

ETHICAL CONSIDERATIONS IN STEM CELL RESEARCH

General remarks

The entire field of biomedical research and technique is changing very fast. It is therefore necessary to try and find basic or fundamental principles that apply generally, and to avoid a situation where ad hoc rules are set up only to be quickly overtaken by further developments.

Stem cell research includes both theoretical (or basic) and applied (or practical) aspects. The main intended benefits are:

- a) Theoretically, advancing understanding of tissue differentiation, development, repair and ageing.
- b) Practically, the therapeutic use of undifferentiated tissue for organ/tissue replacement or repair.

The distinction between theoretical and applied research, in any field, is one of time scale. In the long run, theoretical advances find application. In the short term, research can address immediate problems. Others problems may arise unanticipated, however. If we knew the outcome of research in advance, we would not have to do it in the first place. Therefore, the benefits of research, like its results, cannot be completely specified in advance. The costs, similarly, cannot always be foreseen. Such costs may include ethical and social costs.

Ethical and social issues arise to some extent whenever scientific research is carried out, because the outcome affects people. In particular, such issues arise in biomedical research because the interests of potential beneficiaries may compete with, and may have to be considered together with costs to society or to other individuals, such as donors. There are relatively clear-cut guidelines on research ethics available elsewhere, e.g. US NIH guidelines on research on human embryonic stem cells.

Medical practitioners have obligations to individual patients, and therapeutic or preventive application of research findings has to be moderated on a case by case basis, such that there is a clear and identifiable benefit and no important general principle is contravened.

Then boundary between therapeutic, preventive, and non-therapeutic intervention is difficult to mark clearly. For example, the principle of intervention to improve on natural genetic endowment would seem to have been established by some uses of cosmetic plastic surgery (for example, breast enhancement). Similarly, recourse to abortion as a method of family planning is only loosely therapeutic, (on the argument that proceeding to term jeopardises the mother's mental state) and is primarily a quality of life issue.

Stem cell research raises a number of such issues, which seem to fall naturally into two groups:

- c) Issues surrounding the origins of stem cells, in particular, the use of embryo stem cells. Even if it is assumed or determined that the source embryos would never have been enabled to develop as individuals, the use of such tissues does

raise assumptions about the status of embryos which have to be addressed. Similarly any claim that no further recourse to embryos is needed does not remove the obligation to address the issues, since the need may still recur. In any event moral principles have retrospective application, though the passage of time may blunt their urgency in particular cases.

- d) Issues relating to the use of stem cell tissue. In general the issues are similar to those relating to organ donation and focus on the need for appropriate regulation.

Stem cell research also prompts consideration of the potential non-therapeutic use of biomedical techniques, which might also include cloning, genetic modification, and artificial fertilization. These techniques allow the power to intervene actively in the physical creation, maintenance, alteration or repair of humans. In so doing they call into question many of the conventional assumptions about the propriety of interfering with the creation or modification of people. They may also be seen as threatening the conventional structure of families.

It should be noted that these ethical issues do not hinge upon a distinction between what is natural and what is not. There is no necessary convergence between what is natural and what is best, though there may be (for example, in recommending mothers to breast feed). In its entirety, medical science is concerned with interventions, whether preventive, therapeutic, surgical, emergency, or aimed at improving quality of life and recommending healthy lifestyle choices. In this sense, it is never natural, though it is ultimately based on the scientific study of natural biological phenomena.

The issues raised in 7 and 8 above are considered in more detail in the following sections.

The origins of stem cells and the use of embryos

Stem cells may come from the sacrifice of embryos, or from adults in the form of umbilical cord or bone marrow tissue donations. There is some difference of opinion as to the merits and potential of stem cell lines from these respective sources, and the extent of likely future requirements for embryos. Balance of opinion appears to be that embryo stem cells have greater potency and potential for therapeutic use than adult cells. However, the ethical issues need to be considered anyway.

As regards adult sources of stem cells the sourcing is not very controversial and is considered under the issue of regulation.

Acceptability of the use of human embryo tissue for stem cell supply is more controversial. Such use raises ethical issues centred on the question of whether or not human embryos can be regarded as disposable for benevolent purposes. An embryo used for the sake of its stem cell tissue is not able to develop to term, and a potential human being is denied existence. Regularising the use of embryos in this way in effect devalues their future human potential in favour of their immediate value as a source of tissue. This is not necessarily an unjustifiable priority, since no realistic possibility of development may ever have existed, but it certainly needs to be examined. The extent to which an embryo should be regarded as having a right to life is disputed and raises strong views, even though an embryo is by definition not a foetus.

