The ethics of regenerative medicine

Session organised by

- **EASAC : European Academies Science Advisory Council**

and

- **Hungarian Academy of Sciences (HAS).**

Contribution by Anne Cambon-Thomsen: issues for Europe

- Anne Cambon-Thomsen, MD, Immunogenetics and health ethics, emeritus research director at the French National Centre for Scientific Research (CNRS),
- Work in an epidemiology and public health joint Unit of the National Institute for Health and Medical Research (Inserm) and the University of Toulouse (UT3, Paul Sabatier), France. Interdisciplinary team. <anne.cambon-thomsen@univ-tlse3.fr>
- Active in several bodies in relation to WSF 2019 theme:
  - Member of a societal platform on ethics and biosciences, Toulouse
  - Research Integrity Officer, for University Paul Sabatier
  - Member of the European group on ethics in science and new technologies (EGE)
  - Member of the governing board of EuroScience and of MURS (Universal movement for scientific responsibility - France)
  - Member of the CODATA international data policy committee
  - Ambassador of the Research Data Alliance (RDA), for health sciences and research ethics
- Former champion of the EuroScience Open Forum, ESOF 2018, Toulouse.

Outline

- Introduction : general considerations
- Precaution and the evidentiary timelag
- The EGE works on various aspects in relation with regenerative medicine and gene editing
- Challenges for Europe
- The common dimensions
  - Regulation and ethics
  - Science and ethics
  - The societal dialogue/debate
- Conclusion

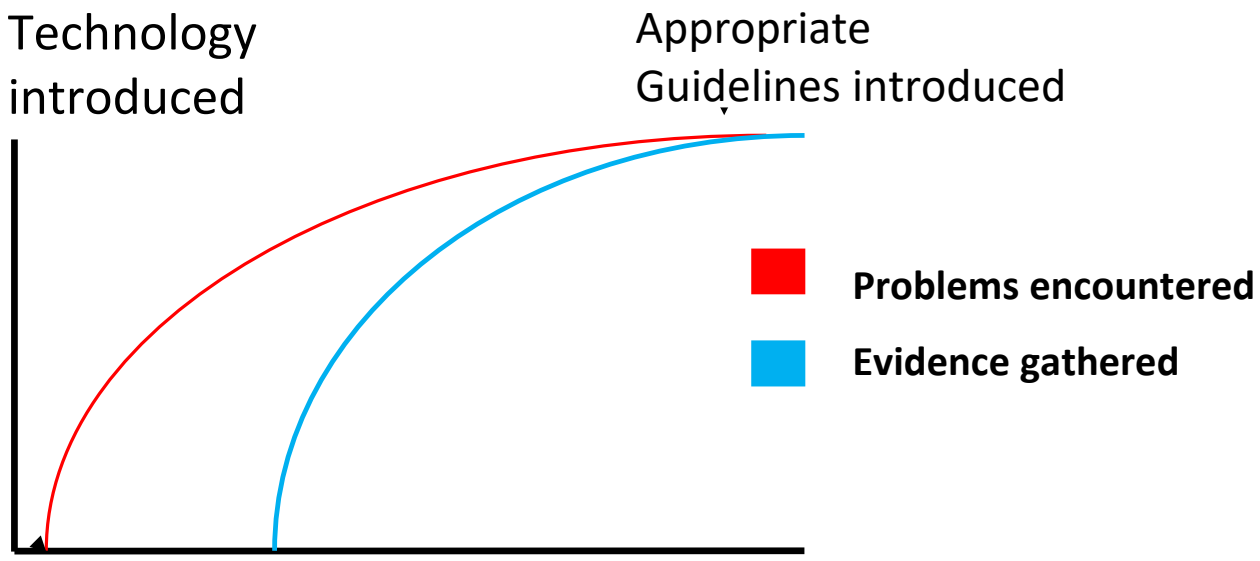
The evidentiary timelag: what is it? (1)

- Decision making in regulating the use of new technologies is depending on numerous factors:
  - technical availability and safety
  - education of professionals
  - public perception
  - adaptation of existing organisations
  - Institutional and other stakeholders responsibilities
  - Economic considerations.
- Whereas research contexts are constantly evolving and intrinsically bound to novelty, applications often suffer from an evidentiary time lag.

The evidentiary timelag: what is it? (2)

- Between the moment when the technology is ready and in principle applicable and the moment when data on issues actually encountered through its application in reality are available there is a time period with lots of uncertainty on how to apply optimally the technology.
- Questions appears without evidence based answers; e.g. what are
  - the good practices?
  - the actual advantages and risks?
  - the best realistic guidelines?
  - the best way of sharing experiences?
- Deciding on a framework to apply new techniques in practice can be difficult.

