

EMBRYO RESEARCH/ CHIMAERA

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INTRODUCTION I

- 1978 Louise Brown was born in England - the world's first test tube baby
- During In-vitro-fertilisation (IVF), human embryos are created outside the body
- IVF procedures often involve the creation of multiple embryos, only some of which are implanted in any given cycle of treatment



INTRODUCTION II

- Common for IVF laboratories to be left with a number of surplus embryos at the end of the process
- The storage and/or disposal of embryos may place burdens on the IVF clinic
- Start of the debate:
 - What to do with surplus embryos?
 - Should research on human embryos be allowed?
 - When does human life begin?

ETHICAL ASSESSMENT

- Two sides of the medal:
 - Novel therapies which could reduce the suffering through sicknesses
 - Fundamental question of protection of life

FULL PROTECTION

- Potentiality argument
 - Every human embryo can develop into a human being and therefore is potentially a human being who needs protection → irrelevant whether an embryo is actually or only potentially able to develop into an adult human or even to be born
- Identity argument
 - It is the same human being at any time of the development
- Continuity argument
 - An embryo's further development is preprogrammed from the time of its creation through nuclear fusion, the embryo is thus a continuum that can be recognised as an individual it is a human being

MULTI-STAGE PROTECTION

- Arguments:
 - A unborn does not necessarily have the same rights like a born human being
 - The identity of the embryo with the future human being is a fiction, the future person does not exist from the beginning of the nuclear fusion, it only evolves in the course of development through social interaction
 - During the embryonic development there are different steps, which are morally relevant, e.g. nidation, formation of nerve system, birth → therefore an embryo in the blastocyst phase can be treated differently compared to a newborn

THE STATUS OF THE HUMAN EMBRYO

- Moral status:
 - The moral value that something has in its own right, independently of the interests or concerns of others
- Legal status:
 - The law must specify the point at which the developing human being becomes a legal subject
- Problem:
 - It is very difficult to reach a consensus on this issue

HUMAN DIGNITY

- Human dignity is inviolable
 - Recognizing the embryo's dignity means protecting the embryo for its own sake
- Questions:
 - Does that apply equally to embryos created by in vitro fertilisation, cloned embryos, totipotent cells produced by fission and human body cells reprogrammed to become totipotent cells?
 - Are human dignity and the right to life inseparable?
 - How similar or dissimilar is an embryo compared to a human being who has been born?

FREEDOM OF RESEARCH

- Right to freedom of research
 - Primary goal of research: to acquire new knowledge
 - Researchers claim a right to freedom of research with regard to subject matter and methods
 - Research should only be restricted by society for good reasons
 - Society may benefit from this, since it can never be known in advance what findings of basic research may yield beneficial applications

HUMAN DIGNITY VS. FREEDOM OF RESEARCH

- The interests of research lie in generating reliable knowledge and not in promoting the welfare and survival of an individual embryo
- Ethical respect and consideration for in vitro embryos and their claim to protection are based on the fact that they are wholly dependent on protection
- Freedom of research and discovery must be respected but scientific adventurism needs to be checked

GRADUALISM

- Moral status is respected, but the «special status» of the embryo is «not absolute»
- Its status is based on «gradualism»: a middle way between full status and no status
- Full status would not permit use of human embryos; no status would contradict the rationale for the law

EMBRYO RESEARCH

- Scope of application:
 - Knowledge about the complex processes during nidation/implantation
 - New insights into the incidence of malformations
 - Improvement of reproductive procedures
 - New concepts for contraception
 - Derivation of embryonic stem cells from human embryos

PROF. GRATWOHL

STEM CELLS

- What are they?
 - In the 1960s, Till and McCulloch and colleagues provided genetic marking evidence that in mouse bone marrow there are rare cells, some of which contain cells that can self-renew
 - Have the capacity to renew themselves
 - Have the potential to differentiate into different cell types

