Stem Cell-Based Embryo Model Governance: Australian Law Contrasted with the UK's New Code of Practice

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Disclaimer

- I held the role of Chair of the NHMRC Embryo Research Licensing Committee (ERLC) from 2018 to 2024
- I speak entirely in my capacity as an independent law academic
- I rely solely on publicly available information

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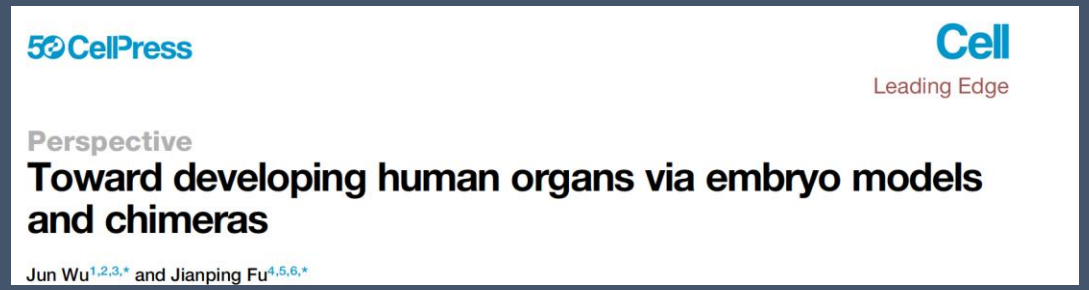
Timeline from human embryonic stem cells to human embryo models

- 1998 human embryonic stem cells
- 2006 human induced pluripotent stem cells
- 2013 human embryonic stem cells derived from embryos created through somatic cell nuclear transfer
- 2016 stem cell-based human organoids
- 2022 stem cell-based human blastoids
- 2023 other stem cell-based human embryo models



Mostly from Eguizabal C, et al, Hum Reprod Open. 2019

Perceived beneficial uses of human embryo models

Improved knowledge of human development

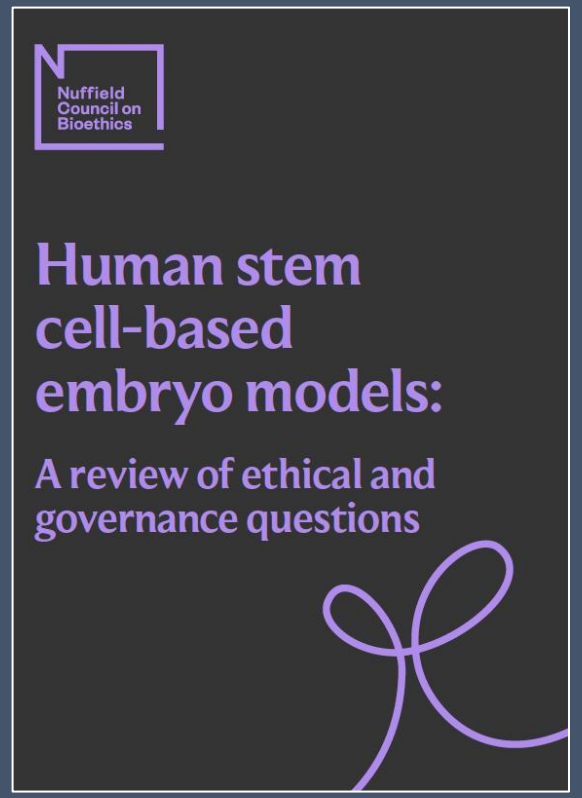
Potential translation into diagnostic and therapeutic interventions for a range of conditions, including infertility

Training of personnel

Refinement and development of IVF techniques

A need to discuss governance – UK perspective

- Lack of a clear governance framework
- Distinct ethical concerns (particularly re unknown developmental potential)
- Public support for oversight
- Oversight that is less stringent than for embryo research but more exacting than for research using stem cell cultures



The Cambridge Reproduction Code of Practice for the Generation and Use of Human Stem Cell-Based Embryo Models (2024)

- To fill the gap in UK governance by addressing the ethical, legal and regulatory questions specific to human stem cell-based embryo models and provide guidance on their responsible use
- To provide guidance in other jurisdictions

