



WAKE FOREST  
INTELLECTUAL PROPERTY  
LAW JOURNAL

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VOLUME 9

2008 - 2009

NUMBER 3

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ETHICAL ISSUES IN REGENERATIVE MEDICINE

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INTRODUCTION

“Regenerative medicine” is an enormous category, encompassing more than a field of medicine and medical research.<sup>1</sup> The name “regenerative medicine” describes a set of innovative approaches to the treatment of illness, injury, and disability, focusing on the growth, replacement, and repair of cells, organs, and tissues specific to the health needs of particular individuals.<sup>2</sup> The extraordinary breadth of application of this approach is clear from an enumeration of just a few of the areas of regenerative medicine research: stem cells, including not only pluripotent embryonic stem cells, but also pluripotent stem cells produced by genetic reprogramming, and multipotent stem cells from fetal, perinatal,

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<sup>1</sup> See ANTHONY ATALA ET AL., *PRINCIPLES OF REGENERATIVE MEDICINE* 2 (Academic Press 2008); COMMITTEE ON THE BIOLOGICAL AND BIOMEDICAL APPLICATION OF STEM CELL RESEARCH, *STEM CELLS AND THE FUTURE OF REGENERATIVE MEDICINE* (National Academy Press 2002).

<sup>2</sup> ATALA ET AL., *supra* note 1, at 28. The term “regenerative medicine” was introduced by Dr. William Haseltine. See William A. Haseltine, *Regenerative Medicine*, BROOKINGS REV., Winter 2003, at 38, available at [http://www.brookings.edu/articles/2003/winter\\_healthcare\\_haseltine.aspx](http://www.brookings.edu/articles/2003/winter_healthcare_haseltine.aspx).

pediatric, and adult tissues;<sup>3</sup> techniques for stimulating endogenous cell growth and repair, which can be applied, for example, to the kidney,<sup>4</sup> the pancreas in the case of diabetes,<sup>5</sup> or digits and limbs in the case of trauma;<sup>6</sup> and the growth of replacement tissues and organs, from blood vessel<sup>7</sup> to bladder<sup>8</sup> to heart.<sup>9</sup> This enormous diversity of applications, all currently in various stages of research and development, arises from a profoundly effective multidisciplinary and interdisciplinary research orientation, which incorporates genetics, informatics, and basic research into the structure, mechanics, development of different tissues, and creative production techniques, as well as a range of other technologies that can scarcely be imagined by nonscientists.<sup>10</sup>

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<sup>3</sup> See Paolo De Coppi et al., *Isolation of Amniotic Stem Cell Lines with Potential for Therapy*, 25 NATURE BIOTECHNOLOGY 100 (2007); Akiva J. Marcus & Dale Woodbury, *Fetal Stem Cells from Extra-Embryonic Tissues: Do Not Discard*, 12 J. CELLULAR & MOLECULAR MED. 730 (2008); Sharon C. Presnell et al., *Stem Cells in Adult Tissues*, 13 SEMINARS CELL & DEVELOPMENTAL BIOLOGY 369 (2002); James A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCIENCE 1145 (1998); A. Vats et al., *Stem Cells*, 366 LANCET 592 (2005); Shinya Yamanaka, *Pluripotency and Nuclear Reprogramming*, 363 PHIL. TRANSACTIONS ROYAL SOC'Y B 2079 (2008); Junying Yu et al., *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*, 318 SCIENCE 1917 (2007).

<sup>4</sup> See Bendetta Bussolati et al., *Contribution of Stem Cells to Kidney Repair*, 28 AM. J. NEPHROLOGY 813 (2008); Laura Perin et al., *Stem Cell and Regenerative Science Applications in the Development of Bioengineering of Renal Tissue*, 63 PEDIATRIC RES. 467 (2008).

<sup>5</sup> See L. Baeyens & L. Bouwens, *Can  $\beta$ -Cells Be Derived from Exocrine Pancreas?*, 10 DIABETES, OBESITY & METABOLISM (SPECIAL ISSUE) 170 (2008); Qiao Zhou et al., *In Vivo Reprogramming of Adult Pancreatic Exocrine Cells to  $\beta$ -Cells*, 455 NATURE 627 (2008); Gordon C. Weir, *Can We Make Surrogate  $\beta$ -Cells Better Than the Original?*, 15 SEMINARS CELL & DEVELOPMENTAL BIOLOGY 347 (2004).

<sup>6</sup> See Ken Muneoka et al., *Regrowing Human Limbs*, SCI. AM., Apr. 2008, at 57; Hitoshi Yokoyama, *Initiation of Limb Regeneration: The Critical Steps for Regenerative Capacity*, DEV. GROWTH DIFFERENTIATION, Jan. 2008, at 13.

<sup>7</sup> See Laurence Bordenave et al., *Developments Towards Tissue-Engineered, Small-Diameter Arterial Substitutes*, 5 EXPERT REV. MED. DEVICES 337 (2008).

<sup>8</sup> See Anthony Atala et al., *Tissue-Engineered Autologous Bladders for Patients Needing Cystoplasty*, 367 LANCET 1241 (2006).

<sup>9</sup> See Shinako Masuda et al., *Cell Sheet Engineering for Heart Tissue Repair*, 60 ADVANCED DRUG DELIVERY REV. 277 (2008); Harold C. Ott et al., *Perfusion-Decellularized Matrix: Using Nature's Platform to Engineer a Bioartificial Heart*, 14 NATURE MED. 213 (2008); Vincent F.M. Segers & Richard T. Lee, *Stem-cell Therapy for Cardiac Disease*, 451 NATURE 937 (2008).

<sup>10</sup> See Paul Kemp, *History of Regenerative Medicine: Looking Backwards To Move Forwards*, 1 REGENERATIVE MED. 653 (2006). See generally ATALA ET AL., *supra* note 1. Kemp's historical perspective is particularly helpful for consideration of the financial, social, and policy contexts in which regenerative medicine is developing. See discussion *infra* at Section III.A.

Fundamentally, however, all of regenerative medicine, in its great complexity, springs from the search for understanding the basic mechanisms of generation—that is, the growth and development of living organisms. In this respect, it is the next step in a long scientific journey toward the efficient restoration of health and wholeness that comes from true knowledge. That noble goal notwithstanding, regenerative medicine’s many applications, areas, and branches together constitute a very early step along the road to fundamental understanding.

Like other novel biotechnologies, regenerative medicine raises a number of interesting research ethics issues. These issues are not new. Instead, as is common in scientific advancement, familiar and longstanding questions, never perfectly or finally addressed, appear in fresh contexts and renew old debates, causing us to reexamine the productive tensions that necessarily arise in research involving human subjects. Thus, just as regenerative medicine’s many scientific components all connect to basic knowledge of human growth and development, the many ethical issues it raises similarly connect to the basic building blocks of bioethics and human relationships in medicine and research.<sup>11</sup>

This article examines some of the novel technologies within regenerative medicine, focusing on: (1) human embryonic and pluripotent stem cell research; and (2) cell, tissue, and organ regeneration research. The range of ethical issues raised by each of these novel technologies is examined in turn, including: some of the most familiar arguments about human embryonic stem cell research; safety concerns raised by induced pluripotent stem cell research; the ethics of research design; issues to consider the first time an intervention is tested in human subjects; and informed consent and the therapeutic misconception. Finally, the article further considers whether regenerative medicine’s innovative technologies may further blur whatever distinction is thought to exist between medical treatment and enhancement, possibly creating more ethical issues to address in the long term. This article concludes by advising scholars and policymakers in bioethics to take the opportunity offered by

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<sup>11</sup> See, e.g., RUTH R. FADEN & TOM L. BEAUCHAMP WITH NANCY M. P. KING, A HISTORY AND THEORY OF INFORMED CONSENT (Oxford Univ. Press 1986); Steven Joffe & Franklin G. Miller, *Bench to Bedside: Mapping the Moral Terrain of Clinical Research*, HASTINGS CENTER. REP., Mar.-Apr. 2008, at 30; Ezekiel J. Emanuel et al., *What Makes Clinical Research Ethical?*, 283 JAMA 2701 (2000); NAT’L COMM’N FOR THE PROT. OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (1979), <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>.

regenerative medicine to reconsider these and other long-standing issues, and to move forward research ethics and policy by examining the issues anew through the lens of this groundbreaking medical science.

