Chimeras

Definition: What are Chimeras? How and why are they produced?

Chimeras are animals composed of cells that originate from two (or more) different species. In the research lab, chimeras are created by introducing cells from one species into the developing embryo or fetus of another. (The name chimera comes from Greek mythology and describes a creature with the head of a lion, the body of a goat, and the tail of a serpent).

The first chimeras helped scientists understand questions about developmental biology. A sheep-goat chimera, created in 1984, had the head of a goat and the woolly coat of a sheep.[i] Chicken-quail chimeras have also been successfully developed.[ii,iii]

Sheep-Goat Chimera
Courtesy of Dr. Gary B. Anderson -University of California, Davis

Now, researchers are developing human-animal chimeras to study disease processes, test new drugs,

and develop organs for future transplant patients. The chimeras are produced by introducing human stem cells into developing animal embryos. The following are some of the major projects utilizing human-animal chimeras underway in the U.S and internationally:

Sheep-to-humans organ transplant project:
At the University of Nevada at Reno, researchers have added human stem cells to sheep fetuses to create chimeras that they hope will someday serve as a reliable source of organs for liver transplant patients. Some sheep now have livers with up to 80% human cells that produce the compounds normally made by human livers. (The cells are not all in distinct liver lobes but spread throughout the tissue. The sheep also have human cells in their hearts and brains).[iv,v]

Pigs-to-humans organ transplant project:
Mayo Clinic researchers in Minnesota are studying how specially-bred pigs could be used as sources of organs for human transplant patients. Part of their work involves determining the risk of transmitting pig diseases to humans who would receive the organs.[vi] They have developed a line of pigs that have pig blood cells, human blood cells, and a new kind of blood cells with characteristics of both humans and pigs.[vii] An unexpected development in this project may help researchers formulate an explanation for the appearance of the AIDS virus in humans.

Mice with human brain cells for the study of neurologic diseases and mice with human immune systems for AIDS drug testing:
At Stanford University, researcher Irving Weissman is heading a project that injects human neural stem cells into mouse fetuses. The result is mice with brains that are about 1% human. The researchers want to increase that percentage to 100% human brains in mice bodies in order to better understand the development of Parkinson's, Alzheimer's, and Lou Gehrig's diseases. Weissman is director of the Stanford Institute of Cancer/Stem Cell Biology and Medicine, which developed a line of mice with immune systems that were almost all human. They were able to use the mice to test the response of the AIDS virus to new drugs.[viii]

Rabbit-human hybrids for stem cell research:
In 2003, for the first time, researchers at the Shanghai Second Medical University developed embryos that contained both human and animal DNA. Working with rabbit embryos, the researchers' goal was to develop a new source of embryonic stems cells for medical research. The resulting embryos contained mostly human DNA (derived from skin cells) and a small amount of rabbit DNA. The researchers harvested the stem cells after a few days, which destroyed the embryos.[ix,x]

Hybrids and chimeras are biologically different. A cell from a chimera contains the genetic material of either one parent species or the other. While each cell from a hybrid animal, such as a mule, contains genetic material from both parent species.

Monkey-human chimeras for the study of Parkinson's disease:
At St. Kitts Biomedical Foundation in the Caribbean, scientists are transplanting immature human brain cells deep into the brains of vervet monkeys. Their goal is to develop a treatment for Parkinson's disease. They inject immature human brain cells into the dopamine-producing area of the monkeys' brains to see whether the cells can grow and increase dopamine production. (The monkeys are taken from the overabundant wild population on the island of St. Kitts.)[xi]

In April, 2005, the National Academies (which advises the federal government and the public on scientific and medical issues) released recommended guidelines for embryonic stem cell research, including research on chimeras. While the guidelines are not legally binding, they are likely to have a significant impact on research in the U.S. because funding agencies and professional societies (through which scientists publish their work) are likely to abide by the guidelines.[xii]

The complete *Guidelines for Human Embryonic Stem Cell Research* are available online at: http://books.nap.edu/catalog/11278.html?onpi_newsdoc04262005.

You can read an announcement and summary of the *Guidelines* online at http://www4.nationalacademies.org/news.nsf/isbn/0309096537?OpenDocument.

Regulations and recommendations on chimera research generally lag behind ongoing projects and vary across international boundaries. For example, while it is ongoing in other countries, Canada bans research on human-animal chimeras.[xiii,xiv,xv]

Top of Page

Ethical Issues

Because human-animal chimeras contain human cells—or even tissues or organs that are primarily human—ethical concerns surround the question of just what *or who* chimeras are. Because they were created under laboratory conditions for research purposes, are chimeras lab animals? Or, will chimeras eventually be developed that are too human to be considered otherwise?

