Stem Cell Network
Réseau de cellules souches

Ethics of Research Using Hybrids, Chimeras and Cytoplasmic Hybrids

By Lori P. Knowles

What are Chimeras, Hybrids and "Cybrids"?

In stem cell research, creating and using human and non-human animal hybrids, chimeras and cytoplasmic hybrids, or "cybrids" as they have been nicknamed, poses some of the most contentious and confusing ethical issues in stem cell science and policy. This confusion arises from different understandings of exactly what hybrids, chimeras and cybrids are. Clear definitions have yet to be firmly established although several authors have attempted to clarify the differences and even offer taxonomies with examples.[1]

In Greek mythology the chimera was described either as possessing the head of a lion, the body of a goat and the tail of a serpent, or as having three heads, one from each animal. Either way, the result was a deadly, repellant monster. This history sets the stage for understanding what a chimera is biologically speaking, and why people often react fearfully to discussions about creating chimeras. Biologically, a chimera is an organism with a mixture of cells from two or more genetically distinct species. Chimeras are mosaics at the cellular level; individual cells are derived from either the host or the donor but not both. Chimeras can be created through transgenesis, a process by which a gene from one species is isolated and inserted in the embryo of another species. Examples of chimeras include humans with pig heart valves, sheep with human liver cells and mice with human neural cells.

Hybrids are created by breeding across species. They are generally the result of combining an egg from one species with sperm from another to form a single embryo. Hybrids contain recombined genetic material throughout their genome and throughout all the tissues in their body. In agricultural experimentation, plant hybrids have been created for over a century through traditional fertilization techniques. The mule is an example of a non-human animal hybrid, being the result of a female horse reproducing sexually with a male donkey.

Cybrids, or cytoplasmic hybrids, are created by taking an egg from a non-human animal and removing the nuclear DNA. This leaves only the cytoplasm or ooplasm of the animal egg which contains a small amount of mitochondrial DNA. Human nuclear DNA or an entire human cell is fused with the enucleated egg to create a cybrid embryo. The resulting embryo possesses human nuclear DNA and animal mitochondrial DNA. The mitochondrial DNA is minute in comparison with the nuclear DNA – approximately 13 genes compared with 23,000 genes. Cybrid embryos are said to be 99.9 percent human, however, it is unclear what effects the mixture of DNA from two different species will have.

Stem cell research and the issue of creating chimeras have been linked for over 10 years. Shortly after the first announcements that human embryonic stem cells and germ cells had been isolated, Advanced Cell Technologies (ACT), a biotech company in Massachusetts, USA announced that it was considering fusing enucleated cow ova with human nuclear DNA to make human/non-human embryos as a cheaper and more ethical source

1 Greely, H.T., "Defining Chimeras ... and Chimeric Concerns" *Am. J. Bioethics* 2003, 3:17–19.

of stem cells than using human ova and embryos. In response, President W. Clinton asked his National Bioethics Advisory Committee to look into the mingling of human and non-human species, saying he was "deeply troubled" by the creation of part-cow, part-human embryos.[2] Although the experiments were not undertaken by ACT and little attention was paid to these inter-species mixes for several years, ten years later the issue of human/non-human animal mixtures in stem cell research has become one of the most current and controversial ethical and policy issues in stem cell science.

Ethical Issues Related to Use of Animals in Research

Most of the ethical issues related to chimeric research are not particular to stem cell science or research. There are experiments that use human/non-human animal chimeras and hybrids in many well-accepted practices. For example, for almost 30 years fertility specialists have been fertilizing hamster eggs with human sperm to test sperm motility. In some ways, chimeric research is an extension of current research in transgenesis to generate 'humanized' animal models for research. But it may also be understood as part of a continuum of techniques within developmental biology established over the past 150 years.[3]

Protocols for chimeric research are well established for embryonic, fetal and adult systems and hundreds of chimeric experiments have been undertaken. Two examples involving human stem cells include the transplantation of human neural cells into the forebrains of a developing monkey in order to assess human stem cell behaviour in monkey development[4] and the insertion of human embryonic stem cells into very young chick embryos to assess human stem cell differentiation in chick development.[5] These experiments are subject to ethical and legal guidelines involving the use of animals in research activities. There have been some stem cell experiments involving cybrids. For example, in 2003 China extracted stem cells from cybrids created using rabbit eggs and human sperm.