## I. HUMAN EMBRYONIC AND PLURIPOTENT STEM CELL RESEARCH

### A. HUMAN EMBRYONIC STEM CELLS

One question about the ethics of regenerative medicine has preoccupied most of the public debate for many years: whether the moral status of the embryo and fetus makes use of human embryonic stem (hES) cells ethically problematic.<sup>12</sup> Embryonic stem cells are highly versatile, able to give rise to all types of cells and to be “immortalized,” or perpetually propagated in a cell line.<sup>13</sup> Their versatility makes them valuable for research and treatment. However, they also have the intrinsic property of forming teratoma tumors.<sup>14</sup> Their source makes them controversial.

Deeply felt differences of opinion about the moral status of the human embryo have raised questions about the sources of embryonic stem cell lines, leading to both ethical and public policy debate.<sup>15</sup> When embryos must be destroyed in order to create new cell lines, moral and religious concerns are raised.<sup>16</sup> Recently, questions have also arisen about the adequacy of consent for research with the embryos used to create approved cell lines.<sup>17</sup> Disagreement is long standing about the moral appropriateness of creating new cell lines, for example from “leftover” embryos created in vitro and donated for

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<sup>12</sup> See generally CYNTHIA B. COHEN, *RENEWING THE STUFF OF LIFE: STEM CELLS, ETHICS, AND PUBLIC POLICY* (Oxford Univ. Press 2007); COMM. ON GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH, *GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH* 34 (National Academy of Sciences 2005).

<sup>13</sup> Junying Yu & James A. Thomson, *Embryonic Stem Cells, as reprinted in* NAT'L INSTS. OF HEALTH, *REGENERATIVE MEDICINE* 2006, at 1, [http://stemcells.nih.gov/staticresources/info/scireport/PDFs/Regenerative\\_Medicine\\_2006.pdf](http://stemcells.nih.gov/staticresources/info/scireport/PDFs/Regenerative_Medicine_2006.pdf).

<sup>14</sup> Davor Solter, *From Teratocarcinomas to Embryonic Stem Cells and Beyond: A History of Embryonic Stem Cell Research*, 7 *NATURE REVIEWS GENETICS* 319, 319-320 (2006).

<sup>15</sup> See COHEN, *supra* note 12; Russell Korobkin, *Stem Cell Research and the Cloning Wars*, 18 *STAN. L. & POL'Y REV.* 161, 171 (2007); John A. Robertson, *Ethics and Policy in Embryonic Stem Cell Research*, 9 *KENNEDY INST. ETHICS J.* 109 (1999).

<sup>16</sup> See COHEN, *supra* note 12.

<sup>17</sup> See Robert Streiffer, *Informed Consent and Federal Funding for Stem Cell Research*, 40(3) *HASTINGS CENTER. REP.*, May-June 2008, at 40.

research purposes,<sup>18</sup> or from stored embryos that have been determined to be “dead.”<sup>19</sup> Recent evidence that hES cell lines can be created from single embryonic cells (blastomeres) without compromising the viability of the donor embryos has not ended the controversy.<sup>20</sup>

Similarly important and pervasive discussions concern the ethical implications of somatic cell nuclear transfer, or “research cloning,” in which the nucleus of a somatic cell replaces the nucleus of an oocyte in order to create a stem cell line that is a match for the individual from whom the somatic cell was taken.<sup>21</sup> This type of research requires large numbers of oocytes, giving rise to concerns about consent and payment in the procurement of human oocytes,<sup>22</sup> in addition to qualms about the use of a technology that is largely identical to what would be used for reproductive cloning.<sup>23</sup> The proposal to use non-human oocytes as hosts for the cloning of human cell nuclei potentially would resolve the procurement concerns, but raises other questions of feasibility and the ethics of creating novel chimaeras.<sup>24</sup>

Two important considerations are likely to influence public discourse about the ethical implications of hES cell research. First, the

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<sup>18</sup> Annie D. Lyerly & Ruth R. Faden, *Embryonic Stem Cells: Willingness to Donate Frozen Embryos for Stem Cell Research*, 316 *SCIENCE*, July 2007, at 46.

<sup>19</sup> See Xin Zhang et al., *Derivation of Human Embryonic Stem Cells from Developing and Arrested Embryos*, 24 *STEM CELLS* 2669, 2669 (2006); Donald W. Landry & Howard A. Zucker, *Embryonic Death and the Creation of Human Embryonic Stem Cells*, 114 *J. CLINICAL INVESTIGATION* 1184, 1184 (2004).

<sup>20</sup> See Young Chung et al., *Human Embryonic Stem Cell Lines Generated Without Embryo Destruction*, 2 *CELL STEM CELL* 113 (2008).

<sup>21</sup> See generally ATALA ET AL., *supra* note 1; COHEN, *supra* note 12; DJ Procop, *Embryonic Stem Cells versus Adult Stem Cells: Some Seemingly Simple Questions*, in *ESSENTIALS OF STEM CELL BIOLOGY*, xxii (Robert Lanza et al. eds., 2006); Alexander Meissner and Rudolf Jaenisch, *Generation of Nuclear Transfer-Derived Pluripotent ES Cells from Cloned Cdx2-Deficient Blastocysts*, 439 *NATURE* 212 (2006); PRESIDENT’S COUNCIL ON BIOETHICS, *MONITORING STEM CELL RESEARCH* 111-12 (2004), [http://www.bioethics.gov/reports/stemcell/pcbe\\_final\\_version\\_monitoring\\_stem\\_cell\\_research.pdf](http://www.bioethics.gov/reports/stemcell/pcbe_final_version_monitoring_stem_cell_research.pdf).

<sup>22</sup> See David Magnus & Mildred K. Cho, *Issues in Oocyte Donation for Stem Cell Research*, 308 *SCIENCE* 1747, 1747-48 (2005). *But see* John A. Robertson, *Technology and Motherhood: Legal and Ethical Issues in Human Egg Donation*, 39 *CASE W. RES. L. REV.* 1, 31 (1989); Josephine Johnston, *Paying Egg Donors: Exploring the Arguments*, 36(1) *HASTINGS CENTER REP.*, Jan.-Feb. 2006, at 28, 30; Debora Spar, *The Egg Trade: Making Sense of the Market for Human Oocytes*, 356 *NEW ENG. J. MED.* 1289 (2007); David B. Resnik, *Regulating the Market for Human Eggs*, 15 *BIOETHICS* 1, 5-9 (2001).

<sup>23</sup> See COHEN, *supra* note 12.

<sup>24</sup> See Stephen Minger, *Interspecies SCNT-Derived Human Embryos—a New Way Forward for Regenerative Medicine*, 2 *REGENERATIVE MED.* 103 (2007).

debate has changed now that presidential policy regarding federal funding of this research has been liberalized.<sup>25</sup> Second, the moral and religious debate is not unique to hES cell research, although it has remained largely focused there. Many of the same issues arise in the extensive assisted reproduction industry, which is largely unregulated in the United States.<sup>26</sup> These issues include the implantation and “selective reduction”<sup>27</sup> of multiple embryos and the permanent storage or destruction of unused but potentially viable embryos.<sup>28</sup> Recent media furor over the birth of octuplets through assisted reproduction has revived interest in these ethical issues, and perhaps also in regulation.<sup>29</sup>

#### B. INDUCED PLURIPOTENT STEM CELLS

The newest and perhaps most interesting development in pluripotent stem cell research is the creation of induced pluripotent stem (iPS) cells—that is, the use of various means of stimulating a somatic cell to “de-differentiate,” or evolve backward to a pluripotent stem cell.<sup>30</sup> Pluripotent stem cells are capable of giving rise to all adult cell types. A key consideration is the risk of harm that could result from the process of generating iPS cells. To stimulate de-differentiation, generally referred to as “reprogramming,” current methods of iPS cell creation require the introduction of genetic material into the cell. This is often achieved by using viral vectors, as in gene transfer research, and thus introduces comparable risks,

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<sup>25</sup> Exec. Order No. 13,505, 74 Fed. Reg. 10,667 (Mar. 11, 2009); Nat’l Insts. of Health, Guidelines on Human Stem Cell Research, 74 Fed. Reg. 32,170 (July 7, 2009), available at <http://stemcells.nih.gov/policy/2009guidelines.htm>.

<sup>26</sup> See generally Am. Soc’y for Reproductive Med., Ethical Considerations of Assisted Reproductive Technologies: ASRM Ethics Committee Reports and Statements, <http://www.asrm.org/Media/Ethics/ethicsmain.html> (last visited Jan. 20, 2010); Am. Soc’y for Reproductive Med., Practice Committee Reports: Guidelines, Statements, and Opinions of the American Society for Reproductive Medicine Practice Committee, <http://www.asrm.org/Media/Practice/practice.html> (last visited Jan. 20, 2010).

