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Commentary

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Therapeutic misconception and stem cell research

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Some are making too good a case for stem cells' medical benefits


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Therapeutic misconception is a problem for all research aimed at developing treatments for human diseases. The term "therapeutic misconception" was originally coined in 1982 to describe a fundamental confusion among research subjects and researchers alike between the goals of research (generalisable knowledge) and the goals of clinical care (improving the health of an individual patient)[1]. However, the phenomenon was recognised and documented as a set of misunderstandings among research subjects about scientific methods such as randomisation and placebo controls, and of underestimation of risk and overestimation of benefit of participating in medical research[1]. The latter is now sometimes distinguished as "therapeutic misestimation"[2].

Dozens of studies have found that therapeutic misconception is pervasive. For example, Appelbaum *et al*. found that 31% of subjects in a research study had inaccurate beliefs about the nature of their treatment (e.g., that they would definitely receive the active treatment as opposed to the placebo because they told the researchers that this was their preference), and 51% had unrealistic beliefs about the nature or likelihood of benefit to themselves of participating in the study[3]. Lidz *et al*. found that 24% of participants in a study reported no risks or disadvantages even though they had been told about such risks[4]. Research by Henderson *et al*. found that a subject's education level and type of disease (e.g., cancer, vs. an inherited condition) correlate with levels of therapeutic misconception about studies of phase I gene transfer trials[5]. A study by King *et al*. analyzed language in consent forms for gene transfer studies and found that many forms combined contentless statements, such as "you may or may not benefit" with statements such as "the hope is that we can improve your symptoms and prolong your life with this treatment", and used terms such as "research" and "treatment" interchangeably[6]. Kimmelman and Levenstadt found in a survey of 286 consent forms that 50% of phase I protocols used the misleading term "gene therapy" and only 23% used "gene transfer research" to describe the intervention. They found similar problems with misleading language in many of the consent forms[7].

Agrawal and Emanuel have claimed that the therapeutic misconception may not be a significant problem in phase I oncology trials[8]. They point out that simply being in a trial confers benefit and that a small, but non-zero probability of remission may constitute a benefit in the absence of any treatment for a fatal disease. Even Agrawal and Emanuel accept a problem for patients who receive subtherapeutic doses (which a substantial portion of phase I oncology subjects receive; see Estey *et al*.[9]). And for frontier research there is less plausibility to the claim of direct benefit and, in the case of gene transfer research, a history of misleading language used in consent forms.

These studies suggest that researchers can and should guard against encouraging the therapeutic misconception, both in informed-consent forms and in publications.

The therapeutic misconception is a particular concern for stem cell researchers for two reasons. First, like gene transfer (formerly misleadingly known as "gene therapy"), stem cell research is a frontier field. The potential for therapeutic misconception is especially large because of the promises already made, such as promotion of California's Proposition 71 to fund stem cell research by slogans such as "save lives with stem cells"[10], and use of the term "therapeutic cloning" before any therapies exist.

Second, some stem cell research will depend upon participation of a class of individuals who are not patients and also not research subjects—egg donors—and for whom a different type of therapeutic misconception can exist. We have argued that this group be called research donors to distinguish them from research subjects[11]. Like organ donors, their participation provides risk but no possibility of benefit. The need for recognising this category of research participants can be seen by considering the difference between women who donate oocytes that fail to be fertilised when undergoing *in vitro* fertilization (IVF) and those who donate specifically for research.

Slogans such as "save lives with stem cells" boost the risk that people will overestimate the benefits and underestimate the risks of participating in stem cell research.

Current regulations in the United States (and California regulations that govern the research funded by the California Institute for Regenerative Medicine) would not recognise these two very different classes of donors as distinct, creating situations in which too much regulation may occur for one class, and not enough for another. Voluntary guidelines for the conduct of human embryonic stem cell (ESC) research issued by the National Research Council–Institute of Medicine recommend that egg donors be treated similarly to research subjects, but again failed to recognise the distinction between research donors and clinical donors[12].

