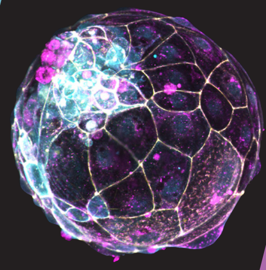
THE SWEDISH NATIONAL COUNCIL ON MEDICAL ETHICS

In brief

Embryo models


N. Rivron/IMBA

Stem cell-based models of human embryos can help researchers understand early human development and contribute to the development of new treatment methods for infertility and foetal damage. At the same time, embryo models spark boundary issues and challenge current regulations.

What are embryo models?

An embryo model is a two- or three-dimensional structure made up of stem cells that mimic a certain stage or event in embryonic development. Developing embryo models is founded on progress in reprogramming, merging, combining and arranging stem cells *in vitro**. The stem cells that make up an embryo model can be derived from an embryo (embryonic stem cells) or from an adult individual (induced stem cells). Currently, the most advanced embryo models are based on cells from mice, although increasingly complex embryo models are also being developed from human cells.

Types of embryo models

Various types of embryo models differ from each other, for instance in terms of the types of cells used, the aspects of embryonic development they are intended to mimic and their capacity for further development. According to the International Society for Stem Cell Research (ISSCR), one fundamental distinction is that between non-integrated and integrated embryo models.[1]

Non-integrated embryo models

Non-integrated embryo models mimic some, but not all, aspects of the early embryo. They generally lack what are known as extraembryonic cells, which are essential for the continuing development of the embryo but do not form part of the embryo itself. They therefore do not have the potential to develop further.[2] One type of non-integrated embryo model is gastruloids, which aim to mimic various aspects of gastrulation – the process through which the body's axes are defined and formation of different organs is initiated.[3] Another example is neuruloids, which mimic the first stages in

* The term in vitro ("in glass") refers to cells, microorganisms or biomolecules that exist outside of their normal biological context, usually in a laboratory environment.

The "In brief" series of publications highlights ethical and societal aspects of a particular topic.

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the formation of the nervous system[4], and PASE (post-implantation amniotic sac embryoids), which mimic events associated with the development of the amniotic sac[5]. In the near future, the development of many more types of non-integrated embryo models is expected, representing a number of different events during the initial months of embryonic development.[6]

Integrated embryo models

Integrated embryo models are intended to represent embryonic development as a whole. They include extraembryonic cells and can become so complex as to be capable of developing further when cultivated *in vitro*.[7] One type of integrated embryo models is blastoids (see fact box), which mimic the final stage of development before the embryo attaches to the uterus (implantation). So far, mouse, monkey and human blastoids have been developed.[8] For mice, integrated embryo models have also been created that mimic several post-implantation stages of development, including gastrulation and the foundation of various organ systems such as the heart, brain/nervous system and gut (ETX/sEmbryos).[9] Human integrated embryo models capable of representing different post-implantation stages are expected to be developed in the not-too-distant future.[10]

Theoretically, integrated embryo models could be created that have the potential to produce viable embryos capable of developing further into an individual. In order to achieve this, a number of significant technical and biological barriers must be overcome. Even so, it is predicted that it may eventually be possible to produce embryo models with the potential to proceed further into later stages of development.[11]

Other terms for embryo models

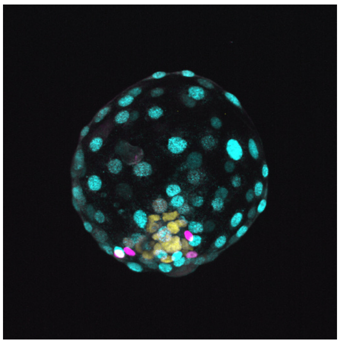
In scientific literature, embryo models are also called stem cell-based embryo models, embryoids, synthetic embryos, artificial embryos, synthetic embryo systems (SES), embryo-like structures (ELS) and synthetic human entities with embryo-like features (SHEEF). "Embryo models" is the term used by the International Society for Stem Cell Research (ISSCR).

