

# Advancing Neuroregenerative Medicine: a Call for Expanded Collaboration Between Scientists and Ethicists

Jocelyn Grunwell · Judy Illes · Katrina Karkazis

Received: 13 June 2008 / Accepted: 9 September 2008  
© Springer Science + Business Media B.V. 2008

**Abstract** To date, ethics discussions about stem cell research overwhelmingly have centered on the morality and acceptability of using human embryonic stem cells. Governments in many jurisdictions have now answered these “first-level questions” and many have now begun to address ethical issues related to the donation of cells, gametes, or embryos for research. In this commentary, we move beyond these ethical concerns to discuss new themes that scientists on the forefront of NRM development anticipate, providing a preliminary framework for further discussion between scientists and ethicists. Fostering strong partnerships between neuroscientists and ethicists that operate and collaborate within this evolving

framework will maximize the translation of NRM discoveries on the brain into cures that are safe and address the needs of science and society.

**Keywords** Empirical bioethics · Neuroregenerative medicine · Stem cell · Animal–human chimeras · Human neural-grafted chimeras · Informed consent · Therapeutic misconception · Therapeutic orphans · Vulnerable research subjects · Cognitive enhancement · California Institute of Regenerative Medicine (CIRM) · Proposition 71 · Scientific emigration · Brain-drain · Medical tourism · Neuroethics · Neuroscience · Batten’s disease

---

J. Grunwell (✉)  
Stanford Center for Biomedical Ethics,  
Stanford University School of Medicine,  
701 Welch Rd., Suite 1105,  
Palo Alto, CA 94034, USA  
e-mail: grunwell@stanford.edu

K. Karkazis  
Stanford Center for Biomedical Ethics,  
701 Welch Rd., Suite 1105,  
Palo Alto, CA 94034, USA  
e-mail: karkazis@stanford.edu

J. Illes  
National Core for Neuroethics,  
The University of British Columbia,  
2211 Wesbrook Mall, Koerner S124,  
Vancouver, BC V6T 2B5, Canada  
e-mail: jilles@interchange.ubc.ca

## Introduction

Over the last decade research showing neurogenesis in the adult brain has fostered hope among scientists, clinicians, and the public that replacement or repair of damaged cells in the central nervous system (CNS) using transplanted stem cells will be an important tool to restore lost or impaired function and to slow the deterioration associated with deeply debilitating diseases such as Parkinson’s Disease, Alzheimer’s Disease, and multiple sclerosis. Although scientists and others are optimistic about the possibilities of neuroregenerative medicine (NRM) to lead to novel strategies and therapies for the treatment of such neurodegenerative diseases, as well as brain injury due to stroke or trauma, answers to a host of ethical

questions about the research and its clinical applications are still elusive. We sought to identify the key concerns of scientists working in NRM with the goal of developing a preliminary framework outlining ethical and social issues raised by the use of stem cells in NRM.

To date, ethics discussions about stem cell research overwhelmingly have centered on the morality and acceptability of using human embryonic stem cells (hESCs) [24, 44]. Governments in many jurisdictions have now answered these “first-level questions” such as whether and how hESCs should be used and whether this research should be supported by public funding [24]. As stem cell research progresses, ethicists, scientists, Institutional Review Boards (IRB) and stem cell research oversight (SCRO) committees have now begun to address ethical issues related to the donation of cells, gametes, or embryos for research [9, 10, 15, 16, 24, 39, 40] and issues around patenting [49, 62]. In this commentary, we move beyond these ethical concerns to discuss new themes that scientists on the forefront of NRM development anticipate. Our discussion is based on in-depth interviews that we conducted with ten senior scientists in the United States under IRB approval from Stanford University. Although our interviews were from a limited geographic pool, early data [19] suggest that scientists working in other countries are grappling with similar ethical challenges as those we discuss here.