Ethical issues of primary concern for bioethicists, researchers, animal rights activists and others interested in chimeras can be divided into two broad categories: a) complete opposition to research of

this kind and b) concerns about particular research methods to be used and outcomes that may ensue.

Opposition to Chimera Research

There are those who are convinced that human-animal chimera research should not be performed at all. The following are their reasons for opposing all such research:

1. **Because it involves research on human embryos.** Even if the embryos are not destroyed, the research combines human and animal genetic material with unknown and perhaps unknowable results.

   Richard Doerflinger, Deputy Director of the Secretariat for Pro-Life Activities at the U.S. Conference of Catholic Bishops, told the *The Boston Globe* regarding human-animal chimeras: "I think it would be basically immoral to create a human whose status we could not determine. We'd have an unresolvable dilemma about how to treat this animal."[xvi]

   William Cheshire, a Mayo Clinic associate professor of neurology in Jacksonville, Florida, and a member of Christian Medical and Dental Associations expressed his concerns in National Geographic: "Research projects that create human-animal chimeras risk disturbing fragile ecosystems, endanger health, and affront species integrity. We must be cautious not to violate the integrity of humanity or of animal life over which we have a stewardship responsibility."[xvii]
2. **Because it disregards the welfare of animals and animal species involved:** The Humane Society of the United States (online at http://www.hsus.org) communicates its opposition to all chimera research in the position statement, "Genetic Engineering of Animals":

   > "The creation of chimeras (organisms composed of cells from individuals of two or more species) involves serious ethical concerns that should be taken into consideration. Creation of chimeras contributes to the debasement of animals, as humankind manipulates nature by combining cells of an array of organisms. As far as current application of chimera research goes, The HSUS is concerned about pain and distress that the animals may undergo and calls on the research community to carefully address the welfare of these animals and to minimize any pain and distress resulting from this type of animal use."

3. **More specifically, because it disregards the welfare of higher primates involved.** Higher primates, especially chimpanzees, are closely related to humans and thus may be seen as ideal research subjects in chimera experiments:

   Jeremy Rifkin, noted biotechnology activist, opposes chimera research because it crosses species boundaries. In his view, animals have the right to exist without being tampered with, especially because he finds that other research methods could lead to the same medical advances.[xviii] (Rifkin is the author of *The Biotech Century*, a best-seller about the biotech revolution.). Together with Dr. Stuart A. Newman, a professor of cell biology and anatomy at New York Medical College, Rifkin applied for a patent on chimera research techniques, including ones that would combine human and monkey or ape cells into a single *humanzee* embryo. In another, human and mouse cells would form a *humouse* embryo. Their goal was to challenge biotechnology efforts that would produce these chimeras.

Rifkin and Newman were pleased when the U.S. Patent and Trademark Office (PTO) turned down their application. “By applying for a patent on the humanzee, humouse, and other part-human embryos and animals, we hoped to alert the general public to the need for regulations and restrictions in this area,” Newman said in an interview with *Science and Theology News*. While the PTO has been issuing patents on living organisms since a 1980 Supreme Court Decision, the human chimera application was rejected in 2005 primarily because the PTO has no way to determine how “human” an organism can be before it is *not* patentable by the 13th Amendment's prohibition of slavery, according to Newman.[xix]

It is still legal to produce these chimeras without a patent, but may not be financially feasible for a biotech company to develop products based on techniques that are not protected by a patent.

—The Humanzee—

“Chimps share 98% of the human genome, and a fully mature chimp has the equivalent mental abilities and consciousness of a four-year-old human. Fusing a human and chimpanzee embryo—which researchers say is feasible—could produce a creature so human that questions regarding its moral and legal status would throw 4,000 years of ethics into chaos. Would such a creature enjoy human rights? Would it have to pass some kind of ‘humanness' test to win its freedom? Would it be forced into doing menial labour or be used to perform dangerous activities?”

—Jeremy Rifkin “Are you a man or a mouse?” March 15, 2005 The Guardian. Available online at http://www.guardian.co.uk/comment/story/0,3604,1437701,00.html

Concerns About Chimera Research

While not completely opposed to the research, some experts and interested members of the public raise concerns about techniques and possible outcomes if initial problems are ignored. Their major concerns are the following:

1. **Could chimeras have human brains?**
   If a chimera's brain is comprised of mostly human neurons with an appropriate structure, experts are questioning whether a human brain—and mind—could develop within an animal or human-animal body. The National Academies *Guidelines for Human Embryonic Stem Cell Research* cautions that experiments in which there is a possibility that human cells could contribute in a "major organized way" to the brain of an animal require strong scientific justification.[xx]
   Projects such as the following give rise to questions regarding chimeras with human brains:

   - Researchers at Stanford University are injecting human neural stem cells into mouse fetuses to study development of neurologic diseases (see project description in Definition section, above). Initial results were mice with brains that were about 1% human, but researchers could increase that percentage to 100% human brains in the laboratory mice. They anticipate that the structures of the brain, and certainly the size, would still be mouse-like even though the neurons of the brain would be 100% human. Responding to

concerns that the experiment could result in brains that were more human than mouse, Stanford University's ethics committee has approved the research on the condition that if the mice developed indicators of human intelligence, such as improved memory or problem-solving, it would be time to stop the project.

