PH427 – Week 6 (Lent Term 2014)

Stem cells and the ethics of therapeutic cloning

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Goals of this lecture:

A) Understand the biology of stem cells:

You know what stem cells are.

You know what stem cells can be used for and how they are used.

B) The ethics of therapeutic cloning:

You know what therapeutic cloning is (as opposed to reproductive cloning).

You can discuss the ethical issues this type of research might raise.

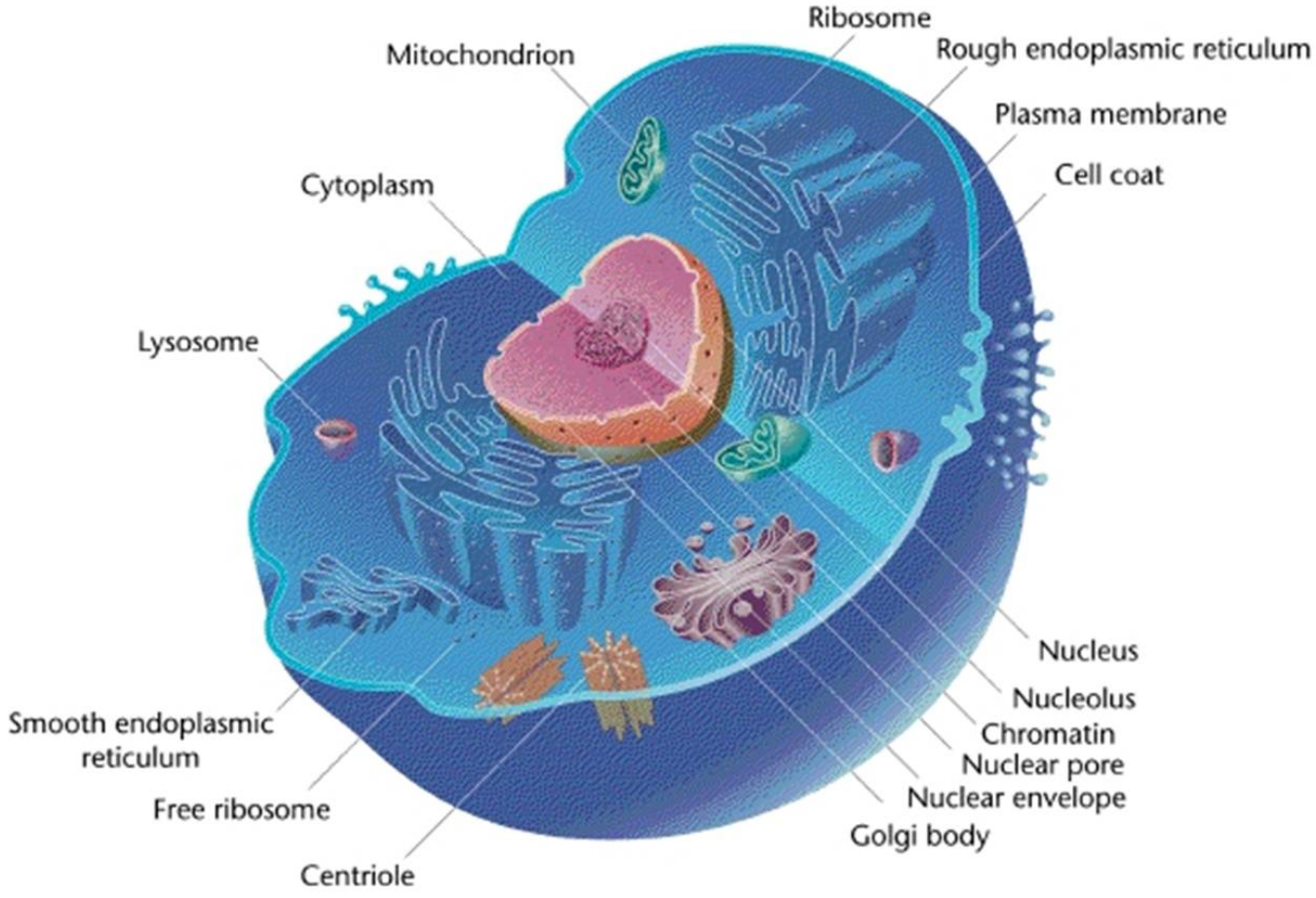
What are stem cells?

Some basic cell biology first:

-What does a cell look like?
-How does a fertilized egg develop into an organism?
-What does ‘differentiation’ mean?

