

Making and managing new biological entities: conceptual, ontological, epistemological, and ethical aspects

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Abstract:

Novel biotechnologies produce new person-related biological entities, such as cell-lines, organoids, and synthetic organisms, that tend to disrupt existing concepts, taxonomies, modes of evidence production, as well as moral norms and values. This urges the question of how we can manage these new person-related biological entities? By identifying and analyzing key conceptual, ontological, epistemological, and ethical aspects of such entities, this article provides a set of suggestions of how to make, manage, and regulate of such entities. In particular: To avoid conceptual vagueness and taxonomic confusion, we need to clarify how person-related biological entities relate to existing concepts, such as person, identity, consciousness etc., and to make new concepts, where necessary. Ontologically, we need to determine the thing- and person-likeness of such entities. Epistemically, we must provide measures to verify the characteristics of person-related biological entities and to provide high-quality knowledge of their implications (outcomes). Ethically, we must clarify the moral status, rights, and responsibility for and of the entities, and how they will change our norms and values. Addressing these generic issues up front may improve our making and managing of person-related biological entities.

Key words: organoid, assistive reproduction, stem cell, embryo, ethics, epistemology, ontology

Introduction

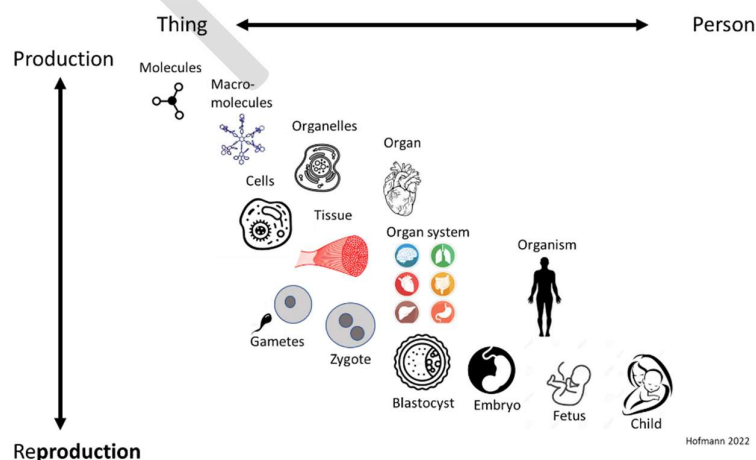
Many fields of medicine are preoccupied with producing or handling person-related biological material. Reproductive medicine has contributed in the making new human beings. Regenerative medicine produces new tissues and organs for replacement or enhancement (Knoepffler et al. 2016; Fangerau 2011). Transplantation medicine has mediated body parts from one person to others and biobanks have managed biological material of all kinds. Moreover, stem cell research has reprogrammed cells and produced cell lines and organoids. Synthetic biology is on the verge of producing new biological entities for the use for or in persons. Together with gene editing we expect to see a wide range of new biological entities in the near future.

The making and handling of person-related biological material has sparked a number of controversies, e.g., who owns an embryo that is frozen (Shapiro 1998) and when brain organoids become persons (Lawrence and Morley 2021). While the areas of reproductive, regenerative, and transplantation medicine, as well as stem cell research, gene editing, and synthetic biology have been separated, they all seem to be caught in the tension between things and person, and between production and reproduction. See Figure 1. Moreover, they are haunted by the same essential questions:

1. What is the moral status of person-related biological entities (e.g., with respect to ownership, rights, responsibilities)?
2. How do these entities relate to traditional categories, such as things, persons, actions?
3. How can we gain knowledge about biological entities (e.g., how can we know whether brain organoids are sentient or have consciousness)?
4. How should we conceptualize such person-related biological entities?

Hence, person-related biological entities raise basic conceptual, ontological, epistemological, and ethical questions. While each type of entities may raise specific issues, this article tries to explore common issues for the generic kind of person-related biological entities (PeBE). If successful, this will make it possible to address basic aspects of PeBE on a generic level and leave more specific issues to the specific fields. It will provide a useful division of labor, avoiding that each specific field that generates new biological entities needs to address generic issues from scratch.