<sup>27</sup> See Liza Mundy, *Too Much to Carry?*, WASH. POST MAG., May 20, 2007, at W14.

<sup>28</sup> See Lyerly & Faden, *supra* note 18.

<sup>29</sup> See, e.g., Stephanie Saul, *Birth of Octuplets Puts Focus on Fertility Clinics*, N.Y. TIMES, Feb 12, 2009, at A1.

<sup>30</sup> See, e.g., Keisuke Okita et al., *Generation of Germline-Competent Induced Pluripotent Stem Cells*, 448 NATURE 313 (2007); Marius Wernig et al., *In Vitro Reprogramming of Fibroblasts into a Pluripotent ES-Cell-Like State*, 448 NATURE 318 (2007); Chad A. Cowan et al., *Nuclear Reprogramming of Somatic Cells After Fusion with Human Embryonic Cells*, 309 SCIENCE 1369 (2005); see also Amy Zarzeczny et al., *iPS Cells: Mapping the Policy Issues*, 139 CELL 1032 (2009).

including the possibility of insertional mutagenesis.<sup>31</sup> Uses of non-viral vectors and non-genetic means of reprogramming cells to a pluripotent state are in development in many laboratories.<sup>32</sup> Once this problem is solved, the intrinsic propensity of iPS cells, like ES cells, to form teratoma tumors may still present a potential risk for therapeutic applications.<sup>33</sup>

Induced pluripotent stem cell research appears extremely promising, both for the study of genetic and other diseases and ultimately for the development of genuinely personalized therapies.<sup>34</sup> Nonetheless, many uncertainties accompany this exciting research; its safety, effectiveness and cost are yet to be determined, and much is still unknown. Thus, it is clearly desirable to continue pursuing the identification and development of multiple sources of human pluripotent stem cells. The availability of iPS cell technology, the collection of potentially pluripotent stem cells from biological waste materials, and other technologies for the identification and production of usable stem cells and cell lines are not alternatives; instead they are complementary.<sup>35</sup>

### C. BIOBANKING

One technology used widely in medicine and research is the collection and storage of biological materials. When biological

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<sup>31</sup> Insertional mutagenesis is the stimulation of potentially deleterious genetic mutations when new genetic material is introduced. It is most likely to be a problem when viral vectors are used to insert new genes, and has long been of concern in gene transfer research. See Salima Hacein-Bey-Abina et al., *A Serious Adverse Event After Successful Gene Therapy for X-Linked Severe Combined Immunodeficiency*, 348 NEW ENG. J. MED. 255, 255 (2003).

<sup>32</sup> See, e.g., Wenlin Li et al., *Generation of Rat and Human Induced Pluripotent Stem Cells by Combining Genetic Reprogramming and Chemical Inhibitors*, 4 CELL STEM CELL 16 (2009); Rudolf Jaenisch & Richard Young, *Stem Cells, the Molecular Circuitry of Pluripotency and Nuclear Reprogramming*, 132 CELL 567 (2008); Keisuke Okita et al., *Generation of Mouse-Induced Pluripotent Stem Cells Without Viral Vectors*, 322 SCIENCE 949 (2008); Takashi Tada, *Genetic Modification-Free Reprogramming to Induced Pluripotent Cells: Fantasy or Reality?*, 3 CELL STEM CELL 121 (2008).

<sup>33</sup> The Food and Drug Administration has clearly indicated that extensive testing of hES cell and iPS cell products will be required, especially with respect to tumorigenicity, before human testing may begin. This safety testing reportedly could take years. See *infra* notes 51 and 55.

<sup>34</sup> See, e.g., Asa Abeliovich & Claudia A. Doege, *Reprogramming Therapeutics: iPS Cell Prospects for Neurodegenerative Disease*, 61 NEURON 337 (2009).

<sup>35</sup> See generally COHEN, *supra* note 12; Mahendra Rao & Maureen L. Condic, *Alternative Sources of Pluripotent Stem Cells: Scientific Solutions to an Ethical Dilemma*, 17 STEM CELLS & DEV. 1 (2008); PRESIDENT'S COUNCIL, *supra* note 21, at 111-12.

materials are stored in order to be made available to share for treatment or research, this is usually called biobanking. Blood banking is the best-known example in which the cells have a limited shelf-life. However, biobanking technology often makes it possible to store usable biospecimens for many years, generally in ultra-low temperature freezers, and even to generate long-lived cell lines so that they can serve indefinitely as a renewable resource.

Regenerative medicine has come to depend on the ability to bank cells for use in so-called “cell therapy” research and treatment. Private umbilical cord blood banking services were developed in the 1980s as an expensive and exclusive option marketed to families concerned about possible future health needs.<sup>36</sup> Public umbilical cord stem cell banking followed, beginning in the 1990s.<sup>37</sup> The rationale for this public banking is to provide a resource for transplantation of blood-forming hematopoietic stem cells to virtually any United States citizen. The use of cord blood stem cells represents an alternative to bone marrow transplantation for many patients.<sup>38</sup> However, technologies have not been developed to date for the expansion of the relatively limited number of blood-forming stem cells present in umbilical cord blood, nor for their differentiation into other types of cells. More recently, broadly multipotent stem cells capable of extensive expansion in laboratory culture have been isolated from what are often considered biological waste products: most notably amniotic fluid and placental chorionic villi,<sup>39</sup> as well as the stromal tissue of umbilical cord.<sup>40</sup> These new findings have heightened interest in large-scale national stem cell banking beyond the existing collection of cord blood.<sup>41</sup> Ideally, large-scale banking efforts could

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<sup>36</sup> Joanne Kurtzberg et al., *Untying the Gordian Knot: Policies, Practices, and Ethical Issues Related to Banking of Umbilical Cord Blood*, 115 J. CLINICAL INVESTIGATION 2592, 2592 (2005).

<sup>37</sup> *Id.*; see also Stem Cell Therapeutic and Research Act of 2005, Pub. L. No. 109-129, 2520 HR 2005 (codified 42 U.S.C. § 274) (providing substantial support for public cord blood banking. The target is to have enough banked umbilical cord blood units to provide good matching for virtually any US citizen.).

<sup>38</sup> Bertram Lubin & William Shearer, *Cord Blood Banking for Potential Future Transplantation*, 119 PEDIATRICS 165, 165 (2007).

<sup>39</sup> M. Minhaj Siddiqui & Anthony Atala, *Amniotic Fluid-Derived Pluripotential Cells*, in 2 HANDBOOK OF STEM CELLS 175 (R. Lanza et al., eds., Elsevier Academic Press 2004); De Coppi et al., *supra* note 3, at 104; Ming-Song Tsai et al., *Clonal Amniotic-Fluid Derived Stem Cells Express Characteristics of Both Mesenchymal and Neural Stem Cells*, 74 BIOLOGY REPRODUCTION 545, 550 (2006).

<sup>40</sup> Alp Can & Sercin Karahuseyinoglu, *Concise Review: Human Umbilical Cord Stroma with Regard to the Source of Fetus-Derived Stem Cells*, 25 STEM CELLS 2886, 2886 (2007).

<sup>41</sup> Senators Burr and Coleman introduced the Amniotic Fluid and Placental Stem Cell Banking Act on March 22, 2007. See Amniotic Fluid and Placental Stem Cell

store enough different lines of broadly multipotent and pluripotent stem cells that might be used in many different regenerative medicine applications to provide good matches for nearly the entire population of the United States.<sup>42</sup>

Systems for the collection, storage, and use of stem cells of different types are, however, still in the early stages, both technologically and from a policy standpoint, and a number of scientific, practical, and ethical issues are raised by this effort. These issues include ensuring the broad availability of matches for those in need, determining access for research as well as for therapeutic uses, refining consent forms, information, and procedures, and developing robust systems for confidentially labeling biospecimens and linking them to the information needed for research and treatment.<sup>43</sup> These practical, ethical and policy questions must be thoroughly and continually addressed before the promise of biobanking, in particular banking of stem cells, can be fully realized.