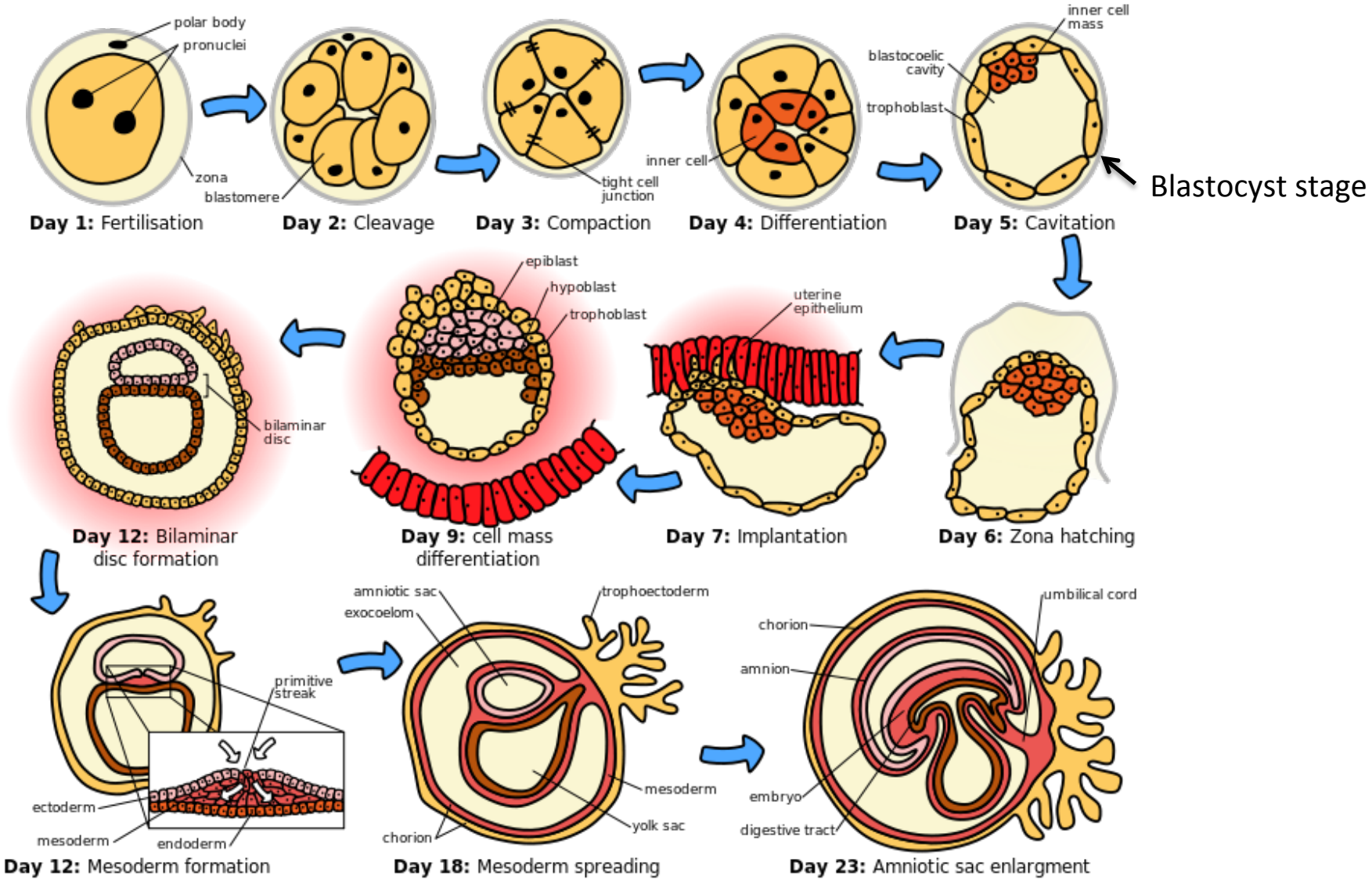
What does a cell look like?

-Human body consists of **about 35 trillion cells** (estimates are highly disputed).
(Source: Bianconi E. et al., *Ann Hum Biol*. 2013 Nov-Dec; 40(6):463-71.)
-Body is built from **about 200 different cell types** (skin cells, neurons, muscle cell,…).



http://commons.wikimedia.org/wiki/File:Eukaryotic_Cell_(animal).jpg

How does a fertilized egg develop into an organism with 200 different cell types?



http://en.wikipedia.org/wiki/File:HumanEmbryogenesis.svg

What does ‘differentiation’ mean?

Differentiation: can be translated as the **specialisation** of a cell. The cell obtains a particular function. To fulfill that function it needs a special set of tools (proteins in this case) and a special structure (cells whose function it is to give stability to a tissue need to be rigid, for example).

But each cell has the same genome, so it has the same genes as all the other cells. How is it made ‘different’ then?

Cells achieve specialisation by only expressing a part of the genes in the genome while other genes are shut down. Each cell type has its own ‘expression profile’.
The cell also shuts down the machinery needed to replicate itself. In a sense it gives itself up, it fully commits itself to that one task. Fully differentiated cells do not undergo mitosis (cell division). Partly differentiated cells still undergo mitosis (see below).

Stem cell biology

-What is so special about stem cells?
-How do we classify them?
-What can they be used for?
-How can we get our hands on stem cells?

What is so special about stem cells? And how do we classify them?

Definition of the term 'stem cell' (from: Alberts et al., Molecular Biology of the Cell, 2008):

"Undifferentiated cell that can continue dividing indefinitely, throwing off daughter cells that can either commit to differentiation or remain a stem cell (in the process of self-renewal)."

-'Undifferentiated' here means 'not fully differentiated'.

-Stem cells have the capability of developing into different cell types, something a fully differentiated cell (majority of our cells) cannot do.

-Stem cells constantly renew themselves. 'Immortal' cell lines can be created.

-Stem cells can be classified according to *source* or *plasticity*.

