Legal and Ethical Challenges of Novel Entities

civis · Organact · anr · cnrs · amU Aix Marseille Université · ADES UMR 7268 · CDSA Centre de droit de la santé. · UMR 7318 Droits international, Comparé et Européen · CERIC

BIP Novel Research and Ethics: from Neuroscience to AI, Athens, 11 December 2024

Course outline

Themes and issues

- Manmade novel entities created by biotechnologies, robotisation, computer sciences
- **Exploration of many more forms of life** that are possible but never occurred on the tree of life
- Blurring of boundaries (between species, between artificial and natural, between animate and inanimate)
- Novel entities with agentic behaviour in various domains
- Question regarding their sentience, consciousness and welfare

→ **Q1: What is their current legal classification and regulation?**

→ **Q2: What are our moral duty towards the welfare of these novel entities?**

Plan of the course

I. Introductory Remarks
- (1) Technical Capabilities
- (2) Definitions
- (3) State of the Art of Consciousness Science

II. Issues Raised by Novel Entities
- (1) Embryoids
- (2) Neural organoids
- (3) Chimeras

III. The Legal Perspective
- (1) Legal Methodology
- (2) *Persons* and *Things*
- (3) European Legal Framework
- (4) Donors' Rights
- (5) Research limits

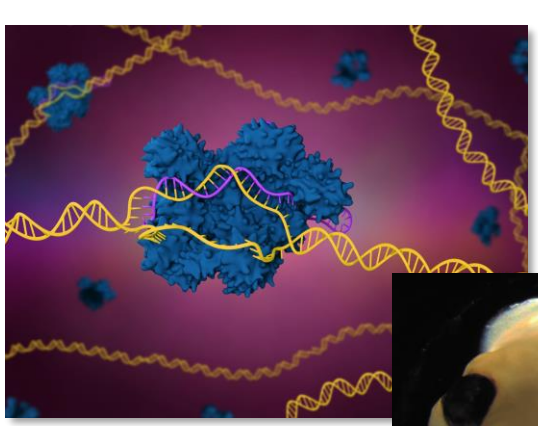
I. Introductory remarks

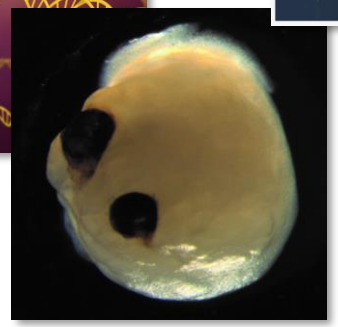
(1) Technical Capabilities

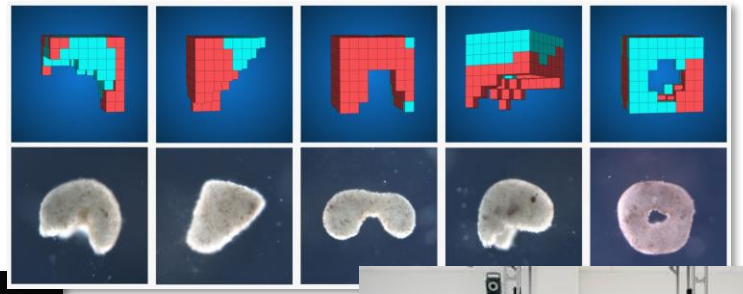
Considerable progress in biotechnology (gene editing, 2D and 3D stem cell cultures, xenotransplantation, synthetic biology, bioprinting etc.) and computer science (robotics, AI, computational biology, *in silico* methods). Convergence of fields.

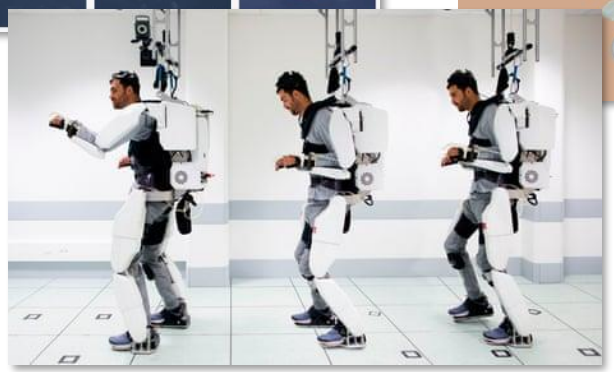
Interoperability of life systems and artificial systems (neural interfaces, exoskeletons, biobots, organs-on-chip etc.)

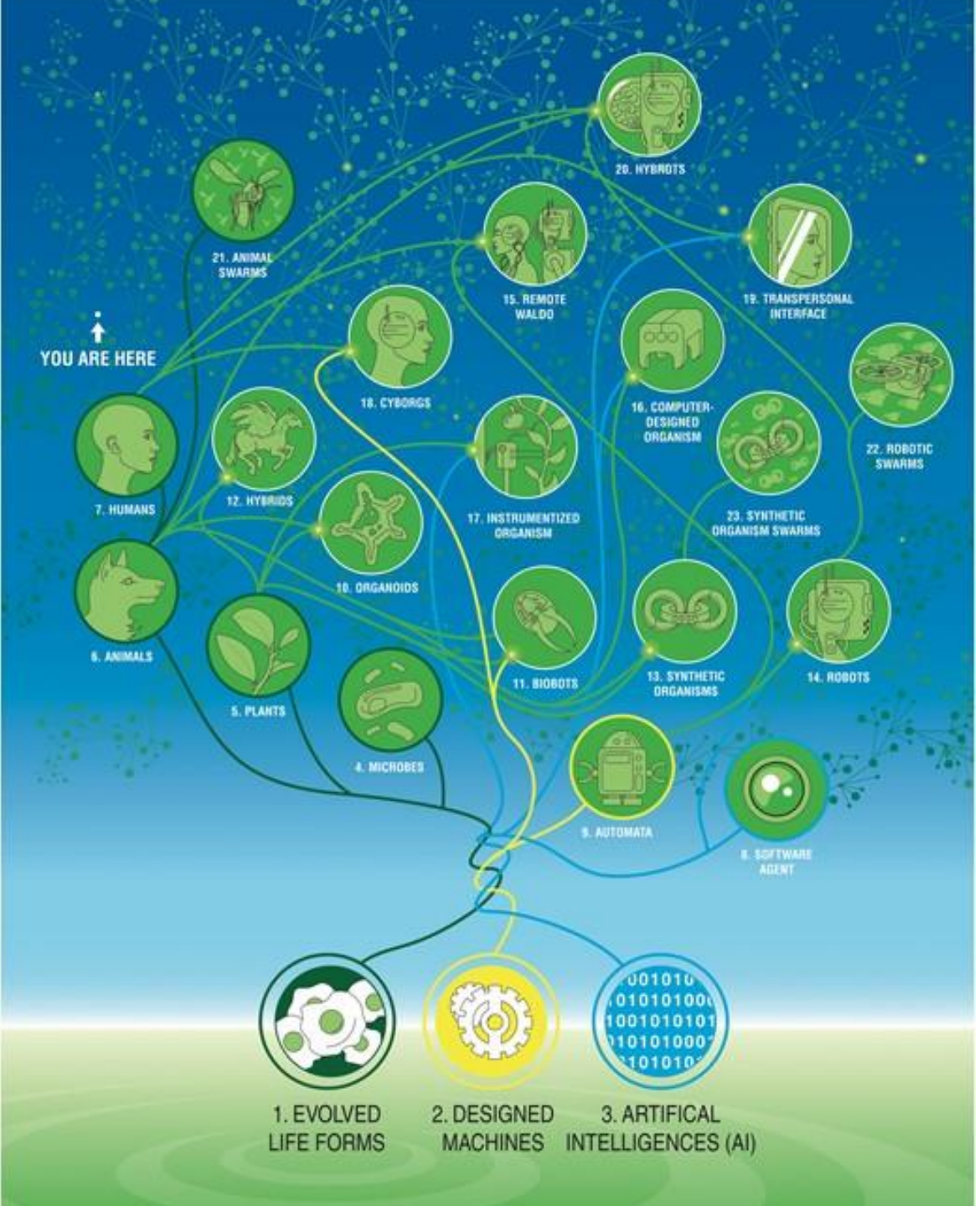
→ Increasing control over the forms that life and agents can take











- There is a great number of possible novel entities
- Some of which are already among us (cyborgs, chimeras, AI software agents, organoids…)

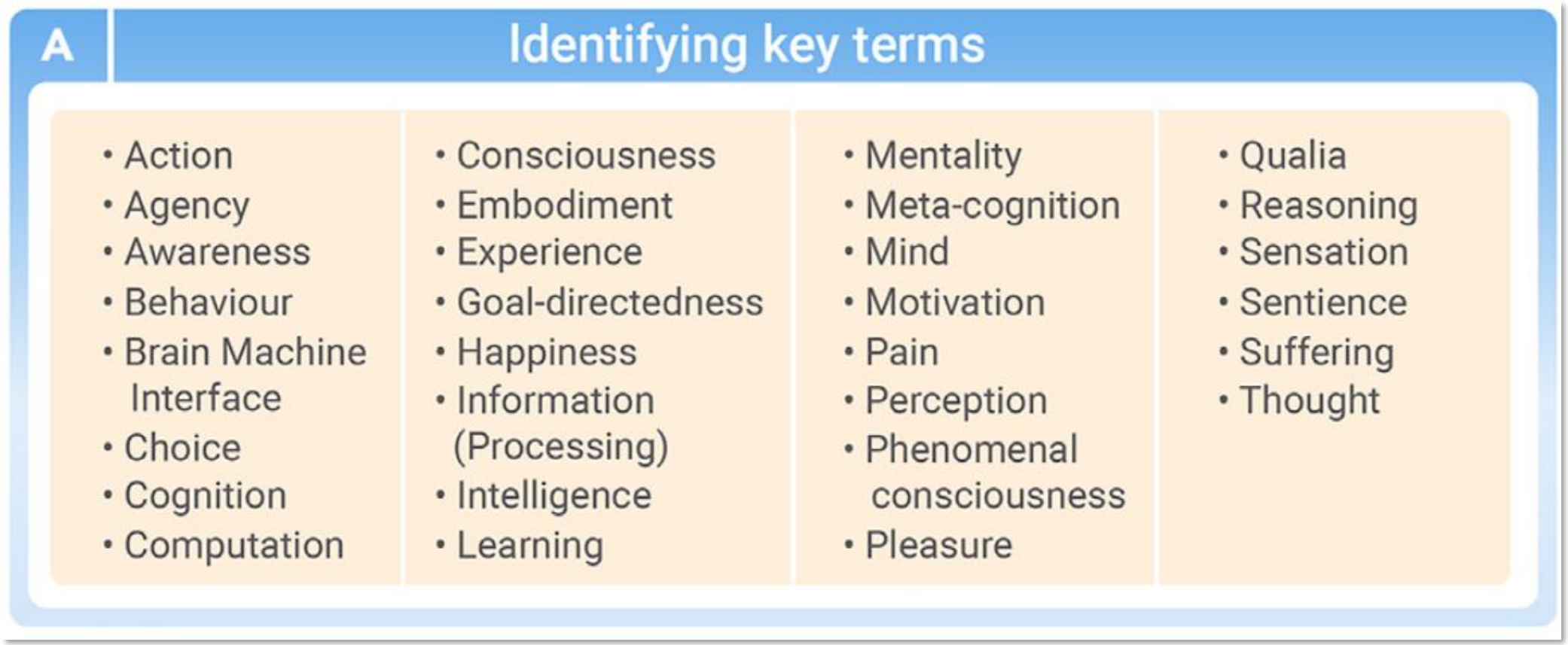
→ Each raising their own set of ethical and legal questions

→ Focus on agency, sentience and consciousness related questions

CLAWSON Wesley P et LEVIN Michael, “Endless forms most beautiful 2.0: teleonomy and the bioengineering of chimaeric and synthetic organisms”, *Biological Journal of the Linnean Society*, juillet 2022, p. blac073.

