

REPORT

FOSTERING GLOBAL RESPONSIBLE RESEARCH WITH CRISPR-Cas9



with the courtesy of the Mc Govern Institute for brain research (MIT, USA)

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Buenos-Aires, Argentina¹

Steering committee:

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25 experts (scientists, bioethicists, policy advisors) were gathered together to discuss the ethical and scientific issues raised by CRISPR/Cas9 and genome editing technologies

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WORKSHOP PROGRAMME

Welcome Coffee

▶ 09.30 – 10.00•

Welcoming remarks

- ▶ 10.00 – 10.30•
- ▷ Florencia Luna, Argentina
Latin American School of Social Sciences (FLACSO) and National Scientific and Technical Research Council (CONICET)
 - ▷ Hervé Chneiweiss, France
Inserm Ethics Committee

I – Setting the scene

▶ **Moderator:** François Hirsch, France
Inserm Ethics Committee

▶ 10.30 – 11.15²• **Human genome editing: Scientific and ethical considerations**
▷ Hervé Chneiweiss, France
Inserm Ethics Committee

▶ 11.30 – 13.00• **A Global thinking**

Wellcome: a funder's perspective³

▷ Katherine Littler, UK
Wellcome Trust

The regulatory framework of Argentina⁴

▷ Fabiana Arzuaga, Argentina
Argentina Regenerative Medicine Commission, Ministry of Science, Technology and Productive Innovation

A Global Position?⁵

▷ Peter Mills, UK
The Nuffield Council on Bioethics

▶ 13.00 – 14.00• **LUNCH BREAK**

² 45 mns talk + 15 mns discussion

³ 15 mns talk + 5 mns discussion

⁴ 25 mns talk + 5 mns discussion

⁵ 25 mns talk + 15 mns discussion

II – Round Table⁶ - What Recommendations?

▶ **Moderator:** **Florencia Luna, Argentina**

Latin American School of Social Sciences (FLACSO) and National Scientific and Technical Research Council (CONICET)

▶ **14.00 – 16.30•**

▷ **Florencia Braga Menéndez, Argentina**

Fundación Investigar and Argentina Federation of rare diseases (FADEPOF)

▷ **Xavier Soberón Mainero, Mexico**

National Institute of Genomic Medicine (INMEGEN)

▷ **Sergio Surugi de Sequeira, Brazil**

Pontifical Catholic University of Paraná

▷ **Federico Pereyra Bonnet, Argentina**

National Council of Science and Technology (CONICET) and University Institute – Medicine School - Hospital Italiano

▷ **Martina Crispo, Uruguay**

Institut Pasteur International Network

▷ **Noemi Sandra Tirado Bustillos, Bolivia**

Genetics Institute – Medicine School – Universidad Mayor de San Andres (UMSA)

III – Wrap-up

▶ **16.30 – 17.00•**

▷ **Fabiana Arzuaga**

Argentina Regenerative Medicine Commission, Ministry of Science, Technology and Productive Innovation

▷ **Carla Saenz**

Pan American Health Organization (PAHO)

⁶ With all attendees

Introduction

▷ **Florencia Luna**

Latin American School of Social Sciences (FLACSO) and National Scientific and Technical Research Council (CONICET)

This meeting is part of a proposed series of discussions to be held around the globe, designed to promote transparent and sound ethical debates, and contribute to the advancement of a necessary global responsible scientific research and innovation.

This meeting aims at promoting Latin-American discussions on the development of genome editing technologies, with particular reference to human applications. International experts will share their experiences with regard to developing critical thinking, policy and best practices on genome editing, before turning the focus to the Latin-American context.

Thus, some of the questions that we want to discuss during this day are: What are the ethical and legal issues in the context of Latin American countries? How to heighten awareness of decision-makers and promote a sound public debate? How to take civil society into account and how the information should be given to them? How to protect the civil society interest and build trust between scientists and the society? What kind of regulations already exists? What is happening in Latin America regarding gene editing? How to allow CRISPR/Cas9 in a responsible way?

