Type of print: Publisher's PDF

Originally published as:

Baylis, F. & Fenton, A. (2007). Chimera research and stem cell therapies for human neurodegenerative disorders. *Cambridge Quarterly of Healthcare Ethics*, 16, 195-208.
DOI:10.1017/S0963180107070211

Chimera Research and Stem Cell Therapies for Human Neurodegenerative Disorders

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In April 2005, the U.S. National Academy of Sciences (NAS) published its *Guidelines for Human Embryonic Stem Cell Research*.[1] These voluntary guidelines are among the most permissive in the world[2]—in a country that prohibits federal funding of research to derive human embryonic stem (hES) cells (cells that can self-renew or differentiate into most cells in the human body).[3] One of the few research prohibitions in the NAS guidelines concerns the creation of certain kinds of human–nonhuman chimeras. A chimera is an organism with a mixture of cells from two different *organisms*, from the same or different species. Figure 1 provides a useful overview of different types of chimeras.

In the NAS guidelines, research involving the transfer of hES cells or their derivatives into nonhuman primate blastocysts is prohibited, as is the transfer of human and nonhuman ES cells into human blastocysts.[4] Meanwhile, other forms of chimera making are explicitly permitted. For example, subject to special ethics review by a local Embryonic Stem Cell Research Oversight (ESCRO) committee, researchers can transfer "hES cells into nonhuman animals at any stage of embryonic, fetal, or postnatal development,"[5] which means that they can transfer hES cells into any nonhuman blastocyst, except those of primates. Having permitted this wide array of interspecies research, the NAS guidelines include a prohibition on breeding nonhuman animals engrafted with hES cells.[6] Interestingly, the guidelines are silent on the creation of human-to-human chimeras, except for the prohibition on grafting hES cells into human blastocysts. This suggests that human-to-human chimeric research is permissible after the blastocyst stage.

In this paper, we critically examine the NAS position on research involving the transfer of hES cells or their derivatives into nonhuman primates. We argue that the moral reason given for the NAS prohibition on grafting hES cells into nonhuman primate blastocysts, namely that this may undermine human dignity, is flawed. We next review alternate proposals for pursuing such research subject to strict research design criteria and conclude that they too are flawed. These conclusions leave us calling for a richer discourse on the ethics of creating novel beings likely to be of a controversial moral status.[7]

This work was supported, in part, by a Stem Cell Network grant to Françoise Baylis and Jason Scott Robert and a CIHR grant to Françoise Baylis. We sincerely thank Alan Fine, Rich Campbell, Cynthia Cohen, and Tim Krahn for helpful comments on an earlier draft of this paper. Thanks are also owed to Tim Krahn for his research assistance. An earlier version of this paper was presented to the Department of Bioethics and the Novel Tech Ethics research team (www.noveltechethics.ca). We thank the participants at each of these meetings for their helpful comments.

Cambridge Quarterly of Healthcare Ethics (2007), **16**, 195–208. Printed in the USA.

DOI: 10.1017/S0963180107070211

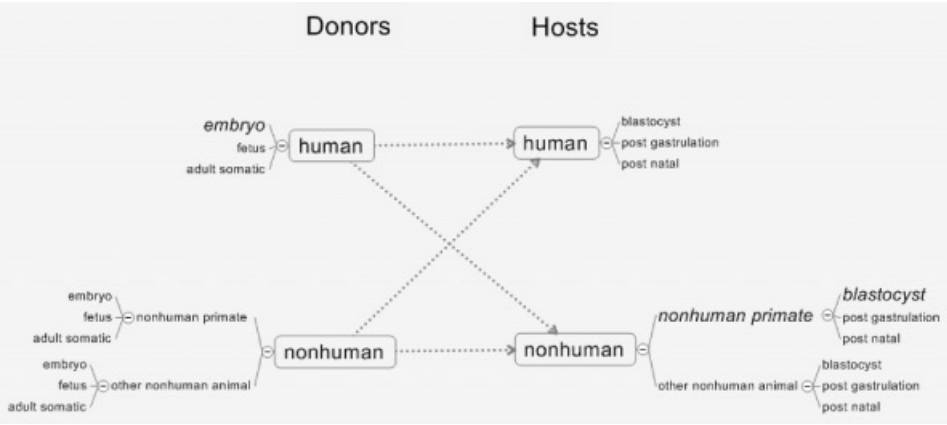

Figure 1. Grafting human or nonhuman stem cells into human or nonhuman hosts at various stages of development.

Reasons for Creating Part-Human Chimeras

The promise of stem cell research for the treatment of degenerative brain diseases like Parkinson's and Alzheimer's is great, as are the scientific and ethical hurdles. One of those hurdles, according to some stem cell scientists, is research involving the creation of part-human chimeras. These scientists maintain that such research is a necessary step on the path to clinical trials—a step that, according to the NAS, "will inevitably be required by the Food and Drug Administration (FDA)."[8] In November 2005, Geron Corporation indicated that it would be seeking FDA approval for clinical trials to test neural derivatives of its hES cell lines in patients with spinal cord injuries. Although this is not research on a neurodegenerative disease, the response to this announcement from physicians and bioethicists is instructive. Serious concerns were expressed about the move to clinical trials based on preclinical research in rodents, without additional research in nonhuman primates.[9] A similar response is to be expected with any proposed first-in-human trials for neurodegenerative diseases.

