Comité
d'éthique
de l'Inserm

FOSTERING GLOBAL RESPONSIBLE RESEARCH WITH CRISPR-Cas9

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Declaration of links of interest

President of the Ethic committee of Inserm (National Institute for Research in Health and Medicine)
Member of the French National Ethic committee (CCNE)
Member of the International Bioethic Committee of Unesco

Head Neuroscience Paris Seine (Inserm/Cnrs/Univ. Pierre & Maris Curie)

I declare that I have no conflict of interest concerning the data contained in this presentation

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Ethical aspects of biomedical research

Trois pôles de l'agir: "*ma liberté, ta liberté, la règle*"
Three dimensions of action: "my freedom, your freedom, the rule »

A l'affirmation par soi de la *liberté*, s'ajoute la volonté que la *liberté de l'autre* soit.
On the assertion of my own freedom, there is in addition the desire for the freedom of the other.

Visée de la vie bonne, avec et pour les autres, dans des institutions justes.
Aiming for the good life, with and for others in just institutions.

Paul Ricoeur

Distinction between ***ethics*** and ***deontology***
importance of one and the other:
* First and open sights of reflection,
* And meet the demands increasingly clear of regulations and limits that is a paradox of our societies concerned with regard to the normative.

Roots of ethics in modern biomedical research

4th century BCE, Hippocrates: "to help and do no harm" (*Epidemics*)

« Le principe de moralité médicale et chirurgicale consiste donc à ne jamais pratiquer sur un homme une expérience qui ne pourrait que lui être nuisible à un degré quelconque, bien que le résultat pût intéresser beaucoup la science, c'est-à-dire la santé des autres. »
Introduction à la médecine expérimentale 1865
Claude Bernard (1813-1878)

"The principle of medical and surgical morality therefore is to never practice on a human being an experience that could only be harmful to her/him at any degree, although the result could be of great interest for science, that is to say the health of others. »
in *Introduction to Experimental Medicine* 1865
Claude Bernard

Roots of ethics in modern biomedical research (2)

Lettre du 22 septembre 1884 de **Louis Pasteur** à l'empereur Pedro II du Brésil pour lui demander d'expérimenter le vaccin contre la Rage et des traitements expérimentaux du choléra sur des condamnés à mort.
Request to test innovative treatments against rabies and cholera on prisoners in the death row.

The **Eugenic ideology** including in democratic countries such as France:

Charles Richet - Nobel Prize 1913 - a freemason (GODF); a Dreyfusard; a pacifist; but the founder of the French Eugenics Society: "... after the elimination of inferior races, the first step towards the *(human)* selection, it is the elimination of the abnormals » - The Human Selection 1913

Alexis Carrel Nobel Prize 1912 " in Germany, the government has taken strong measures against the increase of minorities, of the insane, of the criminals. the ideal situation would be that each individual of this kind is eliminated when he proved dangerous,» Preface to the German edition of the Man, this unknown 1936

1931 in Nuremberg Concept of informed consent

Roots of ethics in modern biomedical research (4)

1979 Tom Beauchamp and James Childress published the first edition of *Principles of Biomedical Ethics* (seventh edition 2013)

1979 The Belmont Report follow-up: guidelines for responsible research using human subjects

1982 Comité Consultatif National en Ethique des Sciences de la Vie et de la Santé

1. **Respect for Autonomy/ Informed consent**
2. **The Principle of Nonmaleficence**
3. **The Principle of Beneficence**
4. **The Principle of Justice**

Ethical issues raised by **Genomic Research** are not necessarily unique or exceptional, **but the significance of the genome in human existence** generates powerful reasons both to intervene when function is damaged and to proceed with caution before intervening without good evidence of safety and benefit

