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HYBRIDA

D1.3: The challenging history of organoid research and its implications for ontology and ethics

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Embedding a comprehensive ethical dimension to organoid-based research and relating technologies

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ABSTRACT:	This document highlights some conceptual difficulties in the history of organoid research. We do not aim at writing a full history of organoid research, but at raising awareness of some conceptual difficulties when considering the dynamics of research. We sketch a standard narrative that presents organoids as a recent breakthrough in research. The conception of organoids as a recent breakthrough corresponds to a certain vision of history, and also a particular role for ethics. Beyond the standard narrative, different genealogies have been proposed for organoids. We suggest that these historical debates are dependent on current conceptual uncertainty in the scientific nomenclature and that these historical debates and nomenclatural uncertainty have implications for framing the ethical debate on organoid research.

Keyword List:	Organoids; gastruloids; assembloids; stem cells; modelling; bioethics.

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EXECUTIVE SUMMARY

This document highlights some conceptual difficulties in the history of organoid research, and shows how these difficulties impact ethics. It discusses also related ontological issues, that is, what organoids are and how we should understand them, with a focus on scientific nomenclature and its uncertainties (the issue of the categorization of biotechnologies as hybrid entities has been raised in D1.2). First, we sketch a standard narrative that can be found in many press accounts, reports, or summaries of organoid research. According to this narrative, the emergence of organoid technology is a recent breakthrough in research (occurring around 2010), leading to the development of new biotechnological entities of increasing complexity. Following this emergence, a subfield of research is progressively structured, focusing on the study of these new entities, and ethical questions arise that have to be addressed by specific moral scrutiny. We show as well that this standard narrative is contested and that it can have some drawbacks. Alternate narratives exist, and a closer look at the genealogy, for instance of stem cell research, suggests that organoids have a longer and richer history. These considerations have implications for ethics. We explore the connections between the historical discourse and the ethical discourse, as exceptionalism in history and in ethics are related: if entities such as organoids are radically new, then we may need to re-think the way we regulate biotechnologies in order to account for them—which might not be the case if we consider that organoids are just slightly more complex cell cultures that have been around for decades. In a second part of the document, we consider issues of definition and nomenclature. This is also related to history and ethics: if one wants to see what is new in organoids that would (i) justify the claim that the emergence of organoids is an historical event and (ii) deserves a tailored ethical treatment, one needs to make assumptions about what organoids are and what they are not. There are also many kinds of organoids and different uses for them. A glance at definitions of and nomenclatures for organoids, in the scientific and ethical literature, suggests that there are many uncertainties at this level, too. Organoid researchers themselves regularly discuss nomenclature issues, as the main terms are not always used in the same sense. Entities such as embryoid bodies and spheroids are definitely not organoids, but things are more complicated for assembloids, gastruloids, organs-on-chip, and so on. Should these entities be assimilated to organoids? Should they be encompassed in an organoid research ethics? These are conceptual issues that deserve further clarification (which will be the goal of D1.4, incorporating the ongoing work of WP2 and WP3). As a preliminary result, we suggest in the third part of the document that debates on definitions and genealogies of organoids might be connected to different visions of what organoids are and should be. For instance, organoids can be seen as models of development, built in the laboratory for the scientific study of natural embryo development and its pathologies. Or, organoids can be seen as the latest stage of long-running research on 'artificial organs' for organ transplant (more genealogies would have to be explored). If organoids are models, these models can be put to use in different ways—mimicking organogenesis, creating artificial organs, and so on. Yet these models are also connected to different conceptions of organoids, different understandings of what these entities are and what they should be in the future. These different visions need to be clarified, as they will likely have implications for framing the ethical debate on organoid research.

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Contents

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1 From the standard narrative to the novelty debate

The following analysis is based on a literature review of historical accounts of organoid research. As there are only very few articles or book chapters doing exactly this task (a history of organoid research),[1] we looked for various sources such as scientific reviews, editorial columns, or comments in major scientific journals presenting organoids as a breakthrough or a notable innovation, grey literature, textbooks, and ethics articles on organoid research.[2] All of these documents sometimes include, to varying degrees, considerations of the history of organoid research, for instance as a 'box' or as an introductory paragraph. Given the scope of the review and the varied nature of the references consulted, the current review has no pretension to exhaustiveness. It appeared during the review that the various sources were mostly consistent on the identification of the main seminal papers (or historical landmarks), which are mentioned below.

1.1 The standard narrative

There are common patterns in many presentations of organoid research and their recent development. In this section, we propose a sketch of what we will call the *standard narrative* of organoid history.[3] In our sense, a narrative is a story with recurrent elements that goes beyond the personal opinion of a particular author. If it is stipulated in a paper, often in passing, that 'organoid research began with X, then came Y,' then this sketch of a history can be identified as a narrative. When the same narrative is found in many papers, it can be identified as a 'standard narrative', or a kind of common knowledge in the field about what the history of organoids is. This does not necessarily mean that authors mentioning this narrative are explicitly defending a thesis on the history of organoid research, as their point is generally elsewhere: to discuss new findings in research, to discuss ethical issues, and so on.

The emergence of organoid technology is dated around 2010, with a few pioneering works between 2008 and 2013, then a constant improvement of the technology that leads to multiple applications in research an potential clinical applications on the one hand and the development of more and more complex biotechnological entities on the other. The standard narrative also often refers to the progressive institutionalization of the field within this timeline: organoid research seen as a specific subfield of research with its own conferences, journals, etc. The last remarkable point in this process of emergence of a new biotechnology is that ethical questions arise subsequent to this emergence and that

[1] Notably, there is no article that can be identified as doing the history of organoid research following the methods of history and philosophy of science (HPS) or science and technology studies (STS). All the accounts listed above, although sometimes very rich and instructive, are recollections of actors of the field (i.e., organoid researchers themselves).

[2] A first collection of articles was gathered by librarian Thibault Hamtiaux (HELESI/SESAME) by browsing several databases such as Scopus or Google Scholar. Supplementary references were added during the literature review by tracking relevant citations and all references were classified (with folders such as ethics/grey literature/textbooks/media…) in a database shared by all three authors of this document.

[3] The following section focuses on the history of organoids, relations to organ-on-chip and embryoid bodies are discussed later (see section 2).

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these questions have to be addressed by specific moral scrutiny. The general pattern would thus be the following:[4]

1/ emergence of a new biotechnology =>

2/ development and structuring of the field =>

3/ urge to deal with ethical issues and regulation

The emergence of organoid research

Many presentations presentations of organoid research point to the work done in the laboratory of Yoshiki Sasai, with a first publication in 2008[5] and others downstream.[6] This series of papers reporting the in vitro formation of "optic cups" (an early stage of eye development) from mouse and human ES cells is often considered as the first work in organoid research.

Another source is a series of papers from the laboratory of Hans Clevers from 2009 onward.[7] Intestinal stem cells are cultured until they form small physiological units which are labeled intestinal or gut organoids.[8] The 2009 article of Sato and colleagues is interesting as it explicitly makes extensive use of the term 'organoid' (which was not the case for the Eiraku and colleagues' papers).