The anticipated benefits of research involving the grafting of human neural stem cells into nonhuman embryos (blastocysts stage and beyond) and human fetuses are twofold. First, this research will permit "the study of human neural development in a live environment paving the way for the generation of new models of human neurodegenerative and psychiatric diseases" (p. 18644).[10] This might be particularly important for the study of disorders where "the [nonhuman] animal model does not entirely recapitulate the neurodegenerative process observed in humans."[11] Second, the availability of chimera models for test purposes will speed up the screening process for therapeutic drugs.

In further explaining the need for and value of research involving the creation of part-human chimeras, the NAS guidelines underscore the following benefits associated with the introduction of hES cells or their derivatives into nonhuman blastocysts and nonhuman postgastrulation and postnatal animals: "[S]uch experiments will be essential to test the potential of hES cells or their derivatives to differentiate into the desired cells and tissues and to ensure that

hES cells or their derivatives do not give rise to inappropriate cell types or to tumors or have any other deleterious consequences."[12] In brief, the research will be invaluable in determining how transplanted hES cells or hES cell-derived neurons and glia respond to particular environments, whether they survive and proliferate, and whether proliferation and functional differentiation is normal or pathological.

Concerns with Creating Part-Human Chimeras

The scientific community is divided with respect to the value of interspecies chimera research.[13] Among those who support such research are those who believe that the research objectives summarized above can be pursued most effectively by grafting human pluripotent or restricted ES cells into nonhuman fetal or postnatal animals and then observing cell growth and cell fate. Others who support this research believe that it should be done in nonhuman blastocysts and embryos as the transplanted stem cells would most likely reveal their full developmental potential in these richly proliferating environments. Ethical concerns have been raised, however, regarding the grafting of hES cells into nonhuman blastocysts and embryos, because at these early developmental stages the transplanted cells could contribute to the inner cell mass. The engrafted nonhuman animal would thus be a mixture of human and nonhuman cells, potentially containing human cells in the germline, brain, or both.

Grafting hES Cells into Postgrastrulation and Postnatal Nonhuman Animals

The NAS guidelines permit the grafting of hES cells into postgrastrulation and postnatal nonhuman animals, including primates, in the belief that there is no serious risk that hES cells would contribute to the germline of the engrafted animal. Erring on the side of caution, however, the guidelines stipulate that this unlikely risk will be managed by prohibiting the breeding of part-human chimeras.[14]

The risk of human cells infiltrating the brains of postgrastrulation or postnatal nonhuman animals is also deemed unlikely, but is not identified as a risk to be avoided. Indeed, according to the NAS guidelines, this possible outcome would be worthy of further study:

> [T]he idea that human neuronal cells might participate in "higher-order" brain functions in a nonhuman animal, however unlikely that may be, raises concerns that need to be considered. Indeed, if such cells are to be used in human therapeutic interventions, one needs to know whether they could participate in that way in the context of a treatment. Thus there are good reasons to explore this sort of issue through animal experiments.[15]

Grafting hES Cells into Nonhuman Blastocysts

The NAS guidelines permit the grafting of hES cells into all nonhuman blastocysts except those of primates. The explicit prohibition on grafting hES cells into nonhuman primate blastocysts is introduced because of the risk of both germline and brain infiltration. This risk is identified as a threat to human dignity, though human dignity is nowhere defined in the guidelines:

> Research in which hES cells are introduced into nonhuman primate blastocysts . . . should . . . not be conducted at this time. These kinds of studies could produce creatures in which the lines between human and nonhuman primates are blurred, a development that could threaten to undermine human dignity.[16]

Human Dignity and Moral Status

Concerns about violating human dignity are shared by Karpowicz and colleagues according to whom "chimeras, by combining the appearance and functional capacities of humans and animals, seem to risk denying human dignity" (p. 333).[17] They write:

> Human dignity is a widely shared concept that refers to being worthy or respected because one is human. . . . Human dignity is based on the recognition that human beings possess, will possess, or have possessed functional and emergent psychological capacities that indicate they are worthy of respect. Humans have the capacity to make moral choices and their actions can be imputed to them because they possess a conscience and a sense of responsibility. Recognition of such human characteristics informs us of our common humanity and reminds us of our reasons to respect and support humanity.[18]

Interestingly, despite a shared concern about possible threats to human dignity, Karpowicz and colleagues reach a different conclusion than that found in the NAS guidelines. In their view, grafting hES cells into nonhuman primate embryos need not "threaten the belief at the core of our social ethic that human beings have a certain distinctive dignity" (p. 129).[19] Why? Because such research need not result in the transfer of "emergent human mental capacities,"[20] "emergent and supercellular psychological human functions,"[21] "human-like psychological alterations,"[22] "psychological characteristics associated with human brains,"[23] or "psychological and cognitive capacities associated with human dignity."[24] Indeed, Karpowicz and colleagues maintain that the risk of humanization is most unlikely because of important differences between the species in terms of brain size and the number of cell cycles during neurogenesis. Nonetheless, to minimize the risk of humanization in grafting hES cells into nonhuman primate embryos they propose a limit on: "(i) numbers of human cells transferred, (ii) choice of host animal for early blastocyst chimeras, and (iii) dissociation of human cells, rather than postanatomical tissue transplants for later embryonic chimeras."[25]

Related to concerns about human dignity are concerns about moral status. Shortly after the NAS guidelines were released, Greene and colleagues published their views on the moral issues associated with grafting human stem cells into nonhuman primates, starting with the worry that such research might change the morally relevant mental capacities of engrafted nonhuman primates.[26] If human–nonhuman primate chimeras were to develop "humanlike cognitive capacities relevant to moral status . . . such as the ability to feel pleasure and pain, language, rationality, and richness of relationships,"[27] then we might have to reexamine socially entrenched differences in moral standing between humans and nonhuman primates.