2 "Clinton Asks Study of Bid to Form Part-Human, Part-Cow Cells," Nicholas Wade, *New York Times*, November 15, 1998.

3 Robert, J.S. "Model systems in stem cell biology" *Bioessays* 2004, 26:1005-1012.

4 Ourednik et. al. "Segregation of Human Neural Stem Cells in the Developing Primate Forebrain," *Science* 7 September 2001: 293(5536): 1820-1824. DOI: 10.1126/science.1060580

5 Goldstein, R.S., "Transplantation of Human Embryonic Stem Cells to the Chick Embryo" in Human Embryonic Stem Cell Protocols, Turksen, K., ed., (Springer, 2006) at 137, as cited in Robert, J.S. "Model systems in stem cell biology" *Bioessays* 2004, 26:1005-1012.

Why use Chimeras, Hybrids and Cybrids?

The main rationale behind the creation of cybrids, hybrids and chimeras in stem cell research is the creation of a non-human model system. This system enables learning about basic developmental stem cell biology. In addition, one particularly promising avenue of research involves the creation of cybrids using DNA of patients with conditions such as Arterial Lateral Sclerosis (ALS) or other genetic diseases such as Alzheimer's and Parkinson's. These animal-human mixes thus provide an invaluable tool for studying the genetic basis and development of a disease and potentially what drugs or therapies might effectively combat that disease.

For many years animals have been used in research to aid human health and medicine. And, while animal models are an invaluable research tool in stem cell research, there are systemic and cellular differences between animal stem cells and human stem cells. The fact that chimeras or cybrids have human DNA means that they are closer to a human model system and therefore, research data should be more predictive and closer related than data in a pure animal model. While this is true, some have raised cautions about the extrapolation of data generated by animal, chimeric or hybrid models to human data, noting that stem cell biology and behavior between species can be very different.[6] In stem cell research much animal model research is conducted using mice. In December 2008 a team from California announced the isolation of stem cells from rats, which is viewed by researchers as a promising advance as rat stem cells provide a closer model to humans than mice.[7]

Of course the best model system for stem cell research and therapies ultimately aimed at human application would be a human model system. There are, however, research projects performed on animals that are ethically and legally prohibited from being performed on humans. Arguments for the creation of human/non-human animal embryos in stem cell research include the practical and ethical difficulties in obtaining human ova. Animal ova are not scarce or expensive and do not have the same ethical issues attendant. However, where production and procurement of animal ova is involved, issues about proper treatment of animals will apply. These issues are not distinct to stem cell research, but are the same in any research endeavour that uses animals as research tools.

6 Robert, J.S. "Model systems in stem cell biology" *Bioessays* 2004, 26:1005-1012.

7 Buehr, M., Meek, S., Ying Q., et al. "Capture of Authentic Embryonic Stem Cells from Rat Blastocysts" *Cell* 2008, 135(7): 1287-1298.

Use of animals and chimeras in research

In stem cell research non-human animals continue to be an important source of stem cells for scientific and medical research. In addition, the use of animals or animal/human "mixes" provides a way of conducting experiments that either cannot be performed ethically or legally on human research subjects or in which it is not practical to use humans. Most countries have human subjects research legislation that defines the circumstances in which it is permissible to use humans for research. In Canada, institutions that accept funding from the three federal research councils (health, natural and social sciences) or which decide to bind themselves are subject to the guidelines articulated in the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans,1998 (with updates of May 2000 and September 2002)*.[8] Great reliance is placed on institutional research review boards, in Canada called Research Ethics Boards or REBs. These boards are responsible for ensuring that research protocols are valid, appropriately designed, and do not pose inappropriate risks to human subjects. In addition, most countries also have legislation and regulations governing the appropriate use of animals in medical and scientific research. These regulations are aimed at ensuring that the use of animals is necessary for a valid scientific aim, and that animal suffering is minimized wherever possible. In Canada, the Canadian Council on the Care of Animals is a good resource for understanding oversight of animal use in experimentation.[9] In addition to legislation, research institutions also have Institutional Animal Care committees that ensure use of animals in research protocols are scientifically valid and adhere to ethical standards.[10]