The evidentiary time-lag *(shutting the stable door)*



Slide from S. Leonard

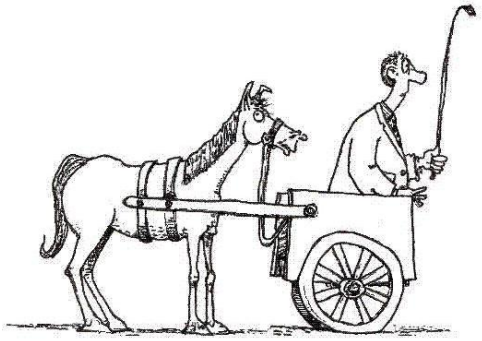
The Cassandra Complex

Ethicists and regulators considered as being
too negative or too late

or

"Just a minute!"

Slide from S. Leonard



Regulations and Recommendations for applications in different domains of regenerative medicine are not stabilised (yet)

As we are technology driven are we…

— *putting the cart before the horse?*

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Ethics at European level

- **Ethics within the competence of the national Member States**
- However the **ethical debate** is present across the European Union and in its institutions
  - EU Charter of fundamental rights,
  - European group on ethics in science and new technologies (counselling EU Commission)
  - Many EU domains incorporate ethics under other « hats » (quality, safety, respect, freedom, protection of citizens (ex GDPR), mobility, health promotion)
  - Ethics components, panels and guidance in research projects
- The EGE : since 1998, 11 **opinions of the European Group of Ethics (EGE)** were related to the uses of stem cells in Europe
- Relation with The Council of Europe Committee on Bioethics (DH-BIO), especially Oviedo Convention (Convention on Human Rights and Biomedicine)

Some ethical challenges for Europe regarding regenerative medicine

- Patient interests first, and involving them into defining those
- Independent and evidence-based sources of information (not publicity!) need to be promoted
- Finding the balance between access to medicine and innovation
  - ✓In the mission letter from the new European Commission President, to the new DG Sante Commissioner, the first priority was *"…to help ensure Europe has the supply of affordable medicines to meet its needs… support the European pharmaceutical industry to ensure that it remains an innovator and world leader."*
- Regulate to fight unregulated provision of regenerative medicine
- Address « medicine » versus « enhancement »

Ethical challenges of genome editing in relation with regenerative medicine

- The EGE works presently on a broad scope on genome editing.
- Some of the elements discussed are related to certain aspects of regenerative medicine

Genome editing : manipulation / *transformation*

- **Genome editing** is a way of making specific changes to the DNA of a cell or organism. An enzyme cuts the DNA at a specific sequence, and when this is repaired by the cell a change or 'edit' is made to the sequence.
- **Available since the 1980s**, these tools have become more efficient and specialized over time
- **A disruptive advance**: Crispr/Cas9 in 2012
  - More specific; easier, cheaper, faster
  - Hence, makes foreseeable possible more efficient genome modifications for therapeutic applications in humans :
    - Somatic cells and germ line modification
  - [As well as in other contexts (animals, plants, microorganisms)]

Genome editing : **rapid dissemination**

- 6 years of massive dissemination/refinement of the technique!
- > 9000 studies published using Crispr/Cas in 6 years
- In humans, clinical trials ongoing (somatic cells) : HIV, thalassemia, cancer…
- Some experiments (not for reproduction) on embryos : **basic research intended to evaluate the efficacy and safety of CRISPR-Cas9 on embryos which will then be destroyed**
- **An experience that shaked the world** (He, a Chinese researcher, who did an experiment of gene modification of humans on two twins who were born in 2018)
- Risks : off-target modifications and mosaicism

Numerous initiatives, statements, organisations

- See : http://ethics-and-integrity.org/ethics/ethicsGenomeEditing.html
- Tools
- **Reports, Statements, and Guidelines > 25 since 2015**
- **Organisation, groups, ethics councils**
- **Industry**
- **Events**
- **Surveys and public dialogues**

EGE statement on gene editing, Jan 2016

- The EGE considers that deliberation regarding the acceptability and desirability of gene editing will require inclusive debate which extends to civil society where diverse perspectives and those with different expertise and values can be heard. This cannot be left to select countries, social groups or disciplines alone. The EGE cautions against reducing the debate to safety issues and the potential health risks or health benefits of gene editing technologies.
- Ethical consideration needs to be given to all applications of gene editing, including the non-human applications. It is likely that many of the practical applications of gene editing will occur in the environmental sphere and will have significant implications for the biosphere.
- call for a broad public debate on these issues and convinced that the EGE will make a useful contribution to these deliberations.

