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Human Embryo Models Made From Pluripotent Stem Cells are Not Synthetic. They Aren't Embryos, Either

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Abstract

Embryo models are potentially highly impactful for human health research because their development recapitulates otherwise inaccessible events in a poorly understood area of biology, the first few weeks of human life. Casual reference to these models as "synthetic embryos" is misleading and should be approached with care and deliberation.

INTRODUCTION

Human stem cell-based embryo models (embryo models) are three dimensional (3D) organized assemblies derived from diploid cells that recapitulate certain aspects of structured embryo development occurring in the pre implantation and early post implantation stages of human life. These novel cellular assemblies have captured the imagination of researchers as an appealingly tractable and controlled approach to understand infertility and early pregnancy loss, the earliest events in human embryo development, or the differentiation of cells in vitro. Traditionally, researchers studying the first few weeks of human development have had to rely on disorganized stem cell differentiation in 2D or 3D, or extrapolations from animal (mammalian) models, all the while knowing that enormous evolutionary differences have arisen in the tissue, cell and molecular strategies associated with the biology of early embryo development across species. The research community has long recognized a pressing need to develop scientific models that more accurately reflect the beginnings of human life itself, in order to develop technologies and therapies for human health and wellbeing.

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DECLARATIONS OF INTEREST

Amander T Clark is an elected officer of the International Society for Stem Cell Research.

Embryo models are made from human biological materials and they are explicitly intended to serve as models of early human life. They are surrogates [1], whose use depends exactly on their status as *not* human embryos. They must be similar enough to human embryos to stand in for them in the study of otherwise inaccessible developmental stages relevant to pressing questions of infertility, reproductive health and stem cell biology; and yet unlike enough that they are decidedly not the same as human embryos that develop in the reproductive tract. Unfortunately, early media coverage and some scientific discussion of these embryo models has landed on the descriptor 'synthetic embryo,' a term that we believe is inaccurate, disrespectful, and potentially harmful when the intent is to generate surrogate models of human life without any intent for reproductive use. Here we argue that the naming of such entities at the dawn of their more widespread use is critical for responsible and accurate science communication, as well as for establishing rational regulatory frameworks that can enable the science to move forward with public trust.

HUMAN EMBRYO MODELS ARE NOT SYNTHETIC

Embryo models are made from human pluripotent stem cells. This could involve starting with human embryonic stem cells (hESCs) derived from pre-implantation embryos, or human induced pluripotent stem cells (hiPSCs) derived from a sample of human tissue that has been reprogrammed or partially reprogrammed to a pluripotent state. Using these starting materials, embryo models can be generated in a variety of ways. Some involve differentiating the human pluripotent stem cells on engineered devices, or specialized tissue culture plates. In other examples, embryo models are generated by differentiating human pluripotent stem cells or partially reprogrammed cells into trophoblast and primitive endoderm cells before combining these cell types together with pluripotent stem cells to promote cellular interactions and organized differentiation. Once made in the lab, embryo models are classified in two ways; non-integrated and integrated [2].

The term "synthetic embryo" emerged with increasing frequency after a 2016 meeting in Paris called 'Engineering the embryo' [3]. While 'synthetic' has a range of connotations, many of them positive, the public is likely to understand it in terms of synthetic chemistry and products such as plastics, 'forever' chemicals, and fake imitations of natural products, such as synthetic leather. Moreover, 'engineering embryos' further amplifies an image of scientists-as-creators, linked to the temporally concurrent, but rather unconnected biotechnological field of endeavor called synthetic biology. Synthetic biology includes major initiatives aimed at re-designing and constructing new cells and organisms for useful purposes, usually through modifying and rearranging DNA [4]. Major synthetic biology projects include the generation of new forms of bacteria, or Saccharomyces cerevisiae. Importantly, the "engineering" inherent in these projects is almost exclusively directed at generating new-to-nature genes and chromosomes, with the assumption that the cellular components, and thus the cells and organisms that these engineered genetic constructs give rise to, will follow the instructions built into them by the scientist at the level of DNA sequence.

Given how current embryo models are made, is there warrant to refer to them as "synthetic"? Certainly, there are broad connections between embryo models and synthetic biology that

arise from speaking in terms of “engineering” in both cases, with its emphasis on building and designing. It was after all an explicit “engineering ideal” for biology that gave rise to Jacques Loeb’s artificial parthenogenesis experiments of the 1890s, which caused an immediate media stir around the “creation of life”; indeed, we might draw a direct line from Loeb’s “technologies of living substance” to today’s embryo models in both science and its public understanding [5]. Yet at the same time, just because one is led by association to “genetic engineering,” and thereby to “synthetic biology,” it is not inevitable – nor it is desirable – to accept this rather sloppy train of thought. Why recapitulate the story of hubris and unwarranted claims to total control of life visible in Loeb and his parthogenic sea urchins that fed into public suspicions about scientists playing God?

