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An ethical framework for human embryology with embryo models

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SUMMARY

A human embryo's legal definition and its entitlement to protection vary greatly worldwide. Recently, human pluripotent stem cells have been used to form *in vitro* models of early embryos that have challenged legal definitions and raised questions regarding their usage. In this light, we propose a refined legal definition of an embryo, suggest "tipping points" for when human embryo models could eventually be afforded similar protection to that of embryos, and then revisit basic ethical principles that might help to draft a roadmap for the gradual, justified usage of embryo models in a manner that aims to maximize benefits to society.

INTRODUCTION

Our perceptions and views of the human embryo have evolved over time with scientific advances. In the last century, it became apparent that embryos did not have to be formed via fertilization but could be also created by transferring the nucleus of an adult cell into an egg,[1] endowing an egg with two sets of the maternal genome,[2] or by forming gametes directly from stem cells and fertilizing them in a dish.[3] More recently, embryo-like structures have been formed *in vitro* directly from animal and human stem cells, therefore bypassing the use of both egg and sperm.[4] Although they are not considered embryos due to their current inability to form fetuses and eventually neonates, these models represent a new way to study development and eventually contribute to medicine. However, they have raised several questions. What is their legal status? For what purpose should we use them? This article argues that answering these questions requires both a refined legal definition and a decision about "tipping points" for embryo models. Firstly, we propose that the legal definition of the embryo should be a group of human cells supported by elements fulfilling extra-embryonic and uterine functions that, combined, have the potential to form a fetus. And secondly, we propose "tipping points" beyond which a model could receive protection similar to embryos. We then revisit largely shared ethical principles in science and medicine that might be useful to guide ongoing discussion about the uses of human embryo models.

RESEARCH WITH HUMAN EMBRYOS AND EMBRYO MODELS

The goals of human embryology

Human embryology grapples with fundamental questions about "how we come to be." And although much is known, a great deal remains to be discovered about the mechanisms by which an oocyte fused with a sperm transforms into an embryo, especially during the first weeks of pregnancy. These insights are relevant for medicine because, for reasons that are largely unknown, about half of fertilized human oocytes fail to develop.[5,6] In addition, some preventable chronic and genetic diseases can originate during early development (e.g., due to abnormal neural and cardiovascular development).[7] Thus, research on this period will impact global health challenges including family planning, fertility decline, and prenatal preventive medicine. Clearly, human embryology is a field with significant impact on public health and the potential for profound worldwide economic, social, environmental, and geopolitical benefits.[8]

The biological definition of an embryo

What is an embryo? For biologists, it is the group of cells that can potentially form the fetus and ultimately the body of the neonate. Human embryos are normally formed by fertilization, when an oocyte fuses with a sperm and produces a totipotent cell (the zygote; Figure 1; glossary in Data S1). This cell divides to form about 32 cells that shape into a hollow structure called the blastocyst (~5 days post fertilization [d.p.f.]; Figure 1). Within this blastocyst, a group of cells forms an internal tissue called the epiblast (~7

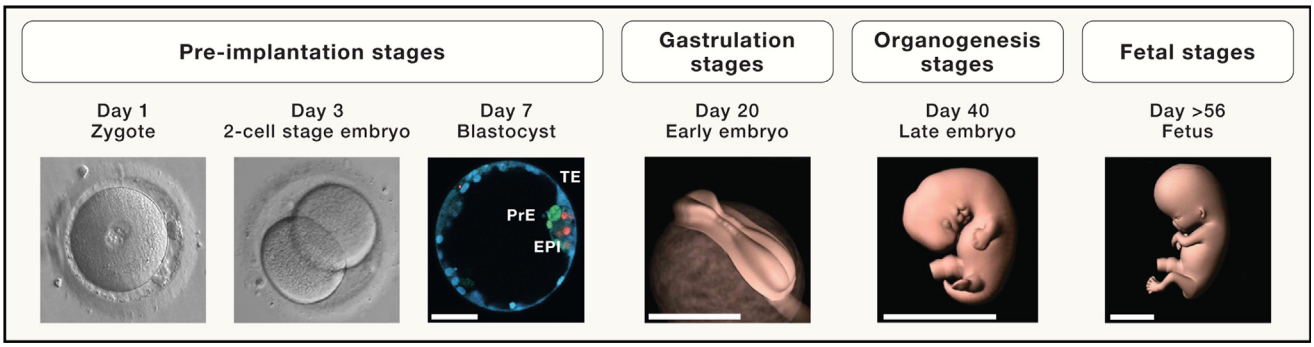

Figure 1. Human embryological development

The development of the human embryo can be characterized by the stages of preimplantation, gastrulation, and organogenesis that lead to the formation of a fetus (day 56). Preimplantation development culminates in the formation of a mature blastocyst consisting of a group of cells that form an internal tissue called an epiblast (EPI, in red), whose potential is largely limited to the formation of the fetus, and extraembryonic cells forming the trophectoderm (TE, in blue) and the primitive endoderm (PrE, in green) that, together, envelop and support the development of the epiblast and mediate implantation in the uterus. After implantation, supported by the extraembryonic and uterine environments, the epiblast continues to develop and forms the outline and the major axis of the body plan (gastrulation process). Once this outline is laid, the embryo forms the organs until the fetus is formed (56 d.p.f.), thereby closing the period of greatest transformation. The image of the zygote and the 2-cell stages are from the European Society for Human Reproduction and Endocrinology. The image of the blastocyst is from the laboratory of Laurent David. The postimplantation stage images are embryos and a fetus from the Kyoto Human Embryo Visualization Project.