Classification of stem cells according to *source*:

Embryonic stem cells: derived from the inner cell mass of the blastocyst.

Perinatal stem cells: derived from umbilical cord blood

Adult stem cells: derived from an adult organism.

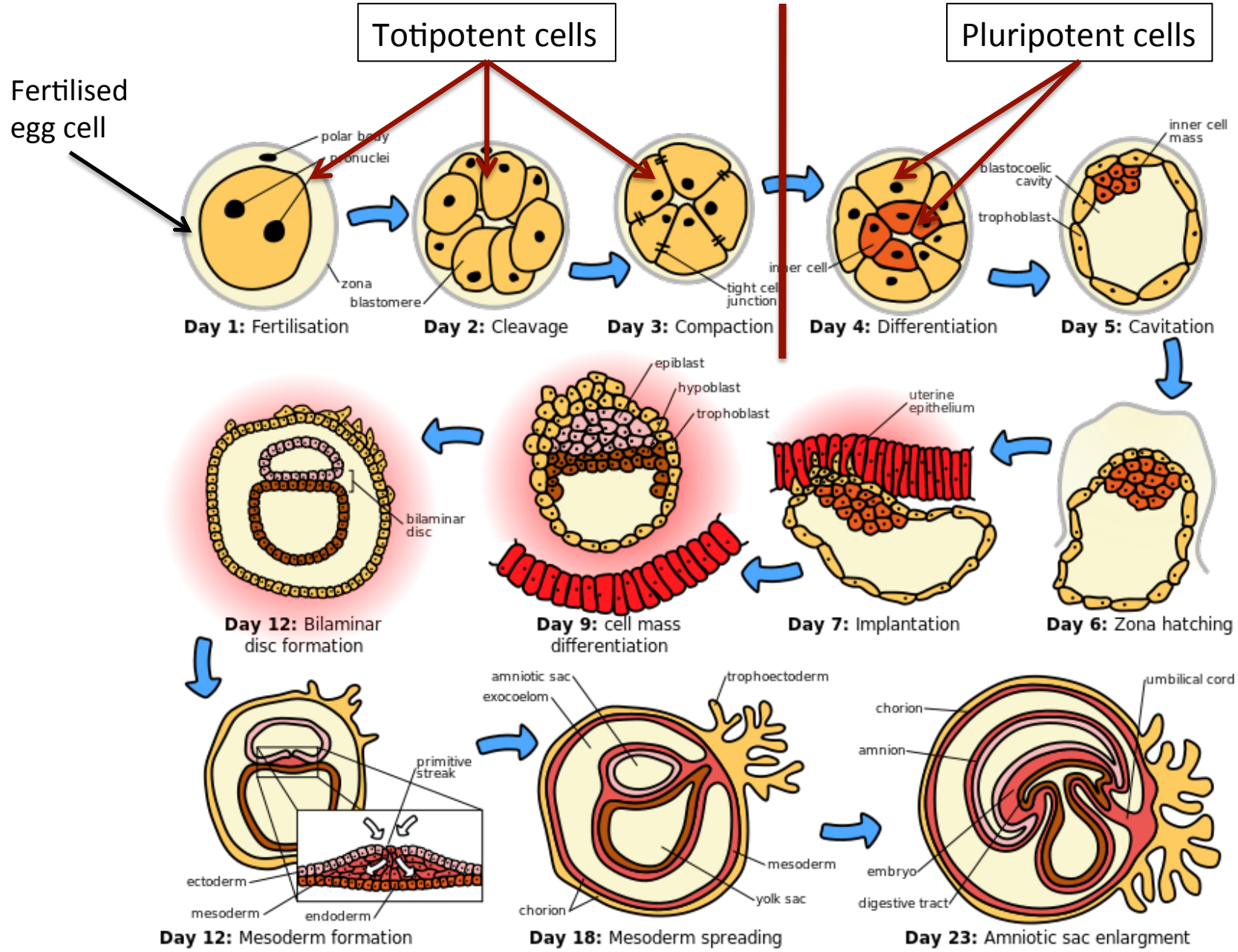
Depending on the source the cells have already undergone more or less differentiation. This also has consequences for their plasticity (developmental versatility).

Classification of stem cells according to *plasticity*:

Totipotent:
can develop into any cell type in a body, including egg cells and placenta cells.
Example: fertilised egg or embryonic cells created during the first few divisions of the embryo (first four days).

Pluripotent:
After four days the clump of cells splits into two layers. Outer layer contains cells that can form a placenta. Inner cell mass of the blastocyst contains cells that give rise to the rest of the body. This is the first differentiation that takes place. Cell of the inner mass can develop into any cell type in a body, but not placenta cells. Hence they are 'pluripotent' and not 'totipotent'.

Multipotent:
Adult stem cells are even more specialised than embryonic stem cells. Are not fully differentiated, meaning they can still develop into different cell types. But they have limited plasticity. Adult stem cells can be found in skin or bone marrow. Are important for the self renewal of tissues.



http://en.wikipedia.org/wiki/File:HumanEmbryogenesis.svg

How and why we use stem cells

Why the interest in stem cells?