The research on organoids is brought to the "next level"[9] by the laboratory of Jürgen Knoblich developing the first human brain organoid from pluripotent SC while engaging in the study of microcephaly with organoids as a model—thus pioneering both the biotechnology of organoid development and their use for purposes of medical research.[10] The first article was published in 2013 and accompanied by a substantial amount of publicity (implying, that is, a sense for a part of the scientific community that this development was indeed a breakthrough, something that was really new in terms of research).[11]

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[4] The present document does not take for granted, or endorse, any of the claims mentioned below, presenting instead the main narrative, without making any comment or decision on who or what is really "pioneering." The purpose of this document is to suggest a reflection on historiography, not to pronounce a historical judgment. Other detailed aspects of history and a scientific review of the field are conducted in WP2.

[5] Eiraku et al. Self-Organized Formation of Polarized Cortical Tissues from ESCs and Its Active Manipulation by Extrinsic Signals, *Cell Stem Cell*, 2008, 3(5): 519–32.

[6] Eiraku et al. Self-Organizing Optic-Cup Morphogenesis in Three-Dimensional Culture, *Nature*, 2011, 472(7341): 51–56. https://doi.org/10.1038/nature09941

[7] Sato et al., Single Lgr5 stem cells build crypt–villus structures in vitro without a mesenchymal niche, *Nature*, 2009, 459(7244): 262-65, https://doi.org/10.1038/nature07935

[8] Sato, T. et al. Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium. *Gastroenterology*, 2011, 141:1762–1772.

[9] Expression used by Oliver Brüstle, Miniature human brains, *Nature*, 2013, 501, to express the complexification of developmental models.

[10] Lancaster et al., Cerebral organoids model human brain development and microcephaly, *Nature*, 2013, 501:373–379, doi:10.1038/nature1251

[11] For a report: Gretchen Vogel, Lab dishes up mini-brains, *Science*, 2013, 341(6149):946-947. See also Oliver Brüstle, op.cit.

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According to the standard narrative, this seminal work—presented as the discovery or invention[12] of new biological entities—is naturally followed by the establishment of a line of research on organoids. We can imagine extending this line of research in two different ways. The first is an increase in the breadth of the research program, here most commonly an extension of the diversity of organs modeled by organoids. Once a methodology has been developed to form brain and gut organoids, it can be adapted to form liver organoids, kidney organoids, and so on. Innovation in breadth can also mean succeeding with different animals (from mouse to human, or chimeras) or from different cell sources (ESC, iPS, adult SC). A typical narrative insisting on breadth would be the following:[13]

> *Early work on embryonic stem cell-derived cortical tissue and on adult stem cell-derived intestinal tissue showed the fascinating capacity for stem cell-derived constructs to organize into complex in vivo–like structures. Now, about a decade later, scientists have reported organoids that model (albeit incompletely) brain, retina, intestine and other organs of the gastrointestinal tract, kidney and liver, among several other organs.*

The second main direction of research is what we might call increasing the depth of organoid research, here the improvement of the quality of the model for each of the above-mentioned organs: brain organoids are improved, gut organoids are improved, and so on. Improvement in depth can be measured through a gain in anatomical and physiological complexity, the longevity of culture, the stages of development reached in vitro (from blastoids to gastruloids…). For instance, a typical narrative along this line is found in a semi-public article entitled "The rise of the organoids" by Willyard:[14]

> *Biologists know that their mini-organs are still a crude mimic of their life-sized counterparts. But that gives them something to aim for, says Anthony Atala, director of the Wake Forest Institute for Regenerative Medicine in Winston-Salem, North Carolina. "The long-term goal is that you will be able to replicate more and more of the functionality of a human organ." Already, the field has brought together developmental biologists, stem-cell biologists and clinical scientists. Now the aim is to build more-elaborate organs — ones that are larger and that integrate more cell types.*

We could find many examples of this teleological view of organoid history: organoids tending to become more and more elaborate organs, and thus getting closer to natural organs. Presentations of assembloids (entities composed of different organoids) and related entities often merge the two trends mentioned above: if scientists are able to build more and more organoids that become more and more elaborate, the possibility of connecting these organoids conjures up the vision of a proto-organism.[15]

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[12] If one considers organoids as artefacts, they are invented; if one considers them as natural entities, they are discovered (this ontological point will be discussed in D1.4).

[13] Natalie de Souza, Organoids, *Nature Methods*, 2018, 15(1):23.

[14] Cassandra Willyard, The Boom in Mini Stomachs, Brains, Breasts, Kidneys and More, *Nature*, 2015, 523(7562): 520–22. https://doi.org/10.1038/523520a. This is a semi-public article: in a scientific journal, a paper by a science writer for a broader audience than specialists of the field.

[15] Jorge-Miguel Faustino Martins et al., Self-Organizing 3D Human Trunk Neuromuscular Organoids, *Cell Stem Cell*, 2020, 26(2):172-186.

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Markers of institutionalization

Once a biotechnological innovation perceived as extremely promising like organoids has emerged, the full development of research on and with such a technology requires the establishment of institutional places specifically dedicated to it. This is a clear sign of the fact that researchers think that they are doing new research with organoids.

This is a classic issue in the history of science. Any innovation has to pass through an institutionalization stage—in other words, it has to find a place in the institutional framework of the science of its time. When a new field of research is emerging, there are debates on how the field is connected to other, existing fields, which is part of the scientific discussion to assess the significance of the innovation. From the claim of a "scientific revolution" to the emergence of a "new discipline," many positions can be held.[16]

We are not going to discuss this issue further here,[17] but it is worth noticing a sociological aspect of organoid research as a new research field, as vindicated in many presentations: There is something such as an 'organoid research field' today, and there was none a decade earlier. What follows is a list of several markers which could indicate that organoid research is a new research field.[18] The existence of one of these indicators is not enough to say that there is a new research field emerging, but taken together these markers suggest that there likely is.

- The existence of a public discourse on the history of organoids: They have been discovered by founding fathers/mothers who can be identified (figures such as Sasai, Clevers, Knoblich, Lancaster[19]…), seminal publications are repeatedly cited in the literature as cornerstones of the field.
- The existence of dedicated textbooks[20] or chapters in textbooks[21] specifically focusing on organoids.
- Summer schools, training sessions, workshops, crash courses for biology researchers dedicated to organoid technology.
- The selection of organoid technology as "method of the year" in *Nature Method* 2017.[22]

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[16] See for instance I. Bernard Cohen, *Revolution in Science*, 1985, Harvard University Press.

[17] Some aspects of it will be studied in WP2.

[18] There is no consensus in the history and sociology of science on what it takes to constitute a field of research. Some of the markers listed below, such as the existence of textbooks or dedicated training, are already mentioned by Thomas Kuhn in the *The Structure of Scientific Revolutions* (1962, University of Chicago Press) to identify a "paradigm." A refined account of what constitutes a scientific field, and of the different kinds of fields that exist in scientific research has notably been produced by Richard Whitley in *The Intellectual and Social Organization of the Sciences* (1985/2000, Oxford University Press). It would be out of the scope of this document to engage in a discussion on what constitutes a field of research and whether organoid research can be counted as one or not.

[19] This list is only intended to stick to some prominent figures already mentioned above, many others could have been identified.

[20] Jamie Davies, Organoids and mini-organs: Introduction, history, and potential, in Jamie Davies and Melanie Lawrence ed., *Organoids and Mini-Organs*, 2018, Academic Press, pp. 3−23.

[21] Christine Mummery, Bernard Roelen, Anja van de Stolpe, and Hans Clevers. *Stem Cells. Scientific Facts and Fiction* (3rd ed.) 2021, Academic Press.