d.p.f.), whose potential becomes largely limited to forming the fetus. By definition, these cells are pluripotent (Figure 1; glossary in Data S1). The remainder of the blastocyst consists of extraembryonic cells that sequentially form the trophectoderm tissue and the primitive endoderm tissues,[9] which give rise to the placenta and the yolk sac, respectively, although this dichotomy is not absolute. For example, mouse primitive endoderm cells contribute to the embryonic gut tube.[10] These extraembryonic cells encase and support the development of the epiblast and mediate the implantation into the uterus (~8 d.p.f.; Figure 1; glossary in Data S1), thereby closing the preimplantation period. Supported by extraembryonic and uterine environments, the epiblast subsequently progresses and forms an outline of the body plan with respect to the main axes of the body through the gastrulation process (Figure 1; glossary in Data S1). Once the body plan is laid out, organogenesis can start. In biology, the term "embryo" is meant to encompass the period of greatest transformation until the fetus forms (the first 8 weeks after fertilization, 56 d.p.f.; Figure 1). Thereafter, the fetal stages consist mainly of growth, maturation, and interconnection of the structures laid down during the embryonic period. Thus, in a strict biological sense, the term "embryo" includes the totipotent cells preceding the blastocyst, the epiblast, and its descendants until week 8 after fertilization, but not the extraembryonic cells. The term "conceptus" (see glossary in Data S1) refers to the product of conception at any point between fertilization and birth. It thus includes the embryo or the fetus (depending on the stage) and all extraembryonic appendages (e.g., the placenta).

Embryo models as a convenient and complementary alternative to the use of embryos for research

Since the 1980s, embryos formed through *in vitro* fertilization (IVF) have been generously donated for research conducted under strict ethical oversight. Yet, embryos are scarce and often of limited quality (because the highest quality ones are used for reproduction), and their experimental manipulations are limited for ethical and technical reasons.[11] Moreover, in many jurisdictions, it is legally prohibited to form human embryos for research purposes and to culture them for more than 14 d.p.f. As an alternative, embryo models have recently been formed *in vitro* from stem cells.[4] These models have different levels of completeness and recapitulate different moments of early development, particularly the periods around implantation. For example, blastoids are relatively complete models reflecting the pre-implantation blastocyst (5–7 d.p.f. in humans), and gastruloids are partial models recapitulating aspects of gastrulation (14–21 d.p.f.). Although we do not yet know how well these models are suited to mimic actual human embryo development, the ability to grow pluripotent stem cells (PSCs) indefinitely *in vitro* allows the generation of vast numbers of these embryo models using established lines either derived from embryos (human embryonic stem cells [hESCs]) or reprogrammed from somatic cells (human induced PSCs [hiPSCs]). Since embryos are not used, these models are a convenient alternative that complements the use of embryos in research.[12] However, these models challenge the current legal definitions of the embryo, and their increasing sophistication warrants ethical justification for their use. It has therefore been necessary to establish ethical guidelines for research using human embryo models.[13]

Implemented guidelines for research on human embryo models: Permissibility, prohibition, and terminology

In 2021, the International Society for Stem Cell Research (ISSCR) established ethical guidelines for research using embryo models. These arose following two years of discussions between a group of geographically and culturally diverse scientists and ethicists, including those from the European Union, Canada, the United States of America, Japan, and China.[14–16] At this group's suggestion, the ISSCR confirmed that embryo models should not be considered embryos, neither in the biological nor legal sense, due to their limited developmental potential, but that research involving them nevertheless requires ethical oversight. These guidelines also distinguished two types of models.[16] First, "integrated embryo models" were defined as models that include both embryonic and supporting extraembryonic tissues (e.g.,

blastoids) and that might one day form fetuses. The guidelines proposed that their use for research should only be permitted after review and approval by specialized scientific and ethical committees. Second, "non-integrated embryo models" were defined as models that form a discrete group of anatomical structures that could support the formation of combinations of organs but lack the potential to generate a fetus (e.g., gastruloids). Guidelines proposed that their use for research should be reported as part of an oversight process, but not reviewed further, at the discretion of the relevant committee and/or local policy.[15,16] In addition, the updated guidelines prohibit practices that are currently unjustified or unsafe, and included in this category the transfer of human embryo models into any uterus, whether animal or human, in part because they could develop abnormally and harm the gestational carrier (e.g., in the case of molar or ectopic pregnancies).