-Tool for treating degenerative diseases

-Modeling human diseases, toxicology screening

-Make reproductive cloning possible

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The principle behind the therapeutic use of stem cells

Stem cells give us a source of new tissue (blood cells, neuron, whatever it is that is vanishing due to the degenerative disease).

Idea: Stem cells are implanted in the body and will form the type of cells present in that tissue. By that they replace the missing cells in that tissue.
In principle the target can be any tissue, i.e. the liver, brain, spinal cord, eye, etc. What matters is that the stem cell is potent enough to form the required cell type.

Important feature of this approach:
We don't need to understand the mechanism of the disease and find a treatment for it. We simply put a *replacement* in place. In a sense we work around the problem.

The problem of the therapeutic approach

Problem:
We cannot use *any* embryonic cell for therapeutic treatments. Same problem as in organ donation: high risk of *rejection*, as our immune system will recognise the donated stem cells as 'foreign', hence it will attack them.

Solution:
We need stem cells that are *indistinguishable from our own cells*.

What is recognised by the immune system are the *proteins* a cell expresses.
The proteins a cell expresses are determined by the genome of that cell, which 'codes' for the protein sequence (see weeks 4 and 5).

-> We need cells that are pluripotent but carry our genome. We need clones.

The idea behind therapeutic cloning

Idea: since the genome of a cell is stored in the nucleus we can obtain a pluripotent stem cell that carries our genome if we transfer a nucleus from one of our cells (donor cell) to a suitable acceptor cell.

This is exactly how cloning works (Dolly was created this way). The method is called **somatic cell nuclear transfer (SCNT)**.

Basically this method is simply the transfer of a (somatic) cell nucleus from one of our cells to an acceptor cell (usually an enucleated egg cell).

[A **somatic cell** is any cell of our body that is not in the germline (the system of cells that produces egg cells or sperm cells)].

Somatic Nuclear Cell Transfer (SCNT)