Figure 1 PeBEs in the tension between things and person, production, and reproduction



Accordingly, the aim of this article *is to identify key conceptual, ontological, epistemological, and ethical aspects of the making of new person-related biological entities*. It will start by providing a short overview of various types of new PeBEs. Then the article will synthesize key conceptual, ontological, epistemological, and ethical aspects of new biological entities. Lastly, it will suggest some measures that we should take when handling and deliberating on person-related biological entities in the future.

Producing new types of person-related biological entities

New person-related biological entities are made in a wide range of fields, such as assistive reproductive technologies (ARTs), cell-line and organoid production, stem-cell research, gene editing, and synthetic biology. Below I will present some examples of the making of PeBEs.

A short note on clarification. The phrase producing or making biological entities refers to the process of producing, conceptualizing, theorizing, producing evidence, and developing moral norms for the new person-related biological entities described in the article, which can also be called “biological constructs”. The term “entity” simply refers to a unit.

Assistive reproductive technologies

The most obvious kind of new biological person-related entities are embryos, and fetuses, e.g., provided by assistive reproductive technologies (ARTs). In-vitro fertilization (IVF) was introduced widely during the 1990s followed by intracytoplasmic sperm injection (ICSI) combined with various types of gamete maturing (MESA/TESE/TESE/PESA)(Verza and Esteves 2019). Gamete selection was supplemented with gamete preparation (sperm washing). Gamete and embryo donation is followed by gamete modification (e.g., Mitochondrial Replacement). Another great step is gamete production (Cohen, Daley, and Adashi 2017), which is expected to help very many people who do not produce their own gametes, but which also is envisaged to be combined with gene editing (see below). Hence a wide range of ARTs produce new types of PeBEs.

Nurturing, gestating, and growth media

Many novel methods for handling gametes and embryos, such as freezing, including for non-medical purposes (e.g., “social freezing”), are applied in the production of PeBE with ARTs. Moreover, various types of culture media have contributed to the production of cells (cell lines) and organoids (i.e., artificially grown masses of cells or tissues that resemble an organ) while new ways to handle biological material have led to 3D printing of biological material.

Importantly, ectogenesis (the growth of an embryo in an artificial environment outside the body in which it would normally be found) is envisioned to contribute to the production of PeBEs in the future and potentially address some of the controversies of surrogacy. This will represent a radical step in the production of PeBEs.

Modifying and producing biological material

New ways to modify biological material have vastly altered the field of producing person-related biological entities. Induced pluripotent stem cells (iPSC) is among the most game-changing techniques for cell modification and “reprogramming” together with gene editing (e.g., by the much renowned CRISPR-cas9). Additionally, synthetic biology is expected to produce a wide range of new

PeBEs in the future. However, synthetic cells have stirred debates on «synthetic life,» «artificial life» (M. Bedau et al. 2010) and on safety (M.A. Bedau and Parke 2009).

Immortal *cell lines* are well-known ways of producing new PeBEs by making cells from a multicellular organism to evade normal cellular senescence (by mutation) and keep it undergoing division and grown for prolonged periods in vitro.

More recently 3D organ-like biological entities of many kinds are produced, i.e., *organoids*. By now there are many kinds of organoids, such as brain organoids; embryo models, such as gastruloids and blastoids; stem cell aggregates, such as organ-on-a-chip, tumoroids, and chimeras (M., Pence, and Botbol-Baum 2022).

Correspondingly, other envisioned PeBEs are *chimeras* and *hybrids*. *Chimeras* are in genetics defined as single biological entities with genetically distinct cells from two (or more) different zygotes, as well as *hybrids* which are defined as offspring resulting from crossbreeding in biology, falling under several categories or natural kinds.

Hence, PeBEs are produced in a wide range of fields. However, what they seem to have in common is that they raise a series of conceptual, ontological, epistemological, and ethical issues.

Conceptual issues

Technologies producing new biological entities challenge established concepts, like person, agency, offspring, and identity (Goekoop et al. 2020).

