Human embryonic stem cell research has emerged as an important platform for the understanding and treatment of pediatric diseases. From its inception, however, it has raised ethical concerns based not on the use of stem cells themselves but on objections to the source of the cells—specifically, the destruction of preimplantation human embryos. Despite differences in public opinion on this issue, a large majority of the public supports continued research using embryonic stem cells. Given the possible substantial benefit of stem cell research on child health and development, the American Academy of Pediatrics believes that funding and oversight for human embryo and embryonic stem cell research should continue. Pediatrics 2012;130:972–977

INTRODUCTION

In the past 10 years, significant progress has been made in basic and translational research using human embryonic stem cells (hESCs), with specific implications for pediatric diseases such as hypoxic-ischemic encephalopathy,1 bone marrow failure syndromes,2 leukemia,3 and congenital heart disease.4 Although the fundamental principle of stem cell research remains the same (ie, the development of undifferentiated cells into committed cell lineages for the purpose of tissue renewal and repair), the science has evolved to encompass many new applications, including cell-based therapies5 and drug screening.6,7 Although these new applications are intriguing, they remain in the early stages of development, and additional research is needed to make the transition from bench to therapeutics. It is anticipated that continued advances will have a substantial impact on the understanding and treatment of pediatric diseases.

hESCs

Three unique properties of hESCs are as follows: (1) they are un specialized or undifferentiated; (2) they can differentiate into more specialized cell types, such as brain, bone marrow, or heart, depending on the developmental signals they receive (referred to as pluripotency); and (3) they can continue to divide and renew themselves for longer periods than differentiated cells.8

Current sources of hESCs include excess embryos that would have been discarded after a successful in vitro fertilization (IVF) process, from previously frozen embryos created as part of an earlier IVF
process, and from de novo synthesis. In addition, hESCs may be generated from embryos with arrested or otherwise abnormal growth that would render them unsuitable for implantation. In these cases, the removal of the cells to form the stem cell line results in the destruction of the embryo. There is some recent evidence that hESC lines can be generated from 1 to 2 cells obtained by a biopsy procedure that does not require destruction of the embryo, but this procedure has not obviated the need to continue to derive stem cells in the traditional manner, which results in the destruction of an embryo. Traditionally created embryonic stem cell lines are needed to serve as a comparison with the newly developed lines to establish whether they are indeed equivalent to traditionally developed lines. Moreover, although a single cell biopsy may be performed in IVF cases to test for genetic diseases, it is unclear whether it would be appropriate to transfer to a uterus an embryo that underwent such biopsy for the creation of stem cell lines. It is not known whether the biopsy makes the embryo less likely to implant. Women undergoing IVF typically choose to transfer to their uterus embryos with the highest likelihood of implantation and, eventually, healthy birth. If embryos that have undergone a biopsy for purposes unrelated to health are not going to be chosen for implantation and will be eventually discarded, then the single biopsy procedure does not result in “spared” embryos (although it may result in a delay in destruction). Research is ongoing to identify novel and more efficient methods of obtaining stem cells from human embryos, and it is anticipated that this area will continue to evolve.

Once small numbers of embryonic stem cells have been isolated from human embryos, they are cultured in the laboratory to generate an ongoing source of cells, referred to as a cell line. Because of the unique self-renewing capacity of stem cells, the lines can often be maintained indefinitely. Because of constraints on the use of federal funds for research that results in the destruction of a human embryo, federal research grants involving hESCs entail the experimental manipulation of existing hESC lines and do not directly fund the acquisition of stem cells from the embryo. To maximize collaboration and access to hESC lines available nationally and internationally, the National Institutes of Health Office of Extramural Research maintains a publicly accessible registry that investigators may access to apply for funds pertaining to a particular cell line. State and private funding of stem cell research may not be similarly constrained.