▷ **Hervé Chneiweiss**

Inserm Ethics Committee

The mission of Inserm Ethics Committee is to manage reflection on ethical issues raised by medical scientific and health research as it is implemented within the Institute.

Based on its own report (December 2015), the Inserm ethics committee organised a meeting on the ethical issues raised by CRISPR/Cas9 on March 16th 2016, with various European stakeholders in order to foster responsible research with CRISPR-Cas9. Stakeholders were able to explain their positions and to suggest recommendations. Following this workshop, the Inserm ethics committee has elaborated a White Paper (submitted for publication at the time of the meeting but available on request) presenting the resulting general principles, which aim at guiding research involving genome editing technology and ensuring satisfactory compliance with ethical standards. Due to rapid scientific advance in this field, these principles will almost certainly require further refinement. However a main aspect of the European consensus is the involvement of all players and the present meeting is intended to involve our Latino-American colleagues in the discussion to gain from their feedback.

I – Setting the scene

Human genome editing: Scientific and ethical considerations ▷ Hervé Chneiweiss

Inserm Ethics Committee

CRISPR/CAS9 and other genome editing technologies (i.e. C2c2) is an incredible pace of scientific discoveries and technical breaks. These technologies come as an essential part of the convergence with cheap high-throughput sequencing since it is possible to buy the human genome for less than \$1000 (whole exome for less than 400\$) and powerful bioinformatics.

The ethical question that CRISPR/Cas9 raises is: What kind of new interventions this may allow on our body (including human embryos and human brain) or on our environment?

The debate on genetic modification is not new (Asilomar 1975) but genome editing is now precise, efficient, rapid and not expensive.

It is our duty to define what is possible, to overview and not automatically to promote.

Scientific considerations focused on human being:

Some potential applications for genome editing of human cells:

1. Basic understanding of human biology: role of specific genes or LncRNA.
2. To create models of human disease in vitro: genetic disorder, cancer.
3. To treat disease targeting somatic cells.
4. Germline changes to avoid/prevent genetic disease.
5. Germline alterations to give “genetic enhancement”.

CRISPR/Cas9 derived methods are not only able to change the architecture of the DNA, but it may also modulate its functions.

There are situations where actual methods such Preimplantation Genetic Diagnosis (PGD) are inefficient to prevent death threatening diseases. The genome editing methods may turn out to be more efficient and perhaps more reliable. But the proof of concept for efficiency, reliability, and absence of toxicity or deleterious side effects such as off-targets hits remains to be done.

Stages at which genome editing could be used to modify the human germline:

- At fertilization
- In zygotes
- 2-cell to blastocyst stage embryos
- Post-implantation stages
- Postnatally
 - (a) maturing eggs in the ovary
 - (b) spermatogonial stem cells

- Via induced-pluripotent stem cells and in vitro-derived gametes

Clinical uses:

- Somatic: intended to affect only the individual who receives them, they can be appropriately and rigorously evaluated within existing and evolving regulatory frameworks for gene therapy, and regulators can weigh risks and potential benefits in approving clinical trials and therapies
- Germline: would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application

Following the European workshop organized by Inserm – 16 March 2016 - a White-Paper has been written with these recommendations:

- Raising 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

The White-Paper reveals the different approaches that European scientists and countries have regarding genome editing. While some were asking for a moratorium, others were more for a free use of CRISPR/Cas9, but with a sound scientific and ethical oversight. It is also essential to clearly distinguish academic research that needs freedom, and translational research or clinical applications that need a careful ethical evaluation.

Ethical considerations focused on human being:

1. The risks of inaccurate (on-target, or off-target) and inefficient (mosaic) editing.
2. Insufficient knowledge of human genes, genomes and genetic variation, and their interaction with environmental factors: The difficulty of predicting effects (positive or negative) that genome editing may have.
3. The obligation to consider implications for the individual born and for future generations who will carry the genetic alteration.
4. Once introduced into the human gene pool, genetic alterations would be difficult to remove and would not remain within any single community or country.
 - Need comparisons with natural mutation rates and the risks associated with human reproduction in the absence of genome editing.
 - If the change being made is to an allele that already exists in human populations, then is this a legitimate concern?
 - The alteration might correspond to a novel linkage with flanking gene sequences. Even then, genome editing could be used to reverse the alteration.