(2) Definitions

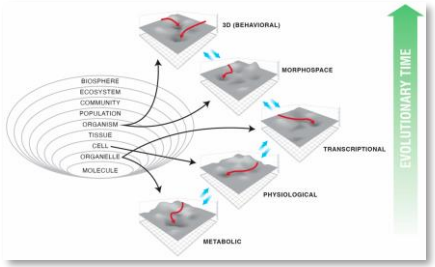
Lack of consensus



KAGAN Brett J., MAHLIS Michael, BHAT Anjali *et al.*, "Toward a nomenclature consensus for diverse intelligent systems: Call for collaboration", *The Innovation*, 5, Elsevier, September 2024, nº 5. https://www.cell.com/the-innovation/abstract/S2666-6758(24)00096-1

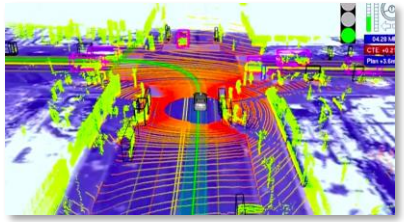
(2) *(Working)* Definitions

Life and Cybernetics: systems and agents



An Agent: coherent, bounded and dynamic system that pursues goals in specific problem spaces.

Agency: capacity to act in an environment by setting goals and solving problems to reach these goals



Awareness: ability of a system to model its environment

Self-awareness: ability of an agent to have a model of itself

A Self: phenomenon manifesting in a first person perspective (including valence, attention and decision-making) for a system that has goals, memories and preferences, that do not belong to its parts

Sentience: ability of to experience feelings and sensation, to have a subjective perspective

Consciousness or Self-consciousness : meta-capability of a self to monitor and analyse subjectively its own mental states

Novel entity: a system created through technological means (biotechnologies, robotics, computer science) demonstrating a level of agency and/or a level of sentience

Empirical question: how do we assess their degree of sentience/consciousness

Ethical question: what obligations do we have regarding their treatment?

(3) State of the Art

Consciousness science

We have multiple theories of consciousness

- Global workspace theory (GWT), Integrated information theory (IIT), Attention schema theory, Entropic brain theory, Projective consciousness model…

→ **Difficult to make testable hypotheses that isolate the "hard problem" of consciousness**

We have assessment and measurement protocols for humans and animals

- Based on behaviour and lack thereof: Neuropsychological assessment (i.e. Glasgow Coma Scale).
- Ethology and frameworks to study animal behaviour

→ **Correlational evidence rather than causal**

- Based on non-behavioural data? Experimental methods: Perturbational Complexity Index (PCI)
- But no mature framework and tests for truely novel entities (such as AI, brain organoids etc.).

→ Current frameworks work best with entities whose biology and behaviour is well studied and close to ours

(3) State of the Art

Consciousness science

→ No unified theory of consciousness

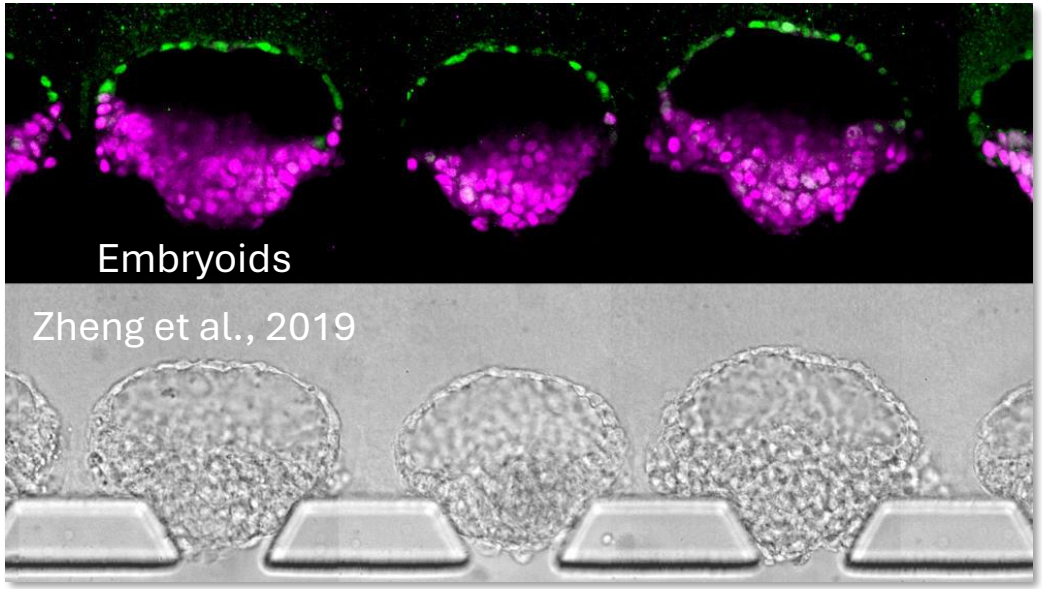
→ No standardized and validated tool to measure consciousness

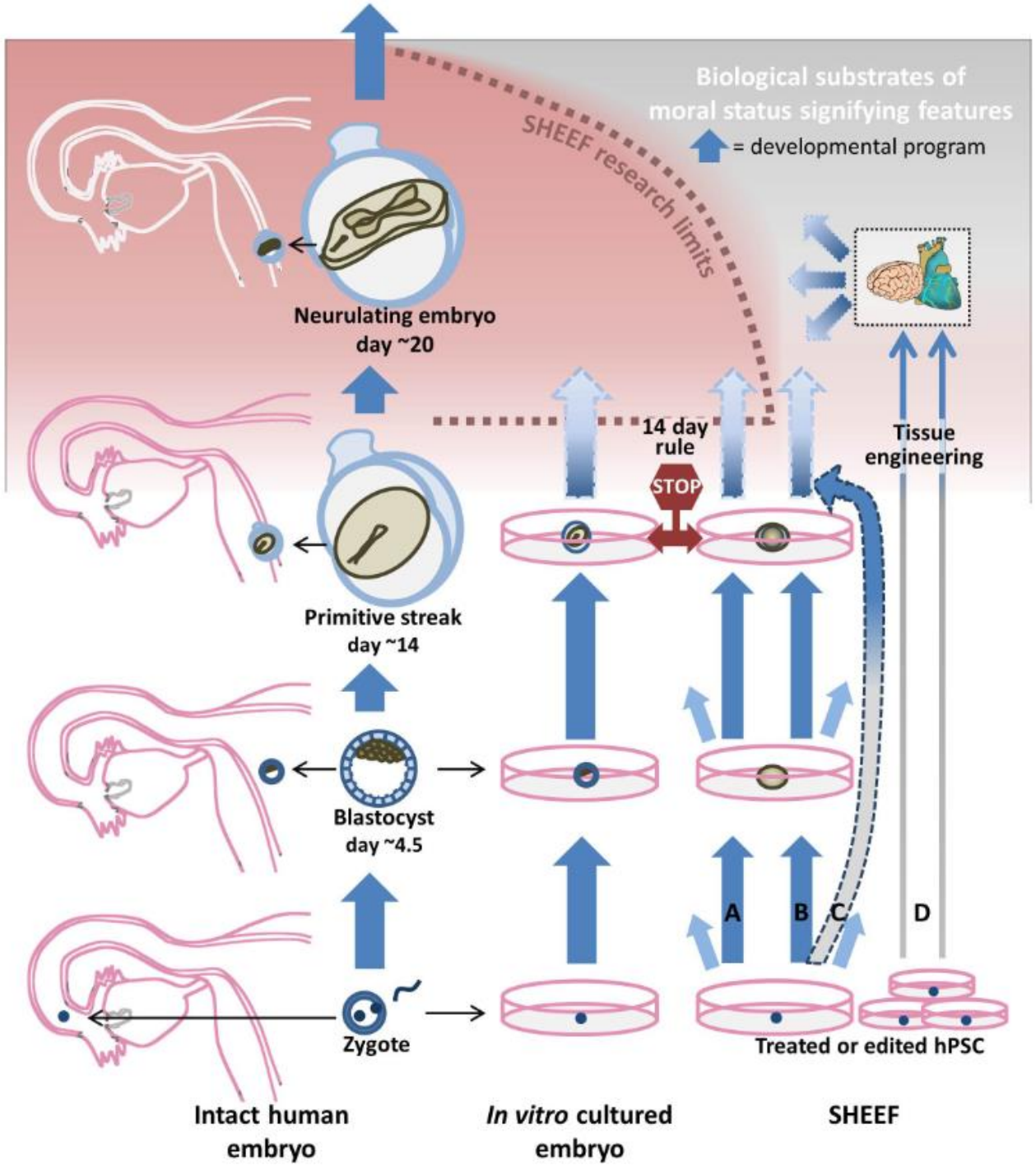
II. Issues Raised by Novel Entities

(1) Embryoids

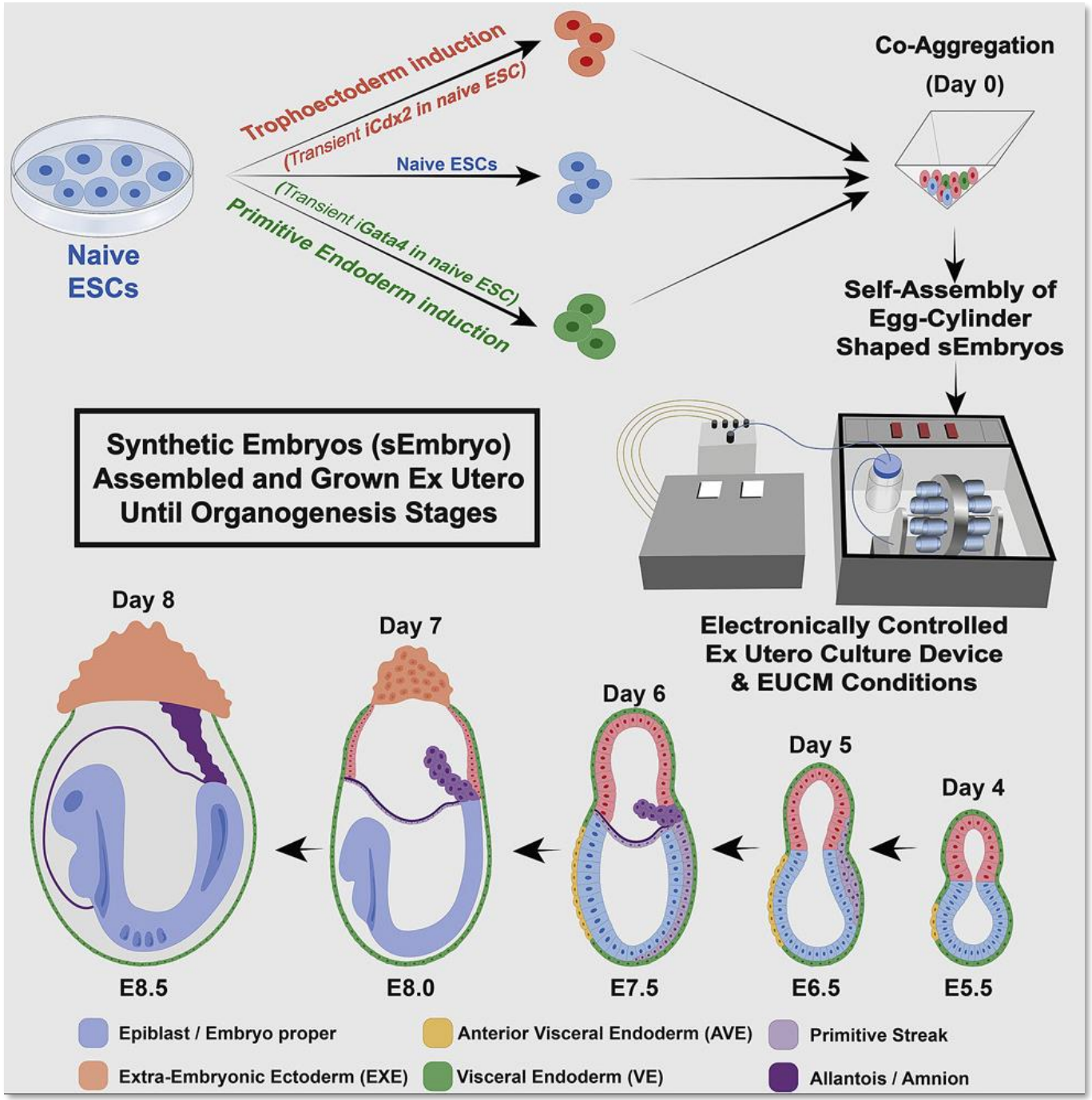
(1) Embryoids – Technical aspects

- **Definition**: Entities derived from embryonnic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) that reproduces stages of embryonic development (without using gametes or an embryo)
- **Terms**: iblastoid, blastoid, gastruloid, embryonic developement model, synthetic human entities with embryo-like features (SHEEF), **embryoid**…
- Broadly two categories: **blastoids** (blastocyst) and **gastruloids** (after gastrulation)
- **Uses**: to study embryonic develoment, embryonic diseases, causes of infertility, early body-plan development. Allow the study of developmental stages that were previously inaccessible