Blastoids

The blastocyst is the final stage before the embryo attaches to (implants in) the uterus (see illustration on p. 3). The blastocyst contains cells that produce both what will become the foetus and extraembryonic structures such as the placenta. Researchers have succeeded in getting cultured stem cells to organise themselves into structures that resemble blastocysts and contain the same cell types as these, known as blastoids. Mouse and monkey blastoids have been successfully implanted in the uterus (though they did not continue to develop)[12], while it has been shown that human blastoids can attach to endometrial cells in vitro[13].

Research on early human development – opportunities and constraints

The potential benefits of research on early human development are numerous. Humans have an unusually high level of early miscarriages compared with other mammals. More knowledge about early embryonic development can provide insights into the causes of early miscarriages and fertility problems and contribute in the long term to the development of new infertility treatments. Other potential benefits are understanding the causes of diseases caused by early embryonic development disorders and developing effective treatments. Knowledge of how cells are differentiated and organs are created could also be used in regenerative medicine to replace or restore damaged tissue and, ultimately, enable the production of synthetic organs.



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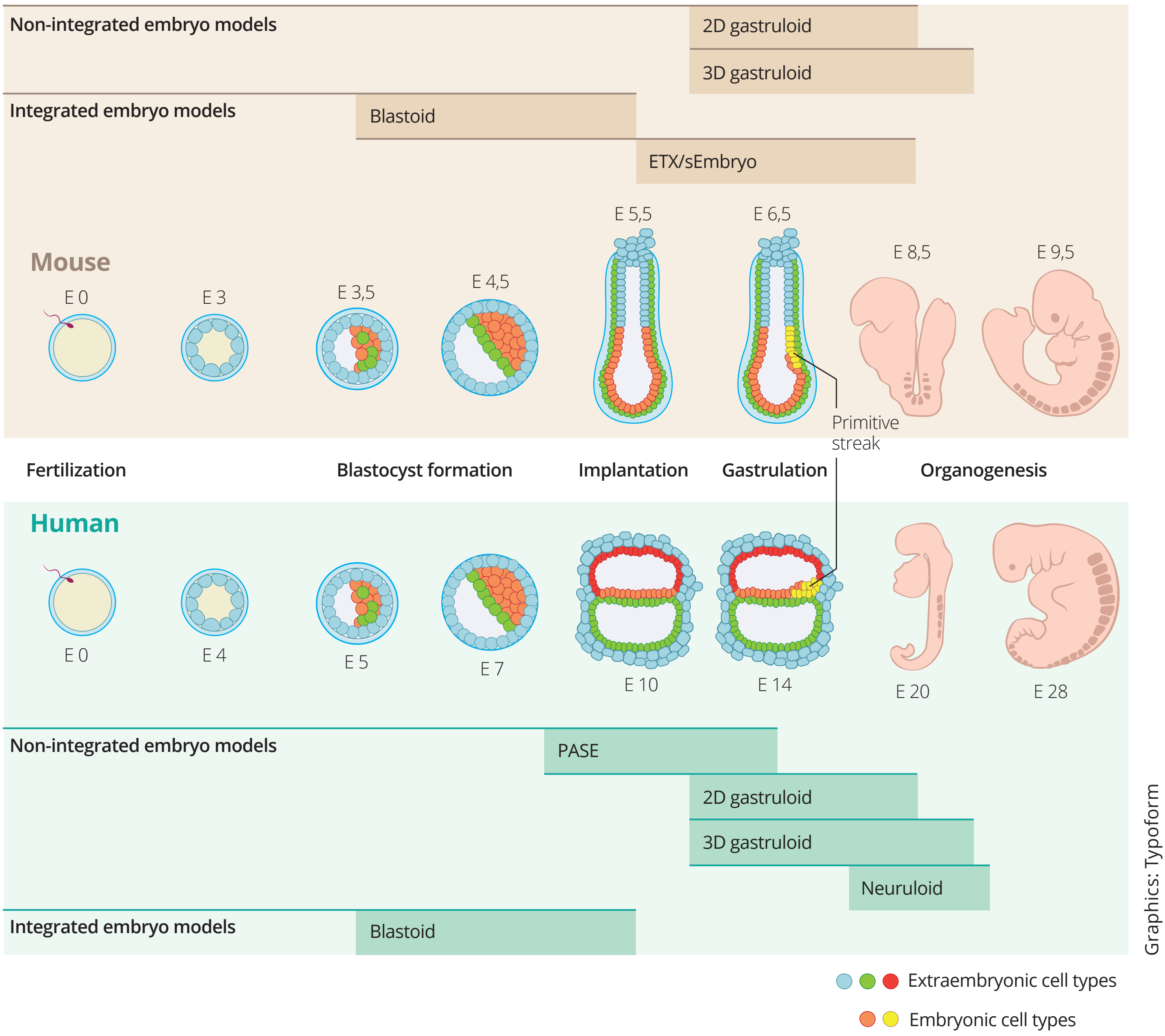
Human blastoid. Blastoids generate different cell types analogous to cell types found in embryos at the corresponding developmental stage. Yellow cells correspond to embryonic cells while magenta and cyan coloured cells correspond to extraembryonic cells.

