OSAKA UNIVERSITY

第1回
資料3

内閣府・生命倫理専門調査会
第１回「多能性幹細胞等からのヒト胚に類似した
構造の作成等に関する検討」に係る作業部会
2023年8月9日

ISSCR（国際幹細胞学会）等における embryo model に関する検討

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(Ethics Committee of the ISSCR, Chair)

国際幹細胞学会（ISSCR）による幹細胞研究・臨床応用に関するガイドライン
“ISSCR Guidelines for Stem Cell Research and Clinical Translation”

- ガイドライン制定の歴史
  - ➢2006年　ヒトES細胞研究について
  - ➢2008年　Translational researchについて
  - ➢2016年　上記2つを統合した。

- 2021年の改訂
  - ➢2019年から準備開始
  - ➢4つの領域（ワーキンググループ）に分けて検討
    1. Genome editing and MRT
    2. Embryos, embryo models and gametogenesis research
    3. Organoid and chimera research
    4. Regulatory, pricing, and access issues

ヒト胚研究の14day ruleについて

補足

原始線条の形成または14日間を超えてのヒト胚の培養

現在のところ、原始線条の形成や受精後14日を超えてヒト胚を培養することは技術的に不可能である。しかし、培養システムが進歩しているため、近い将来、可能となる見込みである。ヒトにおける原始線条、初期胚葉の形成、始原生殖細胞の形成を理解することは、不妊症、体外受精、妊娠損失、着床直後に生じる発生過程の障害に対する理解と治療法を向上させるために非常に重要である。

推奨2.2.2.1：ヒト胚培養の進歩と、このような研究が人間の健康と福祉を増進する有益な知見をもたらす可能性があることを踏まえ、ISSCRは、各国の科学アカデミー、学会、研究助成機関、規制当局に対し、このような研究を許可することによる科学的意義と社会的・倫理的課題について社会との議論をリードするよう求める。国や地域の法域内で社会から広範な支持が得られ、政策や規制によって容認されるならば、専門的な科学的・倫理的監視プロセスによって、科学的目的に照らし、14日を超えて培養することが必要かつ正当性を有するかどうかを検討し得る。その際、研究目的を達成するために使用する胚の数は、最小限であることが担保されなければならない。

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（日本語版）より
（下線や赤字、青字は講演者による） 他のスライドも同様

Embryos, embryo models and gametogenesis research

Stem Cell Reports
Perspective

ISSCR

OPEN ACCESS

Human embryo research, stem cell-derived embryo models and *in vitro* gametogenesis: Considerations leading to the revised ISSCR guidelines

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June 8, 2021

SUMMARY

The ISSCR Guidelines for Stem Cell Research and Clinical Translation were last revised in 2016. Since then, rapid progress has been made in research areas related to *in vitro* culture of human embryos, creation of stem cell-based embryo models, and *in vitro* gametogenesis. Therefore, a working group of international experts was convened to review the oversight process and provide an update to oversight process and the categories of research to be reviewed. A sub-committee of the Task Force to update the ISSCR Guidelines called Working Group 2, was specifically charged with reviewing this area and proposing appropriate revisions to the guidelines. The working group was chaired by Amander Clark and Janet Rossant, and included scientists with relevant expertise and ethicists involved in stem cell/embryo oversight issues (please refer to the author

ISSCR Stem Cell Report:
https://www.cell.com/stem-cell-reports/fulltext/S2213-6711(21)00259-9

