第126回　特定胚等研究専門委員会	資料126-３
令和７年６月３日	

ヒト胚モデル研究の倫理的課題と規制の動向

京都大学iPS細胞研究所 上廣（うえひろ）倫理研究部門
京都大学高等研究院 ヒト生物学高等研究拠点
藤田みさお

受精後14日相当のヒト胚モデル作製成功

The Guardian

Wed 14 Jun 2023

合成胚

Synthetic human embryos created in groundbreaking advance

https://www.theguardian.com/science/2023/jun/14/synthetic-human-embryos-created-in-groundbreaking-advance

The ISSCR Statement on New Research with Embryo Models

PRESS RELEASE

The ISSCR supports research with embryo models derived from human pluripotent stem cells that is conducted with scientific and ethical rigor. ISSCR encourages researchers to continue to follow the ISSCR Guidelines for Stem Cell Research and Clinical Translation when considering research in this emerging area. Recent work presented at the ISSCR 2023 Annual Meeting in Boston, USA this month and additional research posted online as preprints shortly thereafter highlights the rapid pace of progress in the development of stem cell-based embryo models. To aid public understanding of this progress and assist the media in accurate reporting, the ISSCR provides the following information.

...yo models are organized three-dimensional structures derived from pluripotent stem cells that mimic the developmental processes that occur in early human embryos. Recent advances involve the growth of integrated ...dels which contain both embryonic and extra-embryonic structures, from embryonic stem cells or induced pluripotent stem cells in laboratory dishes. Use of these models allows experimental modeling of the early ...mbryonic development that occur in the first few weeks of pregnancy. They can facilitate understanding of early pregnancy loss and placental failure, and help researchers gain basic knowledge of the early ...mental origins of congenital defects in the heart, nervous system, and other organs.

...ke some recent media reports describing this research, the ISSCR advises against using the term "synthetic embryo" to describe embryo models, because it is inaccurate and can create confusion. Integrated embryo models ...either synthetic nor embryos. While these models can replicate aspects of the early-stage development of human embryos, they cannot and will not develop to the equivalent of postnatal stage humans. Further, the ISSCR ...lines prohibit the transfer of any embryo model to the uterus of a human or an animal.

ISSCR's guidelines recommend that research with integrated embryo models can only proceed with a compelling scientific rationale and after careful review and approval by a specialized scientific and ethical oversight process. Integrated embryo models should also be maintained in culture for the minimum time necessary to achieve the scientific objective. And researchers must also comply with local laws and policies. Adherence to these guidelines ensures that stem cell research is ethical, practical, and appropriate.

The continued development of embryo models represents a step toward better understanding the earliest stages of human development and the developmental defects that can occur at this stage. For more information, consider reviewing Toward Guidelines for Research on Human Embryo Models Formed from Stem Cells and the SnapShot: Embryo models, both published in *Stem Cell Reports*, as well as the ISSCR Guidelines.

統合胚モデルは、合成でも胚でもない。これらのモデルは、ヒト胚の初期段階の発生を再現することはできるが、生後段階のヒトと同等の発生をすることはできないし、することもない。

June 26, 2023
https://www.isscr.org/isscr-news/isscr-statement-on-new-research-with-embryo-models

国際幹細胞学会による胚モデルの分類

- 非統合胚モデル（Non-integrated stem cell-based embryo model）
  - 胚外膜を含まない等、胚の一部の発生を再現するモデル
  - 基礎研究としての適切な審査のみで実施可能
    - ガストロイド

- 統合胚モデル（Integrated stem cell-based embryo model）
  - 胚外膜を含む胚全体の統合された発生を再現するモデル
  - ヒト胚や幹細胞研究に関する専門的監視プロセスが必要
    - ブラストイド