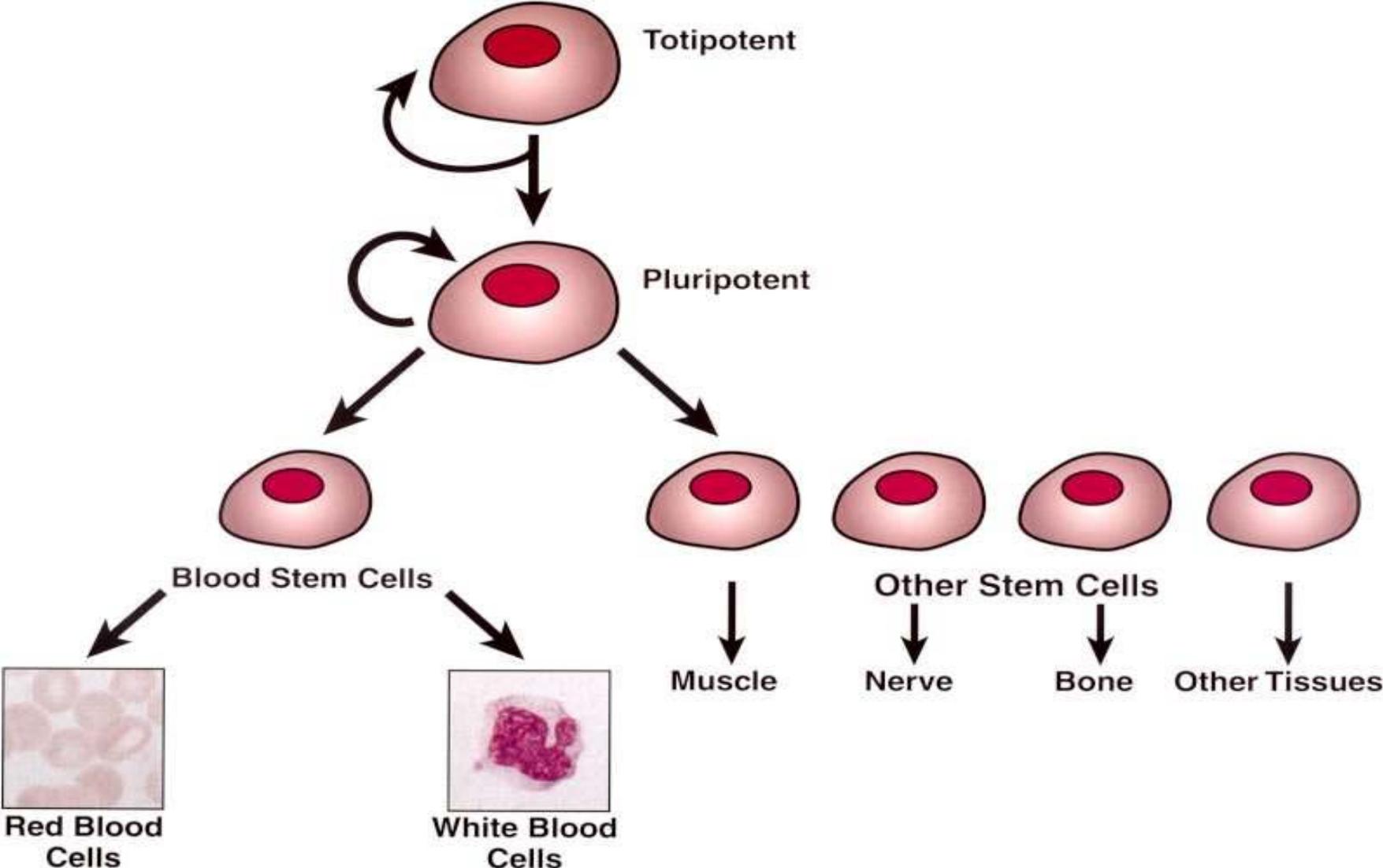
STEM CELLS - CATEGORIES

- Different categories of stem cells by method of production:
 - Stem cells from adult organism/tissue (e.g. bone marrow)
 - Stem cells from cord blood
 - Fetal stem cells from aborted fetuses
 - Embryonic stem cells
 - From surplus embryos after IVF
 - From embryo's that were produced for research

HUMAN EMBRYONIC STEM CELLS (HESCS)