Human biological material is not merely a thing, as it may have belonged to a person and carries characteristics or information of that person (and related persons). Still, biological material is not a person either (Solbakk, Holm, and Hofmann 2009). This makes it difficult to conceptualize and to regulate biological material. Legal systems rooted in Roman Law have been developed to regulate things, persons, and actions (Blumenberg 1985). Many biological entities do not fully fit any of these categories but include aspects of all. While we have “intellectual property” as a category between things and persons, we yet do not have a corresponding “biological property” category (Blumenberg 1985). Therefore, it may be helpful to apply a new category for *person-related biological entities* that warrant special regulation inspired both by norms for things and persons.

Correspondingly, PeBEs raise conceptual controversies with respect to what we call “person” (e.g., with respect to chimeras) and “consciousness” (e.g., with brain organoids) or identity (Goekoop et al. 2020), offspring, and motherhood (B Hofmann 2022; Callaway 2016). The point here is not to review all the conceptual issues related to all kinds of new PeBEs, but to underscore that they raise such issues and that their person-relatedness forces us to take these aspects into account.

Hence, PeBes raise conceptual issues. As we have (had) a propensity to connect concepts to things, the conceptual aspects relate to ontological issues.

Ontological issues

The making of new biological entities can disrupt traditional ontological categories, such as organism, body, thing, and offspring. For example, the making of various biological material and entities have spurred the debates on species characteristics, e.g., what count as “human characteristics” (Mollaki 2021). As John Harris pointed out in his book on *How to be good: the possibility of moral enhancement*: “We have already considered humanimals; now we must consider brave new beings.” (Harris 2016)

Organoids, chimeras, and hybrids challenge us to characterize and classify such entities as things or beings. They do not fit into existing classification systems, like with platypus in the classification of animals (Karlsen 2011).

While we tend to use analogical reasoning to categorize estranged or new things, such as “bio-banks,” we seem to lack good analogies for PeBEs. Moreover, analogies have a conservative tendency not suited to capture completely different things (Bjørn Hofmann, Holm, and Solbakk 2006). Conceptualizing *person-related biological entities* can acknowledge the biological ontology of the entity, but also its relationship to persons (or personhood).

Ontological indeterminacy is connected to conceptual vagueness, normative (ethical and regulatory) unclarity, as well as epistemological uncertainty.

Epistemological issues

If we do not know what things are and how we can grasp them by concepts and classify them, it is difficult to provide knowledge about them. Firstly, it can be difficult to verify what they are, e.g., to verify the organ-likeness of specific organoids or to verify the sentience or consciousness of PeBEs. Second, it can be difficult to document the outcomes of the application of PeBEs: how do we know how they work. Even in straight-forward areas, such as procreational medicine, outcome documentation has turned out to be difficult (Kushnir et al. 2013). In organoid research, there are no clinically relevant outcomes reported from high-quality evidence after more than two decades of research (B. Hofmann et al. 2022).

Hence, the knowledge of existing productions of new biological entities is limited. Additionally, new biological entities may be few in numbers and frequentist approaches may not be applicable. Consequently, the making of novel biological entities may stimulate alternative modes of knowledge production, such as mechanistic (and other types of) narratives (Walker, Bourke, and Hutchison 2019). However, it may also lead us to more biased types of evidence production.

Hence, corresponding to the need to clarify the ontology of PeBEs and provide conceptual clarity, we need to have clear criteria for producing empirical evidence on how they can be identified and classified, how they behave, and their implications (e.g., in terms of clinical outcomes).

Ethical issues

Related to their conceptual, ontological, and epistemological aspects, PeBEs are ethically challenging, as they challenge our norms and values, obligations, conceptions of consequences, and our virtues.