The ISSCR also made recommendations about the communication and terminology of research using embryo models.[15,17] It reiterated that research must ensure that the information obtained is trustworthy, accessible, and exchanged in a timely manner and that researchers are accountable for maintaining public confidence.[14,15,18] This is meant to ensure that colleagues and the public understand the nature and implications of the research (see "Integrity of the Research Enterprise" and "Transparency," ISSCR Guidelines). So far, embryo models are rudimentary—they only partially and imperfectly reflect the conceptus and are not capable of forming animals.[19] To reflect this state of affairs, the ISSCR advised using the term "embryo model."[15,17] Sometimes the term "synthetic embryo" is used, especially in the press. In agreement with the ISSCR,[17] we believe that this term can be misleading, since the stem cells used are relatively similar to the conceptus' cells and spontaneously, albeit imperfectly, execute a "natural" program. In contrast, the term "synthetic embryo" implies the use of synthetic elements—components obtained by synthesis. The term "synthetic embryo" also suggests a high degree of similarity to the embryo, a comparison that is not currently justified. Finally, this terminology is at odds with the historically evolving understanding of the embryo, according to which it should not be defined differently—either as "natural" or "unnatural"—because of its origin (e.g., embryos formed by somatic cell nuclear transfer [SCNT] are still embryos).[20] In other words, the way a human embryo is formed (its *etiology*) is relatively unimportant from a terminological point of view since what matters most is what these cells are and could become.

In summary, the terms "embryo models,"[15,17] "embryonic models,"[21] or "stem-cell-derived embryo models" have the merit of acknowledging their currently limited potential. However, once these models are considered, based on criteria that remain to be defined, sufficiently similar to embryos, they could be named, legally defined, and regulated similarly to embryos regardless of how they were formed.

THE LEGAL DEFINITION OF THE EMBRYO IN LIGHT OF EMBRYO MODELS

The legal definitions of the human embryo

The legal definition of an embryo is different from the biological definition as it does not aim to describe the embryo scientifically, but rather to protect it. Legal definitions should be informed by biological insight, yet they are also crafted based on considerations that vary worldwide, as they are rooted in philosophical, ethical, social, or cultural beliefs.[22] For example, in France, an embryo is legally considered as such when in the context of a parental project.[23] Often, legal definitions of the human embryo express concerns about protecting the potential to (1) form certain cells, tissues, and organs; (2) develop into a human being; (3) develop sentient and conscious individuals capable of experiences; and (4) belong to the human species. Because different jurisdictions will employ specific wording to capture the essence of what they intend to protect[22,24] (see a scope of legal definitions in Data S2), it often serves the scientific community to remain agnostic about the reasons underlying an entitlement to protection.[25] Indeed, it is less important that stakeholders agree on *why* embryos are entitled to protection than to agree that they *are* entitled to protection.[25]

Initially, legal definitions of the embryo referred to a group of cells resulting from fertilization whose completion was signaled by the first cell division or the expulsion of the polar bodies. IVF embryos met this definition and were thereby legally protected, but their availability raised the possibility of culturing them for longer periods in a dish. Following reports from the U.S. Department of Health, Education, and Welfare and the U.K. Warnock Committee,[26,27] a restriction to 14 days of culture or to the appearance of the primitive streak (see glossary in Data S1) was therefore established in many jurisdictions. This time point was partly chosen to assure the public that research would not advance untethered.[26] However, it was discovered that similar to amphibians,[1] mammals (e.g., sheep[28]) can form via the transfer of a nucleus into an enucleated oocyte (through SCNT). These animal embryos bypassed fertilization and therefore were not legally considered embryos. Neither would their human counterparts, an outcome that was considered undesirable. In response, many jurisdictions made an adjustment to describe the embryo as a group of cells having a certified or assumed potential to develop to a certain stage of intrauterine development. These stages ranged from the gastrulation stage in Australia to neonates in Japan.[29] Some jurisdictions, including Australia and Japan, retained the reference to fertilization while adding terms of potentiality and stages. Other jurisdictions, including Germany, Belgium, and the Netherlands, relied solely on potentiality and stages (see a scope of legal definitions in Data S2).[29] Thus, a combination of the terms of potentiality and stages became central to many definitions.

A more precise legal definition of the embryo is needed

It is now clear that scientific advances are narrowing the biological and therefore ethical and legal gaps between embryo models and embryos.[30,31] In the future, embryo models may pass a "tipping point" after which, in our view, most of the ethical distinctions with an embryo would disappear and there would therefore no longer be reason to value and regulate embryo models differently from embryos. Put differently, at some point of refinement, embryo models could pass a "Turing test," meaning that an evaluator testing them without having information about their origin could not distinguish them from embryos. But under what conditions should an embryo model be

considered an embryo? The potential to achieve a specific developmental stage is an obvious answer, but this consideration exposes a lack of agreement on how these terms are considered. To stimulate a broader discussion, we will briefly attempt to refine the current understanding of these terms.