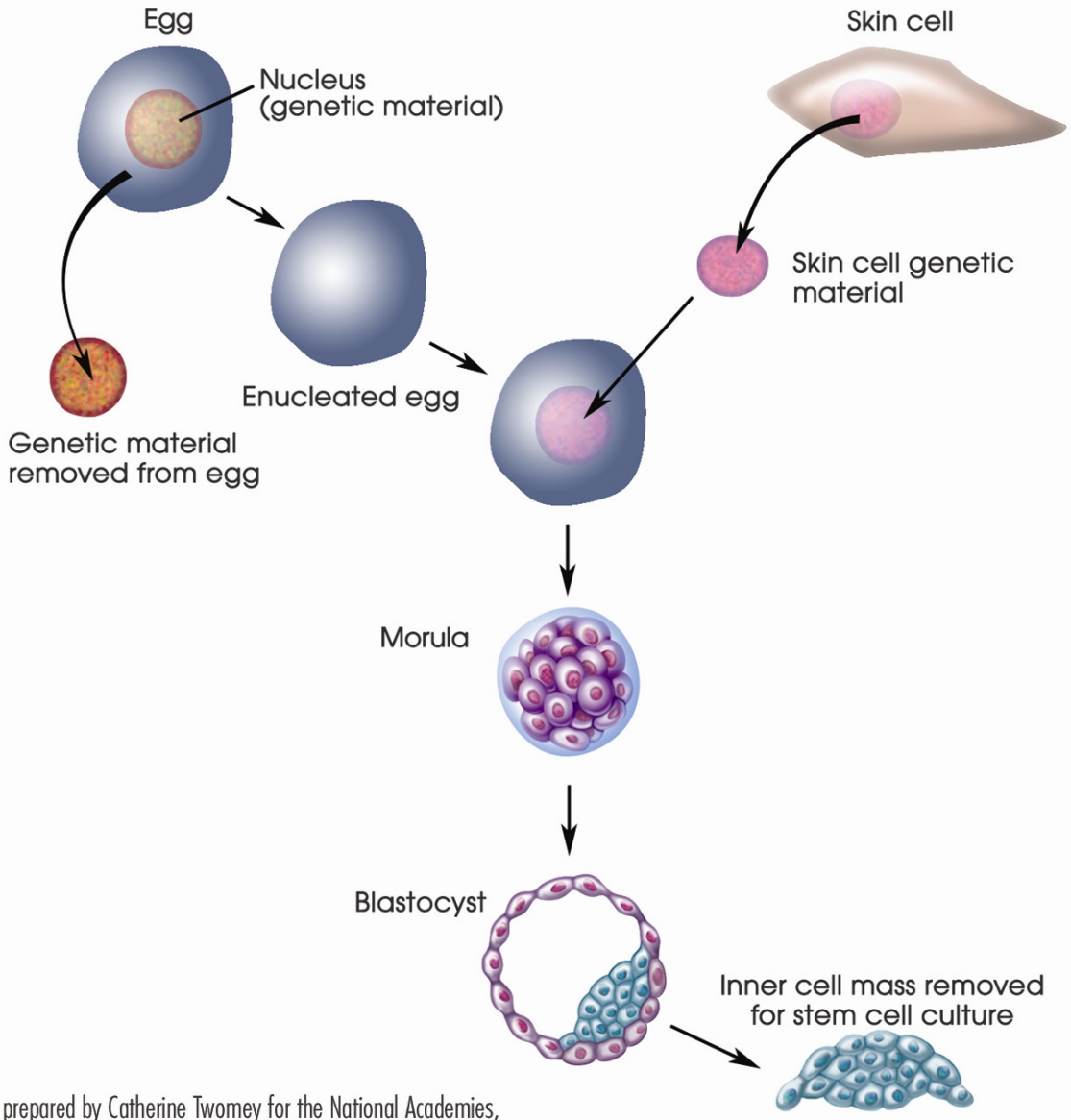
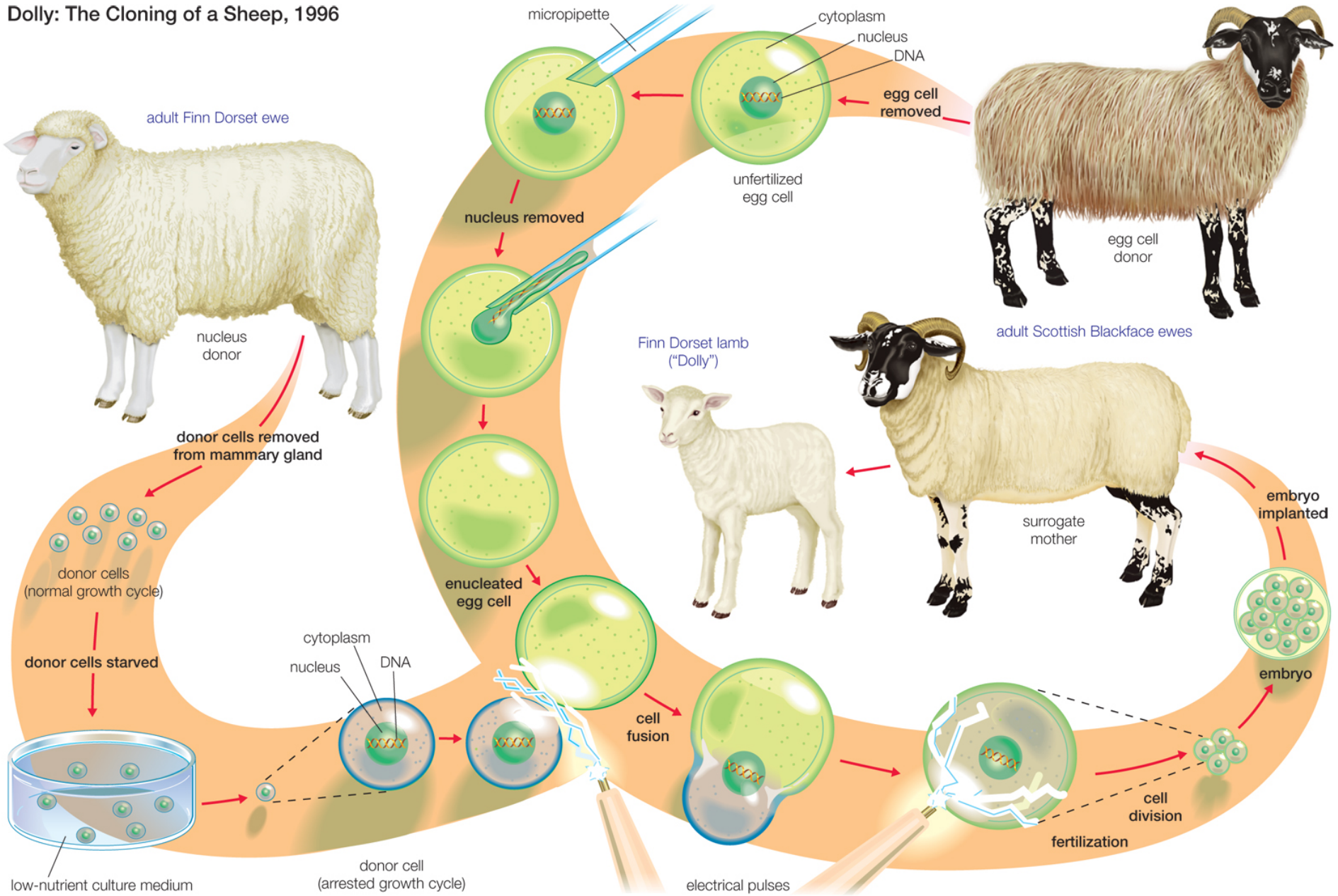


Image prepared by Catherine Twomey for the National Academies,
Understanding Stem Cells: An Overview of the Science and Issues
from the National Academies, http://www.nationalacademies.org/stemcells.
Academic noncommercial use is permitted.

Crucial step: the somatic cell nucleus gets '**reprogrammed**' when it is exposed to the environment of the egg cell. Whereas in the somatic (differentiated) cell only particular genes were expressed, the reprogrammed cell nucleus obtains the ability to express all relevant genes again. The nucleus has been 'reprogrammed'.

Cloning Dolly



Some remarks on SCNT:

-In the case of Dolly the goal was to produce a clone. This is an example of *reproductive cloning*. Ethics of this will be discussed in week 7.

-It is difficult to get the technology working so that a fully grown and viable organism develops (see Dolly's early death and health issues).