For new areas of biological research, such as stem cell research, one of the challenges faced by governing bodies and animal researchers is ensuring that these new developments are adequately covered by existing policies and practices regarding humane animal experimentation. New research areas often develop experimental animal procedures that can introduce animal welfare concerns not covered by current policies and practices. In the case of genetically modified animal models, there has been an overall increase in numbers of animals used in research. This increase runs counter to previous successful efforts to reduce animal numbers – a goal of policies to ensure humane animal experimentation.[11]

Similar to other aspects of stem cell research, governing bodies must be sensitive to whether new developments in animal research captures the contemporary ethical and social concerns about animal use. Unfortunately we know very little about whether or not the use of animals in stem cell research does present new animal welfare challenges. Old research techniques, such as parabiosis (anatomical and physiological union of two organisms), are currently being used in stem cell research. This technique requires high levels of skill and is considered to be a severe procedure in terms of animal suffering.[12] Whether this technique is widely used is unknown. Governing bodies and scientists need to be vigilant to the impacts of their research on the welfare of animals, constantly adapting to new ethical challenges.[13]

In addition to the animal welfare issues, public conversations about animal-human mixes have indicated an ethical unease with these mixes that is reflected in policy. The International Society for Stem Cell Research has addressed some of these issues in its Guidelines for the Conduct of Human Embryonic Stem Cell Research. In particular, they note that the type of tissue that is being transferred (for example brain tissue) and the animal involved, especially other primates may be ethically relevant. The Society suggests that mixing animal and human gametes be carefully monitored. Particular concerns arise when

8 *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 1998 (with updates of May 2000 and September 2002)* (Ottawa: Tri-Council, 1998), online: http://www.pre.ethics.gc.ca/english/policystatement/introduction.cfm

9 Use of animals in research falls under both provincial animal care legislation and under federal criminal prohibitions against cruelty and abuse of animals. While all provinces have animal care regulations in some form, only Alberta, Ontario, Manitoba, New Brunswick, Nova Scotia and Prince Edward Island have legislated with respect to the use of animals in research, teaching and testing. See http://www.ccac.ca/en/CCAC_Programs/ETCC/Module01/toc.html for more information.

10 See http://www.ccac.ca/en/CCAC_Programs/Guidelines_Policies/POLICIES/ETHICS.HTM

11 Ormandy, E.H., Schuppli, C.A. and Weary, D.M. *Worldwide trends in the use of animal research. Alternatives to Laboratory Animals*, In press.

12 LASA (Laboratory Animal Science Association) 1990. The assessment and control of the severity of scientific procedures on laboratory animals. Laboratory Animals 24: 97-130.

13 The author thanks Cathy Schuppi of the University of British Columbia for her assistance on these issues. See Schuppli, C. A., Fraser, D. & McDonald, M. (2004) "Expanding the 3Rs to meet new challenges in humane animal experimentation" *Alternatives to Laboratory Animals* 32, 525-532, and Buehr, M., Hjorth, P. J., Hansen, A. K. & Sandøe, P. (2003) Genetically modified laboratory animals – what welfare problems do they face? *Journal of Applied Animal Welfare Science* 6(4), 319-338.

experiments may transmit genetic changes through reproduction. The Society counsels that chimeric animals should typically not be permitted to breed.[14]

A number of countries have prohibitions on the creation of animal-human mixes including Canada. The *Assisted Human Reproduction Act* (2004, c.2) states in section 5 that it is prohibited to:

(i) create a chimera, or transplant a chimera into either a human being or a non-human life form; or

(j) create a hybrid for the purpose of reproduction, or transplant a hybrid into either a human being or a non-human life form.