Moreover, there are important and profound differences between the approaches central to synthetic chemistry and biology, and the work of generating embryo models through stem cell technologies. Researchers derive embryo models using donated human biological materials from in vitro fertilization (IVF) laboratories or patient biopsies and apply what is known about derivation, reprogramming and differentiation to coax and elicit certain biological trajectories, often dependent on the cells’ capacities for self-organization or inherent behaviors, to generate these models with the capacity to recapitulate developmental sequences. They are not built with artificial chromosomes, they do not arise de novo from new-to-nature DNA sequences put together entirely in a PCR machine. Where the term synthetic, denoting that which is made in the laboratory by combining chemical substances – or referring to an artificial substitute for a natural product - might be appropriate to the building of novel microbial cells with novel properties, it is a poor fit for the embryo models we described above. Along with other stem cell technologies, such as organoids, embryo models are cellular assemblies, as much enabled as they are “built” [6].

EMBRYO MODELS ARE NOT EMBRYOS, THEY ARE MODELS

The second failure of the phrase synthetic embryo lies not only in the adjective, but in the noun. Given the current state of the technology, this phrase improperly suggests equivalency between the construct and the human embryo generated by fertilization. This leads observers to immediately wrestle with the impossible yes-or-no question of whether or not these entities could one day be human embryos by scientific or legal definitions. By contrast, this second half of our commentary presents the positive case for the intentional and careful choice of the language of embryo models. Here the noun – the thing being named – is a model, and the purpose of that model is front and center. From this starting point, we begin to address the questions we think researchers should be asking one another and communicating to the public: are these good models? What are they for? In whose service are they being made? Is their existence warranted by their current or potential role in knowledge production and the improvement of clinical care? Such close attention to grammar may seem pedantic, yet what kind of thing is at stake is of enormous consequence both for science communication and the question of legal regulation in this new arena of scientific activity.

The language of embryo models emerged in 2017 when “embryoid model” was coined to describe a non-integrated amniotic sac model made from human pluripotent stem cells [7].

It was carried forward by scientists and bioethicists to describe the emerging 3D models generated from mouse pluripotent cells [8], and solidified by a 2020 National Academies of Science meeting, “Examining the State of the Science of Mammalian Embryo Model Systems” [9]. Why is it better to think of these as models, and not straightforwardly embryos, just made by a novel route? The first answer is straightforward and points toward a certain humility concerning our current ability to accurately recapitulate the early stages of human life. To date these entities are likely very far from functional [10].

In short, asking first what these entities are models of, and whether they are good models in the sense of fidelity or research utility is essential for critical assessments of the work that remains to be done and realistic communication of the state of the field. The formation of human embryos in the body occurs in the fallopian tubes of the reproductive tract. Fertilization by the sperm triggers the oocyte to complete Meiosis II, releasing a second polar body and generating a zygote, a single cell encased in a thick extracellular matrix shell called a zona pellucida. The zygote is diploid in that it contains chromosomes from both gametes enclosed in their own pro-nuclei. Once formed, the zygote undergoes a cleavage division forming a 2-cell embryo which continues to cleave into smaller and smaller cells generating a morula-stage embryo which undergoes compaction to generate the blastocyst encased in the zona pellucida. Currently, embryo models at no stage have a zona pellucida, they do not develop from an oocyte, sperm or zygote, they do not undergo embryonic genome activation or compaction, and have missing cells, or in some cases extra cells with unknown identity.

The second reason to lean into the status of these entities as models is to foreground their purpose. Why make an embryo model? The simple answer is that these models have tremendous potential in developing knowledge or procedures to address human suffering. Some specific examples of this include infertility; a condition currently treated by IVF yet success rates have not improved in decades. Developmental disorders such as autism; these are complex diseases often with unknown etiologies that in some cases are speculated to originate in the first few weeks of pregnancy. Early miscarriage; a common occurrence for which knowledge on non-genetic causes would be of great benefit. Pre-eclampsia and complications of pregnancy; diseases for which the mother and fetus could be at significant risk if untreated. Stem cell research; researchers may find that the differentiation of cells from embryo models, for example the differentiation of hematopoietic cells, will have increased clinical utility compared to current differentiation approaches [2, 6].

The third reason to foreground the model and its purpose is to face head on the legitimate concern that one day the proxy will become indistinguishable from the original, and the line between human embryo model and human embryo will disappear. This discussion, exacerbated by the unfortunate nomenclature of the “synthetic embryo,” has focused primarily on the ontological status of these laboratory entities as embryos. Instead, the question “is it a model?” should precede “is it an embryo?” in the task of generating responsible oversight and regulation of embryo modeling. If it is not a model and has a purpose other than increasing knowledge about human reproduction, early development and stem cell biology, or is pushed toward biological features that are not essential to the activity

and purpose of modeling, then it should not exist, regardless of current or future similarity or non-similarity to human embryos.