AACH John, LUNSHOF Jeantine, IYER Eswar *et al.*, “Addressing the ethical issues raised by synthetic human entities with embryo-like features”, Watt Fiona M (éd.), *eLife*, 6, eLife Sciences Publications, Ltd, mars 2017, e20674.



TARAZI Shadi, AGUILERA-CASTREJON Alejandro, JOUBRAN Carine *et al.*, « Post-gastrulation synthetic embryos generated *ex utero* from mouse naive ESCs », *Cell*, 185, September 2022, n° 18, p. 3290-3306.e25.

(1) Embryoids – Ethical Aspects

How close are embryoids to “real” embryos? Until what point of complexity can they be developed?

- Empirical question: what structures and functions does the model recapitulate?
- Moral and ethical questions: what is the starting point of human life, how should be treat these early stages of human life?
- At what stage of development the conceptus or its model can start to experience pain? What features of the developing embryo are off limits for research on embryoids?

→ Setting limits: at a specific stage of development? Neurulation? Organogenesis?

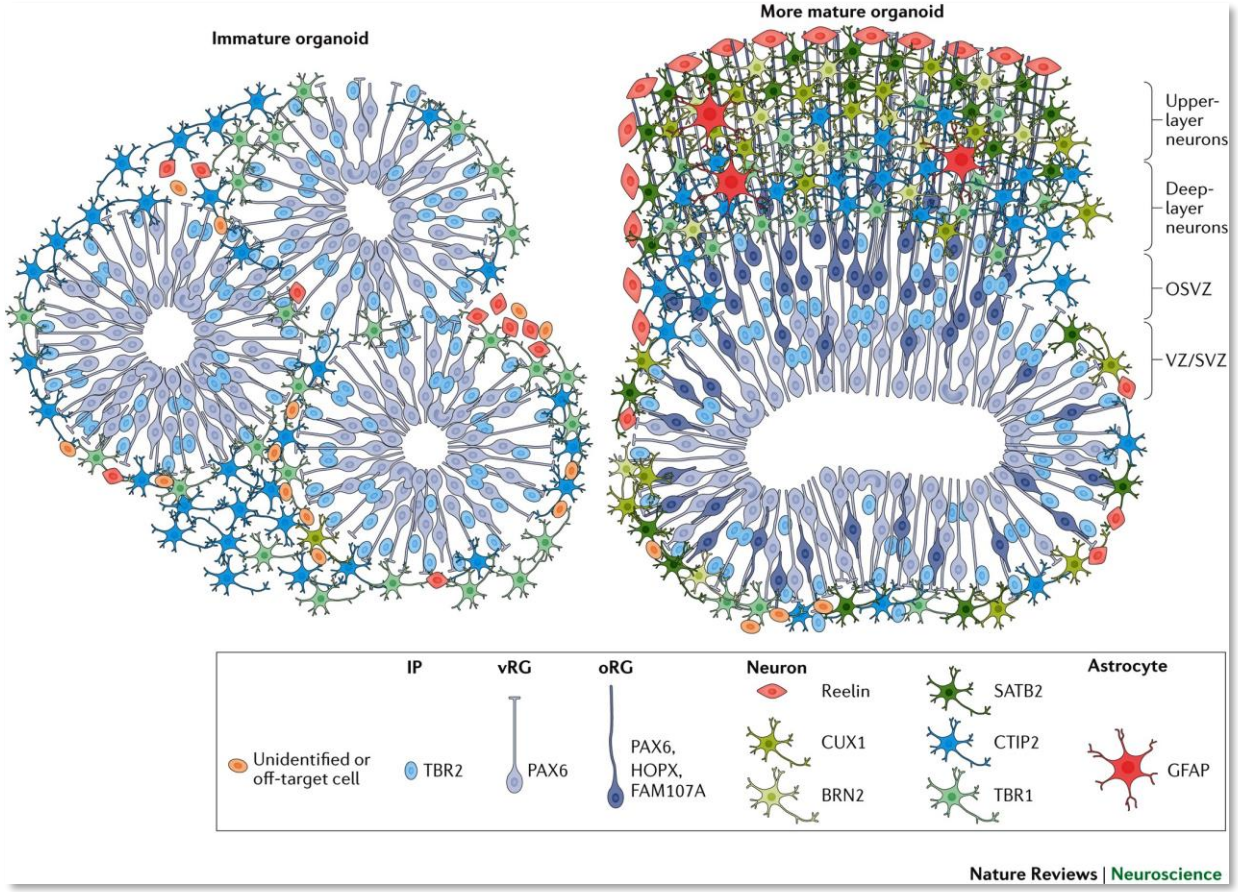
II. Issues Raised by Novel Entities

(2) Neural Organoids

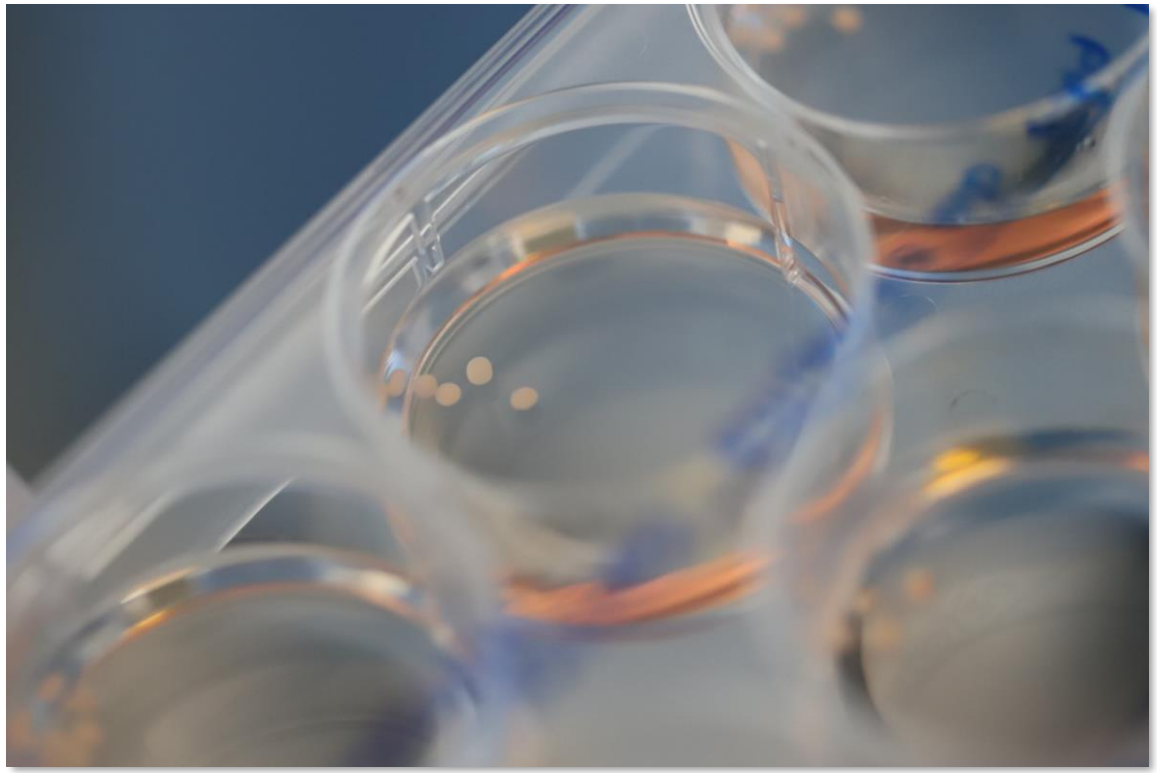
(2) Neural Organoids – Technical Aspects

- **Definition**:
  - Organoids: cellular structures derived from ESCs or iPSC, that are self-organizing in 3D, and reproducing structural and functional features of a tissue or organ (Boers et al., 2018)
  - Neural organoids: organoids made of neuronal cell types
- **Terms**: “mini-brain”, brain organoid, neuronal organoid, cerebroid, **neural organoid…**
- **Uses**: To study developmental biology, neurological diseases, network dynamics of neurons…

(2) Neural Organoids – Technical Aspects



Di Lullo, E., Kriegstein, A. "The use of brain organoids to investigate neural development and disease". *Nat Rev Neurosci* 18, 573–584 (2017). https://doi.org/10.1038/nrn.2017.107



Credits: Fabien Milanovic

(2) Neural Organoids – Technical Aspects

Recapitulate early stages of brain development

“Moreover, the internal cyto-architecture was reminiscent of a laminated neocortex and grew to include equal proportions of projecting neurons expressing deep- and superficial-layer cortical markers. Transcriptional analysis and comparison to the developing human brain revealed that hCSs after 2.5 months resembled the mid-fetal prenatal brain (19–24 post-conception weeks, PCW). Cortical neurons were accompanied by a network of nonreactive astrocytes and were synaptically connected.”

PAŞCA Anca M., SLOAN Steven A., CLARKE Laura E. *et al.*, « Functional cortical neurons and astrocytes from human pluripotent stem cells in 3D culture », *Nature Methods*, 12, juillet 2015, nº 7, p. 671-678.

Neural organoids are used for bio-computing

In this approach—which is termed Brainoware—computation is performed by sending and receiving information from the brain organoid using a high-density multielectrode array. By applying spatiotemporal electrical stimulation, nonlinear dynamics and fading memory properties are achieved, as well as unsupervised learning from training data by reshaping the organoid functional connectivity. We illustrate the practical potential of this technique by using it for speech recognition and nonlinear equation prediction in a reservoir computing framework.

CAI Hongwei, AO Zheng, TIAN Chunhui *et al.*, « Brain organoid reservoir computing for artificial intelligence », *Nature Electronics*, 6, Nature Publishing Group, décembre 2023, nº 12, p. 1032-1039.

