



Organoids and ethical challenges

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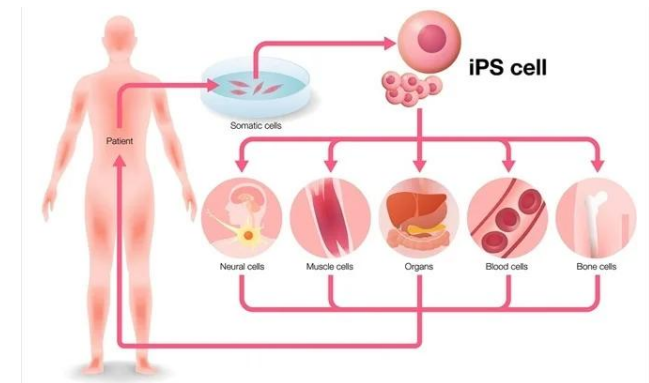
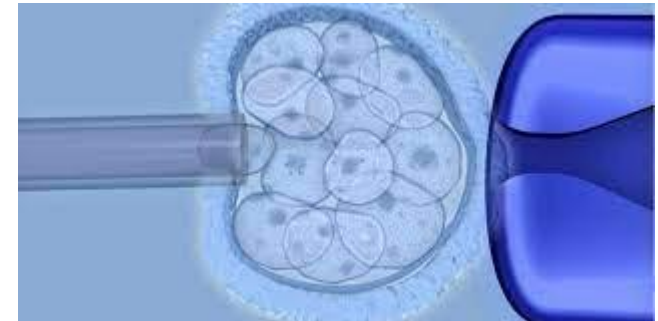


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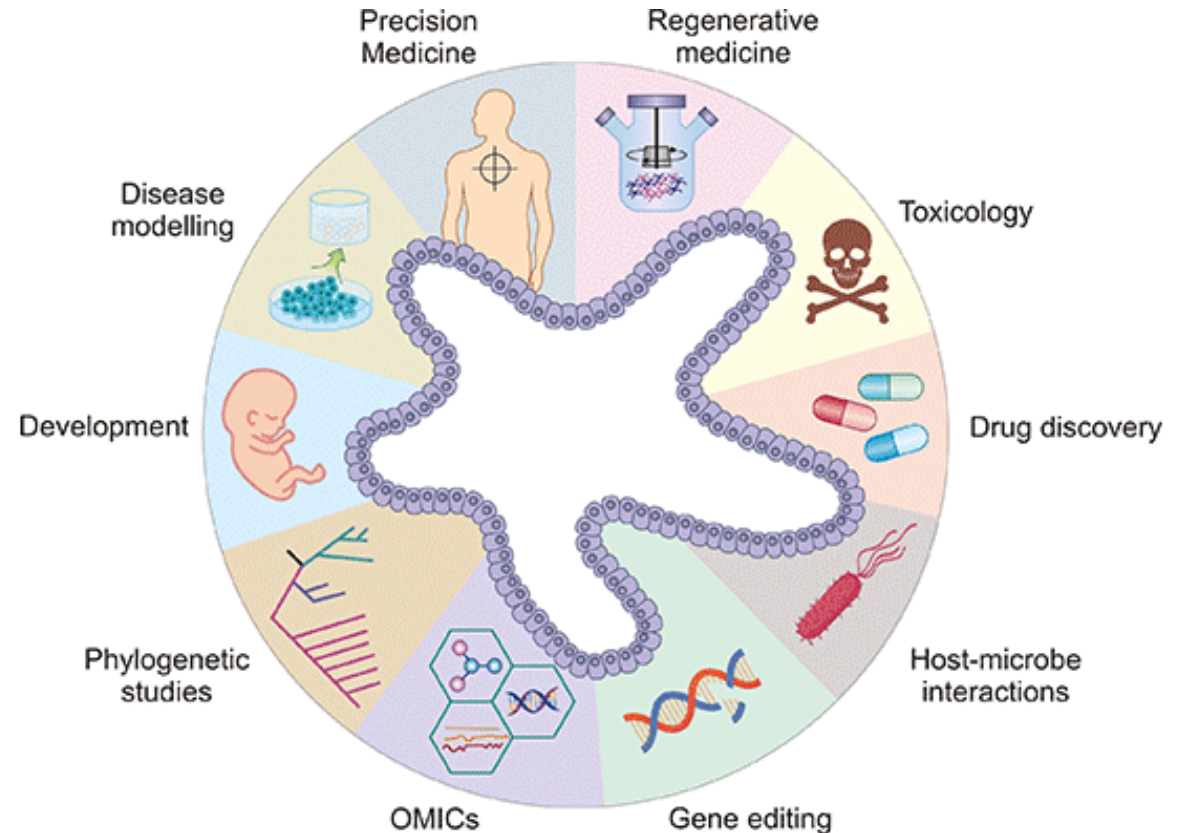
Organoids: what are they?