国際幹細胞学会「幹細胞研究・臨床応用に関するガイドライン」2021年

ヒト胚モデル研究の倫理的課題

科学的意義

- ヒト初期胚の発生過程を模倣
- 不妊症、不育症、先天性疾患の解明及び治療への貢献
- ヒト胚の代替手段

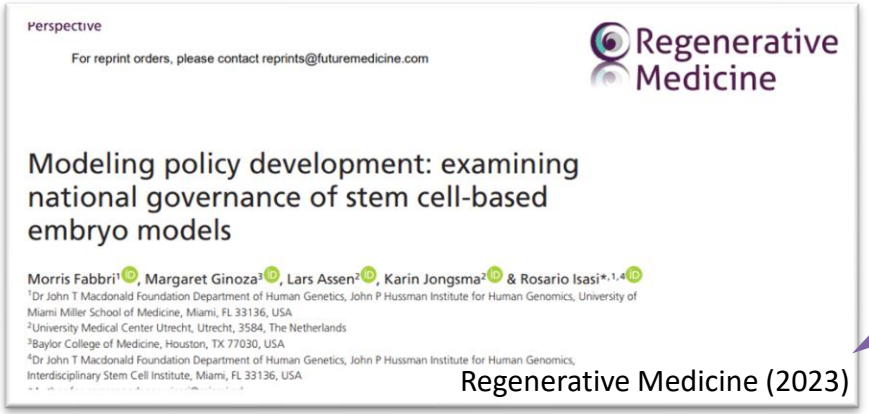
懸念や課題

- ヒト胚に酷似していく可能性
- 法規制上の曖昧な位置づけ
- 国内既存指針間のギャップ
- 研究（培養）期間の設定

本日はこの三点に加え、海外の動向を紹介します。

ヒト胚モデルに特化した規制はない

ほぼ



Perspective

For reprint orders, please contact reprints@futuremedicine.com

Regenerative Medicine

Modeling policy development: examining national governance of stem cell-based embryo models

Morris Fabbri[1], Margaret Ginoza[3], Lars Assen[2], Karin Jongsma[2] & Rosario Isasi*[,1,4]

[1]Dr John T Macdonald Foundation Department of Human Genetics, John P Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL 33136, USA
[2]University Medical Center Utrecht, Utrecht, 3584, The Netherlands
[3]Baylor College of Medicine, Houston, TX 77030, USA
[4]Dr John T Macdonald Foundation Department of Human Genetics, John P Hussman Institute for Human Genomics, Interdisciplinary Stem Cell Institute, Miami, FL 33136, USA

Regenerative Medicine (2023)

2021年に改定されたフランスの生命倫理法は..ヒト多能性幹細胞を用いた胚モデル（SCB-EMs: Stem Cell-Based Embryo Models）研究を生物医学庁に申告することを研究者に義務付け...違反した場合の刑事罰を初めて示唆したものである。

Review

For reprint orders, please contact: reprints@futuremedicine.com

Regenerative Medicine

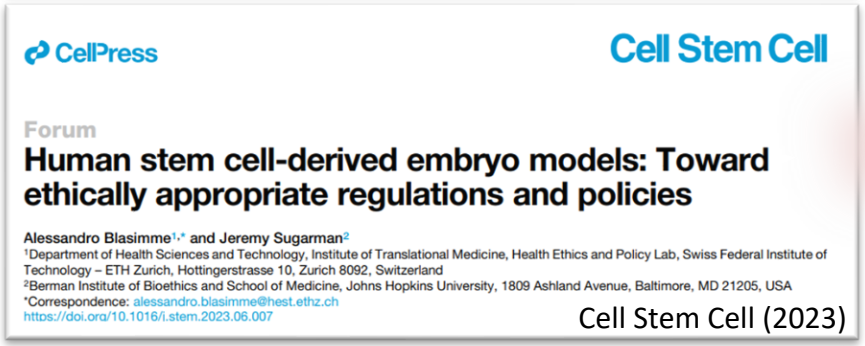
National human embryo and embryoid research policies: a survey of 22 top research-intensive countries

Kirstin RW Matthews*[,1] & Daniel Morali[1]

[1]Baker Institute Center for Health & Biosciences; Rice University; Houston, TX 77005, USA

Regenerative Medicine (2020)

ほとんどの国の法律やガイドラインは、胚モデル（embryoid）研究に関して曖昧で、何が許され、何が許されないのか不明確なままである。



CellPress

Cell Stem Cell

Forum

Human stem cell-derived embryo models: Toward ethically appropriate regulations and policies

Alessandro Blasimme[1,*] and Jeremy Sugarman[2]

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https://doi.org/10.1016/j.stem.2023.06.007

Cell Stem Cell (2023)

ヒト胚モデル研究は、既存の法規制の枠組みの中で行われている

ヒト胚モデル＝？

- 既存の法規制はヒト胚モデルのような新しい研究を想定していない
- ヒト胚の定義は各国の法規制によって異なる
- 既存の法規制におけるヒト胚モデルの位置付けは国毎に異なる

Table 2. Definitions and restrictions to human embryoid research.