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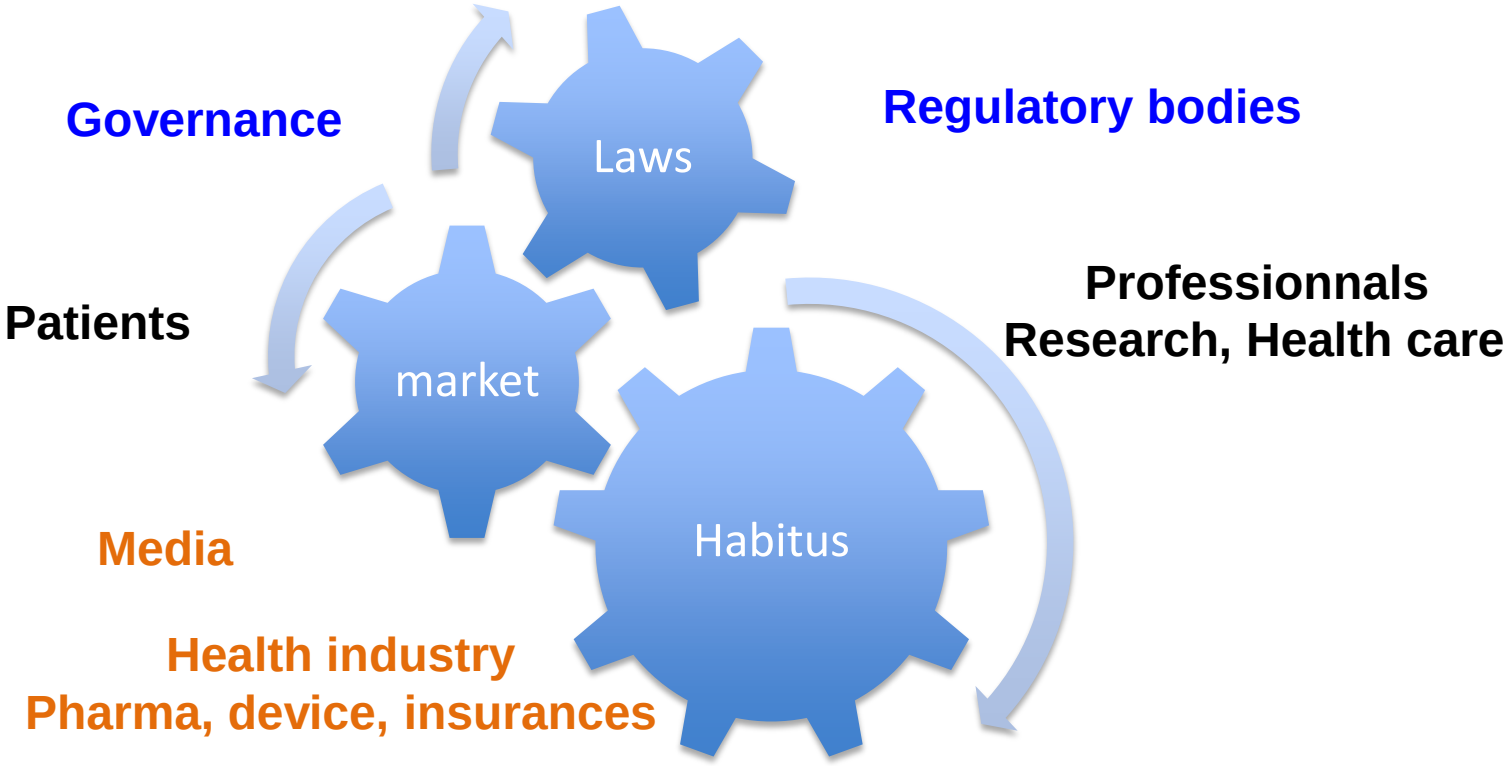
A global challenge (2): multiple stakeholders



Acknowledging that different stakeholders will have different views on what is good or valuable and what ought to be done

Missions of CEI

- Encourage reflection on the ethical issues raised by scientific medical research and health research as it is implemented within the Institute.
- Closely associated with the practice and everyday life at Inserm
- Supports the staff of the Institute to identify and integrate ethical issues into the design of their research projects and their practice
- Coordinate reflection within Aviesan.