ガイドラインで示された研究審査のカテゴリー

カテゴリー1	カテゴリー2	カテゴリー3
1A 専門的な監視プロセスによる審査が免除される ・in vitroで実施されるほとんどの多能性幹細胞研究 ・in vitroで実施されるほとんどのオルガノイド研究 ・出生後の動物宿主へのヒト幹細胞の移植	2 **専門的な監視プロセスによって審査される** ・in vitroでの研究のための胚、または胚を作るための配偶子の入手 ・ヒト胚からの細胞株の樹立 ・胚または配偶子の遺伝情報の改変 ・原始線条が形成されるまで、または受精後14日目までのいずれか早い方の期間、ヒト胚を研究のためにin vitroで培養 ・ヒト細胞を非ヒト胚に移植し、ヒト以外の動物の子宮での妊娠に利用 ・幹細胞由来の統合胚モデル ・MRTを施したヒト胚のヒト子宮への移植	3A **容認されない：現時点で安全ではない** ・子孫に遺伝するゲノム編集 ・ミトコンドリアDNAを改変した胚(MRTを含まない) の子宮への移植 ・ヒト幹細胞から分化させた配偶子の生殖利用
1B **報告可能だが、通常は専門的な監視プロセスによる審査は行われない** ・幹細胞を用いた非統合胚モデル ・キメラ胚のin vitroでの培養 (ヒト細胞を非ヒト胚に移植すること) ・受精や胚の作成を伴わないin vitroでの配偶子の生成		3B **容認されない：説得力のある科学的根拠を欠くか、倫理的に問題がある** ・ヒト幹細胞由来の胚モデルの妊娠への利用 ・ヒト生殖クローニング ・ヒト生殖細胞が存在する可能性のあるヒト–動物キメラの交配 ・ヒト–動物キメラ胚のヒトや類人猿の子宮への移植 ・由来を問わず、ヒト胚の動物子宮への移植

2種類のembryo model

(1) Non-integrated stem cell-based embryo models

2.2.1B: カテゴリー**1B**

専門的な科学的・倫理的監視プロセスを担当する組織に報告は可能だが、監視プロセスを担当する組織の判断により、通常は、さらなる審査または継続的な審査の対象とはならず、当該法域の規制および方針に従う研究。カテゴリー1Bの研究には、以下の活動が含まれる。

a. 胚外膜を含む胚全体が統合された発生を表現することを意図していないヒト幹細胞由来の胚モデルを in vitroで形成する研究。
(Research that entails the *in vitro* formation of human stem cell-based embryo models that are not intended to represent the integrated development of the entire embryo including its extraembryonic membranes.)
（b、cは省略）

なお、ISSCRのワーキンググループとしては、「合成胚 (synthetic embryo)」「人工胚 (artificial embryo)」といった表現は使わないのがよいと提案。

2種類のembryo model (2)

(2) Integrated stem cell-based embryo models:

2.2.2: カテゴリー2

胚、特定のキメラ、幹細胞由来の胚モデルを用いた研究の形態で、専門的な科学的・倫理的審査プロセスを経て審査・承認された場合にのみ容認されるもの。包括的な審査は、人を対象とする研究審査委員会、体外受精（IVF）クリニックの監視組織、動物実験の審査プロセスなど、他の関連する監視活動と連携して行い、研究は現地の法律や政策に準拠しなければならない。このような研究は全て、説得力のある科学的根拠をもとに、代替モデルではなく、これらの試料を使用する必然性がなければならない。研究に用いる胚の数は、科学的目的を達成するために必要最小限にすべきである。以下のような活動が、専門的な審査プロセスによる包括的な審査を必要とする研究の形態である。

（a – f 省略）

g. **胚外膜を含む胚全体の統合的な発生を表現する、幹細胞由来の胚モデル**の作成。これらの幹細胞由来の統合胚モデルを培養するのは、科学的目的を達成するために必要な最短期間にとどめなければならない。

(Generation **of stem cell-based embryo models that represent the integrated development of the entire embryo** including its extraembryonic membranes. These integrated stem cell-based embryo models should be maintained in culture for the minimum time necessary to achieve the scientific objective.)