The *Act* defines "chimera" as the insertion of any non-human animal cell into a human embryo. The *Act* does not, therefore, cover the creation of cybrids or chimeras in which a non-human animal has human genes or cells inserted.

The Canadian Institutes of Health Research Updated Guidelines for Human Pluripotent Stem Cell Research go further than the *Act* with respect to chimeric research. The Guidelines indicate that research in which pluripotent cells, including embryonic stem cells, of human or non-human animal are combined with a human embryo will contravene the Guidelines. In addition, the Guidelines indicate that research in which human ES cells or other pluripotent cells are combined with a non-human embryo is also not sanctioned.[15] It would seem therefore, that in Canada cybrids can be created using enucleated non-human animal eggs.

In September 2007, the British Human Fertilisation and Embryology Authority (the governing regulatory body that hands out licenses to researchers) allowed three licenses for the creation of cybrid embryos as a source of embryonic stem cells after public consultation on the issue. One of these licenses went to Ian Wilmut, creator of Dolly the cloned sheep, to create cybrids with the ALS gene. In 2008, Britain had a contentious public and parliamentary debate over the ethics of permitting mixtures of human and animal cells for research in a new Human Fertilisation and Embryology Bill. An open vote was held in May 2008 and the creation and use of human animal cybrids and hybrids was passed in the Parliament. This makes the United Kingdom one of the world's most liberal nations with regulatory approval of animal/human mixes. In January 2008, Singapore announced plans to hold a public consultation with a view to creating animal/human cybrids for research into specific diseases. Early results indicate that there is a sharp division in public sentiment. A report will be forthcoming later in 2009.

Why not use human ova and create human embryos as a research model?

Using human ova and creating human embryos for research would circumvent the scientific uncertainties about the translation of data generated in non-human animals to humans. These practices, however, raise serious ethical concerns. First, the number of human ova available for research is scarce. This scarcity is the result of the amount of time invested and physical discomfort that must be endured by a woman to produce enough eggs for retrieval from her body. In addition, the process of ova retrieval is onerous and risky. Women who wish to use their ova for IVF or to sell or donate them must undergo weeks of daily hormone injections to induce hyper-ovarian stimulation. They must be monitored daily as they get closer to the ova "ripening" and then undergo general anesthesia and extraction of the ripe eggs through the vaginal wall. These procedures are not without risks.

Hyper-ovarian stimulation and ova retrieval are usually undergone by women hoping to use their own eggs in a "reproductive project"– an attempt to get pregnant through IVF. In order to have human ova for stem cell research, women would have to donate their eggs for research rather than have them fertilized for future implantation. Some have suggested that an agreement to donate eggs for research could be encouraged by lowering prices of IVF treatments. This, however, is problematic since it requires that a woman give up some possible chances at getting pregnant. Others maintain that it affords women who could not otherwise afford IVF the opportunity to have a chance at a baby. These issues about markets in human tissue, including ova, are more fully discussed in Knowles L., "The Use of Human Embryos in Stem Cell Research" Stem Cell Network and Knowles L., "Commercialization and Stem Cell Research" Stem Cell Network.

14 International Society for Stem Cell Research, "Guidelines for the Conduct of Human Embryonic Stem Cell Research" Art. 10. http://www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf

15 The Canadian Institutes of Health Research Updated Guidelines for Human Pluripotent Stem Cell Research, June 29, 2007, Ss. 8.2.4-8.2.6 http://www.cihr-irsc.gc.ca/e/34460.html

Concerns about naturalness and crossing the species boundaries

In the last few years several authors have written about the ethics of using human/non-human animal mixtures in stem cell research. In those articles they examine arguments against mixing human DNA with non-human DNA. The arguments against the creation of the resulting living organisms range from arguments about whether humans ought to be creating living organisms not envisaged by God, to concerns about human dignity and moral confusion and also arguments that crossing the "species barrier" is in various ways morally repugnant and wrong.