[22] Method of the Year 2017: Organoids, *Nature Methods*, 2018, 15(1). https://doi.org/10.1038/nmeth.4575

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- Not only topical collections or special issues of journals dedicated to SC research but a dedicated journal from 2021.[23]
- Initiatives such as the organization of an organoid contest based on the model of the famous synthetic biology contest.[24]
- The establishment of technological platforms dedicated to organoids.[25] These platforms not only centralize and rationalize organoid development, but they are also a sign that organoids are made available to non-specialists so that they can be put to use for medical research or clinical purposes.

Parallels with other fields of research and the specifics of various institutionalization processes could be discussed in more detail, but all these signs suggest that organoid research is on the way to becoming institutionalized (if it has not been already) as a field of research, as nanotechnology or synthetic biology have been in the recent past. This point is important, as institutionalization is an essential aspect of the standard narrative describing the emergence of organoids as new entities. This is also an important step in the recognition of ethical concerns.

Rise of ethical concerns

With the development of a new biotechnology comes questions about its immediate application and its prospective impacts in the long run. Presentations of organoid research so far have insisted on the study of development, on clinical applications for drug testing (see WP2), and have also often mentioned more long-term consequences, in the line of regenerative medicine.

Ethical issues are often raised among the implications and impacts of organoid technology development. Once the biotechnology is invented and in constant progress, there is the feeling that it is going to be applied in more and more domains and used widely. Then the need for an ethical assessment appears obvious, as we can foresee implications of this biotechnology. A theme emerges: there are (or will be) ethical issues with organoid research that deserve to be treated as specific issues, as questions raised by organoids cannot be considered as easy examples of broader ethical issues. The consideration that ethical issues are a growing concern is manifest through several media:

- The mentions of ethical issues in scientific articles or reviews, generally at the end of the paper. This goes also for science communication and public, journalistic reviews of the field.
- The number of editorial columns or commentaries in scientific journals (such as *Cell Stem Cell*) dedicated to ethical issues or organoid research.
- The development of a research literature in the field of bioethics, with articles on ethical aspects of organoid research published in classical venues for bioethics.
- The development of grey literature from bioethics committees and bodies in charge of the regulation of research, publishing on organoid research.

Ethics committees gaining interest in organoid research is generally seen as an important further implication of the development of this field of research. Among recent and remarkable initiatives, one can mention for instance:

[23] https://j-organoid.org
[24] http://inocontest.eu/
[25] One example, out of many, in France: https://www.orgapred.fr/

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- An "Organoids Research Group" at the French Inserm Ethics Committee (report issued in 2020);[26]
- A work package focused on organoids during the revision process of the guidelines from the International Society for Stem Cell Research (ISSCR, report issued in 2021);[27]
- A full report (issued 2021) of the US National Academies of Sciences, Engineering, and Medicine dedicated to ethical, legal, and regulatory issues raised by brain organoids.[28]

The HYBRIDA project itself, of course, is also aimed at providing an ethical framework for the development of organoid research and organoid-related technologies. In other words, the HYBRIDA project is itself a product of this ethical awareness raised after the emergence of the technology (but before the technology has become established, or routinized). This remark should be kept in mind when discussing the articulation of ethics with the public discourse on scientific and technological progress (see section 1.3 for a discussion).

1.2 Dissenting voices and the novelty debate

What we have called the standard narrative is a typical story of any biotech success: invention, diffusion, and questioning. In this sense, organoid research is presented as a breakthrough and we are invited to reflect on organoids as new entities. Because they are new entities, organoids offer new possibilities for research and medicine, and they also raise new ethical questions.

However, there are some dissenting voices to this standard narrative. All technologies have a history, i.e. they rely on previous discoveries and technologies (body of techniques and body of knowledge). One can insist on the continuity of the progress in biotechnological research leading to organoid research and on the dependence of organoid research on other fields of research. This perspective would offer a kind of alternative view on organoid history. Maybe, after all, organoids existed before the 2010s? In the next paragraph, we present what we label the "novelty debate:" did organoids already exist before the recent spread of the keyword? We will rely on two papers discussing the history of organoids.

In a review, Simian and Bissell explicitly defend the idea that organoids existed before 2010.[29] They argue that, from 1980, 'organoids' refer commonly to organ-like cell cultures that are grown from tissue fragments or embryonic cells. In fact, there have been 3D cell cultures for decades, and some of these cell cultures could be considered organoids in the current sense.

> *Before 2005, the word organoid was an extension of 3D cultures. Typically, it referred to small tissue fragments taken from organs, mostly epithelial tissues, separated from stroma by mechanical and enzymatic digestion and grown in different types of 3D gels to produce an organ-like structure…*

[26] Inserm Ethics Committee, *Organoids Research: What are the ethical issues?*, April 2020.
[27] ISSCR, *ISSCR Guidelines for Stem Cell Research and Clinical Translation*, May 2021.
[28] National Academies of Sciences, Engineering, and Medicine, *The Emerging Field of Human Neural Organoids, Transplants, and Chimeras: Science, Ethics, and Governance*, 2021, The National Academies Press.
[29] Marina Simian and Mina Bissell, Organoids: A Historical Perspective of Thinking in Three Dimensions, *The Journal of Cell Biology*, 2017, 216 (1): 31–40, https://doi.org/10.1083/jcb.201610056.

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Examples described by the authors include in vitro differentiation of cells, the orientation of cells in the milieu (proto-organization), and even secretion of milk from pseudo-mammary glands.

> *Rodent mammary fragments were grown in collagen gels to produce a branching structure resembling branching in the mammary gland of virgin mice.*

Simian and Bissell state interestingly that "*Whether we call these 3D cultures or organoids is like calling a rose by any other name. What we should keep in mind is that the essence is the same*." We could label this position the 'continuity thesis': organoids were already an object of research in the 1980s, and as such, they did not appear around 2010.

To take a deeper look at this position, consider another example offered by the history of organoids narrated by Davies in a dedicated textbook on methods.[30] Davies is also a proponent of the continuity thesis, stating that the boom of organoids in the 2010s was "*not because the technology was new*" but "*because it had suddenly become much more pervasive and visible thanks to some high-profile research papers*." While Wilson's experiments on sponges are mentioned as precursors, Davies's description of organoid research begin in the 1940s. For instance, an organoid is made from chicken cells in the 1950s[31]–yet this organoid was not obtained through differentiation and development of ESC but from disaggregation-reaggregation of embryonic cells. The emphasis is on the natural capacity of embryonic cells to self-organize, showing that cells contain sufficient information to organize themselves, even when spatial relations are lost. In the 1940s, experiments aggregating tissues from different species were also made to prove that cells with similar functions spontaneously group together, even across species boundary.

For Davies, this research in the mid-twentieth century is not only the *prehistory* of organoid research, as past research paving the way to real innovations to come, but is part of the history of organoid research. This remark may seem incidental, but it has important implications for how we consider contemporary organoid research.

Davies, while insisting on continuity, also acknowledges organoids' novelty. He says that "For decades, almost all work and commentary on organoids was done from the point of view of basic developmental biology,"[32] implying that the fact that contemporary organoid research leaves the field of developmental biology is in itself an innovation.[33] Another interesting expression is: "*simple* neuronal organoids were constructed in the 1980s and 1990s from foetal brain cells…"[34] The adjective "simple" is quite confusing here. The author wants to claim that there were organoids before the current boom, but are "simple organoids" organ-like enough to qualify as organoids? Some would point out that Davies might

[30] Davies, op.cit.