Valuable knowledge can be obtained through studies on the embryos of other mammals. However, studies have shown that embryonic development differs in many respects between humans and other species, including non-human primates.[14] This means that animal studies cannot completely replace studies on human embryos. At the same time, research on human embryos raises ethical questions, associated in particular with the issue of their moral status (see fact box on p. 4). Research on human embryos is, as a rule, subject to restrictions. Most countries that allow research on human embryos apply the 14-day rule (see fact box on p. 5). The rule states that research on human embryos may last for no more than 14 days after fertilisation. This means that developments beyond day 14 – a period that includes formation of the most important organ systems – are unavailable for research on human embryos.

Many countries prohibit the production of human embryos solely for research purposes and only allow research on embryos that have been



Embryonic development in mouse and human. Different types of embryo models mimic different parts of this development. For monkeys, blastoids have been created that develop up to gastrulation, see reference 8.

left over from IVF treatment and been donated by IVF patients.[15] These embryos would otherwise have been destroyed and many countries therefore accept using them for research. One drawback is that donors have sought treatment for infertility issues and the embryos that are left over are those considered to be of the lowest quality. Another disadvantage is that the availability of such embryos is limited.

Human embryo models in research, development and treatment

Research on embryo models developed from human stem cells can contribute to knowledge of early human development and the causes of disease and infertility.[16] Unlike embryos left over from IVF treatment, embryo models can be produced in large quantities. Another advantage is that embryo models produced using cells from the same stem cell lineage are genetically identical, while embryos left over from IVF have a unique DNA. Embryo models can also be genetically and physically modified in a way that can be difficult in human embryos. Genetically identical embryo models modified in different ways could be used to examine the impact of genetic or environmental factors on embryonic development and the risk of miscarriage, and to discover and test new drug candidates.[17]

The early post-implantation period is a particularly difficult period of embryonic development to study, because the embryo is still very small while at the same time embedded in the uterine tissue. Human embryo models that mimic different stages and events in the post-implantation period and can be cultivated outside of the uterus (*in vitro)* could help to provide insights into this important period of embryonic development.[18]

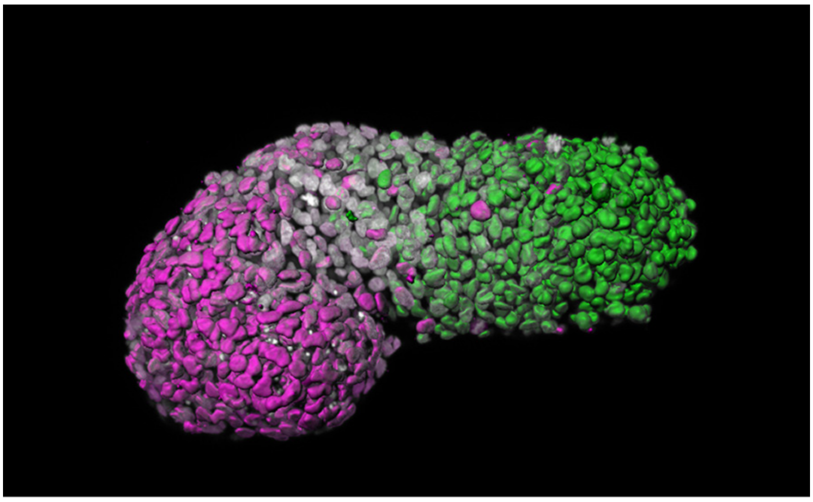
The moral status of the human embryo

Someone or something having moral status means that we are obliged to consider its interests, not because it benefits anyone else, but because these interests have a moral weight in themselves.[19] Some consider moral status to be something one has in full or not at all, while others believe that different entities can have moral status to a greater or lesser extent.[20]

There are different views as to whether the early human embryo has moral status, how this status potentially changes as the embryo develops, and which of the embryo's characteristic(s) provide(s) the basis for this moral status.[21] Even those who find that human embryos have moral status can have different views on what their interests are, and thus how they may be treated, at different stages of development.