As alluded to, source and ownership issues are key to a wide range of makings of biological entities, such as cell lines, organoids (Mollaki 2021) and gametes (Cohen, Daley, and Adashi 2017). The vast and vivid debates on the HeLa- cell line and the cell line after John Moore's spleen (Gilgenkrantz 2014; Littlefield and Pollock 2011; Wilson 2016; Landecker 1999) are but two historical examples. With organoids, patients in general seem to be positive, but they express ethical concerns for brain organoids (Sawai et al. 2022) and gonadal organoids (Bollinger et al. 2021). Embryo-like structures made from pluripotent stem cells for modeling natural embryos (embryoids) have stirred ethical debates on personhood, moral status, and ownership (Nicolas, Etoc, and Brivanlou 2021).

Autonomy and consent issues have widely been acknowledged but not solved for a wide range of new biological entities (Mollaki 2021). Parenthood issues have been raised in the case of mitochondrial treatment (Callaway 2016) and will increase its relevance with gene editing, hybrids, and chimeras.

PeBEs raise identity issues (Shoemaker 2008; Goekoop et al. 2020) as a person's cells are part of the person and make (up) the person, but are not the person. The same goes for tissues and organs, with a potential exception of the brain, which has stirred foundational controversies (Wiseman 2020). Accordingly, moral status of new biological entities is a crucial issue that has been discussed in the literature, e.g., with respect to whether entities are sentient or conscient (Capps 2017), e.g., in cerebral organoids (Cheshire Jr 2020; Lavazza 2021; Jeziorski et al. 2022). Related is the issue of whether PeBEs can become "other minds" (Sebo 2018) or "artificial moral agents" (Tigard 2021; Wallach, Allen, and Franklin 2011; Himma 2009).

The person- or thing-relatedness is crucial for the question of objectification and commercialization of PeBEs where some argue about organoids that "commercialisation of organoids is legitimised by a detachment of the instrumental and commercial value of organoids from their associations with persons and their bodies" (Boers, Van Delden, and Bredenoord 2019) while others would argue that it will introduce a new form of ownership over persons ("biological slavery") (Goekoop et al. 2020). Relatedly, PeBEs raise crucial questions about which rights we have to new biological entities, e.g., in terms of patents, licenses etc (McMahon 2021).

According to the "moral principle of complexity" for organoids (Barnhart and Dierickx 2022b), "the more ontologically and epistemologically complex the (current or potential) organoid-entity, the greater the moral consideration is needed regarding that entity." (Barnhart and Dierickx 2022b) This seems highly relevant for other PeBEs as well.

Corresponding to the issues of moral status and implications of PeBEs are ethical questions of responsibility of the making of new biological entities. Accordingly, it is crucial to assess the rights of novel (biological) beings. Can PeBEs hold rights and what criteria should be fulfilled for them to do so? What kind of right claims could PeBEs make (Jowitt 2021)? Relatedly, the necessary criteria that novel beings would need to fulfil in deciding to end their own lives have also been considered (Black 2021).

Additionally, there are many issues with respect to research ethics and research integrity identified in specific fields, such as organoid research (Barnhart and Dierickx 2022a), that are relevant for new bioethical entities in general.

Hence, PeBEs raise wide range of specific ethical issues. However, the point here is that PeBEs raise a set of basic ethical issues related to their moral agency and status, our responsibility for and rights to PeBEs that are generic and crucial to such entities. Taking these into account for existing and emerging PeBEs appears to be crucial for grasping and regulating such entities.

Crucial aspects for making and managing PeBEs

While the types of novel biological entities are diverse, there tend to be some general trends. Firstly, the biological entities are getting ever more complex and do not easily fit into existing conceptual (taxonomic), ontological, epistemological, and ethical frameworks, as already illustrated. Secondly, the disruptive potential and moral relevance of PeBEs tends to increase with their complexity (Barnhart and Dierickx 2022b). Thirdly, the traditional division between things and persons (in the life sciences) is blurred and the distinctions between reproduction and production is evading.

All these trends make biological entities difficult to grasp (conceptualize, in German: be-greifen) and to regulate. Nonetheless, the conceptual, ontological, epistemological, and ethical aspects seem to be common to PeBEs and make it relevant to apply PeBE as a concept. Table 1 tries to summarize the conceptual, ontological, and ethical aspects that are common to PeBEs.