[31] Moscona & Moscona, The dissociation and aggregation of cells from organ rudiments of the early chick embryo, *Journal of Anatomy*, 1952, 86:287–301.

[32] Op. Cit., p.9.

[33] The nature of the model would have changed when entering putative clinical applications: an organoid as a model for understanding a developmental process is a different entity from an organoid as an–even still putative–full organ for clinical use in regenerative medicine. See section 3 for a discussion.

[34] Op. Cit., p.10.

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be referring here to "embryoid bodies," and not proper organoids. At some point, a "simple organoid" just does not look like its target organ. The problem is that similarity is always a matter of degree.

To sum up, we could contrast two approaches in the history of organoids. On the one side, the breakthrough thesis, stipulating that scientists have developed organoids in the time since the early 2010s, with a slow start between 2008 and 2013 and a subsequent boom in innovation. According to this perspective, previous cell cultures that can retrospectively be considered as precursors of organoid technology were far from the current achievements. On the other side, the continuity thesis states that, even if one should acknowledge that significant progress has been made in the last decade, *in vitro* organoids existed since the middle of the twentieth century, or even earlier. We propose to label the confrontation between these two theses the "novelty debate."

1.3 Implication for dealing with ethical issues

As noted above (end of section 1.1), the HYBRIDA project is itself a product of the awareness that organoids might raise new ethical issues, with the underlying assumptions that these issues deserve to be treated by a variety of stakeholders, including scientific, philosophical, and legal perspectives. This assumption would be perfectly in line with the breakthrough thesis: organoids are new entities, and as a consequence, we need to launch a discussion and develop new guidelines or adopt new rules governing this unprecedented research. Nonetheless, should the HYBRIDA project's members and documents adhere naively to the standard narrative? We think they should not. Proponents of one version or another of the continuity thesis would suggest that all the current excitement about organoid research is unjustified. In other words, this is part of a hype cycle that is poised to calm down if we take stock of the long course of research. This claim has an ethical counterpart: if organoids are not novel, then we have already been pursuing cell cultures for decades, hopefully with appropriate ethical rules, and there is no need to revisit the ethical questions that they raise. For instance, one can claim that there are existing rules for dealing with informed consent of cell line donors for storage in biobanks, and if organoids are not a radical innovation, we don't need to change these rules (or we might discuss the improvement of rules for various reasons, but independent of the actual progress of the subfield of organoid research).

Moreover, according to this perspective, ethics can be seen as part of the hype. The very fact that ethical issues related to organoids are presented as new issues, the very fact that large-scale inquiries into the governance of organoids are launched, would be factors contributing to the image of organoid research as radically new research. There is a co-construction of ethics and science in this regard. The HYBRIDA project should be aware of the following conundrum, which is an adapted version of the Collingridge dilemma:[35] either we do not pay attention to novelty in technology, in which case we could miss something and fail to regulate an innovation, and fail in our job as ethicists of technology to have an impact on the very development of these technologies; or we do too much, endorsing a futuristic discourse on medical progress, before promises have a chance to become reality, and by doing so we distort the image of science and technology (and maybe miss concrete, current ethical issues raised by laboratory research).

[35] David Collingridge, *The Social Control of Technology*, 1980.

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We formalize this conundrum as follows. There are several ways to articulate the technological novelty, or ontological novelty (the fact that new entities are coming into existence, or not), and ethical novelty (the urge for new norms, new rules). Depending on whether one embraces the technological novelty discourse or not and one's position on ethics, we can schematically describe 4 possible attitudes, or stances: [36]

new rules / novel entity	yes	no
yes	A	C
no	D	B

Stance A embraces both the novelty of the biotechnology and the need for a renewed ethics. It would correspond to the following claims: *There is something radically new in organoids; as a consequence, we need a specific regulatory framework* or *We urgently need to think about a code of conduct or regulation because there is something radically new happening in biotechnology*. This stance is likely the assumption motivating the revision of the ISSCR guidelines, the public report of the NAS, and the SwafS call for proposals which gave rise to the HYBRIDA project itself. Most ethical reflections on organoid research in line with the standard narrative can be seen as grounded in an assumption of this nature. For example, one can argue that if cerebral organoids can feel pain, then we obviously need a regulation to deal with these *in vitro* artificial sentient entities. It is worth noticing that one does not have to embrace fully the discourse on biotechnological novelty. That is, the ethical discourse following technological innovation is not necessarily biotechnology-enthusiastic or progressive. It can even propose to regulate, limit, or forbid some developments. However, the ethical discourse has still to buy at some point the discourse on technological novelty, as the existence of the ethical debate itself is justified by the recognition that there is something new at the ontological level.

Stance B rejects both the discourse on biotechnological novelty and the idea that a new ethics is required. It would correspond to the following claims: *There is nothing radically new with organoids; as a consequence, there is no need for supplementary regulation (or even ethical considerations)* or *We have done cell cultures for decades and there is nothing radically new with organoids, so we should stick to the existing rules.* This position endorses a kind of skepticism or conservatism, or at least a deflationary attitude regarding the novelty discourse. It can be interpreted as a reaction to A, against biotechnological or even ethical hype. As a reply to the previous example: Cerebral organoids cannot feel pain, there are just neural cell cultures, so all we need is informed consent from the cell donor, and, as we already have procedures for collecting consent, nothing ethically pressing appears. In a way, the position endorsed by the ISSCR during its revision of 2016 guidelines in 2021 might be closer to B than A. After investigating the case, the conclusion was indeed that the technology is not mature enough to justify a change in the ethical

[36] This preliminary work based on the literature review will be developed once results from other work packages become available (for instance, WP3's expert interviews and WP4's interaction with mini-publics). We might need to refine the nomenclature and discussion according to future findings.

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guidelines right now. From this perspective, one could interpret this position as a claim that organoid technology at this stage is not different from other kinds of cell cultures, classical studies conducted in the laboratory.

Stance C endorses the ontological novelty but rejects the need for a new ethics. It would correspond to the following claims: *There is something radically new in organoids, but existing tools of ethics and legislation are already equipped to deal with these new entities*. This position acknowledges that there are new features in organoid technology that were not present in basic cell culture until the recent developments in the field. But this is not to say that these new features are not compatible with the existing regulatory framework. For example, models of embryos made from stem cells in vitro are ontologically different from real embryos (they are entities of a different nature). Yet the rules that apply to embryos can apply a fortiori to these new entities: no implantation of (models of) human embryos made for research, in vitro culture is allowed only until a certain period or stage of development, etc. This would be a kind of adjustable ethics position, as we make a place for the novel biotechnology in the existing ethical framework. One might wonder whether this position is really coherent: maybe the simple consideration of possible adjustments to fit the novelty is enough to say that the framework has changed, or that ethical novelty has occurred.