Greene and colleagues do not present a consensus view on the moral acceptability of grafting hES cells into nonhuman primate embryos: "[S]ome of us believe that engraftment of human neural cells into great apes should not be permitted, particularly early in neural development. Others argue against outright prohibition."[28] It appears that the authors agree, however, on a framework for research design. They maintain that to minimize the risk of introducing significant changes to the cognitive and emotional capacities of engrafted nonhuman animals (capacities that are deemed relevant to moral standing), there should be particular attention to the "(i) proportion of engrafted human cells, (ii) neural development, (iii) NHP [nonhuman primate] species, (iv) brain size, (v) site of integration, and (vi) brain pathology."[29]

Flawed arguments

A first problem with arguments in support of limited research involving the grafting of human stem cells into nonhuman primates is that such arguments appear to accept unchallenged the claim that creating interspecies chimeras is a necessary step in the development of safe and effective stem cell therapies for human disease. But what about the problem of inference from cross-species research to human research given known differences between the biology of nonhumans and humans? Biological differences such as the possible absence of the rostral migratory stream in the human brain after infancy may well limit the ability to extrapolate research findings from part-human chimeras to humans.[30] The inferential gaps associated with chimera research may be significant, even in the face of counterexamples suggesting important similarities between human and nonhuman stem cells. Tolerance for the problem of inference is perplexing, when this problem could be eliminated or, at the very least, significantly reduced by some kinds of within-species research, including human-to-human research, nonhuman-primate-to-nonhuman-primate research, and rodent-to-rodent research.

Those who advocate part-human chimeric stem cell research as a means to the end of regenerative medicine suggest that this research is imperative in part because the human-to-human chimera research would be unethical. But this statement may be far too sweeping. For example, following current guidelines in Canada, the United Kingdom, and many other countries, human embryo research, though morally controversial, is permitted up until 14 days. Why preclude human-to-human chimera research within the 14 day time limit?[31]

Also, what about nonhuman-primate-to-nonhuman-primate research (with appropriate stringent restrictions on the care of nonhuman primates in research facilities)? Admittedly there are fewer available nonhuman primate stem cell lines and nonhuman primate hosts are an expensive animal model for preclinical research, but *if* this research could successfully sidestep certain moral and scientific problems, why not pursue this alternative and plan to move directly from nonhuman-primate-to-nonhuman-primate studies into human clinical trials? At this time, there is no reason to think that the inferential problems will be greater with grafting nonhuman primate stem cells into nonhuman primates as contrasted with grafting human stem cells into nonhuman primates, though admittedly different research strategies may be needed for efficacy than for safety.

With respect to safety, there is the claim that interspecies research is necessary to test for tumorigenicity. Recent research, however, suggests that ES cells may be

more likely to generate tumors when grafted into a host that is of the same species as that from which the cells were derived.[32] If so, observations of tumor formation (or absence of same) resulting from hES cells being grafted into nonhuman hosts (whether rodents or nonhuman primates) may have little bearing upon determinations of the risk of tumor formation by hES cells grafted into humans.[33] From another perspective, it is unclear how the potential benefits of chimera research should be weighed against the potential harms, especially when one considers that the benefits and harms devolve onto different creatures.

With respect to efficacy, there is the apparent assumption that nonhuman primates are the ideal animal model for diseases affecting the human brain, so that we are right to have more confidence in the relevance of preclinical data from human–nonhuman primate chimeras than from human–rodent chimeras. Evidence in support of the view that nonhuman primates are the better animal model for research relevant to the human brain is lacking, however. Here, it is perhaps instructive to consider the development of the related field of fetal neural transplantation for the treatment of Parkinsonism. The first published clinical trial of this approach[34] was undertaken prior to completion of any nonhuman primate studies, largely on the basis of rodent experiments. Results of initial nonhuman primate studies[35] were favorable and used to justify further human clinical trials. Yet the nonhuman primate studies were no more successful than the rodent studies in predicting the debilitating dyskinesias that have prevented the widespread acceptance of these procedures.[36] It follows that nonhuman primate chimeras may not be the best animal model for all diseases affecting the human brain. More generally, the ideal nonhuman animal model to study the properties of stem cells in vivo may be disease or disorder specific, and may or may not be a part-human chimera.

A further problem with arguments limiting research involving the grafting of human stem cells into nonhuman primates is the failure to address head-on the moral quandary, namely that the primary scientific reason for wanting to pursue research involving the creation of human–nonhuman primate embryonic chimeras and the primary ethical reason for limiting such research are one and the same—nonhuman primates most closely approximate humans. Instead of squarely confronting this quandary, considerable intellectual energy is expended insisting on the potential scientific benefits of biological humanization while seeking to minimize the risk of moral humanization.