(2) Neural Organoids – Technical Aspects

“Organoid intelligence”

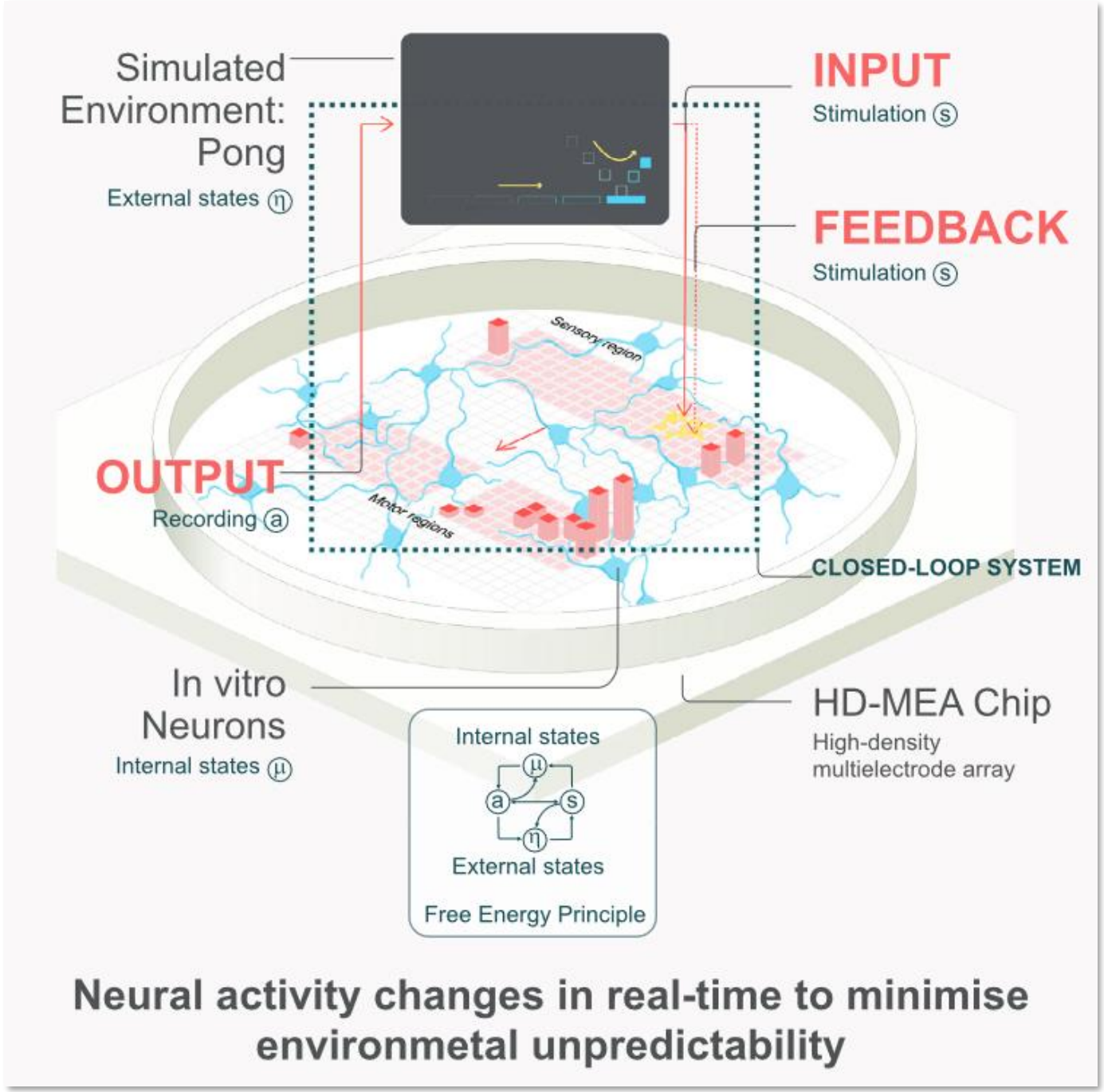
Neurons perform computation for very low energy consumption compared to silicon-based computers. Their networks are inherently reconfigurable, are actively adapting to inputs (neuronal plasticity) and producing outputs

→ Still an early research field but start-ups are already sprouting

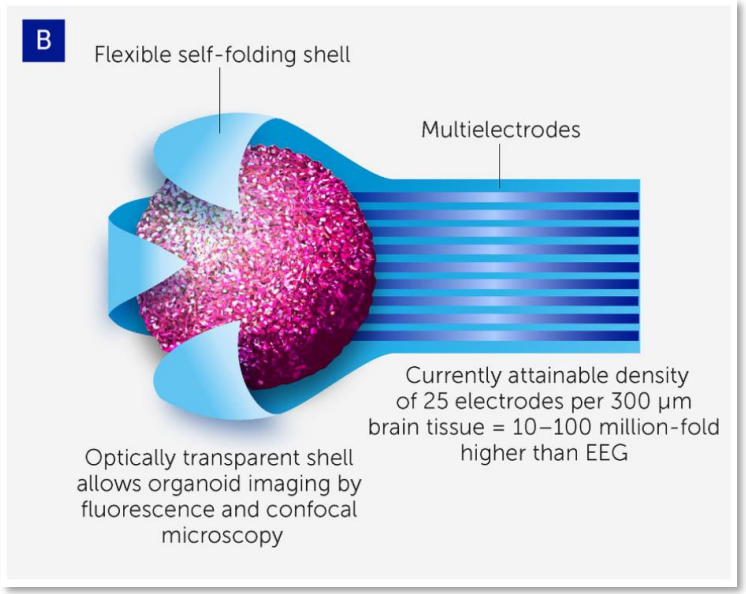
FINALSPARK

JORDAN Fred D., KUTTER Martin, COMBY Jean-Marc *et al.*, “Open and remotely accessible Neuroplatform for research in wetware computing”, *Frontiers in Artificial Intelligence*, 7, Frontiers, May 2024.

Habibollahi, F., Kagan, B.J., Burkitt, A.N. et al. Critical dynamics arise during structured information presentation within embodied in vitro neuronal networks, Nat Commun 14, 5287 (2023)



KAGAN Brett J., KITCHEN Andy C., TRAN Nhi T. *et al.*, “In vitro neurons learn and exhibit sentience when embodied in a simulated game-world”, *Neuron*, 110, December 2022, nº 23, p. 3952-3969.e8.



SMIRNOVA Lena, CAFFO Brian S., GRACIAS David H. *et al.*, « Organoid intelligence (OI): the new frontier in biocomputing and intelligence-in-a-dish », *frontiers in science*, February 2023.

TABLE 1 Comparison of the latest supercomputer (June 2022) and a human brain.

	Frontier supercomputer (June 2020)	Human brain
Speed	1.102 exaFLOPS	~1 exaFLOPS (estimate)
Power requirements	21 MW	10–20 W
Dimensions	680 m^2 (7,300 sq ft)	1.3–1.4 kg (2.9–3.1 lb)
Cost	$600 million	Not applicable
Cabling	145 km (90 miles)	850,000 km (528,000 miles) of axons and dendrites
Memory	75 TB/s read; 35 TB/s write; 15 billion IOPS flash storage system, along with the 700 PB Orion site-wide Lustre file system	2.5 PB (petabyte)
Storage	58 billion transistors	125 trillion synapses, which can store 4.7 bits of information each

(2) Neural Organoids – Ethical Issues

Could neural organoids have a minimal degree of sentience? Would it be ethical to conduct experiments on them if this is the case? Should we farm human cognition at scale?

- Greely dilemma:

"When we avoid unethical research by making living models of human brains, we may make our models so good that they themselves deserve some of the kinds of ethical and legal respect that have hindered brain research in human beings. If it looks like a human brain and acts like a human brain, at what point do we have to treat it like a human brain—or a human being?"

GREELY Henry T., "Human Brain Surrogates Research: The Onrushing Ethical Dilemma", *The American Journal of Bioethics*, 21, Taylor & Francis, January 2021, nº 1, p. 34-45.

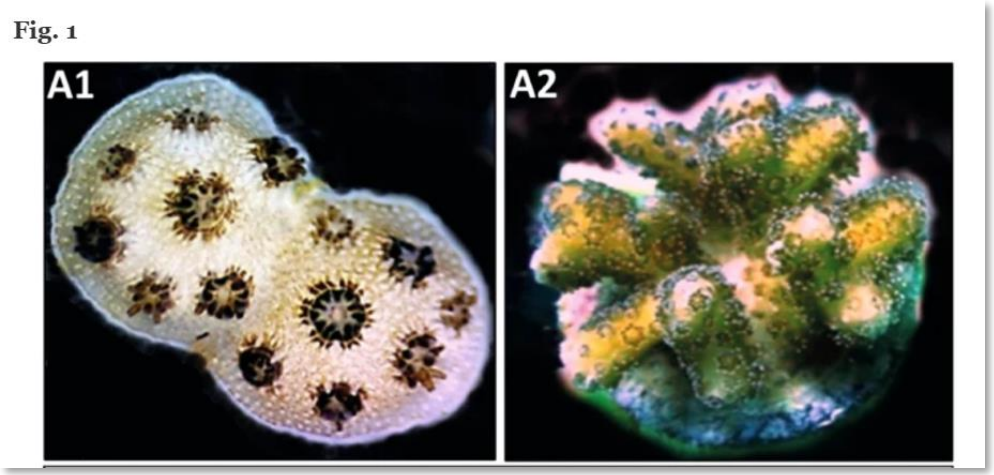
- What happens when we scale that human biological computing? What if we run AI models on such infrastructure?

II. Issues Raised by Novel Entities

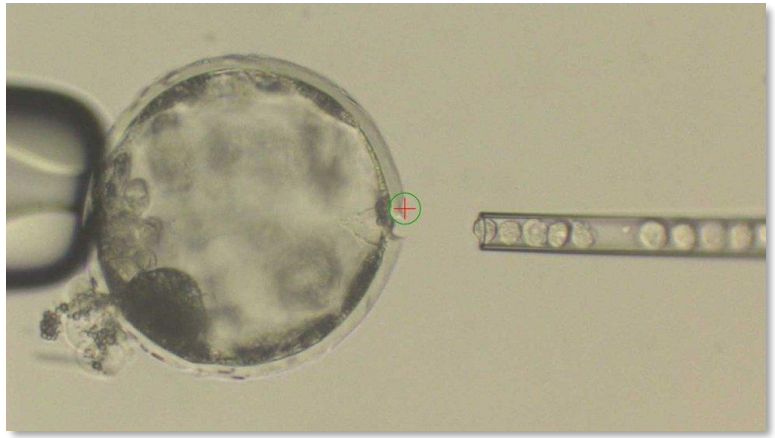
(3) Chimeras

(3) Chimeras – Technical Aspects

- **Definition**: an organism constituted of two or more varieties of cells from different genetical background, but without mixing the genetical material itself
- **Terms: "Natural" chimerism** (symbiotic chimerism) // **"artificial" chimerism** (chimeric embryo)



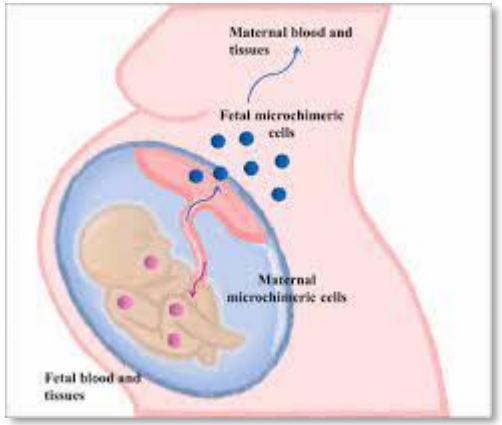
Vidal-Dupiol, J., Harscouet, E., Shefy, D. *et al.* Frontloading of stress response genes enhances robustness to environmental change in chimeric corals. *BMC Biol* 20, 167 (2022).