Understanding potentiality to better define the embryo

Although the use of the term "potentiality" has been criticized,[32–34] we believe it is increasingly important for assessing embryos with different etiologies.[2–4,28] However, it would be useful to clarify this term.

Firstly, in this context, potentiality refers to the intrinsic ability of cells to develop to a certain developmental stage. But it has been demonstrated that human nucleated cells (e.g., skin cells) can be reprogrammed into iPSCs that have the assumed potential to form all fetal and extraembryonic cell types under the right circumstances. If any human nucleated cell can be reprogrammed into potent cells, potentiality is arguably ubiquitous. This *reductio ad absurdum* warrants a distinction between an active potential to develop into a fetus under the right supportive circumstances and a passive potential that requires an intervention (e.g., nuclear reprogramming) to acquire a similar capacity.[32] Secondly, the circumstances that enable the acquisition and realization of the potential to form a fetus also depend on extrinsic factors. During pregnancy, the embryo cannot develop without the support of the extraembryonic and maternal environments, the latter beginning with the uterine environment (e.g., growth factors, hormones, and exchange of gasses and waste products). Recently, the necessity for this support has been confirmed by experiments showing that (1) embryo models organize properly only under certain conditions (e.g., supported by extraembryonic cell types);[4] (2) mouse concepti can develop *in vitro* only in a supportive environment mimicking the uterus;[35] and (3) human embryo failure can be caused by a suboptimal uterine environment.[36] Importantly, the nature of the support necessary for the proper development of a neonate likely involves cognitive, social, and other external elements as well.[37] Therefore, we now better recognize that the realization of an intrinsic cellular potential to form a fetus is conditioned by, and contingent on, extrinsic factors.

As such, the description of potentiality should include the active capacity of cells and the right supportive circumstances that, when combined, enable the formation of a fetus. The distinction between passive and active potential has been discussed widely in the philosophy and ethics literature.[33,34] Here, we make our distinction a biological one, which might be sufficient to support the formulation of sensible legislation and guidelines for embryo models.

Understanding the stages of human embryonic development

There is a broad, though not unanimous, consensus that the level of protection of the conceptus increases over time. Given this gradual approach to ethics and policy, how should we identify discrete stages in a developmental continuum? And what do we hope to protect? Below, we outline a set of watersheds of human embryonic stages and highlight some features that might require legal protection. We acknowledge that this proposition and its implications for regulation of research both require wider discussion amongst the scientific, ethics, and regulatory communities, carried out in the context of public review.

Completion of fertilization and implantation

This period corresponds to 0 to 12 d.p.f. (Carnegie stages 1–5c). During that time, the blastocyst forms and implants in the uterus. Here, the ethical concerns involve ensuring that the use and disposition of biological materials (e.g., DNA, cells) is regulated.

Gastrulation and the formation of specialized cells

This period corresponds to 12 to 24 d.p.f. (Carnegie stages 6–8). During this time, the implanted blastocyst progressively undergoes gastrulation, and many concepti fail and are lost. However, a successful implantation and gastrulation significantly increases the gradually realized potential to form a neonate.

Organogenesis

This period corresponds to 25 to 56 d.p.f. (Carnegie stages 9–23). Some embryos form an overall recognizable outline that will soon become a fetus (56 d.p.f.) and contains most tissues and *primordia*, which represent organs in their earliest recognizable form (e.g., forebrain, eyes, limb buds; see glossary in Data S1). The formation of integrated *primordia* requires that their use and disposition is regulated and signals a further increased realization of the potential for development toward full term.

Passing the bottleneck of pregnancy

Some embryos form a fetus (from 56 d.p.f.; Carnegie stage 23) and pass the bottleneck of pregnancy (80% of miscarriages occur within the first 84 d.p.f.[38]). Passing the bottleneck of pregnancy considerably increases the potential to form a neonate.

In summary, although human development is continuous, for legislative purposes it is possible to identify watersheds that correspond with a gradual and mostly cumulative acquisition of features raising ethical concerns (Figure 1).

Proposition for the definition of the embryo

For regulatory purposes, we stress that it does not matter how the embryo originated. We also suggest that realization of the potential to become a fetus requires both potent cells and adequate support from elements fulfilling extraembryonic and uterine functions. Based on these considerations, we surmise a definition of an embryo in legal terms as "a group of human cells supported by elements fulfilling extraembryonic and uterine functions that, combined, have the potential to form a fetus" (Figure 2). Which fetal stage is appropriate for that legal definition is an important topic for further discussion. Embryonic cells capable of forming all the cells of the body but without the support necessary for fetal development should therefore not legally be considered embryos. However, these same cells, if properly supported, could eventually form a fetus. Were that to happen, this ensemble of cells could be legally considered an embryo. Of note, this contextuality is already used in the legal definition of the embryo in Spain, which is contingent on its presence in a uterus (see a scope of legal definitions in Data S2).