The Argument from Human Dignity

It is difficult to assess the NAS claim that grafting human cells into nonhuman primate blastocysts "could threaten to undermine human dignity" without first understanding the meaning of the term *human dignity*. This is no easy task, as there are a number of candidate definitions.[37]

Human dignity is often used as a stand-in for autonomy,[38] respect for persons (as persons),[39] human equality,[40] and that which (properly) underlies a sense of self-respect.[41] Taken individually, each of these definitions is problematic insofar as each would appear to be either under- or overinclusive. Underinclusive definitions would be those that improperly exclude some humans—namely, those who do not meet the conditions implied by the definition. For example, human nonpersons, like individuals in a persistent vegetative state or human embryos,

would fail to possess human dignity understood as either autonomy, respect of persons (as persons), or that which (properly) underlies a sense of self-respect. Further, human persons lacking self-awareness, like very young children and some individuals with severe mental disabilities would fail to possess human dignity understood as that which (properly) underlies a sense of self-respect. In sharp contrast, human dignity understood as human equality is perhaps too strong insofar as it would include human zygotes and blastocysts. Because each of these definitions has implications in tension with how the notion of human dignity is used in ethical debate, we have reason to reject each definition in turn as inadequate for the task. For the same reason, clustering these definitions is also problematic.

But what of the definition of human dignity offered by Karpowicz and colleagues, who, like the NAS, worry that grafting human stem cells into nonhuman primates may violate human dignity? In their view,

> [h]uman dignity is a widely shared notion that signifies that humans typically display certain sorts of functional and emergent capacities that render them uniquely valuable and worthy of respect. It is not only the capacities for reasoning, choosing freely, and acting for moral reasons, as Kant argues, or for entertaining and acting on the basis of self-chosen purposes, as Gewirth holds, that are at the core of what we mean by human dignity. The notion also encompasses such capacities as those for engaging in sophisticated forms of communication and language, participating in interweaving social relations, developing a secular or religious world view, and displaying sympathy and empathy in emotionally complex ways.[42]

The problem with this definition when it is used to clarify what types of chimera research would or would not violate human dignity is that it implicitly relies on the species integrity argument (disclaimers to the contrary notwithstanding). Indeed, there is an inherent tension in Karpowicz and colleagues' criticism of the use of the species concept and their own use of their concept of *human* dignity. It appears to us that they want to both (a) value certain human functions and capacities for their own sake and not because they are human[43] and (b) value certain human functions and capacities because they are human and not for their own sake.[44] At the same time, both of these points in tension rely on an implicit appeal to a principle conferring intrinsic moral value on x if x belongs to a class A that contains members who manifest certain cognitive or emotional capacities, even if x herself does not. X is thus valued, or possesses moral significance, because x is a member of class A. In this case, the class is all humans.

The problem with implicitly opting for, while at the same time denying the value of, species integrity is that this introduces a significant logical problem. If Karpowicz and colleagues believe that human capacities are to be valued for their own sake and not because they are human, then they can't conclude that creating human–nonhuman primate chimeras with these capacities in any way threatens human dignity. Alternatively, if their position is that human capacities are to be valued because they are human and not for their own sake, then they can conclude that creating human–nonhuman chimeras risks violating human dignity but, per force, must acknowledge that their argument relies on presuppositions about species integrity.

Karpowicz et al. are resistant to relying on a species integrity argument, but this comes at a price. If the species classification/demarcation truly plays no role in the analysis of human dignity and if nonhuman primates have dignity-associated capacities "that resemble those of humans in several respects,"[45] which Karpowicz and colleagues acknowledge, then logic and justice demand that we accord human and nonhuman primates the same "human dignity" by virtue of the dignity-associated capacities manifested by members of the respective species.

In sum, we agree with Karpowicz et al. that human capacities "for carrying out discursive and moral reasoning, engaging in complex communication, and forming multifaceted social relations"[46] are inherently valuable (from our human perspective). We do not agree with them, however, that human dignity is somehow reduced by research that results in nonhuman primates being revealed as, or even becoming, creatures that have these capacities. It is not obvious to us that creating nonhuman primates with the capacity "to develop human psychological, cognitive, or other capacities associated with human dignity"[47] (or increasing these valued capacities among nonhuman primates who already display many of these capacities) in any way denies the dignity of humans, unless the dignity of humans depends on the separation of species, which Karpowicz et al. want to reject.

From another perspective, it is difficult for us to understand how the use of nonhuman primate hosts for the creation of part-human chimeras represents an objectionable affront to "human dignity" (and for this reason should be prohibited or strictly regulated), whereas the use of other nonhuman hosts seemingly does not constitute such an affront (and therefore does not need to be prohibited or strictly regulated). Surely the threat to human dignity, if there is such a threat, would be all the more significant with efforts to "humanize" our more distant nonhuman relatives? Would not a "thinking, talking" mouse à la Stuart Little be more of a threat to human dignity (such as it is) than a "thinking, talking" Cornelius from Planet of the Apes?[48]

From our perspective, it seems logically possible to engage in human-to-nonhuman primate neural grafting without adversely affecting the dignity of humans. Nothing about this process entails that human persons or even human beings (if we wish to make this distinction) will lose their status as autonomous individuals, persons, or equal moral citizens (of the global moral community). Nor is there any reason to suppose that this will undermine their self-respect. As such, while there may be sound ethical concerns with grafting hES cells into nonhuman primates, it would seem that these concerns have little or nothing to do with human dignity (at least relative to the definitions of human dignity that we have canvassed).

