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# Practical Considerations in Regenerative Medicine Research: IACUCs, Ethics, and the Use of Animals in Stem Cell Studies

*Susan VandeWoude and Bernard E. Rollin*

What is the purview of the institutional animal care and use committee (IACUC) in reviewing stem cell research?

The intent of US federal laws mandating IACUC review of animal-related activities was to satisfy contemporary socioethical concerns by introducing deliberations about ethics and animal welfare into the research process when animals are used. These laws and the system they chartered have worked well for the most part in providing opportunities for consideration of animal welfare as a vital part of animal research. As a result, investigators today are far less naïve about the ethical issues raised by research on animals and typically more sympathetic about the need for such consideration. As evidence of this growing awareness, the literature on and use of analgesia and other modalities for controlling pain (and, more recently, distress) in research protocols have grown exponentially, and the issue of environmental enrichment for animals used in research continues to challenge the research community to consider animal husbandry beyond uniformity in animal care and the provision of a clean cage with food and water.

## Good Ethics and Bad Ethics

Anyone professionally involved in animal experimentation knows that IACUC oversight has had a significant impact on how research is performed. Perhaps less obvious is the role of the IACUC in helping to educate the general public about issues that some people believe are matters of ethics but that in fact are not.

Questions about ethics and morality arise most often across the range of biotechnological investigations, in a phenomenon that has been dubbed a “Gresham’s Law of ethics” (Rollin 1995). Gresham’s Law in economics states that “bad

money drives good money out of circulation.” Thus, for example, in post–World War I Germany, when paper *deutsche* marks were essentially valueless (vast amounts of currency were required to buy a loaf of bread), citizens capitalized on the opportunity to pay off large debts (such as mortgages) with the valueless currency rather than with gold. With respect to the current topic, Gresham’s Law of ethics refers to dicta lacking genuine ethical import. Such dicta proliferated in the absence of the research community’s articulation of the genuine ethical issues that arose in the wake of genetic engineering or cloning; examples of these nonethical pronouncements include “cloning violates God’s will” and “genetic engineering desacralizes nature” or “blurs species boundaries” or “does not show proper respect for the gift of life.” Since such assertions lack clear meaning, they cannot be dispatched by simple responses. How, for example, does one determine the truth of the claim that “cloning violates God’s will”?

Such inflammatory claims unfortunately play well with a scientifically illiterate public. That public sees species as fixed and immutable “natural” kinds and is upset by the rapidity of change in organisms that can be effected by biotechnology, as opposed to the slow change traditionally created by natural and artificial selection. Biotechnology, perhaps more than any other area of investigation, tends to elicit “Gresham’s Law of ethics” because it is seen as tinkering with “the very nature of life.” It may thus raise questions for some IACUC members that go beyond genuine ethical issues.

However strongly felt, matters that allegedly violate religious principles or metaphysical perspectives should not rise to the level of ethical issues in a secular society that strives to separate church and state, as has been discussed in detail regarding stem cell technology (Rollin 2006). Therefore, we argue that the general issue of **the “ethicality” of stem cell use, versus specific implications for animal welfare engendered by animal model-based studies, is beyond the purview of the IACUC** insofar as that issue is largely theologically based.

Politicians and political activists have heatedly debated the morality of stem cell use, resulting in a spate of regulations that may concern the IACUC but do not directly require its oversight. A well-known example is the significant limitation imposed by recent administrations restricting the use of fetal tissue for stem cell development. Regardless of whether this decision is logical based on secular American societal ethics, it remains a major concern in some quarters.

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Thus the IACUC, perhaps in partnership with the institutional review board (IRB) that reviews research on humans or internal committees specialized in reviewing research with human embryonic stem cells, must ensure that researchers scrupulously adhere to all regulations regarding sources of fetal material. However, it is outside the scope of the IACUC's charge to debate the "morality" of stem cell research or to require investigators to address the nuances of public debate surrounding the origin and sanctity of life if they propose to use stem cells to address a scientific question using animal models.

## Chimeras and Clones

A significant and problematic spurious issue will arise when human stem cells, whether derived from fetal tissue or not, are inserted into an animal, creating a chimeric xenograft. Although this process is arguably similar to the use of animals to grow human tumors, tissues, or proteins—routinely practiced in other scientific investigations—the specter of intermixing species genotypes using primordial germ cells would predictably be more likely to raise public concerns. Chimeric entities are, after all, the stuff of nightmares—gorgons, werewolves, mermaids—and the possibility of creating them raises fear of "the Frankenstein syndrome" (Rollin 1995). Such research can elicit cries of "mixing humans and animals," "debasement of human dignity," "failing to respect human nature," and variations on such themes. This sort of response is, as mentioned, unanswerable in rational terms, but nonetheless needs to be addressed and the results of the discussion documented and disseminated.