5. The possibility that permanent genetic “enhancements” to subsets of the population could exacerbate social inequities or be used coercively (including by governments).
→What constitutes an “enhancement”? And would these be different from other types of enhancement already in use?
6. The moral and ethical considerations in purposefully altering human evolution using this technology.
→But could there be situations where this becomes necessary?
7. The danger of “rogue” clinics offering unsafe, untested, genome editing methods to ‘treat’ or avoid genetic disease or for enhancements, and either preying on desperate individuals or on the ego and foolishness of others – whether for somatic or heritable germline genetic alterations.
→ Robust regulation and oversight are needed.

A Global thinking

Wellcome: a funder’s perspective ▷ Katherine Littler

Wellcome Trust

The Wellcome has stated its position in the ‘Initial joint statement’; however it is committed to reviewing this, in light of ongoing ethical reflections, public discussions and scientific advances. Wellcome would also like to bring more partners on board and consider how to reflect the views of non-UK based funders in the statement.

The Wellcome supports full and inclusive exploration of scientific innovation, including the social context, the ethical complexities and public engagement, and so the use in research and in clinical trial when using somatic cells, and also the therapeutic potential of genome editing. Nothing should be automatically ruled in or out before it has been fully explored.

The engagement of the Wellcome concerns the funding of studies to review past engagement activities, participating and funding regional discussions, learning lessons from other similar technologies from international experiences, producing material to help to explain the technology, so that the public can engage in discussions around the topic.

Wellcome Trust specifies that there is a need to engage the government in the debate as early as possible.

Next:

- work in partnership and focus on an ethical engagement
- Bill & Melinda Gates Foundation is working on principles for funding studies using genome editing technologies, with specific reference to gene drives

The regulatory framework of Argentina ▷ Fabiana Arzuaga

Argentina Regenerative Medicine Commission, Ministry of Science, Technology and Productive Innovation

How to think and promote regulatory framework for technologies that have no regulation at all?

In Argentina, there are 2 commissions: an interdisciplinary commission and a biobank commission. The patients association is the biggest in Argentina, gathering together 40 patients associations. The ministry of Science is the main founder for national and international research projects.

For stem cells researches, we talk about advanced therapies and try to harmonize the legislation with the international standards. Regarding the biobanks, there is no regulation. The role of the Ministry of Science is then to think about the main issues and to promote communication with the public organisms and population. The ministry points out the gaps in the law, which come from the lack of information to the legislators.

The problem is that political decision-makers do not understand exactly the extended uses of these new technologies, their risks. In the same time the federal system of Argentina limits the likeliness to take decisions and set them in motion. Political decision-makers do not have the enforcement powers.

In 2016 the Ministries of Science and Health have designed a bill on advanced therapies, the creation of a comprehensive regulatory framework, supported by soft law aspects working with ethics committees, communicators, patients associations.

Cellular therapies were regulated under the regulation of proceeding more than as a product, but it did not guarantee to the patient community the best practices of manufacturing. Now it is considered as a medical product with all the requirements for the commercialization of a medicament.

One of the issues is a social justice aspect, the accessibility of the product to all the population.

CRISPR/Cas9 and GMOs:

Argentina is one the biggest exporter of GMOs. In lab, researchers must comply with a lot of rules and regulations, and have authorization from the agricultural commission (CONABIA).

It has been agreed that CRISPR/Cas9 cannot be considered as a GMO, because it is not adding a new genetic material.

Gene therapy is a product obtained through a set of manufacturing processes and CRISPR/Cas9 is a molecular tool; for a better control of this, it will receive a special legal categorization.