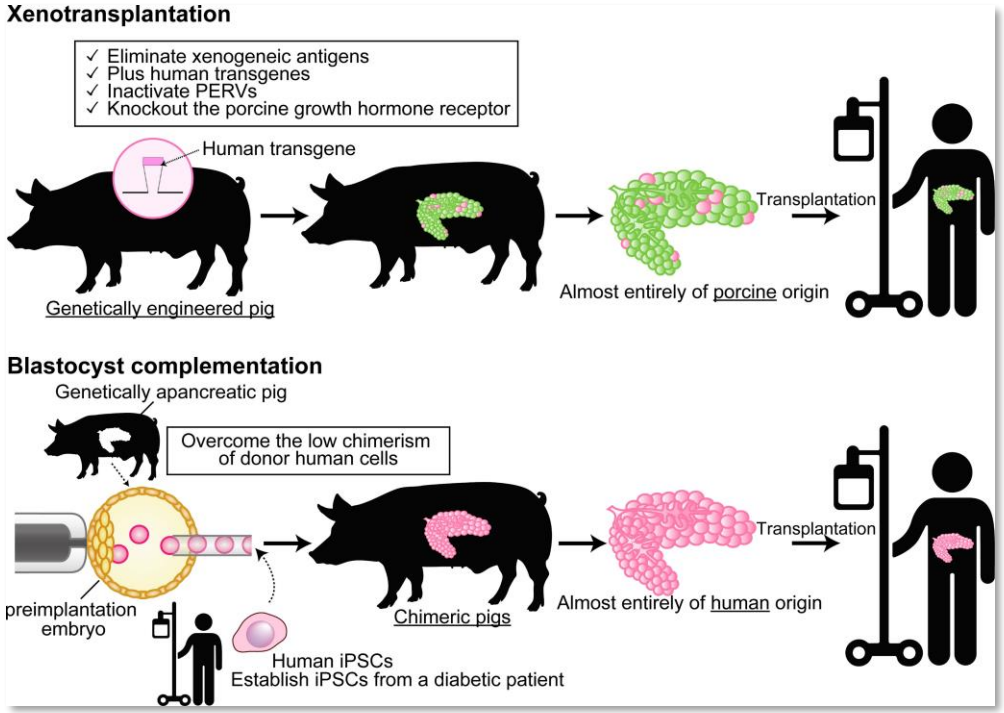


Credits: BBC

(3) Chimeras – Technical Aspects

Microchimerism (fetomaternal microchimerism) // **“macro-”chimerism** (xenotransplantation)

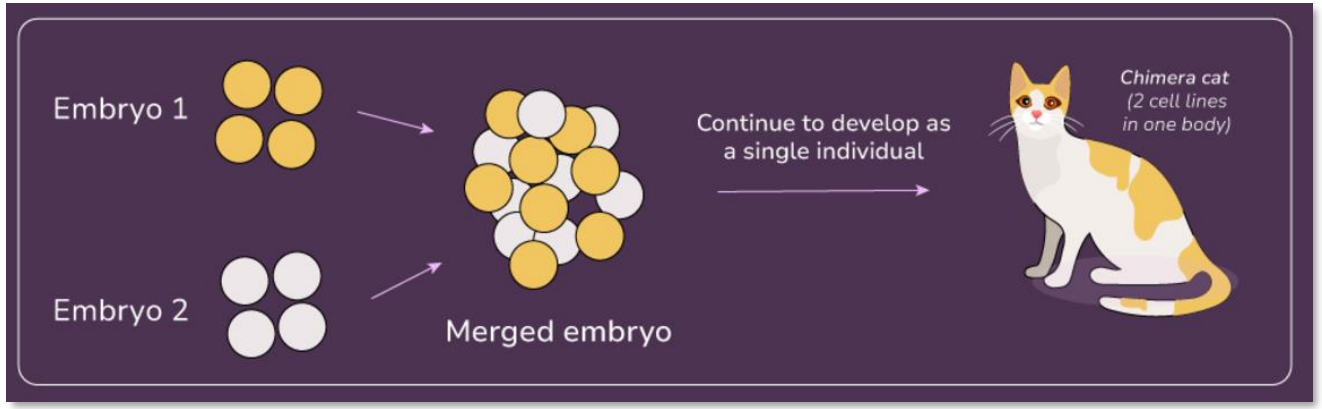




Kano M, Mizutani E, Homma S, Masaki H and Nakauchi H (2022) Xenotransplantation and interspecies organogenesis: current status and issues. *Front. Endocrinol.* 13:963282. doi: 10.3389/fendo.2022.963282

(3) Chimeras – Technical Aspects

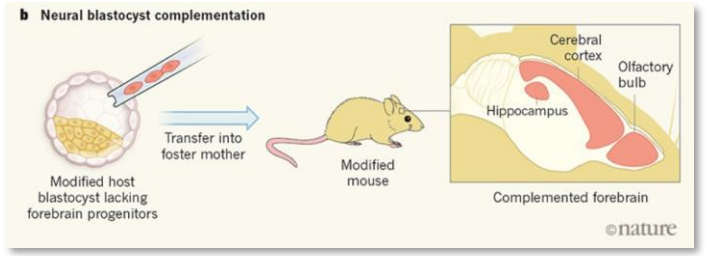
Intraspecies (cat-cat chimera) // **interspecies** (mice-rat chimera)



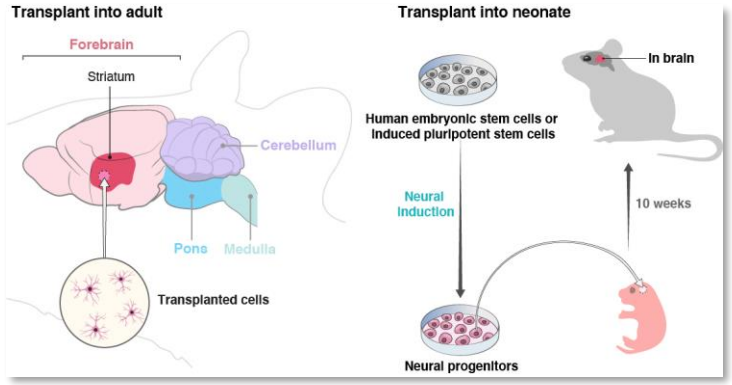
(3) Chimeras – Technical Aspects

3 main types of human-animal cerebral chimeras

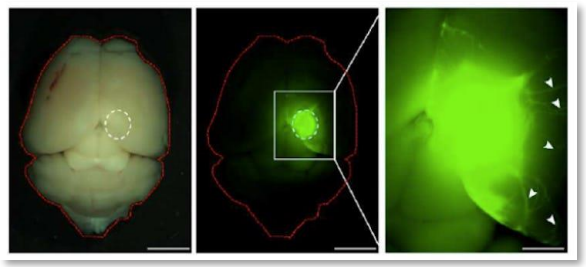
- Blastocyst complementation
- Animal grafted with neural tissue
- Animal implanted with human brain organoid



ANDERSEN Jimena et PAŞCA Sergiu P., "Absent forebrain replaced by embryonic stem cells", *Nature*, 563, November 2018, nº 7729, p. 44-45.



Washington, D.C., National Academies Press, (2021) https://www.nap.edu/catalog/26078



MANSOUR Abed AlFatah, GONÇALVES J. Tiago, BLOYD Cooper W. *et al.*, "An in vivo model of functional and vascularized human brain organoids", *Nature Biotechnology*, 36, Nature Publishing Group, May 2018, nº 5, p. 432-441.

(3) Chimeras – Technical Aspects

- **Uses**:
  - Transplant of brain organoids allows for the vascularisation of the organoid, it allows to study the functional integration of the organoid in the nervous system of the host, to study diseases and developmental biology etc.
  - Blastocyst complementation allows the study of organogenesis, developmental disorders, test new therapeutic approaches. Most importantly, leads to the generation of human organs in animals for xenotransplantation.

(3) Chimeras – Technical Aspects

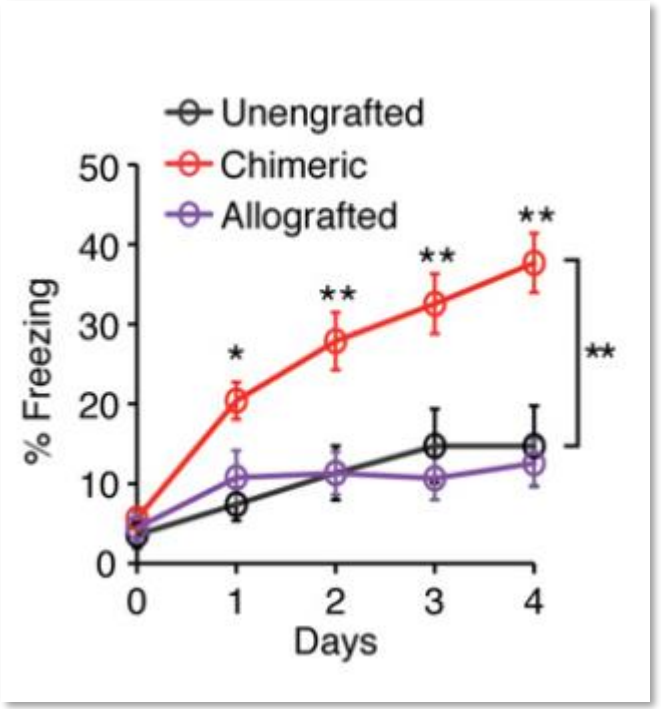
Functional integration of brain organoid and alteration of cognitive functions in host

Alteration of biological function:

human astrocytes replaced host glia in mice engrafted with human glial progenitors, they enhanced long term potentiation in the adult murine hippocampus, they propagated calcium waves more quickly, there was a strengthening of excitatory transmission and synaptic plasticity caused by the engrafting of human glial cells…

Behavioural changes:

"After just a single pairing of the tone with foot shock, the human glial chimeric mice exhibited a significant enhancement in learning of the tone foot shock association: they showed greater fear to the tone as measured by scoring freezing behavior (the cessation of all movement except for respiration) than did either allografted chimeras or unengrafted controls (n = 5–20, 9.6 ± 1.0 months old, F = 18.9, two-way repeated-measures ANOVA, $p < 0.001$). Moreover, after 3 continuous days of training, humanized chimeric mice also showed enhanced AFC during the 3 remaining days of testing, as manifested by their higher levels of freezing in response to the conditioned tone ($p < 0.01$, post hoc Bonferroni test)."



HAN Xiaoning, CHEN Michael, WANG Fushun *et al.*, "Forebrain engraftment by human glial progenitor cells enhances synaptic plasticity and learning in adult mice", *Cell Stem Cell*, 12, mars 2013, nº 3, p. 342-353.

(3) Chimeras – Ethical Issues

To what degree are chimeras "humanised"? Are there moral and ethical limits to chimerisation?

Boundary between species

- Human cells ending in gonadal tissue or in animal brain
- Altered cognitive abilities, enhanced abilities (what do we look for? Purely histological modifications, or cognitive and behavioural alterations?)
- The boundary with great apes might be even thinner

Welfare of the animal

- Replace, Reduce, Refine (3Rs)
- Welfare needs of cognitively enhanced animals?

III. The Legal Perspective

(1) Legal Methodology

Innovation, Society and Law

Temporality and Co-production of Norms

- Sometimes law is lagging behind innovation.
  Sometimes it anticipates it.
- Innovation and societal views influence law.
  Law influences innovation and societal views.
- Sometimes regulation is decided in a top-down manner.
  Sometimes regulation emerges in a bottom-up manner.

→ **Dynamic co-production of norms**

How does law function?