## Neuroexceptionalism

One of the key issues framing the ethical concerns surrounding NRM is the idea of neuroexceptionalism. Compared to other types of biomedical research, neuroscience discovery concerns the brain, which is critical to self-identity, cognition, memory and consciousness. Moreover, neuroimaging methods can unveil biological signals associated with morally relevant capacities such as rational thought and decision-making [e.g., 29, 50]. The notion of neuroexceptionalism thus suggests that basic neuroscience research and the translation of this research out of the laboratory and into the clinic poses unique ethical and social challenges that deserve heightened attention because of the brain’s special status and the implications of interventions on the brain for privacy,

confidentiality and, perhaps most importantly, identity and personhood [28]. Echoing earlier disputes over genetic exceptionalism that figured prominently in public debates over the uses of genetic technology, ethicists are divided over the significance of neuroexceptionalism [61, 63].

Although scientists we interviewed recognized the utility of experiments that could potentially lead to a deeper understanding of how humans learn, remember, and perceive feelings, for example, their enthusiasm was tempered by the as yet unknown consequences of such interventions. As one respondent cautioned, “if you do those experiments, you better be thinking about how you could delete the cells you put in.” The reasoning has much to do with the brain’s special status: “the ability to get those cells out is going to be a lot harder than it would be for your liver because you can easily take out a part of your liver.” Citing not simply the unique status of the brain more generally, some expressed concern that interventions on the frontal cortex and limbic areas of the brain, which are critical for executive decision-making and emotions, may fundamentally change the self: it’s not just a matter of enhancing an organ’s function. It’s potentially changing who we are.” As one observer has asked, “How much can we reweave the cerebral tapestry without creating a new self, a new identity?” [26].

Other scientists, however, did not believe that NRM interventions would alter the consciousness of a person and viewed them as akin to a side-effect of the treatment rather than an ethical problem per se. Scientists’ and ethicists’ varying degrees of concern about whether NRM would change one’s identity or consciousness suggests that the question of neuroexceptionalism will prove important in both scientific discussion and public debates over the uses of NRM, where the complexities, risks, and consequences of such interventions are likely to be assessed differently by scientists, ethicists, patients, the public, health care providers, the media, and policy makers. Ethical issues around stems cells—an already complex and highly debated area of research—will only be compounded by interventions on the brain, which as one scientist said “comes closest to what we fear, what we love, what we understand.” It will be imperative to consider the unique ethical issues raised by both stem cell interventions and those on the brain before scientific advances are translated from the laboratory into clinical settings.

## Animal–Human Chimeras

A critical obstacle to realizing the promise of NRM research is that there is no adequate model system to understand how neural progenitor cells will proliferate, differentiate, integrate, and function in the immature and adult human brain. Because of these technical hurdles, the United States Food and Drug Administration will likely require preclinical trials on animals with human neural progenitor cells implanted into their brains. Researchers are working toward creating such human neural-grafted chimeras not only to study human brain development and disease, but to accelerate the screening process for therapeutic drugs and to provide a source of stem cells for xenotransplantation [6, 45, 52]. Redmond and colleagues, for example, implanted neural stem cells into the brains of monkeys with the hope they will supply dopamine to help people with Parkinson’s disease [51, 58]. Others have conducted or proposed similar experiments [23, 45].

Scientists and ethicists alike recognize that chimeras must have enough biological similarity to humans to be scientifically useful [52]. A central concern, however, is that chimeras will develop brains capable of human-like cognitive or mental characteristics [64]. Indeed, the bulk of the ethics literature on stem cells in NRM has centered chiefly on whether scientists would “confer humanity” on these animals [e.g., 25, 31, 32, 53, 59]. Scientists we interviewed, however, felt such concerns were misplaced; they did not believe that a human neural-grafted animal would yield human qualities such as language, cognition, and emotion. Rather, the scientists in our cohort were more concerned with the experimental problems of rejection, transfer of viral infections, and different physiological environments. As one scientist asked, “The big question is, How do you get your treatment to where you want it to go, and selectively so it doesn’t misdirect wires or cause abnormal signaling patterns in other parts of the brain that are not effected?”

Although scientists expressed minimal concern about conferring human qualities on animals, the creation of animal–human chimeras continues to be socially, politically, and ethically controversial in the United States and elsewhere, and concerns about their creation may pose significant risks to the public support of NRM research if not addressed. Societal

concerns over animal–human chimeras have prompted legislators in the United States, for example, to propose a bill criminalizing the practice [55], and similar debates have taken place in Canada and in Europe.