-However, these are *not problems if we use SCNT for therapeutic use*. The embryo that forms does not need to get past the blastocyst stage. All we are interested in are the pluripotent cells in the inner cell mass of the blastocyst. After this extraction we can dispose of the embryo.

-> This is obviously where the ethical problems of this use of SCNT begin.

Ethical/technical problems of the therapeutic use of stem cells (I)

1) The destruction of embryos

Technical problem: You have to **destroy an embryo** to obtain pluripotent cells (Remember: pluripotent cells are collected from the inner cell mass of the blastocyst). This problems applies both to cloning and to the use of pluripotent cells for therapy more generally.

Ethical problem: Depending on the moral status you attribute to the embryo you can be seen as committing murder when you destroy an embryo.

Also: in the case of cloning you create life only to destroy it. Instrumentalisation of living being.

Ethical/technical problems of the therapeutic use of stem cells (II)

How to get around the ethical problems?

A) *Find a way to get pluripotent cells without having to destroy the embryo.*

Problem with this approach: in case you are after immune-compatible stem cells then you still have to create life only for an instrumental reason. You cannot use frozen/discarded embryos from in vitro fertilisation (IVF) treatment. The extra embryos you create are likely to die, as cloning of human beings is not there yet. And if the technology allows them to survive, then you have created a clone of you simply to get some cells for therapy. Host of additional issues come up at this point (see next week on the ethics of reproductive cloning).

B) *Problem is conditional on the definition of 'personhood*'. If an embryo is not seen as having any specific moral rights then destroying an embryo is not problematic, especially if it used for good reason (see Douglas and Savulescu, 2009).

Ethical/technical problems of the therapeutic use of stem cells (III)

Douglas and Savulescu 2009: Why it is ok to destroy an embryo

Douglas and Savulescu discuss two lines of reasoning that could be used to defend embryos and save them from destruction:

1) Embryos are persons. Same moral status as any other person. We can't just do as we like.

2) Embryos are living beings and destroying them means killing them. Ethics of killing apply (mental capabilities, species membership, depriving living being of valuable future).

Douglas and Savulescu claim that:

a) *embryos are not persons*, hence they have not the same rights as any other developed human being (they draw the line at fetal stages of development, it seems).

b) the *ethics of killing either does not apply or gives us insufficient reason* not to kill.

Ethical/technical problems of the therapeutic use of stem cells (IV)

2) **Cloning requires unfertilized eggs**:

Technical problem: You need eggs to do SCNT. The collection of unfertilized eggs is not an easy procedure (can be painful, requires hormone treatment and so on).

Ethical problems: Because eggs are often donated in exchange for money, this step of the procedure raises issues of exploitation, informed consent, etc.

How to avoid these problems?

Interestingly, since both problems discussed here (egg collection and destruction of embryo) have their source in a technical problem, there is also a technical fix for them:

induced pluripotent stem cell (iPS cells)

The principle behind induced pluripotent stem cells

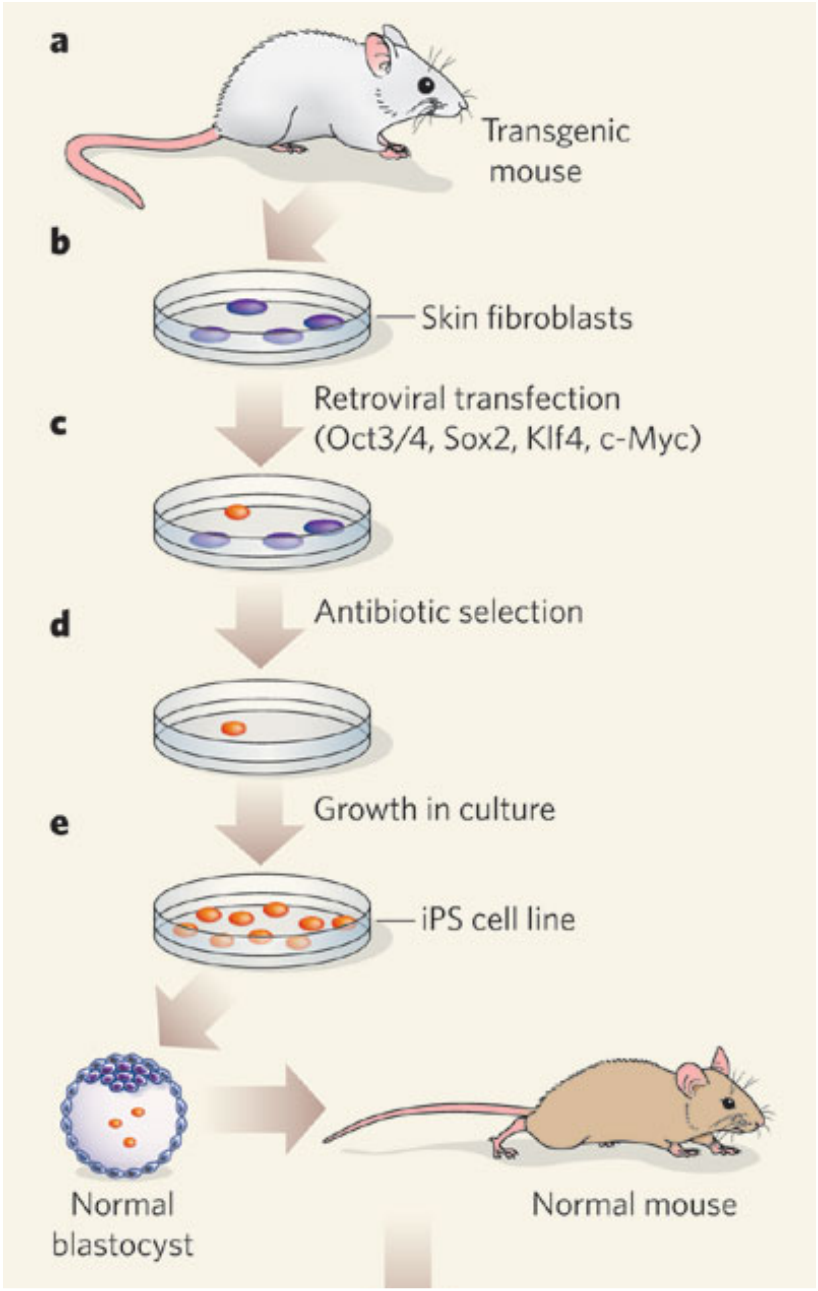
The **basic idea** behind induced pluripotent stem cells is that in principle *any somatic cell can be induced by a particular stimulus to go back to an undifferentiated state*.