## II. CELL, TISSUE, AND ORGAN REGENERATION RESEARCH

The ethical issues arising from the design and conduct of research into cell, tissue, and organ regeneration are distinctive and interesting, though not novel. Most of these issues are common to all early-phase research in novel biotechnologies—for example, gene transfer research, often misleadingly called “gene therapy.”<sup>44</sup>

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Banking Act, S. 957, 110th Cong. (2003). Reps. Lipinski, McIntyre, Shuler, Ellsworth, Melancon, and Donnelly introduced the National Amniotic and Placental Stem Cell Bank Act on April 17, 2007. See National Amniotic and Placental Stem Cell Bank Act, H.R. 1892, 110th Cong. (2007).

<sup>42</sup> Ruth R. Faden et al., *Public Stem Cell Banks: Considerations of Justice in Stem Cell Research and Therapy*, 33(6) HASTINGS CENTER REP., Nov.-Dec. 2003, at 13.

<sup>43</sup> *Id.*; see also Jeremy Sugarman et al., *Ethical Issues in Umbilical Cord Blood Banking*, 278 JAMA 938, 938 (1997). Many of these issues are currently being addressed in umbilical cord blood banking. Future extensions to multipotent stem cells, such as those in amniotic fluid, may be easier in some respects—for instance, the cells can be perpetuated and thus will not be used up when samples are taken to treat an individual patient, or for a particular research use. Other issues may be more difficult to translate. For example, the processing cost for amniotic fluid stem cells is likely to be greater than for umbilical cord blood. In addition, since amniotic fluid stem cells are expected to have a broader range of (still unproven in the clinic) potential uses, their use may necessitate broader consent forms.

<sup>44</sup> See Larry R. Churchill et al., *Genetic Research as Therapy: Implications of “Gene Therapy” for Informed Consent*, 26 J.L. MED. & ETHICS 38 (1998); Nancy M. P. King, *Rewriting the “Points to Consider”: The Ethical Impact of Guidance Document Language*, 10 HUMAN GENE THERAPY 133 (1999); Nancy M. P. King, *Defining and Describing Benefit Appropriately in Clinical Trials*, 28 J.L. MED. & ETHICS 332 (2000) [hereinafter King 2000].

Although some of the research into the regeneration of cells, tissues, and organs uses hES cells and iPS cells or cells from fetal tissues, most current regenerative medicine research uses less controversial types of stem cells derived from a variety of adult and perinatal cell sources. These different types of stem cells are variously named and categorized, according to where they are found and the stage of development when they are derived. The range of stem cell types within this large group may be best described as creating a continuum of potentiality, from “adult” stem cells, able to give rise only to the cells of the tissue from which they are derived, to adult and perinatal stem cells believed to be more versatile—perhaps able to give rise to specialized cells corresponding to organs and tissues different from that of their source.<sup>45</sup> “Cell therapies” used in research and treatment employ stem cells of all types. Examples of cell therapy include: widespread use of hematopoietic stem cell transplants in cancer treatment,<sup>46</sup> research addressing autoimmune diseases,<sup>47</sup> and increasing tolerance for solid organ transplantation; injection of stem cells into the brains of patient-subjects with nervous system disorders like Parkinson’s disease,<sup>48</sup> or into patient-subjects with diabetes, in an effort to stimulate the growth of healthy cells that can replace those damaged by disease.<sup>49</sup> Another promising type of cell therapy research seeks ways to stimulate self-repair of damaged cells, or to turn one type of cell into a needed cell type, through injection of chemical or gene transfer agents directly into target organs and tissues.<sup>50</sup>

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<sup>45</sup> ATALA ET AL., *supra* note 1, at 347 (determined stem cells are found in small quantities in adult organs and tissues). Some stem cells have also been called “multipotent.” Scientific debate about the potentiality of stem cells and their categorization is ongoing.

<sup>46</sup> Edward A. Copelan, *Hematopoietic Stem-Cell Transplantation*, 354 NEW ENG. J. MED. 1813, 1813 (2006).

<sup>47</sup> Richard K. Burt et al., *Clinical Applications of Blood-Derived and Marrow-Derived Stem Cells for Nonmalignant Diseases*, 299 JAMA 925, 927 (2008).

<sup>48</sup> Ole Isacson & Jeffrey H. Kordower, *Future of Cell and Gene Therapies for Parkinson’s Disease*, 64 ANNALS NEUROLOGY (SUPPLEMENT) S122, S122 (2008); see also Ninette Amariglio et al., *Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient*, 6(2) PLOS MED. 221, 222 (2009) (apparently demonstrating that tumorigenicity is a risk not limited to hES and iPS cells).

<sup>49</sup> Mark E. Furth & Anthony Atala, *Stem Cell Sources to Treat Diabetes*, 106 J. CELLULAR BIOCHEMISTRY 507, 507 (2009).

<sup>50</sup> Promising research is underway testing the ability of such injections to restart insulin production in non-functioning pancreatic islet cells, and perhaps even to turn (“reprogram”) non-insulin-producing cells in the pancreas into the insulin-producing cell type. See generally Zhou et al., *supra* note 5, at 627.

In late January 2009, the Food & Drug Administration approved the first clinical trial of an hES cell-based experimental intervention for spinal cord injury.<sup>51</sup> This phase I study is a good example of how regenerative medicine research raises ethical questions common to all early-phase research. The industry-sponsored study plans to enroll eight to ten subjects with recent, severe spinal cord injuries.<sup>52</sup> The goal of the study, like that of phase I research generally, is only to determine safety.<sup>53</sup> Like many other phase I studies, however, it must enroll not healthy volunteers (as is usual in pharmaceutical research) but instead patients with the condition of interest (as is usual in cancer research, gene transfer, and numerous other areas). Thus, potential subjects, investigators, regulators, reporters, investors, and the general public may all have heightened and perhaps unrealistic expectations of potential benefit for the subjects, derived from the hope that this promising research could ultimately become an effective treatment. This “therapeutic misconception”<sup>54</sup> might be compounded by the enrollment of subjects who are patients with new, severe injuries—presumably chosen in order to provide the best data on the intervention’s potential for efficacy—rather than patients with less severe and less recent injuries, who have

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<sup>51</sup> See Karen Kaplan, *Stem Cell Therapy To Be Tested on Spinal Cord Injuries*, L.A. TIMES, Jan. 24, 2009, available at <http://www.latimes.com/news/printedition/front/la-sci-stemcells24-2009jan24,0,5005078.story>; Andrew Pollack, *Milestone in Research in Stem Cells*, N.Y. TIMES, Jan. 23, 2009, at B1; Press Release, Geron Receives FDA Clearance to Begin World’s First Human Clinical Trial of Embryonic Stem Cell-Based Therapy (Jan 23, 2009), available at <http://geron.com/media/pressview.aspx?id=1148> (providing information about the study and its sponsor, Geron Corporation).

<sup>52</sup> See sources cited *supra* note 51.

<sup>53</sup> See 20 CFR 312.21(a) (2010).

<sup>54</sup> Paul S. Appelbaum et al., *The Therapeutic Misconception: Informed Consent in Psychiatric Research*, 5 INT’L J.L. & PSYCHIATRY 319 (1982); see also Rebecca Dresser, *The Ubiquity and Utility of the Therapeutic Misconception*, 19 SOC. PHIL. & POL’Y 271 (2002); Gail E. Henderson et al., *Clinical Trials and Medical Care: Defining the Therapeutic Misconception*, 4 PLOS MED. 1735 (2007); Gail E. Henderson et al., *Therapeutic Misconception in Early Phase Gene Transfer Trials*, 62 SOC. SCI. & MED. 239 (2006); King 2000, *supra* note 44, at 332; Nancy M. P. King et al., *Consent Forms and the Therapeutic Misconception: The Example of Gene Transfer Research*, 27(1) IRB: ETHICS & HUMAN RES., Jan.-Feb. 2005, at 1 [hereinafter King 2005]; Sam Horng & Christine Grady, *Misunderstanding in Clinical Research: Distinguishing Therapeutic Misconception, Therapeutic Misestimation, & Therapeutic Optimism*, 25(1) IRB: ETHICS & HUMAN RES., Jan.-Feb. 2003, at 11 (2003); see generally George J. Annas, *Questing for Grails: Duplicity, Betrayal and Self-Deception in Postmodern Medical Research*, 12 J. CONTEMP. HEALTH L. & POL’Y 297 (1996); Matthew Miller, *Phase I Cancer Trials: A Collusion of Misunderstanding*, 30(4) HASTINGS CENTER REP., July-Aug. 2000, at 34.