Current policies on stem cell research from the International Society for Stem Cell Research (ISSCR), the National Academy of Sciences (NAS), and the California Institute of Regenerative Medicine (CIRM) are well-tuned to the prevailing ethical and social concerns. The ISSCR, for example, upholds the need for special consideration for human neural-grafted chimeras, and although this international body does not legislate or enforce policy, its goal is to reach consensus to facilitate international research collaboration. NAS and CIRM guidelines prohibit the transfer of hESCs into non-human primate blastocysts and the transfer of *any* species ESCs into human blastocysts. In addition, the breeding of any animals into which hESCs have been transferred at any time is not allowed.

There are few mechanisms, however, to gauge the extent to which research scientists and institutions are following ISSCR and NAS guidelines. By contrast, CIRM has an enforcement mechanism incorporated into their mandate: funding for research is tied to approval of the research plan by stem cell research oversight committees (SCROs) [8]. That scientists and ethicists disagree about the ethical risks to personhood posed by animal–human chimeras suggests that instituting policies to address this concern is but one hurdle. Despite scientists’ belief that conferring human qualities on a neural-grafted human–animal chimera is extremely unlikely and will be scientifically difficult to assess, most thought that a step-wise approach to neural grafting with experimental stopping points was a responsible and viable solution to the ethical dilemma. Policy interpretation in light of each proposed study will prove equally challenging, and will require sustained deliberation between scientists and ethicists, among other stakeholders.

## Informed Consent, Therapeutic Misconception, and Therapeutic Orphans

Ethicists have long recognized that research participants often fail to understand that the studies in which

they enroll will not yield a therapeutic benefit—a misunderstanding known as the therapeutic misconception [1]. Several scientists we interviewed felt that any novel NRM therapy will necessarily raise patients' false hopes of a cure and that the therapeutic misconception may be especially problematic in NRM because many patients with neurodegenerative diseases, and families of patients with cognitive dysfunction, have exhausted the available treatment options and may be desperate for a cure or be more likely to expect a benefit, however small [18]. Scientists were especially concerned that the acceptability of a high-risk procedure would increase in the face of increasingly severe illness. As one scientist noted, "You just don't know how what you say will be interpreted. It's frequently misinterpreted as being overly positive and overly hopeful. We will have to be very careful about how we carry out those studies, and we'll have to be very aware of creating false hope."

Since it was first conceived, numerous studies have found that the therapeutic misconception is widespread not only across clinical trials but within them. Evidence from phase I oncology and gene transfer trials, for example, reveal a very high rate of therapeutic misconception among participants who are motivated by the idea that they may benefit from participation [27, 36], in some cases as high as 74% of participants. The therapeutic misconception often assumes that the problem is with research participant's misinterpretation of information. Research has shown, for example, that the readability of consent forms decreases as the riskiness of the intervention increases [17]. The problem, however, may also be that forms may contain misleading terms (such as "therapeutic cloning" or "gene therapy") or contradictory statements [36]. Moreover, observations of informed consent sessions, reveal that investigators can play an active role in "creating and sustaining the confusion between research and treatment" by "casting unlikely outcomes as plausible, alternating between the scientific and popular meanings of terms, and selectively highlighting different features of the proposed trial" [56: 442]. Sankar suggests this has to do with awareness rather than overt deception.

There are other concerns about informed consent specific to the population that might enroll in NRM trials. An individual's capacity to consent may be compromised by impairment of the same brain

processes that are the target of intervention. As one clinician observed regarding NRM therapy trials, volition is a principal concern: "Very often, exactly what you want to try to do something about in the brain is what makes a person least able to evaluate what might be done to them." As [57] notes, individuals who are newly disabled (and their families and caregivers) may "overestimate the long-term emotional impact of a recent injury" and thus might be more likely to agree to a risky trial in the short-term than they would later after time passes and their expectations change. In other words the patient and their families are responding to the concept of neuroexceptionalism. These concerns are well-founded as injury effecting the brain affects one's capacity to understand and learn about the consequences of interventions to mitigate that insult.