IMPROVING THE REGULATION OF RESEARCH WITH HUMAN EMBRYOS AND EMBRYO MODELS

Tipping points for embryo models to become legally similar to embryos

Now that we have proposed a more precise definition of the embryo in legal terms, we believe we are better equipped to

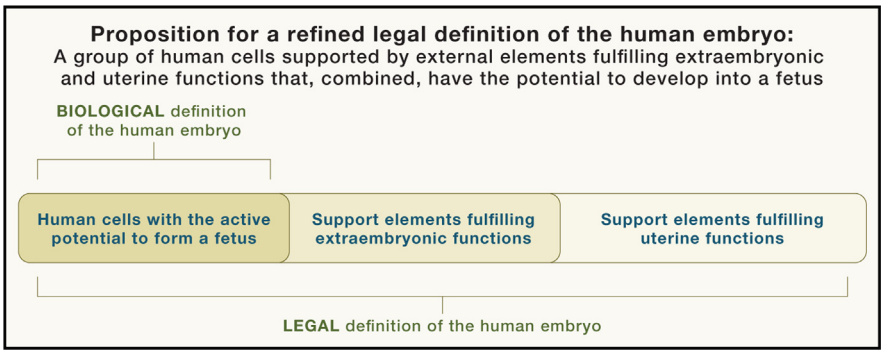

Figure 2. Refining the legal definition of the human embryo

The formation of embryos and embryo models using methods that bypass fertilization makes the consideration of developmental potential necessary for a refined definition. Because potential, as manifested in a fetus, is the result of a combination of intrinsic cellular potential and extrinsic support, we propose that cells capable of forming all the cells of the body (referred to as pluripotent stem cells for the period between 7 and 14 d.p.f.) should be considered differently when they are isolated versus when they are in a supportive environment fulfilling, at least, extraembryonic and uterine functions.

consider when a model would become an embryo. Based on the necessity of supporting elements, integrated embryo models are the ones most likely to breach the gap toward an embryo. However, because the ISSCR guidelines prohibit the transfer of human embryo models into any uterus, the direct Turing test cannot be performed, and indirect tests are required.

We propose two indirect Turing tests to identify whether a tipping point has been reached. The first test is based on the potential for a human embryo model formed by a particular method to develop efficiently and faithfully *in vitro*. Currently, technologies to support this *in vitro* development are rudimentary, and cells acquire detrimental genetic and chromosomal aberrations faster than embryos. But, when protocols are refined, embryo models might progressively pass certain watersheds. Assuming this were to be achieved efficiently and faithfully based on standards that remain to be established,[19] how should we determine the duration of this test? We argue for a gradual assessment, because although failure to develop properly at early stages raises few concerns, failures at later stages would be increasingly problematic due to the accumulation of features entitled to protection. The duration of this test should therefore reflect a balance between a brief period of *in vitro* culture, which would be deemed acceptable based on the entitlement to protection of emerging features, and a sufficiently long period to allow a better evaluation of the model's potential. This balance should be discussed in jurisdictions to fit local values and could be decided gradually when progress is made (Figure 3).

The second test is based on the potential for a similar embryo model to form live and fertile animals. Here, fertility is used as a proxy for animal health but should not be interpreted as relevant for the human case. Such a test may start with mice, but since human development is notably different from murine development, passing the second test should additionally require the formation of fertile animals in several species more similar to humans, such as pigs[39] or non-human primates.[40] The range of species used could reflect a compromise between those with a lower entitlement to protection and those with capacity to develop in a manner more similar to humans, which would need to be discussed in light of local values (Figure 3).

When both tests are passed, we think it is appropriate to assume that a model has a potential similar to the human embryo and that it should fall under its definition and be subject to similar norms. Of note, embryos formed via different methods (e.g., fertilization, SCNT, stem cells) might be considered legally similar, but additional layers of regulation should determine their usage (e.g., for research or reproduction). Jurisdictions will have to decide whether they will continue to allow embryos formed from stem cells to be used for research, as was the case for SCNT embryos, and if they could be used for human assisted reproduction. However, attempting to use human embryos formed from stem cells for assisted reproduction would require an exhaustive prior discussion and evaluation on whether it is safe, socially, and ethically justifiable and desirable to do so.

Potential ethics principles for adapting the regulation of human embryology

In addition to the legal status of embryos and models, ethical principles are also needed to formulate guidelines and policies. The guidelines of the ISSCR contain several fundamental principles that are used for human embryology. They originate from largely shared principles in science and medicine (Nuremberg Code; Declaration of Helsinki of the World Medical Association[41]; Department of Health, Education, and Welfare[42]; European Science Foundation[43]; Medical Professionalism Project[44]; Institute of Medicine; Council for International Organizations of Medical Sciences,[45] UNESCO Universal Declaration on Bioethics and Human Rights [UDBHR][46]). Here, we briefly revisit some of these principles and then suggest how they might be applied specifically to human embryology done with embryo models (Box 1).