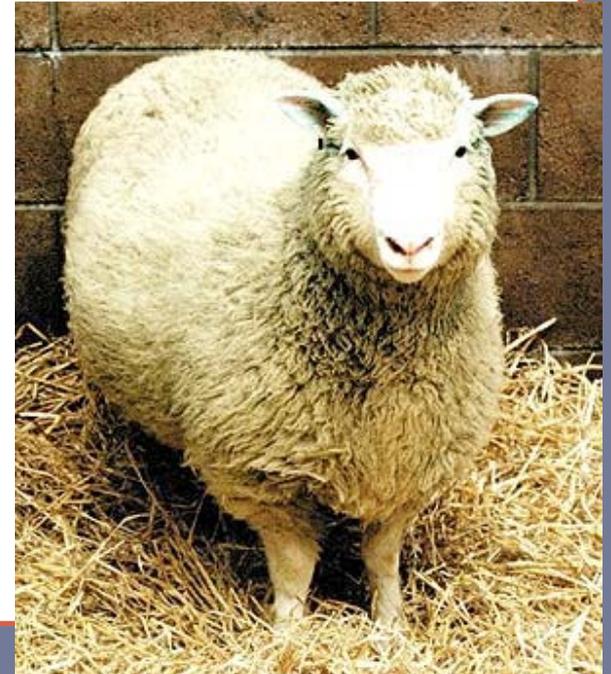
- Early original cells with high multiplication as well as unilateral and multilateral polarization potential
- Different types, or potencies of stem cells:
 - *Totipotent*: one of the most important stem cell types, have the potential to develop into any cell found in the human body
 - *Pluripotent*: derived from totipotent cells, have the potential to differentiate into almost any cell in the body
 - *Multipotent*: formed from pluripotent cells, can only give rise to one or two closely interrelated type of cells

Hierarchy of Stem Cells



«CLONING»

- Producing a genetically identical copy of an organism by replacing the nucleus of an unfertilized ovum with the nucleus of a body cell from the organism
- Dolly: 5 July 1996 - 14 February 2003
 - Cloned by Ian Wilmut, Keith Campbell and colleagues at the Roslin Institute near Edinburgh in Scotland

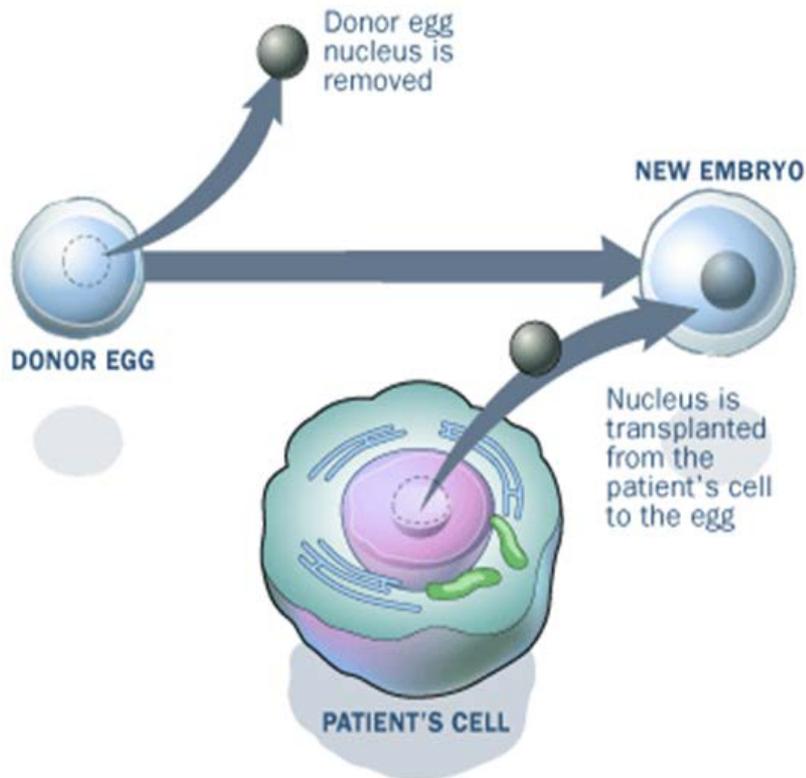


CELL NUCLEAR TRANSFER (CNT)