ADULT STEM CELLS AND INDUCIBLE PLURIPOTENT STEM CELLS

In an attempt to find alternative sources for stem cells, several additional methods have been developed over the past 15 years. These include the isolation and genetic reprogramming of specific adult cells (usually skin fibroblasts) into inducible pluripotent stem cells (iPSCs). The development of these methods has not replaced the use of hESCs but has offered additional insight into the biology of cell differentiation, dedifferentiation, and aging in new biological models. Most mature tissues have small populations of stem cells that facilitate continued tissue growth and repair. These were first recognized in bone marrow, and advances in their isolation and expansion have revolutionized the treatment of hematologic and other malignancies. Bone marrow transplantation with hematopoietic stem cells is now the standard of care for pediatric high-risk leukemia as well as for certain solid tumors, immune deficiencies, and metabolic disorders. Stem cells have also been identified in the brain, cardiac muscle, connective tissue, and bone. Most evidence suggests that these cells are not pluripotent, as are hESCs, but could be induced to accelerate their repair mechanism in cell-based regenerative therapy, such as the use of native neural stem cells to repair spinal cord injury. Traditionally, this technology has been limited by the fact that adult stem cells are more differentiated, are harder to isolate from tissue, exist in relatively small numbers, and are more difficult to maintain in long-term culture when compared with hESCs. The generation of iPSCs from adult cells represents a major advancement in the understanding of the molecular mechanisms of cell differentiation. In 2007, iPSCs were successfully generated from human fibroblasts by engineering them to express genes implicated in dedifferentiation and the maintenance of “stemness.” These cells were capable of differentiating into all 3 embryonic germ layers (endoderm, mesoderm, and ectoderm). It is anticipated that, as the technology evolves, iPSCs will have important implications for pediatric diseases, including the study of tumor differentiation, hematopoiesis, and neurodegenerative disorders, and damaged tissue regeneration. Opponents of funding for hESC research believe that advances in the use of iPSCs obviate the need for cells derived directly from the human embryo. Although the use of iPSCs appears to hold great promise, there is evidence that, when compared with embryonic cells, iPSCs tend to retain their “molecular identity” and may, therefore, be less stable and efficient.
when programmed to develop into a particular cell line. Their cellular growth parameters may also be altered and have an increased susceptibility to unregulated growth similar to a neoplastic process, raising cancer concerns. In addition, some iPSCs may be susceptible to silencing of genes required for fetal development and differentiation. This concept of lineage bias will continue to be an active area of research requiring ongoing comparison of the pluripotency of iPSCs and hESCs. For example, the gene involved in fragile X syndrome, the most common inherited form of mental retardation in children, produces a protein vital to normal brain development in normal patients but acquires a silencing mutation in those with the disease. Researchers have shown that this gene functions normally in human embryonic cells and becomes silenced as the cells differentiate. In iPSCs, however, the gene is already silenced before the cells begin to differentiate. The use of iPSCs in human trials is problematic, given the high level of manipulation of these cells and the resulting concerns about how they will function in vivo. Whether iPSCs will prove a useful substitute for hESCs has yet to be determined. At this time, comparative studies using iPSCs will require an ongoing source of hESCs, which are still considered the scientific gold standard for embryonic cell lines.

hESC RESEARCH AND PEDIATRIC DISEASE

The American Academy of Pediatrics supports hESC research because current research reveals it may positively affect the treatment of pediatric diseases. In the past decade, several promising advances have been made with specific applications in pediatrics. hESCs have been programmed to differentiate into type II alveolar lung cells capable of producing surfactant, optimizing gas exchange, and protecting against pathogen invasion. Continued developments in this area could enhance the treatment of neonatal lung disease, a leading cause of morbidity and mortality in preterm infants. Insulin-secreting populations of pancreatic islet cells have been developed. Additional research is needed to stimulate these cells to produce enough insulin to be physiologically functional. If achieved, this could serve as a powerful therapy for children facing lifelong insulin replacement and morbidity associated with type I diabetes mellitus. A new technique for culturing hESCs has allowed for their differentiation into skin cells that expand rapidly and may serve as a replacement for autologous skin grafts and their long-term cosmetic sequelae. A direct comparison of the tumor-killing capacity of natural killer cells derived from hESCs versus umbilical cord blood stem cells found hESCs to be more efficient at killing leukemias and solid tumors as well as protecting against metastasis and recurrence in an in vivo model. Further work in this area will be particularly beneficial to children, in whom the late effects of cancer chemotherapy have been of increasing concern.

ETHICAL ISSUES

There are few ethical concerns raised about the use of isolated hESCs. Rather, concerns focus on the sources of the cells and, particularly, on the need to destroy a human embryo to derive the cell lines. If the destruction of a human embryo is a morally wrong act, then the use of stem cells derived from the destruction of the embryo may also be morally problematic. Some people who object to the destruction of embryos do not similarly object to the use of stem cells derived from those embryos but see the 2 acts as separate. People who do object argue that the use of such stem cells is morally illicit. In some ways, this concern may be time-limited (eventually, an alternative mechanism for deriving cell lines that does not result in the destruction of an embryo may be discovered). But, as pointed out earlier, even as new mechanisms are developed, traditionally derived stem cells must be used to set the standard against which to compare the newly derived lines.