In the end, discussions of whether human dignity is adversely affected seem focused on the wrong beings. Though no human beings are adversely affected by human-to-nonhuman primate neural grafting at early developmental stages, and so human dignity (whatever it might mean) remains unthreatened, nonhuman primate beings may be adversely affected by such research. The possibility of harm to nonhuman primates is difficult to assess at this juncture in the debate, however.[49] If the engrafted early-stage developing animals are not brought to full-term, or if they are not allowed to mature after birth, then there need not be any nonhuman primate beings adversely affected by the relevant procedure. If the relevant nonhuman primate embryos are allowed to mature,

however, then concerns about the moral status of the maturing nonhuman primates become pertinent. Thus, we now turn our attention to examining the moral status of nonhuman primate chimeras.

The Argument for Protected Human Moral Standing

Greene and colleagues appear to believe that grafting hES cells into nonhuman primates may alter those primates' cognitive and emotional capacities in ways that might change their current moral status.[50] This risk is greatest when using nonhuman great apes at a very early stage of development.[51]

There are several problems with the article by Greene and colleagues, not the least of which is the contradiction between the claim that there is no scientific or philosophical ground for maintaining a strict theoretical division of the species,[52] and the discussion that follows that in so many ways belies this claim. In our view, the socially entrenched distinction between human and nonhuman primates is under strain from at least two directions. The first direction concerns the collapse of strict species distinctions resulting from the rise of Darwinian evolutionary theory as the dominant interpretative framework in modern biology.[53] The illusion of a strict species distinction between humans and other animals arises in part from the lack of extant hominids that are members of other species of the genus *Homo*. The existence of such hominids would arguably serve to highlight, and perhaps force a more adequate integration of, human primate identity.[54] The second direction concerns the well-studied variety of cognitive capacities or abilities that range over humans of varying degrees of cognitive health or development. It is no longer plausible to highlight a particular cluster of cognitive properties as both necessary and sufficient for inclusion in humanity. To do so would inevitably lead either to the exclusion of some humans from, or the inclusion of some of the nonhuman great apes in, the human "family." This problem is not simplified by identifying clusters of properties whose family resemblances allow us to talk of all members of each "cluster class" (containing members who manifest the properties of the relevant cluster) as human. As will be implied below, there is no prima facie reason for supposing that nonhuman animals, particularly great apes like chimpanzees or bonobos, would not qualify as members of one of these cluster classes (and so qualify as human).

In our estimation, talk of nonhuman primates who might acquire humanlike characteristics as a result of hES cell grafting, and so become worthy of a moral status akin to that accorded such humans as young children or the mentally challenged, is deeply problematic. There simply is no good reason to think that there is a class of mental states, or a set of classes related through family resemblance each containing a set of mental states, properly described as human that are *unique* to *all* humans. Arguably, to think otherwise is to fail to appreciate the remarkable diversity of cognitive capacities found throughout the human species. What we see among humans is a broad spectrum of cognitive capacity from the very simple (e.g., infants and toddlers) to the complex (e.g., human adults who enjoy a degree of cognitive health that falls within what is considered to be statistically normal, possess linguistic skills, and have a to-be-specified level of education). When we include various pathological or degenerative conditions in this analysis, the diversity of cogni-

tive capacities among humans only increases. The "simpler" the cognitive capacity exhibited by humans, the less likely it is that this capacity is unique to humans. Indeed, considerations of evolutionary parsimony lead us to expect that similar behaviors in closely related species are to be explained by similar proximate causes, and this is no less true for the human and chimpanzee than it is for wolves and domestic dogs.[55]

Greene et al. suggest some characteristics they believe confer on humans a unique moral worth, including linguistic capacity, rationality, and a capacity for sufficiently rich social relationships.[56] Though it may appear unproblematic to suggest that only humans possess these characteristics, advances in such animal sciences as ethology, primatology, animal psychology, and behavioral ecology suggest otherwise. Individuals belonging to each species of nonhuman great ape have been involved in language research, and some chimpanzees and bonobos have revealed proto-linguistic abilities, acquiring a competence in sign language akin to that achieved by young human children who are hearing impaired.[57] Savage-Rumbaugh's work with Kanzi (*Pan paniscus*) has received a great deal of attention.[58] Arguably, Fouts' work with Washoe (*Pan troglodytes*),[59] Miles' work with Chantek (*Pongo pygmaeus*),[60] and Patterson's work with Koko (*Gorilla gorilla*) deserve equal attention.[61] Kanzi, Washoe, Chantek, and Koko are each capable of communicating some of their wants or desires to those humans working with them.[62] This is not to claim that some of these nonhuman primates have acquired a mastery of sign language (whatever that might mean), but it is relatively uncontroversial to suggest that they can communicate after a fashion not unlike a very young human child.[63] Rationality, understood as means-to-ends reasoning, is now well evidenced (albeit to varying degrees of complexity) among several nonhuman primate species, including capuchins (or members of the genus *Cebus*),[64] macaques (or members of the genus *Macaca*),[65] chimpanzees (*Pan troglodytes*),[66] and bonobos (*Pan paniscus*).[67] The stone tool use of free-living *Pan troglodytes verus* is a striking example of this rational capacity.[68] The richness of social relationships in several species of nonhuman primates is now receiving a great deal of attention. Within groups of free-living nonhuman primate species like capuchins, macaques, and chimpanzees, there are complex dynamic social hierarchies that require a certain degree of cognitive sophistication to successfully navigate. Within such groups, opportunistic alliances to secure resources or ensure some level of protection are widespread.[69] Reconciliation behavior, hypothesized to be necessary to maintaining important social relationships,[70] can also be observed within groups of nonhuman primates like macaques and chimpanzees.[71]

