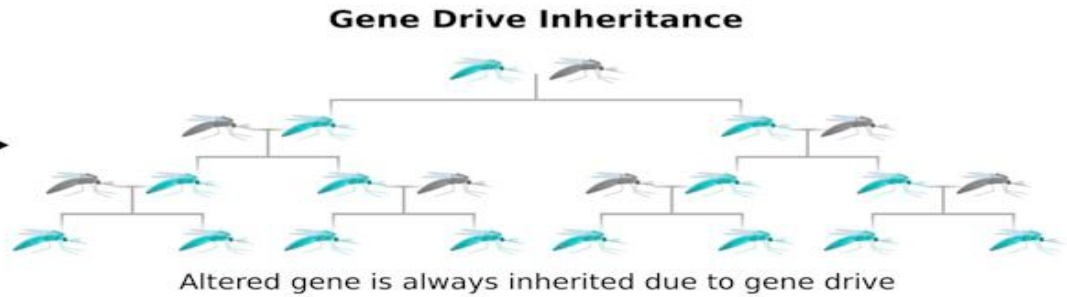
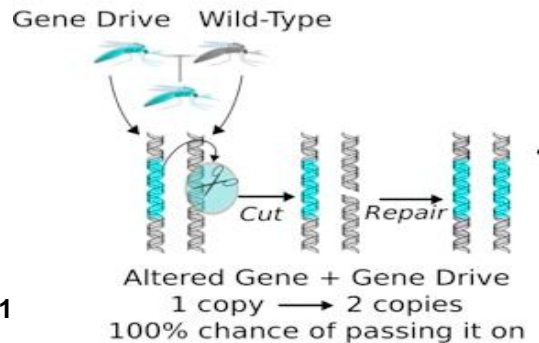
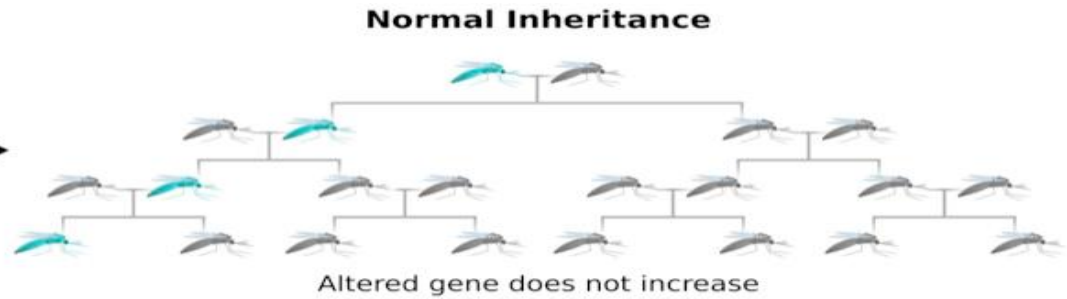
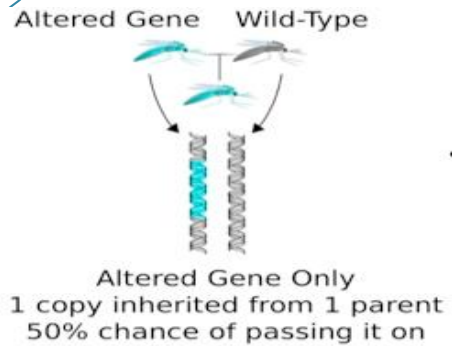
*Oviédo convention 1997, art 13: « an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aims is not to introduce any modification in the genome of any descendants »*

An objective for **ARRIGE** should be to help international and national research institutions in defining guidelines.

This would mean international cooperation with political decision-makers to determine common strategies and define clear positions from the ethical standpoint on what kinds of translational research are admissible and what kinds are not.



# Ethical Issues Relative to Transmissible DNA Direct Action on the Inheritance of Certain Genetic Traits using Gene drives



# Some ethical questions about gene drive

- 1- **Feasibility** in the wild: need evaluation of dissemination and long term stability but also the great genetic diversity of mosquito populations
- 2- the risk of **off-target** effects of the inactivation of a gene other than the target gene.
- 3 - the risk of **transversal diffusion** of the guided gene which would contaminate organism populations other than that of the target population.
- 4 - the **environmental impact** resulting from the eradication of a “harmful” population/pathogenic to humans, but that may nonetheless play an important role for biodiversity.
- 5- the risk of **unwanted side effects of the guided gene for man** (appearance of other pathologies associated with guided gene).
- 6- **Adaptability** of Malaria parasites to other hosts
- 7- **Cultural representations** of mosquitoes and living organisms/ acceptability

# The potential adverse effects of a gene drive ought to be thoroughly evaluated and mitigated before any clinical or environmental trials are undertaken outside the laboratory

Assessment of a benefit-to-harm balance in the long-term,

The **Steering Committee** will produce

- \* risk analysis matrices,
- \* devise realistic scenarios
- \* will produce recommendations for reversibility strategies in the case of adverse effects harmful for humans or for biodiversity.