As a result of these issues, consent in NRM clinical trials will need to be given as a function both of research design and illness as well as the severity of that illness. In many cases, not only will informed consent forms need to be painstakingly crafted so as to avoid fostering or even exploiting the therapeutic misconception, but informed consent will need to be given over a period of time, and those giving the informed consent will need heightened awareness as to how their language may foster the therapeutic misconception. Even with these safeguards in place, however, it is still possible that extraclinical factors such as overly optimistic media representations of stem cell research may nevertheless contribute to the therapeutic misconception.

Children are another vulnerable research population that requires special attention. Children cannot categorically be excluded as research subjects—and indeed the NIH has mandated and provided incentives for the inclusion of children in research—in part to avoid having them become "therapeutic orphans" denied access to research and its benefits [5]. As some diseases only afflict children, pediatric research is the only option for developing treatments for them. This explains in part why some frontier studies that have not been carried out in adults may gain approval in children despite the considerable risks involved. In fact, the first clinical trial of neural stem cell transplantation began in 2006 on children with Batten's disease. Batten's disease, a lysosomal storage disorder leading to neuron loss, is a fatal pediatric disorder in which children suffer from seizures and

progressive loss of motor skills, sight and mental capacity. There is no cure for Batten's disease, and the symptoms can only be managed for a short period before the child succumbs to the disease.

Using Batten's disease as a case study, Martin and Robert [43] have questioned whether pediatric research without the prospect of direct benefit is ever justified due to the therapeutic misconception, the hype surrounding the promise of stem cell research, and parents' desperation that make it challenging, if not impossible, to obtain true informed consent—a conundrum acknowledged by our interviewees. Indeed as one parent of a child enrolled in this trial said, “He was a little boy who was basically waiting to die, now he's waiting to get better” [2]. When asked whether there was a higher threshold for safety and efficacy for NRM therapies in children participants expressed a range of opinions from the idea that the same standards should apply to children as to adults, to the view that the benefits of the intervention should greatly outweigh the risks for studies performed in children.

Although current regulations do not seek to curtail pediatric research, if interpreted strictly, it would make it impossible to conduct much research on children. As a result, reviewers of proposal for NRM clinical trials face difficult decisions about how to interpret justifications for the research, and whether to assess risks and benefits using objective standards or relative standards that take into account the child's disease state [42, 65]. Despite the clarity of the language in the Common Rule, there is widespread inconsistency among different institutional review boards (IRBs) in applying guidelines for the oversight of pediatric research to specific pediatric research protocols [21, 33]. This problem has prompted the federal government to charge three commissions over the last decade to address the issues [21].

As the minimal risk standard for research on children is difficult to meet, ethicists [60] have noted a “benefit creep” [35] in which IRBs may “exaggerate or even invent benefits to subjects” or include “collateral” or “inclusion” benefits in their assessment of direct benefits so that research that they believe to be both sound and likely to benefit society can be conducted [38]. Thus, both research with no prospect for direct benefit and research that promises to deliver a benefit raise concerns regarding the motivations for entering a trial and whether child participants will be adequately protected—concerns that are more prob-

lematic for frontier research that has not been proven in humans. As one scientist summarized his concern, “The only time I think they [children] should be able to participate [is] if they want to be an experimental animal because in the early trials, that's what they'll be.”

For the first decade of gene transfer clinical trials, it was unlikely or impossible that the Phase I research would offer any direct benefit to the subjects enrolled and the field was accused of exploiting the therapeutic misconception by not dispelling the idea of medical benefit in these trials. As Kimmelman notes, that guidelines for informed consent have changed in such trials speaks to the important reflection the concept of the therapeutic misconceptions has stimulated [34]. For innovative research such as NRM there will be ongoing difficult and contentious challenges over determining when the pre-clinical data are sufficient to justify pursuing clinical trials in humans, when there is adequate knowledge about the benefits and risks of the proposed intervention to proceed, and whether children should be the first human subjects in these trials.

### Enhancement Versus Therapy

There have been intense debates over the last few decades over the propriety of using medicine not simply to treat illness and disability, but to improve, enhance or modify human capacities and characteristics. These issues emerged perhaps most directly with genetic technology, but in recent years have centered as well on psychotropic drugs and surgical interventions to affect areas of memory, attention, and mood [4, 7, 11, 20, 22, 47, 48]. The ethics debates surrounding interventions for enhancement have generally sought to delineate medical goals from societal goals. Whereas medical goals involve the cure of illness and the ease of suffering, societal goals are to augment the ordinary traits of healthy people to improve quality of life. As NRM progresses, more effective medical technologies will not only be available to treat illness but will help individuals beyond therapeutic use to enhancement.

