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Ethical-legal aspects of organoids and their use in research. Manage risks and legal constraints for the development of ethical research.

Aspetti etico-legali degli organoidi e loro utilizzo nella ricerca. Gestire rischi e vincoli legali per lo sviluppo.

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Abstract

Gli organoidi, detto in sintesi e semplicità, sono repliche in miniatura di organi e tessuti umani: derivano da cellule staminali pluripotenti indotte (iPSC) o da cellule e tessuti adulti, anche di tipo tumorale. Rappresentano un importante strumento per la medicina personalizzata e per la sperimentazione dei farmaci in generale. Al momento il quadro giuridico è lacunoso e l'attenzione è piuttosto sui temi etici e tutela della privacy. Il saggio si concentra sul framework giuridico cercando risposte qualificatorie che possano coniugare sviluppo della ricerca e tutela la persona.

Organoids, briefly and simply stated, are miniature replicas of human organs and tissues: they derive from induced pluripotent stem cells (iPSC) or from adult cells and tissues, including tumors. They represent an important tool for personalized medicine and drug testing in general. At the moment the legal framework is incomplete and the focus is rather on ethical issues and the protection of privacy. The essay focuses on the legal framework looking for qualifying answers that can combine research development and protection of the person.

Keywords: organoids; developmental biology; regenerative medicine; disease modelling.

Summary:

1. Premise.

The term organoids indicate three-dimensional (3D) cell structures that contain a multitude of organ-specific cells that are formed by organization and differentiation of stem cells.

The similarities that organoids share with organs make them a promising research tool for studying more complex biological functions. The use of organoids has already found application in areas such as developmental biology, regenerative medicine, disease modeling, drug discovery, and personalized medicine.

Moreover, from the point of view of the "Do No Significant Harm (DNSH)" principle, according to which no measures financed by the notices must damage the objectives environmental, and according to ecological transformation PNRR mission, organoids may represent, in specific conditions, either a suitable alternative or a complementary approach to animal experimentation. It is important to note that there is no in vitro model that can replace all animal models, and, at the same time, there are experiments unfeasible in animals but tailored for in-vitro 3D models.[1]

Organoids also represent a key for advanced drug and personalized medicine therefore in line with the PNRR mission of innovation, competitiveness in fact as said they can be used for the development of new pharmacological products. Some studies analyze the ethical issues raised by organoids and recommend measures that must be taken at various levels to ensure the ethical use and application of this technology. It lacks a keen legal perspective connected to ethical and medical issues and a deep insight of boundaries between human and non-human.

This paper proposes strategies to support organoid research and ensure that we do not lose any of the potential benefits that organoids offer maintaining DNSH perspective.

To do that a multi-factor action is needed: the legal issues (the theory of goods, the body availability, industrial property issues in respect of product of the body) together with and not separate from the ethical perspective above mentioned, public engagement action, and dialogue law-medicine.

[1] C Horejs, 'Organ chips, organoids and the animal testing conundrum' (2021) 6 Nat Rev Mater, 372–373.

2. State of art.

Organoids are usually identified in three-dimensional (3D) cell structures that contain a multitude of organ-specific cells that are formed by self-organization and differentiation of stem cells.

They can be used for:

Developmental Biology – Tissue Biology: matured organoids display functional organ sub-structures and have been used to investigate both adult tissue homeostasis and embryonic organ development.

Regenerative medicine: next to in vitro applications, organoids have been used in transplantation studies to assess regenerative potential.

Disease modelling - "Organ Pathology in a Dish": in disease modelling, organoids generated from human cells can overcome several limitations of animal models.

Drug discovery and personalized medicine: organoids are attractive for drug discovery, since they can be produced on a relatively large scale for an array of subtypes capturing disease heterogeneity and long-term biobanked.

Research using organoids gained momentum in 2009 when single stem cells were first used to produce self-organizing intestinal crypt-villus units. Since then, the number of international, peer review papers increased from 10 to over 2000/year

There are two main types of organoids based upon the choice of stem cells. The first is derived from PSCs that include both embryonic stem cells (ESCs) and iPSCs and the second type is derived from organ-specific adult stem cells (ASCs).