- Organoids are mini organs, grown as 3D cell structures in the lab
- They display architectures and functionalities similar to *in vivo* organs
- They derive from:
 - Embryonic Stem Cells (ESCs),
 - induced Pluripotent Stem Cells (iPSCs),
 - adult stem cells, and
 - tissue-specific progenitors
- They have the ability to self-organize, they are multicellular and can be grown indefinitely

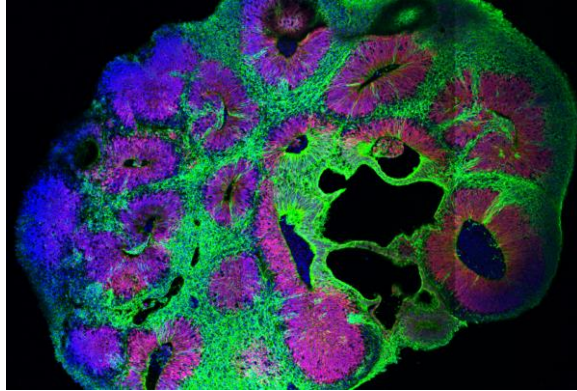


Organoids: utility and promises

- Drug discovery
- Alternatives for drug testing in animals
- Disease modelling
- Precision medicine
- Gene editing
- Regenerative medicine
- Models of organ development
- Transplantation, etc.