Scientists we interviewed felt that future NRM technologies will enable increasingly sophisticated manipulations of the brain but allowed that every positive enhancement may risk unpleasant or even

debilitating side effects. For example, one researcher expressed concern that enhancement of memory could “bring on-line other cognitive functions that are not comfortable, that are not enjoyable, that don’t make their lives better. I’d be willing to take chances with unproven therapies where there’s a reasonable chance for success, but in a setting of illness.” Many participants saw the issue of enhancement of cognitive and emotional brain function, as opposed to the treatment of frank pathology, as analogous to the role of cosmetic surgery in the enhancement of physical beauty. Like cosmetic surgery, “cosmetic neurology” [12–14] will be faced with the interpretational question, subject to societal values, of what constitutes health and disease and thus enhancement versus therapy, as well as unfair advantages for some and dis-enfranchisement of others [30]. Interviewees expressed that this was not a concern of NRM bench scientists, however, but that it will be an important challenge for clinician scientists involved in translation and ultimately clinicians in the health care arena.

## Policy

There has been a debate about whether regulations governing hESC research should be centralized at the international, federal, state, or institutional level to achieve the goal of advancing NRM as rapidly as possible [3, 41]. ISSCR, for example, was designed to facilitate international hESC collaboration. NAS developed hESC guidelines, but the US federal government suspended funding for the creation of new hESC lines in 2001. In response, California voters passed Proposition 71, allocating \$3 billion for hESC research over 10 years and created CIRM. Scientists we interviewed suggested that, in the absence of a federal funding and enforcement structure, CIRM provides a best-practice solution allowing NRM research with hESCs to progress. Most believed that the CIRM scientist-citizen oversight committee (SCRO) facilitates productive ethical debates. One scientist remarked that poorly developed and implemented oversight and funding policies will also lead to emigration of scientists to places where hESC research is supported. This is not an unfounded concern as “brain-drains” have been documented [46, 54]. Medical tourism, another type of migration phenomenon that is characterized by the pursuit of

treatments not locally available or at significantly lower cost off-shore, has also been widely reported [37, 66]. Most of the scientists we interviewed felt patients had the right to seek any medical care that they thought would help them. However, there was the strong belief that promises of stem cell therapies abroad are overstated and potentially doing more harm than good due to the lack of regulatory oversight of the protocols: “Most of the examples that I’ve heard about are really random, crazy experiments. They seem like the desperate acts of patients who are without hope. It’s understandable and sad more than it is threatening to the future of regenerative medicine.”

## Conclusion

Scientists we spoke to about issues at the nexus of NRM, neuroscience, and ethics believed it will be essential to address the ethical issues raised by NRM research. While we were able to identify only a small representation of views and philosophies at the juncture of the disciplines, they nonetheless provide a preliminary framework for further discussion between scientists and ethicists. The extent to which the brain holds a special status, and thus transplanting human stem cells into a human or animal brain is fundamentally different from transplanting them into another organ, will be critical to how ethical issues raised by NRM are framed and addressed. Prevailing elements of this framework include assessing concerns about the possibility of interventions that may reshape the self or conferring humanness on animals; determining when pre-clinical data justify moving from pre-clinical to clinical studies and whether children should be the first human subjects; and addressing concerns both about the potential for informed consent and how to assess benefits and risks for vulnerable subjects. Perhaps most importantly, to foster public trust in NRM, ensure that experts adequately versed in the complexities of the scientific and ethical issues of NRM research review proposed studies, and avoid major setbacks, academic medical centers will need to ensure IRBs and SCROs provide adequate scientific and ethical review of all NRM research [57, 67]. Thus far the US FDA has approved only one stem cell trial for a neurological disorder (Batten’s disease). If stem cell trials are to avoid going the route of earlier gene transfer trials in

which the widely reported death of a study participant eroded public confidence in gene transfer research, strong partnerships between neuroscientists and ethicists that operate and collaborate within this evolving framework will need to be fostered to maximize the translation of NRM discoveries on the brain into treatments that are safe and address the needs of science and society.