Organoids can be generated by both unguided and guided methods. The unguided approach relies on PSC aggregates to undergo spontaneous morphogenesis and their capacity for intrinsic differentiation, whereas the guided approach induces PSCs to differentiate towards desired lineages by supplementing external patterning factors and scaffolds. This method also fosters an entirely new technical approach called bio-printing.

From this synthetic information on what organoids are, and on what they are going to be used for, joint to the development of dedicated biotech and ICT branches with broad economic impact, it emerged that they present new legal and ethical issues.

Their legal statute is missing, and the proposed solutions regarding to ethical issues in the experimentation on human cells, on their statute, etc. are not fully applicable here as the organoids, in the end, are other than the human component that gave them origin, they are distinct from the original cells. This distinction becomes even more significant as the technology advances further in their creative process. Hence the importance of the above distinctions.

Some studies put in evidence ethical challenges.[2] In order to permit the development of an organoid it is important to map legal risk and constraints and implement the ethical and legal studies on the phenomenon. At the same

[2] D de Jongh, EK Massey; VANGUARD consortium, EM Bunnik, 'Organoids: a systematic review of ethical issues'(2022) 13 Stem Cell Res Ther, 337; BBaertschi, HAtlan, M Botbol-Baum, B Bed'hom, H Combrisson, et al., 'Organoids Research: What are the ethical issues? ' 2020; S Boers & al., 'Organoids as Hybrids: Ethical Implications for the Exchange of Human Tissues ', (2018) 45 Journal of Medical Ethics, 2.

time, it is important to raise citizens' awareness on organoids' nature, their promise but also their limitations, in order to avoid mystifications of such new technologies, so important for human and animals' health.

Research in this field holds the potential to address numerous ethical and non-ethical issues, such as the shortage of grafts for transplantation, the welfare and treatment of animals for in-vivo and ex-vivo experiments, the equitable access to innovative therapies. It is conceivable that the debate around organoids will have an impact on the direction of future research. This debate can help prioritizing the investment of the limited financial resources, avoiding avenues that lack a solid scientific basis, even if they may appear popular or "fashionable".

Although a list of issues would be difficult and incomplete, some are already burning: 1. The evaluation of risks, benefits, and safety; 2. The moral status of organoids; 3. The creation of chimeras by xenotransplantation. At the moment ethical studies are mostly focusing on brain organoids, on ethical issues and consciousness assessment of organoids, especially cerebral organoids.[3] Some studies aimed to analyze the ethical issues surrounding organoid research recommend measures: informed consent and privacy of cell donors, the moral and legal status of organoids, the potential acquisition of human "characteristics or qualities", use of gene editing, creation of chimeras, organoid transplantation, commercialization and patentability, issues of equity in the resulting treatments, potential misuse and dual use issues and long-term storage in biobanks. Existing guidelines and regulatory frameworks that are applicable to organoids are discussed and offer only partial solutions.[4]

This paper intends to propose strategies to promote research on organoids that allow to reduce animal research and arrive at advanced results and personalized medicine, finding solution to legal and ethical issues.

3. Open Issues, General Object and specific objectives/proposed strategies.

Studies on organoids left some open issues:

What are the relationships between the concept of organoids and the concept "part of the body" in the present interaction between technology and medicine? To give an answer it is necessary to define the legal status of organoid by considering the different medical and pharmacological methodologies applied to organoid research.

Do organoids have legal protection? Are they organs, tissues, intellectual goods? Who owns the organoids? How can they circulate between research institutes, for example? What rights does the researcher who created them have over them? Is it possible to destroy them? What rights do subjects have over information obtained from research on organoids derived from their cells?

[3] B Baertschi, H Atlan, M Botbol-Baum, B Bed'hom, H Combrisson, et al., 'Organoids Research: What are the ethical issues?' (n. 2).

[4] V Mollaki, 'Ethical Challenges in Organoid Use' (2021) 10 BioTech, 12.

The question of obtaining explicit consent from patients for the use of their cells to create specific types of organoids (neural, renal, cardiac, etc.) raises important ethical considerations. Starting from the importance of pseudonymisation rather than anonymizing in order to maintain the link between information derived from the cell and its use and the medical history of its donor, in what terms can pseudonymisation be performed as an alternative to anonymisation? Can the donor deny the pseudonymization and ask for anonymity?