More generally, the issues regarding CRISPR/Cas9 are similar to those of the biotechnologies. Nevertheless, gene editing definition is not contained in the gene therapy

definition: it is a molecular tool and referred as a medicinal product. In terms of sanitary control, both have different approaches. Regarding the clinical uses in human, there are not enough data to justify applications in human reproductive contexts.

The lack of information at the societal and legislative levels can be filled by a context and social values analysis.

A Global Position? ▷ Peter Mills

The Nuffield Council on Bioethics

A global position on genome editing does not exist, but we can try to think about whether and to what extent a global position/consensus might be possible and desirable, with consequences of subsidiarity and differences in cultural diversity.

Nuffield Council still does not have a position, it has published the first piece of work looking at genome editing from the point of view of the technology and thinking about the conceptual questions raised and a more normative consideration of 2 areas applications of genome editing: in human being and in livestock.

Genome editing technologies raise societal challenges, as being part of a set of emerging technologies having an impact on society. The main point is to pay attention to the fact that technologies depend on convergences to a number of different technologies, not only a simple technic and also underlines the knowledge, skills, practices shown through the use of the technic, and it is more concretized for particular purposes.

In this piece of work 3 key characteristics of the emerging biotechnologies are identified:

- ambiguity: find the appropriate frame: which social values?
- uncertainty: the fact that it is often very hard to anticipate the outcomes, the risk management of the implementation of the technology
- transformative technology: the technology never stops to be improved.

The use of genome editing technologies needs to be specified, to think about the kind of organisms, the kind of model we are thinking about, trying to define and to arrive to a global position with the different attitudes regarding the alteration of different types of organisms, like human embryos. We also have to think about the purpose and the context the technic is being used (law, knowledge, culture, technologies, etc.). There are thus 2 cases where there is perhaps a **global public interest**:

- gene drive (infection diseases)
- biomedical technologies, especially gene therapy and human reproductive applications

What it means to define a global position in genome editing?

Regarding the geoethics – geography of ethical interest on genome editing, the key thing is how the interest of the global communities are played into the way technologies are deployed.

There are 2 ways of approaching this, 2 framings:

- a question of public health, it is a question of welfare and social justice
- there are questions that come from environmental ethics: sustainable, precautions, intergenerational justice.

It transforms the natural world through its application. Artefacts have politics, and artefacts bring ethics with them, and there is a lack of care about the ways in which different technological solutions structure our interactions with each other, about the risks derogating the interest of certain groups and communities.

Biomedical research is one area where there is an attempt to create a global position. There are a lot of initial positions taking: UK research funders, Hinxton group, National Academies of Sciences and Medicine/Royal Society/Chinese Academy of Sciences, Inserm.

The question arises to what extent this is a possible and relevant and successful enterprise. But the thesis of this potentially fails, because of the nature of the technologies. Unlike the DNA technology, which was at the time capable to be achieved by a small number of scientists, the use of CRISPR/Cas9 is much less constrained to that, because it needs fewer resources in terms of money, scientific knowledge.

The separation that Asilomar and the other initiatives implicitly tried to do between research and applications on the one hand, between technic and technology on the other hand is constantly under threat, and risks failing. One reason for that is the character of this technology, but also there is a kind of reached through the public interest into genome editing research. The research has already different kind of applications.

Consequences of that are that the decisions cannot be entirely retained, even now for basic research. We have to distinguish 3 particular kinds of ethical concerns that arise:

- 1- the notion of technological dimension: technology has its own forward forth and excludes decision points of human agency
- 2- the familiar slippery slide walking: something that becomes acceptable, but moved down through a change of reasoning to a point where there is the absurd consequence that you are effectively committed to approve something you would not
- 3- the idea of function creep: when a new technology is introduced to do one thing (one function), and is later used for an entirely different thing.

Ultimately, the more feasible, 4- the ethical arbitrage: characterised as a process that would annihilate differences between more and less restrictive jurisdictions through free movement among them.