Table 1 Conceptual, ontological, epistemological, and ethical aspects with PeBEs in general and what we can do to address them

Field	Issues	What we can do
Conceptual	Vagueness, unclarity: PeBEs do not fit traditional conceptual categories, such as things, persons, agents, offspring, identity, consciousness.	Clarify how the PeBE relates to existing concepts, such as person, thing, identity, consciousness etc. Make new concepts, if necessary.
Ontological	Indeterminacy with respect to what the PeBE is, e.g., as a thing or person	Try to determine the thing- and person-likeness of PeBEs.
Epistemological	Uncertainty: difficult to provide knowledge (verification of identity and implications / outcomes)	Provide measures to verify PeBEs and to provide knowledge of high quality of their implications (outcomes).
Ethical	Normative disruption: PeBEs challenge our norms and values, our obligations, conceptions of consequences and moral status, and our virtues	Clarify moral status, responsibility, and how PeBEs will change our norms and values.

These issues also indicate what we can do in order to manage PeBEs. Conceptually, we should clarify how the PeBE relates to existing concepts, such as person, thing, identity, consciousness etc. If they do not fit existing concepts (or combinations thereof), we may need to make new concepts. Moreover, we should reduce indeterminacy by providing clear definitions and robust taxonomies.

Ontologically it is crucial to determine the thing- and person-likeness of PeBEs. Epistemically, we should provide empirical knowledge of high quality (trustworthy, demonstrable, and independent of specific subjective beliefs or biases) in particular with respect to verification of their ontological status (e.g., are they “liver organoids”) and implications (outcomes).

Ethically, we should assess the value of making these person-related biological entities (intrinsically and/or extrinsically) and in particular clarify the moral status of, responsibility for, and the normative framing of PeBEs.

The point here is that addressing these issues upfront with new PeBEs can help us managing the making of new person-related biological entities. Additionally, each type of PeBE will have special issues that need to be addressed. But having a framework for addressing the general issues with PeBEs will make the task more structured and hopefully improve the deliberation on and regulation of PeBEs.

New names for new phenomena

I have suggested that person-related biological entities have conceptual, ontological, epistemological, and ethical aspects in common but have not given them a special name beyond PeBE. As pointed out by Blumenberg: «The earliest and not the least reliable form of familiarity with the world is to find names for what is undefined.» (Blumenberg 1985) PeBEs is obviously not a good name (as it is an acronym without meaning). Some suggestions are available from the literature.

“Subjects” has been suggested as a term for naming body parts, divorced from a human body and not yet implanted in another (Hoeyer 2013). With reference to the work of Lesley Sharp (Sharp 2006) and others Fredrik Svenaeus has proposed the concept of “subject” for blending “subject” and “object” (Svenaeus 2015). He argues that “the ontology of subjects is changing quickly and is dependent on medical technologies that may take turns we are presently not even aware of.” (Svenaeus 2015) Svenaeus argues that “subjects presently found in the world most often have a clear point of origin and belonging. They come from an individual person, living or dead, and thus have a form of home that they have been exiled from. Subjects are consequently body parts in exile that may find a new home – or be rejected and discarded – by being put into a new body, a body of another human being, who needs the body parts to heal and prosper in some way or other (Sharp 2006). These subjects include blood, bone, and skin cells, as well as a number of human organ and tissue types – kidney, heart, liver, lung, pancreas, uterus, hand, and face – that can presently be transplanted (Gunnarson and Svenaeus 2012).”

While subjects include many of the biological entities discussed in this article, they exclude those that do not have a “home that they have been exiled from.” We could therefore extend the definition of subject to include such entities, or we could add new concepts to biological entities that do not satisfy the criteria of origin. However, “subjects” has also been applied in arts to discuss the interrelationship between subject and object (Lloyd II 2013). This suggests that we might need a new concept: “person-related biological entity,” “personhood-related biological entity,” and “personal biological entity”, are but three suggestions. So far, I have found it fruitful to apply person-related biological entity, PeBE.

Other approaches of unifying agency and objects, such as actants in the philosophy of technology (Latour 1999) are certainly also relevant, but are beyond the scope of this article.