まとめ１

- 胚モデルは、胚ではない。
- 非統合胚モデルと統合胚モデルは区別しなくてはならない。
- ヒトの統合胚モデルは、ヒト胚ではないが、倫理審査を経て研究される必要がある。
- ヒトの胚モデルは、動物やヒトの子宮に移植されてはならない。

Magdalena Zernicka-Goetzらによる発表
（2023年6月　ISSCR年会　Boston）

Synthetic human embryos created in groundbreaking advance

Exclusive: Breakthrough could aid research into genetic disorders but raises serious ethical and legal issues

Analysis: advances leave legislators needing to catch up

14 June 2023 ガーディアン紙の記事

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

Scientists have created synthetic human embryos using stem cells, in a groundbreaking advance that sidesteps the need for eggs or sperm.

Scientists say these model embryos, which resemble those in the earliest stages of human development, could provide a crucial window on the impact of genetic disorders and the biological causes of recurrent miscarriage.

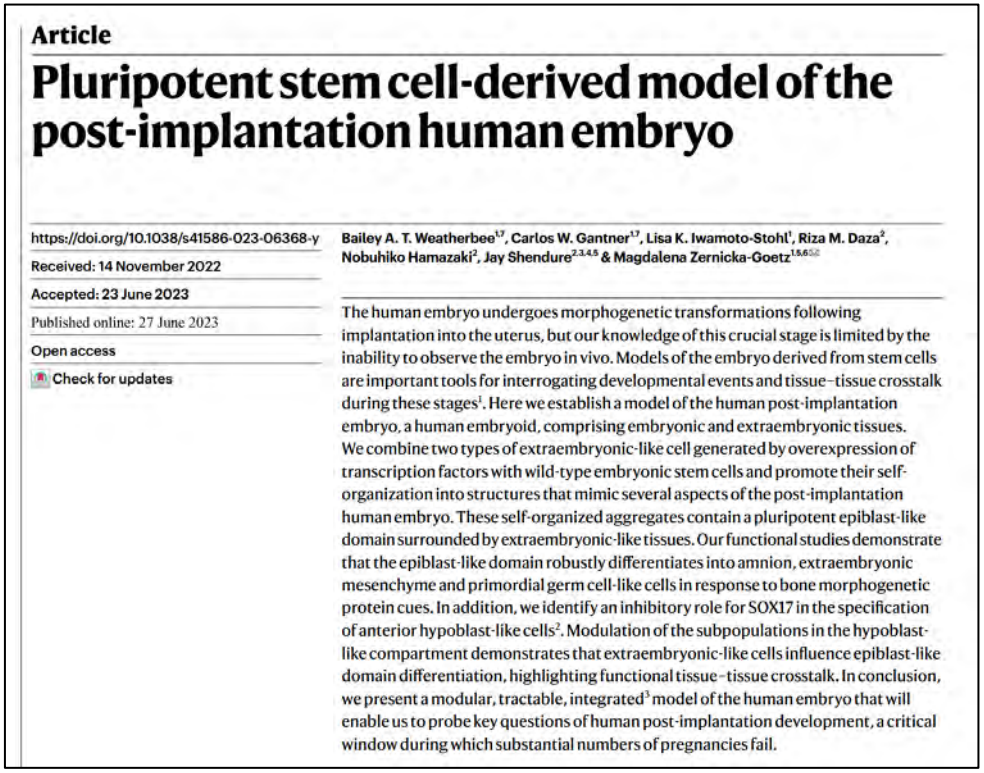
However, **the work also raises serious ethical and legal issues as the lab-grown entities fall outside current legislation in the UK and most other countries.**

The structures do not have a beating heart or the beginnings of a brain, but include cells that would typically go on to form the placenta, yolk sac and the embryo itself.