When we talk about governing genome editing responsibly, we talk about scientific regulation, self-regulation, and the reached through the public interest. It raises that question: how that public is constituted and how that interest is articulated?

Regarding the human rights, in a democratic system approach, what is important is going up reflective activities that engage interested persons, in order to constitute the public interest. How do you interest the different groups that become the public interest? Because of the transformative nature of genome editing technologies, ambiguous, they require redoubled attention to broader and different ways of valuing and imaging the cause.

For more information see Peter's blog:

<http://nuffieldbioethics.org/blog/2016/crispr-south-america-case-liberation-genomics/>

II – Round Table What Recommendations?

▷ **Florencia Braga Menéndez** (Not present)

“Running A GE Animal Facility In Uruguay” ▷ **Martina Crispo**

Institut Pasteur International Network

Use CRISPR/Cas9 on rats, mice and sheep: transfer embryos into surrogate females.

The Lab has used different techniques:

- DNA microinjection
- Homologous recombination in ES cells
- Lentiviral transgenesis
- Transposons
- Lately CRISPR/Cas9

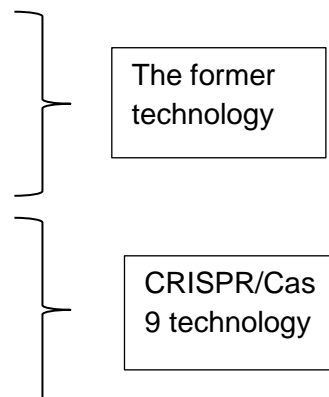
Example 1:

CRISPRs system improves the overall efficiency in small transgenic facilities

Maria Noel Meikle¹, Geraldine Schlapp¹,
Ana Paula Mulet¹, Adrián Capoano², Adriana Geisinger²,
Martina Crispo¹

Our results showed that 24 ES cells microinjection sessions were needed to produce three chimeras that were fertile but unable to transmit the mutation to the germline. The post injection embryo survival rate was 87.6 % (990/1130) while the global transgenesis rate was 0.30 % (3/990). Additionally, 280 female mice were used as embryo donors and 60 foster mothers for embryo transfer. On the

other hand, 31 mutant mice were produced in only four CRISPR injection sessions, 12 of them showing double mutation. Moreover, at least one of these males was fertile and produced 100 % mutant pups (13/13). The embryo survival rate after microinjection was 60.8 % (275/452) and the global transgenesis rate was 11.3 % (31/275). Furthermore, 31 females were used as embryo donors and eight females as recipients. Our data indicates that CRISPR



Transgenic Res (2016) 25:195–270

Example 2: CRISPR/Cas9 system injected into cytoplasm of ovine zygotes to produce

MSTN mutant lambs.

Overall efficiency.

- 50% of mutant embryos = very high, before very difficult
- 45% of mutant lamb born

Sheep are still alive and continue to grow.

It is more efficient with knock-out than knock-in.

The Lab is using CRISPR/Cas9 for 2 years now. It has a huge applicability, very efficient. CRISPR/Cas9 facilitates knock-out animal regulation for animal consumption, which will be for scientists very good, able to work faster and easier.

“Fostering global responsible research with CRISPR-Cas9-INMEGEN point of view”

▷ **Xavier Soberón Mainero**

National Institute of Genomic Medicine (INMEGEN)

Bioethics discussion from the outset:

Fact: Following the recently reported birth of a child conceived using a technique of mitochondrial donation conducted by a US research team, public IVF services in Mexico had been suspended.

INMEGEN was created to conduct research around the human genome to improve health, including gene therapy (Law of the National Institutes of Health), and in the same time the Organic Statute was required by the same “Diputados” that passed the previous law, creating the Institute, to specifically forbid: “In no case will it conduct research on human stem cells from live embryos, or those obtained by nuclear transplant”.

Quite a few scientists have worked with transgenic mice and flies without opposition. All this has started to change with CRISPR-Cas9, e.g. new work with Zebra Fish and *C. elegans*, human cancer cell lines, at least, but there is no work with human embryos.