The use of primordial germ cells to create "clones" of an animal also raises concerns in certain sectors of society. While the existence of identical twins might indicate that this phenomenon occurs naturally, and in fact companies have been founded to preserve genetic material from beloved pets, the creation of Dolly the cloned sheep sparked much discussion about the "ethics" of cloning using tissue from adult animals. Public concern was enflamed by the specter of persons creating genetically identical humans to serve some sinister purpose, but this is the hyperbole of disturbing science fiction.

Again, the debate regarding these issues is beyond the purview of the IACUC's regulatory authority. However, since much research is done with public money and with the permission of the public, scientists cannot be contemptuous or dismissive of public opinion. While not required by statutory authority, the IACUC minutes might reflect discussions of societal concerns, particularly if these involve "hot button" issues such as those described here, in the hope of clarifying the difference between real and spurious ethical issues.

## Practical Guidelines

Reasonable guidelines (adapted from NRC 2005) suggest that protocols incorporating the use of human embryonic stem (hES) cells address the following questions:

- Are hES cells required, or can cells from other primates or animals or nonembryonic human tissue be used?
- Has sufficient animal work preceded the proposed work involving hES cells?
- Might the cell transfer result in the animal's acquiring characteristics that are valued as distinctly human?
- If hES cells are to be transferred into an animal embryo or fetus, have studies (for example, with ES cells from other species or interspecies chimeras) suggested that the resulting creature would exhibit human characteristics that would be allegedly ethically unacceptable to find in an animal?
- If visible human-like characteristics might arise, have all those involved in these experiments, including animal care staff, been informed and educated about this?

Several of these points may have relevance for IACUC or animal care program oversight of hES experimentation, and thus are provided here as a point of reference.

## Issues Relevant to IACUC Review

The ethical issues associated with stem cell research in the context of experimental studies using animals concern possible harm, pain, distress, and disease that may accompany the animal manipulation. For example, standard approaches to transplanting animal stem cells may require induced or genetically engineered immunosuppression, creating the potential for significant morbidity and requiring intensive monitoring and pharmacological management. The IACUC therefore must ensure that the investigator has devoted adequate resources to the monitoring and management of resulting opportunistic infections or tissue damage related to cytotoxins or radiotherapy, for example.

Similarly, stem cell therapies are being targeted to treat diseases that are often severe and debilitating (e.g., diabetes mellitus, arthritis, and neurodegenerative disorders, as discussed in this issue; Joers and Emborg 2010; Song et al. 2010). Animal model systems designed to evaluate stem cell therapy interventions for such diseases must replicate the disease states, which are likely to cause pain and distress in control animals or in animals for which the therapies are ineffective. Because there are often no modalities for controlling the pain and distress occasioned by these diseases even in human patients, the IACUC must consider and weigh the potential for detection and mitigation of pain and distress in these animals, and must carefully evaluate experimental endpoints for these studies. In some cases—for example, when researchers wish to study the full course of the disease—early endpoints are not an option to curtail suffering (Rollin 1995).

Considerations such as immunosuppression and chronic disease expression are not unique or specific to stem cell therapy and have been reviewed elsewhere (e.g., NRC 2008, 2009). Investigators and animal care staff should

- be aware of potential complications of induced disease, immunosuppression, and other conditions that may result in studies involving the use of stem cells in animals,

- be able to recognize symptoms that demonstrate animal pain and distress,
- take actions to symptomatically minimize distress associated with sequelae (e.g., provide ready access to food and water if ambulation is impaired, provide analgesics if possible, maintain hydration), and
- establish well-defined observation frequencies and endpoints for euthanasia in response to anticipated adverse effects.

## Conclusion

While stem cell experiments raise concerns about the dominion of humans in manipulating animals at the level of the genome, most of the issues debated in the press and political arenas about stem cell experiments do not fall under IACUC regulatory authority. It may be prudent to discuss such issues when they are presented during protocol review as a matter of public responsibility, but the primary IACUC issues raised

by animal experimentation involving stem cells recapitulate the common issues of animal welfare attendant upon the induction of immunosuppression or chronic diseases.

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