Reasons for suggesting that it is acceptable or actually morally desirable to use embryo tissue hinge on arguments that propose that the embryo (as distinct from the foetus), is not entitled to full human status, plus arguments to the effect that the embryos which may be used in stem cell research would never in any event have developed as people. Specifically it can be argued that :

- e) An embryo is only a potential foetus. It has undifferentiated tissues and its form and stage of development are not yet recognisably human. It has no differentiated nervous tissue and so cannot feel pain.
- f) A potential foetus and an actual human should not stand in a relation of equality where human rights are concerned. The needs of adult humans or children deserve more consideration than the needs of embryos, where there is a conflict. This is because adults or children carry an investment of experience (realised potential) and are self-aware.
- g) By extension of (b) it could paradoxically diminish respect for human life to extend the rights and privileges of an adult human to an insentient embryo and treat them as equivalent. It could be seen as implying that awareness and sentience entail no corresponding consideration.
- h) Embryos available as a source of stem cells are in practice those that would in any event not have been allowed to develop to term, having been engendered for other purposes such as fertility treatments.
- i) It is morally objectionable to deny people the benefits of embryo stem cells if (a) to (d) above are accepted. There is ample precedent for sacrificing foetuses in abortions, so an embryo, which is the precursor to a foetus, cannot rationally enjoy a more privileged position if the benefits are deemed as great or greater.
- j) The requirement for further embryos may be very modest.
- k) Creation of embryos specifically for stem cell tissue might be deemed justifiable under (a) to (c) above, but practically speaking it is preferable to outlaw this practice on the utilitarian grounds that the less respect for human life is apparently called in question in the use of embryo stem cells, the better. Moreover, there are objections to reproductive cloning of embryos (see below). It might be useful occasionally to create an embryo for therapeutic cloning, i.e. as a source of stem cells genetically identical to the anticipated host. However, to eliminate the danger of facilitating an illegitimate reproductive cloning attempt, it might be wiser to simply outlaw all cloning.

However, the arguments set out above will not satisfy those who maintain that from the moment of conception an embryo is a human being and should be treated accordingly. Arguments for according full human status for embryos can be summarised as follows:

- l) It diminishes respect for human life not to treat embryos as de facto humans, the arguments above notwithstanding.
- m) By extension of (a), once a decision is made to deny human status in principle to embryos, a precedent will have been set which may extended to other categories of human beings such as the profoundly disabled or the elderly infirm.
- n) Using embryo tissues conflicts with some religious convictions.

This particular issue is not one that is likely to be rationally resolved to the satisfaction of all parties, because the commitments to positions are often driven by moral or religious conviction. However, the following considerations seem salient from the point of view of developing a policy:

- o) Singapore is a secular state, and in the interests of religious tolerance and social harmony specific religious convictions cannot be the basis for determining policy. However, no-one should be compelled to act contrary to their religious or moral convictions. Therefore, if an embryo is to be used in stem cell research, it cannot be in contradiction to an expressed religious or conscientious objection by persons in loco parentis, if any.
- p) Similarly, no person should be compelled to destroy or help destroy an embryo in contradiction to religious conviction.
- q) There is already established legal and medical precedent in Singapore that a foetus does not in all circumstances enjoy the rights of a post-partum child.
- r) The line between an embryo and a foetus is not arbitrary.
- s) The argument that respect for the disabled or elderly infirm will be undermined by regarding embryos as expendable in some circumstances might be mitigated by recognition that a potential benefit of stem cell research is the means to assist these very groups. It is arguable that respect for life actually benefits from the appropriate and controlled use of embryo stem cells.
- t) Sources that rely on the principle of voluntary donation by informed consent of adult donors are preferable to sources that rely on termination of embryo potential, all else equal.

Two fallacious arguments may be mentioned:

- u) Many embryos spontaneously abort anyway, so it is acceptable to utilise embryos in research. The fact that something is frequent does not mean it is acceptable; moreover, spontaneous abortions may reflect biological unviability of particular embryos, and cannot be a ground for asserting the general expendability of embryos.
- v) Destroying an embryo might be destroying a potential genius. This argument is sometimes produced in debates over abortion, but it is fallacious on two grounds. It is selective (it overlooks the fact that one might as easily be destroying a potential retardate), and it is inequitable (implicitly asserts a greater moral right to life of a particular class of people, viz., potential geniuses).