In part, much of the controversy about creating admixtures comes from a view that mixing human and animal DNA upsets a natural order. That is, the products of this research are unnatural in morally relevant ways and/or the process of creating these entities is unnatural and therefore, should be foregone. These arguments are not new to bioethics. Arguments about the moral acceptability of creating unnatural entities (entities not found in natures) or doing unnatural things (things that do not naturally occur outside the laboratory) are found in criticisms of agricultural, animal, environmental and human biotechnology.

Many people express feelings of repugnance or wrongness toward cross-species hybrids. Intuitive negative feelings that some idea or practice is repugnant have been identified as a "yuck" factor.[16] The yuck factor is often used as evidence of the intrinsic moral wrongness of the practice. While the yuck factor has been called the wisdom of repugnance by some noteworthy bioethicists,[17] others caution against using such feelings of disgust as a moral barometer without an appeal to evidence or rational explanation of the wrongness of the practice.[18] Individual and societal concepts of disgust can change over time. Interracial marriage, women voting, and same-sex marriage are all examples of practices that have evoked feelings of repugnance in certain segments of society and have changed or are changing over time.

Before dismissing the yuck factor, however, the feelings need to be unpacked and analyzed to determine if there are compelling moral intuitions at work. First, the idea of creating an entity by interbreeding distinct species is morally repugnant to many. The term "crossing the species barrier" signals a world view in which each species is distinct and "walled off" from every other species by natural reproductive barriers. This "biological understanding of species" in which species are isolated from one another by an inability to reproduce across species lines is pervasive but not persuasive. It does not address the world's most numerous species – those that do not reproduce sexually. There are others notions of what compromises a species, including "natural kinds" or evolutionary lineages but no one definition is entirely compelling. Nonetheless, the biological understanding of species remains the most popular understanding of what categorizes one species from another.[19]

The biological understanding of species also grounds a religious objection to creating entities that were not envisaged or created by God. By creating new living species not found in nature, we move ourselves from "created" to "creator" and may step into the territory generally thought of as "divine providence." Other religious thinkers however, believe the scripture in the Bible that asserts human dominion over all living things entitles us to act as a creative force. The "playing God" argument however, is rarely used to oppose the thousands of hybridized plant species created by humans over several hundred years. Additionally, the use of life-saving xenotransplants in humans such as pig heart valves or the introduction of human DNA into sheep to produce life-saving insulin for diabetics does not occasion much opposition on these grounds. And so, one can suppose that there may be something else at work in these objections.

Still others find the alteration of natural physical characteristics the source of their unease or repugnance. This is especially true when a resulting hybrid or chimera does not fit comfortably into the known cluster of characteristics that we associate with a particular species. So, the introduction of a jelly fish gene into monkeys such that the monkeys glow in the dark is wrong to many people because it breaks the rule "monkeys do not glow in the dark." A reaction to sheep that produce human insulin may be less negative because the sheep still look like sheep. Alternatively, the goal of the research may be judged to fall below the threshold of importance needed to outweigh the costs of doing a very unnatural

16 Midgely, M., "Biotechnology and Monstrosity," *Hastings Center Report*, Sept-Oct 2000; 7-15.

17 Kass, Leon R. "The Wisdom of Repugnance." New Republic Vol. 216 Issue 22 (June 2, 1997).

18 Nussbaum, M.C., "Danger to Human Dignity: The Revival of Disgust and Shame in the Law" *The Chronicle of Higher Education*, August 6, 2004, B6-9.

19 Robert, JS., Baylis, F., "Crossing species boundaries" *Am. J. Bioethics* 2003; 3(3):1-13.

thing. In other words, if the goal of the unnatural process is immediate and life-saving therapy it might be more morally acceptable than remote laboratory research of some future indeterminate benefit.