lived with their disability longer and would also have more time to decide about research participation. Finally, use of an agent that has shown only moderate success in research with animals has provoked another question frequently asked about first-in-human studies: Is this really ready for prime time?<sup>55</sup>

Organ and tissue regeneration is an even more precise and complex process than cell therapy research. It requires collaborative, deliberate, and extensive pre-clinical knowledge-building research. The prototypical example is the regeneration of hollow organs, such as human bladders, which Dr. Atala has pioneered.<sup>56</sup> The exogenous building of hollow organs, including blood vessels, bladders, and uteruses, requires technological sophistication and pragmatic understanding of human development and function. The regeneration of solid organs adds many further complexities, including vascularization, tissue oxygenation prior to vascular regrowth, pre-implantation development, and a host of other complex considerations.<sup>57</sup> Limb regeneration is yet another distinctive area of research, as yet in the early stages of understanding of the triggers for, and controls on, development and differentiation of complex structures.<sup>58</sup>

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<sup>55</sup> See Nancy M. P. King & Odile Cohen-Haguenaer, *En Route to Ethical Recommendations for Gene Transfer*, 16 *MOLECULAR THERAPY* 432 (2008). Determining when to move into human trials, or “from the bench to the bedside,” is now often referred to as a “translational” research issue. General consideration of the quantity and quality of preclinical evidence underpins the readiness question. For any proposed clinical research involving the study of ES cell-derived products as a potential therapy, a specific concern arises: that residual undifferentiated ES cells are likely to cause teratoma tumors. The general view is that these would be “benign”—but it is still a significant safety concern. Geron has been required to complete extensive testing to provide data indicating that potentially tumorigenic cells have been eliminated from the specialized oligodendrocytes (derived from hES cells) in this cell product. Indeed, in August 2009, the trial was placed on “clinical hold” by the FDA, pending completion of a confirmatory preclinical study in an animal model of cervical injury, owing to a higher than expected incidence of cyst development at the site of the cervical spinal lesion in animals receiving the ES cell-derived product. See *hESC-Derived Oligodendrocytes—GRNOPCI*, Geron, <http://www.geron.com/products/productinformation/spinalcordinjury.aspx> (last visited Apr. 13, 2010). Patient-subjects are likely to need immune suppressive drugs to avoid rejection of non-HLA-matched ES cells, and little is known about their possible effects on tumor growth, making the risk of tumorigenesis in such research particularly concerning.

<sup>56</sup> Atala et al., *supra* note 8, at 1241. For the media’s take on the research, see Stephanie Smith, *Doctors Grow Organs From Patient’s Own Cells*, CNN, Apr. 5, 2006,

<http://www.cnn.com/2006/HEALTH/conditions/04/03/engineered.organs/index.html>.

<sup>57</sup> See Mark E. Furth & Anthony Atala, *Producing Organs in the Laboratory*, 9 *CURRENT UROLOGY REPS.* 433 (2008).

<sup>58</sup> See Muneoka et al., *supra* note 6; Yokoyama, *supra* note 6.

The ethical issues raised by regenerative medicine research in these areas are intriguing. As in the phase I spinal cord injury study described earlier, long-standing research ethics questions are brought into sharp focus in the context of this new technology. These issues, some of which could appear to be of heightened significance in this context, include the following: design and ethics in early-phase research; subject selection, informed consent, and the therapeutic misconception; and the distinction between treatment and enhancement.

#### A. ETHICAL ISSUES IN RESEARCH DESIGN

One recurring ethical concern about any novel technology is captured by the question “Is the practice morally acceptable under the circumstances?” The answer, of course, depends on what count as the relevant circumstances. One of them is always cost. Asking about resource allocation and regenerative medicine research requires us to consider this cutting-edge research in its social context, alongside other health needs and priorities, such as local and global health disparities.<sup>59</sup> The perennial question, of course, is: Who should determine funding priorities, and on what basis? What is arguably new—or at least highlighted—in regenerative medicine is that these priorities are being determined not only by federal funders, but also by investors with private capital, and by intellectual property considerations.<sup>60</sup> Most of these considerations, however, are addressed explicitly by others in this symposium.

A notable aspect of regenerative medicine, which relates to questions about cost and resource allocation, is its recognition of the need to standardize and streamline production. This production perspective is an important step in lowering costs and increasing access to new technologies, but it could also have interesting ethical implications. Because the regeneration of cells, organs, and tissues is specific to the health needs of particular individuals, the trajectory of regenerative medicine research could be characterized as moving from the individual in early phase studies outward to progressively larger groups in later research phases, through the testing of increasingly

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<sup>59</sup> See, e.g., Alex John London & Jonathan Kimmelman, *Justice in Translation: From Bench to Bedside in the Developing World*, 372 LANCET 82 (2008); Heather L. Greenwood et al., *Regenerative Medicine and the Developing World*, 3 PLOS MED. 1496 (2006); Faden et al., *supra* note 42.

<sup>60</sup> See Faden et al., *supra* note 42; Greenwood et al., *supra* note 59; London & Kimmelman, *supra* note 59; see also Kemp, *supra* note 10; David B. Resnik, *The Commercialization of Human Stem Cells: Ethical and Policy Issues*, 10 HEALTH CARE ANALYSIS 127 (2002).

standardizable production methods. The move from individually tailored research toward standardization is arguably a distinctive trajectory, scientifically and ethically distinguishable both from traditional drug development<sup>61</sup> and from so-called “personalized medicine.”<sup>62</sup>

In conventional clinical research, as typified by drug development, the number of subjects typically increases from one trial phase to the next. At the same time, however, the risks of harm and potential for benefit also become better characterized, and ideally, risks of harm decrease and evidence of potential efficacy increases as the research progresses from early to later study phases.<sup>63</sup> In contrast, in the new category of “personalized medicine,” the research trajectory moves from the large-scale development of genetic screening and testing to the application of test results to tailor interventions precisely for each individual.<sup>64</sup>

In order to make organ and tissue regeneration feasible and affordable outside the research context, regenerative medicine research seeks to move from individually tailored interventions toward the development of production methods that can reduce the investment of time, labor, and cost. This “reverse trajectory” is necessary and admirable if regenerative medicine is to become meaningfully available to those who need it. Attention to this goal distinguishes regenerative medicine from new technologies like gene transfer, where standardization, the development of platform technologies, and attempts at large-scale, cost-reducing production are in their infancy.<sup>65</sup> This emphasis on standardization and development of large-scale production, however, raises the atypical possibility that the risks of harm for individual subjects could increase over the research trajectory, and the potential for efficacy could decrease.<sup>66</sup> Thus, the

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<sup>61</sup> Nat’l Library of Med., U.S. Dep’t of Health & Human Servs., FAQ: ClinicalTrials.gov – Clinical Trial Phases (Apr. 18, 2008), <http://www.nlm.nih.gov/services/ctphases.html>; see also OFFICE OF BIOTECHNOLOGY ACTIVITIES, NAT’L INSTS. OF HEALTH, NIH GUIDANCE ON INFORMED CONSENT FOR GENE TRANSFER RESEARCH (2003), [http://oba.od.nih.gov/oba/rac/ic/pdfs/temp\\_pdf.pdf](http://oba.od.nih.gov/oba/rac/ic/pdfs/temp_pdf.pdf).

<sup>62</sup> See, e.g., Allen Buchanan et al., *Pharmacogenetics: Ethical and Policy Options*, 12 KENNEDY INST. ETHICS J. 1 (2002); Thomas J. Hudson, *Personalized Medicine: A Transformative Approach Is Needed*, 180 CAN. MED. ASS’N J. 911 (2009); Jesse J. Swen et al., *Translating Pharmacogenomics: Challenges on the Road to the Clinic*, 4 PLOS MED. 1317 (2007); David J. Triggle, *Drug Discovery and Delivery in the 21st Century*, 16 MED. PRINCIPLES & PRAC. 1 (2007).

<sup>63</sup> See Nat’l Library of Med., *supra* note 61.

<sup>64</sup> See sources cited *supra* note 62.

<sup>65</sup> See King & Cohen-Haguenauer, *supra* note 55.

<sup>66</sup> The principal advantage of “personalized” tissue and organ regeneration is avoidance of immune rejection. Use of the patient’s own cells is likely to be more labor-intensive and costly than if organs could be produced “off the shelf” with

design, ethics, and policy questions that arise throughout this research trajectory include questions about how best to balance cost and access, safety and scale in the development of production processes.