Country	Definition	Embryoid restriction	Ref.
Australia	Human embryo means a discrete entity that has arisen from either: (a) the first mitotic division when fertilisation of a human oocyte by a human sperm is complete; or (b) any other process that initiates organised development of a biological entity with a human nuclear genome or altered human nuclear genome that has the potential to develop up to, or beyond, the stage at which the primitive streak appears; and has not yet reached 8 weeks of development science the first mitotic division	Yes	[66–68]
Austria	Fertilized oocytes and cells derived from them shall be considered viable cells. Developmentally capable cells may not be used for purposes other than medically assisted reproductive†	Yes	[52]
Belgium	Embryo: the cell or the organic set of cells capable, as they develop, of becoming a human being†	Yes	[63]
Brazil	NA	No	[41–43]
Canada	Embryo means an a human organism during the first 56 days of its development following fertilization or creation, excluding any time during which its development has been suspended, and includes any cell derived from such an organism that is used for the purpose of creating a human being. (Assisted Human Reproduction Act)	No	[69,70,74,75]
China	NA	No	[65,78]
France	NA	No	[47,48]
Germany	Embryo is any totipotent cell which, if the necessary conditions are met, is able to divide and develop into an individual. (2002 Act) For the purpose of this act, the embryo is the fertilized, developable human oocyte from the time of nuclear fusion, and any totipotent cell taken from an embryo, which, if the necessary conditions are met, can be divided and become an individual.† (1990 Act)	Yes	[53–55]
India	Human embryo: It is the development stage from [the] time of fertilization until the end of the eight week of gestation, after which it is known as a fetus. The term 'early embryo' covers stages of development up to the appearance of [the] primitive streak i.e., until 14 days after fertilization	No	[79]
Israel	NA	No	[44–46]
Italy	NA	No	[58]
Japan	Embryo- a cell (except for a Germ Cell) or a cell group which has the potential to grow into an individual through the process of development *in utero* of a human or an animal and remains at a stage prior to placental formation†	Yes	[65,76,77]
Netherlands	Embryo: cell or set of cells with the capacity to grow into a human†	No	[80]
Russia	The Law establishes…the inadmissibility of creating a human embryo for the production of biomedical cell products; the inadmissibility of using biological material obtained by suspension or interruption of the development of a human embryo or fetus for the development, production and use of biomedical cell products	Yes	[59]
South Korea	EMBRYO: a fertilized oocyte (or segmented cells) from the moment of fertilization to the point of time at which all organs of the given organism have developed embryologically	No	[65,83]
Spain	Embryo is the stage of embryonic development from the moment the fertilized oocyte is implanted in the uterus until the onset of organogenesis, which ends at 56 days post fertilization. Pre-embryo is an *in vitro* embryo from the fertilization of the oocyte through 14 days post fertilization†	No	[81,82]
Sweden	No 'embryo' definitions in the law, instead uses the term 'fertilized egg'†	No	[62]
Switzerland	Embryo means the offspring, from the fusion of the cell nuclei (karyogamy) to the completion of organ development	No	[60]
Taiwan‡	EMBRYO: Human embryos for research (hereafter referred to as embryos for research): refer to the embryonic tissue that have been available for research in accordance with these regulations and have not been divided for more than 14 days and the primitive streak has not appeared (Human Embryo and Embryonic Stem Cell Act). Embryo: refers to a fertilized oocyte that has undergone division for less than eight weeks (Assisted Reproduction Act)	No	[65,71–73]
Turkey	NA	No	[56,57]
United Kingdom	Embryo means a live human embryo and does not include human admixed embryo (as defined by section 4A[6]), and references to the embryo include an egg that is in the process of fertilization or is undergoing any other process capable of resulting in an embryo	No	[13,61]
United States	The term 'human embryo or embryos' includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning or any other means from one or more human gametes or human diploid cells	Yes§	[13,50]