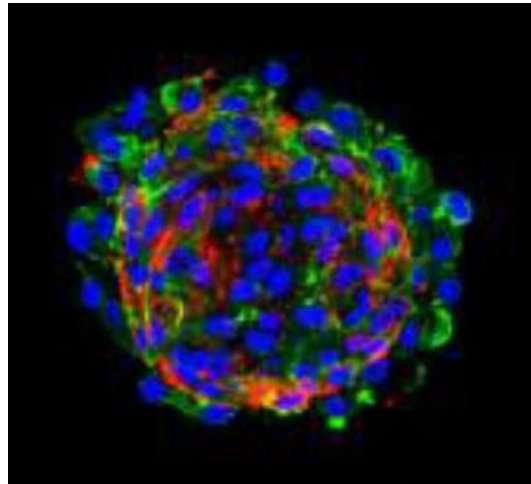
Types of organoids



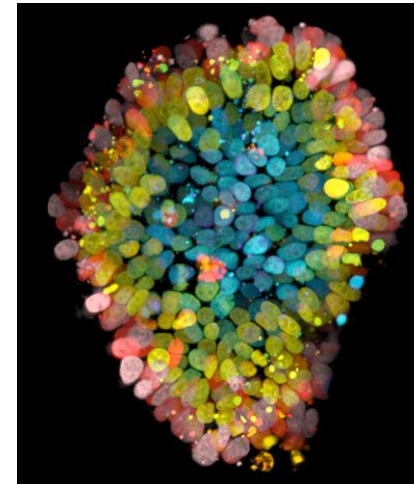
Brain organoid



Embryo model

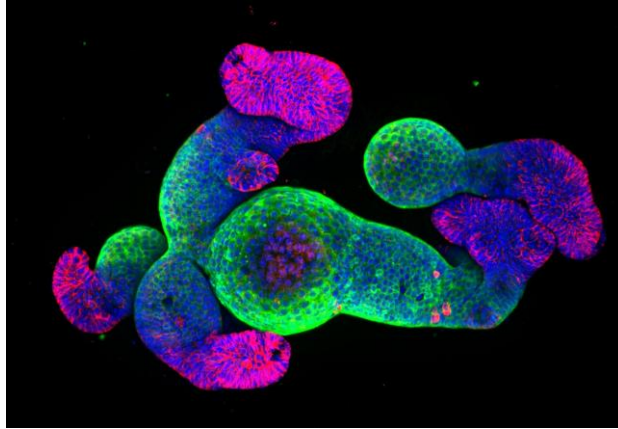


Testicular organoid

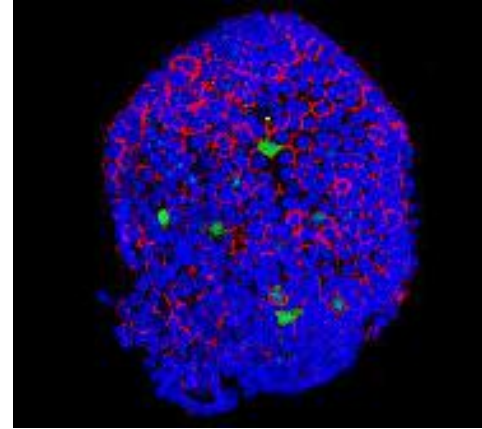


Ovarian
organoid

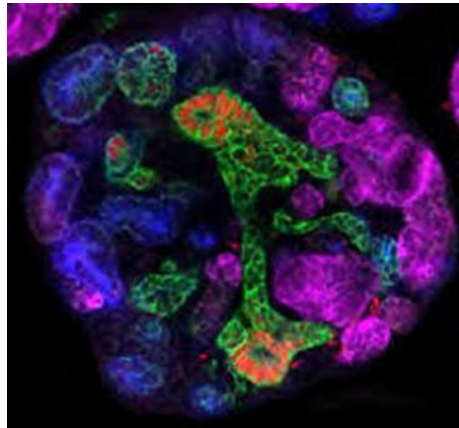
Types of organoids



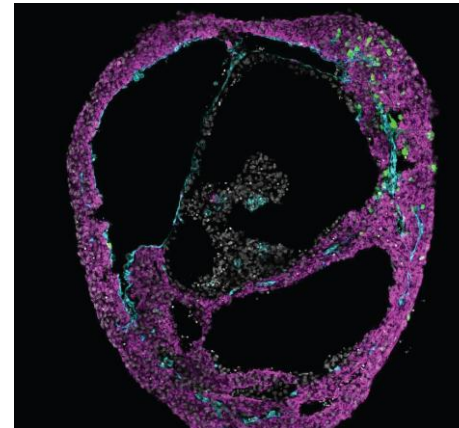
Gut organoid



Lung organoid

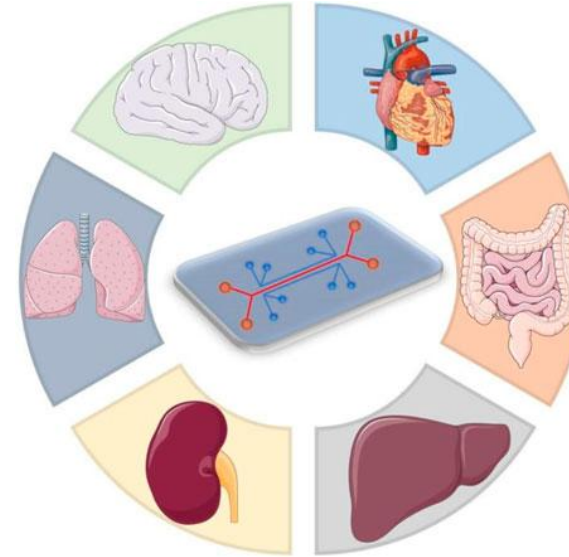
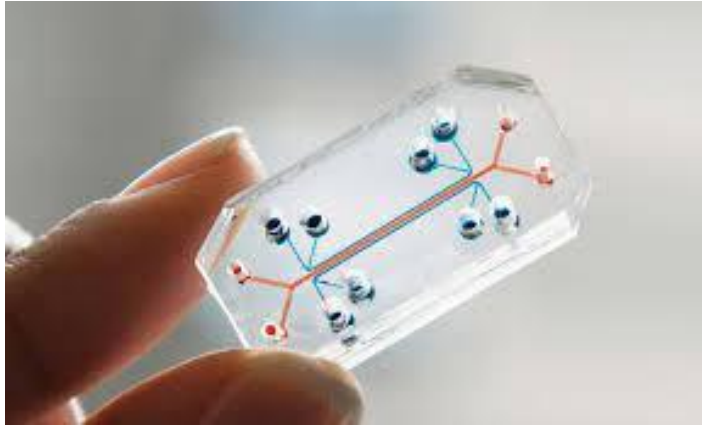


