Stem cells – what are they and what is all the fuss about?

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Stem cell session overview

- Stem cells – what are they and what is all the fuss about? – Dr Katie Allen
- Will stem cells deliver the goods – lessons from cystic fibrosis – Prof Bob Williamson
- The politics of embryonic stem cells – is it religion or regulation? – Prof Andrew Sinclair

Talk overview

- What are stem cells?
  - Definitions
  - Scientific criteria for defining a stem cell
- What are the pros/cons of the adult versus embryonic stem cell research?
- What is cloning?
- Where has Dolly gone?

What are stem cells ?

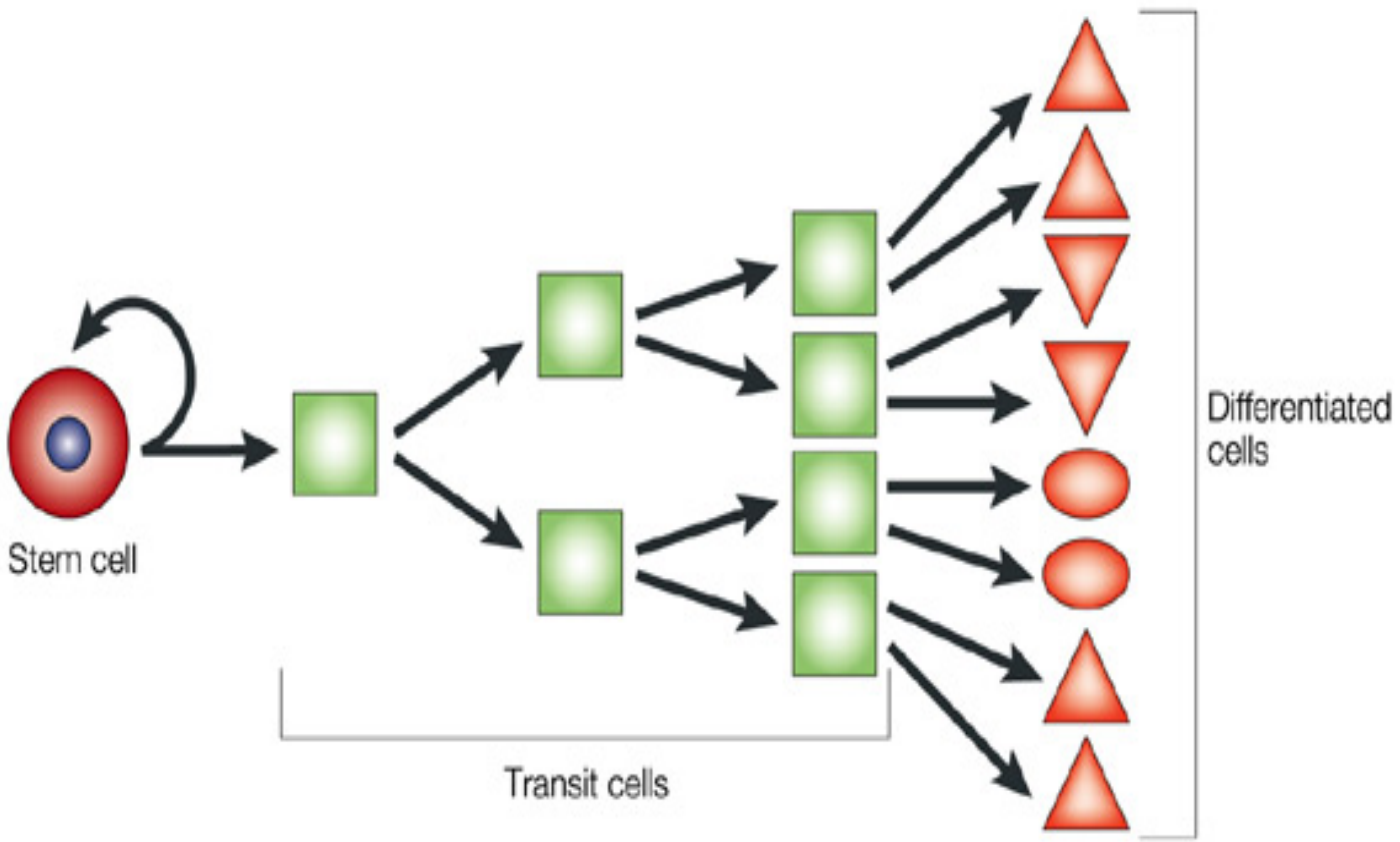
Stem cells are cells in the body that can:

Reproduce themselves

AND

Produce different cell types (differentiation)

Diagram of stem cell differentiation



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Why are stem cells so important?