**Acknowledgements** This work was supported by NIH/NINDS #NS 045831 and the Foundation of Ethics and Technology (JI), Canadian Institutes of Health Research (CIHR) 73411 (Abdallah Daar) and CIHR CNE-85117 (JI). We extend our appreciation to Abdallah Daar and Adrian Ivinson for valuable feedback on the interview guide.

## References

- Appelbaum, P.S., L.H. Roth, C.W. Lidz, P. Benson, and W. Winslade. 1987. False hopes and best data: Consent to research and the therapeutic misconception. *Hastings Center Report* 17:20–24.
- Associated Press. 2006. *Child who received stem cells from aborted fetus on way home*. San Diego: San Diego Union-Tribune.
- Baylis, F., and J.S. Robert. 2006. Human embryonic stem cell research: An argument for national research review. *Accountability in Research* 13:207–224.
- Bioethics, P. s. c. o. 2003. *Beyond therapy: Biotechnology and the pursuit of happiness*. New York: Dana.
- Blumer, J.L. 1999. Introduction. *Pediatrics* 104:582.
- Brüistle, O., K. Choudhary, K. Karram, A. Huttner, K. Murray, M. Dubois-Dalcq, and R.D. McKay. 1998. Chimeric brains generated by intraventricular transplantation of fetal human brain cells into embryonic rats. *Nature Biotechnology* 16:1040–1044.
- Butcher, J. 2003. Cognitive enhancement raises ethical concerns. Academics urge pre-emptive debate on neuro-technologies. *Lancet* 362:132–133.
- California Institute for Regenerative Medicine. 2005. *California code of regulations*. San Francisco: California Institute for Regenerative Medicine. title 17, division 4.
- Caulfield, T., U. Ogbogu, and R.M. Isasi. 2007a. Informed consent in embryonic stem cell research: Are we following basic principles? *Canadian Medical Association Journal* 176:1722–1725.
- Caulfield, T., U. Ogbogu, E. Nelson, E. Einsiedel, B. Knoppers, M. McDonald, F. Brunger, R. Downey, K. Fernando, J. Galipeau, et al. 2007b. Stem cell research ethics: Consensus statement on emerging issues. *Journal of Obstetrics and Gynaecology Canada* 29:843–848.
- Chan, S., and J. Harris. 2006. Cognitive regeneration or enhancement: The ethical issues. *Regenerative Medicine* 1:361–366.
- Chatterjee, A. 2004. Cosmetic neurology: The controversy over enhancing movement, mentation, and mood. *Neurology* 63:968–974.
- Chatterjee, A. 2006. The promise and predicament of cosmetic neurology. *Journal of Medical Ethics* 32:110–113.
- Chatterjee, A. 2007. Cosmetic neurology and cosmetic surgery: Parallels, predictions, and challenges. *Cambridge Quarterly of Healthcare Ethics* 16:129–137.
- Cho, M.K., and D. Magnus. 2007. Therapeutic misconception and stem cell research. *Nature Reports Stem Cells*. doi:10.1038/stemcells.2007.88.
