HTA of organoids HYBRIDA

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

Title: Health Technology Assessment of emerging and disruptive technologies: organoids

(Virtual) Hosting organization: Centre for medical ethics, University of Oslo, Norway.

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Planning: preferably starting December 2020; 4 d/w; completion by June 2021 (minimum of 4 months on a full-time basis) with the opportunity to continue to work on the project (payed).

Format: long distance, weekly discussions with BH and GJvdW, bi-weekly discussion with GJvdW + JHS+BH, monthly discussions with all; face-to-face meetings where and when possible, prevailing COVID-19 regulations permitting.

Remuneration: optional, depending on tasks, the institutes will contribute in-kind.

Language of reporting: English

Project background

Organoid research comes with ambitious promises of revolutionizing biomedical research in the future and with it our view of the human organism and life itself. As such a train leaves the station, it is vital that ethics not only follows, but is there on the train, shaping the journey as it is charted.

An organoid is an organized cluster of cells generated *in vitro* from different kinds of stem cells (either pluripotent or derived from some types of adult tissue) through the use of 3D tissue culturing methods.[1] By using organ-specific cell types, such entities might serve as "three-dimensional culture models"[2] mimicking the structural and functional properties of different organs,[3] both human and non-human such as the retina, heart, brain, intestine, kidney, pancreas, liver, inner ear and skin.

[1] Munsie,M.,Huyn. I., and Sugarman, J. (2017).Ethical issues in human organoid and gastruloid research. Development 144, 942-945 doi:10.1242/dev.140111.

[2] Barcellos-Hoff, M.H., J. Aggeler, T.G. Ram, and M.J. Bissell. (1989). Functional differentiation and alveolar morphogenesis of primary mammary cultures on reconstituted basement membrane. Development. 105:223–235, and Petersen, O.W., L. Rønnov-Jessen, A.R. Howlett, and M.J. Bissell. 1992. Interaction with basement membrane serves to rapidly distinguish growth and differentiation pattern of normal and malignant human breast epithelial cells. Proc. Natl. Acad. Sci. USA. 89:9064–9068. http ://dx .doi .org /10 .1073 /pnas .89 .19 .9064.

[3] Simian, M, and Bisell, M.J (2017). Organoids: A historical perspective of thinking in three Dimensions. J. Cell Biol. Vol. 216 No. 1 31–40. https://doi.org/10.1083/jcb.201610056.

Since Roman law, all entities have been categorized and regulated either as persons or as things (subjects or objects).[4] Organoids, however, are entities, and organoid research and organoid-related technologies are examples of disruptive research and innovation[5] that challenge this conceptual, epistemological and regulatory dualism. That is, the dualistic normative framework pertaining to health and life science research are disrupted by three different kinds of uncertainty.

The HYBRIDA project will address **how three kinds of uncertainty** (conceptual, epistemological, and regulatory) **arise in organoid research** and will **develop a conceptual and regulatory framework able to overcome this dualism** between persons and things. From this follows the need to **communicate the potential and possible pitfalls of organoid research** in ways that convey realistic- instead of hyped scenarios.

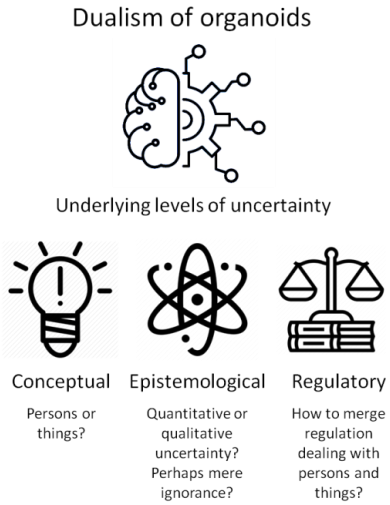

Figure 1: Levels of uncertainty stemming from the dual nature of organoids.

One crucial part of this project is to conduct a comprehensive mapping of organoid research and a HTA of organoids.

