The closer the knit, the tighter the fit: conceptual and ethical issues of human embryo modelling

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VIEWPOINT

The closer the knit, the tighter the fit: conceptual and ethical issues of human embryo modelling

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INTRODUCTION

Recent publications reporting the generation of human blastocyst-like structures (also known as 'blastoids'; *Liu et al., 2021*; *Yu et al., 2021*) mark an important further step in the modelling of human embryogenesis. This emerging field of research uses advanced (stem) cell technologies and culture systems to enable new insights into early human development and reproductive health. Moreover, it promises to do so in a way that overcomes current limitations on human embryo research. Unlike human embryos, stem cell-based 'embryo-like structures' (ELS) – such as 'blastoids' or 'gastruloids' – can be created and modified *ad libitum*, enabling studies that require large numbers of genetically identical entities, while bypassing the need for oocyte donation. What is more, ELS-research provides a bottom-up approach to human embryology, which is not possible with fertilization-derived ('natural') embryos. In addition to overcoming shortages of research material and expanding scientific possibilities, the main benefit of ELS research presumably lies in its potential to circumvent the ethical sensitivities and legal restrictions associated with human embryo research.

ELS RESEARCH AS A 'WIN–WIN' POLICY

The destructive use of human embryos, even for important purposes, remains highly controversial due to conflicting views on the moral status of early human life. In jurisdictions where human embryo research is allowed, it is only permitted within 14 days post-fertilization (the so-called '14-day rule') and often only if conducted with surplus embryos. However, insofar as ELS are just models, these restrictions simply do not apply. It is therefore not surprising that furthering ELS research is widely regarded as a 'win–win' policy, promising scientific progress and its ensuing societal benefits, while avoiding the restrictions and burdens of human embryo research. The Dutch government, for instance, has launched a €14 million programme for research consortia on the advancement of human ELS explicitly with an eye to making human embryo research as redundant as possible.

This is of course assuming that ELS are and will remain just that: embryo models, rather than embryos. Where concerning 'non-integrated' ELS, such as present-day human gastruloids for instance, this is not really an issue. Although clearly promising tools for both fundamental and applied research (e.g. toxicity testing), they lack relevant cell types and have a limited developmental potential (*Moris et al., 2020*). Indeed, for answering many specific research questions, ELS need not be 'perfect replicas' of human embryos in every respect. But with the human blastoids that were recently created, ELS-research has taken an important step forward in precisely that direction (*Zheng and Fu, 2021*). Despite their remaining limitations, these 'integrated' blastocyst-like models represent all the cell types needed for the development of both the fetus and supporting tissues. Still, the hurdles on the road to creating high-fidelity human ELS remain considerable. As stressed in a recent review, important challenges include benchmarking these models against 'natural' embryos, on which (comparative) studies are lacking (*Posfai et al., 2021*). The development of ELS that are functionally capable of replacing 'natural' embryos will therefore itself require parallel human embryo research (also beyond 14 days), which should serve as a sobering note for those counting on immediate benefits of the aspired 'win–win' policy.

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Once these hurdles are overcome, it may become increasingly difficult to distinguish between the functional properties of ELS and those of 'natural' embryos. While this would support claims of sufficient similarity to replace embryos in research, it would also raise the question of how to ethically and legally distinguish between ELS that are (still) just models and ELS that should be regarded as (stem cell-derived) embryos. The paradox that emerges here is that the better these models become, the less useful they may be precisely as (embryo-replacing/saving) models (*Pereira Daoud et al., 2020*). There is a tipping point beyond which greater similarity collapses into identity, and ELS research into human embryo research. Where precisely this tipping point lies is not a question that can be easily resolved. Whereas with animal ELS the ultimate test would be the birth of healthy and fertile offspring (*Posfai et al., 2021*), this route is for obvious ethical reasons inaccessible where human ELS are concerned.

In order to maintain the benefits of embryo modelling over embryo research, it may thus be prudent to err on the side of safety and steer clear of attempts to create the 'perfect replica' – not because crossing into territory where ELS might be more than just models would be ethically problematic in itself, as some authors seem to suggest (*Moris et al., 2021*), but rather because so doing would ultimately bring back the ethical and legal restrictions ELS research meant to circumvent, thereby also revoking debates about whether and how these restrictions should be revised. Of course, acknowledging that there is a limit to the envisaged 'win–win' policy does not detract from the value of developing ELS as a context for bottom-up and decoupled approaches to exploring principles of development.