In what terms can individuals who have a connection with the donor (children, grandchildren) access postmortem information?

Genetically edited cells, which legal status do they have with the donor?

If the result of the research is susceptible to economic valorisation, in what terms can it be valued? Within what limits must the social aim remain?

How it is possible to ensure that the input of the public will play a role in the decision- making process? Public engagement seeks to ensure that decisions are sustainable by making all participants aware of the various interests and points of view surrounding an issue or decision.

This will be reached by addressing the following specific objectives: to allow both general and specialised public to access information about the project progress and its outcomes; -to ensure a successful run-time and dissemination of project achievements and results to all relevant stakeholders; to foster contact between researchers, potential end-users of the results and decision makers.

The general object the paper, as said, is to promote ethical research on organoids that allows to reduce animal research and arrive at advanced results and personalized medicine.

Specific objectives consisting in the strategies proposed are:

- qualification of Organoids under the legal categories;
- mapping legal and ethical risks and constraints related to organoids;
- management of legal / ethical risks and constraints: informed consent models, guidelines and protocols, standard form of agreements to manage problems related to industrial property;
- fostering the citizens awareness on what organoids are, their potentials and limitations.

All these actions, generally speaking, permit to foster curiosity-driven research on the determination of new boundaries between part of the bodies and industrial production taking into account the different processes to produce an organoid: form stem cells or from engineered adult cells converted in stem cells, usage of guided or unguided methods.

Organoids represent a key for advanced drugs, being therefore in line with the NextgenerationEU mission of innovation and competitiveness: in fact, as said, they are suitable for the development of new pharmacological products, or for the re-purpose of existing drugs, in human-like models.

Some studies analyse the ethical issues raised by organoids and recommend measures that must be taken at various levels to ensure the ethical use and application of this technology. However, these studies lack a more legal perspective connected to ethical and medical issues: what is the legal status of organoids? Do organoids have legal protection? Who owns the organoids? How can they circulate between research institutes, for example? What rights does the researcher who created them have over them?

Only thanks to the interaction between jurists and scientists, it will be possible to consider ethical issues in a new perspective considering the different methodologies applied to organoids and their different uses in medicine and pharmaceutical research. All the problems will be considered in a casuistic perspective without black or white solutions and in the prospect of a "reasonable accommodation" in the composition of opposing interests. Furthermore, scientific, legal and ethical issues will be considered related. Thus, issues relating to the donor's right to anonymization will be dealt with starting from the legal status of the organoids and their different use.

With respect to the inter- and transdisciplinary approach, this paper considers two aspects, which may limit the exploitation of organoid-based research in Italy: the ethics-by-design method applied to all projects, based on applicable toolkits, and a mutual recognition and fruitful empowerment between scientists and citizens.

A new communication strategy will be dedicated to the communication to the citizenships and to the public engagement in order to disseminate scientific research even among non-experts and thus share knowledge to develop an informed debate on the research in progress.

4. Legal framework for solutions

All the above-mentioned questions find a legal framework and a legal key point.

The legal framework includes: consent of the donor; privacy right; intellectual property rights.

With regard to the consent of the donor, a new concept is emerging to better protect the dignity of the donor: the consent for governance, which shifts the ethical issues from the initial consenting process to ongoing obligations for governance.[5]

Initial consent consists barely of informing participants of any known future uses of the human tissue.

This consent for governance structure includes transparency on management of data and tissue, identification of potential commercial uses, details on how clinical benefit for the donor too and a plan for longitudinal ethical oversight which consider all the issues involved and not only ethics and privacy right.

Regarding the Protection of Privacy, de-identification of data of the donor have also been critical aspects of ethical research when the anonymization is not possible and, more importantly, not preferable in the social interest and in the interest of the donor.[6]

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[5] A Lavazza, FG Pizzetti, ' Human cerebral organoids as a new legal and ethical challenge' (2020) 9;7(1) J Law Biosci.