Beneficence and *non-maleficence* refer to the duty to promote some valuable good and to do no harm or the least possible harm (UDBHR Article 4).[46] In the context of human embryology, this means that the use of embryos should be justified by virtue of scientific or clinical research that produces a valuable good, and the putative harm necessary to achieve research aims (e.g., the destruction of a human embryo) should be either avoided or kept to a minimum. In addition, human embryology should meet the

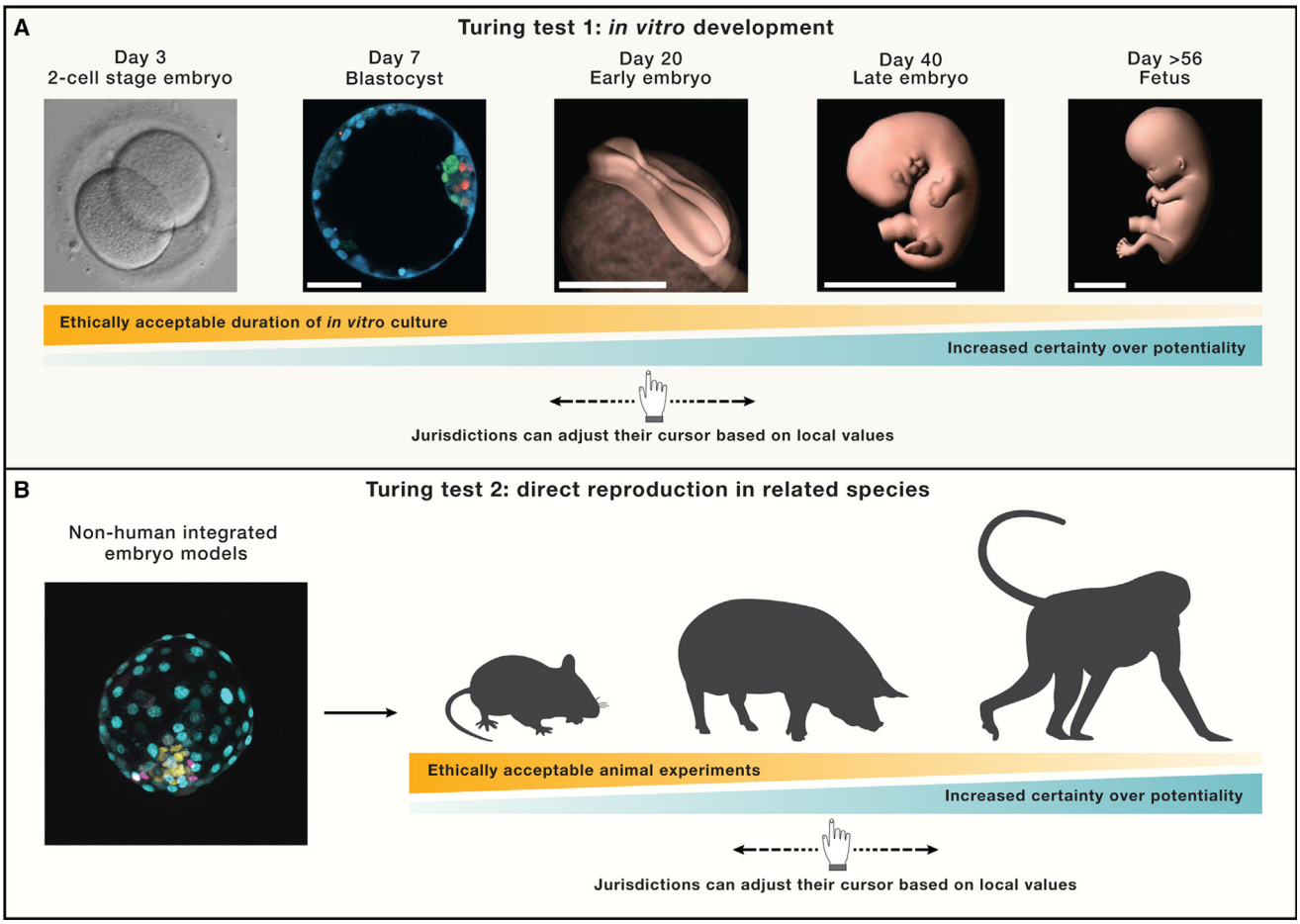

Figure 3. Tipping points for human embryo models to become legally considered embryos

A human embryo model could be legally considered similar to a human embryo if it has shown a potential to form a fetus. Once it has passed this tipping point, it could become fully entitled as an embryo, regardless of how it formed. Because the Turing test would require the transfer of human embryo models *in utero*, which is prohibited due to justified ethical concerns, indirect tests can be used. We propose that human embryo models pass the tipping point when two tests are successfully passed.