Missions of CEI

- **Anticipate conditions for implementation of innovative researches and advice on ethical rules to support them, particularly from the perspective of their impacts and consequences**
- **Educate research staff on the importance of ethics, to ensure a fair balance between intellectual freedom and duties vis-à-vis the Institute and society**
- **Contribute to the organization of public debates, in emerging areas of biomedical innovation.**

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Methods

- Sixteen members appointed for a period of 3 years
- Diversity according to Gender (9/7), activities (Bio / SHS; Inserm / other), geographical origin (Belgium, Switzerland), 1 rep. asso. Patients
- Interface with other bodies concerned with INSERM ethical issues: CS, BIC, DIS, collective expertise, GRAM, Workshops Inserm
- Interface with other EC research organization

- Working groups with auditions of experts
- Plenary session each month to discuss the progress draft reports
- Open draft papers
- Annual open meeting (last meeting 13th June 2016, next 14th June 2017)

- Notes on-line
  - **Research on human embryo: proposals. Coord. P. Jouannet**
  - **Unexpected discoveries in biomedical research. Situation analyzes and proposals of management methods. Coord. F. Eisinger**
  - **Gender and research in health and medicine. Coord. C. Vidal, J. Merchant, M. Botbol-Baum**
  - **Management of research in the South Coord. C. Longuet**
  - **Saisine Marthe Gautier. Coord. M. Brodin**
  - **Saisine Declaration of links of interest Coord MC Lecomte & G. Moutel**
  - **Saisine IRESP Addiction to money games Coord. G. Moutel**
  - **Ethical challenges of CRISPR/Cas9 technologies Coord. H. Chneiweiss**

- **http://www.ethique.inserm.fr/qu-est-ce-que-l-inserm/l-ethique-a-l-inserm/saisines-et-avis-du-comite-d-ethique#**

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Instituts thématiques

Inserm

Institut national
de la santé et de la recherche médicale

Pour tout contact avec le comité d'éthique de l'Inserm

Comite-ethique@inserm.fr

Many thanks to the Steering committee:
Fabiana Arzuaga, Solveig Fenet, François Hirsch, Adrienne Hunt, Katherine Littler, Florencia Luna

Thank you for your attention

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Ethics in biology of reproduction research

Three propositions of discussion:
1- genetic tests / choice of the sex
2- genome editing of gametes
3- iPS and gametes

The integrity violations may include all activities of the researcher:
the research themselves,
student training
evaluation,
the dissemination of knowledge to the workplace, donors and the general public

The most serious cases involved the fabrication, falsification, plagiarism and data retention, the latter having potentially significant consequences for the advancement of knowledge, particularly in translation toward clinical trials.

Less severe cases, but more frequent, concern the "voluntary forgetting" of an author on a publication or on the contrary abusive signing, undisclosed conflict of interest in an evaluation process, the non-retention of experimental data or inadequate supervision of students.

One particular area concerns the scientific training deficiencies, particularly in statistics, leading to the publication of good faith of potentially false data.

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Some Reported Reproducibility Concerns in Preclinical Studies

Author	Field Reported	Concerns
Ioannidis et al (2009)	Microarray data	16/18 studies unable to be reproduced in principle from raw data
Baggerly et al (2009)	Microarray data	Multiple; insufficient data/poor documentation
Sena et al (2010)	Stroke animal studies	Overt publication bias: only 2% of the studies were negative
Prinz (2011)1	General biology	75% to 80% of 67 studies were not reproduced
Begley & Ellis (2012)	Oncology	90% of 53 studies were not reproduced
Nekrutenko & Taylor (2012)	NGS data access	26/50 no access to primary data sets/software
Perrin (2014)	Mouse, in-vivo	0/100 reported treatments repeated positive in studies of ALS
Lazic & Essioux (2013)	Mouse VPA model	Only 3/34 used correct experimental measure
Haibe-Kains et al (2013)	Genomics/cell line analysis	Direct comparison of 15 drugs and 471 cell lines from 2 groups revealed little/no concordant data
Elliott et al (2006)	Commercial antibodies	Commercial antibodies detect wrong antigens
Prassas et al (2013)	Commercial ELISA	ELISA Kit identified wrong antigen
Baker et al (2014)	Journals Top tier	fail to comply with agreed standards for animal studies
Vaux (2012)	Journals	Failure to comply with their own statistical guidelines