[6] SN Boers, AL Bredenoord, 'Consent for governance in the ethical use of organoids' (2018) 20 Nat. Cell Biol., 642–645.; SN Boers, JJ Delden, H Cleversand, AL Bredenoord, 'Organoid biobanking: Identifying the ethics: Organoids revive old and raise new ethical challenges for basic research and therapeutic use' (2016) 17

IT solutions are available that allow both to maintain the security of personal data and to increase the efficiency of access to data in biobanks. Disclosure filters are discussed as a strategy to combine European public expectations concerning informed consent with the requirements of biobank research.[7]

With regard to Intellectual Property Right (IPR), the combination of human biomaterial and research activity raise IPR issues: to what extent are human biomaterials patentable? As many authors remember the US Supreme Court decision in the case of Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al. ruled that the creation of new products from human biomaterials with the creation of entities that are not naturally occurring are patent-eligible.[8]

As many authors stressed, this has important implications for increased costs that both could impact progress and restrict patients from accessing monetary or clinical benefits of organoid research.[9]

The key legal point is the qualification of organoid in the circulation of goods. It is possible to not consider organoids as goods and consider them as part of the body. However, this conclusion can have tremendous implication considering the evolution of research. It is possible to consider them as goods, because they represent something new respect to body of the donor, with a circulation assisted by the consent for governance of the donor.

With reference to the information, we have met similar instances as well.[10] Also in this case, even though they are considered assets subject to circulation, particular statutes have been identified aimed at protecting the different interests involved (nb not only interests of a physical person):

1. the fairness of financial market (see the prohibition of insider trading or the buying and selling of securities of a specific company by subjects who, due to their position in the within the same or for their professional activity, have come into possession of confidential information, i.e. not in the public domain.);
2. the secrecy obligations present in commercial contracts and in employment relationships where in general it is forbidden for the worker to disclose news pertaining to the company and its production methods, or to use them in order to cause damage or prejudice to it, and finally

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EMBO Rep., 938–941; SN Boers, JJ M van Deldenand, AL Bredenoord, 'Broad consent is consent for governance' (2015) 15 (9) Am. J. Bioeth., 53-55; SN Boers, JJM. van Deldenand, AL Bredenoord, 'Organoids as hybrids: Ethical implications for the exchange of human tissues' (2019) 45 J. Med. Ethics, 131-139.

[7] M Mostert, AL Bredenoord, MC Biesaart, JJ van Delden, 'Erratum: Big data in medical research and EU data protection law: Challenges to the consent or anonymise approach' (2016) 24 Eur. J. Hum. Genet., 1096.

[8] J Eder, H Gottweis, K Zatloukal, 'IT solutions for privacy protection in biobanking' (2012) 15 Public Health Genomics, 254-62.

[9] M Roberts, IB Wall, I Bingham, D Icely, B Reeve, K Bure et al., 'The global intellectual property landscape of induced pluripotent stem cell technologies' (2014) 32 Nat. Biotechnol, 742–748.; M Hoppe, A Habib, R Desai, L Edwards, C Kodavali, NS Sherry Psy and PO Zinn, 'Human brain organoid code of conduct' (2023) Front. Mol. Med.

[10] M Roberts, IB Wall, I Bingham, D Icely, B Reeve, K Bure et al., 'The global intellectual property landscape of induced pluripotent stem cell technologies' (2014) 32 Nat. Biotechnol, 742–748.; M Hoppe, A Habib, R Desai, L Edwards, C Kodavali, NS Sherry Psy and PO Zinn, 'Human brain organoid code of conduct' (2023) Front. Mol. Med.

3. the protection of personal data closest to the object in question considering that human cells carry information about the person from whom they are drawn.[11]

At the end, organoids can be considered as *legal goods that include personal information*. The relevance of the legislation on the acts of disposition of the body concerns the prodromal moment to the creation of the organoids or the removal of cells. Cells will then be subjected to treatment for the creation of the organoid, which at the end of the production process is some way different, even if the DNA is the same of the donor, from the part of the body from that originates it even in case of organoids from iPCS They are the result of cell engineering processes.

An organoid made up of primary cells, i.e. cells derived directly from the dissociation of a tissue, healthy or diseased (for example from a tumor, or gut) can maintain the complexity of the primary tissue in term of cell heterogeneity and extracellular matrix. Thus, organoids contain personal data and with regard to these aspects, norms on Data Protection will be applied. However, they often display high variability limiting the possibility of "standardization", a prerequisite for some applications such as drug development.