- There is a worldwide shortage of organ donors and an increasing demand

Stem cells can be used to replace any tissue in the body

Stem cells can replicate and renew themselves

- They are therefore the ideal cell to overcome the shortage of organs for transplantation

Why are stem cells so important?

Stem cells could provide cells:

1. for liver cell transplantation, islet cell transplantation, bone marrow transplantation
2. be grown to provide tissue, eg burns patients or sports injuries
3. Be used for drug testing *in vitro*

There are different types of stem cells

Totipotent – stem cells that can form EVERY sort of cell in the body (eg embryonic stem cells)

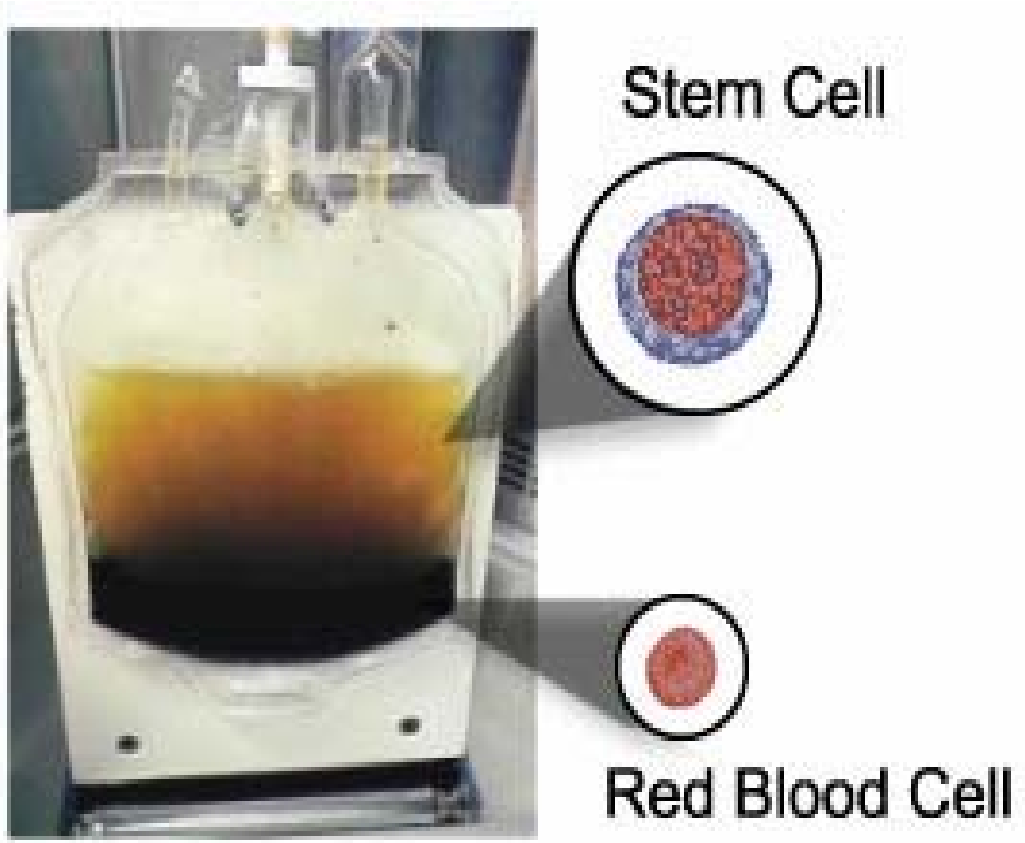
Pluripotent – stem cells that can form MANY different cell types (eg adult stem cells)

What is the difference between embryonic and adult stem cells?