While regulating the activity of embryo modeling and the ontological status of the model are of course related, emphasizing who and what the model is for in terms of knowledge or clinical care, better equips us to include and engage tissue donors, scientists, and potential beneficiaries as stakeholders. There are precedents for the consensus-driven regulation of modeling with embryos. Cloned embryos are generated in an embryology lab by transferring a diploid somatic nucleus into an enucleated oocyte. The purpose of creating cloned embryos was to demonstrate the possibility of human nuclear reprogramming, a key step to the later wide-spread technology of induced reprogramming used to generate hiPSCs which transformed stem cell research. Due to an international consensus, and in some jurisdictions laws that prohibited the transfer of cloned human embryos to a uterus, a regulatory framework allowing some research with cloned embryos as a model was established. Action around the prohibition of the transfer of embryo models to a uterus seems a sensible precautionary step regardless of the state of the science. Moreover, it would underline the point that the purpose of these models is to address human suffering, not to create new human beings.

Indeed, by spotlighting the current status of embryo models, and the purposes towards which they are being developed, researchers will be better positioned to navigate the definitional swamp that faces human embryo research more generally. Many definitions of embryos are already strategic in that they incorporate a sense of the purpose of scientific or medical activity into the definition. For example, a position statement led by the International Committee for Monitoring Assisted Reproductive Technologies including profession societies that perform reproductive care from, Europe, Asia, Africa, Middle East, USA and Latin America defines the embryo as a biological organism resulting from the division of a zygote and ending eight completed weeks after fertilization or ten weeks of gestation [11]. The decision to refer to an embryo as beginning from the 2-cell stage (and not the zygote) enabled reproductive care in countries where embryo cryopreservation was not allowed.

Paradoxically, the very challenge that engenders the need for such models – working directly on actual human embryos in these early stages or in vivo – also makes it difficult to know just how like or unlike they are to the real thing. As with other biotechnologically-generated reproductive materials, using legal definitions to try and determine whether embryo models are embryos simply leaves one with the answer that it depends on the definition and the jurisdiction. Such misfit between scientific and legal definitions stalls research and publications, leaving embryo models to linger in regulatory uncertainty. This points to the need for robust, publicly-engaged, scientifically honest discussion and debate about where embryo models stand in terms of existing regulations, and what steps need to be taken to develop guidelines where none exist.

THE CONVERSATION WE SHOULD BE HAVING

We suggest, in light of the above arguments, that the research community would be best served by the existing plain-spoken and direct terminology of the embryo model. There are reasons beyond accuracy for this choice. First, the use of *synthetic* is disrespectful to the human origins of the materials used in this scientific work, and to the donors' intentions, whose predominant motivation, documented in many qualitative studies, is to provide embryos or tissues for research with the belief that their cells will help others [12]. Whether or not these donors ever know that the donated cells end up as embryo models, we should not be emphasizing the scientist as creator in this narrative. Open and respectful characterization of these entities as models, given shape by science, that play a crucial role in knowledge production, is preferable to pretensions that they come purely from the hand of the inventor. We need to discuss and amplify all the different senses in which embryo models are composed of human materials and imbued with human intention. This is a launching point for a more concerted public participation in and discussion of this science, not the point at which to shut it down by obscuring the material origins of research tools.

Second, we must not to lose sight of the fact that these are models, used as proxies to investigate pressing questions of human health. We have argued that it is inaccurate to call embryo models synthetic. Furthermore, it is doubly misleading to use the term embryo as a noun unmodified by any term other than synthetic. By contrast, continued insistence on the model keeps the question of intention front and center: models of what? For whom? The value of highlighting and exploring the differences between human embryo models and human embryos proper is an important step for scientific humility about the power and limits of these tools. It also emphasizes the needs that these proxies could answer: understanding and alleviating infertility, recurrent miscarriage, fostering developmental health or improving stem cell differentiation. Calling these entities synthetic embryos or muddying the waters with Frankenstein narratives might make for good headlines in an ever-shorter news cycle, but it inaccurately portrays the science as being bent on the making of replicant human beings. The purpose of embryo models is not to make human beings directly from these *in vitro* entities. It is to use them to explore human biology in ways that are not harmful to nascent or actual human persons.

Concerns have been voiced that these embryo models could potentially one day cross the line between human embryo models and human embryos [6]. This is reason enough to continue to insist in both word and deed that the aim is to make a good model, not to make persons. Models must allow the accurate study of early development and implantation biology with living human materials, yet be constrained by widely agreed upon measures that limit threats to social and ethical boundaries around personhood. These boundaries will always be contested, but their open and inclusive debate within and beyond science is best served by discussion that honors the human origins and intent of the donated materials with which embryo models are made, foregrounds the need to which these models answer, and dispenses with hubris as a starting principle.

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