Concerns About Human Dignity

Some objections to animal/human mixtures enlist notions of human dignity. One commentator articulates the connection between the yuck factor and notions of human dignity in this way, "...in this age in which our given human nature no longer commands respect.... [r]epugnance may be the only voice left that speaks up to define the central core of humanity." The existence of human dignity is a relatively uncontroversial concept in Canada (where it is invoked in the *Tri-Council Statement on Ethics in Research* and in the preamble to the *Assisted Human Reproduction Act*) and in Europe. By contrast it is rarely part of policy and ethics discourse in the United States, where it is often regarded as a fuzzy, ambiguous term. This is in part due to cultural differences which place an emphasis on societal welfare in Canada and Europe and an emphasis on individual autonomy in the United States, but also because human dignity is hard to define in a pluralistic society. At its core, human dignity is something unique and sacred to human identity and membership in the human community, and exists in a rights-based ethical framework. In part, those who argue that animal-human mixtures threaten human dignity are asserting either that human tissue is sacred or that unique and sacred human characteristics are threatened by theses mixtures.

This argument is not new to stem cell research, chimeras and cytoplasmic hybrids, but has been used in conjunction with any number of biotechnological alternations that have been made to the human body. A question that arises is whether creating humans with artificial parts or parts from animals somehow confuses their humanity or compromises their human dignity? So, in 1974 when Barney Clark received the first artificial heart, musings about whether his humanity was compromised and what artificial organ transplants meant for humans took place. Similar discussions occurred in 1984 when Baby Fae received the first xenotransplant heart from a non-human primate (something that is no longer considered medically appropriate). Over time, as these types of interventions become more common we, as a society, often change our views about what they mean for the human race. We have grown accustomed to people with artificial knees, hips and breasts. Similarly, we do not consider people with pig valves in their hearts to be less human or have less human dignity than any other human. There are however, certain hybrids or chimeras that many agree do have implications for human dignity.

Human-Mouse Neural Transplant Research

The question remains open as to whether there is any threshold level of xenotransplantation beyond which a transplant recipient's humanity would be in question. Similar questions exist if animals receive certain human tissue or DNA. As of yet, no animal has been the recipient of numerous human organs. If an animal received say, a human heart, human lungs and human kidneys would we still look upon that animal the same way? Should we? Would we think it was deserving of special respect? These sorts of questions have been raised in the context of experiments that anticipated implanting mouse (murine) brains with human brain (neural) stem cells. These experiments were proposed by Dr. Weissman at Stanford University to learn more about human brain trauma and to lead to potential clinical and pharmaceutical therapies.

Prior to the commencement of the experiments Dr. Weissman consulted with Stanford ethicists. These ethicists[20] and subsequent commentators[21] made the following observations. The type of human tissue involved in the creation of human and non-human animal chimeras is morally significant. The creation of animals with human genes is not novel, but chimeras and hybrids that involve transplantation of human neural tissue or use of human gametes are of particular ethical concern. In these cases it is important to be careful that any resulting animal chimeras not develop uniquely human characteristics such that it might lead to the conclusion that some "degree of humanity" or human dignity has been conferred on the resulting entity.

In part this responds to the same sort of concern about conferring unusual physical characteristics on animals (see above). If animal-human mixes were to exhibit human-like behaviors they would break our rules about characteristics that do and do not belong to distinct species. In other words, we do not want to see mice

20 Greely, HT, Cho, MK, Hogle, LF, Satz, DM "Thinking about the human neuron mouse" *Am J Bioethics* 2007; 7: 27–40.

21 Baylis, F., Robert, JS, "Part-Human Chimeras: Worrying the Facts, Probing the Ethics" *Am J Bioethics* 2007; 7: 41–45; Cohen, C., "Beyond the Human Neuron Mouse to the NAS Guidelines" *Am J Bioethics* 2007; 7: 46–49.

playing chess or exhibiting problem-solving behavior that we associate solely with humans. This would raise issues of the dignity of life these creatures possessed, whether they held some sort of intermediate human dignity and how, in light of the former answer, they were to be treated. Such a blurring between human and non-human animals might lead some to devalue characteristics thought to be sacred due to their uniquely human status and/or to something called "moral confusion."