Prof Magdalena Żernicka-Goetz, of the University of Cambridge and the California Institute of Technology, **described the work in a plenary address on Wednesday at the International Society for Stem Cell Research's annual meeting in Boston.**

2023年6月　ネイチャーの論文公表

23 June 2023



Article

Pluripotent stem cell-derived model of the post-implantation human embryo

https://doi.org/10.1038/s41586-023-06368-y

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Open access

Check for updates

Bailey A. T. Weatherbee[1,7], Carlos W. Gantner[1,7], Lisa K. Iwamoto-Stohl[1], Riza M. Daza[2], Nobuhiko Hamazaki[2], Jay Shendure[2,3,4,5] & Magdalena Zernicka-Goetz[1,6,8]

The human embryo undergoes morphogenetic transformations following implantation into the uterus, but our knowledge of this crucial stage is limited by the inability to observe the embryo in vivo. Models of the embryo derived from stem cells are important tools for interrogating developmental events and tissue–tissue crosstalk during these stages[1]. Here we establish a model of the human post-implantation embryo, a human embryoid, comprising embryonic and extraembryonic tissues. We combine two types of extraembryonic-like cell generated by overexpression of transcription factors with wild-type embryonic stem cells and promote their self-organization into structures that mimic several aspects of the post-implantation human embryo. These self-organized aggregates contain a pluripotent epiblast-like domain surrounded by extraembryonic-like tissues. Our functional studies demonstrate that the epiblast-like domain robustly differentiates into amnion, extraembryonic mesenchyme and primordial germ cell-like cells in response to bone morphogenetic protein cues. In addition, we identify an inhibitory role for SOX17 in the specification of anterior hypoblast-like cells[2]. Modulation of the subpopulations in the hypoblast-like compartment demonstrates that extraembryonic-like cells influence epiblast-like domain differentiation, highlighting functional tissue–tissue crosstalk. In conclusion, we present a modular, tractable, integrated[3] model of the human embryo that will enable us to probe key questions of human post-implantation development, a critical window during which substantial numbers of pregnancies fail.

Nature：https://www.nature.com/articles/s41586-023-06368-y

Synthetic human embryo raises ethical issues

By James Gallagher
Health and science correspondent

15 June 2023

BBC　News：
https://www.bbc.com/news/health-65914934.amp

ISSCRによる声明

講演者による仮訳

June 26, 2023

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

ISSCR Statement on New Research with Embryo Models

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.

Embryo 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 embryo models, 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 stages of embryonic 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 developmental origins of congenital defects in the heart, nervous system, and other organs.

Unlike 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 are neither 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 Guidelines 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.

- ISSCRは、科学的・倫理的に厳格に実施されヒト多能性幹細胞由来の胚モデルを用いた研究を支援する。
- ISSCR2023の年会やその後のプレプリントでの発表はこの分野の研究が急速に発展していることを示している。
- 胚モデルの研究により、妊娠の最初の数週間に起こる胚発生の初期段階を実験的にモデル化することができる。また、心臓や神経系、その他の臓器における先天性欠損の発生の起源に関する基礎知識を得るのにも役立つ。
- 最近のメディア報道とは異なり、**胚モデルを説明するために「合成胚」という用語を使用することは不正確であり、混乱を招きかねないため、使用しないように忠告する。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発生を再現することはできるが、生後のヒトと同等の段階まで発生することはできない。さらに、ISSCRガイドラインは、胚モデルをヒトや動物の子宮に移植することを禁止している。
- ISSCRのガイドラインは、統合胚モデルを用いた研究は、説得力のある科学的根拠があり、専門的な科学的・倫理的監視プロセスによる慎重な審査と承認を経た後にのみ進めることができると推奨している。

