THE HASTINGS CENTER

EXECUTIVE SUMMARY OF THE *HASTINGS CENTER REPORT*'S SPECIAL REPORT *CREATING ANIMALS CONTAINING HUMAN CELLS: SEEKING CLARITY ON ETHICS AND OVERSIGHT*

For decades, researchers have inserted different types of human cells into nonhuman animals at various stages of development to advance understanding of human biological processes. Today, advances in human stem cell science and gene editing are enabling scientists to more extensively and precisely insert human cells into nonhuman animals at any stage of development, from in vitro experiments with chimeric embryos to in vivo studies that create chimeric animals. We use the word "chimeric" to describe animals, embryos, and other organisms that contain a mix of human and nonhuman animal cells, and to describe the research involving the insertion of human cells into nonhuman animals at any stage of development.

Many people hope that chimeric research will yield enormous benefits, including more accurate models of human disease, inexpensive sources of human eggs and embryos for research, and sources of tissues and organs suitable for transplantation into humans. But there are several ethical concerns about this type of research, which raises questions such as whether the moral status of nonhuman animals is altered by the insertion of human stem cells, whether it is morally appropriate to cross species boundaries in this way, and whether these studies should be subject to additional prohibitions or oversight beyond that generally imposed on research involving somatic cells donated by human subjects and research with nonhuman animals.

Consequently, stem cell-based chimeric research has been surrounded by cross-disciplinary debate about whether such scientific work should take place and how best to respond to the ethical and policy issues it raises.

Existing guidance regarding the ethics of chimeric research is not sufficiently conceptually clear or operationalizable, and optimal ways of organizing the oversight of chimeric research are not yet known.

Researchers at The Hastings Center and Case Western Reserve University conducted an interdisciplinary research project to develop clear, reasoned, and practical recommendations and educational materials to assist researchers, research institutions and their oversight bodies,

funders and the public in identifying, understanding, and managing the ethical issues associated with chimeric research. This mixed-methods research project included:

1. Reviewing existing guidelines and policies (e.g., in stem cell science, bioethics, and animal studies) pertaining to research with human stem cells and nonhuman animals;
2. Conducting 35 audio-taped in-depth interviews with relevant scientists and regulators to better understand the strengths and challenges of current oversight approaches for chimeric research;
3. Analyzing a sample of the more than 20,000 public comments the U.S. National Institutes of Health received in response to the agency's proposed funding policy for certain types of human stem cell research with nonhuman animals; and
4. Creating an interdisciplinary Work Group composed of: scientists engaged in human stem cell research with nonhuman animal embryos and post-natal nonhuman animals; members of relevant oversight bodies; and academic researchers in philosophy, law, bioethics, and nonhuman animal studies.

Below is a selection of the research project's main findings and recommendations:

1. Animal welfare is a primary ethical issue and should be a focus of ethical and policy analysis as well as the governance and oversight of chimeric research.
2. Chimeric studies raise the possibility of unique or novel harms resulting from the insertion and development of human stem cells in nonhuman animals, particularly when those cells develop in the brain or central nervous system.
3. Oversight and governance of chimeric research is siloed, and public communication is extremely limited. Our project recommends enhanced communication between the different committees involved in oversight at each institution as well as mechanism for a national discussion amongst those involved in oversight of these studies. We also recommend additional support for improved public communication about this area of research.
4. Scientists, journalists, bioethicists, and others writing about chimeric research should use precise and accessible language that clarifies rather than obscures the ethical issues at stake. The terms "chimera," which in Greek mythology refers to a fire-breathing monster, and "humanization" are examples of obscure, frightening, ethically laden, or overly broad language to be avoided.

In the Publication

Karen J. Maschke, Margaret M. Matthews, Kaitlynn P. Craig, Carolyn P. Neuhaus, Insoo Hyun, and Josephine Johnston, ed., *Creating Animals Containing Human Cells: Seeking Clarity on Ethics and Oversight*, in the *Hastings Center Report,* November-December 2022 supplement.