Background: the concept of organoids

Organoid research can be traced back to 1906 when Ross Harrison introduced the "hanging drop" tissue culture technique to recapitulate organogenesis in culture.[6]The use of the word "organoid" has changed over time; in the 1950's and 60's it was used to characterize research on intracellular structures and it was also used for tumors and abnormal cellular growths. From the 1980's, however, research papers started to use the term "organoid" as a synonym for 3D cultures.[7]In addition to the organ-specific kinds of organoids here mentioned, so-called gastruloids have also been created.[8]These are organoids generated from human pluripotent stem cells (hPSCs) with the potential to mimic aspects of early embryonic development to such an extent that they undergo processes resembling gastrulation, the event in development that naturally occurs by day 14. In vitro culture beyond this point is in most countries prohibited and this is what the "14-day rule" is intended for. It has been suggested that such entities be

[4] Solbakk, J.H. (2011). Persons versus things. *Nature*; 478: 40-41.
[5] Poole, E.S., Comber, R., and Hoonhout, J. (2015). Disruption as a research method for studying technology use in homes. Interacting with computers 27.1: 13-20.
[6] Harrison, R.G. (1906). Observations on the living developing nerve fiber. Exp. Biol. Med. 4:140–143. http ://dx .doi .org /10 .3181 /00379727 -4 -98; Simian, M, and Bisell, M.J (2017). Organoïds: A historical perspective of thinking in three Dimensions. J. Cell Biol. Vol. 216 No. 1 31–40. https://doi.org/10.1083/jcb.201610056, p. 33.
[7] Simian and Bisell, 2017, p. 32.
[8] Warmflash, A., Sorre, B., Etoc, F., et al. (2014). A method to recapitulate early embryonic spatial patterning in human Embryonic stem cells. Nat. Methods 11, 847-854; van den Brink SC, Alemany A, van Batenburg V, et al. (2020). Single-cell and spatial transcriptomics reveal somitogenesis in gastruloids. Nature. Feb 19. doi: 10.1038/s41586-020-2024-3.

referred to as "synthetic embryos"[9]thus distinguishing them from "non-synthetic embryos",[10] i.e. embryos formed from zygotes in culture or through sexual intercourse or assisted insemination.

While the creation of organ-specific organoids has not generated much debate, "synthetic embryos" and cerebral organoids (which are often inaccurately called "mini-brains"), as well as human organoids containing gonad-like structures with gametes, will become the subject of much more public and political debate. The first kind of entity will create attention because of its moral "family" resemblance with non-synthetic human embryos whilst human cerebral organoids might generate the same kind of reactions for two reasons. First, because of their potential to mimic, at least aspects of, human cognitive functions, and, second, in chimera research (as a subset of organoid research), because of the possibility of integration of human cerebral organoids into the central nervous system of animals raises the concern that by "biologically humanizing a research animal, scientists might inadvertently morally humanize the resulting chimera".[11] Likewise, the introduction of human gonad-like organoids into animal models - to create hybrids -might raise concerns about the possibility of inadvertent cross-species fertilization involving human and non-human gametes.[12]

As indicated above, organoid research makes use of two concepts or metaphors, hybrids and chimeras, that have been in use in different cultural and religious contexts for millennia, in Christian, Egyptian, Greek, Indian and Nordic mythology as well as in epic narratives.[13] Artistic representations of human-animal hybrids and chimeras have also been a recurrent theme in painting since the beginning of humanity.[14]The concept of hybridity derives from the Latin word *hybrid* and was first used to describe the offspring of a tame sow and wild boar, but Horace, the leading Roman lyric poet at the time of Augustus, also used the word to describe Roman soldiers of mixed descent.[15]By the late 18th century, hybridity had come to be used in a scientific context to describe the offspring of two animals or plants of any different species but hybrids were still widely considered to be violations of nature and most held the view that all species had been created by God and were immune to change. A biological definition of a hybrid is an animal that occurs by mating of two different species.[16]

Biologically speaking, organoids, with the possible exception of human-animal gonad-like hybrids, are not hybrids per se but it has been suggested that morally and legally speaking it makes sense to consider organoids as hybrids.[17] The reason for this is that organoids possess not only *instrumental* moral value as things, but also *relational* moral value as persons; first, because "they could relate to the bodily integrity of donors and recipients"; second, because "they relate to the personal identity and values of donors", and third, "because they relate to the privacy of donors".[18]

A chimera is an animal composed of cells with two different DNA sets (e.g liver parenchymal cells from a human source, vascularized by endothelial cells from a mouse after being transplanted under the