Matthews & Morali, (2020) Regenerative Medicine

オーストラリア：統合胚モデル＝ヒト胚

Article

Modelling human blastocysts by reprogramming fibroblasts into iBlastoids

https://doi.org/10.1038/s41586-021-03372-y
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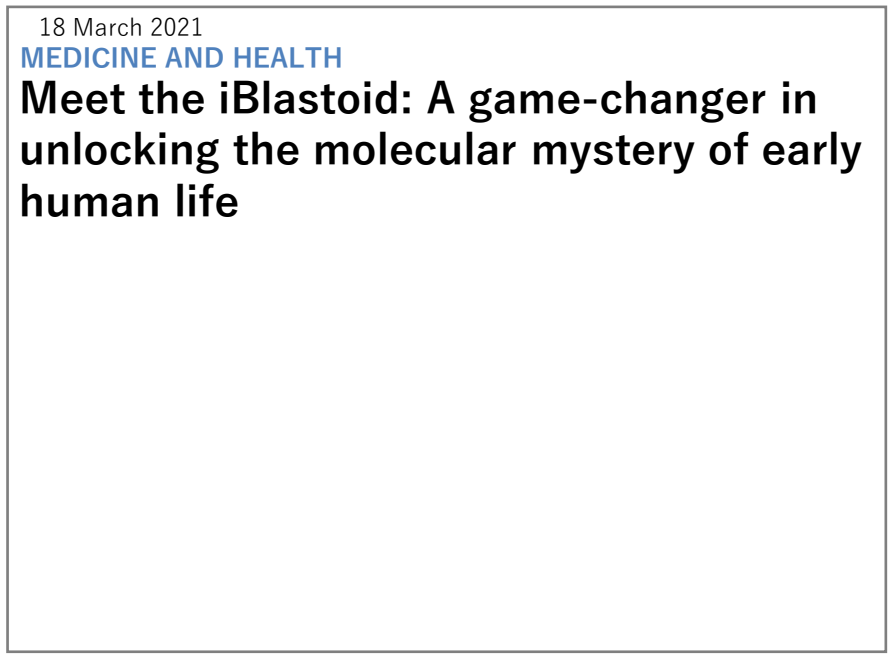


18 March 2021

MEDICINE AND HEALTH

Meet the iBlastoid: A game-changer in unlocking the molecular mystery of early human life

- Research Involving Human Embryos Act (2002)
  - ヒト胚とは、以下いずれかから発生した個別の実体

  a) ヒトの精子によるヒトの卵子の受精が完了したときの最初の有糸分裂 、または

  b) ヒト核ゲノムまたは改変ヒト核ゲノムを有する生物学的実体の組織的発生を開始するその他の過程であって、原始線条が現れる段階まで、またはそれを超えて発生する可能性を有するもの

  かつ、最初の有糸分裂から8週間を経過していないもの

規制当局は、iBlastoidsをヒト胚と同等とみなし、研究者と大学に法に基づくライセンスの取得を要求した。

https://lens.monash.edu/@medicine-health/2021/03/18/1382960/meet-the-iblastoid-a-game-changer-in-unlocking-the-molecular-mystery-of-early-human-life

https://www.nhmrc.gov.au/about-us/news-centre/nhmrc-statement-iblastoids

日本：統合胚モデル≠ヒト胚

- ヒトに関するクローン技術等の規制に関する法律（2000）
  - **胚** 一の細胞（生殖細胞を除く。）又は細胞群であって、そのまま人又は動物の胎内において発生の過程を経ることにより一の個体に成長する可能性のあるもののうち、胎盤の形成を開始する前のものをいう。
  - **ヒト受精胚** ヒトの精子とヒトの未受精卵との受精により生ずる胚（当該胚が一回以上分割されることにより順次生ずるそれぞれの胚であって、ヒト胚分割胚でないものを含む。）をいう。
  - **人クローン胚** ヒトの体細胞であって核を有するものがヒト除核卵と融合することにより生ずる胚（当該胚が一回以上分割されることにより順次生ずるそれぞれの胚を含む。）をいう。

既存指針間のギャップによる課題

- iPS 細胞由来の胚モデル：
  →人を対象とする生命科学・医学系研究に関する倫理指針
- ES 細胞由来の 胚モデル：
  →ヒトES 細胞の使用に関する指針