Stance D rejects the discourse on biotechnological novelty but acknowledges that the ethical framework needs to evolve. It would correspond to the following claims: *There is nothing radically new with organoids, but we need an update in the regulation*. At first sight, it does not seem that this position makes sense at all. If nothing new is emerging, then we will find a way to deal with these entities, as we already have ethical directives for ongoing research. However, one could claim that even if organoids are not novel entities, their potential uses will make their commodification and commercialization different from what was done with cell lines, and we may need to regulate that. For example, when organoids are going to be used as tools for clinical tests and research, they might carry some sensitive personal information that will be revealed only through time—some disease that could not be revealed by genetic screening and that might appear when researchers develop an organoid from the cell line. In this light, anonymization will become an issue, and maybe there will be a need to adapt the regulation regarding cell lines. This position would be a cautionary position, anxious to avoid hype and premature discourses about biotechnological novelty, but at the same time attentive to ethical issues emerging in the course of research. If one compares all possible options, D may be a very interesting choice in the end, as it is both deflationary ontologically and cautionary ethically. This is a perfectly reasonable aim: we want to avoid hype but we do not want to miss any ethical issue emerging in the course of research. This being said, D might face serious conceptual issues, as we would have to justify where we put the bar for "biotechnological novelty." As a first objection, one could answer that if there is something to regulate, that means that the organoid has a property that the simple cell culture does not have, and that an entity with a new property is a new entity, and then we would be back to option A.

The simplified picture of 4 positions can of course be nuanced and discussed in more detail. Unfolding all these options can be useful as it goes beyond the classical conservative vs. progressive opposition (for or against technological innovation) that often frames the debate on novel biotechnologies. It matters also for the HYBRIDA project to integrate a kind of self-reflection and to be aware of its own role, as an ethics project, in the general public discussion on organoid research.

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2 What is an organoid? Issues of definition and nomenclature

The debate on the novelty of organoids is correlated to the underlying discussion on the very definition of an organoid. The position that one is likely to adopt regarding the "novelty debate" depends on the understanding of what an organoid is and on which entities should be considered as organoids. In a way, to solve the novelty debate, we would have to reach a consensus on the definition of an organoid.

Histories of biomedical research that defend the existence of organoids before 2010 argue (whether implicitly or explicitly) that the entities developed in laboratories in previous decades were similar to current organoids, or to what we call organoids today—no matter what we called them at the time. Inversely, one cannot argue for the existence of the mere term 'organoid' to identify the existence of organoids as biotechnological entities. For instance, Davies suggests that the term 'organoid' was used at the end of the nineteenth century as a synonym for 'organelle,' that is, any intracellular structure[37] (although 'organelle' seems more frequent and 'organoid' was of marginal use). More widely, in the second half of the twentieth century, the term 'organoid' was used to designate cancer cell aggregates. Depending on the context, 'organoid' could refer to any kind of unusual multicellular structure or malformation that manifests some similarity with an organ, such as teratomas or carcinomas that look like organs instead looking like an embryo (grounded on the intuitive meaning of –oid as resemblance).

We think of the utmost importance not to mistake the concept of organoid for its use as a keyword. A keyword does not make a concept (see D1.2 for a discussion on the role of language): a concept refers to a class of entities that can be circumscribed in nature. By contrast, a keyword is a term that circulates in certain linguistic communities. A keyword might be used by many, but may not correspond always to the same concept, that is, people using the word do not have necessarily the same object in mind. In our case, scientists might use the same keyword to refer to different things: they have a different concept in mind, although pronouncing the same word. Inversely, we might also use different terms to refer to the same concept. Claiming that organoids existed before 2010 is equivalent to say that, even if there was no keyword 'organoid' at the time, there were entities that had similar properties.

In this section, we review the specific vocabulary surrounding organoid research and examine several ambiguities in the nomenclature (organoids, assembloids, gastruloids...).

2.1 Organoids

There have been many attempts to define organoids. Here are some definitions of organoids collected in the literature:

[37] Such as the mitochondria, Golgi complex… This is an analogy: the organelle is to the cell what the organ is to the body. In other words, the organelle/organoid is an entity that looks like an organ, although we know that it is not an organ because it is located inside the cell. There is no possible confusion with the current meaning of 'organoid.'

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- "A collection of organ-specific cell types that develops from stem cells or organ progenitors and self-organizes through cell sorting and spatially restricted lineage commitment in a manner similar to *in vivo*" (Lancaster & Knoblich 2014)[38]
- "A structure in which pluripotent or progenitor stem cells are differentiated into multiple cell populations that self-organize/assemble into a tissue that resembles an organ *in vivo*." (Simunovic & Brivanlou 2017)[39]
- "We define an organoid as a unit of function of a given organ that is able to reproduce, in culture, a biological structure similar in architecture and function to its counterpart in vivo" (Simian & Bissell 2018)
- "A three-dimensional assembly that contains cells of more than one type, arranged with realistic histology, at least at the micro-scale" (Davies 2018)
- "An organoid is now defined as a 3D structure grown from stem cells and consisting of organ-specific cell types that self-organizes through cell sorting and spatially restricted lineage commitment" (Clevers 2016)[40]
- "Bioengineering of stem cell-derived, self-organizing, three-dimensional (3D) cell cultures"… "brain organoids are… 3D aggregates of neural tissue that resemble human brain regions" (Amin & Paşca 2018)[41]
- "Organoids are in vitro miniaturized and simplified model systems of organs" (Hofer & Lutolf 2021)
- "Stem cell-derived, self-organizing miniature organs" (Park, Georgescu, & Huh 2019)[42]
- "An organoid has been defined as a stem cell-derived complex 3D structure with the architecture and functionality of a normal organ. In other words, a mini organ made from stem or progenitor cells." (Mummery et al. 2021)

Although all of these definitions overlap up to a certain point, there are important nuances. If one wants to identify organoids as members of a natural kind, one should ask: what are the essential properties that an entity should have to be an organoid? From the previous list, we can extract some criteria that a cell culture should fulfill to be qualified as an organoid.

1. An organoid is a development of a 3D, tridimensional cell culture.
2. An organoid comes from stem cells that differentiate. It can come from embryonic stem cells, induced pluripotent stem cells, adult stem cells, progenitor cells.[43]
3. An organoid looks like an organ of the body or a tissue at a specific stage of development. That is, it shares at least some structural/spatial/architectural properties of the target organ (crypts for intestines, cups for retinas…).

[38] Madeline Lancaster and Jürgen Knoblich, Organogenesis in a Dish: Modeling Development and Disease Using Organoid Technologies, *Science*, 2014, 345(6194) 1247125. https://doi.org/10.1126/science.1247125.

[39] Mijo Simunovic and Ali Brivanlou, Embryoids, Organoids and Gastruloids: New Approaches to Understanding Embryogenesis, *Development*, 2017, 144 (6): 976–85. https://doi.org/10.1242/dev.143529.

[40] Hans Clevers, Modeling Development and Disease with Organoids, *Cell* 2016, 165(7): 1586–97. https://doi.org/10.1016/j.cell.2016.05.082.

[41] Neal Amin and Sergiu Paşca, Building Models of Brain Disorders with Three-Dimensional Organoids, *Neuron*, 2018, 100 (2): 389–405. https://doi.org/10.1016/j.neuron.2018.10.007.

[42] Sunghee Estelle Park, Andrei Georgescu, and Dongeun Huh, Organoids-on-a-Chip, *Science*, 2019, 364 (6444): 960–65. https://doi.org/10.1126/science.aaw7894.

[43] The question whether progenitor cells are stem cells or not is another issue, likely with a minimal impact on the current debate.

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4. An organoid shares some function(s) with the target organ.
5. An organoid has the capacity of self-organization, self-assembly.