These facts suggest to us that the worry with grafting hES cells into nonhuman primate blastocysts, in relation to concerns about moral standing, is not so much a worry about nonhuman primates acquiring human-*like* characteristics, as they already have these. Rather, it would appear that the worry is more about nonhuman primates *becoming* human.

Conclusion

In the face of repeated claims about the need for human–nonhuman primate chimera research as a necessary step along the way from bench to bedside in the treatment of neurodegenerative diseases, it is important to identify and

carefully assess the arguments for and against such research. As we have shown, the moral reason given for the NAS prohibition on grafting hES cells into nonhuman primate blastocysts—the argument from human dignity—is flawed. So too, however, are the arguments given by Karpowicz and Greene and their respective colleagues for permitting such research.

Beyond this, we have identified the need to critically examine the following beliefs (some of which appear to undergird arguments about the ethics of creating human–nonhuman primate chimeras): that the natures of species are fixed; that human beings have a certain distinctive dignity; that moral standing is a function of genetics, higher cognitive capacities, or both; that enhancing the psychological and cognitive capacities of nonhumans is a priori a bad thing; that preclinical research in the human embryo is de facto unethical or unlikely to yield answers to interesting and important scientific questions and potential stem cell therapies; that the scientific and economic challenges with nonhuman-primate-to-nonhuman-primate research are not worth exploring; or that the nonhuman primate (or part nonhuman primate) model is the preferred model for Parkinson's and Alzheimer's research. The time has come for us to question these beliefs and, in so doing, to squarely address the moral status of novel part-human beings.

Notes

1. Committee on Guidelines for Human Embryonic Stem Cell Research, National Research Council. *Guidelines for Human Embryonic Stem Cell Research*, 2005. Washington, D.C.: National Academy of Sciences; 2005. Available at: http://newton.nap.edu/books/0309096537/html/.
2. Robert JS, Baylis F. Stem cell politics: The NAS prohibitions pack more bark than bite. *Hastings Center Report* 2005;35:15–6.
3. White House. Fact sheet: embryonic stem cell research. 2001 Aug 9. Homepage available at: http://whitehouse.gov/news/releases/2001/08/20010809-1.html (accessed 2005 Dec 1).
4. See note 1, Committee on Guidelines for Human Embryonic Stem Cell Research, National Research Council 2005:8, 57, and 124.
5. See note 1, Committee on Guidelines for Human Embryonic Stem Cell Research, National Research Council 2005:7, 57, and 124.
6. See note 1, Committee on Guidelines for Human Embryonic Stem Cell Research, National Research Council 2005:8, 58, and 125.
7. Robert JS, Baylis F. Crossing species boundaries. *American Journal of Bioethics* 2003;3:1–13.
8. See note 1, Committee on Guidelines for Human Embryonic Stem Cell Research, National Research Council 2005:39.
9. Hall SS. Stem cells: A status report. *Hastings Center Report* 2006;36:16–22.
10. Muotri AR, Nakashima K, Toni N, Sandler VM, Gage FH. Development of functional embryonic stem cell-derived neurons in mouse brains. *Proceedings of the National Academy of Sciences, USA* 2005;102:18644–18648.
11. See note 10, Muotri et al. 2005:18648.
12. See note 1, Committee on Guidelines for Human Embryonic Stem Cell Research, National Research Council 2005:39.
13. Robert JS. Model systems in stem cell biology. *BioEssays* 2004;26:1010.
14. See note 1, Committee on Guidelines for Human Embryonic Stem Cell Research, National Research Council 2005:39–40.
15. See note 1, Committee on Guidelines for Human Embryonic Stem Cell Research, National Research Council 2005:39–40.
16. See note 1, Committee on Guidelines for Human Embryonic Stem Cell Research, National Research Council 2005:55.
17. Karpowicz P, Cohen CB, van der Kooy D. It is ethical to transplant human stem cells into nonhuman embryos. *Nature Medicine* 2004;10:331–335.
18. See note 17, Karpowicz et al. 2004:333.