The importance of respect for human life is not in question, but it is best expressed by regulating, not prohibiting, the use of embryos.

Issues relating to the use of stem cell tissue.

Normally the keeping or disposal of human organs or tissue is treated with respect or even reverence, because it is a part of some individual person, or even a complete person, and because it is normally evidence of death. The exception is when organs or tissues are donated. A stock of stem cell tissue has somewhat the character of a stock of blood in a blood bank. Taken together, developments in transplant technology and stem cell research might be held to undermine the idea that there is anything special about human tissue per se. Rather, it supports the view that tissue is quite separate from the individuals whom it comprises. This argument is developed in 20-23 below.

Over time, the constituent cells of the body, other than neurons, replace themselves. Even neurons, however, grow and alter their synaptic connections. These facts make it impossible to reduce an individual's identity to a collection of tissues, because these tissues change over time though the person they instantiate does not. People are therefore defined by the integrated action of their tissues.

If the function of a tissue is maintained, its physical embodiment can change without prejudice to the integrity of the person as a whole. Some, in defining a person, would wish to argue an additional immaterial but essential constituent such as a soul or a mind. Others of a more materialist persuasion might feel that we have no need for recourse beyond the fully functioning brain to account for individuality. In either case, however, there would be wide agreement that integrated functioning is important for a coherent person to exist, i.e. that it is the nature of the system as a whole and not merely its parts that is important. This reflects a shift from structure to function as the defining mark of a person.

If this is granted, it follows that tissue derived from stem cells can be used to repair or construct body organs, as can artificial materials, without any ethical complications arising from an unnecessary sense of residual ownership. For example, if animal tissues, say, or artificial hearts, or synthetic blood, functioned equivalently to the corresponding

natural human article, they could be used in therapeutic ways without incurring any ethical dilemmas. Tissues are just tissues.

Clearly some implications of this dissociation of tissues from people as individuals could offend taste or religious belief. For example, many people might find the idea of animal tissues or organ transplants distasteful, or in some cases prohibited by their religions, but taste and prohibitions are not ethical issues. Treatment is voluntary and no-one need undergo a procedure they find unacceptable. Tissue donation and organ transplants have been generally recognised as acceptable. The exceptions tend to be belief systems generally hostile to medical or surgical interventions, preferring in principle other forms of therapeutic intervention, or none. No-one, however, is compelled to accept medical or surgical interventions, and debate tends to arise only over in the case of minors, where the beliefs of parents or guardians can conflict with the rights of minors as recognised in law.

A further implication is that an individual does not retain ownership of tissue once donated, nor do they have any unique claim on the benefits of research. This does not preclude arrangements analogous to autologous blood donations in any situation in which stem cells could appropriately be maintained for the benefit of the donating individual.

Examples of acceptable donations and their ethical justification include:

- w) Blood donation: immediate saving of life, minimal risk to donor.
- x) Bone marrow transplants: long term saving of life or delaying death. Slight operative risk to donor.
- y) Kidney donation: long term saving of life, sparing the expense and inconvenience of dialysis; some operative risk to donor and recipient, and long term loss of reserve function in donor, who has to rely on a single remaining kidney.
- z) Organs donated upon death of the donor: long term saving of life at no cost to the donor; some potential pain or distress to relatives in the process of securing permission where required (i.e. other than under prearranged donation schemes), or where relatives may object to donation for their own reasons irrespective of the donor's wishes.

The ethical principles that apply in cases like this can be summarised as follows:

- aa) Donor choice. People are free to donate tissue or organs. However, as there may be a risk to the donor, this choice should be one made freely. For this reason donations are not acceptable where there is a conflict of interest such that a donor might feel impelled to donate despite a health disadvantage. Examples arise when tissue or organs are sold, or donated for a consideration. Only autologous or unpaid anonymous donations avoid this problem.
- bb) Donor information. It is necessary that donors be clear, and if necessary reassured, as to the scope and limitations of use of donated tissue, including their agreement to relinquish rights over the tissue and the research or treatments that use it, which have to be determined by research and clinical criteria.

- cc) Donor competence. When the donor is incompetent, being dead, or not of sound mind, decisions have to be made by proxy. The default is that donation does not occur unless the law provides for an alternative default or other provisions have been made.

The donation of stem cell tissue by consenting informed adult donors, whether for research or therapeutic purposes, does not seem to raise additional ethical issues per se, over and above those inherent in donation generally. The risks are low, or non-existent.