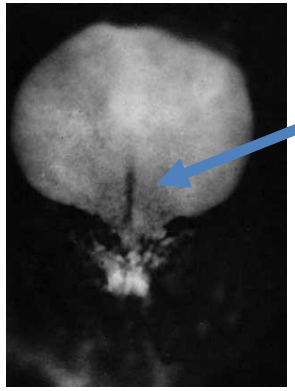
倫理審査が必要な場合と必要でない場合？

国への届出が必要な場合と必要でない場合？

ヒト胚モデルを用いる研究のためだけに指針を新規に作成することは、無用に指針の種類を増やすこととなることから、規制方針が類似する「ヒトｉＰＳ細胞又はヒト組織幹細胞からの生殖細胞の作成を行う研究に関する指針」、「ヒトＥＳ細胞の使用に関する指針」、「ヒトＥＳ細胞の樹立に関する指針」、又は「ヒトＥＳ細胞の分配機関に関する指針」といった既存の指針を改正し、ヒト胚モデルを用いた研究に適用することが適切と考えられる。

14日ルール

- 受精後14日（又は原始線条の形成）以降、胚を培養してはならない
  - 1979 US Ethics Advisory Board
  - 1984 UK Warnock Committee



原始線条
「胚が個体としての発生を開始する出発点」
Warnock (1985) A Question of Life

- 胚盤内の最初の特徴的変化
- 一卵性双生児となる限界

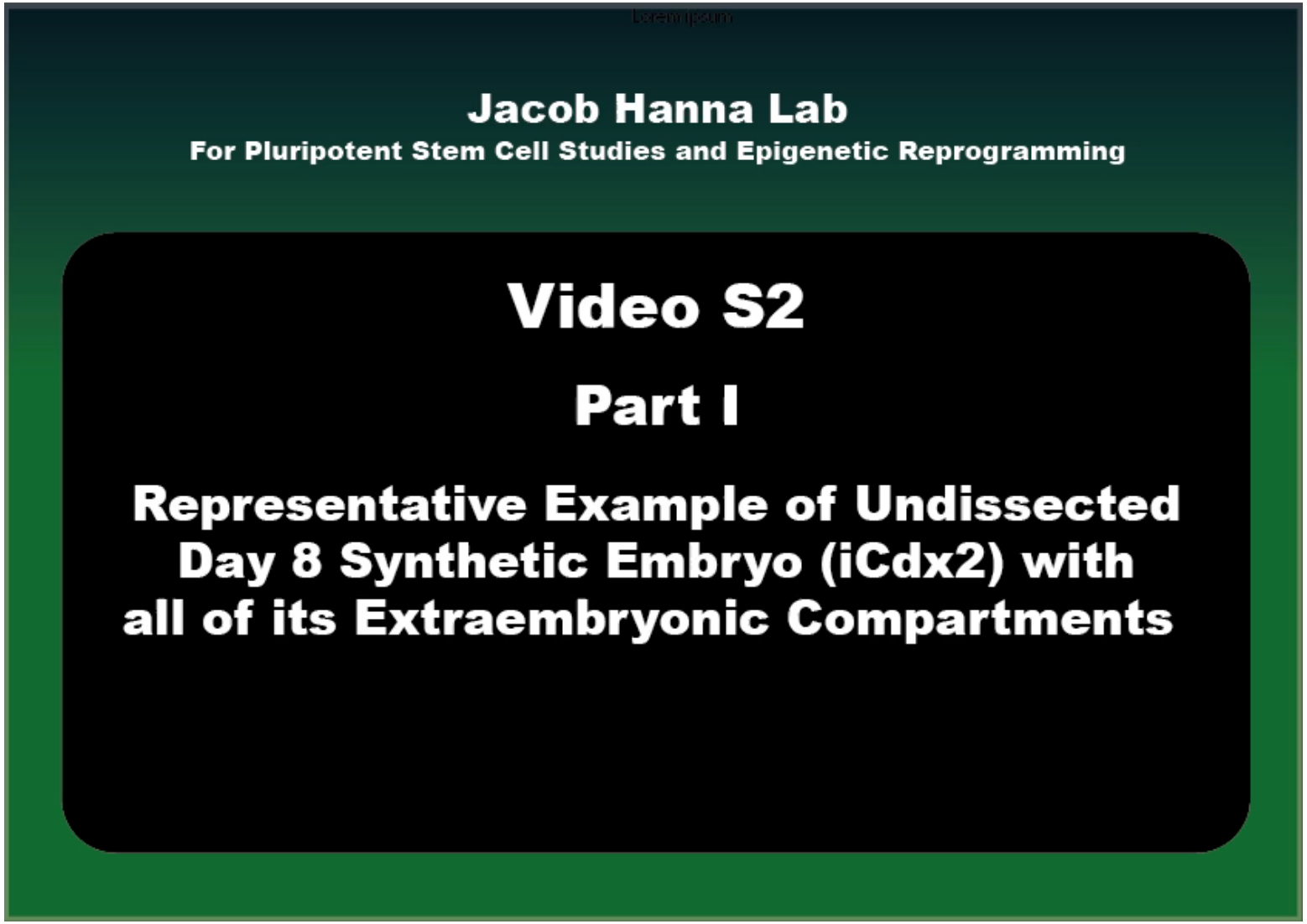
Kyoto Collection
(https://embryology.med.unsw.edu.au/embryology/index.php/Carnegie_stage_7)