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[9] Denker HW. 2014. Stem cell terminology and 'synthetic' embryos: a new debate on totipotency, omnipotency, and pluripotency and how it relates to recent experimental data. *Cells Tissues Organs* 199: 221–227. doi:10.1159/000370063, PMID: 25547645; Shahbazi MN, Zernicka-Goetz M. (2018). Deconstructing and reconstructing the mouse and human early embryo.Nat Cell Biol. Aug; 20(8):878-887. doi: 10.1038/s41556-018-0144-x; Clark, A.T. (2019). Human embryo implantation modelled in microfluidic channels. Nature. Sep;573 (7774): 350-351. doi: 10.1038/d41586-019-02563-y. ; Zheng, Y., Xue, X., Shao, Y., et al. (2019). Controlled modelling of human epiblast and amnion development using stem cells. Nature.Sep;573(7774):421-425. doi: 10.1038/s41586-019-1535-2.

[10] Aach, J., Lunshof, J., Iyer, E, et al. (2017). Addressing the ethical issues raised by synthetic Human entities with embryo-like features. eLife 2017;6:e20674. DOI: 10.7554/eLife.20674.

[11] Munsie,M.,Huyn. I., and Sugarman, J. (2017).Ethical issues in human organoid and gastruloid research. Development 144, 942-945 doi:10.1242/dev.140111.

[12] Ibid, p. 944.

[13] Kuře, J. (2009). Etymological background and further clarifying remarks concerning chimeras and hybrids. In J. Taupitz and M. Weshka (Eds.). CHIMBRIDS – Chimeras and Hybrids in Comparative European and International Research. Scientific, Ethical, Philosophical and Legal Aspects. Springer Dordrecht Heidelberg London New York, pp. 7-20, p. 12.

[14] Chippindale, C. and Tacon, P.S.C. (1998), (Eds.), *The Archaeology of Rock-Art***,** CUP, 1998.

[15] Horace, *Satires* 1.7.

[16]Stross, B.(1999). The Hybrid Metaphor: From Biology to Culture. *The Journal of American Folklore* 112, (445), Theorizing the Hybrid: 254-267**.**

[17] Boers, S.N, van Delden J.J.M, and Bredenoord, A.L. (2019). Organoïds as hybrids: ethical implications for the exchange of human tissues. J Med Ethics 2019;45:131–139. doi:10.1136/medethics-2018-104846 131.

[18] Ibid, p. 133.

mouse kidney capsule (a frequent procedure), or a brain organoid made of neurons from humans and monkeys – for whatever research reason.

In Greek mythology Chimera was the name of one of the monster-offspring of Ehidna, depicted as half-woman and half-snake. Homer describes Chimera as "a thing of immortal make, not human, lion-fronted and snake behind, a goat in the middle".[19]But as monster Chimera was unique, "the ultimate monster of monsters",[20]not in terms of her fate, which was death at the hands of a hero as most monsters, but because she became ''the protoype of every possible composite, every hybrid''.[21]

However, the "mythic accretions gathered around the term chimera" and these narratives' "grip on the modern imagination" is prevalent not solely in non-scientific settings; they have also "made their way deep into biology".[22] In 1961, Tarkowski published a paper in Nature entitled, "Mouse chimaeras developed from fused eggs".[23] Thirty seven years later, he acknowledged the impact of these myths in chimera research by stating that mouse chimaeras were: ''in a way a bow and a tribute paid by experimental embryology to ancient mythology which created monsters of dual, triple or even multiple origin''.[24] The mixture of repulsion, fear and "fascination with the fantastic"[25] that certain parts of organoid research and the creation of artificial hybrids and chimeras, or chimbrids,[26] receive among the public outside science cannot be fully explained by just pointing to people's ignorance; these reactions are themselves - at least partly - nurtured by the same ancient myths, narratives and images that have impacted the conceptual and narrative landscape of organoid and chimera research.

During the last decade, **organoid, blastoid and gastruloid research and related technologies have become increasingly important** as a complementary approach to existing 2D-culture methods and animal model systems in the study of developmental biology, disease pathology, cell biology, drug toxicity, pharmacokinetics, pharmacodynamics and drug efficacy testing.[27] Although this research approach is still in its infancy, future biomedical visions promise that it **holds a tremendous potential** for regenerative and precision medicine and for understanding developmental defects during reproduction, while at the same time **raising a whole range of ethical, epistemological and regulatory challenges**. Some of these challenges can be addressed in isolation or in a piecemeal fashion such as rights and privacy issues of donors of material for organoid research, while other challenges cannot be dealt with in a socially robust way without taking into account three underlying uncertainties.