Moral confusion

Although the argument is made that the blurring of lines between the human and non-human animal species may compromise human dignity, another perspective is that such blurring raises moral confusion. About this confusion Baylis and Roberts say, "When faced with the prospect of not knowing whether a creature before us is human and therefore entitled to all of the rights typically conferred on human beings, we are, as a people, baffled. One could argue further that we are not only baffled but indeed fearful."[22] We understand our world by classifications. Some categories are watertight. In the law all entities are either people or property and one cannot be the other. Where the two become blurred (patents on human genes) we run into controversy as to how and whether to proceed.[23] Humans are female or male but not both, and when the line gets blurred it causes us to feel discomfiture and an uncertainty as to how to categorize and treat the person who is both genders (transgender or hermaphrodite).

Likewise chimeras and hybrids raise issues of moral confusion. What is an animal that has human tissue? Do we need to treat it differently or dispose of it with the respect and ceremony normally due to humans? Does this blurring of the line between human and non-human animals somehow compromise our human dignity? In fact, the human-mouse neural transplant experiments did not go forward, but the discussion of the issues has informed how to move forward with care and forethought in this area. Where cytoplasmic hybrids are concerned, it is generally agreed that the resulting entities should not be allowed to breed and have offspring. Many have recommended that the hybrid embryos be destroyed at the standard regulatory 14 day limit. Additional limits can be found in the section on regulatory oversight, see Knowles L., "Canada's Regulatory Oversight of Stem Cell Research" Stem Cell Network. The public, policy and regulatory discussions and limits placed on the use of chimeras, hybrids and cybrids in stem cell research reflect the ethical issues of using animals in research and of creating new life forms. These issues will not disappear, but only grow more complicated. Continuing communication on why and how stem cell research impacts these issues is needed.

References

Bordet, S., Feldman, S., Knoppers, B.M. Legal Aspects of Animal-Human Combinations in Canada. (2007) 1:1 McGill Health Law Publication, 83.

Bubela, T., Caulfield, T. 2007 When human dignity is not enough: embryonic stem cell research and human cloning in Canada, in *Emerging Technologies: Hindsight and Foresight* ed. Einsiedel, E. (Vancouver: University of British Columbia Press, 2007).

Buehr, M., Meek, S., Ying, Q., et al. "Capture of Authentic Embryonic Stem Cells from Rat Blastocysts" Cell 2008, 135(7): 1287-1298.

Buehr, M., Hjorth, P. J., Hansen, A. K. & Sandøe, P. (2003) Genetically modified laboratory animals – what welfare problems do they face? Journal of Applied Animal Welfare Science 6(4), 319-338.

Caulfield, T., Chapman, A., Human dignity as a criterion for science policy, *PLoS Med.* 2005 Aug;2(8):e244. Epub 2005 Aug 2.

The Canadian Institutes of Health Research Updated Guidelines for Human Pluripotent Stem Cell Research, June 29, 2007 http://www.cihr-irsc.gc.ca/e/34460.html

Donnelley, S., The Brave new world of Animal Biotechology, 1994, Special Supplement, The Hastings Centre Report.

International Society for Stem Cell Research, "Guidelines for the Conduct of Human Embryonic Stem Cell Research" http://www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf

Kaebnick, G., "Are chimeric embryos natural? And does it matter?" Bioethics forum online, http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=466

Karpowicz, P., Cohen, CB., van der Kooy, D., "It is ethical to transplant human stem cells into nonhuman embryos." *Nat Med.* 2004 Apr;10(4):331-5.

Karpowicz, P., Cohen, CB., van der Kooy, D., Developing human-nonhuman chimeras in human stem cell research: ethical issues and boundaries. *Kennedy Inst Ethics J.* 2005 Jun;15(2):107-34.

Robert, JS. 2004 Model systems in stem cell biology *Bioessays* 26 1005-1012.

Schuppli, CA., Fraser, D. & McDonald, M. (2004) "Expanding the 3Rs to meet new challenges in humane animal experimentation" *Alternatives to Laboratory Animals 32*, 525-532.

22 Baylis, F., Robert, JS, "Part-Human Chimeras: Worrying the Facts, Probing the Ethics" *Am J Bioethics* 2007; 7: 41-45.

23 Knowles, L., "Property, Progeny and Patents," *Hastings Center Report* 1999; 29(2).