Request for an EGE Opinion on gene editing

- Commissaire Moedas, July 2018

Whereas the precise scoping of the Opinion is of course for you to independently outline, it is important to note that there is tremendous need for your advice both on the bigger picture of this issue and on specific aspects of concern.

The bigger picture pertains to crossing the dividing lines which otherwise limit the ethical analysis: human and non-human; somatic and germline; research and therapeutic and enhancement purposes; agricultural, health, environmental and further areas; existing and future technologies and implications.

As to the specific aspects of concern, they pertain to gene editing applied to animals as well as gene editing in the context of biodiversity and ecosystems, in particular with regard to the development and release of organisms engineered with gene drives.

With regard to animal testing, there is a need to focus on on the development and use of transgenic techniques in non-human primates.

Some issues in human somatic gene editing

- safety, efficacy and the availability of existing treatments alternatives.
- justice and fair access that other costly advanced medical treatments imply for solidarity-based financing of healthcare systems
- novelty or continuum ethical continuum with existing gene therapies ?
- considerable care necessary with respect to ethical aspects linked to consent, rigorous safety assessments, patient oversight and access, basic and clinical research on somatic gene editing should continue given the potential benefits they hold for human health.

Some issues in human germ line gene editing

- highly ethically contentious area
- questions of **safety, harm and risk-opportunity** analyses (drawing on ethical concepts of non-maleficence and beneficence)
- longstanding debates on the moral status of embryos and positions vary
- **Human dignity, protection of life and integrity** feature as core ethical principles
- Debate around whether the technology can ever be deemed 'safe enough' to apply in a clinical setting
- evaluating the **necessity of germline interventions and the availability of alternatives**
- **Dimensions of solidarity and justice.**

Regulatory aspects in human germ line editing

- Oviedo Convention :
  - Article 13: “An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.”
  - Article 18: forbids the creation of human embryos for research purposes, restricting research activities in the field of germline editing in the countries that have ratified the Convention.
- revised Clinical Trials Regulation which is due to come into force in 2020 will continue to prohibit clinical trials that result in modifications of the human germline.
- many of the concepts used in relevant legal documents are vague and ambiguous, including the distinction between research and clinical applications and basic definitions.

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Public views, public debate

- Ref : Public views on gene editing and its uses, Nature Biotechnology · November 2017, 35, 1021-23
- DOI: 10.1038/nbt.3958
- 25 authors with 1st author G Gaskell (The London School of Economics and Political Science, very experienced in Eurobarometers)
- Online quota sample surveys on 1,000 respondents in Austria, Denmark, Germany, Hungary, Iceland, Italy, the Netherlands, Portugal, Spain, UK (EEA-10 countries) and the United States (*n* = 11,716)

Results (1)

- Female respondents were more cautious about gene editing in general
- Support is consistently greater for treatment than enhancement
- Greater support across all countries for intervention on adults than prenatals
- Adult therapy, 75% of the comments were positive evaluations of gene editing
- Prenatal therapy the proportion of support for gene editing declines to 60%
- Only 11% of comments on prenatal enhancement are positive

Results (2)

- As with many other technologies, the public's attention is on the applications or uses; these drive moral judgments.
- Yet scientific experts tend to focus on the technology itself.