(A) A given human embryo model shows the potential to efficiently and faithfully produce the complete embryo *in vitro* as it normally forms up to a certain stage of development. This time point will be a compromise, based on local values, between a brief enough period of *in vitro* culture that is ethically acceptable and a sufficiently long period of *in vitro* culture that allows better evaluation of the model's potential.

(B) An embryo model formed by the same methodology has the potential to produce live and fertile animals in multiple species, particularly those closely related to humans, including pigs and non-human primates. The choice of species should represent a trade-off between their entitlement to protection and a development similar to that of humans. This balance should be evaluated in the context of local values.

demands of *integrity* and *equity*, which entail that practices should be overseen by an appropriate oversight commission evaluating if they meet scientific, ethical, legal, and societal standards and that the results should be widely shared with society (see UDBHR Articles 15 and 20).[46] Human embryology should also meet the demands of *proportionality* and *subsidiarity* to appropriately balance means and ends. *Proportionality* demands that the ends must justify the means and that the value that is brought about should outweigh the associated burden. *Subsidiarity* refers to the demand that embryology's aims must be pursued in the least morally problematic or controversial way.[47] Specifically, answering a scientific or medical question should involve the means with the least ethical concerns. Lastly, given that it is not always possible to ascertain the full scope of risks and harms, it is advisable to err on the side of caution. Following what we would call a *principle of precaution*,[48] respect for and protection of embryos should outweigh the potential benefits when the adverse consequences are unknown or largely uncertain.

Application of these principles to human embryology with embryo models

How can we interpret these ethical principles to draw a roadmap for the use of embryo models? These principles suggest that there might be unjustifiable activities where the risks and harms outweigh potential benefits. One of these is the transfer of human embryo models into a uterus, primarily because it is likely to develop abnormally and harm the gestational carrier (e.g., in the case of molar or ectopic pregnancies). The ISSCR guidelines currently prohibit the transfer of human embryo models to any

Box 1. Possible applications of basic ethics principles to embryo models

- Human embryo models should not be transferred into a uterus, whether animal or human, because of the risk of developing abnormally, resulting in possible harm to the gestational carrier and resulting fetus (already implemented in the ISSCR guidelines).[14,15]
- Permission from an ethics committee to culture human embryo models throughout developmental stages of increasing worthiness of protection should require a proportional increase in potential benefit.
- Permission from an ethics committee to culture human embryo models for a specified period of time should take into account the quality of the model, justification of the objectives, technical feasibility, and consistency of the practice with local and international values.
- For a specific goal, forming an embryo model that is more complete than necessary might yield equal benefits but cause more concerns. Therefore, if possible, less complete models should be preferred. Consequently, while the use of human integrated embryo models is justified in the early stages of development, alternatives might make their use less justified at later stages.

uterus of any species. These principles might also guide discussions related to three additional issues: (1) the duration of *in vitro* culture of human integrated embryo models, (2) the scope of scientific and medical applications of embryo models, and (3) the permissibility of generating embryos for research.

Justifying human embryology requires that its potential benefits outweigh its burdens. Because ethical concerns increase as development progresses, the use of embryo models is more justifiable at early stages than at late stages. Permission by an ethics committee to culture human embryo models throughout development would therefore require a proportional increase in potential benefits to offset the increasing worthiness of protection.

As it is now, the *in vitro* culture of human integrated embryo models is not formally regulated. However, if these models are improved, they might form a fetus. Scientific societies and ethics committees could regulate the extent of *in vitro* development by balancing the opportunity for research with the need to protect the features emerging from these models. Importantly, ensuring the quality of the models is crucial to justifying the research and assessing whether the potential societal benefits are achievable. Scientific societies and ethics committees could implement quality checks using specific assessments (e.g., faithfulness, efficiency, reproducibility[19]) that researchers would need to fulfill before they would be permitted to attempt culturing human models toward later stages. This would also limit the incentive to rush into stages with widespread ethical concerns without broad consultation and allow for public discussion up front, thereby aligning embryology with societal goals and maintaining public trust. Overall, a decision over the duration of *in vitro* culture could be granted by scientific societies and ethics committees if the quality of the model, the justification of the objectives, their technical feasibility, and public discussions lead to consistency with local and international standards.

These principles also lead to the consideration that when pursuing a particular goal, models that are less entitled to protection should be preferred. Forming an embryo model that is more complete than necessary might provide the same benefit but raise more concerns. Therefore, if possible, less complete models should be preferred. For example, if the goal is to form a specific organ, the minimal required features (e.g., progenitors and supporting tissues) could be formed without promoting the development of a more complete embryo model (e.g., blastoids). This can be achieved by channeling development, as seen in assemblies of organoids and non-integrated embryo models (e.g., gastruloids). As a consequence, although the use of human integrated embryo models is justified in the early stages of development, alternatives may make their use less justified in the later stages.