- The nucleus from an adult cell is inserted into an egg from which the nucleus has been removed
- The resulting embryonic cells contain nuclear DNA identical to that of the donor of the adult cell
 - Therapeutic Cloning (for regenerative therapy for the individual donating the adult cell)
 - Reproductive Cloning (procedure that created Dolly)
- Slippery slope:
 - If we allow therapeutic cloning, then reproductive cloning will be the next step

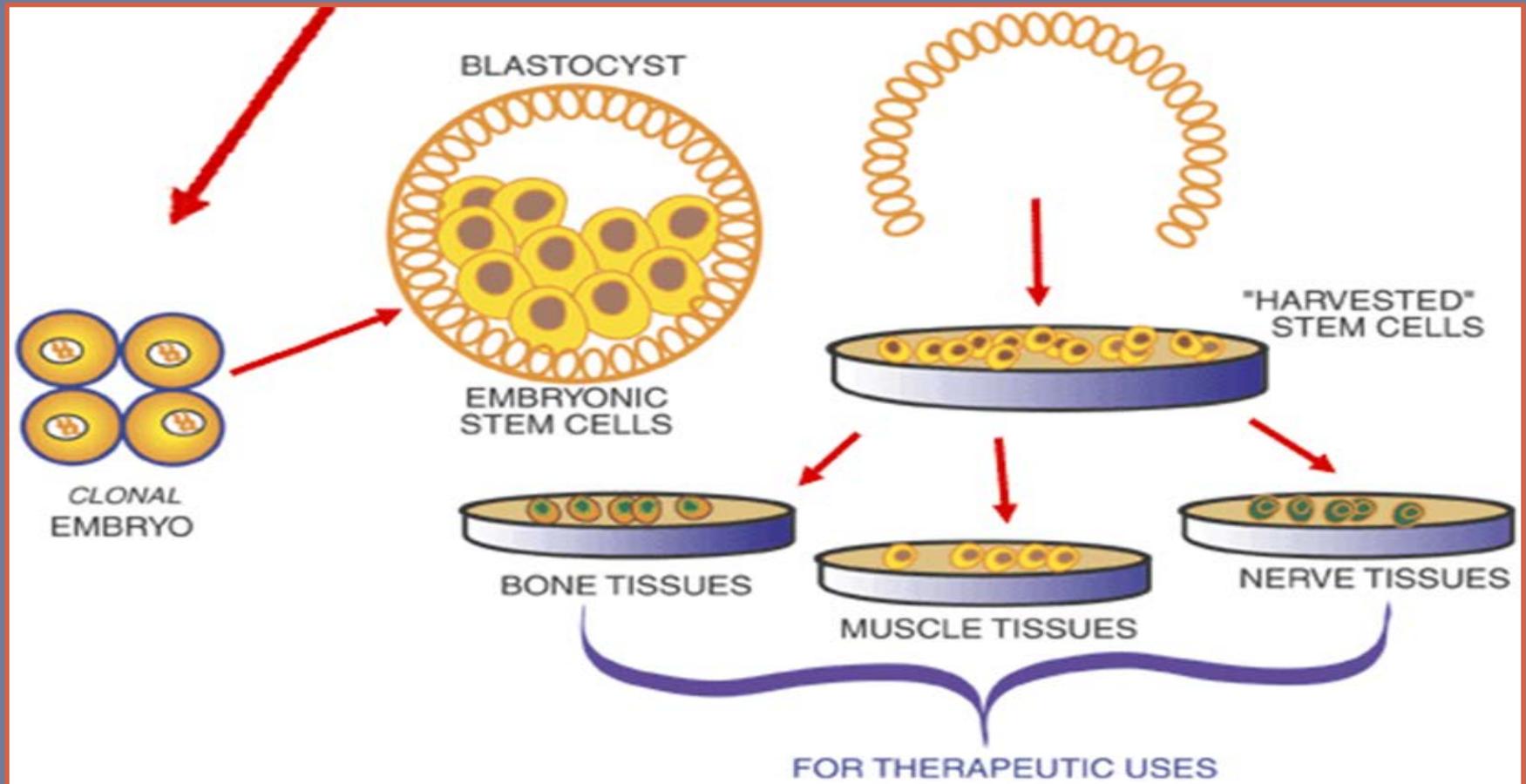
THERAPEUTIC CLONING I

How Stem Cells Work: Therapeutic Cloning