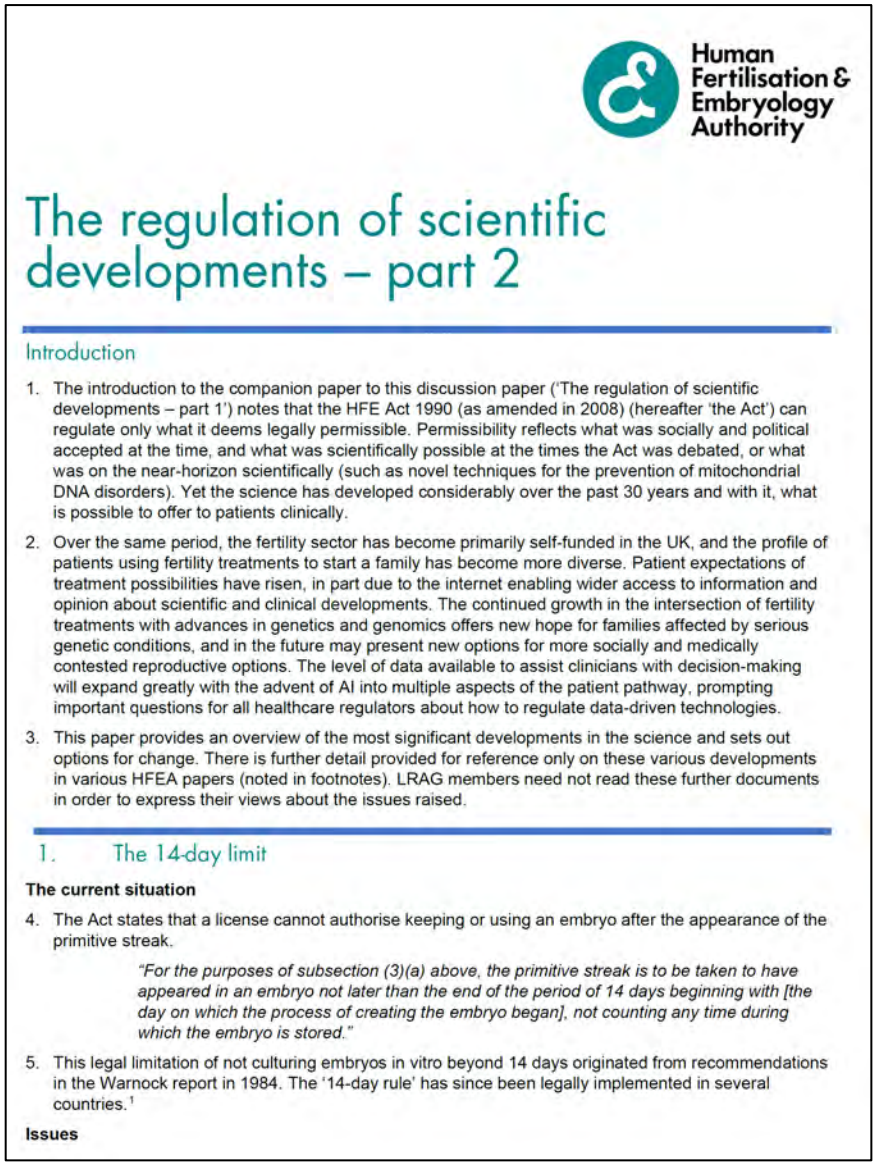
ISSCR：https://www.isscr.org/isscr-news/isscr-statement-on-new-research-with-embryo-models

規制の必要性や見直しに関する検討は各国で開始されている

英国HFEA（Human Fertilisation and Embryology Authority)によるdiscussion paper June 2022：

・https://www.hfea.gov.uk/media/qfljx3i2/2022-06-27-hfea-the-regulation-of-scientific-developments-part-2.pdf

・https://www.hfea.gov.uk/about-us/our-authority-committees-and-panels/legislative-reform-advisory-group/



Human Fertilisation & Embryology Authority

The regulation of scientific developments – part 2

Introduction

1. The introduction to the companion paper to this discussion paper ('The regulation of scientific developments – part 1') notes that the HFE Act 1990 (as amended in 2008) (hereafter 'the Act') can regulate only what it deems legally permissible. Permissibility reflects what was socially and political accepted at the time, and what was scientifically possible at the times the Act was debated, or what was on the near-horizon scientifically (such as novel techniques for the prevention of mitochondrial DNA disorders). Yet the science has developed considerably over the past 30 years and with it, what is possible to offer to patients clinically.
2. Over the same period, the fertility sector has become primarily self-funded in the UK, and the profile of patients using fertility treatments to start a family has become more diverse. Patient expectations of treatment possibilities have risen, in part due to the internet enabling wider access to information and opinion about scientific and clinical developments. The continued growth in the intersection of fertility treatments with advances in genetics and genomics offers new hope for families affected by serious genetic conditions, and in the future may present new options for more socially and medically contested reproductive options. The level of data available to assist clinicians with decision-making will expand greatly with the advent of AI into multiple aspects of the patient pathway, prompting important questions for all healthcare regulators about how to regulate data-driven technologies.
3. This paper provides an overview of the most significant developments in the science and sets out options for change. There is further detail provided for reference only on these various developments in various HFEA papers (noted in footnotes). LRAG members need not read these further documents in order to express their views about the issues raised.