Kidney organoid



Heart organoid

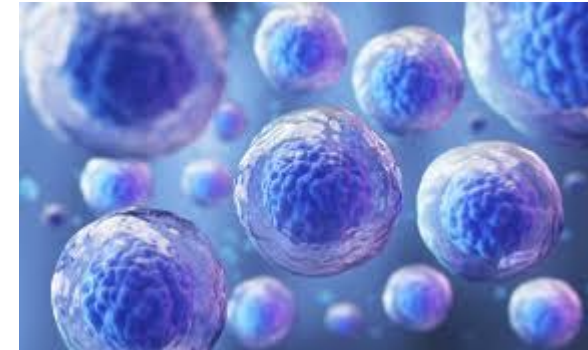
Types of organoids



Organ-on-a-chip system
and multi-organoid
complexes

Ethical issues: Source of Stem Cells

- ESCs can self-renew and differentiate into any cell type of the human body, thus ESC-derived organoids are outstanding *in vitro* models
- But ESCs are isolated from embryos, raising significant ethical concerns
- Controversial issue: the **moral status of the human embryo** (from human tissue to a human being) (Brown, 2018)
- Ethical concerns on the **value of human life** and respect to human dignity
- This has also legal ramifications, as the human embryo is subject to stringent regulation in most jurisdictions



Ethical issues: Informed Consent

- The **purpose of donation** may be unclear to donors. Consent to:
 - development or novel therapies?
 - research in organoid technology in general?
 - development of disease models?
- Even for researchers such questions are not always straight forward
- Proper **informed consent strategies** for both research and clinical purposes is necessary:
 - blanket (not a real consent)
 - broad with restrictions (prevents from losing potential social benefits)
 - tiered for certain areas (e.g. cancer) or diseases (e.g. breast cancer) (provides control to donors)
 - continuous (impractical requiring investment of time and resources)
 - Two-step consent (CHANGER, <https://zenodo.org/records/18865183>)
- For brain organoids and embryo models donors may have objections for certain uses - **Opt-out** options should be available according to their personal values/beliefs



Ethical issues: Data Protection

- **Sample anonymization** is applicable for organoid biobanks for research purposes
- Anonymization is NOT appropriate for clinical applications (personalized treatments, precision medicine, transplantation)
- The unclear legal status of organoids and the ambiguous ownership status have implications on the ownership of the genotypic/phenotypic data produced
- In any case, biobankers are legally and ethically obligated to protect sensitive data of donors and take **appropriate measures** to minimize the risk of unauthorized parties having access



- The long-term storage and use of “live” organoids demands meticulous, continuous **ethics review and oversight** by independent ethics bodies with high level expertise

Ethical issues: Chimeras

- Is it ethically acceptable to use human brain and gonadal organoids in human-animal chimeras?
- Does it **violate human dignity and human nature**?
- If human brain organoids develop sentience or consciousness, such chimeras are ethically highly problematic
- If gonadal organoids are used in animals, this raises the additional possibility of cross-species fertilization
- Existing legal frameworks on human-animal chimeras affect organoids, e.g. Greece, Cyprus, Italy and Germany prohibit chimeric research
- Competitive disadvantage over countries allowing chimera research (e.g. UK, China)



Ethical issues: Commercialization

- If commercialization of organoids is prohibited then the risk of placing obstacles in biomedical research is apparent
- On the other hand, if organoids can be “traded” as commodities, then the interests of third parties ultimately have more value than the rights of tissue donors
- According to normative national or European documents and guidelines, the **human bodily parts** (including not only whole organs but also human tissues) **shall not give rise to financial gain**
- Some countries have not ratified the relevant conventions leaving room for the commercial practice of tissue procurement and transfer
- Organoid technology with its enormous potential should have a clearer regulatory framework on whether commercialization is legitimate or not

Ethical issues: Patentability

- Organoids derive from human cells after manipulation, thus are patentable interventions
- Patents have already been granted for various organoids or methods to develop organoids (USA, Japan)
- In the EU patent system, the type of organoid may define eligibility (e.g. Brüstle v Greenpeace, EU Courts of Justice)
- Due to their special moral value, **embryo models and brain organoids could be excluded from patents** based on the notion of morality or on the general prohibition against the patenting of immoral inventions (human characteristics)
- Differences in the patenting system between EU and non-EU countries may lead to a competitive disadvantage for the EU