Begley & Ioannidis Circulation Res. 2015

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Quality to reproducibility Challenges

Recommandations

1. Increase the quality and transparency of scientific records, digital registries
2. Engage our institution in international actions for quality and transparency *Replicability initiative*, EQUATOR, *AllTrials initiative*, *Proposed Principles and Guidelines for Reporting Preclinical Research*, ...
3. Replication initiative for selected results with potential high translationnal impact
4. Contribute to international gold standards for "*reporting guidelines*" and data sharing

Codes éthiques fondateurs	Code de Nuremberg (traduction française in [27])	Déclaration d'Helsinki	Rapport Belmont
Quand, où ?	1947, Etats-Unis	1964, Finlande (dernière révision de 2000)	1978, Etats-Unis
Qui ?	Juges du Tribunal militaire américain de Nuremberg	Association médicale mondiale (AMM)	Commission nationale américaine pour la protection des sujets humains dans la recherche biomédicale et comportementale
Pourquoi ? Précisions	• Expériences des médecins nazis sur des prisonniers en camp de concentration • Trois officiels nazis et vingt médecins impliqués, dont : – Heinrich Himmler : mécène et directeur de la médecine nazie, parfois surnommé «le meurtrier du Siècle». Met en œuvre la solution finale – Josef Mengele : tortures, sévices corporels lors d'expériences médicales absurdes et inhumaines entraînant souvent la mort, à Auschwitz – Aribert Heim : vivisection humaine sur les détenus de Mauthausen	• Fait suite aux atrocités de la Seconde Guerre mondiale • AMM : association internationale de médecins (fondée en 1947 à Paris) dont le but humanitaire est de mettre en place les normes les plus rigoureuses dans le domaine de la médecine, l'éthique et l'enseignement médical	• Création le 12 juillet 1974 du National research act (Loi publique 93348 sur la recherche) • Tuskegee : expériences sur la syphilis (1932-1972, Etats-Unis) : ouvriers agricoles noirs et pauvres, non traités par les médecins (diagnostic donné : «mauvais sang») pour observer l'évolution de la maladie, et ce même après l'efficacité avérée du traitement à la pénicilline. L'expérience cesse en 1972, lorsque le Washington Star [28] révèle l'affaire. N'a jamais donné de résultats concluants • Willowbrook : étude sur l'hépatite (1950-1960, Etas-Unis) : virus délibérément inoculé à des enfants placés en établissements psychiatriques. Selon le formulaire de consentement signé par les parents, est administré un vaccin et non le virus. Justification d'alors : ces enfants seraient infectés de toute manière ; en participant à l'étude, ils seraient mieux soignés.
Principes généraux	• Bienfaisance : rapport risque/bénéfice favorable • Respect du sujet de recherche : consentement volontaire, capacité de consentir, possibilité de quitter l'essai • Justice : utilité pour la société	• Bienfaisance : rapport risque/bénéfice favorable • Respect du sujet de recherche : consentement informé • Justice : distinction entre recherche thérapeutique ou non • Responsabilité : pas uniquement au chercheur, avis extérieur nécessaire (comité d'éthique)	• Bienfaisance : rapport risque/bénéfice favorable (distinction entre risques «minimes» et risques «plus que minimes») • Respect du sujet de recherche : consentement éclairé • Justice : sélection équitable des sujets
Forme	Dix principes fondamentaux	Loi consensuelle, nombreux paragraphes	Paragraphes agencés en trois catégories éthiques et applications

Chenaud et al. Rev Med Suisse 2008;2691-2695