A 3D-system derived from cell-lines or tissue-derived naïve cells lines undergoing extensive manipulation *in-vitro* to acquire homologous and standardized characteristics, can be hardly classified as an "organoid" in strict terms. However, these systems are more reproducible and further development of bioengineering techniques and advances in biomaterials may allow them to approach a standard mimicking the biochemical, metabolic and mechanic properties of naïve tissue. Cell lines are easier to grow in the laboratory than primary cells, but they do not represent the natural differences that exist between individuals. They therefore do not allow researchers to test whether certain therapies work on specific groups of patients. iPSC-derived cells maintaining the genetic and epigenetic profile of the naïve cells are suitable patient-specific models but their differentiation into "adult-like" phenotype is often incomplete (e.g., cardiomyocytes or neurons).

Finally, ethical issues need to be considered moving from the different moral significance of organoids like in case of cerebral organoids which pose analogous problem as other case of replication of brain functions like in case of Artificial Neural Networks (ANNs).[12]

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[11] Having regard to information as economic good we have to consider the peculiar cost and value of such good. In Economics the concept of information is defined broadly. See A. Marshall, *Principles of Economics* (8th edn, MacMillan and Co. 1930). Thus information can be considered economic goods but with some peculiarities - 'The value of information is probabilistic, rather than deterministic, and depends on the returns from the (future) use of that information. The expected value of information at any particular point, so defined, was called its stock value. Second, that the stock value of information may be affected by the transfer of the information to others, thus making such changes in stock value a valid component of marginal cost considerations of the exchange of information goods': BJ Bates, 'Information as an Economic Good: A Re- Evaluation of Theoretical Approaches' in BD Ruben & L. A. Lievrouw (Eds.), *Mediation, Information, and Communication. Information and Behavior*, Vol3, Routledge, 2018, 379-394.

[12] M Morrison, J Bell, C George, S Harmon, M Munsie, J Kaye, 'The European General Data Protection Regulation: challenges and considerations for iPSC researchers and biobanks ' Regen Med. (September 2017).

Even countries that have already regulated the use of organoids in scientific research (such as the United States and Australia [13]), propose regulatory frameworks for brain organoids that have not kept pace with the associated emerging ethical concerns. For instance, Australian regulation related to organoid research, similarly to United States provisions, clarifies the donor's right to informed consent, the participant's right to know the research results and the welfare of donors, however it does not take into consideration the unique ethical concerns of cerebral organoid research. Specifically, in Australia, the National Health and Medical Research Council's National Statement on Ethical Conduct in Human Research, which governs the regulation of organoid research, stipulates requirements for the collection and utilization of human biospecimens for research, informed consent from tissue donors, and the dissemination of research findings to participants. However, brain organoids differ structurally and functionally from normal adult human brains, raising relevant and specific considerations and ethical issues regarding the potential for consciousness in brain organoids. There are ethical concerns associated with the use of current brain organoid models which in the case of Australian regulation are limited to those related to the treatment of human biospecimens, as the National Statement addresses the ethical implications concerning the well-being of tissue donors but does not address the unique question of considering the well-being of the organoids themselves. Similarly, regulations in the United States pertaining to brain organoid research do not encompass the distinct ethical issues associated with the consciousness and well-being of brain organoids. The existing regulations and guidelines in both Australia and the United States primarily focus on matters such as the origin, procurement, and handling of human tissue, without imposing specific research constraints based on the moral status of brain organoids.[14]

The technique of producing organoids can lead to the creation of more complex organisms. Recently the team, led by Professor Magdalena Zernicka-Goetz from Cambridge, announced that they developed the embryo model without eggs or sperm, and instead used stem cells – the body's master cells, which can develop into almost any cell type in the body. Researchers have created the world's first synthetic human embryos, obtained from stem cells, without using oocytes and sperm. The cells aggregated spontaneously, forming

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13 Such as, respectively, by: the National Institute of Health (NIH) Guidelines for Human Stem Cell Research and the 'Common Rule', included in the Federal Policy for the Protection of Human Subjects; National Health and Medical Research Council's National Statement on Ethical Conduct in Human Research.