Although the view of the human embryo's moral status varies, there is a broad perception that the human embryo, in its capacity of the origin of human life, merits special protection and that this must be weighed against the value of knowledge about early development of human life. This means that research on human embryos needs to be subject to restrictions that do not apply to other biological materials of human origin.

Besides providing an alternative to human embryos in research into early human development, it has also been proposed that advanced embryo models could eventually be used to produce cells and tissues for transplants.[22]



N. Moris/University of Cambridge

Human gastruloid

Ethical aspects

Reduced need for research on human embryos

It is hoped that embryo models could partially replace human embryos in research into early human development, thereby offering an alternative that avoids the ethical, legal and social questions arising from research on human embryos. Not least, there are hopes that embryo models will open up new opportunities for research into development after day 14, when research on human embryos is not permitted in many countries.[23]

However, embryo models cannot entirely replace human embryos in research, because models need to be compared with human embryos to ensure that they produce reliable results.[24] This also applies to models that mimic stages of development occurring later than day 14. The need to be able to validate such embryo models is one of several arguments that have been expressed in favour of permitting research on human embryos for more than 14 days, now that this appears to be technically feasible (see fact box).[25]

Reduced need for animal research

An alternative to research on human embryos could be research on animal embryos, particularly embryos from non-human primates. However, such research raises its own ethical questions concerning to the welfare of the laboratory animals from which the embryos are derived. The possibility of research on human embryo models instead could reduce the need for animal research.

Ethical issues raised by embryo models

There is an expectation that human embryo models, which have not been developed from fertilised ova but created from reprogrammed stem cells, will enable studying early human development without having to consider the ethical and legal constraints that apply to human embryos. There is inherent tension here, however. On the one hand, embryo models are assumed to be sufficiently different from human embryos in essential respects so as not to be subject to the restrictions applying to the latter. On the other hand, they need to sufficiently resemble human embryos to enable generating results that are valid for those too.[30] As increasingly advanced human embryo models are developed, it might become more and more difficult to avoid the ethical issues presented by research on (natural) human embryos. Some embryo

The 14-day rule

According to the 14-day rule, research on human embryos may last up to a maximum of 14 days after fertilisation, or until the appearance of the primitive streak, whichever occurs first. The rule was first formulated in 1979 and has since been included in the legislation of many countries.[26]

The primitive streak, which begins to form after approximately 14 days, is the first stage in the formation of the various organs, including the nervous system. One argument for setting the limit at 14 days was that the risk of causing pain to the embryo could thus be ruled out. Another argument was that after the emergence of the primitive streak, the embryo can no longer divide and form identical twins. Only at this point can the embryo thus be regarded as a distinct individual.[27]

Most people hold that the rule should be seen as a pragmatic compromise between conflicting moral views, rather than an expression of the view that the embryo, at the very point of 14 days, gains moral status. The purpose of the rule has been to enable important research and, at the same time, to show respect for the existence of different moral views on the origin of life.[28]

The rule has long been of limited practical importance, as it has not been possible to cultivate human embryos for as long as two weeks. Recently, however, methods have been developed that allow cultivation up to at least day 13/14, when the studies have been discontinued.[29]

"Embryo models need to be compared with human embryos to ensure that they produce reliable results."

models could exhibit characteristics that make them require similar moral considerations as human embryos. In that case, there may be a need to regulate how they may be preserved and researched.