1. The 14-day limit

The current situation

4. The Act states that a license cannot authorise keeping or using an embryo after the appearance of the primitive streak.

> *"For the purposes of subsection (3)(a) above, the primitive streak is to be taken to have appeared in an embryo not later than the end of the period of 14 days beginning with [the day on which the process of creating the embryo began], not counting any time during which the embryo is stored."*

5. This legal limitation of not culturing embryos in vitro beyond 14 days originated from recommendations in the Warnock report in 1984. The '14-day rule' has since been legally implemented in several countries.[1]

Issues

Stem-cell based embryo models

Issues

25. Researchers have also exploited the potential of stem cells to derive embryo-like structures directly, without the need for a fertilisation step. This involves the creation of embryos from stem cells, rather than through fertilisation. A number of different terms have been used for such entities in recent years, but the 2021 ISSCR guidelines seek to standardise the terminology so that these entities are known collectively as 'stem-cell-based embryo models'.

26. Guidelines divide these stem-cell based embryo models into two categories. 'Integrated' stem-cell-based embryo models containing not just embryo-like cells, but also cells resembling extra-embryonic material – for example, cells of the kind that develop into the placenta.

27. 'Non-integrated' stem-cell-based embryo models do not have (and cannot develop) such additional cells and resemble only the embryo proper (or a part of it).

Options for change

30. All of these developments – in vitro derived gametes, embryo like entities, and stem cell-based embryo models – pose significant challenges to our understanding of human reproduction and may therefore require wider public debate before any changes in regulation were contemplated. However, we can sketch out some key options at this stage.

31. Prior to any changes in regulation, informed Parliamentary debate should take place. Any changes in regulation would need clear articulation of the differences between use of these entities within scientific research and their use within human assisted reproduction.

32. **Status quo** – this work is progressing outside of any regulatory regime and there is therefore an argument for continuing as is. However, drawbacks of this approach include the lack of security and safety accorded to researchers, and the lack of regulatory oversight and control if at some point, there were moves to use these developments within assisted reproduction.

33. **Bring some, or all of these developments under regulatory oversight** - the benefits of bringing in-vitro derived gametes, embryo-like entities, and stem-cell based models under the regulatory framework is that this would ensure that as they become increasingly similar to their human counterparts, there is strong regulatory oversight. Some scientists are proactively requesting the HFEA for cooperation in this matter and would welcome further regulatory oversight in the field. Increased regulation could afford scientists a greater level of protection.

34. The development of techniques to create human-like gametes and embryos is likely to create significant public discomfort as these models become very similar to 'actual' human embryos. Public discussion should consider the future possibilities these new developments may offer. It seems plausible that regulating this field would increase public trust.

英国としての具体的なオプションが書かれている。

まとめ2

- 胚モデルは、胚ではない。
- 非統合胚モデルと統合胚モデルは区別しなくてはならない。
- ヒトの統合胚モデルは、ヒト胚ではないが、倫理審査を経て研究される必要がある。
- ヒトの胚モデルは、動物やヒトの子宮に移植されてはならない。

- 課題
  1. 胚モデルはどのように位置付けるべきか。科学的に、および規制面で。
  2. 将来、胚モデルが、幹細胞由来でないヒト胚と同じような性質を持つことがあるだろうか。その際の規制はどうすればよいか。