- Law functions with finite legal categories or “concepts”. Each concept has its associated legal regime.
  - A legal regime is all the rights, freedoms or obligations and prohibitions that govern a behaviour or concept. Ex: marriage

- Different categories in biolaw : substance of human origin (SoHO), medicinal product, medical device, animals used for scientific purposes, embryos

- Different levels of legal systems

Levels of Legal Systems

National level

European Union (EU)

Council of Europe (CoE)

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

International level

unesco

OECD

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

What are the legal challenges raised?

- Bring about innovation in a responsible manner: evaluation of risks, benefits and safety. Ensure access to novel therapies.
- Protect donors: respect their integrity and their preferences
- Ownership over the entity: intellectual property, reification of human biology and even of human neural computing
- Societal issues: moral status of new entities, transhumanism, human enhancement and eugenics
- Animal ethics: 3Rs and alternative methods, xenotransplantation

→ **What about the welfare of the novel entities themselves?**

Current Unresolved Legal Issues

Theory of law

- Classification among *persons* or *things*
- Protection of Human dignity

Specific fields of enquiry

- Research limits
- Protection of human health and animal health
- Patients and donors' rights

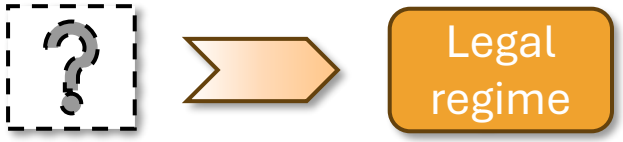
Decision making

- Precautionary principle and risk management
- Protection of societal values
- Democratic versus experts

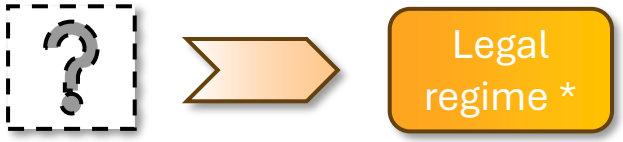
How do we approach these roblems as lawyers?

<u>When encountering a new object, a few questions are in order</u>

1) Is this object **already covered** by legal regulations?
   - If yes, are they appropriate?



2) Do these regulations need to be **adapted**?



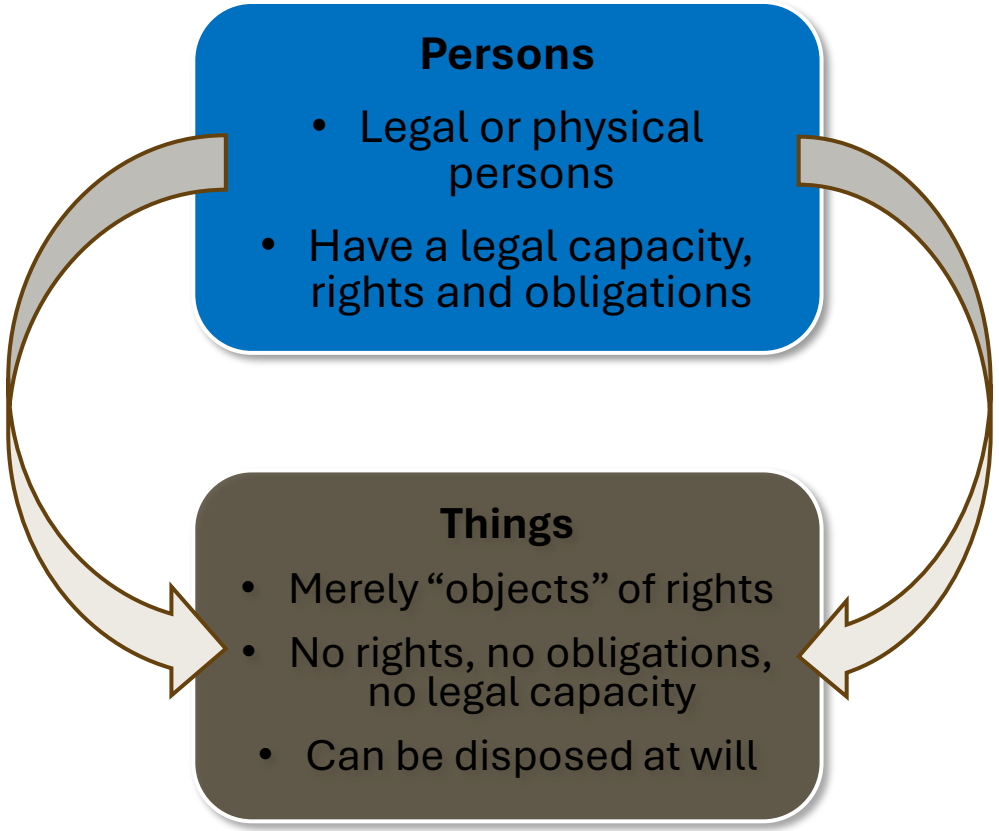
3) Is there a need for a new legal regime?
   - Identify the **specificity** of that object, the objectives and values associated with it that would deserve a new regulation

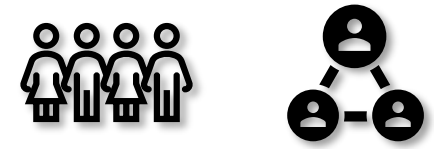
III. The Legal Perspective

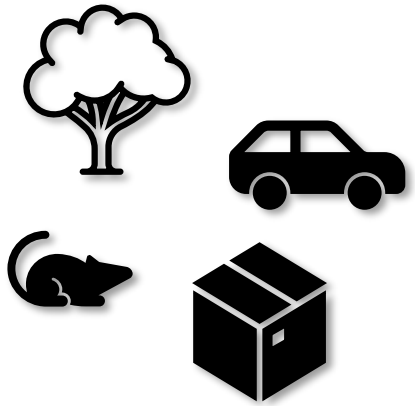
(2) *Person* and *Things*

The Historical Legal Dichotomy

Persons and *things*







What about… an embryo or a fetus?

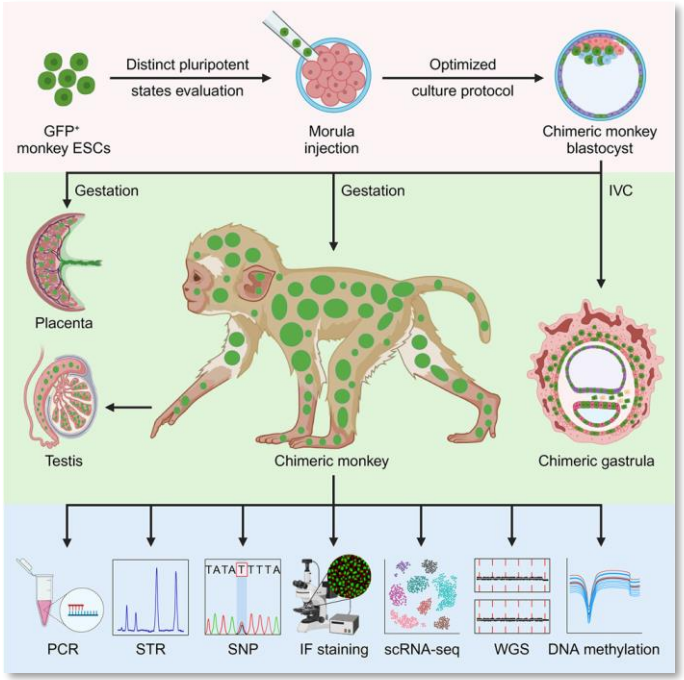
Persons

- Legal or physical persons
- Have a legal capacity, rights and obligations

Things

- Merely “objects” of rights
- No rights, no obligations, no legal capacity
- Can be disposed at will

What about… an animal or a chimera?



Persons

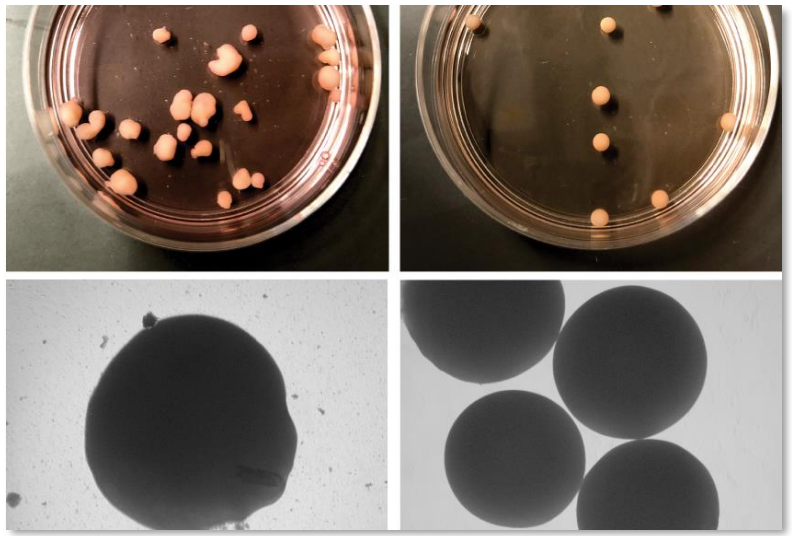
- Legal or physical persons
- Have a legal capacity, rights and obligations

Things

- Merely "objects" of rights
- No rights, no obligations, no legal capacity
- Can be disposed at will

CAO Jing, LI Wenjuan, LI Jie *et al.*, « Live birth of chimeric monkey with high contribution from embryonic stem cells », *Cell*, 186, Elsevier, novembre 2023, nº 23.

What about… a brain organoid?



Persons

- Legal or physical persons
- Have a legal capacity, rights and obligations

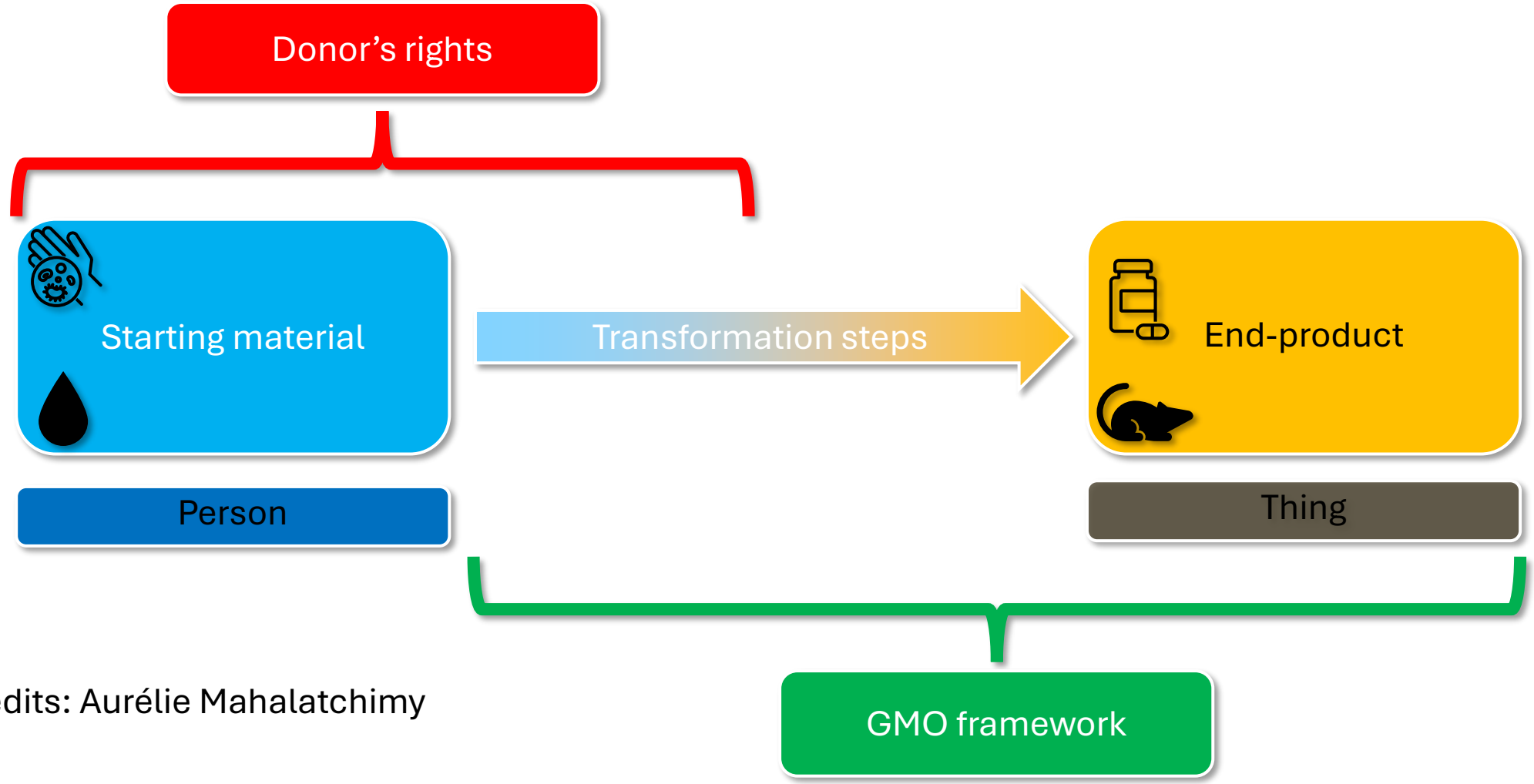
Things

- Merely “objects” of rights
- No rights, no obligations, no legal capacity
- Can be disposed at will