CONCEPTUAL ISSUES: THE POLITICAL USE OF EMBRYO DEFINITIONS

The fact that we lack a universal definition of what, for ethical and legal purposes, should count as a human embryo complicates matters even further. For researchers, it means that research with (particular 'types' of) human ELS – especially if improved – may be severely limited in some jurisdictions, while not requiring the same (or any) level of regulation in others (*Matthews and Morali, 2020*). For politicians, some definitions open up the possibility to have it both ways: benefiting from research with ELS (however perfected), while taking the moral high ground with regard to embryos.

The historical precedent for this is how countries that (like Spain) continue to define the embryo as the fusion of a human oocyte by a human sperm could proceed to ratify the Oviedo Convention – with its ban on creating research embryos – while still allowing somatic cell nuclear transfer. The price, of course, was to deny that Dolly the cloned sheep originated from an embryo. Should it become possible to create offspring from perfected animal ELS, countries with fertilization-based qualifications may follow this precedent and maintain that, by definition, human ELS are not embryos, however perfected they may become.

Similar strategies are possible in jurisdictions that define the embryo exclusively in terms of its developmental potential (e.g. Belgium and the Netherlands). On this score, human embryos that – for whatever reason – are incapable of growing into a child are not embryos for legal purposes. Whereas in earlier debates commentators have called it a problem that this denies the very existence of non-viable human embryos, the Dutch government now seems to see this as an opportunity. Case in point being the aforementioned funding for ELS research, of which a quarter is destined for a consortium developing so-called 'non-viable IVG-embryos', i.e. embryos created through the fertilization of stem cell-derived gametes (in-vitro gametogenesis, or IVG) that have been pre-emptively genetically modified to ensure non-viability. The funding call refers to these as further 'embryo models' with the specific advantage of allowing research on fertilization and post-fertilization processes, stages too early to model with present-day ELS. The political motive is obvious: developing 'non-viable IVG-embryos' would allow the Netherlands to invest in research on early human development without having to lift its ban on research embryos, an issue that still strongly divides Dutch politics and society. Similarly, if scientists were to programme 'suicide genes' in ELS, these models would also fall outside the Dutch embryo definition, regardless of how perfected they are. Politically loaded definitions such as these are problematic insofar as they are used to avoid, rather than address, the ethical and legal questions raised by new developments in ELS research.

ETHICAL ISSUES: POTENTIALITY AND BEYOND

The human blastoids developed by Yu's and Liu's groups (*Liu et al., 2021*; *Yu et al., 2021*) underscore the urgency of reconsidering the moral bearing of the so-called 'potentiality argument'. Some scholars argue that the cellular convertibility demonstrated in ELS comes to show that the whole idea of an 'intrinsic' and 'active' potential is simply unfeasible (*Stier and Schoene-Seifert, 2013*). For these scholars, ELS research is evidence that developmental potential is entirely a matter of contingent factors that can be arbitrarily switched on or off. If proven correct, a cornerstone argument that has generally been taken to grant early human embryos special moral treatment is no longer available: the idea of the human embryo as autonomously capable of growing into a human being under the proper circumstances. From an ethical perspective, this would mean more room for human embryo research, including research beyond the 14 days that legislation currently allows.

But the case against potentiality remains an issue for further analysis and debate (*Hyun, 2013*), with some authors conversely arguing that ELS research may precisely demonstrate a stem cell capacity to initiate autonomous development under the right conditions (*Denker, 2021*). Supposing, for the sake of argument, that the potentiality argument withstands, two side-notes are still worth making. One, it is a misunderstanding that 'active' potentiality would entail 'full moral status'. In fact, the argument is perfectly compatible with the view that human embryos have only limited moral status and can, therefore, be used for research purposes under conditions of proportionality and subsidiarity. Two, many advocates of the argument have argued that 'active' potentiality presupposes numerical identity between the different stages of the developing organism (*Buckle, 1990*). This would entail that 'active' potentiality can only gain moral traction if natural twinning is

no longer possible, meaning that only post-implantation stage embryos or ELS would qualify for protection on this basis, and blastocysts or blastoids would not (Pereira *Daoud et al., 2020*).

Other ethical issues can be expected to emerge precisely with regard to ELS that are clearly not embryos and that, for that reason, would not be bound to the restrictions imposed on human embryo research (such as the 14-day limit). If these ELS are used to model human organogenesis, beating hearts or early brains may be regarded by society as especially sensitive, leading to discussions similar to those raised by brain organoids. Of note, brain cells are not replicated in present human gastruloids, but this may change with their further improvement. Even so, apart from the hypothetical concern that entities with (very) rudimentary brains could become sentient and feel pain, it is unclear why such issues should be regarded as categorical cut-off points for research. Whereas, in developing embryos, beating hearts and early brains might be regarded as markers of what the embryo is growing into, and thus merit some degree of *symbolic* value, no such argument is available where ELS are concerned that are clearly models, and not embryos (Pereira *Daoud et al., 2020*).

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