As long as it is not manipulating genomics technologies, but just studying and understanding the genome, there is no significant reject. Nevertheless, the risk is the revamping racism and discrimination. The anti-movements concern more animal rights and GMOs.

There is no regulation in genome editing, but on GMOs uses in agriculture. It is subject to high scrutiny. Every works on DNA should be approved and registered. It is then becoming urgent to have specific legislation pertaining to gene editing of human tissues, and the 3 parents baby will force the debate. This legislation should distinguish germline and somatic gene therapy.

People know about it, but as it is not used in the country, there is no real debate. Politically, the conservatives will be very active, specially trying to stop any form of manipulations of the embryo, but there would be people promoting gene therapy and basic research.

There is a regulation that is being passed, which is more a prohibition, especially research in gamete, what is going to happen in the private sector?

The law will apply to the private sector, and the project prohibits certain manipulations of the embryos that would mean prohibit mitochondrial replacements. This law is a backwards, it would be in discussion, and it should take into account that there are different technologies and different applications, a case by case analyze.

In Mexico city, some of the politicians are more liberal (abortion has been legalized), but the majority of politicians will remain in the conservative cloud.

Regarding the civil society in general and the engagement community, we do have patients groups that their rights are not denied, but those groups are not so visible.

Assisted reproduction is done, but it is unregulated, and recently, it has been stopped.

“Gene Editing in Brazil-Brief remarks on the current scenario of ethics in research”

▷ Sergio Surugi de Siqueira

Pontifical Catholic University of Paraná

Legal and regulatory issues in Brazil concerning genetic manipulation:

Legal and regulatory bodies:

- CNTBio-National Biosafety Technical Commission is a multidisciplinary consulting and deliberating collegiate which provides technical support to the Government.
- ANVISA-Brazilian National Health Surveillance Agency is responsible for the approval, inspection and regulation of any products which involves the possibility of risk to health obtained as the result of genetic engineering.

Regarding the genome editing engineering:

- Just one article (6th) in the National Law of Biosecurity (Law 11.105 – March 24th, 2005): “...It is banned genetic engineering in human germinal cells, human zygotes and human embryo.”
- This law has 41 articles and primarily was directed to legislate on genetically modified crops.
- Due the lack of specific legislation on human research and assisted reproduction, the guidelines in these issues are the resolutions (not laws) enacted by CONEP or CFM.

There are no relevant initiatives to regulate it.

- CONEP/CNS-Brazil’s National Committee for Ethics in Research, whose members are appointed by the Health Ministry’s National Health Council (CNS).

CNS Resolution #466/2012 (main guideline for ethics in research in Brazil) has no reference to the issue of human embryo research, but merely determine that all researches in the country, must be evaluated by an ethics committee in research.

Gene editing in Brazil:

As researches involving human genome manipulation of embryonic stem cells are forbidden in Brazil, these researches are focused on *in vitro* or *ex-vivo* gene editing in somatic cells. The discussions, at this time, are restricted to some scientific associations and universities and this issue is ignored of the current discussions at the political level.

Regarding the public interest, social movements and religious instances are not yet expressing opinions or guidelines specifically on this subject.

The scientific community, which has started working with CRISPR/Cas9 is asking for an ethical and a legal framework, and for this, scientists should work together with the legislators in the promotion of a regulatory framework on genome editing technologies.

Regulatory bodies in Brazil have become more flexible regarding the application of genetic engineering. An example is the recent CNTBio approval of the use of genetically mosquitoes to fight dengue epidemics.

The experiments with germlines in Brazil are forbidden. There exists one law on biotechnologies, which is an umbrella law prohibiting those practices. There is no research in germlines. The main concern because it is very cheap: how can we control if someone use it?

We need to engage the regulatory agencies, but scientists' community is not here now, because the issue is to catch up the technology. Nevertheless, we should be prepared for this kind of discussion the regulatory agencies. The initiative of self-regulation should arise from the scientists, knowing that evidence based knowledge is not the basis of the politicians.