In general, therefore, the issues of regulation appear very much capable of accommodation within the rules applicable to organs, and there need be no qualms about research with, or therapeutic use of, adult stem cell tissues.

Non-therapeutic use of biomedical techniques

Emerging biotechnologies, including stem cell research, offer the potential for proactive use of technology to actually design or improve humans, as opposed to therapeutic uses that correct defects, repair injuries, or cure diseases. This implies a great increase in the control that can be exerted over people and society. How then is this control to itself be regulated? This is the concern that lies behind the catchphrase 'playing God'. It may be noted that the concern is over the design. For example, we at present grant parents more or less unlimited rights to produce accidental children by unassisted natural reproductive processes.

To illustrate the problems raised by proactive genetic engineering consider the following hypothetical scenario. If we could in fact freely specify the genotype - as affecting characteristics, personality, ability, physical form and gender of our infants - what restrictions would we want to put upon that choice, and how administer them? If we take a time frame of, say, 20 years, it is by no means clear that this scenario is entirely hypothetical. However, it is instructive to try and imagine, given relatively unlimited power of design, the ways in which we might then see reasons to curb it.

For example:

- dd) Possibility of choice raises the possibility of losing it and substituting totalitarian control.
- ee) The interests of parents may conflict with each other, or their children, or state interests (e.g. gender choices under a one child policy).
- ff) Ignorance of pleiotropic genetic effects or interactions might subvert good intentions.
- gg) It undermines the notion of individual autonomy to (in effect) create designer children, because the designer (parent, doctor, etc.) carries the responsibility for the kind of person created.
- hh) The intentions of parties may not necessarily be benevolent.
- ii) Insofar as an argument from what is natural has any force, it has force in arguing for a conservative approach to engineered change, because human nature, being a product of evolutionary pressures, is an integrated whole. Piecemeal 'improvement' may prove undesirable in the long run in unforeseen ways.
- jj) Those who reject an evolutionary approach for religious reasons would however see engineered change as ethically objectionable or even blasphemous because it usurped the role of the creator.

Examples of potential active interventions designed to improve and design people might include

- kk) Selecting or creating foetuses with favourable genetic characteristics or of a desired gender (as against aborting or discarding those with unfavourable characteristics, actual genetic defects, or of undesired gender).
- ll) Attempting or planning to clone children (the nearest equivalent being the natural occurrence of monozygotic twins).
- mm) Delaying the implantation/birth of a twin to optimise child-rearing (for example, by spacing out children, or in order to gain the experience of difficulties facing the first twin which could then be anticipated in a second identical sibling).
- nn) Using stem cell tissue for organ improvement (as against therapeutic replacement or repair).

Such possibilities would be controversial precisely because they actively go beyond the therapeutic and remedial. As long as medical science was essentially remedial, it enjoyed an accepted ethical position embodied in the Hippocratic oath (cure your patients, do no harm, keep secrets). Once it became possible to go beyond therapy, other issues were raised. Even within therapeutic medicine and surgery there are of course many ethical issues, for example those surrounding consent with children or assisted death, but new ones are raised by new technologies which allow, in effect, a eugenic or design component.

In addition, human societies in general, and certainly in Singapore, take the family unit as core to society as we know it or wish it to be, and techniques that seem to affect or undermine the norm of the family are apt to be found objectionable. It is where families are concerned that the idea of a natural way of doing things has its greatest appeal. Much of the resistance to alternative family arrangements, such as same sex marriages or

voluntary single parenthood, extends also to biomedical techniques that extend the frontiers of what might be possible. Thus, questions arise if, for example, post-menopausal mothers seek to bear children, or parents seek to take action to replace a lost child with another of the same sex, or with a cloned offspring. In the normal way of things, parents have no say in determining the genotype of their offspring. A cloned or genetically modified individual, however, is beholden to his or her creators/modifiers for specific characteristics. This obligation is different from and somewhat beyond the normal family obligations of a natural child. In a very definite sense a designed child therefore less an autonomous or unique individual. The possibility of invidious comparisons also arises once the possibility of an element of 'design' is introduced.