[14] Some scholars point out that: 'Organoids vary widely in their complexity, so it becomes important to consider if, and where, different organoids fall on this continuum of moral significance. For example, an organoid using a protocol, which generates a cerebral organoid with varying populations of cells from different brain regions,would likely be lower on the hierarchy than a region-specific organoid, which contains more mature organization. Moving up the pyramid, co-culturing region-specific organoids creates reciprocal connections that begin to form primitive circuits. Connectoids offer even further maturation of function. The addition of more region-specific organoids, non-neural cell types like endothelial cells or microglia, external perfusion systems, and bioengineering will allow organoids to grow in size, cell number, and synaptic density. This will continue to increase the complexity and thus the moral significance of such organoids': M Hoppe, A Habib, R Desai, L Edwards, C Kodavali, NS Sherry Psy, PO Zinn, 'Human brain organoid code of conduct' (2023) Front. Mol. Med. With regard to ethical implications in ANNs see F Shao, Z Shen, 'How can artificial neural networks approximate the brain?' (2023) Front. Psychol.; R Cummins, D Cummins, 'Minds, Brains, and Computers: An Historical Introduction to the Foundations of Cognitive Science' (2000) Oxford: Blackwell Publishers Ltd.

a structure very similar to a human embryo, but which is unable to complete development or be implanted in the uterus. If we were able to create embryos capable of completing development, we would have an entity that would be difficult to qualify as an asset since further development would be mainly the result of biological processes. Moreover, from the side of the ethical aspects, as a matter of fact, we would have a much higher level of moral significance than in the case of the reproduction of a single organ.

All these issues must be taken into account when considering the obstacles to a complete replacement of animal-based experimentations and the risk of an overexpectation on organoid exploitation for health or industrial purposes.

5. Conclusions.

Organoids are a key tool for knowledge enhancements, technological innovation and / or industrial applications in the pharmaceutical sector and in medicine, strengthening the international scientific community. They can be used for:

- Developmental Biology – Tissue Biology

  Matured organoids display functional organ sub-structures and have been used to investigate both adult tissue homeostasis and embryonic organ development. Investigation of adult tissue homeostasis using organoids has, for example, provided insight into the structure of intestinal crypts and the nature of the stem-cell niche, that ensures the renewal of the intestine epithelial layer. More recently, a detailed study explored differentiation mapping of the enteroendocrine regulators by using organoids in combination with in vivo models.

- Regenerative medicine

  Next to in vitro applications, organoids have been used in transplantation studies to assess regenerative potential. The interest for this is two-fold. Firstly, if transplantation into disease murine models leads to an increased survival rate, organoid functionality is confirmed. Secondly, successful transplantations could open up new avenues for using organoids in regenerative medicine applications as tissue-engineered grafts. In proof-of-concept studies organoids have been used as tissue grafts for both liver and intestine. Building on these insights, efforts were made to establish large-scale production methods of liver buds derived from human PSCs of up to 108 cells, and long-term culturing methods for liver organoids.

- Disease modelling - "Organ Pathology in a Dish"

  The therapeutic applications of organoids have been of interest to researchers for several reasons. In disease modelling, organoids generated from human cells can overcome several limitations of animal models. Next to the ethical considerations, some animal models cannot fully recapitulate the human condition, such as with lung tissue.

- Drug discovery and personalized medicine

  Organoids are attractive for drug discovery, since they can be produced on a relatively large scale for an array of subtypes capturing disease heterogeneity and stored long term, creating biobanks. Organoid biobanks provide opportunities to test drug safety and efficacy. Toxicology studies can be used to assess safety. For efficacy testing, several high-throughput methods have been developed that can generate results for drug response within a week.

  When using organoids for personalized medicine, patient-to-patient differences could be captured, but response indications should be producible with clinically relevant timescales.

Certainly, their qualification in terms of goods and intellectual property must not lose sight of the ethical implications most considered up to now. The solution consists in a revision of the theory of the circulation of goods in the light of the ethical implications concerning the goods in question which include personal data and origin from parts of the body and replicate part of the body. A different issue concerns the need to combine medical and pharmacological research with solidarity requests that enhance its social function. But this aspect concerns more general reflections that do not concern only organoids.