Embryonic stem cells (ES cells) are derived from fertilised eggs that are about 4 days old (BEFORE the egg has implanted in the lining of the womb)

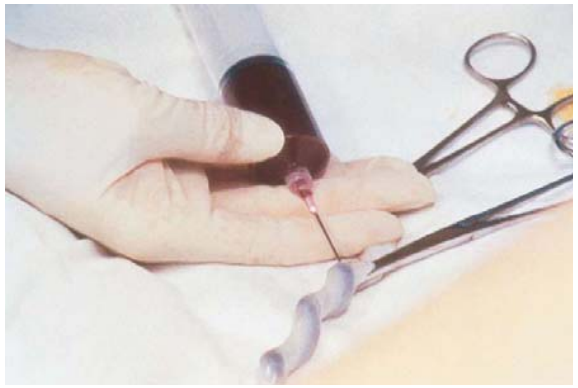
Adult stem cells are derived from tissue such as bone marrow in adults

Adult stem cells reside in many tissues including bone marrow and blood but probably in liver and muscle too

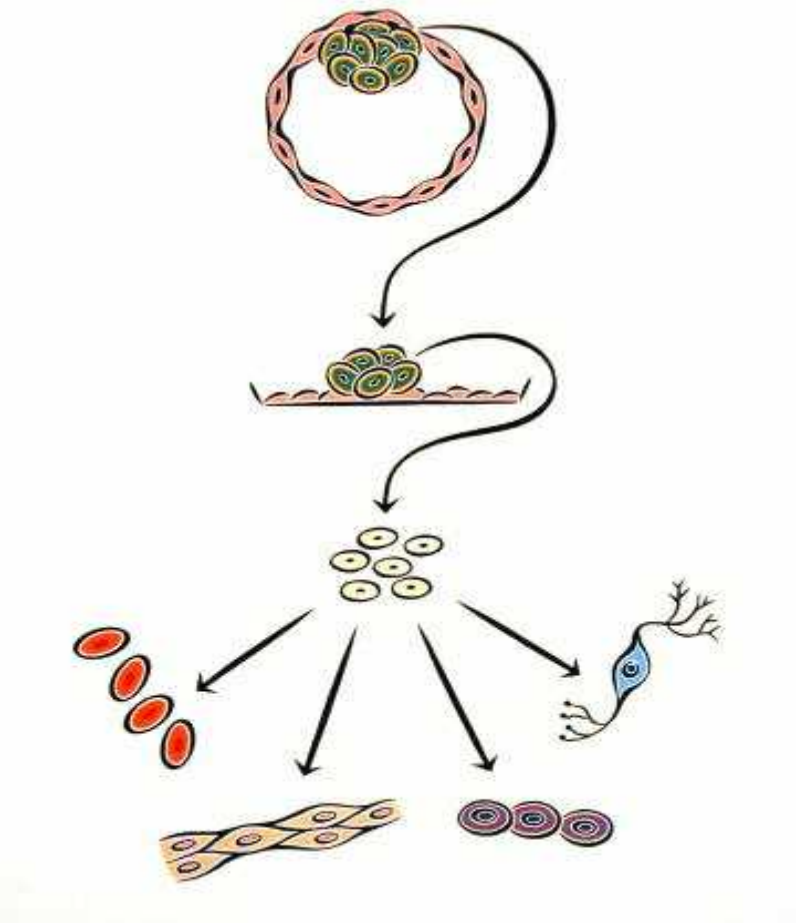


Cord blood stem cells

- similar properties to haematopoietic stem cells but more easily harvested and close HLA matching not so essential



Embryonic stem cells are derived from embryos



What is the controversy over embryonic stem cells?