Because regenerative medicine research is such a vivid exemplar of early-phase clinical research, it also raises important, under-addressed questions of design, ethics, and policy relating to first-time-in-human trials with small numbers of subjects drawn from patients with limited treatment options. Such trials pose difficult questions for reasons of subject vulnerability,<sup>67</sup> the difficulty of providing information when there is considerable uncertainty,<sup>68</sup> and the potential divergence of subjects' desire for clinical benefit from the scientific goals of early-phase research.<sup>69</sup> There has been insufficient scholarly attention to the problems of early-phase research with patient-subjects, but interest in addressing these challenges is increasing, especially as novel technologies like regenerative medicine suggest or even require new study designs and translational pathways.<sup>70</sup>

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standardized donor cells. For many patients the cells needed to “personalize” the intervention may not be obtainable by biopsy. This could be due to a variety of reasons: disease condition may eliminate them or make them difficult to obtain safely (e.g., in a cancer patient, they might be contaminated by tumor cells; in a diabetes patient, the pancreatic insulin-producing cells have been destroyed already by an autoimmune mechanism; for elderly patients the cells may not grow well, as compared to younger patients). The great appeal of iPS cell technology in this context is that it, in principle, offers a way to make any cell type with the patient's own genetic constitution. Unfortunately, the cost associated with making an iPS cell line for every patient, then validating its safety (especially with regard to teratoma formation) and efficacy could well be prohibitive. Intermediate solutions like partial matching of cell types and limited use of immunosuppressive drugs would fit the model of the “reverse trajectory.” (The more complete solution would be a technological breakthrough in the induction of selective immune protection/tolerance for transplanted engineered tissues/organs).

<sup>67</sup> See, e.g., Carol Levine et al., *The Limitations of “Vulnerability” as a Protection for Human Research Participants*, 4(3) AM. J. BIOETHICS 44 (2004); see also Rebecca Dresser, *First-in-Human Trial Participants: Not a Vulnerable Population, But Vulnerable Nonetheless*, 37 J.L. MED. & ETHICS 38 (2009).

<sup>68</sup> See Jerry A. MENIKOFF WITH EDWARD P. RICHARDS, *WHAT THE DOCTOR DIDN'T SAY: THE HIDDEN TRUTH ABOUT MEDICAL RESEARCH* (2006); see also King 2005, *supra* note 54.

<sup>69</sup> See sources cited *supra* note 54; see also Kevin P. Weinfurt et al., *Expectation of Benefit in Early Phase Clinical Trials: Implications for Assessing the Adequacy of Informed Consent*, 28 MED. DECISION MAKING 575 (2008).

<sup>70</sup> See BARUCH BRODY, *THE ETHICS OF BIOMEDICAL RESEARCH: AN INTERNATIONAL PERSPECTIVE* (Oxford U. Press 1998); King & Cohen-Haguenauer, *supra* note 55.

## B. THE FIRST SUBJECTS

Regenerative medicine research, at least as practiced at Wake Forest Institute of Regenerative Medicine, has distinguished itself by the care and caution with which decisions have been made about when to begin human studies. Safety is paramount in first-in-human trials. Yet, when the first human subjects are patients with the disease or condition of interest, as is necessarily the case in regenerative medicine research, it is especially challenging to protect subjects from harm if the intervention is both uncertain and potentially irrevocable. This combination is by no means unique to regenerative medicine research, or even to research at all. Many medical treatment decisions similarly involve standard treatments of uncertain efficacy and high risk that require irrevocable decisions.<sup>71</sup> Certainly, however, the issues raised by these extremely difficult decisions arise even more starkly in the regenerative medicine research context, where what is uncertain and unknown may be more apparent than in standard treatment. Patient-subjects, whether seriously injured, terminally ill, moderately disabled, or chronically impaired, must weigh the likelihood that an experimental or standard intervention may be inefficacious or harmful, and compare experimental and standard apples and oranges, on a regular basis.<sup>72</sup>

Organ regeneration research resembles surgical research, in that it often must necessarily offer a prospect of direct benefit to patient-subjects in order to be justifiable.<sup>73</sup> Surgery's clinical research tradition is relatively weak, since surgical innovation has historically

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<sup>71</sup> The ongoing course of decision-making about treatment for advanced or difficult-to-treat cancers is one familiar example; similarly, decision-making about surgical repair and rehabilitation in traumatic injury is another. *See, e.g., A DEATH RETOLD: JESICA SANTILLAN, THE BUNGLED TRANSPLANT, AND THE PARADOXES OF MEDICAL CITIZENSHIP* (Keith Wailoo, Julie Livingston, & Peter Guarnaccia eds., 2006). Media sensations like face transplantation and the artificial heart are by no means the only examples. Most organ transplantation falls into this category of difficult decisions.

<sup>72</sup> In oncology, it is common to present patients with a range of choices, including both standard treatment and enrollment in research protocols, at a meeting called an "options interview." *See generally* Elisa J. Gordon & Christopher K. Daugherty, 'Hitting You Over the Head': *Oncologists' Disclosure of Prognosis to Advanced Cancer Patients*, 17 *BIOETHICS* 142 (2003).

<sup>73</sup> This is why research protocols that include sham surgery arms have been so controversial. *See, e.g.,* Sam Horng & Franklin G. Miller, *Ethical Framework for the Use of Sham Procedures in Clinical Trials*, 31 *CRITICAL CARE MED.* S126 (2003); *see also* Larry R. Churchill et al., *Assessing Benefits in Clinical Research: Why Diversity in Benefit Assessment Can Be Risky*, *IRB: ETHICS & HUMAN RES.*, May-June 2003, at 1 (2003) (on the perceived need to offer direct benefit to research subjects in early phase trials).

not been viewed as research.<sup>74</sup> This perspective is changing, however,<sup>75</sup> in part because of regenerative medicine research.

The goals of first-in-humans research in regenerative medicine are both to minimize risks of harm and to maximize potential efficacy.<sup>76</sup> In regenerative medicine research, therefore, it will be difficult to maintain the distinction between research and treatment, and to reduce the likelihood that either subjects or investigators fall prey to the therapeutic misconception.<sup>77</sup> The urgency of research progress may pose risks of conflict of interest in at least two ways: research may move forward too quickly when (1) research sponsors have financial stakes in the success of the field,<sup>78</sup> and (2) when investigators are true believers in what is yet unproven.<sup>79</sup> Finally, when catastrophic illness or injury defines the subject population, as in the spinal cord study, narrow temporal decision making windows may adversely affect understanding and consent. This has been an issue in emergency research,<sup>80</sup> and might also be the case for limb regeneration research focusing on civilian and military combat injuries.<sup>81</sup>

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<sup>74</sup> See generally Nancy M. P. King, *The Line Between Clinical Innovation and Human Experimentation*, 32 SETON HALL L. REV. 573 (2002).

<sup>75</sup> See *id.*

<sup>76</sup> The potential efficacy in early studies will nonetheless remain limited and uncertain. See generally Jonathan Kimmelman, *The Therapeutic Misconception at 25: Treatment, Research, and Confusion*, HASTINGS CENTER REP., Nov.-Dec. 2007, at 36; Mildred K. Cho & David Magnus, *Therapeutic Misconception and Stem Cell Research*, NATURE REPORTS STEM CELLS, Sept. 27, 2007, available at <http://www.nature.com/stemcells/2007/0709/070927/full/stemcells.2007.88.html>.

<sup>77</sup> See generally Cho & Magnus, *supra* note 76; Ricki Lewis, *Stem Cells and Genetic Testing: The Gap Between Science and Society Widens*, 8(4) AM. J. BIOETHICS, Apr. 2008, at 1; see also sources cited *supra* note 54.

<sup>78</sup> See, e.g., Robin Fretwell Wilson, *Estate of Gelsinger v. Trustees of University of Pennsylvania: Money, Prestige, and Conflicts of Interest in Human Subjects Research*, in HEALTH LAW AND BIOETHICS: CASES IN CONTEXT 229 (2009).

<sup>79</sup> See, e.g., Gail E. Henderson et al., *Uncertain Benefit: Investigators' Views and Communications in Early Phase Gene Transfer Trials*, 10 MOLECULAR THERAPY 225 (2004); Miller, *supra* note 54; Annas, *supra* note 54.