Ethical issues: Access to Treatment

- Commercialization and patentability of organoids have an impact on the cost of the produced treatments
- Existing examples of ATMPs have shown that SC therapies are expensive, raising serious ethical concerns over patient access to effective therapies



- But iPSCs are relatively easy to obtain, so, **in the future**, organoids derived from iPSCs may indeed provide a **more affordable** option for treatment

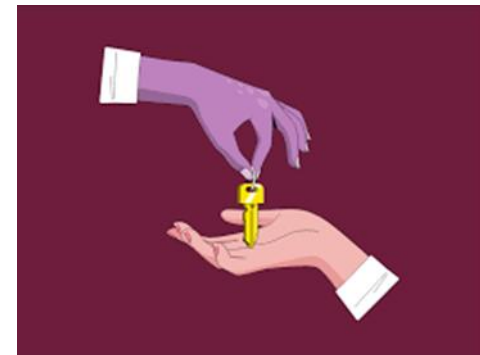
Ethical issues: Misuse and Dual Use

- Organoids can be used for bioterrorism
- E.g. lung and brain organoids can be used to **test the toxicity** of new chemical weapons or toxins, or to assess the infectivity of biological agents (Rinaldi & Colotti, 2019)
- **Biobots** combine robots and human tissues, raising dual-use concerns, particularly for brain organoids connected to a robot
- Special regulations may not be necessary for dual and malevolent use of organoids, but current legislations can be applicable in organoids, too



Ethical issues: Ownership

- There are no binding rules defining the rights and duties of donors and organoid biobankers
- The ambiguous moral and legal status of organoids further complicates the issue of **who owns** the cell-derived organoids
- Organoids are biological entities that do not clearly fall into the categories of cells, gametes, tissues or organs which are legally regulated under relevant laws
- Defining the legal status of organoids (esp. for brain organoids), is **the cornerstone for consent** and subsequent uses (research, clinical, not-for profit, for-profit)
- Existing biobanks storing human biological materials have agreed to be **custodians** (act as the organization that actually holds the assets) **or** **trustees** (act as managers of the assets)



Ethical issues: Multi-Organoid Complexes

- Presenting characteristics of life: cells, homeostasis, energy use, metabolism and excretion, response to environmental stimuli
- Could society perceive them as entities that **exhibit** (some kind of) **life** or as “**in vitro twins**”?
- Cell donors feel more closely related to an entity capable of mimicking physiological functions of his/her body, compared to a single, detached organoid
- The degree of homology to the human body is a key issue, depending on:
 - The **number of organoids** included in a system (more organoids better mimic physiological functions of the body)
 - The **type of organoids** (e.g. brain, gonadal) since they can be considered “more humanized”
- If they can be sentient, conscious, react to stimuli, do they deserve **special protection** (e.g. like non-human primates)?

Ethical issues: Organoid Biobanks

- Organoids from human tissue biopsies can grow **indefinitely**
- Organoids can be stored and serve as **living biobanks**
- Source of biological material, but also information on organ **physiology and function**