This point needs elaboration. Once it becomes possible to create or modify individuals, the concern arises that those who are less favoured may feel more discriminated against or made to feel excluded more than they otherwise would, because of the implication that imperfection could have been avoided, and that someone is culpable. This is a known effect in certain conditions, such as dyslexia, schizophrenia and autism, where for many years parents were made to feel guilty and children inadequate, because it was believed, in some quarters, that these conditions were a result of inadequate instruction or parenting. The acceptance of dyslexia as having a neuropsychological basis removed this guilt; the idea of the 'schizophrenogenic mother' is not now widespread; and autistic children are no longer regarded as the product of aloof and detached parents. However, some of this guilt might be restored if it became possible to avoid dyslexia, or schizophrenia, or autism, by suitable genetic engineering or by choice of embryos. A similar argument extends by analogy to any mental or physical condition such as intelligence or looks, where an element of genetic modification is possible.

The general claim is therefore that the unpredictability of the individual genome is critical to preservation of individuality.

It would seem therefore, that considerations such as those under 30-35 above should lead to a reluctance to countenance proactive non-therapeutic interventions and eugenic trends generally.

Conclusion

Given that stem cell research is likely to yield benefits for organ and tissue repair and replacement, the ethical issues it raises are those of supply and regulation. In the actual use of stem cell tissue in this way there is no general ethical objection. The issue of obtaining embryo stem cells is ethically resolvable.

When active non-therapeutic techniques are considered, including techniques using stem cells, a conservative position is recommended, since there are a number of reasons for caution, especially ignorance of the consequences and concerns as to the implications for individual integrity.

Issues raised by the Bioethics Advisory Committee

BAC 1. The potential benefits do seem to justify stem cell research, because

- oo) There is obvious benefit in exploring ways in which tissues or organs might be repaired using non-differentiated tissue. The entire principle of using tissue in this way is a new one, and while it is too soon to know the limits of what will prove possible, there can be little doubt but that the possibilities ought to be pursued.
- pp) The benefits and outcomes of research cannot be fully specified in advance.

BAC 2. The merits of embryonic stem cells over other stem cells are debated, but there are grounds for arguing that they have the greatest pluripotency and are in general preferable to cells from other sources. The concerns over sacrificing embryos are not sufficient to outweigh this merit.

BAC 3. It is hard to argue for a restriction on stem cell research to areas with a high level of benefit. This is an issue of prioritisation in research, and priority in funding and support might be given to areas likely to show the greatest benefit. However, the uncertainty of the research enterprise is such that rather than restrict it, a policy of selective prioritisation might be more appropriate. There are no ethical reasons for an actual prohibition on research in advance. Individual research proposals will in any case need to be considered by ethics committees which will take into account both the details for the proposed procedures and its likely theoretical or practical benefit.

BAC 4. Clear guidelines exist elsewhere for informed consent, and should be adopted in Singapore also. In general, however, the donation of stem cells should not be linked to financial benefits or benefits in treatment.

BAC 5. A code of conduct analogous to those governing the management of donated organs or tissues generally will be needed.

BAC 6. It is argued that it is ethically acceptable to utilise embryos. It is probably neither necessary nor desirable to create embryos for research or as a source of stem cells. It might be ethically justifiable to do so should the need exist, but in practice the need can apparently be met from embryos or fetuses incidental to other procedures such as abortion or fertility treatment, and there need be no ethical objection to their use for research. Specifically,

- qq) Ethically, stem cells from aborted fetuses could be used, but practically are not an ideal source.
- rr) Embryos from fertility treatment can ethically be used whenever there is no prospect of such embryo ever developing to term.
- ss) It should not be necessary to create embryos for research in vitro.
- tt) In theory, therapeutic cloning is ethically acceptable, but in practice it might be wiser to ban it.
- uu) Reproductive cloning should certainly be disallowed
- vv) Sale and commercial supply of embryos should be disallowed.

BAC 7.

- ww) Xenografting and xenotransplantation raise no unique ethical problems so long as the principle of voluntary agreement to treatment is observed. There need be no objection in principle to research in this area.
- xx) Sale and commercial supply of stem cells should preferably be disallowed, in favour of some system of distribution that recognises and evaluates the clinical and research intentions of prospective users

BAC 8. It is difficult to see specific ethical objections to cross-species experimentation per se. However, there is widespread public concern over issues of genetic modification generally. It would be advisable to limit cross-species experimentation except in cases where a clear anticipated benefit is unattainable by other means.

BAC 9. The issues raised regarding trials appear no different from those in other areas of research. For example, the extent to which trials might need to be conducted on animals or humans is determined by the need for reasonable certainty as to the safety and efficacy of a procedure.

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