19. Karpowicz P, Cohen CB, van der Kooy D. Developing human–nonhuman chimeras in human stem cell research: Ethical issues and boundaries. *Kennedy Institute of Ethics Journal* 2005;15:107–134.
20. See note 17, Karpowicz et al. 2004:333.
21. See note 17, Karpowicz et al. 2004:334.
22. See note 17, Karpowicz et al. 2004:334.
23. See note 17, Karpowicz et al. 2004:334.
24. See note 19, Karpowicz et al. 2005:128.
25. See note 17, Karpowicz et al. 2004:334; see also note 19, Karpowicz et al. 2005:129.
26. Greene M, Schill K, Takahashi S, Bateman-House A, Beauchamp T, Bok H, et al. Moral issues of human–nonhuman primate neural grafting. *Science* 2005;309:385–6.
27. See note 26, Greene et al. 2005:385.
28. See note 26, Greene et al. 2005:386.
29. See note 26, Greene et al. 2005:386.
30. Sanai N, Tamontin AD, Quinones-Hinojosa A, Barbaro NM, Gupta N, Kunwar S, et al. Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. *Nature* 2004;427:740–4.
31. Robert JS. The science and ethics of making part-human animals in stem cell biology. *Federation of American Societies for Experimental Biology* 2006;20:838–845.
32. Erdo F, Buhrle C, Blunk J, Hoehn M, Xia Y, Fleischmann B, et al. Host-dependent tumorigenesis of embryonic stem cell transplantation in experimental stroke. *Journal of Cerebral Blood Flow & Metabolism* 2003;23:780–5.
33. Lindvall O, Kokaia Z, Martinez-Serrano A. Stem cell therapy for human neurodegenerative disorders—How to make it work. *Nature Medicine* 2004;10(Suppl):S42–50.
34. Madrazo I, Leon V, Torres C, Aguilera MC, Varela G, Alvarez F, et al. Transplantation of fetal substantia nigra and adrenal medulla to the caudate nucleus in two patients with Parkinson's disease. *New England Journal of Medicine* 1988;318:51.
35. Sladek JR Jr, Redmond DE Jr, Collier TJ, Blount JP, Elsworth JD, Taylor JR, et al. Fetal dopamine neural grafts: Extended reversal of methylphenyltetrahydropyridine-induced parkinsonism in monkeys. *Progress in Brain Research* 1988;78:497–506; Fine A, Hunt SP, Oertel WH, Nomoto M, Chong PN, Bond A, et al. Transplantation of embryonic marmoset dopaminergic neurons to the corpus striatum of marmosets rendered parkinsonian by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Progress in Brain Research* 1988;78:479–89.
36. Olanow CW, Goetz CG, Kordower JH, Stoessl AJ, Sossi V, Brin MF, et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. *Annals of Neurology* 2003;54:403–14.
37. See Macklin R. Dignity is a useless concept. *British Medical Journal* 2003;327:1419.
38. See note 17, Karpowicz et al. 2004; see also note 19, Karpowicz et al. 2005; Kant I. *Grounding for the Metaphysics of Morals*. Ellington JW, trans. Indianapolis: Hackett Publishing, Inc.; 1981:40–1.
39. See Thomas A. Mappes and David DeGrazia's discussion of human dignity in the general introduction of their anthology *Biomedical Ethics*, 4th ed. New York: McGraw-Hill; 1996:17–8. See also SC Crawford's discussion of the physician–patient relationship in *Hindu Bioethics for the Twenty-first Century*. Albany: State University of New York Press; 2003:103.
40. Something like this seems to be informing Crawford's discussion on this issue in *Hindu Bioethics for the Twenty-first Century*. See note 39, Crawford 2003:29.
41. See Wilson JSJ. Proposed definitions of dignity. *British Medical Journal* (A Rapid Response found on the Internet to Ruth Macklin's article "Dignity Is a Useless Concept") 2004 Feb 26 (accessed 2005 Dec 1). Available at: http://bmj.bmjjournals.com/cgi/eletters/327/7429/1419#51703. See also Ingle RF. Nuts and bolts of dignity? (A Rapid Response found on the Internet to Ruth Macklin's article "Dignity Is a Useless Concept") 2004 Mar 1 (accessed 2005 Dec 1). Available at: http://bmj.bmjjournals.com/cgi/eletters/327/7429/1419#51703.
42. See note 19, Karpowicz et al. 2005:120.
43. "[H]umans are not considered to have dignity because they are *Homo sapiens*, but because they possess a cluster of capacities that matter ethically and that members of that species generally exhibit." See note 19, Karpowicz et al. 2005:121.
44. "The family of capacities associated with human dignity seems to belong uniquely to human beings . . . [A]nimals, including those with capacities that resemble those of humans in several respects, have a different sort of worth from that of humans." See note 19, Karpowicz et al. 2005:122.
45. See note 19, Karpowicz et al. 2005:122.