INTERNATIONAL AGREEMENT

（14日ルールを採用する国を色分けした世界地図）

Hyun, et al. (2016) Nature

マウス胚モデル研究の進化



Tarazi et al., (2022) *Cell*

ヒト胎児モデル？

（顔写真）

Jacob Hanna

https://hannalabweb.weizmann.ac.il/?page_id=69

RenewalBio

https://www.renewal.bio/

MIT Technology Review

This startup wants to copy you into an embryo for organ harvesting

August 4, 2022

https://www.technologyreview.com/2022/08/04/1056633/startup-wants-copy-you-embryo-organ-harvesting/

培養期間の設定

- 「14日ルール」は考えなくてよい
- 培養期間に制限が必要というコンセンサスはできつつも対応は多様
- 28日まで培養可とする国も
  - 通常の発生を遂げず科学的意義がない
  - 他のモデルで代替可能
  - 胎児組織の研究利用が可能

Table 1 International comparisons of regulation on human embryos and SCBEMs

Country	Definitions of Human SCBEM vs embryo	Time limit on *in vitro* maintenance of human SCBEMs
Australia	Integrated SCBEMs fall within the definition of a human embryo.[18,140]	The Embryo Research Licensing Committee (ERLC) of the National Health and Medical Research Council restricts the maintenance of integrated SCBEMs in culture to morphological and/or molecular stages equivalent to a normally developing human embryo 14 days post fertilisation.[18,140,141]
Austria	There is no explicit regulation of SCBEMs, and research on human embryos is not practised. Research using hESCs derived outside Austrian territory is permitted.[142,143]	There is no explicit regulation of SCBEMs but the ethics committee of the Austrian Academy of Sciences has delivered licenses on a case-by-case basis.[45,142,143]
France	In September 2023, the Agence de la biomédecine's Conseil d'orientation proposed that SCBEMs cannot be considered embryos due to differences in their origin and intentionality.[144]	The Conseil proposed to allow the *in vitro* maintenance of integrated SCBEMs up to 28 days.[144]
Netherlands	In October 2023, the Health Council of Netherlands proposed that integrated SCBEMs should qualify for the same protection as human embryos.[130]	The Council proposed to allow the *in vitro* maintenance of integrated SCBEMs up to 28 days.[130]
UK (including devolved nations)	As of February 2024, there is no explicit regulation of SCBEMs.	As of February 2024, there is no explicit regulation of SCBEMs.

These countries were chosen as examples to depict the differences in regulation of SCBEMs.

UK Parliament POST (2024)
https://researchbriefings.files.parliament.uk/documents/POST-PN-0716/POST-PN-0716.pdf