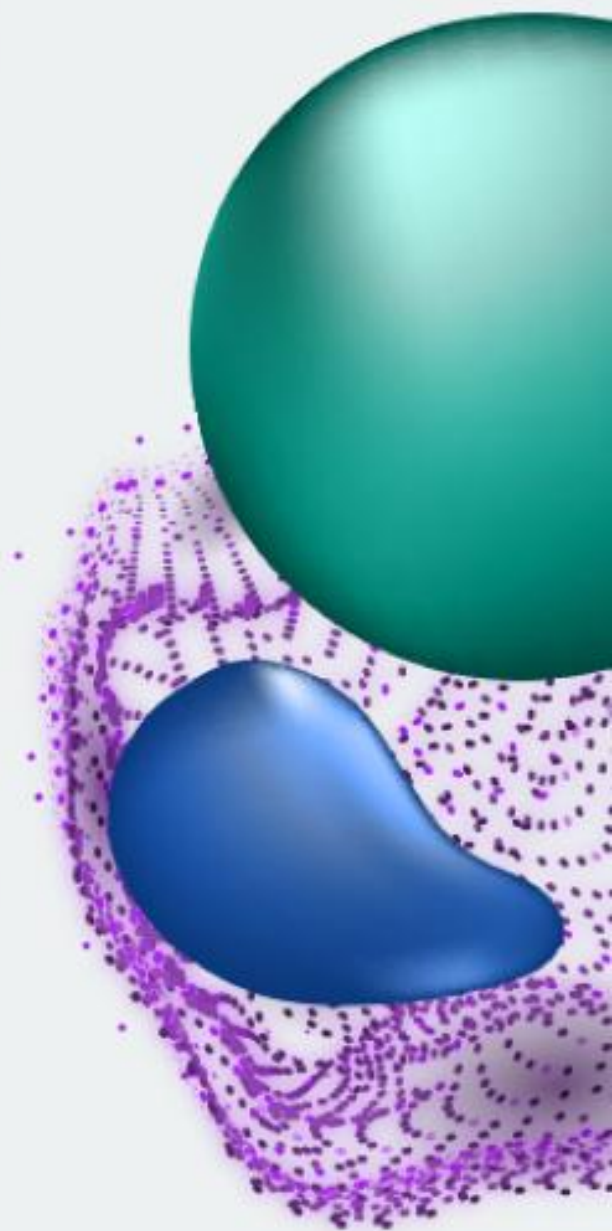


- Future applications and uses of organoids **cannot be defined**

CHANGEL

CHALLENGES AND INNOVATIVE CHANGES IN RESEARCH ETHICS REVIEWS

A 3-year European HORIZON Project aiming to promote changes in research ethics reviews, fostering ethics by design and supporting ethics committees.



The partnership

Project partners

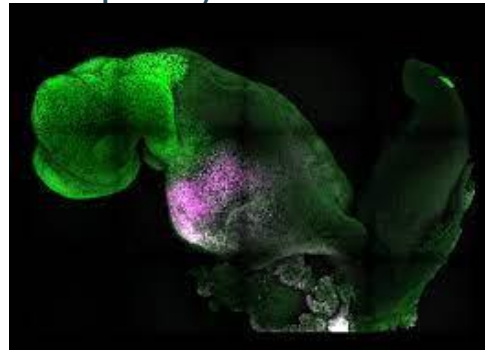


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Ethical issues: Embryo models

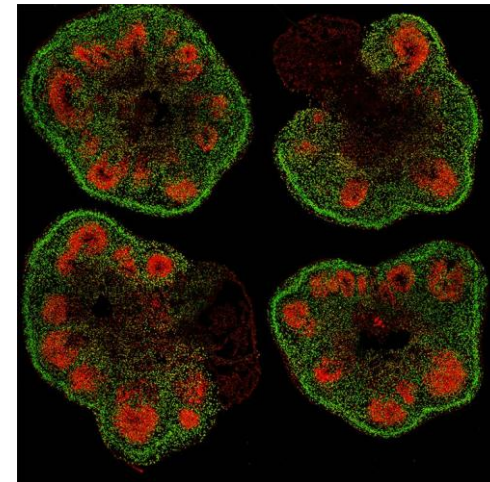
- Similar morphology and gene expression to human embryos, unique model for embryo development beyond the 14-day limit
- Integrated embryo models mimic the entire conceptus (Denker, 2016), is the 14-day limit relevant (?)
- What is their **moral and legal status**? (Highly debatable, they don't constitute zygotes derived from eggs and sperm)



- iPSC-derived embryo models could they be considered as **cloned embryos**? (genetically identical to cell donors)
- Necessary to have a consensus on a definition of an embryo?

Ethical issues: Brain Organoids

- Human brain development cannot be studied in animal models (different complexity, physiology, mechanisms)
- Brain organoids are useful to investigate the complex processes of the brain
- They constitute **neural entities** of human origin: could they obtain cognitive abilities, consciousness or sentience? (Lavazza, 2020)
- What is the **moral status** of brain organoids with potential to exhibit human characteristics?
- How could such an issue be reflected in an informed consent?
- If they are sentient, they may require **special protection** (e.g. similar to the 3Rs in animals)



Ethical issues: Gonadal Organoids

- Source of reproductive cells for IVF, e.g. when no viable oocytes can be extracted or prepubescent girls undergo chemotherapy
- A gonadal organoid developed by **male** iPSCs can be used to generate **oocytes** and vice versa, challenging established social standards requiring a male and a female donor for reproduction
- An **explicit** consensus needed on whether gonadal organoids could be used for reproductive purposes
- If prohibited, the scope should be defined:
 - banned for clinical use (transfer to the uterus)?
 - allowed for research purposes to investigate infertility?