- Deriving stem cells from embryos destroys them

HOWEVER

- Embryos do not have brain or neural tissue before 14 days of age (similar to brain dead organ donors)
- Legislation permits use of embryos destined to be discarded (by law) by IVF programs

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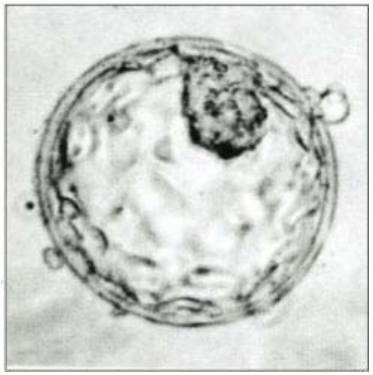
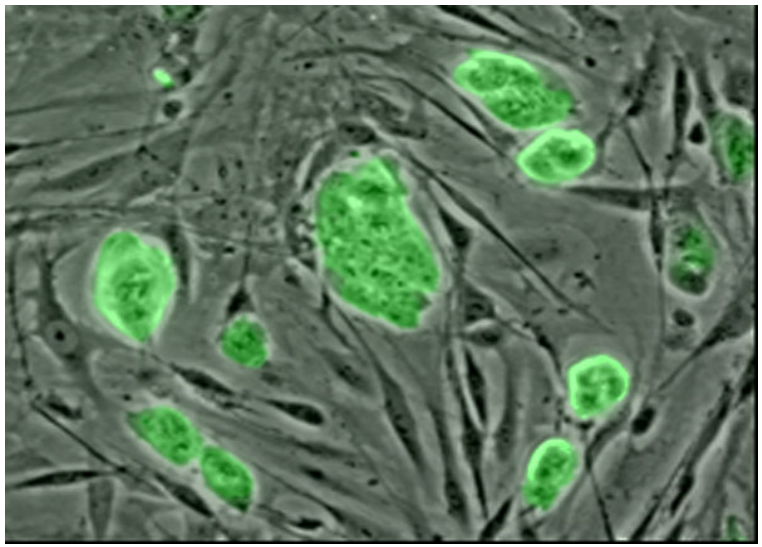
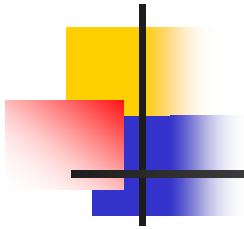
Embryonic Stem Cells





What are the pros and cons of embryonic stem cells?



Pros

- *Should* be able to produce any cell in the body – only truly totipotent cell

Cons

- Considerable ethical dilemmas
- No research to date has reliably shown that human ES cells can be made to differentiate
- No idea whether they will function once they have been differentiated in vitro
- No idea whether they will be immunogenic

The ethical debate centres around

- Should research be prevented just because we are not sure it won't work?

versus

- Why should embryos be unnecessarily destroyed just to satisfy scientific curiosity?

Are there alternatives to destroying embryos for research?

1) Can adult stem cells be reprogrammed to behave as embryonic stem cells

- Recent report from Japan – 4 proteins can re-progam mouse “skin” cells to form mouse ES cells
- Potential to apply this approach to human cells
- Unlawful in Australia if performed on human cells

2) can ES cells be obtained without harming the embryo?

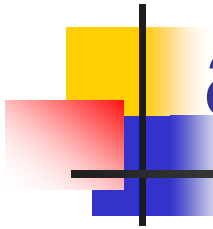
- Recent research – stem cells from one cell taken from eight cell embryo
- Unlawful in Australia
- May be unethical to remove cell for research and then implant seven-cell embryo for pregnancy as embyro may be impaired

3) why don’t scientists do research only on adult stem cells?

- Adult stem cells may have less potential than ES cells (harder to locate, smaller number, DNA may be damaged with age)
- Most scientists advocate researching both areas

Adult Stem Cells

What are the pros and cons of adult stem cells?