Overall project objective

The overall objective of HYBRIDA is to develop a comprehensive regulatory framework for organoid research and organoid-related technologies.

In order to obtain this objective, we will map organoids and adapt Health Technology Assessment for organoids. The objective of this part of the project (WP2) is:

Specific Objective 2:	**Reduce epistemological uncertainty in organoid research and produce improvements in impact assessment of organoïd-related technologies**
Main outcome:	An in-depth and comprehensive HTA of the issues that arise when organoids are translated from the research to the routine use context (clinical or industrial) (**WP2**)

[19] Homer, *Iliad* 6.179–182.
[20] Warner, M. (1994). Managing Monsters. London: Random House, p. 19.
[21] Bompiani, G. (1989) The chimera herself. Fragments for a History of the Human Body 1: 369–409.
[22] Hinterberger, A. (2017). Marked 'h' for human: Chimeric life and the politics of the human. BioSocieties Vol. 13, 2, 453–469; see also Kuře, 2009, p. 9.
[23] Tarkowski, A. (1961) Mouse chimaeras developed from fused eggs. Nature 190: 857–860.
[24] Tarkowski, A.K. (1998) Mouse chimaeras revisited: Recollections and reflections. International Journal of Developmental Biology 42: 903–908, p. 904.
[25] Warner, M. (2007). Monsters of Our Own Making: The Peculiar Pleasures of Fear, p. 243.
[26] Taupitz, J. and Weshka, M. (2009). CHIMBRIDS – Chimeras and Hybrids in Comparative European and International Research. Scientific, Ethical, Philosophical and Legal Aspects. Springer Dordrecht Heidelberg London New York.
[27] Lancaster &Knoblich, 2014; Huch& Koo, 2015; Kretzschmar&Clevers, 2016; van den Brink SC, Alemany A, van Batenburg V, et al., 2020.

WP2: Map organoids and adapt Health Technology Assessment for organoids

Mapping activities: The two kinds of mapping activities (mapping of the organoid field and mapping of current and planned development and translation from research to clinical or industrial use) will be based on literature searches of academic and grey literature, co-citation analysis, patent searches, and searches of trade publications and business databases. Based on the mapping, WP2 will then use the methodologies of Health Technology Assessment to analyse the interaction between the conceptual and practical uncertainties raised by different types of organoids and the ethical and regulatory issues that organoids raise when conceived as health technologies.

HTA activities: WP2 will perform a traditional HTA of organoids by applying existing evidence for efficacy, effectiveness, safety, and cost-effectiveness.[28]Based on the amended HTA methodology WP2 will then perform a complete health HTA to assess organoids as health technologies. Instead of statistical assessment of effectiveness and efficiency focus will be on relevance, plausibility, and amenability.[29]

The project will be able to hire and pay one or more candidates for conducting the work according to their contributions.

Specific project tasks

Tasks	Description	PM
T2.1	Mapping of the organoid field based on literature searches of academic and grey literature, co-citation analysis, patent searches, and searches of trade publications and business databases	3
T2.2	Mapping of current and planned development and translation from research to clinical or industrial use based on literature searches of academic and grey literature, co-citation analysis, patent searches, and searches of trade publications and business databases	3
T2.3	Analyse the interaction between the conceptual and practical uncertainties raised by different types of organoids and the ethical and regulatory issues that organoids raise when conceived as health technologies. Methodology: HTA	
T2.3a	a) Scoping review	3
T2.3b	b) Traditional HTA of organoids by applying existing evidence for efficacy, effectiveness, safety, and cost-effectiveness.[30]	6

[28] Lampe, K., Makela, M., Garrido, M.V., Anttila, H., Autti-Ramo, I., Hicks, N.J., et al. (2009). The HTA core model: a novel method for producing and reporting health technology assessments. *Int J Technol Assess Health Care*, 25 Suppl 2, 9-20