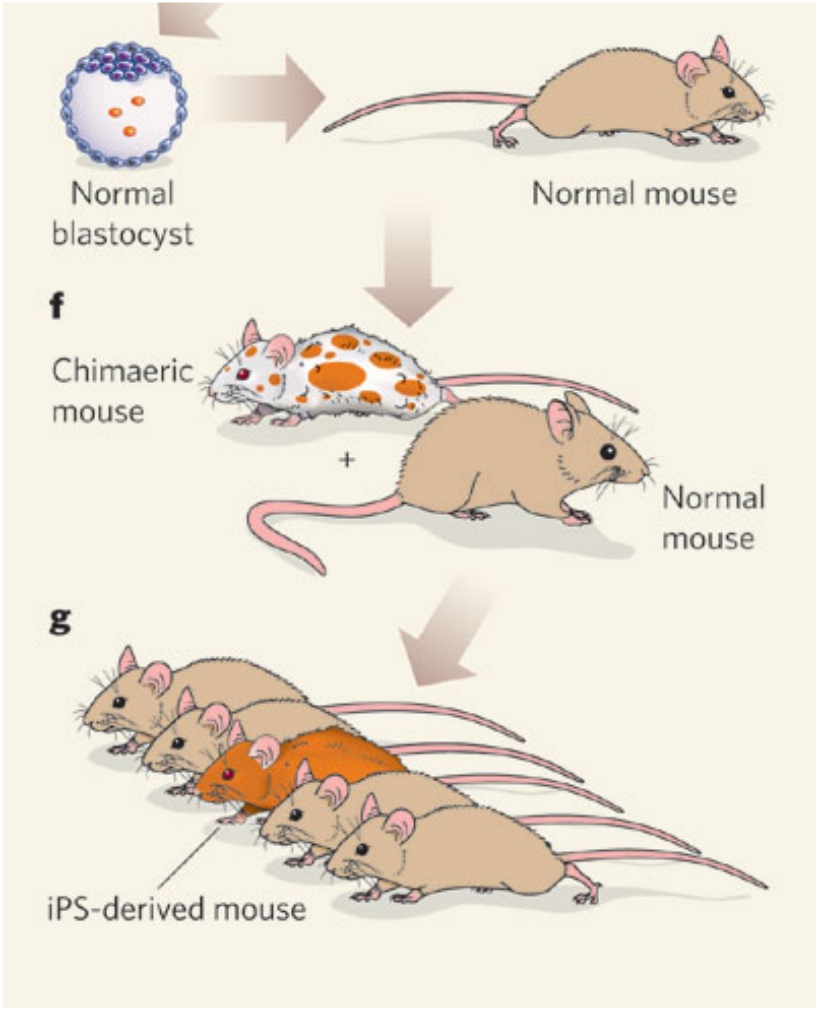
One reason for believing this was research from the 1960s that showed that **nuclei from differentiated cells can be reprogrammed** (meaning that they can be brought back to an undifferentiated state). This was shown most convincingly with SCNT and the development of Dolly in 1997. What did the reprogramming here was the environment of the (enucleated) acceptor egg cell.

The challenge was **to find a set of factors that can induce reprogramming** of a cell (genome to be precise) without having to use egg cells. Shortcut from somatic cell to pluripotent cell was the goal.

It was known since the 1980s that a particular class of proteins plays a crucial role in this reprogramming, namely so called '**transcription factors**'. These are factors that regulate which proteins are expressed in a cell.
Researchers therefore set out to find a set of transcription factors that could, if introduced into any somatic cell, transform this cell into a stem cell (hence the name 'induced' pluripotent stem cell).

Creating induced pluripotent stem cells (iPS cells)





2007 Nature Education Rossant, J. Stem cells: The magic brew. Nature 448, 260–262 (2007).

What changes in the age of iPS cells?