Pros

- Easily available with no ethical issues
- Known to work for replacement of bone marrow

Cons

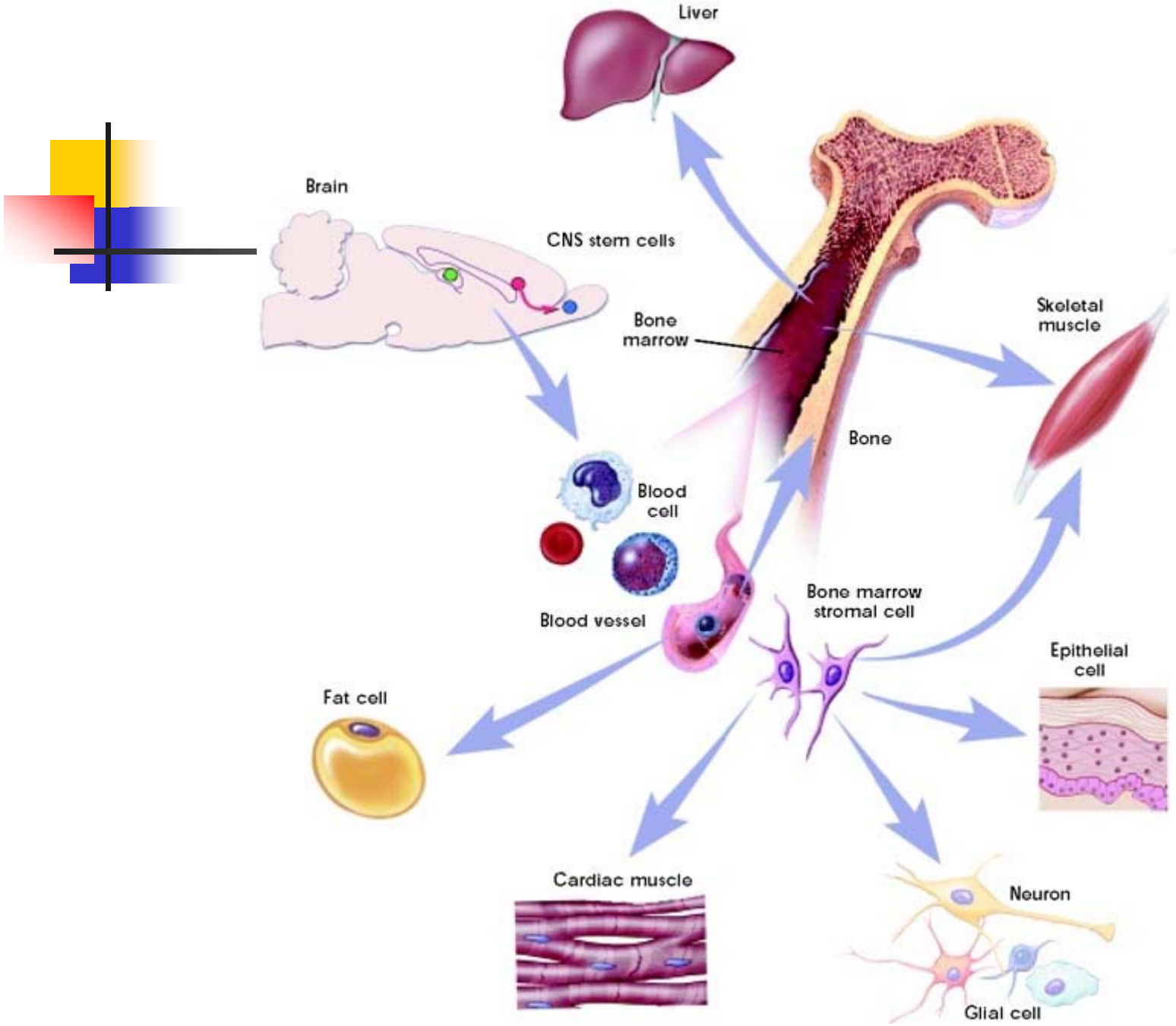
- Highly immunogenic unless autologous
  - Myeloablation and immunosuppression required for allogeneic
  - Large banks needed to improve matching likelihood
  - Currently no genetic or metabolic disease that are treatable with your own cord blood
  - Recent British private/public bank – Richard Branson
- Unclear whether differentiation into other tissue types really occur

Are adult stem cells a feasible alternative?