Biomedical Revolution

From the *source* to the *final product*

Legal Regimes Applying to the Life Cycle of a Biotechnological Product



Credits: Aurélie Mahalatchimy

III. The Legal Perspective

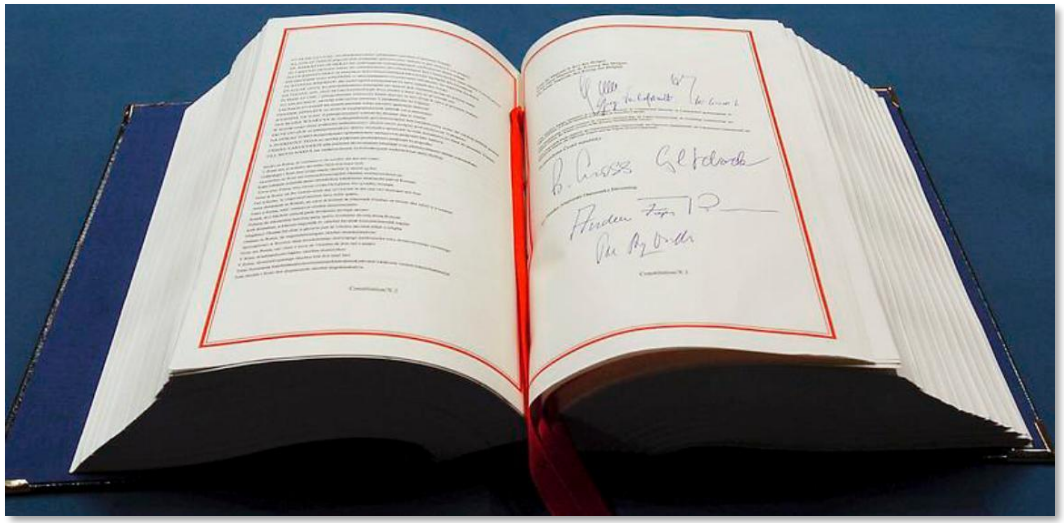
(3) European Legal Framework

EU Legal Framework

Selected instruments related to biotechnologies

The European Charter of Fundamental Rights, 7 December 2009

- Respect of human dignity (art. 1), right to the integrity of the person (art. 3), protection of health (art. 35), freedom of the arts and science (art. 13)



EU Legal Framework

Selected instruments related to biotechnologies

Substances of human origin

- **SoHO Regulation:** Regulation (EU) 2024/1938 of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application
- **Organ Directive:** Directive 2010/45/EU of 7 July 2010 on standards of quality and safety of human organs intended for transplantation

Pharma

- **MP Directive:** Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use
- **ATMP Regulation:** Regulation (EC) No 1394/2007 of 13 November 2007 on advanced therapy medicinal products
- **Clinical trials Regulation**: Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use
- **MD Regulation**: Regulation (EU) 2017/745 of 5 April 2017 on medical devices
- **IVDMD Regulation**: Regulation (EU) 2017/746 of 5 April 2017 on in vitro diagnostic medical devices

EU Legal Framework

Selected instruments related to biotechnologies

Intellectual property

- Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions

Animal experimentation

- Directive 2010/63/EU of 22 September 2010 on the protection of animals used for scientific purposes

GMOs

- Directive 2001/18/EC of 12 March 2001 on the deliberate release into the environment of GMOs
- Directive 2009/41/EC of 6 May 2009 on contained use of genetically modified microorganisms

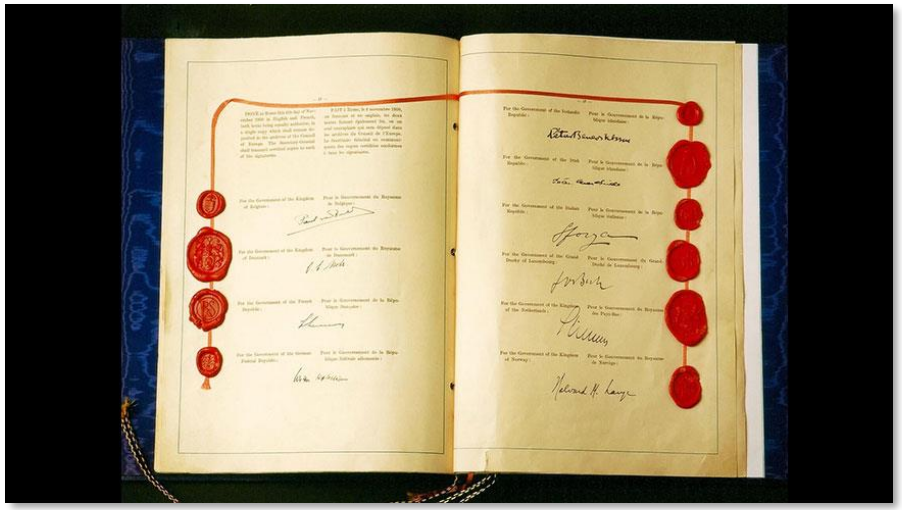
Council of Europe Framework

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

<u>European Convention on Human Rights (ECHR), 3 September 1953</u>

- Right to life (art. 2), right to respect for private and family life (art. 8) - (healthcare)
- Freedom of expression (art. 10) - (freedom of research)
- Right to property (art. 1 prot. 1) - (IP rights)



Council of Europe Framework

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

Convention on Human Rights and Biomedicine (Oviedo Convention), 1 December 1999

Article 2 – Primacy of the human being

The interests and welfare of the human being shall prevail over the sole interest of society or science.

- Art. 10 Private life and right to information, art. 11 Non-discrimination, art. 16 Protection of persons undergoing research…

- Two significant provisions for embryo research:

Article 18 – Research on embryos *in vitro*

1 Where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo.

2 The creation of human embryos for research purposes is prohibited.

III. The Legal Perspective

(4) Donors' rights

SoHOs and Donors' Rights

Regulation (EU) 2024/1938 of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application (SoHO Regulation)

- **Scope**: all SoHOs, except solid organs
- **Objective**: Greater protection of donors and recipients of SoHOs (Chapter VI)
  - Information and consent, volontary and unpaid donations
- **Sources**: Technical norms mainly elaborated by scientific experts organisms active in the sector
- **Procedures** :
  - Registering of entities exercising their activities that have an impact on the security and quality of SoHOs before the national competent authorities (art. 17)
  - Authorisation of establishments that are processing, storing, releasing, importing or exporting SoHOs (art. 17)
  - Authorisation of preparations containing SoHOs (art. 19)
- **Applicable starting 7 August 2027**

Donors' Consent

Review | Open access | Published: 23 July 2022

Organoids: a systematic review of ethical issues

Dide de Jongh, Emma K. Massey, the VANGUARD consortium & Eline M. Bunnik

Stem Cell Research & Therapy **13**, Article number: 337 (2022) | Cite this article

10k Accesses | **19** Citations | **58** Altmetric | Metrics

- What **information** do you put on a consent form for donors?
- Challenges to **informed** consent**:**
  - Fast changing technical opportunities ;
  - Lots of interested stakeholders (donors, biobanks, researchers, investors) ;
  - Relational value between donors and final uses of their donation ;
  - Free donation versus commercial uses
- How **specific** is the consent? Especially regarding sensitive uses (embryoids, neural organoids, chimeras…)
- Reflections surrounding **new consent forms models**
  - Instead of broad consent, allow for opt-in/opt-out, for dynamic consent, or governance models
- **Right to withdraw consent**
  - Limits to that right?

III. The Legal Perspective

(5) Research Limits

Research Limits – (a) Biomedical Research

Binding and non-binding instruments

- Binding provisions mostly found at the national level because it is a highly culture-dependent matter. They are enforceable before a judge (hard law).
- Even if international non-binding guidelines are very influential, they are not enforceable (soft law).

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Research Limits – (a) Embryo Research

By country

- **Some countries have no specific legislation** on embryo research
- **Permissive legislations** allow the use of the majority of techniques concerning embryo research, with the exception of reproductive cloning, which is universally banned: Embryo and hESC research; Derivation of new hESC lines; Creation of embryos for research; Nuclear transfer.
- **Permissive legislations with restrictions** allow research on embryos and hESC lines, as well as the derivation of new lines from supernumerary embryos. However, the nuclear transfer technique and the creation of embryos for research purposes are prohibited.
- **Restrictive legislations** prohibit research on embryos (and therefore the derivation of hESC lines), but allows research using imported lines, possibly with conditions concerning the date of derivation of the lines.
- **Prohibition regimes** forbid all research practices on the embryo and hESCs.

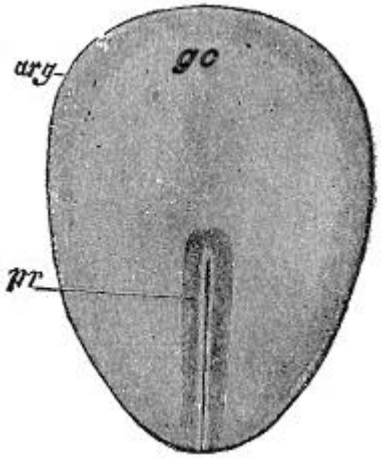
Legal Regime	Country
No specific legislation	Europe: Bulgaria, Cyprus, Estonia, Lithuania, Luxembourg, Latvia, Malta, Poland, Portugal, Romania, Slovakia
Permissive	Europe: Belgium, United Kingdom, Sweden. In the rest of the world: Russia, Israel, China, Japan
Permissive with restriction	In Europe: Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Netherlands, Norway, Portugal, Slovenia, Spain and Switzerland.
Restrictive	In Europe: Germany, Hungary, Italy.
Prohibition	In Europe: Austria, Ireland, Lithuania, Poland, Slovakia. In the rest of the world: Tunisia, Morocco, Jordan, Vietnam, Philippines, Malaysia, Colombia, Ecuador, Peru, Uruguay, Venezuela, Chile.

AGENCE DE LA BIOMÉDECINE, « Encadrement juridique international dans les différents domaines de la bioéthique, Actualisation 2024 », 2024.