- Cho, M.K., G. McGee, and D. Magnus. 2006. Research conduct. Lessons of the stem cell scandal. *Science* 311:614–615.
- Christopher, P.P., M.E. Foti, K. Roy-Bujnowski, and P.S. Appelbaum. 2007. Consent form readability and educational levels of potential participants in mental health research. *Psychiatric Services* 58:227–232.
- Dresser, R. 2002. The ubiquity and utility of the therapeutic misconception. *Social Philosophy & Policy* 19:271–294.
- Emerson, C., and A. Daar. 2008. Neuroethics, Paper presented at: Annual meeting of the RMethnet (Toronto, Canada).
- Farah, M.J., J. Illes, R. Cook-Deegan, H. Gardner, E. Kandel, P. King, E. Parens, B. Sahakian, and P.R. Wolpe. 2004. Neurocognitive enhancement: What can we do and what should we do? *Nature Reviews. Neuroscience* 5:421–425.
- Fisher, C.B., S.Z. Kornetsky, and E.D. Prentice. 2007. Determining risk in pediatric research with no prospect of direct benefit: Time for a national consensus on the interpretation of federal regulations. *American Journal of Bioethics* 7:5–10.
- Glover, J. 1984. *What sort of people should there be? Genetic engineering, brain control, and their impact on our future world*. New York: Penguin.
- Greely, H.T. 2003. Defining chimeras...and chimeric concerns. *American Journal of Bioethics* 3:17–20.
- Greely, H.T. 2006. Moving human embryonic stem cells from legislature to lab: Remaining legal and ethical questions. *PLoS Medicine* 3:e143.
- Greene, M., K. Schill, S. Takahashi, A. Bateman-House, T. Beauchamp, H. Bok, D. Cheney, J. Coyle, T. Deacon, and D. Dennett. 2005. Ethics: Moral issues of human-non-human primate neural grafting. *Science* 309:385–386.
- Grisolia, J.S. 2002. Cns stem cell transplantation: Clinical and ethical perspectives. *Brain Research Bulletin* 57:823–826.
- Henderson, G.E., M.M. Easter, C. Zimmer, N.M. King, A. M. Davis, B.B. Rothschild, L.R. Churchill, B.S. Wilfond, and D.K. Nelson. 2006. Therapeutic misconception in early phase gene transfer trials. *Social Science & Medicine* 62:239–253.
- Hyman, S.E. 2004. Introduction: The brain's special status. *Cerebrum* 6:9–12.
- Ilg, R., K. Vokeley, T. Goschke, A. Bolte, J.N. Shah, E. Poppel, and G.R. Fink. 2007. Neural processes underlying intuitive coherence judgments as revealed by fmri on a semantic judgment task. *Neuroimage* 38:228–238.
- Juengst, E.T., R.H. Binstock, M.M. Mehlman, S.G. Post, and P. Whitehouse. 2003. Biogerontology, "Anti-aging medicine," And the challenges of human enhancement. *Hastings Center Report* 33:21–30.
- Karpowicz, P., C.B. Cohen, and D. van der Kooy. 2004. It is ethical to transplant human stem cells into nonhuman embryos. *Nature Medicine* 10:331–335.

