Fostering Responsible Research with Genome Editing Technologies: a European Perspective

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“Fighting Malaria with CRISPR Cas9”
An incredible pace of scientific discoveries and technical breaks:
- CRISPR-Cas9 but also C2c2 and more
- The human genome for less than $1000 (exome for less than 400$)
- In vitro human embryos till day 13 post-fertilization

What kind of new interventions this may allow on our body (including human embryos and human brain) or on our environment?
Genome-editing using CRISPR-Cas9
Comité d’éthique de l’Inserm

Genome-editing using CRISPR-Cas9
FOSTERING RESPONSIBLE RESEARCH WITH CRISPR-Cas9

European Experts Meeting
March 16th, 2016
Biopark Paris
Purposes of the 16th march 2016

• Rising a european concertation
• Exchange views and present state of regulatory discussions
• Define a process to raise shared guidelines at the european level
• Set-up an advisory group of the european research institutions to survey and report on the rapid progress and emerging ethical, legal and societal impacts of genome editing technologies
What means “Genome editing”? 

• Concept associated with the word « editing » : correction, enhancement, improvement but not modification, alteration

• Not new but easier, faster, cheaper and highly efficient

• High speed growing field, race in science (including credits for honors) and an economical challenge with IP fights and big investments: may we control this rapid and multiform dissemination?
Ethical questions

• Human applications versus animal versus plants
• Research versus medical and/or commercial use
• Transmission/dissemination
• Precautionary principle

I/ Application of this technology to **humans**, which essentially raises the question of changes in the **germ line**;

II/ Application of this technology to **animals**, especially to “harmful” species, which raises the question of a possible lateral gene transfer and the emergence of irreversible damage to biodiversity; additional: ethic of animal experimentation (muscle dogs, mini-pigs..)

III/ Risk of damage to the **environment**.

IV/ **Genetic Engineering**: what is a GMO
Common Technical risks

• On-target: 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 mosaisism 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 must be assessed.
Ethical Issues Relative to Transmissible DNA
Direct Action on the Inheritance of Certain Genetic Traits using Gene drives

Normal Inheritance

Gene Drive Inheritance

Altered gene does not increase

Altered gene is always inherited due to gene drive
Some ethical questions about gene drive

1- the risk of off-target effects and an inactivation of an other gene than the target gene.

2- the risk of transversal diffusion of the guided gene which would contaminate organism populations other than that of the target population.

3- the environmental impact resulting from the eradication of a “harmful” population/pathogenic to humans, but that may nonetheless play an important role for biodiversity.

4- the risk of unwanted side effects of the guided gene for man (appearance of other pathologies associated with guided gene).
Wrap-Up / Proposals

• A moratorium seems implausible because the idea does not seem to be benefitting from the same international consensus as the 1975 Asilomar conference did.
  • Example Bärbel Friedrich quoting the Leopoldina 2015 report « research should not not be halted or hampered »

• 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
  • Katherine Littler (Wellcome Trust) « nothing should be automatically ruled in or out before it had been fully explored »

• 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.
  • We also have heard Anne-Sophie Lapointe (patients association) : “we are here for help and hope.”

• 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.
Therefore we propose the following principles:

**Encourage research** aimed to evaluate the efficacy and safety of CRISPR technology in experimental models that would allow on a case-by-case basis to determine the risk/benefit ratio of a certain therapeutic application, including possibly on germ cells and the embryo and/or gene drive.

**New approaches** should be encouraged. Pluri-disciplinarity. For example learning from evolution/coevolution to learn more about transversal gene transfer and its impact on physiology.

On a general point of view we need to **think systemic** and to be aware of the ecosystem instead of focusing only on one single gene.

**Increase awareness of scientists**
Encourage research aimed at creating the tools to evaluate the efficacy and safety of CRISPR technology in experimental models that would allow on a case-by-case basis to determine the risk/benefit ratio and the needs for a rationale guidance.

We need to set-up an international steering committee of experts to determine the methods that will raise standards and references. These methods and standards will evaluate:

- Acceptable level of off-targets
- read-out for off-target, mosaicism..
- read-out for epigenetic effects

The Steering committee should co-opt stakeholders for an open and transparent process.
The potentially adverse effects of gene drive should be evaluated before any use outside of a laboratory/open field and should fulfill containment rules already in place for other genetic modifications. Evaluations should be done over long periods taking into account the transmissibility of the gene-drive.

Measures of reversibility should be laid down for exhaust or adverse effects.

Such analysis and the development of multiple scenarios require the creation of multidisciplinary teams combining expertise ranging from molecular biology {ecology and various social sciences, with a careful evaluation of the benefit / risk in the long term.
Draw attention to the more philosophical questions that juxtapose the plasticity of living matter with the idea of human nature as being solely based on biological invariants. The objective should be to raise awareness on necessary distinctions to be made between utopian desires and dystopias that certain therapeutic promises can provoke.

As such, ethical debates within the life sciences require the necessary acculturation to our disciplines, and situate science at the heart of culture and society as a whole. Recommendation to create a monitoring group interested in the societal aspects of genomic technologies.

The need to be pro-active to prevent hijack by extremists

Open and transparent process

But we also have to face our diversity: science, culture and geopolitics
Paris 16/03/16 was the **Initial** step

White paper to come: « Fostering Responsible Research with Genome Editing Technologies: a European Perspective »

Vienna 07/09/16 “Fighting Malaria with CRISPR/Cas9: Ethical implications”

Buenos-Aires 01/11/16 as a satellite symposium of the GFBR

India end of February 2017 with ICMR and DBT

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