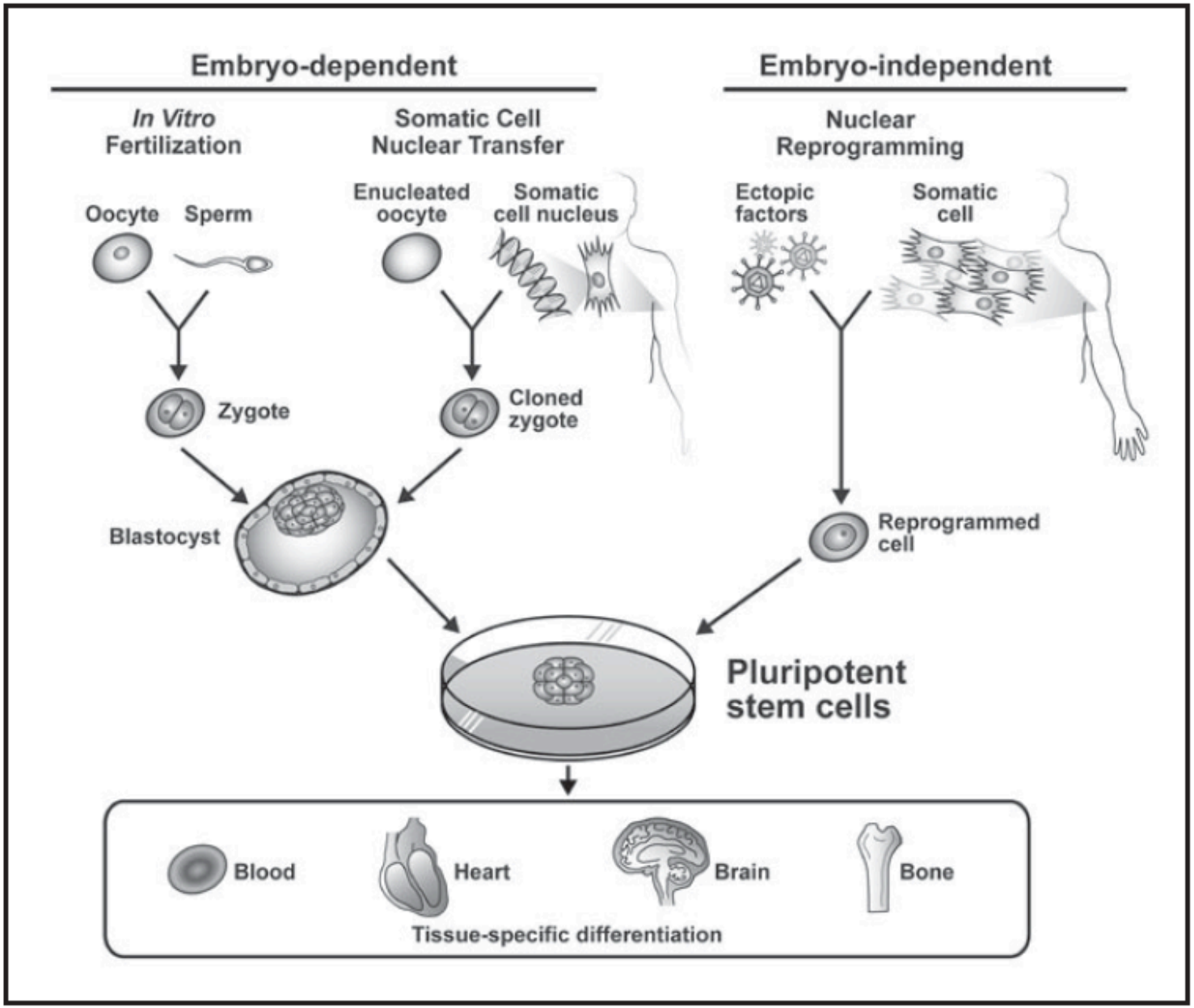
Do we still need embryonic stem cells?

If we have a way to create stem cells that are clones of our own cells without the need for embryonic stem cells, this means that the whole discussion around the ethics of embryo creation and destruction simply vanishes. We simply don't need embryonic stem cells to do research and develop therapies for degenerative diseases.

-> **Technological development of iPS cells has made the ethical discussion obsolete?**

But:
iPS technology is not there yet. Human embryonic stem cells still are the gold standard for pluripotency. Further research on iPS and their behaviour must be done and this needs the comparison to the gold standard. Could turn out that iPS do show some signs of pluripotency but don't work when you put them into an organism.

Overview: the different ways of obtaining pluripotent stem cells



Source: Zacharias, DG. *et al.*, Mayo Clin Proc., July 2011; 86(7):634-640

Timeline of the key developments in stem cell technology

1980:	first extraction of mouse embryonic stem cells
1997:	SCNT established in sheep (Dolly)
1998:	human embryonic stem cells extracted for the first time
2004:	first claims about successful SCNT in human cells. Turns out to be fraud.
2006:	mouse iPS cells established
2007:	human iPS cells established
2013:	SCNT in human cells established
2014:	STAP cells established (Stimulus-triggered acquisition of pluripotency) (Fraudulent data as well? See current debate in science columns)