A scientific discussion of the definition of an organoid, based on an extensive examination of all the cases described in the literature is beyond the scope of this document. We do not want to add another version to the already long list of existing definitions. Neither is our purpose here to be normative. Yet we can say that, from this short list, we can figure out at least the typical or focal concept of an organoid: a stem cell culture that self-organizes in a small biological entity resembling an organ both in its structure and function. This being said, it can be seen that some definitions are partially at odds with this concept and that some conceptual issues will emerge.[44]

2.2 Embryoid bodies and spheroids

Regardless of whether we consider the emergence of organoids historically or conceptually, it is interesting to understand what organoids *are not*. At this point, it seems rather clear that they are neither embryoid bodies nor spheroids—other 3D cell cultures derived from stem cells. Both terms have a long history.

'Embryoid bodies' was regularly used throughout the second half of the twentieth century in reference to a certain type of cancer. A teratoma is a cancer of pluripotent cells developing in several tissues, leading to tumors containing body parts or even entities that look like small fetuses—hence 'teratoma,' monster tumor: Researchers on teratomas observed what they called 'embryoid bodies' in tumors. These cancerous cells were isolated and developed in cultures and studied as a model of development before embryonic stem cells themselves were developed *in vitro* in the 1980s.[45]

The term 'spheroid' is also very intuitive as it refers to a spatial configuration. Any kind of 3D cell culture shaped like a sphere could qualify to be a spheroid—and spheroid can also be used as an adjective, which is even less ontologically laden than the noun.[46] Sometimes the terms 'embryoid bodies' and 'spheroids' are used interchangeably.

Even if there is some conceptual uncertainty surrounding both terms in science as well, there is clearly something lacking in the simpler definitions of embryoid bodies and spheroids when compared to organoids. Contrary to organoids, embryoid bodies and spheroids do not exhibit a specific structure, an organization, or any kind of anatomical structure that is 'organ-like.' There would be here a clear line between organoids, spatially organized like organs, and these other, more primitive entities composed of differentiated stem cells.[47]

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[44] See also future work in D1.4.

[45] Doetschman et al., The in vitro development of blastocystderived Embryonic stem cell lines: formation of visceral yolk sac, blood islands and myocardium, *Journal of Embryology and Experimental Morphology*, 1985, 87:27-45. See WP2, Richard Davies, Embryoid bodies.

[46] For instance, a review on embryos bodies suggests that first models of mouse embryogenesis from stem cells in vitro were termed 'embryoid bodies' "because of their ability to form spheroid aggregates mimicking postimplantation embryonic tissues" (Desbaillets et al., Embryoid bodies: an in vitro model of mouse embryogenesis, *Experimental Physiology*, 2000, 85(6)).

[47] The label of 'organ spheroid' can be more confusing in this regard (see for instance Pașca, The rise of three-dimensional human brain cultures, *Nature*, 2018, 553). Although, note a research paper from the same team referring to 'cortical spheroids' for 3D neural cultures on a focus on astrocytes: the goal of the study (development

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If these simpler terms might not be sources of conceptual uncertainty, the following ones may be.

2.3 Biotechnological entities that may be, or not, identified as organoids

Gastruloids. The term was forged when reporting a phenomenon typical of gastrulation[48] (symmetry breaking, germ layer specification…) observed in vitro from mouse embryonic stem cells.[49] Cells behave *"in a process that is reminiscent of some of the movements of gastrulation. For this reason, we call these aggregates 'gastruloids'."* Here we have a model of a developing embryo, developed for the study of embryogenesis. A gastruloid is a self-organizing entity derived from stem cells and presenting some anatomical and physiological patterns similar to the phenomenon of interest. In this regard, it could be categorized as an organoid—and it is in many documents and reviews.[50] Yet a gastruloid lacks an obvious feature of an organoid: it is not *organ-like*. If we redefine organoids as 3D models of development, it is tempting to include gastruloids in organoids, but obviously, there is no specific organ that is exhibited in a gastruloid. Furthermore, regarding conceptual uncertainty: gastrulation is a process, hence a gastruloid is a model of a process. Considering a gastruloid as an entity might even be problematic.[51] For obvious reasons, this remark might also apply to 'blastoids,' although we are also used to think of blastocysts as entities.

At a different scale, a comparable remark could hold regarding brain organoids. By default, from a naïve point of view, a brain organoid, or 'cerebroid,' as we read sometimes, would be a model of the whole developing brain. Yet neuroscientists like to say that the brain is itself composed of many different organs (i.e., brain regions), and organoids developed in laboratories are now modeling the development of many different parts of the brain. A whole-brain organoid and an organoid of a specific brain region are not likely to be on an equal footing ontologically (nor in terms of clinical applications, study of development, potential ethical issues…).

Organs-on-chip. An organ-on-chip (OOC) refers to a small microphysiological system that reproduces at least one function of a target organ. Defined as a "microfluidic cell culture device that contains perfused chambers in which living cells are arranged to simulate tissue-level and organ-level physiology,"[52] organs-on-chip are a product of a reverse engineering approach to biology. Once the functional units of the target organ are identified, its anatomy is reduced to it basic elements and an artificial structure is built, containing chambers in which stem cell cultures are introduced.[53] The artificial structure allow the reproduction and control of the chemical environment and mechanical constraints of the target organ.

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and maturation of astrocytes) is certainly not to make a mini-brain, see Sloan et al., Human Astrocyte Maturation Captured in 3D Cerebral Cortical Spheroids Derived from Pluripotent Stem Cells, *Neuron*, 2017, 95:779–790.

[48] Gastrulation is one of the first event of embryogenesis (the mass of embryo cells turns into an organized shape with first tissue specification).

[49] Suzanne van den Brink et al., Symmetry breaking, germ layer specification and axial organization in aggregates of mouse embryonic stem cells, *Development*, 2014, 141(22):4231-42.

[50] Reflections on Organoid Ethics: Jeremy Sugarman and Annelien Bredenoord, *Cell Stem Cell*, 2019, 24:849-51.

[51] See D1.2, distinction process/entity.

[52] Rossi et al., Progress and potential in organoid research, *Nature Reviews Genetics*, 2018, 19 671-687.

[53] Sunghee Estelle Park and al., Organoids-on-a-chip, op. cit.

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Depending on the context, 'organoid' is considered as a generic term encompassing all kinds of microphysiological systems, including OOC,[54] and in other contexts, a strict distinction is maintained between organoids and OOC. In the latter case, organoids self-assemble until they take the shape of an organ, while OOC are cellular cultures mounted on artificial devices.

Bioprinting. Another family of biotechnologies that would deserve consideration in this regard is that produced by bioprinting and the development of so-called 'artificial organs.' The reference to 'artificial organs,' usually researched with the goal of producing organs for transplantation, has a long genealogy that is out of the scope of this document. Yet we can see in what sense an organoid is not purely artificial but is also in a way, as a model of development, a natural organ. It seems rather easy to make a distinction between organoids and bioprinting, as no one seems to confuse one for the other. In bioprinting, tissues are assembled by mechanical constraints, whereas organoids self-organize by themselves. But some definitions can be confusing, for instance when assimilating organoids to "in vitro miniaturized and simplified model systems of organs."[55] Indeed, in the review mentioned here, the authors present OOC as the future of organoid research (see next section 3.3 of this document for a discussion). This remark suggests how important issues of definition and nomenclature can be when discussing the scope of a certain field of research.