- Previously thought adult stem cells could not form all cell types (ie were not totipotent)

BUT

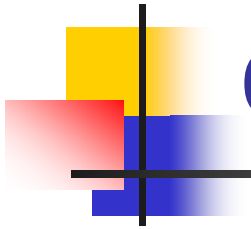
- There is some evidence that human bone marrow cells can become brain, liver, neural, muscle and bone cells


Liver
Brain
CNS stem cells
Bone marrow
Skeletal muscle
Bone
Blood cell
Blood vessel
Bone marrow stromal cell
Epithelial cell
Fat cell
Cardiac muscle
Neuron
Glial cell

What is the research evidence that adult stem cells can treat disease?

- Human studies – co-localisation studies (use immunohistochemistry to show that eg albumin and Y chromosome are co-localising in a female patient who had received a male bone marrow transplant)
- Animal studies – similar findings – for liver mechanism now believed to be due to cell fusion
- Very few studies demonstrating disease correction for any organs post adult stem cell transplant

Definition of a “working” stem cell



- Cell can be driven down the differentiating path in vitro – “biochemist approach”
  - Use morphology, PCR and RT-PCR to show that cell is looking and acting like a differentiated cell
- Disease within organ engenders cell repair – “environmentalist approach”
  - Assess disease correction in a mouse model
  - Very few models have shown this for any sort of adult stem cell – either it they can’t correct disease or there are not the “right” sort of environment for disease correction to occur

What research needs to be done before clinical work can be tried?

- Techniques need to be developed to provide the large number of cells that are required
- Must be “space” in recipient organs to accept the cells
- Immunosuppression is necessary for stem cell therapy unless the cells have been derived from the patient