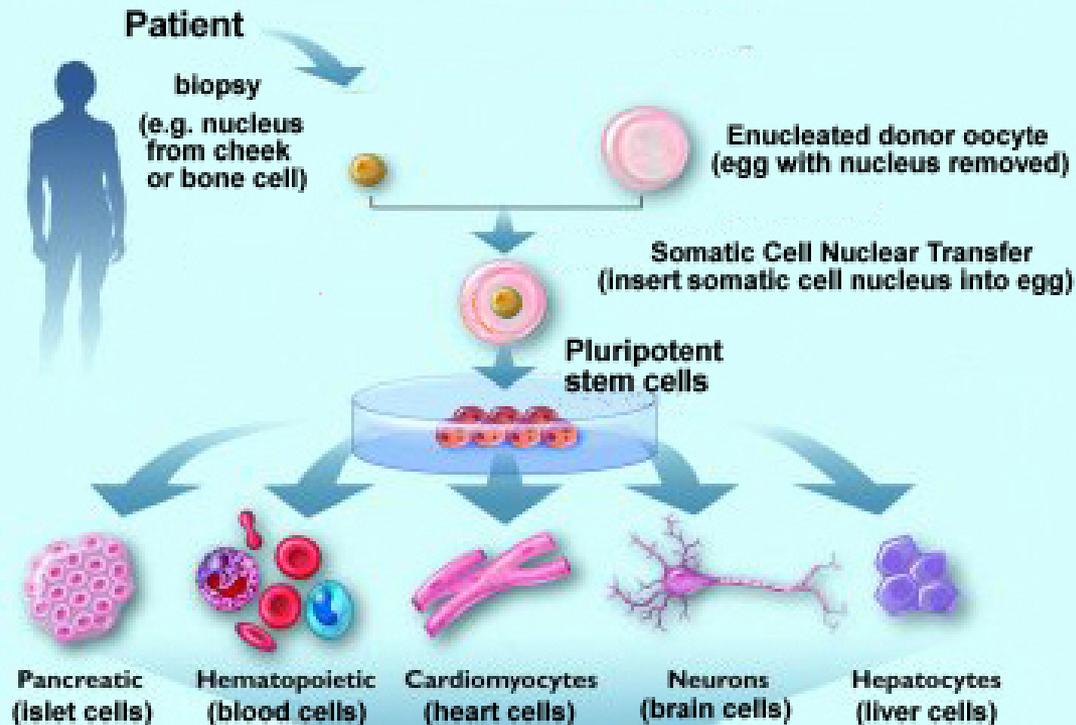


- Source of embryonic stem cells or other tissues, which might be used as the basis of various life-saving medical therapies
- These cells would be genetically identical to the DNA donor's own cells, the problem of tissue rejection would not arise

THERAPEUTIC CLONING II



Human Therapeutic Cloning (SCNT)

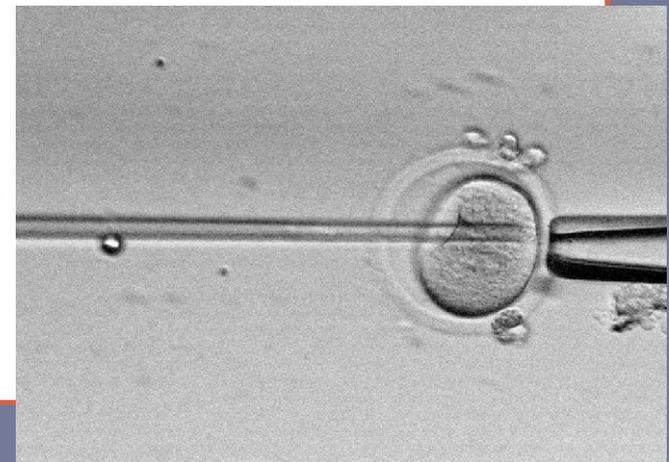


Note: Tissue restoration is NOT the only aim of SCNT. The research is expected to deepen our understanding of disease origins and development, and to improve the testing of new medications.