Lead Article

- Josephine Johnston, Insoo Hyun, Carolyn P. Neuhaus, Karen J. Maschke, Patricia Marshall, Kaitlynn P. Craig, Margaret M. Matthews, Kara Drolet, Henry T. Greely, Lori R. Hill, Amy Hinterberger, Elisa A. Hurley, Robert Kesterson, Jonathan Kimmelman, Nancy M. P. King, Melissa J. Lopes, P. Pearl O'Rourke, Brendan Parent, Steven Peckman, Monika Piotrowska, May Schwarz, Jeff Sebo, Chris Stodgell, Robert

Streiffer, and Amy Wilkerson, “Creating Chimeric Animals: Seeking Clarity on Ethics and Oversight,” in the *Hastings Center Report,* November-December 2022 supplement.

Essays

- Amy Hinterberger, “Composite Animals: Then and Now,” in the *Hastings Center Report,* November-December 2022 supplement.
- Jeff Sebo and Brendan Parent, “Human, Nonhuman, and Chimera Research: Considering Old Issues with New Research,” in the *Hastings Center Report,* November-December 2022 supplement.
- Carolyn P. Neuhaus, “Threats to Benefits: Assessing Knowledge Production in Nonhuman Models of Human Neuropsychiatric Disorders,” in the *Hastings Center Report,* November-December 2022 supplement.
- Patricia Marshall, Kaitlynn P. Craig, and Insoo Hyun, “Moral Status in the Oversight of Research Involving Chimeric Animals,” forthcoming in the *Hastings Center Report,* November-December 2022 supplement.
- Kaitlynn P. Craig, Lori R. Hill, Robert Kesterson, Angelika Rehrig, and Christopher Stodgell, “How Chimeric Animal Research Impacts Animal Welfare: A Conversation with Animal Welfare Experts,” in the *Hastings Center Report,* November-December 2022 supplement.
- Kaitlynn P. Craig, Ali Brivanlou, May Schwarz, and Lorenz Studer, “A Conversation with Chimeric Animal Researchers,” in the *Hastings Center Report,* November-December 2022 supplement.

The Research Team

The Hastings Center

- Josephine Johnston
- Karen J. Maschke
- Carolyn P. Neuhaus
- Margaret M. Matthews
- Isabel Bolo

Case Western Reserve University

- Insoo Hyun (now at *Museum of Science, Boston*)
- Patricia Marshall
- Kaitlynn P. Craig

The Work Group

- Kara Drolet, *Oregon Health & Science University*
- Henry T. Greely, *Stanford University*
- Lori R. Hill, *MD Anderson Cancer Center*
- Amy Hinterberger, *King’s College London*
- Elisa A. Hurley, *Public Responsibility in Medicine and Research*
- Robert Kesterson, *University of Alabama at Birmingham*
- Jonathan Kimmelman, *McGill University*
- Nancy M. P. King, *Wake Forest University School of Medicine*

• Geoffrey Lomax, *California Institute for Regenerative Medicine*
• Melissa J. Lopes, *Harvard University Embryonic Stem Cell Research Oversight Committee*
• P. Pearl O'Rourke, *Harvard Medical School*
• Brendan Parent, *NYU Grossman School of Medicine*
• Steven Peckman, *University of California, Los Angeles*
• Monika Piotrowska, *State University of New York at Albany*
• May Schwarz, *The Salk Institute for Biological Studies*
• Jeff Sebo, *New York University*
• Chris Stodgell, *University of Rochester*
• Robert Streiffer, *University of Wisconsin-Madison*
• Lorenz Studer, *Memorial Sloan Kettering Cancer Center*
• Amy Wilkerson, *The Rockefeller University*

Other Publications

Isabel Bolo, Ben C. Wills, and Karen J. Maschke. "Public Attitudes toward Human-Animal Chimera Research May Be More Complicated than They Appear." *Stem Cell Reports* 16, no. 2 (2021): 225-6.