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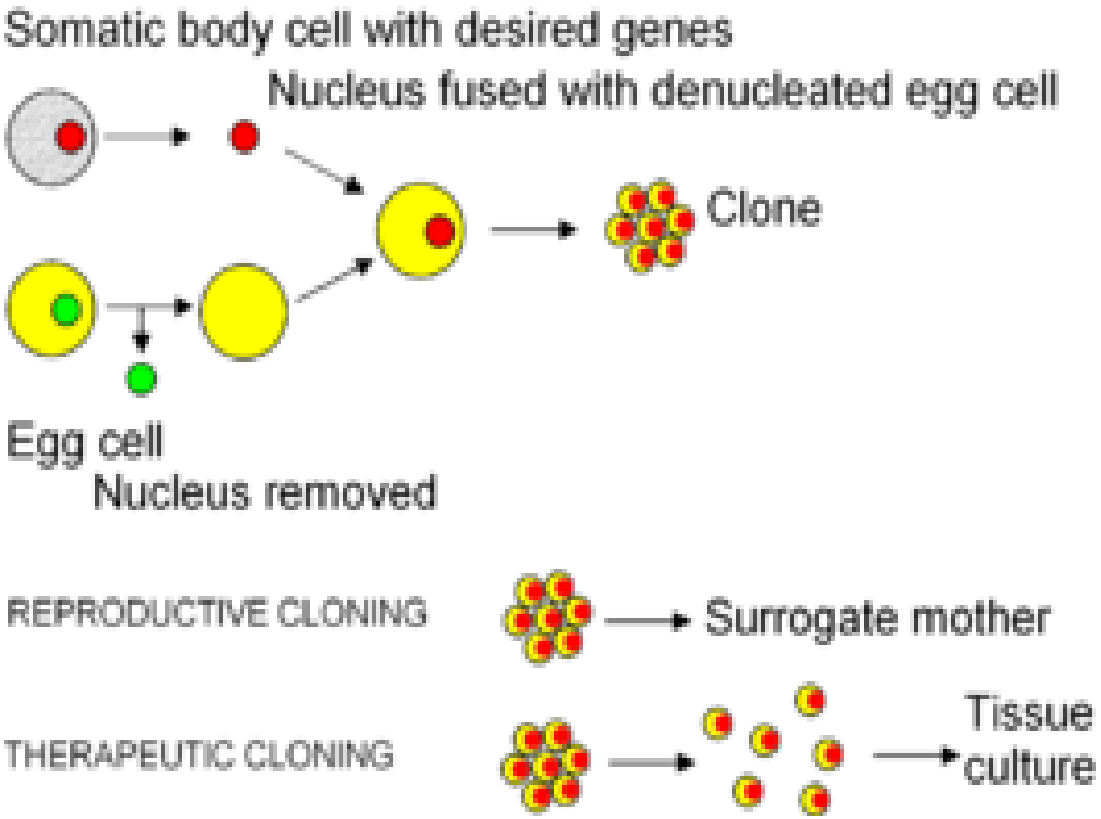
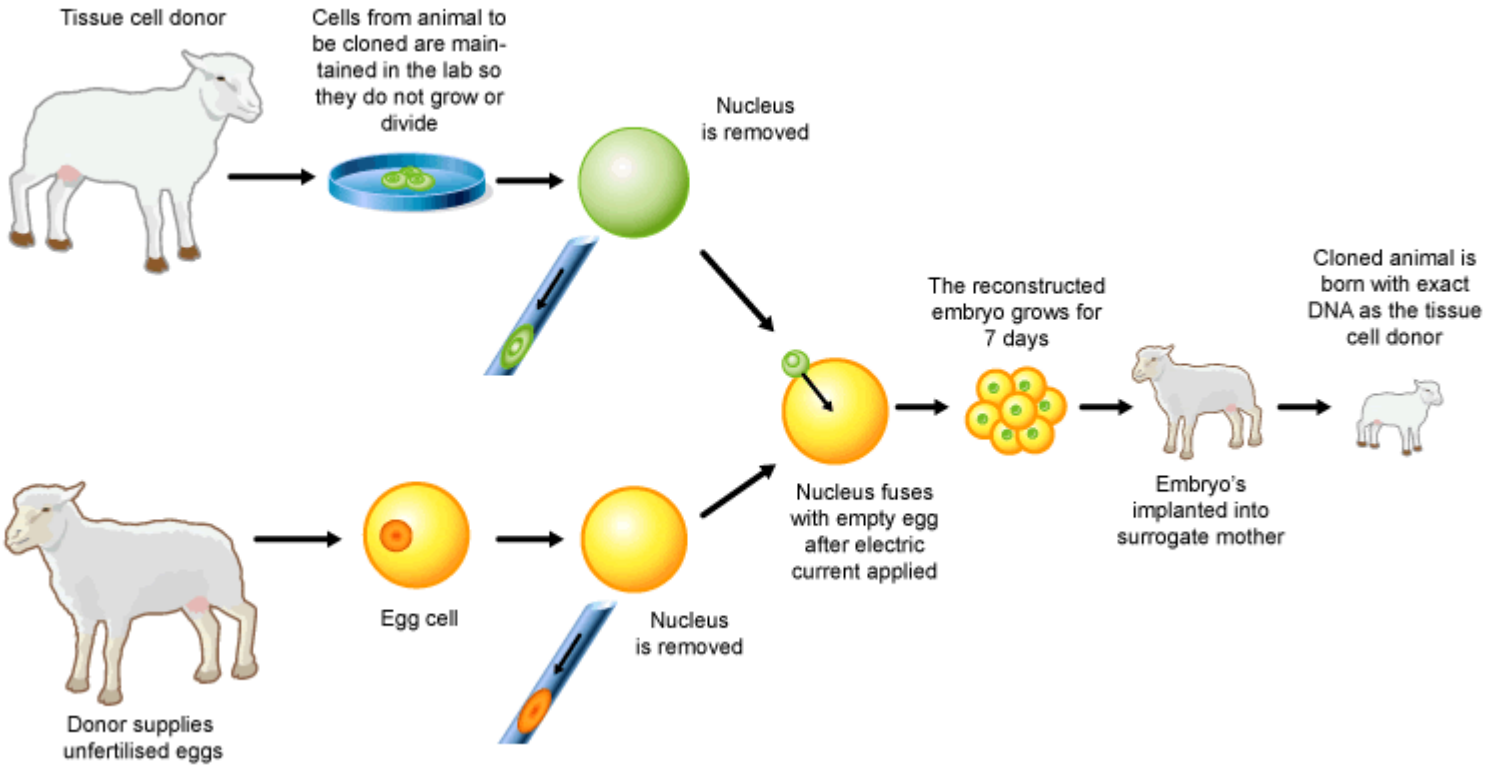
- Where has Dolly gone?
- A cautionary tale!