**Immunologically
Compatible
Transplant**

REPRODUCTIVE CLONING

- Might play a central role in the development and application of clinical procedures that would allow the sourcing of tissue for rejection-free transplantation and other therapies
- Might serve as a new technology of assisted reproduction that could allow couples suffering from certain forms of infertility to have children who are «genetically related» to them



INDUCENT PLURIPOTENT STEM CELLS (IPS) - ADULT STEM CELLS

- Adult cells that have been genetically reprogrammed to an embryonic stem cell-like state by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells

AIM OF STEM CELL RESEARCH

- Treatment of cancer, diabetes, nervous tissue disease, immunity disease and genetic disease
 - Therapy for multiple sclerosis
 - Replacement of destroyed brain cells for Parkinson's or Alzheimer disease
 - Renewal of destroyed heart muscle cells after heart attack
 - Renewal of bone cells in cases of osteoporosis
 - Production of organs for transplantation

IS EMBRYONIC STEM CELL RESEARCH NECESSARY?

- Your opinion...
- Possibility of differentiating adult stem cells into a wide range of different cell types obviates the need for continuing research on embryonic stem cells

POSSIBLE POLICY OPTIONS

1. No human embryo research is permitted
2. Research is permitted only on existing embryonic stem cell lines, not on human embryos
3. Research is permitted only on surplus embryos
4. Research is permitted both on supernumerary embryos and on embryos created specifically for research through IVF or SCNT

SWISS LEGISLATION I

Art. 119 Swiss Constitution - Reproductive medicine and gene technology involving human beings

2. The Confederation shall legislate on the use of human reproductive and genetic material. In doing so, it shall ensure the protection of human dignity ... and shall adhere in particular to the following principles:
 - a. all forms of cloning and interference with the genetic material of human reproductive cells and embryos are unlawful.
 - c. the procedure for medically-assisted reproduction may be used only if infertility or the risk of transmitting a serious illness cannot otherwise be overcome, but not in order to conceive a child with specific characteristics or to further research; the fertilization of human egg cells outside a woman's body is permitted only under the conditions laid down by the law; no more human egg cells may be developed into embryos outside a woman's body than are capable of being immediately implanted into her.
 - d. the donation of embryos and ... are unlawful.

SWISS LEGISLATION II

- Stem Cell Research Act
- Reproductive Medicine Act (FmedG)

INTERNATIONAL LEGISLATION

- Germany
 - 1991 - German Embryo Protection Act (Embryonenschutzgesetz - ESchG)
 - 2002 (2008) - German Stem Cell Act (Stammzellgesetz - StZG)
- United Kingdom (Least restrictive country)
 - Warnock Report 1984:
 - Basis of the Human Fertilisation and Embryology Act
 - «The status of the embryo is a matter of fundamental principle which should be enshrined in legislation»
 - 1990 (2008) - Human Fertilisation and Embryology Act: set up a statutory body to regulate research on human embryos
 - Has not signed the 1997 Convention on Human Rights and Biomedicine in part because this prohibits the creation of embryos for research

RECOMMENDATIONS

- 2006 - Swiss National Advisory Commission on Biomedical Ethics (Nationale Ethikkommission im Bereich Humanmedizin - NEK)
 - The period within which embryo research is permissible should be restricted to the blastocyst stage (6-day limit)
 - An extension of the time frame e.g. to 14 days, as in certain other countries, is not recommended
- National Academy of Science (NAS) U.S.
 - They allow the creation of human embryos for research purposes so long as they are destroyed prior to 14 days of development or the appearance of the primitive streak

CROSS-SPECIES

- Background:
 - Cross-species:
 - Differentiated into chimaera and hybrids
 - Chimaera:
 - Connotes the ancient Greek mythological creature comprising the head of a lion, midsection of a goat, and tail of a snake
 - Hybrids:
 - Already known between animals which are closely related within the zoological systems



HYBRIDS

- Hybrids (Genetic crosses):
 - 1:1 genetic mixes which arise through crossing, created by breeding animals of different species or varieties
- Examples:
 - Hybrid cross between Lion and Tiger: Liger, Tiglon
 - Hybrid cross between Horse and Donkey: Mule, Hinny