<sup>80</sup> See CTR. FOR DRUG EVALUATION & RES., FOOD & DRUG ADMIN., GUIDANCE FOR INSTITUTIONAL REVIEW BOARDS, CLINICAL INVESTIGATORS, AND SPONSORS: EXCEPTION FROM INFORMED CONSENT REQUIREMENTS FOR EMERGENCY RESEARCH (2006), <http://www.fda.gov/RegulatoryInformation/Guidances/ucm127635.htm>; see also Ken Kipnis, Nancy M.P. King & Robert M. Nelson, *Trials and Errors: Barriers to Oversight of Emergency Research*, 28(2) IRB: ETHICS & HUMAN RES., Mar.-Apr. 2006, at 16 (highlighting the controversial nature of the exception).

<sup>81</sup> Press Release. U.S. Dept. of Defense, *New Armed Forces Institute for Regenerative Medicine to Lead Way in Caring for Wounded* (Apr. 17, 2008), available at <http://www.defenselink.mil/releases/release.aspx?releaseid=11842>.

### C. INFORMED CONSENT

Familiar questions of information and consent in early-phase research arise in regenerative medicine research as well. They include, as already mentioned, the challenges of discussing uncertainty, especially when potential subjects believe they have no other viable choices. For organ and tissue regeneration research, discussion of available alternatives, the irrevocability of some decisions, and adverse consequences may be especially difficult, especially when the science appears exciting and full of promise to investigators and potential subjects alike. This is a well-recognized problem in other early-phase research, including oncology research, gene transfer, and even face transplantation.<sup>82</sup>

Notably, the caution and care with which organ and tissue regeneration research has been conducted to date has shown that the therapeutic misconception is not inevitable. Decision-making about research participation, however, is difficult nonetheless. Limb regeneration research is a novel instance of the decision-making challenges that arise routinely in trauma care. Trauma patients often face difficult and irrevocable choices: between amputation and attempting limb preservation, between different approaches to amputation that match with differences in the number and type of reconstructive surgeries needed, different limb prostheses with different mechanisms and functional capacities, different rehabilitation regimens with different potential, and so forth. The consequences of initial decisions are often unpredictable, unforeseeable, and unchangeable. The addition of novel and uncertain treatment options complicates decision-making and consent even further, especially when innovation and improvisation rapidly change the context of every choice. Including limb regeneration research compounds the difficulties of this dynamic decision matrix, especially if early and rapid decision-making about research participation is necessary. Choosing between enrollment in an experimental limb regeneration protocol and embarking on a more established, but constantly changing, course of attempted limb preservation and repair, or amputation and prosthetics, is not easy. Careful consideration of

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<sup>82</sup> See W. Y. Cheung et al., *The Quality of Informed Consent Forms for Oncology Clinical Trials*, 26 J. CLINICAL ONCOLOGY (SUPPLEMENT) 6544 (2008); J. Kimmelman & N. Palmour, *Therapeutic Optimism in Consent Forms for Phase I Gene Transfer Trials: An Empirical Analysis*, 31 J. MED. ETHICS 209 (2005); Osborne P. Wiggins et al., *On the Ethics of Facial Transplant Research*, 4 AM. J. BIOETHICS 1 (2004); Laurie Barclay, *First Face Transplant Raises Ethical Issues*, Medscape Med. News, Dec. 16, 2005, <http://www.medscape.com/viewarticle/520031>; see also sources cited *supra* note 54.

informed decision-making as an ongoing collaborative process, based in an ethically robust researcher-subject relationship, is essential.<sup>83</sup>

This leads to a final point about informed consent in research: the often-neglected discussion of what it really means to be a subject, especially in early-phase research involving novel biotechnologies. Many research subjects who are also patients are allowed or even encouraged to see themselves as patients only—that is, to focus only on the potential for direct benefit from research participation. As a result, the requirements and burdens of long-term follow-up may not be emphasized or even discussed in the consent process.<sup>84</sup> Some study teams assume that this focus is necessary to ensure adequate enrollment.<sup>85</sup> Many novel biotechnological interventions, however, must be followed for the life of the patient-subject in order to gather much-needed information about their real benefits and harms over time. Life-long follow-up may be especially necessary for regenerative medicine interventions, which are intended, like many gene transfer interventions, to persist in the body over the long term. If the patient-subject's role as subject is not described in detail—and not supported by the investigative team—then many subjects will be lost to follow-up, having viewed themselves as receiving treatment that is now completed. The development of a genuine investigator-subject partnership, in which the patient-subject's contribution to knowledge is ongoing, is essential not only to the subject's informed participation but also to successful research. While every research subject remains free to leave the research at any time, consistent with safety concerns,<sup>86</sup> such partnerships make it possible for subjects to make knowledgeable choices about leaving or staying.

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<sup>83</sup> See Nancy M. P. King et al., *Introduction: Relationships in Research: A New Paradigm in BEYOND REGULATIONS: ETHICS IN HUMAN SUBJECTS RESEARCH* 8 (Nancy M. P. King, Gail E. Henderson & Jane Stein eds., 1999) (“Respect for persons . . . includes both respect for the choices of autonomous persons and protection of the rights, needs, and interests of persons who lack the capacity to decide for themselves or have constraints upon their freedom of choice. This principle requires that the autonomy of subjects and potential subjects be supported in the informed consent process . . .”); Faden et al., *supra* note 11.

<sup>84</sup> See OFFICE OF BIOTECHNOLOGY ACTIVITIES, *supra* note 61, at 6.

<sup>85</sup> Variations on the statement “If we tell the truth, they won’t enroll!” are commonly heard in discussion sessions after bioethics scholars give informed consent talks to clinical researchers and study staff members.

<sup>86</sup> General requirements for informed consent include: “A statement that participation is voluntary . . . and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.” 45 C.F.R. § 46.116(a)(8) (2008); see also OFFICE OF BIOTECHNOLOGY ACTIVITIES, *supra* note 61, at 16.

### III. TREATMENT VERSUS ENHANCEMENT?

The last area for discussion is perhaps the most distinctive for regenerative medicine research: how regenerative medicine could change our understanding of the difference between treatment and enhancement. “Treatment” in medicine is generally understood as a restoration to the norm.<sup>87</sup> “Enhancement” is generally understood as deliberately intervening to exceed individual or population norms.<sup>88</sup> Enhancement has been widely discussed in contexts like lifespan extension and the alteration of individual characteristics like height, strength and endurance, or even behavior.<sup>89</sup> Of course, what is considered normal changes continually over time, making the distinction an inherently moving target. Some areas of research have uncovered a different but equally inevitable blurring of the distinction; for example, we seek to prevent, and even treat, disease by strengthening the immune system beyond that which is considered normal—that is, by means of enhancement.<sup>90</sup>

The ideal of regenerative medicine, with its prospects for regeneration of perfectly tissue-matched organs, is in one respect a reflection of changing treatment norms—simply the next step in progress, for example, from dialysis to kidney transplantation to kidney regeneration. Yet the blurring of treatment and enhancement, while inevitable and in some respects uncontroversial, poses ethical challenges.<sup>91</sup> For instance, although success in regeneration of “matching” body parts can readily be assessed by comparison with the normal functioning of an original, it may be harder to assess or predict partial functioning in terms of efficacy in an imperfectly or

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<sup>87</sup> See Norman Daniels, *Normal Functioning and the Treatment-Enhancement Distinction*, 9 CAMBRIDGE Q. HEALTHCARE ETHICS 309 (2000).

<sup>88</sup> *Id.*

<sup>89</sup> See, e.g., Eric T. Juengst et al., *Biogerontology*, “Anti-Aging Medicine,” and the *Challenges of Human Enhancement*, 33(4) HASTINGS CENTER REP., July-Aug. 2003, at 21; Peter J. Whitehouse et al., *Enhancing Cognition in the Intellectually Intact*, 27(3) HASTINGS CENTER REP., May-June 1997, at 14; see also Nancy M.P. King & Richard Robeson, *Athlete or Guinea Pig? Sports and Enhancement Research*, 1 STUD. ETHICS L. & TECH. 1 (2007), available at <http://www.bepress.com/selt/vol1/iss1/art1/> (the inaugural issue of this journal is dedicated exclusively to human enhancement through genetic engineering and features articles from a range of viewpoints).

<sup>90</sup> Eric T. Juengst, *Can Enhancement Be Distinguished from Prevention in Genetic Medicine?*, 22 J. MED. PHIL. 125 (1997).