The moral status of preimplantation ex utero human embryos may never be truly settled, and debates about the ethics of stem cell research are ongoing. Despite differences in public opinion on this issue, a majority of the public supports continued research using embryonic stem cells. Those people who disagree may argue that preimplantation ex utero human embryos should be accorded equal moral status to fully developed humans, but others counter that they have lesser moral status. Those in the latter category may argue that preimplantation ex utero human embryos have no moral status (because they lack relevant characteristics, such as sentience or ability to feel pain), or instead they may attempt to place embryos along a moral status hierarchy with other biologically alive entities, such as nonhuman animals. Even those who believe these embryos have little or no moral status may still believe they should be treated with respect or that there are certain limits to what may be done with a human embryo. Alternatively, those who believe that the preimplantation

*Moral status refers to the determination that an entity "counts" or that its interests must be taken into account, from a moral (as opposed to legal) point of view. Not all entities with moral status will have legal status (eg, nonhuman animals). Not all entities with legal status will have moral status (eg, corporations).
The destruction of embryos, there are a number of other ethical issues that arise in this context. For example, there are ethical concerns regarding acquisition of embryos from different sources. The most common source is excess embryos from the IVF process. But embryos may also be created specifically for stem cell research. For those who believe that embryos have some moral status (whether it is equivalent to that of fully developed humans), the creation of embryos for research purposes may be more ethically problematic than the use of excess embryos that would otherwise be destroyed. Even those who believe the embryo has no moral status may be uneasy about creating them for purely research uses. Because there are fewer objections to the use of embryos already created, research in this area may be limited to cells derived from excess IVF embryos. This would be congruent with the view that embryos have some moral status as well as the view that embryos have little or no moral status but should nonetheless be treated with respect.

The use of excess IVF embryos creates other ethical issues. Couples undergoing IVF may be both emotionally and financially vulnerable. Care must be taken to ensure that the informed consent process for research donation has adequate protections. Under no circumstances should couples feel obligated to donate, and they should be fully informed about the relevant issues, including other choices they can make regarding their excess embryos. Moreover, couples should not feel that their IVF care is in any way dependent on their decision to donate. Finally, it would be improper to offer financial incentives to couples in exchange for donating their embryos for the creation of stem cells because such incentives raise concerns about undue inducement. In addition, for some, payment for embryos may seem to commodify children or even demonstrate disrespect for the embryo (although payment of money can also be viewed as a way of demonstrating respect). Because of the varying positions on this issue and the absence of a need to pay donors for any time, effort, or risk involved in creating the excess embryos, the American Academy of Pediatrics finds financial incentives to be inappropriate in this context. Payment for the time, effort, and risks involved in gamete donation raises different issues and is beyond the scope of this statement.

If embryos are created by using genetic material from multiple individuals, it may be unclear who should provide the consent for research. Most IVF clinics do not look to gamete donors specifically, but rather to the individuals (or individual) who are planning to use the embryos for reproductive purpose to make decisions about disposition, including research. Consent forms for gamete donation should make clear that the recipients will have this dispositional authority. Similarly, agreements between parties who are creating embryos should set forth terms of disposition at the outset of the process, including what to do in cases of disagreement, separation/divorce, or death. hESCs should only be derived from embryos donated for research under either a previous agreement or current consent from parties with dispositional authority.

CONCLUSIONS

In a pluralistic society, substantive disagreements may be addressed through the legislative or regulatory process. The National Institutes of Health has issued guidelines on human stem cell research that identify eligibility for federal funding (setting standards for donation, consent, and the use of cells derived before the guidelines took effect). The guidelines.
serve as an important roadmap for using hESCs in research and attempt to strike an acceptable balance between the potential scientific benefits, the ethical issues and concerns surrounding this research, and the need for proper protection of human subjects. In particular, the American Academy of Pediatrics supports the following restrictions on hESC research:

a. hESCs should be derived from embryos that were created by using IVF for reproductive purposes and are no longer needed for this purpose.

b. The individuals who sought reproductive treatment must give voluntary written informed consent for the human embryos to be used for research purposes.

c. No payments, cash or in kind, should be offered for donated embryos used for hESC derivation.

d. There is a clear separation between the prospective embryo donor(s)’s decision to create human embryos for reproductive purposes and the prospective embryo donor(s)’s decision to donate human embryos for research purposes.

REFERENCES


Human Embryonic Stem Cell (hESC) and Human Embryo Research
COMMITTEE FOR PEDIATRIC RESEARCH and COMMITTEE ON BIOETHICS
Pediatrics 2012;130;972
DOI: 10.1542/peds.2012-2482 originally published online October 29, 2012;

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/130/5/972

References
This article cites 28 articles, 4 of which you can access for free at:
http://pediatrics.aappublications.org/content/130/5/972#BIBL

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Current Policy
http://www.aappublications.org/cgi/collection/current_policy
Committee on Bioethics
http://www.aappublications.org/cgi/collection/committee_on_bioethics
Committee on Pediatric Research
http://www.aappublications.org/cgi/collection/committee_on_pediatric_research

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.aappublications.org/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
http://www.aappublications.org/site/misc/reprints.xhtml