Mule Production



CHIMAERA

- Chimaera (Cell crosses):
 - Organisms composed of cells of different embryonic origin
 - Mixtures of cells; can be combined either in the early development stage or after an individual is fully developed
 - 1998, Washington D.C. - first try to patent chimaeric embryos and animals with human cells by Stuart Newman, finally unsuccessful in 2005
- Examples:
 - 1984 Sheep-goat chimaera → «Geep»
 - Established experimental models
 - Transplantations of human tumour tissue to the nude mouse
 - Mouse chimaera: used to study liver diseases/to test antiviral drugs



STATE OF THE ART

- A wide range of genetically altered and chimaeric animals are used
 - The use of adult animal tissue in humans for therapeutic purposes e.g. animal heart valves, is largely accepted
 - Has made significant contributions in many fields
 - Is likely to be even more used in the future

BUT

- The creation of cross-species has certain biological limits
 - Usually they are not capable of development (fertile hybrids are known to be rare and usually unsuccessful, the combination of sheep-goat embryos is an exception)

PURPOSE

- Cross-species consisting of cells and genetic material of animals and humans are generated for various purposes
 - For the purpose of research
 - For human medical therapy (organ transplantation - xenotransplantation)

REASONS

- To understand human bodily functions and human diseases where cell - or computer based alternatives alone will not suffice
- To determine the role of a specific piece of human DNA, by seeing what effect it has in a living animal
- To assess cell behaviour upon transplantation, especially migration, division and determination
- To test and develop methods of diagnosis, drugs and other treatments for human disease
- To use enucleated nonhuman oocytes transplanted with human DNA as stem cell sources

ETHICAL ISSUES

- Focus of the debate:
 - Protection and dignity of humans - how the resultant animals might threaten «human dignity»
 - To a lesser extent the protection and dignity of the animal

SOCIETY'S CONCERN: WHERE DOES BEING HUMAN BEGIN? WHERE DOES THE ANIMAL END?

- Chimaera research could confer upon an animal the moral status of a human adult
- No clear dividing line between the combination of animal species and human species
- Fear of «Humanisation» - the more the human element in such combinations increase, the more it is perceived as problematic:
 - If a gene of human origin is introduced into an animal, it is not yet «humanised»

BUT

Is it a question of percentage? Your opinion!

SPECIAL TOPIC I

- Reserach involving the brain:
 - Introduction of human neural (nerve) stem cells into primate brains to support research on Parkinson's disease
 - Key question is wether populating an animals brain with human cells could result in that animal developing some elements of human consciousness, or 'human-like' behaviour and awareness

SPECIAL TOPIC II

- Reserach involving the reproductive system:
 - Animals containing human DNA and tissue are used to explore the role of human genes in many aspects of reproduction from the development of eggs and sperm through to the process of birth
 - Some work does result in the presence of functional human sperm and/or egg cells in animals which raises the remote possibility that fertilisation between human and animal germ cells might inadvertently occur (in practice this is unlikely)

SPECIAL TOPIC

- Reserach involving human appearance or behavioural traits:
 - When experiments significantly alter the appearance or behaviour of animals in characteristics that distinguish humans most from our close evolutionary relatives

PROBLEM

- Could have a wide array of unexpected and/or deleterious effects, these might not emerge immediately but only as offspring are produced
- Zoonic infections:
 - Experiments that bring human and animal tissues close together might lead to the activation of dormant human or animal viruses within an animal and allow them to recombine, swap their genetic material and possibly create new diseases risks
- Experiments of this kind should be subject to thorough risk assessment and appropriate control measures

SWISS LEGISLATION I

- Article 119, paragraph 2, letter b, Federal Constitution of the Swiss Confederation:
 - «Non-human reproductive and genetic material may neither be introduced into nor combined with human reproductive material»
- St. Gallen Commentary on the Federal Constitution
 - «The combining of human and animal can harm not only the dignity of humanity but also the human dignity and personality of the unique individual human being»

SWISS LEGISLATION II

- Article 36, Swiss Federal Act on Reproductive Medicine (Fortpflanzungsmedizingesetz)