## Principles for Sponsors and Supporters of Gene Drive Research

HIROs  
Washington  
march 2017

Nasem Oct 2016  
Science Nov 2017

PRINCIPLE	STATEMENT
Advance quality science to promote the public good	The pursuit of gene drive research must be motivated by, and aim to promote, the public good. Funded research shall embody high scientific quality and ethical integrity, consistent with the current best practice guidance set by the research community and relevant decision-making bodies.
Promote stewardship, safety and good governance	Researchers and sponsors are stewards of science and the public trust. It is imperative that good governance is demonstrably shown in all phases of the research, and especially in relation to risk assessment and management. This requires compliance with applicable national and international biosafety and regulatory policies and standards. Research conducted with respect for the broader ecosystem in which humans live, taking into account the potential immediate and long-term effects through appropriate ecological risk assessment, is a hallmark of both good stewardship and good governance.
Demonstrate transparency and accountability	Knowledge sharing is not only essential for the advancement of science, but for transparency to foster public trust in emergent technologies. The timely reporting of results and broad sharing of data shall be the norm in gene drive research, consistent with the tradition of openness established in its parent communities of genetic and genomic science. Measures of transparency and accountability that contribute to building public trust and a cohesive community of practice will be supported.



# Comité d'éthique de l'Inserm

<p>Engage thoughtfully with communities, stakeholders, and publics</p>	<p>Engagement with communities, stakeholders, and publics is critical for ensuring the best quality science as well as building and sustaining support and public confidence in the research. Funded research shall include the resources needed to permit robust, inclusive, and culturally appropriate engagement to ensure that the perspectives of those most affected are taken into account.</p>
<p>Foster opportunities to strengthen capacity and education</p>	<p>Strengthening capacities in science, ethics, biosafety and regulation is essential for enabling agile and steady progress in gene drive research. Opportunities to partner, educate, train, co-develop and co-own the technology, shall be supported throughout all phases of the research, from the early stages to deployment, with particular emphasis on strengthening capabilities within affected countries for informed participation and decision-making.</p>

## AN ETHIC OF RESPONSIBILITY

Through alignment with the Principles, sponsors of gene drive research aim to **contribute to an adaptive and data-informed toolbox of policies that can support the responsible development of** gene drive research, in accordance with recommendation 8-9 of the NASEM report. Such a toolbox affords the flexibility to respond to new technical advances and knowledge, while ensuring the long-term safety of human health and the environment. Principles serve as a moral compass to ‘anchor the actionables’, so that only the highest quality research endeavors, consistent with the best practice guidance and standards set by the scientific community, will be supported.

## **Need to be pro-active to prevent the technology being hijacked by those with extreme views**

Avoid abusing public expectation with overinflated promises

Research institutions should contribute to national and international initiatives addressing questions of freedom of research and of medical ethics.

Participation in such international initiatives by experts from developing countries should be greatly promoted and facilitated, since all people worldwide are concerned, and since local experts need to appropriately control unethical research.

## The philosophical question that opposes the dynamic and plasticity of any living organism to an inadequate idea of human nature founded solely on biological determinism.

- Raise awareness about the distinction between the care/treatment of human diseases and human enhancement.
- Certain therapeutic promises might engender dystopic expectations.
- The ethical debate surrounding the life sciences partakes in the necessary acculturation of the society to our disciplines and puts science back into the centre of culture and society as a whole.
- creating a monitoring group led by all stakeholders concerned with genome editing mentioned above (i.e. the European Steering Committee, European research ethics committees, patient organizations, European research institutions and political decision-makers) to **promote an open debate on the societal aspects** of genomic technologies, before a necessary translation into international legislation becomes possible.

## Concrete aims of the initiative

- **How do we identify ourselves?**
- **What do we offer that is not already there?**
- **What do we promote? A coherent approach (consensus) or diversity/multiplicity?**
- **How do we manage our disciplinary diversity?**
- **How can we mobilize our national, linguistic, religious, geographical diversity**
- **How do we work together in a meaningful way as a group and also respond in real-time to the accelerated developments in GE**

**Be more inclusive and think together**



## Concrete aims of the initiative : a preliminary meeting (Paris Nov 2017) & discussions on the list

- 1- Offering a **reliable platform** for information regarding GE technology and for discussion of ethics issues in connexion therewith. This as already started with the launch of a mailing list [crispr.esc@cnb.csic.es](mailto:crispr.esc@cnb.csic.es) that is now [arrige@cnb.csic.es](mailto:arrige@cnb.csic.es) and the web site which is now [www.arrige.org](http://www.arrige.org) thanks to Lluís Montolui.

Multidisciplinary group of stakeholders will allow explicit awareness of all biases at work from the members.

- 2- **A permanent forum** where there is no rush to reach a final view and where the dynamic of science and of ELSI that need to accompany this movement are valued. Future uses of GE to be foresighted.
- 3- Creating an **ethic tool box** and informal guidance for GE technology users
- 4- Getting involved in **governance of GE technology** with governmental/intergovernmental stakeholder
- 5- develop a particular reflection on the **role of the lay public** in this debate

# How to reach these goals the challenge of ARRIGE organisation

- ? A professional Society: International Radiation Protection Association (IRPA) created in 1965 by the gathering of national Health Physics societies. But many professional societies already exist in the fields of human genetics or environment
- ? An official body embedded in an international organization such as IPPC
- ? A specific international association

# ARRIGE

- More than 200 people from all continents registered at <http://arrige.org>

Should continue  
[join@arrige.org](mailto:join@arrige.org)

Thank you for your attention