Research Limits – (a) Embryo Research

The 14-days rule and beyond

- The **14-days rule** (Warnock Report 1984): the 14-day limit corresponds to the appearance of the **primitive streak.** The embryo becomes **individualised** (there is no longer any possibility of twinning) and the embryo's cells undergo their first differentiation, giving rise to the ectoderm, which can be considered to be the very **first outline of the central nervous system**.
- The **creation of embryos for research purposes under the Oviedo Convention is prohibited**.
    - Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Greece, Finland, France, Hungary, Iceland, Lithuania, Latvia, Norway, Portugal, Romania, Slovenia, Slovakia and Spain.



→ Are embryoids embryos? Is it a scientific question and/or a legal question?

Australia assimilates embryoids and embryos = licence required to conduct research.

The UK does not assimilate them = relies on Cambridge guidelines.

→What limits for embryoids if they are not embryos?

- Time periods are not particularly suitable for embryoids. Instead, set limits with developmental markers?

Research Limits – (b) Embryoid Research

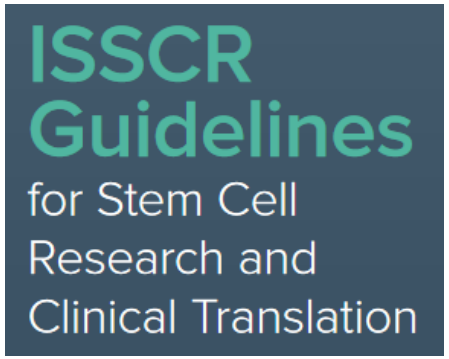
The ISSCR Guidelines

Classify various types of stem cell protocols among three categories for ethical review

Cat. 1 : Protocols not requiring a specific ethical review process

Cat. 2 : Protocols requiring a specific ethical review process

Cat. 3 : Prohibited protocols

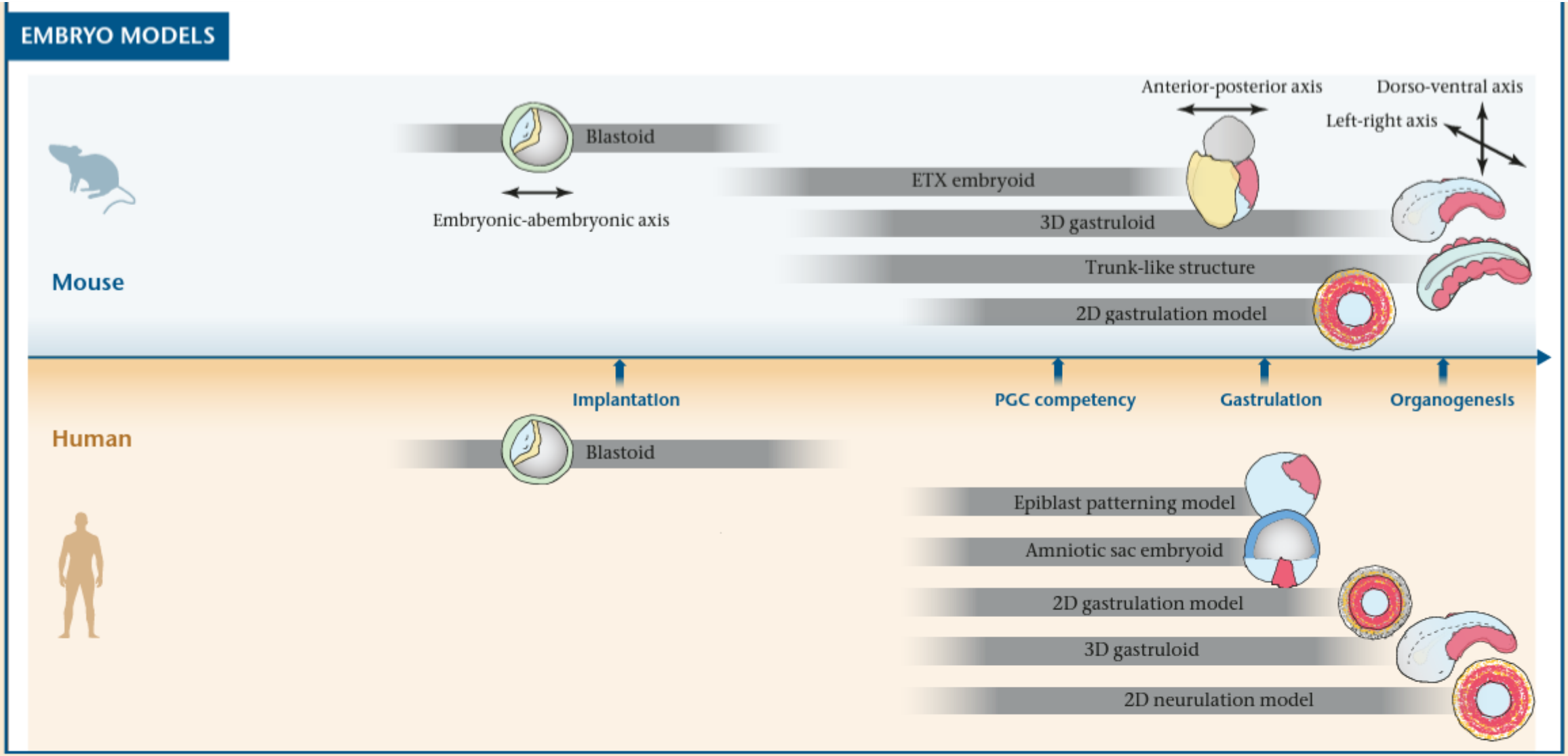


International society for stem cell research, « ISSCR Guidelines for Stem Cell Research and Clinical Translation », May 2021

Suggest to distinguish "integrated embryonic development model" from "non-integrated embryonic development model"

***Non-integrated stem cell-based embryo models**: These stem cell-based embryo models will experimentally recapitulate some, but not all aspects of the peri-implantation embryo [...]. These stem cell-based embryo models do not have any reasonable expectations of specifying additional cell types that would result in formation of an integrated embryo model. Gastruloids are an example of a nonintegrated stem cell-based embryo model.*

***Integrated stem cell-based embryo models**: These stem cell-based embryo models contain the relevant embryonic and extra-embryonic structures and could potentially achieve the complexity where they might realistically manifest the ability to undergo further integrated development if cultured for additional time in vitro. [...] Blastoids are an example of an integrated stem cell model.*



See online version for legends and references

Research Limits – (c) Brain Organoid Research

The ISSCR Guidelines

ISSCR recommendations concerning brain organoids (as of 2021)

- Most *in vitro* organoid research should be exempt from review by a specialized oversight process (cat. 1)
- Instead, a simple assessment by appropriate committees for laboratory research

ORGANOID RESEARCH

At this time, there is no biological evidence to suggest any issues of concern, such as consciousness or pain perception with organoids corresponding to CNS tissues, that would warrant review through the specialized oversight process. However, researchers should be aware of any ethical issues that may arise in the future as organoid models become more complex through long-term maturation or through the assembly of multiple organoids (Hyun *et al.* 2020).

Research Limits – (c) Brain Organoid Research

In the literature

Policy	Summary
Legal endorsement of existing research best practices	Even highly developed brain organoids do not and should not have a legal status comparable to that of embryos or born human being. Current best practices must be passed in law (Taupitz, 2022).
"20 weeks" threshold	Applications of 3R principles to human brain organoids that are equivalent to 20 weeks' *in vivo* brain development or more. For brain organoids with the potential to develop advanced cognitive capacities additional considerations apply (Koplin and Savulescu, 2019).
Graded spectrum of caution	The emergence of cortical structures, the generation of cortical neural oscillations and the response to the "Zap & Zip" test warrant caution. The more milestones incorporated the higher the chances to achieve consciousness (enabling structures, input & output, embodiment) (Jeziorski et al, 2022).

Research Limits – (d) Animals

At the EU level

Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes

- **Scope** (art. 1) : all live, non-human vertebrate animals and also to certain invertebrates which are likely to feel pain (cuttlefish, octopuses, etc.). The use for testing of non-human primates is subject to restrictions, and the use of great apes (chimpanzees, bonobos, gorillas and orangutans) is forbidden.
- **Objective:** To protect laboratory animals and enable research to advance further, these measures aim at limiting animal testing to an absolute minimum and setting up compulsory standards concerning the use, housing and care of the animals. 3Rs (art. 4).
- **Procedures**: Evaluation of projects involving experimentation on animals (art. 36 to 38)
  - The use of animals for experimental purposes is authorised in cases where no satisfactory substitute method exists.
  - Projects involving experiments on live animals must be assessed by the competent authority. They may not begin until they have received a positive assessment demonstrating that the use of animals is justified and that the expected advantages outweigh the harm caused to the animal, taking into account ethical considerations.
  - The number of animals used in a project must be reduced to a minimum, without however compromising the objectives of the project.
  - The living conditions and methods used in the procedures must minimise any unnecessary pain, suffering or distress to the animals.
- **Other provisions** : size of housing, enrichment techniques for social animals, methods of killing (Annex III and IV)

→ How do we deal with the welfare of new animal entities like chimeras, when their need might be unknown?

Research Limits – (e) Chimeras

Which regulation at the state level?

<u>Regulation at the state level</u>

Regulations on chimeras vary from state to state. Most countries require prior authorisation from a review committee.

- Countries prohibiting the creation of chimeras : Canada, South Korea…
- Countries authorising the creation of chimeras : China, Denmark, India, Japan, United Kingdom, United States, France…

The **prohibition on implanting a chimeric embryo in a human womb** is shared by all countries.

→ What limits for research on chimeras?

- Absolute ban? Ban on certain types of chimeras?
- If we have a graduation in the types of chimerisms allowed, what are the cut-offs? A percentage of cells? Of specific cells? Of specific cognitive characteristics?

Research Limits – (e) Chimeras

The ISSCR Guidelines

<u>Recommendations from the ISSCR</u>

- Pre-natal implantation protocols
  - **Animal research oversight committee** with an expertise in stem cell or developmental biology
  - Set **timepoints** to assess degree and scope of chimerism
  - Favor strategies of **targeted chimerism**
  - **Should exclude great and lesser apes**
- Post-natal implantation protocols
  - broadly consistent with common animal research review standards
  - traditional animal research oversight

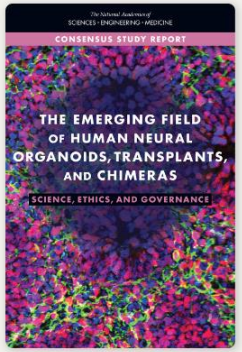
Research Limits – (e) Chimeras

US National Academies Guidelines

<u>Recommendations from the consensus report from the US national academies</u>

- **Precautionary approach**
  - pausing research when changes from species-typical behaviour
  - assess the qualitative changes and whether it has an ethical significance
- Monkey chimeras
  - More sensitive due to evolutionary proximity
  - More likely to be seen as violating human dignity and boundaries between species

NATIONAL ACADEMIES Sciences Engineering Medicine



The Emerging Field of Human Neural Organoids, Transplants, and Chimeras

Science, Ethics, and Governance

(2021)

Conclusion

How do we assess?

- Urgent need in consciousness science for more robust theories of consciousness and evidentiary tools
- Where possible, adapt ethological methodologies to novel entities

How do we regulate?

- Already applicable legal regimes: donors' rights, GMOs, IP law, embryo and stem cell research, animal experimentation…
- To what extent do they cover all issues raised? Mere adaptation, with new standards and professional guidelines? Or need for a real overall?
- What are the ethical boundaries? Each country will have different limits.

Thank you for your attention!

Contact: adrien.bottacci@univ-amu.fr

This work has been supported by ANR-funded Organact (ANR-22-CE41-0012-03).