Assembloids. Assembloids are an assembly of organoids: several functional organ-like structures are developed separately and linked together afterward. For instance, some parts of the brain are differentiated and grown separately and then connected to study neuronal connections and the development of brain circuitry.[56] While in the original paper the authors do not use the term 'assembloid' but 'assembly of spheroids,' this work is often referred to as a pioneering work in assembloids, a term now widely used in the ethics literature as well.[57] As is often the case for gastruloids and OOC, reviews of scientific literature and ethical reviews of organoids also include sometimes references to assembloids. Even when an assembloid is identified as a 3D stem cell culture differentiating by itself (in which connections between organoids are not forced and are left to biological development), they might still lack the organ-like character of an organoid. In some cases, the assembloid aims at modelling an organ (for instance, when different brain organoids are put together to form a model of a brain), but in most cases, they are composed of different organs that are not to be subsumed as a single organ at the end. From the biological point of view, any collection of separate organs, even interconnected, does not make *one organ*. This is precisely the distinction between organs and the organism, in which organs fulfill a specific function. A recent review of the nomenclature for gut organoids proposes the term 'multi-organ organoid' for entities exhibiting inter-organ organization and connectivity (what are designated in other

[54] See for instance Rossi et al., op. cit.

[55] Hofer and Lutolf, op. cit.

[56] Fikri Birey et al., Assembly of functionally integrated human forebrain spheroids, *Nature*, 2017, 545(54).

[57] Nita Farahany et al., The Ethics of Experimenting with Human Brain Tissue, *Nature*, 2018, 556(7702): 429-32, https://doi.org/10.1038/d41586-018-04813-x; Isaac Chen et al., Transplantation of Human Brain Organoids: Revisiting the Science and Ethics of Brain Chimeras, *Cell Stem Cell*, 2019, 25(4):462-72, https://doi.org/10.1016/j.stem.2019.09.002; Hyun, Insoo, J. C. Scharf-Deering, et Jeantine E. Lunshof, Ethical Issues Related to Brain Organoid Research, *Brain Research*, 2020, 1732, https://doi.org/10.1016/j.brainres.2020.146653.

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papers as assembloids).[58] The term has the advantage of highlighting the plurality of organs represented in the biological entity so obtained. However, one can wonder why an entity composed of several organ models would still be called an organoid, where the focus of the study will precisely be in the development of connections between organs, not on the development of one organ per se.

2.4 Discussion

What conclusions can be drawn from this? There are two "extreme" options regarding the nomenclature of organoids and organoid-related technologies, which constitute the ends of a spectrum: the restrictive view and the liberal view.

According to the restrictive view, organoids are strictly speaking *models of organs*. That is, we can identify an entity as an organoid only when we can identify a specific target organ behind it. Other entities mentioned above will thus be classified either as organoid-related technologies or as other entities. For instance, assembloids will be categorized as organoid-related technologies, as there are no assembloids without organoids, but assembloids do differ in nature from organ-like entities. Organ-on-chip would be another kind of entity, as it does not resemble, in the way that has been discussed above, any target organ. In that case, organoids and OOC could be both categorized as subspecies, at the same level, of a much broader category of microphysiological systems. An embryoid body (EB) is in a way an organoid-related technology, as it may be a component in the process of the making of an organoid (especially for brain organoids). In that case, an EB can be seen as an organoid-related technology: a building block for an organoid, or a primitive entity that will be developed into an organoid. But in other cases, we can consider EB as entities that are not related to organoids, when they are not included in a protocol designed for organoid development and are developed for other purposes. If there were EB before organoids existed, then there must be a way to understand and build EB independently of organoids.

According to the liberal view, on the other hand, the label 'organoid' encompasses all these kinds of hybrid entities, which are to be understood as subspecies of organoids. In this sense, OOC, spheroids, assembloids, would all be qualified as organoids. Organoid will be thus a broad label embracing different subspecies of laboratory entities. We could then introduce nuances to account for ontological differences between those subspecies. For instance, one could forge the idea that OOC are rather artificial organoids, spheroids are rather primitive organoids, assembloids are rather complex organoids, and so on. Organ-like organoids, i.e., models of a single organ with an architecture that resembles a real developing organ, would be typical organoids.

Now, should we embrace the liberal view or the restrictive one?

It seems that the liberal view is less accurate in terms of both the historical development of organoid technologies and the scientific rationale behind the use of all these different entities. Also, it might not do justice to the differences between the entities listed above. Furthermore, there might be something rather disturbing in insisting on the term 'organoid,' even in reference to entities that are not organ-like. Yet, the nomenclature mentioned above[59] (see the last paragraph of the previous section), as

[58] Marsee et al., Building consensus on definition and nomenclature of hepatic, pancreatic, and biliary organoids, *Cell Stem Cell*, 2021, 28.

[59] Marsee et al., op. cit.

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a work resulting from the consensus of 60 experts, suggests that there is a tendency in the scientific community to adhere to the liberal view, or at least that scientists are not afraid of making the term 'organoid' take on a much larger meaning than, strictly speaking, "organ-like entity." This point has to be explored further, as it might also be an artifact of the deliberation process: if we invite all identified stakeholders to sit around a table and say "let's discuss organoids," every participant will push to include his/her entity of interest in the discussion, and we would end up discussing many entities, with the impression that they all fall under the label of 'organoids.' There is also a simple phenomenon that we could label 'keyword hegemony:' once a keyword is successful and attracts interest from all parties concerned by research, many research lines have interest to re-qualify and embrace this keyword for reasons of visibility, publicity, funding… Again, a comparison with synthetic biology, nanotechnology, and so on, comes to mind. There would thus be a tendency to apply the term organoid to as many entities as possible, as the label of an organoid has already attained a dominant position in the public discourse, which would lead us to see different concepts merging under the same keyword for pragmatic reasons.

There is a reason specific to public debate why the liberal view might be worse than the restrictive one. To see it, consider the role and nature of concepts in science and public discussion (see D1.2). We cannot take for granted that concepts used in a public discussion conform to a specific definition (i.e., a set of properties necessary & sufficient to identify the entity as a member of a category). If we consider the context of a specific research article, we might find only one definition of organoids holds. The authors of the paper will, in at least some cases, give a specific definition of their entity of interest and stick to it. Often there is even no need for an explicit definition, as in experimental research the context of research and the experimental procedures are speaking for themselves—the name does not matter as long as readers understand what kind of entity is produced. Now in a public discussion, and sometimes even in a review paper, concepts are used in different ways. Concepts in these cases are better understood as types, or exemplars, that is, a particular image or a particular object in the world that I consider as the model for categorizing entities as belonging to this category or not. In this regard, it seems clear that, at least in the outreach and ethical literature, 'organoid' refers mainly to a 'mini-organ,' or an 'organ-in-a-dish.' That is to say that, when we use the term 'organoid,' we are very likely to raise this kind of image. The liberal view is more likely than the restrictive one to be a source of confusion in this respect. There is the risk of raising misguided intuitions, linked to a typical organoid when it comes to entities that do not have the same nature. For instance, we will think of mini-organs while discussing models of gastrulation, which are models of an organism, and not an organ; or we will be prone to think of self-organization and natural architecture (properties of organoids strictly speaking), which does not apply to bioengineered organ-on-chip entities.