The 14-day rule is not suited to embryo models

For human embryos, the 14-day rule governs which research is permitted. In many bodies of legislation, regulation proceeds on the basis of zygotes (fertilised ova) and embryo models thus fall outside of the scope of the rule by definition.[31] The rule is also difficult to apply to embryo models. An embryo model is created directly to mimic a particular stage of development, and a model younger than 14 days can mimic a stage that occurs later than 14 days in an embryo. Rules stipulating that certain stages of development – such as the emergence of the primitive streak – must not be surpassed do not work for embryo models either, because models that are created to mimic later stages of development can 'bypass' the earlier stages.[32]

Alternative limits

The difficulties in applying the 14-day rule to embryo models have led some to call for regulations governing embryo models that are not based on age, but that rather proceed directly on the basis of the characteristics that are considered morally relevant and that can make certain embryo models require special protection. The next step will be to determine the biological structures that provide the basis for these characteristics and ensure that research on models that exhibit these biological traits is appropriately regulated.[33]

In one view, it is its potential to develop into a new human that gives the human embryo special status compared to other human cells and tissues.[34] For many, it is the very possibility that certain embryo models may be capable of developing further that causes concern.[35] According to ISSCR, research on integrated embryo models, which may be capable of developing further, should be examined in a special review process (see fact box). However, it has been pointed out that it is difficult to determine definitely the development potential of an embryo model without implanting it in a uterus, which most consider to be ruled out on ethical grounds.[36]

Besides development potential, an important basis for moral status is often considered to be sentience. One argument in favour of setting the limit for research on human embryos at 14 days has been to rule out the possibility of the embryo potentially feeling pain, since development of the nervous system has not started at that point.[37] It has been pointed out that it may soon be possible to produce human embryo models that develop nervous systems. Since such embryo models might potentially have the capacity to feel pain, research on them may raise ethical issues similar to those concerning research on human embryos and may therefore require regulation.[38]

"For many, it is the very possibility that certain embryo models may be capable of developing further that causes concern."

ISSCR's guidelines for research on embryo models

The International Society for Stem Cell Research (ISSCR) has recently updated its guidelines for stem cell research, including research on different types of embryo models.[39] According to the guidelines, research on non-integrated embryo models does not require any further ethical examination beyond customary ethical review. Research on integrated embryo models, however, should be examined in a specialized scientific and ethical review process. According to ISSCR, integrated embryo models should be maintained in culture for the minimum time necessary to achieve the scientific objective. The guidelines do not permit the transfer of human embryo models to the uterus of animals or humans, as there is broad international consensus that this lacks scientific rationale and is unethical.

According to another outlook, moral status is determined not only by inherent characteristics of an entity such as development potential and ability to feel pain, but also by biological and social relations with its surroundings. An embryo that has been left over from IVF, which will never become a person and will eventually be destroyed, has different relational characteristics than an embryo that is intended to be implanted and result in a pregnancy. For that reason, the moral status of the former embryo may be lower than that of the latter.[40] Similarly, an embryo model, which has the sole purpose of being used for research, may be perceived as having lower protective interests than a human embryo with the same inherent characteristics.

View on humanity

One way of avoiding the ethical difficulties could be to develop embryo models that lack the very characteristics that can make them require special protection. These could be models that have all the organ systems apart from the brain and nervous system, and which thus cannot feel pain or develop consciousness. One perceivable objection could be that this would amount to unacceptable objectification of human beings. The problem here is not primarily the effects for the embryo models, but how what we do with them affects our view on humanity, and hence ourselves.[41] This objection could also be raised against intentions to use embryo models as a source of cells and tissues for transplants.

Public confidence i research

Research on human embryos houses a conflict between the value of knowledge of early human development, and the need for special protection of the human embryo that many consider essential. The 14-day rule is considered to have been important in balancing these interests and enabling research into the beginnings of human life while preserving public confidence in research.[42] If human embryo models exhibit characteristics that make them comparable with human embryos from an ethical angle, without the existence of regulations that appropriately safeguard their protection, public confidence in research may be undermined.

Conclusion

Human embryo models provide an opportunity to gain knowledge of early human development that could have major implications for human health and well-being, while avoiding the ethical difficulties presented by research on human embryos. Embryo models also open up for new types of studies that cannot be conducted on human embryos. However, as increasingly advanced embryo models are developed, the question may have to be raised as to whether certain human embryo models might have properties that raises ethical issues similar to those raised by research on human embryos. This in turn raises the question of how to establish a regulatory framework that balances different interests such as the need for knowledge, respect for varying moral perspectives on the origin of life and preservation of public confidence in research.

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