Key elements of the Code of Practice

- All embryo models should be subject to oversight
- All should be subject to an *in vitro* culture limit
- Research using models should not proceed unless it meets a range of conditions (including accordance with donor consent)
- Transfers to reproductive tracts of humans and non-humans should be prohibited
- Standardised best practices should be promoted

Comments

Incredibly rapid turn around

Useful guide to considerations needed in developing a governance framework ***where one is absent***

A guide to governance – but not governance per se

Described by Soren Holm as ‘distinctly thin’

Contrast with the Australian regulatory landscape

Australia comprehensively regulates use of *human embryos* for research

- *Research involving Human Embryos Act 2002, Prohibition of Human Cloning for Reproduction Act 2002*
- Can only use excess ART embryos for research under licence
- Could also possibly use (under licence) for research:
  - embryos unsuitable for implantation
  - pre-embryos (eg zygotes up to first mitotic division)
  - embryos created by processes other than fertilization
- All require compliance with the 14 day rule

What is a human embryo

- ***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;

- …

What are the consequences if human embryo models are human embryos?

- Creation and research use up to 14 days must be licensed by the ERLC
- Research use after 14 days for embryo models created before this, and creation and research use of embryo models after this are all prohibited
- Institutional ethical approval is required

What are the consequences if human embryo models are not embryos?

- Creation and research use does not require a licence from the ERLC
- Institutional ethical approval is required

What is a paragraph (b) human embryo: an exercise in statutory interpretation

- The entity is human cells with a human nuclear genome or altered human nuclear genome; and
- It is discrete, capable of being identified or counted;
- It has the potential to develop up to, or beyond, the stage at which the primitive streak appears (even if it doesn't actually go through this process);
- It does not show the morphological features of an embryo after 8 weeks development;
- It has arisen from fertilisation or any other process that initiates organised development of a biological entity. Questions to ask:
  - does it have developmental attributes contributing to spatial and/or temporal organisation within the entity?
  - is it an intact conceptus, having the potential to develop the full complement of parts of a normally developing embryo (including embryonic and extraembryonic tissues)?
- The entity is not required to exist independently to fulfil this requirement.

Abridged from: https://www.nhmrc.gov.au/research-policy/embryo-research-licensing/commonwealth-and-state-legislation/determining-whether-embryo-model-regulated-erlc

Reported outcomes to date

- ERLC has decided that:
  - a 3D iblastoid model ***meets the definition of human embryo*** and therefore is required to be licensed. Cut off at 14 days – measured by by morphological and molecular features.
    - Thus, it must be licensed via an application specific to embryo models
  - a 3D gastruloid model ***meets some of the definition of a human embryo*** but does not fully demonstrate 'organised development of a biological entity'. It is not an intact conceptus with the potential to develop the full complement of parts of a normally developing embryo as it does not have all extraembryonic cell lineages.
    - Thus ERLC lacks jurisdiction
- And further, that:
  - other 3D gastruloid models ***may meet the definition of a human embryo*** - researchers are encouraged to consider attributes of each specific model before commencing research and to seek advice from ERLC

Ethical review: required for all research involving human embryo models under the National Statement (2023)

Exemptions from ethical review only apply to information and data, not cells

- Paragraph 5.1.17
  - Research that may be eligible for exemption from ethics review includes research that carries a lower risk to participants or the community **and** satisfies one or more of the conditions in (a)–(d), below:
    - (a) the research involves the use of collections of information or data from which all personal identifiers have been removed prior to being received by the researchers
- …

Use of stored biospecimens for research requires some form of ethical review

- Paragraph 3.2.3
  - If the research involves only use of stored biospecimens and involves no more than low risk, then the provisions of 5.1.10–5.1.14 for non-HREC levels of review may apply
- Paragraphs 5.1.10–5.1.14
  - Review pathways determined by risk levels
  - HREC review required for research projects assessed as having more than low risk
  - Alternative review pathways for lower risk research

My final thoughts

- Australian legislation, though created in 2002 and amended in 2006, has stood the test of time
- Currently, we have a workable regulatory framework
- It largely corresponds with the attributes of a governance framework proposed in the UK Code of Practice
- The 14 day rule provides a limit on *in vitro* culture for licensed embryo models, but there is no limit for other models. This may need to be reviewed
- There is a need to provide further guidance to institutions on risk and ethical review pathways for proposals to create and use embryo models