国際幹細胞学会ガイドライン（2021年改定）

カテゴリー1
基礎研究に必要な審査のみ

非統合胚モデル

ヒト幹細胞から胚モデルを作製する基礎研究（胚体外膜を含む胚全体の統合された発生を説明する意図のないもの）

CATEGORY 1	CATEGORY 2	CATEGORY 3
1A **Exempt from review by a specialized oversight process** • Most *in vitro* pluripotent stem cell research • Most *in vitro* organoid research • Transfer of human stem cells into postnatal animal hosts	2 **Reviewed by a specialized oversight process** • Procurement of embryos, or gametes for the creation of embryos, for *in vitro* research • Derivation of cell lines from human embryos • Genetic alteration of embryos or gametes • *In vitro* culture of human embryos for research until the formation of the primitive streak or 14 days from fertilization, whichever occurs first • Human cells transplanted into nonhuman embryos that are gestated in a non-human uterus • Integrated stem cell-based embryo models • Transferring human embryos following MRT into a human uterus	3A **Not allowed; currently unsafe** • Heritable genome editing • Transferring mtDNA-modified (not including MRT) embryos into a uterus • Using gametes differentiated from human stem cells for reproduction
1B **Reportable, but not typically reviewed by a specialized oversight process** • Non-integrated stem cell-based embryo models • *In vitro* culture of chimeric embryos (human cells into non-human embryos) • *In vitro* gametogenesis without fertilization or generation of embryos		3B **Not allowed: lacks compelling scientific rationale or is ethically concerning** • Gestating human stem cell-based embryo models • Human reproductive cloning • Breeding human-animal chimeras where there may be human germ cells. • Transferring human-animal chimeric embryo(s) to a human or ape uterus • Transferring human embryo(s), irrespective of origins, to an animal uterus

カテゴリー2
ヒト胚・幹細胞に関連する専門的な審査が必要

統合胚モデル

幹細胞を用いた胚モデル（胚体外膜を含む胚全体の統合された発生を説明するもの）を作製する（培養は科学的目的の達成に必要な最短期間）

カテゴリー3
禁止

幹細胞を用いたヒト胚モデルの動物/ヒト胎内移植

ヒト胚モデル研究に関するガイドラインのみ改定し、近日中に公開の予定。

改定予定とされる内容

- （胚体外膜の有無に限らず）3D構造を持つ全てのヒト胚モデル
  - カテゴリー2（専門的審査が必要）
  - 審査の厳格さ、培養期間は当該モデルの複雑さによって決定
- バイオプリントされた2Dの分化モデル
  - カテゴリー1B（専門委員会に報告可能）→1A（基礎研究に必要な審査のみ）
- トロフォブラストと卵黄嚢オルガノイド
  - カテゴリー1A
- 胎内移植（人・動物）/生存可能性を持つin vitroシステムでの培養
  - カテゴリー3（禁止）

https://www.progress.org.uk/event-review-isscr-embryo-models-working-group-summary-of-findings-and-recommendations/

ヒト幹細胞を用いた胚モデルの作製と使用に関する実施規定

Cambridge Reproduction と Progress Education Trust による約2年のプロジェクト
https://www.repro.cam.ac.uk/scbemcode

- 統合/非統合モデルを区別しない
- 専門的な審査が必要
- 研究目的に照らして最小限の培養期間を専門的審査で個別判断
- 人/動物の生殖器官への移植禁止
- 体外で成育可能な状態に発生させることの禁止
- 倫理審査申請・承認の登録と概要の公開を推奨

生倫調報告書：国際的動向と整合的

1. 「ヒトＥＳ細胞の使用に関する指針」等と同様の審査手続き（倫理審査委員会による審査、国への届出）を取ること
2. 許容されない研究（ヒト胎内や動物胎内への移植、ヒトの個体産生に繋がる研究）を規定すること
3. 個々の研究において研究計画書に科学的目的を達成するために必要な範囲で最小限の培養期間を設定し、倫理審査委員会で審査すること
4. 研究機関は研究成果の公開を行うこと。研究実施者は、あらゆる機会を利用して、研究に関する情報提供を行うとともに、国民の理解を深めるための普及啓発に努めること
5. ヒトｉＰＳ細胞等を由来とするヒト胚モデルについては「生命・医学系指針」に則ったＩＣを取得する又はオプトアウトの手続きを行うこと

生命倫理専門調査会「ヒト胚モデルの取扱いについて（中間まとめ）」令和6年11月7日

まとめ – なぜ規制が必要なのか

- ヒト胚モデルに関する課題の特徴
  - ヒト胚の模倣を目指す以上、研究の進展に伴い、将来ヒト胚モデルがヒト胚にさらに近づいてくことは論理的な帰結
  - 既存の規制ではヒト胚モデルの位置付けが明確でなかった

- **ヒト胚モデルに対する規制の明確化が求められる**
  - 規制の厳格さ：ヒト胚＞ヒト胚モデル＞ヒト（幹）細胞
  - 培養期間の制限を設けることはコンセンサスになりつつある
  - 多様なヒト胚モデル研究の可否、および研究目的に照らした研究（培養）期間を個別判断する場合、倫理委員会の役割が重要に