Discussion

In this article I have tried to show how new biotechnologies disrupt existing concepts, taxonomies, modes of evidence production, as well as moral norms and values. These challenges seem to be characteristic of a new type of person-related biological entities. Accordingly, addressing specific conceptual, ontological, epistemological, and ethical issues up front may improve our making and managing of such entities. In lack of a better name, I have called them person-related biological entities.

I have not provided a stringent definition of PeBE or detailed analyses of the various forms of PeBEs, but only illustrating examples. As the objective has been to provide a generic conception and an overarching framework, several specific issues still need clarification. First, I have not been specific about the person-relatedness. How much must a biological entity relate to one or more persons – and in what way? This clearly will vary – and so will the conceptual, ontological, epistemological, and ethical aspects. The person-relatedness of a blood sample in a biobank differs from that of a (genetically modified) embryo. However, the point here has been to provide a framework for what is common and not for the differences.

Second, I have not been specific on what is meant by biological. There are many definitions of what counts as biological, and with the development of synthetic biology this may come to change significantly in the future. Hence, here I have bluntly referred to general conceptions of biology as it is applied in the fields that I have discussed.

Third, I have not been specific about what is meant with entity either. There may be difficult questions about what counts as one entity, e.g., with respect to chimeras. This topic warrants a separate study, but an overarching conception of entity suffices for the present study. Here I have taken a pragmatic (exemplary) approach referring to entities discussed in the literature.

Moreover, the initial overview of various types of PeBEs is not exhaustive. For example, frozen biological entities, such as deceased persons («cryons») have not been included. Surely, cryons are PeBEs, and there are many more to come in the future. The purpose of the initial overview was to provide examples to illustrate the breadth of the field of person-related biological entities, and not to provide a complete list (which is impossible as the field moves forward so fast).

Certainly, many have suggested specific approaches for addressing various aspects of special types of biological entities. For example, Ankeny, Munsie, and Leach have proposed a reflexive, anticipatory, and deliberative (RAD) approach from iBlastoids (Ankeny, Munsie, and Leach 2022). Moreover, the destabilizing effect of biological (created) creatures has been discussed in the literature, e.g., by Donna Haraway (Haraway 2013). I fully acknowledge such approaches and several of them have inspired this analysis. However, the limited scope and space of this article has not allowed detailed discussion of the very many suggested frameworks and approaches.

Additionally, there are types of and modes of producing biological entities that have not been addressed in this article. Bioprinting is but one example of this. Hence, the article is not exhaustive with regards to the production of novel biological entities. I have selected those that seem to be most relevant in terms of conceptual, epistemological, ontological, and ethical aspects, and may rightly be criticized for my selection.

Moreover, there are many types of novel beings, for which this framework may be relevant, such as “synthetic organisms” and “uploaded minds” (Lawrence and Morley 2021). While the framework may be expanded to include such entities, this article has focused on biological entities. Hence, new forms of sentient, even sapient intelligent life, created by computer science and artificial intelligence have not been included and addressed.

Conclusion

This article illustrates how novel biotechnologies produce new person-related biological entities that disrupt existing concepts, taxonomies, modes of evidence production, as well as moral norms and values. Analyzing such entities indicates that they have common conceptual, ontological, epistemological, and ethical aspects. Addressing these generic aspects may help us in making, managing, and regulating of such entities. To avoid conceptual vagueness and taxonomic confusion, we need to clarify how PeBEs relate to existing concepts, such as person, thing, identity, consciousness etc., and to make new concepts, where necessary. Ontologically, we need to determine the thing- and person-likeness of PeBEs. Epistemically, we must provide measures to verify PeBEs’ characteristics and to provide high-quality knowledge of their implications (outcomes). Ethically, we must clarify the moral status and responsibility of PeBEs, and how they will change our norms and values. Addressing these generic issues up front may improve our making and managing of person-related biological entities.

Acknowledgement

A very early draft of this manuscript has been presented at the 16th World Congress of Bioethics in Basel in July 2022.

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