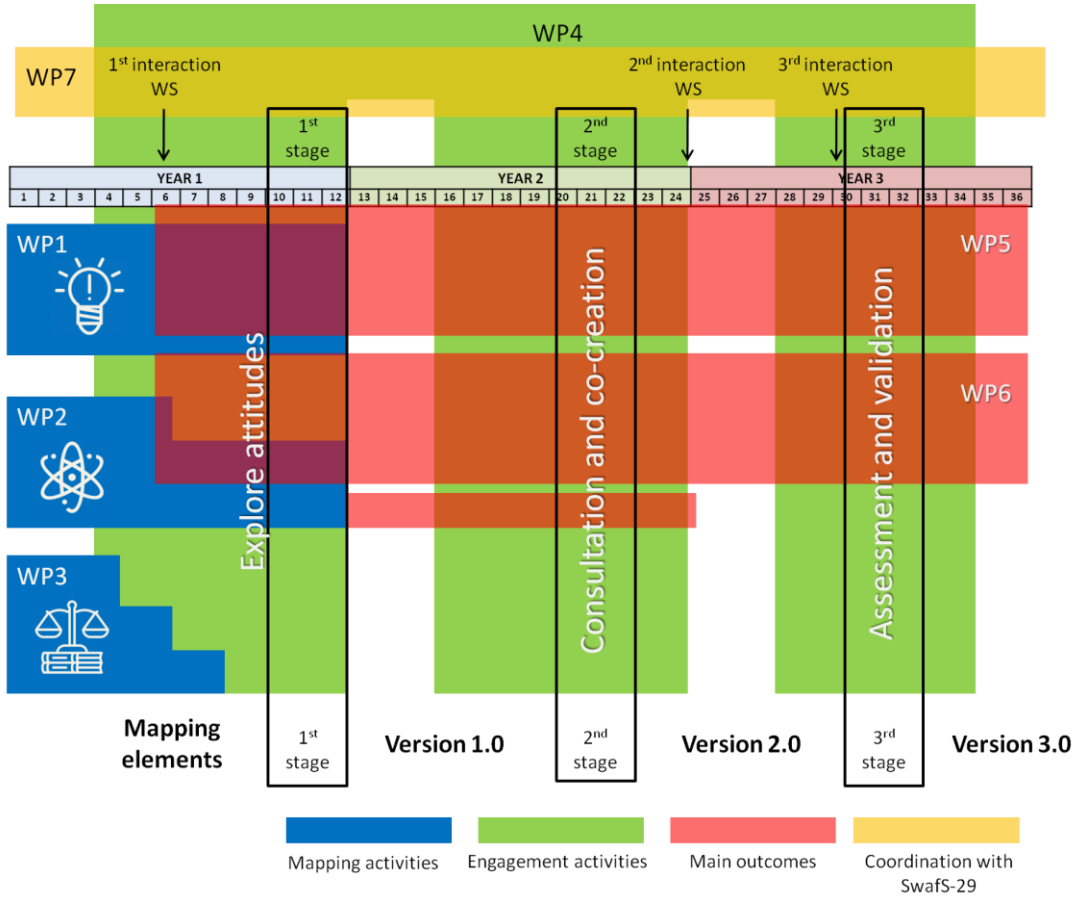
[29] Oortwijn, W., & van der Wilt, G.J. (2016). Challenges in contemporary health technology assessment: a view from the outside. *Int J Technol Assess Health Care*, 32, 1-2.

[30] Lampe, K., Makela, M., Garrido, M.V., Anttila, H., Autti-Ramo, I., Hicks, N.J., et al. (2009). The HTA core model: a novel method for producing and reporting health technology assessments. *Int J Technol Assess Health Care*, 25 Suppl 2, 9-20

T2.3c	c) Based on the amended HTA methodology WP2 will then perform a complete health HTA to assess organoids as health technologies. Instead of statistical assessment of effectiveness and efficiency focus will be on relevance, plausibility, and amenability.[31]	6
T2.4	Report	1

Time plan

HYBRIDA will start on February 1st, 2021 and end on Januray 31, 2024. WP2 will start on February 1st, 2021 and end on January 31, 2023.



[31] Oortwijn, W., & van der Wilt, G.J. (2016). Challenges in contemporary health technology assessment: a view from the outside. *Int J Technol Assess Health Care*, 32, 1-2.