Generation of Clones, Chimeras and Hybrids:

«The generation of a clone, chimaera or hybrid is punishable by imprisonment. Anyone who transfers a chimaera or hybrid to a woman or animal will also be punished»

RECOMMENDATIONS I

- Swiss National Advisory Commission on Biomedical Ethics (NEK)
 - The possible development by the chimaera of a rudimentary form of the perception, sensibility, experience or consciousness of humans or another animal species can not be excluded
 - Reservations in relations to the formation of organ parts or partial structures of humans in animals and in relation to interspecies chimaeras in human research or therapeutic purposes are justified from a *human ethical perspective*

RECOMMENDATIONS II

- 2005 National Academy of Science (NAS) U.S.
 - Prohibit the transfer of hESCs into nonhuman primate blastocysts and the transfer of any embryonic stem cell (including hESCs) into human blastocysts and prohibit the breeding of any animals into which hESCs have been transferred at any time
 - Arguing that «if the recipient blastocyst were from an animal that is evolutionary closer to a human, the potential for human contributions would appear to be greater»
- International Society of Stem Cell Research (ISSCR)
 - Recommends that institutions prohibit the implantation into a human or a nonhuman primate uterus of any embryo into which hESCs have been introduced
 - «Research with the known, intended, or well-grounded significant potential to create humanized cognition, awareness, or other mental attributes, while not absolutely prohibited, should be subject to close scrutiny, taking the most careful steps to collect data pertinent to ethical protection of animal subjects, and an extraordinary degree of justification»

DIFFERENCES IN LEGAL REGULATIONS

- Swiss legislation is highly restrictive and far more stringent than that of the United Kingdom where the generation of chimaeras for research is allowed
- Guidelines developed by international scientific groups can encourage common standards
 - BUT: all this creates uncertainty about what is acceptable and opens up the possibility of researchers seeking to locate their work in certain countries to avoid particular restrictions
 - Consistency in standards or research practice and of ethics at an international level would be helpful and desirable

WHAT IS NEEDED?

- Specialist knowledge
- Sensitive judgement
- To draw up appropriate guidelines for researchers
- National expert body
 - To maintain trust and ensure accountability, this body needs to operate transparently and to engage with the public, as well as with the scientific community

CASE VIGNETTE - EMBRYO RESEARCH

CASE VIGNETTE - CHIMAERA

- Is there a need to distinguish between the use of apes and all other non-human-primates for research?

CASE DISCUSSION

- Discussion of the morality of therapeutic cloning has focused on the ethics of creating and destroying embryos for the purpose of medical procedures
- Instrumentalization and destruction of human life
- By modern biomedical technology, it is possible to produce every tissue from hECSs to repair and replace the pathological or decrepit tissue and organ of human
- Countless symbiotic alien organism and endoparasites reside permanently in every human being and animal

ETHICAL ASSESSMENT

- Playing god - unnatural
- Precautionary principle: «Better safe than sorry»
- These sensitive experiments warrant careful scientific and ethical thought by the national body of experts before they are carried out

PROBLEM

- When it comes to an elevated alien species proportion, when structures, organ parts or organs are formed using human cells in an animal organism, when control is taken of the development of the host organism and when, in the case of transplantations into the brain, the characteristics of humans or another animal species arise in the animal

SWISS LEGISLATION III

- Comes under the definition of animal experimentation, regulated by the corresponding provisions of the Swiss animal protection legislation
- The effect of chimaera/hybrid generation on the animal is legally restricted solely by the animal protection legislation - Swiss Federal Act on Animal Protection (Tierschutzgesetz)
- The regulations require interpretation and are not linked with any clear ethical statements on the justifiable boundaries in the generation of cross-species

- The legal system cannot provide a definitive answer to the meaning of life, all it can do is to acknowledge that all forms of human existence, however small and inconspicuous they are, have meaning and dignity
- The technology to clone a human being does not currently exist, the ability to use iPS cells to make a chimaeric human may be much closer
- This technology has immense power and it is imperative that an effort is made by scientists and governments to understand the ramification of this new breakthrough and to ensure that it is used in an ethically responsible way for the benefit and progress of humanity