32. Karpowicz, P., C.B. Cohen, and D. van der Kooy. 2005. Developing human–nonhuman chimeras in human stem cell research: Ethical issues and boundaries. *Kennedy Institute of Ethics Journal* 15:107–134.
33. Kimberly, M.B., K.S. Hoehn, C. Feudtner, R.M. Nelson, and M. Schreiner. 2006. Variation in standards of research compensation and child assent practices: A comparison of 69 institutional review board-approved informed permission and assent forms for 3 multicenter pediatric clinical trials. *Pediatrics* 117:1706–1711.
34. Kimmelman, J. 2007. The therapeutic misconception at 25: Treatment, research, and confusion. *Hastings Center Report* 37:36–42.
35. King, N.M. 2000. Defining and describing benefit appropriately in clinical trials. *Journal of Law, Medicine & Ethics* 28:332–343.
36. King, N.M., G.E. Henderson, L.R. Churchill, A.M. Davis, S.C. Hull, D.K. Nelson, P.C. Parham-Vetter, B.B. Rothchild, M.M. Easter, and B.S. Wilfond. 2005. Consent forms and the therapeutic misconception: The example of gene transfer research. *IRB* 27:1–8.
37. Kurlantzick, J. 2007. Medical tourism; sometimes, sight-seeing is a look at your x-rays. *New York Times*.
38. Lantos, J.D. 1999. The “Inclusion benefit” In clinical trials. *Journal of Pediatrics* 134:130–131.
39. Lo, B., V., Chou, M.I., Cedars, E., Gates, R.N., Taylor, R.M., Wagner, L., Wolf, and K.R. Yamamoto. 2003. Medicine. Consent from donors for embryo and stem cell research. *Science* 301:921.
40. Lo, B.V., Chou, M.I., Cedars, E., Gates, R.N., Taylor, R.M., Wagner, L., Wolf, and K.R. Yamamoto. 2004. Informed consent in human oocyte, embryo, and embryonic stem cell research. *Fertility and Sterility* 82:559–563.
41. Magnus, D. 2006. Stem cell research: The California experience. *Hastings Center Report* 36:26–28.
42. Magnus, D. 2007. Playing it safe. *American Journal of Bioethics* 7:1–2.
43. Martin, R.A., and J.S. Robert. 2007. Is risky pediatric research without prospect of direct benefit ever justified. *American Journal of Bioethics* 7:12–15.
44. McHugh, P.R. 2004. Zygote and “Clonote”—the ethical use of embryonic stem cells. *New England Journal of Medicine* 351:209–211.
45. Muotri, A.R., K. Nakashima, N. Toni, V.M. Sandler, and F.H. Gage. 2005. Development of functional human embryonic stem cell-derived neurons in mouse brain. *Proceedings of the National Academy of Sciences of the United States of America* 102:18644–18648.
46. Owen-Smith, J., and J. McCormick. 2006. An international gap in human es cell research. *Nature Biotechnology* 24:391–392.
47. Parens, E. 1998. *Enhancing human traits: Ethical and social implications*. Washington, D.C.: Georgetown University Press.
48. Penttila, N. 2007. *The neuroethics of enhancement: How smart are smart drugs*. Washington, D.C.: Dana Foundation.
49. Plomer, A., K.S. Taymor, and C.T. Scott. 2008. Challenges to human embryonic stem cell patents. *Cell Stem Cell* 2:13–17.
50. Pujol, J., J. Reixach, B.J. Harrison, C. Timoneda-Gallart, J.C. Vilanova, and F. Perez-Alvarez. 2007. Posterior cingulate activation during moral dilemma in adolescents. *Human Brain Mapping* 29:910–921.
51. Redmond, D.E. 2002. Cellular replacement therapy for parkinson’s disease—where we are today? *Neuroscientist* 8:457–488.
52. Robert, J.S. 2006. The science and ethics of making part-human animals in stem cell biology. *FASEB Journal* 20:838–845.
53. Robert, J.S., and F. Baylis. 2003. Crossing species boundaries. *American Journal of Bioethics* 3:1–13.
54. Russo, E. 2005. Follow the money—the politics of embryonic stem cell research. *PLoS Biol* 3:e234.
55. US Congress 2005. *S. 1373 109th Congress. A bill to amend title 18, United States code, to prohibit human chimeras*. <http://thomas.loc.gov/cgi-bin/query/z?c109:s.659>
56. Sankar, P. 2004. Communication and miscommunication in informed consent to research. *Medical Anthropology Quarterly* 18:429–446.
57. Scott, C.T. 2008. Stem cells: New frontiers of ethics, law, and policy. *Neurosurgical Focus* 24:E24.
58. Shreeve, J. 2005. The other stem-cell debate. *N Y Times Mag*, 42–47.
59. Streiffer, R. 2005. At the edge of humanity: Human stem cells, chimeras, and moral status. *Kennedy Institute of Ethics Journal* 15: 347–370.
60. Taylor, H.A. 2007. Instead of revising half the story, why not rewrite the whole thing? *American Journal of Bioethics* 7: 19–21.
61. Tovino, S. 2007. Functional neuroimaging information: A case for neuro exceptionalism? *Florida University State Law Review* 34:415–489.
62. Vrtovec, K.T., and C.T. Scott. 2008. Patenting pluripotency: The next battle for stem cell intellectual property. *Nature Biotechnology* 26:393–395.
63. Wachbroit, R. 2008. The prospects for neuro-exceptionalism: Transparent lies, naked minds. *American Journal of Bioethics* 8:3–8.
64. Wade, N. 2005. Chimeras on the horizon, but don’t expect centaurs. *NY Times (Print)*, F1, F8.
65. Wendler, D. 2004. Risk standards for pediatric research: Rethinking the grimes ruling. *Kennedy Institute of Ethics Journal* 14:187–198.
66. Woodman, J. 2007. *Patients beyond borders: Everybody’s guide to affordable, world-class medical tourism*. Chapel Hill: Healthy Travel Media.
67. Zettler, P., L.E. Wolf, and B. Lo. 2007. Establishing procedures for institutional oversight of stem cell research. *Academic Medicine* 82:6–10.