Inversely, campaigning for the adoption of the restrictive view raises the risk of being at odds with common usage. We have to find a convenient way of communication that makes room for many laboratory practices and encompasses all kinds of ongoing research. If everyone agrees on the label of 'organoid' to refer to a vague set of entities that is not even fixed (as research is progressing), why would a strict nomenclature help? The main goal, and the main difficulty, is after all to identify what is at stake ethically, that is, what kinds of entities we want to take into account in our regulation proposal.[60]

[60] It will be important to analyze the results of the ongoing mapping of the literature in WP2 in this regard.

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3 From genealogy to vision

In this section, we justify the need for a discussion of conceptual uncertainty in nomenclature by arguing that there are different visions of organoids. Of course, organoids, as models, can be put to use in different ways. But there is also a deeper issue here: not only a matter of using organoids in different ways, but ways of conceiving organoids as different entities, different understandings of what they are and what they should be. Different visions lead to different practices and prospects—mimicking organogenesis, creating artificial organs, and so on.

Taking into account the uncertainty in the nomenclature that still exists today (section 2), we go back to the debate on the genealogy of organoids (section 1). We suggest that various genealogies proposed in existing historical accounts of organoid research each highlight a particular vision of what an organoid is or should be. The breakthrough thesis and the continuity thesis are themselves linked to different visions: a discourse of revolution on the one side, and a discourse in line with the long term of research on the other. Interestingly, as genealogy can point to different lines of research, they can suggest different understandings of organoids. But this is not only about the interpretation of the past: different genealogies imply different perspectives for the future.[61]

3.1 Organoids as models of development

Consider first the genealogy proposed by Davies,[62] insisting on the previous work on the self-organization of living entities. Organoids are interesting because they are entities that take shape naturally. By looking at the development of organoids, we could look at the emergence of forms in nature and study the ability of living entities (assemblies of cells) to self-organize. This is what Moscona did in the 1950s and this is still what organoid researchers (or a subpart of them, this is precisely our argument) do today. In this sense, organoids are best understood as models of development: a process that occurs naturally and that scientists successfully capture in vitro. Other accounts of organoid research adhere to this vision:[63]

> *"I didn't really know what they were…" Lancaster realized that the cells had assembled themselves into something unmistakably like an embryonic brain, and she went straight to her adviser, stem-cell biologist Jürgen Knoblich, with the news. "I've got something amazing," she told him. "You've got to see it…" Still, biologists have been amazed at how little encouragement cells need to self-assemble into elaborate structures. "It doesn't require any super-sophisticated bioengineering," says Knoblich. "We just let the cells do what they want to do, and they make a brain."*

In this account, organoids develop by themselves, in what seems to be complete autonomy from researchers. Researchers are presented as sole observers of nature, and nature unfolds (almost literally, as we are speaking of spatial organization) under their eyes.[64] Organoids are natural entities, and as models of development, we understand that they are above all objects of study. We want to observe them, to let them grow, in order to study development.

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[61] In the context of this report, we present only a brief sketch here.

[62] Davies, op. cit.

[63] Willyard, op. cit.

[64] See for instance Lorraine Daston and Peter Galison, *Objectivity*, 2007, Princeton University Press.

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3.2 Organoids as cellular therapies

Another genealogy is made by Hans Clevers.[65] In line with the definitions we saw in the last section, all observers would agree that organoid research is a subfield of stem cell research. Clevers further insists on the importance of cell culture, and claims that the main innovation that led to organoid research was the shift from the culture of tumorous cells to the culture of non-pathological stem cells. If we look at the prospects of the field of stem cell research since its emergence, maybe we see another image of the organoid: a tremendous progress in biomedical research looking for cellular therapies over a period of decades. The insistence is not on the natural development of a model of nature, but rather on sound tissues, normal cells, that could potentially be grafted at the end of the journey. Constructing 3D tissues from stem cells paves the way for skin grafts, for instance. Gene editing and other new technologies offer many new possibilities. By pointing to this line of research, organoid research is understood as clinical stem cell research and as a part of regenerative medicine or personalized medicine offering individual therapies.

3.3 Organoids as artificial organs

Another genealogy is proposed by Hofer and Lutolf, as they see organoids as the latest development of artificial organs, or hybrid organs, or bioartificial organs—which is also what their definition of an organoid suggests: "organoids are in vitro miniaturized and simplified model systems of organs." According to this view, living tissues are materials that can be engineered at will by chemical techniques or mechanical constraints.[66] Above all, organoids are a bioengineering success, not a miracle of nature unfolding by themselves, and maybe not even an immediate promise for therapy. They are a technological achievement. For supporters of this vision, organs-on-chip are the future of organoid research. What matters is not that the new entity respects a certain natural spatial organization, but that it reproduces efficiently a target function. In this regard, OOC may be more efficient than organ-like organoids.

There is also a clinical component in this discourse, as the long-term goal of developing artificial organs is to supplement the failure of natural organs in the human body. However, we might not refer to regenerative or personalized medicine but maybe to a transhumanist or cyborg vision, building artificial components as repair parts for the human body.

3.4 Consequences for the bioethics debate

This is a brief sketch and we do not want to claim either that the above-mentioned authors explicitly endorse one of these visions or that they reject other visions or prospects. Different visions can develop in parallel, and they can also converge at some point.[67] The only point that we want to make here, for the sake of the bioethics debate, is that a public discussion of organoids runs the risk of endorsing one vision or another while not being aware of it.

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[65] Clevers, op. cit.

[66] See also the reference to synthetic biology, but it may be another genealogy again.

[67] Some of the references used here make the claim for a convergence of the organoid research line and the OOC research line, see for instance Sunghee Estelle Park et al., op. cit.; Hofer and Lutolf, op. cit.; Takanori Takebe, Boyang Zhang, and Milica Radisic, Synergistic Engineering: Organoids Meet Organs-on-a-Chip, *Cell Stem Cell*, 2017, 21:297-300.

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At the most general level, ethical discussions are mostly discussions about visions,[68] before being a discussion of specific laboratory practices. In this regard, we think that it is important to make clear the visions that are in use. If visions are related to the definitions of organoids, their nomenclature, or the historical narrative that we share, it is important to make them explicit. If we do not, we might mistake one vision for another, or not be clear enough on the plurality of potential visions. In other words, even if it might seem obvious that studying small models of development in a petri dish is not equivalent to building repair parts for your body, we still have to find a framework for the public discussion that does not conjure up all these images at the same time.

4 Conclusion

Our main thesis is that the ethical debate faces different challenges due to conceptual uncertainty surrounding organoid research. To conclude, let us just sum up the three intermediate conclusions of the three sections by a series of questions.

1. A first challenge is to measure the significance of the novelty debate for ethics: Do we really have to claim that organoids are a new biotechnology? If we don't, isn't there the risk of missing something? How can we avoid contributing to the hype, even by the mere existence of an ethical debate on organoids?
2. A second challenge is to agree on common terms and definitions: What should be discussed in the ethical discussion? On what grounds do we include certain entities and exclude others? What terms do we use to refer to the entities of interest? How do we decide a nomenclature? Are efforts to defend a standardized nomenclature vain in the end?
3. A third challenge is to navigate from laboratory practice to visions: How can we delineate different visions of and prospects for organoid research? How can we avoid misplaced intuitions about what organoids are and what they are going to be? How do we go from these different visions and prospects back to laboratory practice?

[68] See also future work on vision assessment in WP2.

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