Lastly, improved models will blur the distinction between embryos created for reproduction and embryos created for research, the latter of which are prohibited in some countries. In the scope of research, it might be arbitrary to allow the use of human embryos formed from stem cells yet prohibit the use of human embryos formed via fertilization. How should we consider the different aims of creating embryos? A first and significant aim is to enable persons to become parents. A second aim is to increase knowledge and improve people's lives (e.g., providing solutions to infertility, miscarriage, and developmental abnormalities). In our view, both aims are worthy of consideration. Therefore, it seems timely and reasonable to open the discussion on which aims justify the use of embryos, including embryos generated from stem cells.[49]

CONCLUSIONS

Definition of the embryo

Advances in forming human embryo models demand a reconsideration of the legal definitions of human embryos. We suggest that this definition should be based on the developmental potential to form a fetus, which incorporates not only the intrinsic capability of cells but also the provision of a supporting environment integral to realizing this potential. We surmise a definition of an embryo in legal terms as a group of human cells supported by elements fulfilling extraembryonic and uterine functions that, combined, have the potential to form a fetus.

Tipping points for embryo models

While no human embryo model is yet suspected of having the potential to form a fetus, it is possible that some models may do so in the future. As long as this potential remains unproven, we suggest using the terms "embryo models," "embryonic models," or "stem-cell-based embryo models." But when these models have passed a defined tipping point, we suggest they should then become fully entitled as embryos, regardless of how they came into being. The definition of a tipping point requires a Turing test that is complicated by the fact that transferring human embryo models into the uterus of any species is prohibited. We propose that human embryo models could be

Box 2. Executive summary

- Scientific research using human embryo models made from stem cells has great potential to advance our understanding of development, infertility, pregnancy loss, birth defects, and the developmental origins of adult diseases.
- As human embryo models become more similar to the human embryo, a refined legal definition of the human embryo is needed to determine the conditions under which the models could be granted similar protection.
- As part of a refined definition, the potentiality of cells to develop into a fetus should take into account both an intrinsic developmental potential and an absolute requirement for support normally provided at least by the extraembryonic cells and the uterine environment.
- We surmise a refined definition of the human embryo as "a group of human cells supported by elements fulfilling extraembryonic and uterine functions that, combined, have the potential to form a fetus."
- Because it is prohibited to evaluate the potential of a human embryo model by transfer to a uterus, we propose that if (1) a given human embryo model is capable of efficiently and faithfully forming the entire embryo up to a given stage of development and (2) the same embryo model has the capacity to form living and fertile animals in multiple species, particularly non-human primates, then that human embryo model has reached a "tipping point" and should be considered similar to a human embryo for ethical and regulatory purposes.
- It is crucial that scientific societies and ethics committees ensure that the *in vitro* development of human embryo models happens gradually and that the quality and reproducibility of results are assured before researchers are allowed to explore later stages. This quality justifies the research, limits the likelihood of precipitous research in areas of widespread ethical concern without broad consultation, and allows assessment of whether societal benefits can be achieved.
- Because, for a specific goal, a human embryo model that is more complete than necessary might yield equal benefits but raise more concerns, less complete models should be preferred when possible. Consequently, while the use of human integrated embryo models is justified in the early stages of development, alternatives might make their use less justified in later stages.

deemed equivalent to embryos when: (1) they have been shown to have the potential to efficiently and faithfully develop *in vitro* as normally formed up to a moment to be decided upon based on local ethical and regulatory considerations and (2) when equivalent animal embryo models are shown to have the potential to form living and fertile animals in multiple species, including the ones that are the closest to humans (e.g., pigs, monkeys).

Basic ethics principles

We likewise propose a wider discussion based on the application of fundamental ethical principles largely shared in science and medicine that take into account the quality of the model, the justification of the goals, their technical feasibility, and whether public discussions result in a match with local and international values. This discussion would be important to decide (1) what limits to impose on the duration of *in vitro* culture of human integrated embryo models, (2) what are the justifications of the scientific and medical aims for using embryo models with different levels of completeness, and (3) the extent to which human embryology using stem cells is a desirable alternative complementary to the classical use of embryos.

An executive summary can be found in Box 2.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.cell.2023.07.028.

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AUTHOR CONTRIBUTIONS

All authors have participated in the conceptualization and in the writing of the manuscript.

DECLARATION OF INTERESTS

N.C.R. is an inventor on the patents "Blastoid, cell line based artificial blastocyst" (EP2986711) and "Blastocyst-like cell aggregate and methods" (EP21151455.9) that are both licensed to dawn-bio, a company he co-founded. A.M.A. and N.M. are inventors on the patents "Polarised three-dimensional cellular aggregates" (PCT/GB2019/052668) and "human polarised three-dimensional cellular" (PCT/GB2019/052670), maintained by Cambridge Enterprise.

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