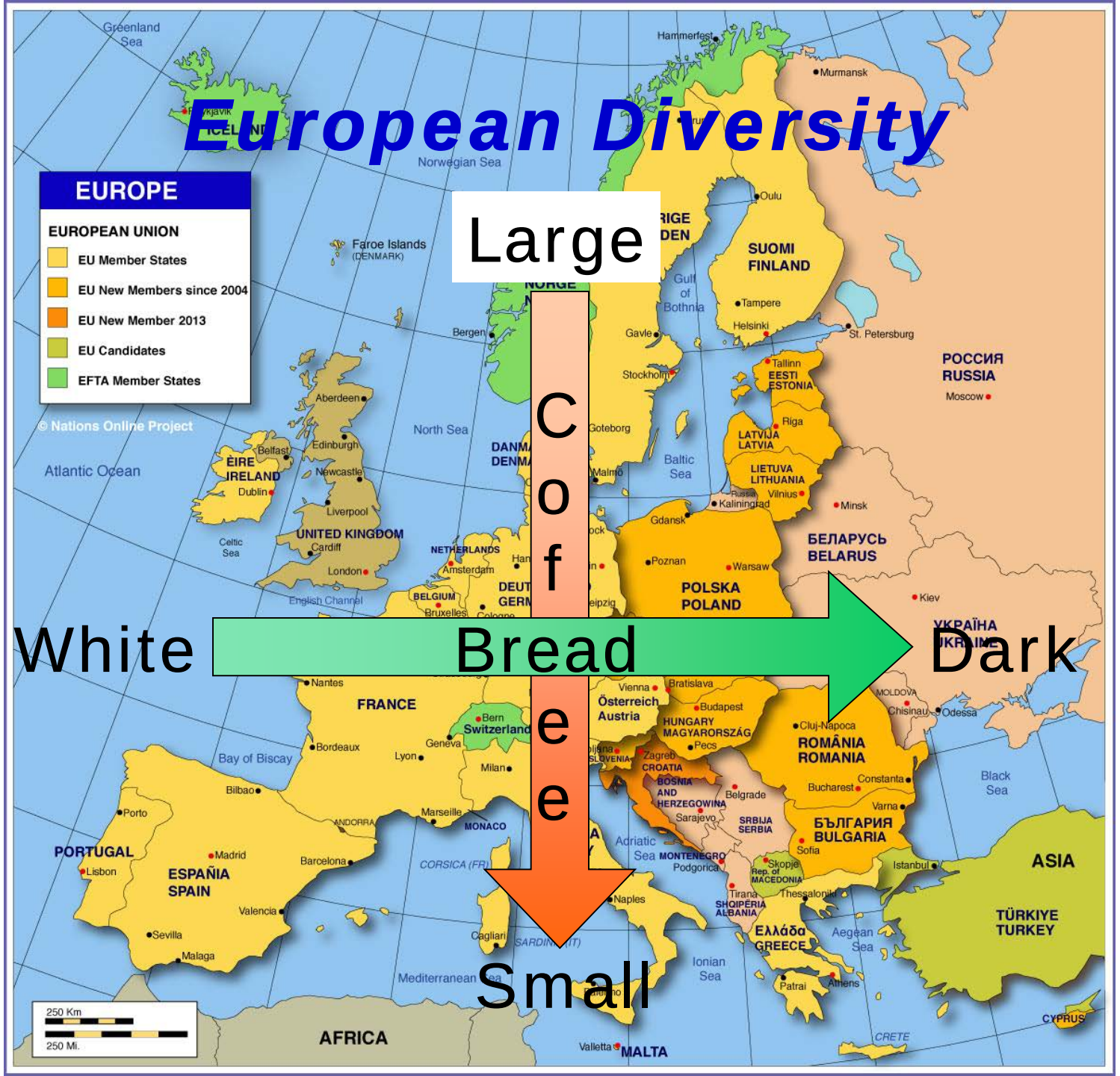
- « Value of surveys in this controversial territory. Public opinion cannot and should not tell us what is right to do. However, as the NAS report notes, "Public participation should be incorporated into the policy-making process for human genome editing and should include ongoing monitoring of public attitudes, informational deficits, and emerging concerns about issues surrounding enhancement. »

Elements of debate

- clear need for honest dialogue and the inclusion of all the public in framing the decision-making process for introducing new treatments to the health systems/ market
- ensuring the veracity of the information provided to the public
- Ensuring clarity in regulations / responsibilities

BUT

We have 1) to keep in mind the variation in ethical positioning even in Europe and 2) to define well the levels where harmonisation can be achieved.