Remark from François Hirsch: In France the regulatory agency for medicine has appointed a person who surveys the new technologies and guides scientists on the regulation in force.

"CRISPR the new Bio-revolution in the bench" ▷ Federico Pereyra Bonnet

National Council of Science and Technology (CONICET) and University Institute – Medicine School - Hospital Italiano

Not all is about the DNA sequence. There are a lot of marks over the DNA that regulate the gene expression: epigenetics. Nowadays the genome is compared to a computer hardware because is rigid; and the epigenome is the software because is plastic and can change all the time.

There are variants of CRISPR, one of them is called CRISPR-ON. CRISPR-ON is almost the same that traditional CRISPR but the scissors are broken, so the DNA will not be cut. If we change the epigenetics marks from one gene we are doing epigenetic editing and it is very different to gene editing because we are not making transgenesis. In addition, if these changes are focused to treat one disease and we use it directly in the patients, we are doing “Epigenetic Therapy”. For instance, using CRISPR-on we activate the INS gene in fibroblasts from patients with Diabetes, changing only their epigenetics marks.

CRISPR-ON does not cause genetic modifications. This is a clear advantage if we are thinking about translational medicine. The CRISPR-ON system could be used for future epigenetic therapies. As all new technologies, CRISPR must be still restricted to research to be deeply tested, before it becomes a real option to treat human diseases.

Question 1: Can we regulate the expression of one gene changing only its epigenetic marks?

Question 2: Can CRISPR change these epigenetic marks without modifying the DNA sequence?

There are a lot of regulations and ethical committees, but now we need a law.

Publication: Giménez, C. A., Ielpi, M., Mutto, A., Grosembacher, L., Argibay, P., and Pereyra-Bonnet, F. (2016). CRISPR-On system for the activation of the endogenous human INS gene. *Gene Therapy*. [Online]
<http://www.nature.com/gt/journal/v23/n6/full/gt201628a.html>

Comments:

In countries like Peru, there is a regulation for clinical trials, but not for CRISPR/Cas9. Researchers are looking for guidance to know until where there are allow to do research and where they have to stop.

Genetic Research in Bolivia ▷ Noemi Sandra Tirado Bustillos,

Genetics Institute – Medicine School – Universidad Mayor de San Andres (UMSA)

Noemi is a research professor at the Genetics Institute, responsible for the Genetic Toxicology Unit, assessing genetic damage and risk in human populations exposed to environmental contaminants such as heavy metals, pesticides, chemicals and radiation. Technical approaches include effect biomarkers (Micronuclei in buccal cells and binucleate cells in lymphocytes, keratin assay and sister chromatid exchanges), individual genetic susceptibility biomarkers (PCR genotyping and RTPCR of different genes related to detoxification enzymes, DNA and cancer).

The results obtained allow us to alert the population of the effects of an exposure in the genetic material, anticipating a degenerative disease or cancer.

Bolivia is a multicultural and multiethnic population. All researchers are approved by the REC of the University. There is also a national ethics committee. Nevertheless, there is a lack of specific legislation on assisted reproduction and for manipulation of stem cells.

There is no research on gene editing, but all the advances in genetics in Bolivia were carried out with counterparts in collaboration with other developing countries:

- Genetic microbiology
- Genetic toxicology
- Nutraceutical food
- Human genetics through biomarkers

As they do not use these technologies, there are no discussions, but there is a need for a debate before introducing these technologies in Bolivia.

There are only some made for crops, access to the genetic sources. A law exists to protect these genetics sources, done in 2013 (Law nº 530).

We have to take into account many aspects as Latin America:

- Sociocultural issues
- Technological development
- Respecting principles of bioethics as no maleficence, beneficence, autonomy and equity
- Human rights, public health sustainability precaution intergenerational

There should be a multidisciplinary work in order to regulate, to have some rules to work with gene editing technologies.