Cloning


Somatic body cell with desired genes
Nucleus fused with denucleated egg cell
Clone
Egg cell
Nucleus removed
REPRODUCTIVE CLONING
Surrogate mother
THERAPEUTIC CLONING
Tissue culture

Reproductive cloning



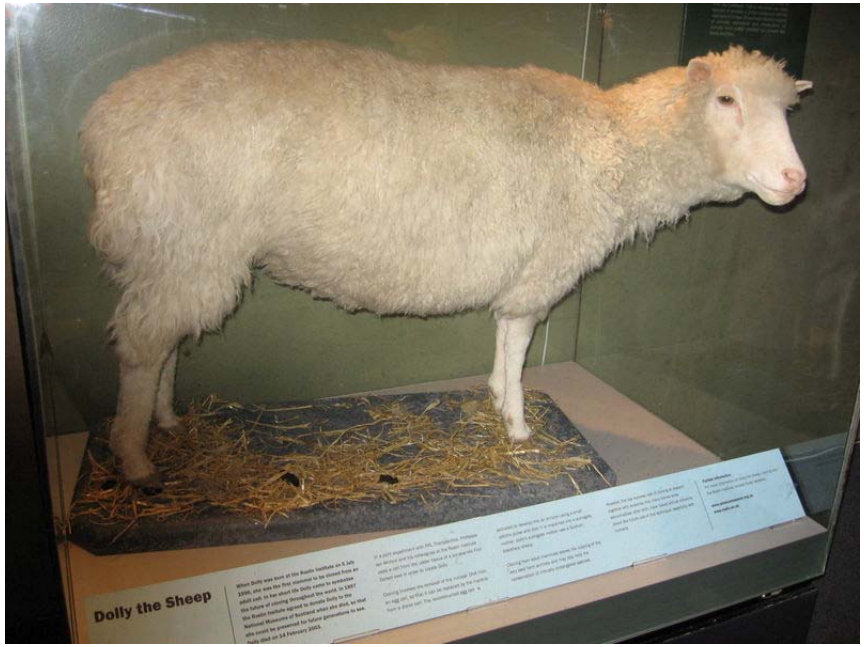
The making of Dolly

- Dolly was the first mammalian clone produced from an adult somatic cell.
- Cloned in 1996 from a mammary cell, named "Dolly", after Dolly Parton
- 277 eggs were used for somatic cell nuclear transfer (SCNT), which created 29 viable embryos, 3 survived until birth and 1 until adulthood

The demise of Dolly

- Controversy when Dolly developed suggestive signs of premature aging at age 3 – shortening of telomeres
- Died at age 5yo, April 2003
- Ovine pulmonary adenocarcinoma, a fairly common disease of sheep caused by the retrovirus JSRV

She remains at Edinburgh's Royal Museum



What is the future of reproductive cloning?

- Many other large mammals have been cloned, including horses and bulls
- However, reproductive cloning is considered a promising tool for preserving endangered species, ...usually by those who do not work in species conservation
- Human reproductive cloning is banned

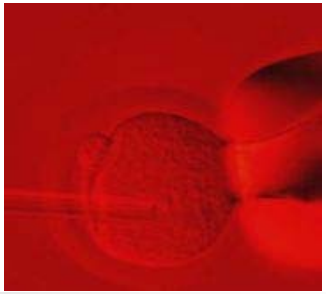
Therapeutic cloning

- Is now referred to as “somatic cell nuclear transfer”
- Endpoint is production of tissue or cells – not an organism

The future of SCTN

- Stem cells have to be *successfully isolated and grown in the laboratory.*
- To be encouraged to *turn into specific cell types.*
- They have to be *proven usable* in treating patients with diseases, injuries, or disorders.
- The transplanted tissue must develop normally and must not represent significant *risks to the patient.*

Conclusions



- The exploration of stem cells for the treatment of disease is of exciting potential

however

- there are significant hurdles before patients benefit from laboratory-based research into stem cell transplantation.