Karen J. Maschke. "Animals with Human Cells in Their Brains: Implications for Research," *Hastings Center Report* 49, no. 5 (2019): 36-37.

Nienke de Graeff, Karin R. Jongsma, Josephine Johnston, Sarah Hartley, Annelien L. Bredenoord, "The Ethics of Genome Editing Technologies in Non-human Animals: A Systematic Review of Reasons Reported in the Academic Literature," *Philosophical Transactions of the Royal Society B* 2019; 374: 20180106. http://dx.doi.org/10.1098/rstb.2018.0106

Insoo Hyun. "Ethical Considerations for Human-Animal Neurological Chimera Research: Mouse Models and Beyond," *The EMBO Journal* 38, 2019; https://doi.org/10.15252/embj.2019103331.

Presentations and Educational Materials
Karen J. Maschke and Josephine Johnston developed a module titled "Human-Animal Chimera Research" for *Technology Ethics*, a new online course offered to U.S. research institutions by The Collaborative Institutional Training Initiative (CITI Program).

Isabel Bolo, Ben Curran Wills, Karen J. Maschke, and Josephine Johnston presented a poster session titled "Which Public, What Comments? An Analysis of Public Comments on Human-animal Chimera Research Submitted to the U.S. National Institutes of Health" for the World Congress of Bioethics in June 2020.

Josephine Johnston participated in a plenary panel on interspecies chimeras at the International Society for Stem Cell Research (ISSCR) Annual Meeting in June 2020. Her remarks focused on ethical and policy issues, drawing on the project's literature review and policy analysis.

Josephine Johnston, Isabel Bolo, and Carolyn Neuhaus presented a panel, “Chimera Research with Humans and Non-Human Primates: Implications for Human and Primate Flourishing” at the American Society for Bioethics and the Humanities (ASBH) in October 2020. They discussed gaps in oversight and governance mechanisms, public concerns about the research, and other ethics issues related to “humanization” and flourishing.

Kaitlynn Craig presented at the American Society for Bioethics and Humanities (ASBH) in October 2020 on interview data collected from scientists, researchers, and oversight committee members surrounding human-animal chimera research. Her presentation focused on how oversight for chimera research is utilized by different stakeholders, how chimera research could bring up unique ethical issues, and where we go from here.

Insoo Hyun presented on the ethics of chimera research in a Members' Briefing Session for the International Society for Stem Cell Research (ISSCR) on November 11, 2020.

Insoo Hyun presented on the ethics and institutional oversight of chimera research at the request of the National Academies of Science, Engineering, and Medicine (NASEM) on November 13, 2020. Dr. Hyun spoke to the committee that drafted the NASEM report on the ethics of brain organoid and chimera research.

Kaitlynn Craig, Isabel Bolo, and Ben Wills gave two presentations and discussed their research as part of the National Human Genome Research Institute’s Ethical Legal and Social Implications Program (ELSI), “ ELSI Conversations” in March 2021. Ms. Craig reviewed interview data and subsequent analyses conducted as part of the empirical portion of the grant and Ms. Bolo and Mr. Wills discussed preliminary findings from their public comment analysis. The presentations are available online at www.elsihub.org.

Insoo Hyun and Josephine Johnston presented a 75-minute webinar called “Chimeras, But Don't Call Them Chimeras: An Introduction to the Ethics and Policy Debate” in September 2022 for Public Responsibility in Medicine and Research (PRIM&R).

Josephine Johnston, Insoo Hyun, Carolyn P. Neuhaus, Kaitlynn P. Craig, Ben Curran Wills will deliver a 3-hour online conference workshop titled “Clarifying the Ethics and Oversight of Chimeric Research” in December 2022 for the Annual Conference of Public Responsibility in Medicine and Research (PRIM&R).

For more information on this report, contact: communications@thehastingscenter.org.