Miscellaneous from the round table

- What should be the role of the pharmaceutical industries?
- Among problems the region already faces with the GMOs: what will happen with MOGE (modified organisms by genetic engineering). There is a need for a case-by-case analysis including toxicology.

If there are successes with this technology, the early engagement of the community is crucial, because the public needs to understand the concepts: **who would drive this issue?**

- The academic level could be the first stage of initiatives, because it is able to explain goals and purposes to the population about scientific knowledge.

We have to prepare the patients before CRISPR/Cas9 arrives to Bolivia. Examples:

- Cultural diseases: patients are informed of the existence of these technologies and use it to have a good health for their babies, that these stem cells are able to treat everything

- Some private companies enroll people to do some clinical trials: there is a gap and to regulate the applications of the new technologies is the most important, not too much regulations for the researchers, or regulate both.

- Related to the situation in Bolivia, in Chile, scientists would have to drive the initiatives, and not the agencies or political decision-makers to set regulations into motion.
- Scientists would be much better served if they concentrate on the real needs of the population and treat patients with genetic diseases.
- We need to have specific vectors for specific patients; we have to think about the empowerment of the local systems that need to be fostered.
- This kind of technologies will also raise the question of costs, social justice, and assurance. Society is not about equity in Latin America. Politicians are conscious about the political powers and the industrial companies are concerned about the economic interests: so those issues are not at all in the political agenda. Regarding this technology, the main effort should be not to speed up things but to develop slowly and steadily a system which will be able to lead scientific process with social justice.
- The process should be simplified. Isn't the role of bioethicists to fill the gap, to provide that community engagement (public education and sensitization)? The public can understand the issues involved. And bioethicists, a social force, will know how to drive the process, and engagement will follow with political initiatives.

III – Wrap-up

Conclusion ▷ Carla Saenz

Pan American Health Organization (PAHO)

It has been acknowledged by everyone that CRISPR/Cas9 has a great potential overall. The main ethical challenges are in its use in the germ line because of the transformative nature of technology, which implies risks for future generations. What should we do? How should we assess risks?

In the Latin-American region there are additional concerns such as the risk of revamped racism and discrimination, the lack of laws and regulations, and the "backwards" laws currently in the works in some countries.

What should we do?

A consensus is a starting point, and it is important to underline that nothing should be automatically ruled in or out before it has been fully explored.

We should proceed with a case by case analysis, since no simple solution does the work. There should be no "moratorium", because research is important and has great potential. It is also not possible to produce some "general law" that dictates how to proceed in every circumstance regarding genome editing technologies. Specific characteristics must always

be taken into account when doing rigorous case by case evaluations, which must be informed by the correct understanding of science. In order to do so, experts will have to be trusted. The engagement with the civil society, legislators and policy-makers is crucial.

Procedural approach:

1. We need a process of ethical arbitrage to ensure responsible governance:
 - Rigorous evaluation of each case
 - Risks and benefits assessment
 - Consensual assessment of risks (at the regional or global level because of the wide potential impact)
 - Legitimacy
2. Engagement
 - Foster wide dialogue, include civil society
 - Accuracy, effectiveness and equity should play a key role.

Can we build on the "lessons learned" in other areas of research ethics?

We should stay away from categorical prohibitions or overregulation that cancels the potential of these technologies while ensuring that the conduct of research and the use of technologies is ethical (responsible).

Scientists, ethicists, legislators and regulators should figure out early on what is right from a legal / regulatory perspective, and find a balance to allow for thorough case by case evaluations while avoiding "predatory" practices.

Ethicists and regulators need to provide meaningful guidance. It is also necessary to enhance trust in each element of the research ethics system by promoting productive collaboration between all the stakeholders: scientists, ethicists, regulators, decision-makers, civil society, and by proactively informing the population.

After this workshop, the next goal is to know how we can catalyze ethical CRISPR/Cas9 research and the ethical use of such research. The Regional Program on Bioethics of PAHO proposes to serve as a forum to discuss these issues, raise awareness, and advance consensus.



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