European Diversity
EUROPE
EUROPEAN UNION
EU Member States
EU New Members since 2004
EU New Member 2013
EU Candidates
EFTA Member States
© Nations Online Project
Large
Coffee
White
Bread
Dark
Small
Atlantic Ocean
North Sea
Baltic Sea
Norwegian Sea
Greenland Sea
Bay of Biscay
Mediterranean Sea
Black Sea
Adriatic Sea
Ionian Sea
Aegean Sea
Celtic Sea
English Channel
Gulf of Bothnia
Faroe Islands (DENMARK)
ÍSLAND
SUOMI FINLAND
EESTI ESTONIA
LATVIJA LATVIA
LIETUVA LITHUANIA
РОССИЯ RUSSIA
Moscow
Minsk
БЕЛАРУСЬ BELARUS
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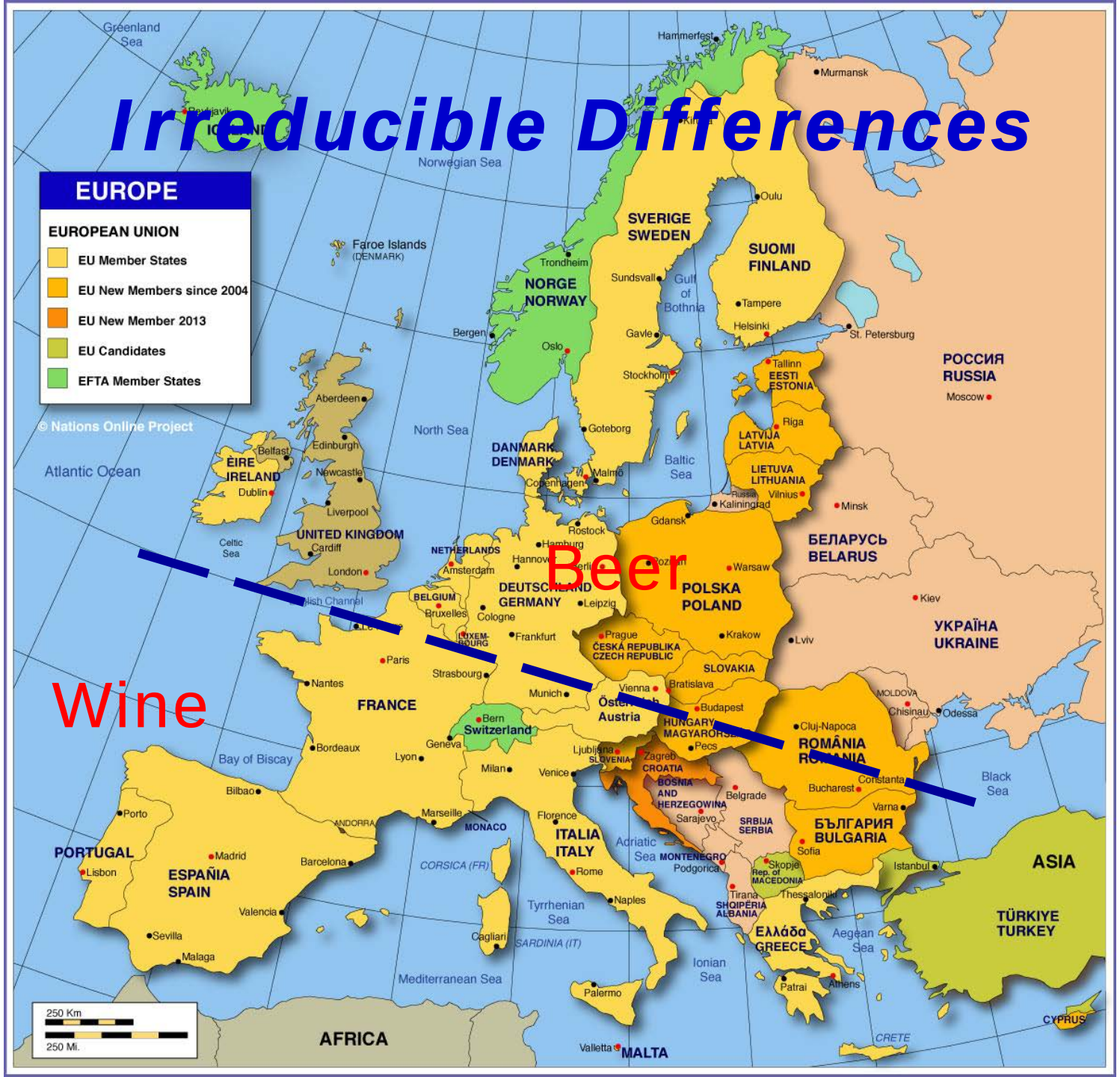
Bucharest
Varna
Sofia
Skopje
Tirana
Thessaloniki
Istanbul
Naples
Cagliari
Patrai
Athens
Chisinau
Odessa
250 Km
250 Mi.

Irreducible Differences



Panel discussion, World Science Forum, Budapest 22/11/2019

Conclusion

- The various dimensions and domains of regenerative medicine have each their specific issues
- Concerns about implementation and regulation is transversal
- Necessity of dialogue to take into account informed stakeholders views and avoid hype
- The applicability and subsequent ethical considerations of the gene editing techniques to various domains are influencing the general debate
- Time line revive classical questions: is the speed for obtaining a result creating an issue?
- Some classifications are re-questioned

Thanks a lot for your attention