<sup>91</sup> See, e.g., Maxwell J. Mehlman & Jessica W. Berg, *Human Subjects Protections in Biomedical Enhancement Research: Assessing Risk and Benefit and Obtaining Informed Consent*, 36 J. L. MED. ETHICS 546 (2008); Sarah Chan & John Harris, *Cognitive Regeneration or Enhancement: The Ethical Issues*, 1 REGENERATIVE MED. 361 (2006).

incompletely regenerated organ or limb than in conventional replacement or repair.<sup>92</sup> Thus, at least in early-phase research, it may be hard to provide information for potential subjects that can help them to compare partial success in research and in conventional treatment. An exogenously grown kidney can perhaps be tested, to a limited extent, before implantation. Will incomplete endogenous stimulation of healthy cell growth result in partial kidney function? An attempted surgical repair of an injured hand may gain the patient sufficient partial function, or require later amputation. Will a partially successful regeneration be functional at all?<sup>93</sup>

Once again, questions like these are common to novel technologies in their early stages. For example, every phase I dose escalation study involving a biologic agent must confront profound uncertainties about the dose-response relationship. The dose-response curve is fairly well understood for many pharmacologic agents, where higher doses are more likely to do both good and harm.<sup>94</sup> However, cancer chemotherapy research has shown us that more toxicity is not always paired with greater efficacy.<sup>95</sup> Potential harms and benefits at different doses are even more different for biologics, where there may be no expectation that higher doses will be more effective, or lower doses safer. Every new agent may have a new dose-response curve, such as the “elbows” or “thresholds” seen in some gene transfer research, whereby all doses are equally without effect below a certain level, and toxicities move from minimal to profound with small

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<sup>92</sup> In regenerative medicine, there is the unusual expectation that maximum benefit may not be derived for months to years after a procedure is done.

<sup>93</sup> *Id.* Given the expectation that there will be considerable ongoing maturation of the implanted organ, getting good predictors of outcome will be a slow process. Thus, the pace of rehabilitation hoped for by patient-subjects, and the time points at which success will be measured by investigators, may not coincide.

<sup>94</sup> See, e.g., Edward V. Flynn, *Pharmacodynamic and Pharmacokinetic Principles of Pharmacology and Gene Therapy*, 27 J. NEUROLOGIC PHYSICAL THERAPY 93, 94-95 (2003); King & Cohen-Haguenauer, *supra* note 55, at 436.

<sup>95</sup> To cite one well-known example, despite a media furor and much litigation against health insurance companies for denying coverage for this experimental procedure, high-dose chemotherapy combined with autologous stem cell transplant has not been shown to be more beneficial for treatment of high risk breast cancer patients than standard chemotherapy regimens, though the former is far more toxic. See Cynthia M. Farquhar et al., *High Dose Chemotherapy for Poor Prognosis Breast Cancer: Systematic Review & Meta-Analysis*, 33 CANCER TREATMENT REVIEWS 325, 325-326, 335-36 (2007); DT Vogl & EA Stadtmayer, *High-Dose Chemotherapy and Autologous Hematopoietic Stem Cell Transplantation for Metastatic Breast Cancer: A Therapy Whose Time Has Passed*, 37 BONE MARROW TRANSPLANTATION 985, 985-87 (2006); see also Nancy M.P. King & Gail W. Henderson, *Treatments of Last Resort: Informed Consent and the Diffusion of New Technology*, 42 MERCER L. REV. 1007, 1014 n. 39; 1021 n. 77 (1991).

changes in dosage.<sup>96</sup> Nonetheless, the way this issue arises in regenerative medicine research is somewhat distinctive, again highlighting a familiar issue in a novel way.

Finally, a more speculative but still significant ethical issue arises from considering not only individual research subjects but also the future of regenerative medicine technologies themselves. Returning to the larger ethical issues raised when new biotechnologies are introduced, we would do well to consider now some of the longer-term implications of success in regenerative medicine. As this area of research moves forward, it will inevitably create shifts in human norms, again and again. If cells, organs, and tissues become easier to replace, then humans may begin to take on the character of George Washington's hatchet:<sup>97</sup> all new parts many times over. The relationship between treatment of disease, injury, and disability and enhancement in the form of life extension is thus raised by the "piecemeal" application of regenerative medicine. But the same relationship is also implicated by the obvious next step: from George Washington's hatchet to the human salamander.<sup>98</sup> Mastery of the mechanisms of regeneration at the level not of the organ but of the organism presents the same questions about life extension and the alteration of human norms.<sup>99</sup> When medical science can readily

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<sup>96</sup> After the death of Jesse Gelsinger, the investigator, James Wilson, told the Recombinant DNA Advisory Committee that he had not anticipated the shape of the dose-response curve that appeared in the study, which he described as an "elbow." "Asked what he would have done differently, Wilson replied, 'Including not having done this at all, the trial could have been designed differently [with respect to] the half-log increments. The increments should be smaller.' He noted that the dose-toxicity relationship appeared to be 'elbow shaped' and that at the half-log increment the difference in dosage between the later cohorts is significantly greater than that between the earlier ones and 'may be breaching that elbow.' A RAC member agreed that there appeared to be a narrow window between early and severe toxicity, requiring meticulous measures." Fran Pollner, *Gene Therapy Trial and Errors Raise Scientific, Ethical, and Oversight Questions*, NIH CATALYST, Jan-Feb 2000, at 7, available at <http://www.nih.gov/catalyst/2000/00.01.01/page1.html>. See also Wilson, *supra* note 78.

<sup>97</sup> See James Baldwin, *George Washington and His Hatchet*, in FIFTY FAMOUS STORIES RETOLD (2005) (summarizing the story on which the analogy is based).

<sup>98</sup> See, e.g., Wyatt Andrews, *Medicine's Cutting Edge: Re-Growing Organs*, CBSNews.com, Mar. 23, 2008, <http://www.cbsnews.com/stories/2008/03/22/sunday/main3960219.shtml#>; *Salamanders Regrow Lost Limbs, Could Human Medicine Benefit from Understanding Regeneration*, SCIENCE DAILY, Apr. 1, 2007, <http://www.sciencedaily.com/releases/2007/03/070330111307.htm>; Larry Shaughnessy, *Salamander Therapy May Aid Injured Vets*, CNN.com, May 27, 2008, <http://www.cnn.com/2008/HEALTH/05/26/regrowing.body.parts/index.html>.

<sup>99</sup> See H. TRISTRAM ENGELHARDT, REGENERATIVE MEDICINE AFTER HUMANISM: PUZZLES REGARDING THE USE OF EMBRYONIC STEM CELLS, GERM-LINE GENETIC

stimulate regrowth of cells, tissues, and organs in humans, then we may have permanently altered not just human norms but humanity itself. In this respect, regenerative medicine research is one of the premier components of so-called “anti-aging medicine”<sup>100</sup>—a topic of considerable interest, profound controversy, and lively debate, now and for a long time to come.

#### IV. CONCLUSION

Regenerative medicine is a broad, complex, nuanced, and potentially groundbreaking area of research. It is not necessary, or necessarily helpful, to invent novel ethical issues or to exaggerate the novelty of ethical issues as applied to the new biotechnologies that regenerative medicine investigates. It is instead essential to acknowledge the persistence of fundamental issues of long standing: the nature of the medical research enterprise, the relationships between researchers and patients who are research subjects, and how medical research and medical practice complement and reshape each other in contemporary society. It is also worth noting that new technologies and new research designs are often presented as obviating some of these persistent ethical issues, but generally fail to achieve that goal.

An ethics and policy framework for further consideration of ethical issues in regenerative medicine research should include the following “points to consider:”

- Regenerative medicine research raises ethical issues in common with other first-in-human studies.
- Regenerative medicine research raises ethical issues in common with other clinical trials enrolling patients as research subjects.
- Regenerative medicine research raises ethical issues related to trial design, which should be considered as important as the ethical issues related to protecting the rights and welfare of human subjects.
- Regenerative medicine research raises ethical issues related to financial and nonfinancial conflicts of interest.
- Regenerative medicine research, like other new and costly medical technologies, raises ethical issues related to cost and access, including the role of public-private partnerships, venture capital, and intellectual property considerations.

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<sup>100</sup> Nicholas Wade, *The Stem Cell Debate: Apostle of Regenerative Medicine Foresees Longer Health and Life*, N.Y. TIMES, Dec. 18, 2001, at F5 (interview with William Haseltine); see also Juengst et al., *supra* note 89.

Regenerative medicine research thus provides scholars and policymakers in bioethics and law with a fresh opportunity to consider, discuss, and move forward on all these issues by examining them through the lens of this groundbreaking medical science.