Although it is obvious for healthy egg donors that they will not directly benefit from participation in ESC research as donors, it is likely that they will be recruited from populations of those whose family members have particular diseases and disabilities under study. Even though the likelihood of potential egg donors misconstruing benefit to themselves is very low, and they are by definition participating mainly out of altruism, it is still possible and even likely that some will have a therapeutic misconception about the potential benefit to family members. It is especially important to avoid this misconception, because these research donors face significant physical risks that they would not otherwise incur. Egg donors are thus distinct from sperm donors and from couples undergoing IVF for reproductive purposes.

It is especially important not to abuse or mislead this group of people because, although nearly half of couples undergoing IVF for reproduction reported being somewhat or very likely to donate their embryos for research purposes[13], egg donors have not been forthcoming. As of June of this year, Harvard has been unable to recruit a single egg donor, although hundreds responded to ads[14]. Pursuing oocyte donors from families who are afflicted with disease that are potential targets of future or present stem cell research is likely to be a more successful strategy than attempting to procure them from among healthy young women who typically are paid thousands of dollars to "donate" oocytes for infertile couples. But it will be imperative that these donors comprehend the well-understood risks of being an oocyte donor and also understand that

human ESC research is in its infancy. Even CIRM's strategic plan recognises that it is unlikely that there will be any treatments within the next decade. Women's voluntary donation of oocytes may be critical to research, but it is far too early for women to do so with the expectation that their donation is going to lead to cures anytime soon.

Thus, although all researchers working with human subjects must guard against the therapeutic misconception, stem cell scientists have a particularly heavy burden to make sure that research donors and research subjects alike understand that, so far, experiments are exactly that.

References

1. Appelbaum, P., Roth, L. & Lidz, C. The therapeutic misconception: informed consent in psychiatric research. *Int. J. Law Psychiatr.* **5**, 319–329 (1982).
2. Horng, S. & Grady, C. Misunderstanding in clinical research: distinguishing therapeutic misconception, therapeutic misestimation, and therapeutic optimism. *IRB: Ethics Hum. Res.* **25**, 1–16 (2003).
3. Appelbaum, P., Lidz, C. & Grisso, T. Therapeutic misconception in clinical research: frequency and risk factors. *IRB: Ethics Hum. Res.* **26**, 1–8 (2004).
4. Lidz, C., Appelbaum, P., Grisso, T. & Renaud, M. Therapeutic misconception and the appreciation of risks in clinical trials. *Soc. Sci. Med.* **58**, 1689–1697 (2004). | **Article** | **PubMed** |
5. Henderson, G. *et al*. Therapeutic misconception in early phase gene transfer trials. *Soc. Sci. Med.* **62**, 239–253 (2006).
6. King, N. *et al*. Consent forms and the therapeutic misconception: the example of gene transfer research. *IRB: Ethics Hum. Res.* **27**, 1–8 (2005).
7. Kimmelman, J. & Levenstadt, A. Elements of style: consent form language and the therapeutic misconception in phase 1 gene transfer trials. *Hum. Gene Ther.* **16**, 502–508 (2005).
8. Agrawal, M. & Emanuel, E. Ethics of phase 1 oncology studies: reexamining the arguments and data. *J.A.M.A.* **290**, 1075–1082 (2003).
9. Estey, E. *et al*. Therapeutic response in phase I trials of antineoplastic agents. *Cancer Treat. Rep.* **70**, 1105–1115 (1986). | **PubMed** | **ISI** | **ChemPort** |
10. Kimmelman, J., Baylis, F. & Glass, K. Stem cell trials: lessons from gene transfer research. *Hastings Center Rep.* **36**, 23–26 (2006).
11. Magnus, D. & Cho, M. Issues in oocyte donation for stem cell research. *Science* **308**, 1747–1748 (2005). | **Article** | **PubMed** | **ChemPort** |
12. Institute of Medicine and National Research Council Committee. *Guidelines for Human Embryonic Stem Cell Research*. (National Academies Press, Washington, DC, 2005).
13. Lyerly, A. & Faden, R. Willingness to donate frozen embryos for stem cell research. *Science* **317**, 46–47 (2007).
14. Dizikes, P. Reluctance of egg donors stymies Harvard efforts. *Boston Globe*, June 7, 2007.

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