46. See note 19, Karpowicz et al. 2005:123.
47. See note 19, Karpowicz et al. 2005:124.
48. Having said this, it is worth noting that although the claim above is logical, it may not always be true to human psychology. In many ways "proximity" is relevant to the perception of "threat." The fact that nonhuman primates (unlike rodents) are similar to us in so many ways makes their cognitive and emotional enhancement more threatening than it might be with other species that appear more distant from humans. This point was drawn to our attention by T. Krahn.
49. Streiffer R. At the edge of humanity: Human stem cells, chimeras, and moral status. *Kennedy Institute of Ethics Journal* 2005;15:347–70.
50. See note 26, Greene et al. 2005:385.
51. See note 26, Greene et al. 2005:386.
52. See note 26, Greene et al. 2005:385.
53. Ereshefsky M. Eliminative pluralism. In: Hull D, Ruse M, eds. *The Philosophy of Biology*. New York: Oxford University Press; 1998:353–4; Rachels J. *Created from Animals: The Moral Implications of Darwinism*. Oxford: Oxford University Press; 1991; Dunbar RIM. What's in a classification? In: Cavalieri P, Singer P, eds. *The Great Ape Project: Equality Beyond Humanity*. London: Fourth Estate; 1993:110–1.
54. This point informs Jane Goodall's musings on the similarities and differences between chimpanzees and humans in her book *Through a Window: My Thirty Years with the Chimpanzees of Gombe*. Boston: Houghton Mifflin; 1990:174; Dawkins R. Gaps in the mind. In: Cavalieri P, Singer P, eds. *The Great Ape Project: Equality Beyond Humanity*. London: Fourth Estate; 1993:82–5.
55. De Waal FBM. Foreword. In: Mitchell RW, Thompson NS, Miles HL, eds. *Anthropomorphism, Anecdotes, and Animals*. Albany: State University of New York Press; 1997:xiv–xv.
56. See note 26, Greene et al. 2005:385.
57. See Gómez's comment to this effect in his own footnote in Gómez JC. *Apes, Monkeys, Children, and the Growth of Mind*. Cambridge, MA: Harvard University Press; 2004:282.
58. See Greenfield PM, Savage-Rumbaugh S. Grammatical combination in *Pan paniscus*: Processes of learning and invention in the evolution and development of language. In: Parker ST, Gibson KR, eds. *"Language" and Intelligence in Monkeys and Apes: Comparative Developmental Perspectives*. New York: Cambridge University Press; 1990:540–78; Savage-Rumbaugh S, Shankar SG, Taylor TJ. *Apes, Language and the Human Mind*. New York: Oxford University Press; 1998.
59. See Fouts RS, Fouts DH. Chimpanzee sign language research. In: Dolhinow P, Fuentes A, eds. *The Nonhuman Primates*. Mountain View, CA: Mayfield Publishing Company; 1999:252–6; Fouts RS, Jensvold MLA, Fouts DH. Chimpanzee signing: Darwinian realities and Cartesian delusions. In: Bekoff M, Allen C, Burghardt GM, eds. *The Cognitive Animal: Empirical and Theoretical Perspectives on Animal Cognition*. Cambridge, MA: The MIT Press; 2002:285–91.
60. Miles HLW. The cognitive foundations for reference in a signing orangutan. In: Parker ST, Gibson KR, eds. *"Language" and Intelligence in Monkeys and Apes: Comparative Developmental Perspectives*. New York: Cambridge University Press; 1990:511–39.
61. See Patterson F, Linden E. *The Education of Koko*. New York: Holt, Rinehart and Winston; 1981.
62. Some of Savage-Rumbaugh's retelling of her experiences with Kanzi are most suggestive in this regard. See her brief account of her research with Kanzi in (see note 58), Savage-Rumbaugh et al. 1998:3–74.
63. See some insightful comments on this matter in (see note 57) Gómez 2004:281–9. Do note, Kanzi does not use sign language, or elements of sign language, in communicating with Savage-Rumbaugh. Rather, Kanzi uses a keyboard containing symbols when communicating with his human "interlocutors." A picture of some of these symbols can be seen in (see note 58) Savage-Rumbaugh et al. 1998.
64. See some cautious comments on this matter in (see note 57) Gómez 2004:109–12.
65. Tanaka I, Eishi T, Haruo T, Toshio H. Tube test in free-ranging Japanese macaques: Use of sticks and stones to obtain fruit from a transparent pipe. In: Matsuzawa T, ed. *Primate Origins of Human Cognition and Behavior*. Tokyo: Springer-Verlag; 2001:509–18.
66. Matsuzawa T. Field experiments on use of stone tools by chimpanzees in the wild. In: Wrangham RW, McGrew WC, de Waal FBM, Heltne PG, eds. *Chimpanzee Cultures*. Cambridge, MA: Harvard University Press; 1994:351–70; Matsuzawa T, Yamakoshi G. Comparison of chimpanzee material culture between Bossou and Nimba, West Africa. In: Russon AE, Bard KA, Parker ST, eds. *Reaching into Thought: The Minds of the Great Apes*. Cambridge, UK: Cambridge University Press; 1996:211–32.

67. Ingmanson EJ. Tool-using behavior in wild *Pan paniscus*: Social and ecological considerations. In: Russon AE, Bard KA, Parker ST, eds. *Reaching into Thought: The Minds of the Great Apes*. Cambridge, UK: Cambridge University Press; 1996:190–210.
68. For an excellent discussion of this tool use, see note 66, Matsuzawa T. 1994:351–70.
69. See FBM de Waal's extended discussion of the social interactions of macaques, chimpanzees, and bonobos in his book *Peacemaking among Primates*. Cambridge, MA: Harvard University Press; 1989.
70. See de Waal FBM. Conflict as negotiation. In: McGrew WC, Marchant LF, Nishida T, eds. *Great Ape Societies*. Cambridge, UK: Cambridge University Press; 1996:161–2.
71. See note 69, de Waal 1989.