- At St. Kitts Biomedical Foundation in the Caribbean, scientists are transplanting immature human brain cells into the brains of vervet monkeys, generating a human-monkey chimera.[xxi] This kind of research could create human-primate chimeras, with human brain cells.

An expert panel was convened by John Hopkins University in 2005 to study the potential for just such human-primate experiments to significantly change the cognitive and emotional capacities of primates—in effect, to humanize them.

The Working Group on Interspecific Chimeric Brains consisted of primatologists and other scientists, ethicists, and lawyers. They concluded that any shift in brain capacities toward the human end of the spectrum would be more likely to occur if human brain cells were introduced early in the development of the brains of great apes. Experiments in which small numbers of human cells were grafted into healthy adult brains of the most distantly related monkey species were the least likely to raise concerns.[xxii]

—The Working Group on Interspecific Chimeric Brains—

"Many of us expected that, once we'd pooled our expertise, we'd be able to say why human cells would not produce significant changes in non-human brains. But the cell biologists and neurologists couldn't specify limits on what implanted human cells might do, and the primatologists explained that gaps in our knowledge of normal non-human primate abilities make it difficult to detect changes. And there's no philosophical consensus on the moral significance of changes in abilities if we could detect them."

— Mark Greene, Ph.D., professor at the University of Delaware and Working Group member. In: Johns Hopkins Medicine - Office of Corporate Communications. Experts discuss use of human stem cells in ape and monkey brains. July 14, 2005. Available online at http://www.hopkinsmedicine.org/Press_releases/2005/07_14_05.html

2. **What is the potential for humanized chimeras?**
If human embryonic stem cells were to be injected into an animal embryo very early in its development, the human cells might spread through *every* organ system in the animal embryo. Conversely, animal embryonic stem cells could do the same thing when introduced into an early-stage human embryo. The results of such techniques could be a humanized animal (or animalized human), with physical features and behaviors that are distinctly human.

Considering this possible outcome, the National Academies' *Guidelines for Human Embryonic Stem Cell Research* say that no animal embryonic stem cells should be transplanted into a human blastocyst (early embryo). In addition, approval by an Embryonic Stem Cell Research Oversight committee should be secured before any human embryonic stem cells are put into an animal.

3. **Could chimeras mate and produce human offspring?** If a female chimera with human ova

(egg cells) mated with a male chimera with human sperm cells, scientists believe that it would be possible for a human fetus to be the result. Potentially, a chimera could give birth to a human. To address this issue, the National Academies *Guidelines for Human Embryonic Stem Cell Research* states: “No animal into which human embryonic stem cells have been introduced at any stage of development should be allowed to breed.”

4. **How will human-primate chimeras be treated?**
   While already being used a t St. Kitts Biomedical Foundation (mentioned above), primates are likely to be the animal of choice in some human-animal chimera projects because of their close genetic similarities (especially in chimpanzees) to humans. While the guidelines state that “no human embryonic stem cells should be put into nonhuman primate blastocysts [early embryos],” they do not exclude chimera research at a later stage of development. While some oppose this research outright, others are assuming that human-primate chimeras will become more widespread in research and question whether they will be treated as humans or animals.

   A.M. Chakrabarty, of the University of Illinois College of Medicine, asks:

   > "What is a human? This is not a question of the moral dilemma to define a human but is a legal requirement as to how much human material a chimpanzee must have before it is declared a part human and therefore falls under the protection of the Thirteenth Amendment….We must move beyond moral and philosophical discussions of hybrid human-nonhuman animals and be prepared to tackle the difficult legal questions that will attend not-so-distant attempts at creating such hybrids say for organ harvesting, for use as a subhuman species to perform hard manual labors, or simply for curiosity’s sake.”[xxiii]

Top of Page

Links

The National Academies issued a press release summarizing the recommendations for stem cell research —including chimera research—made in their publication, Guidelines for Human Embryonic Stem Cell Research . The April 2005 press release is online at http://www4.nationalacademies.org/news.nsf/isbn/0309096537?OpenDocument.

The complete Guidelines are available online at: http://books.nap.edu/catalog/11278.html?onpi_newsdoc04262005

Findings of the Working Group on Interspecific Chimeric Brains are announced by Johns Hopkins Medicine in this press release, “Experts discuss use of human stem cells in ape and monkey brains,” dated July 14,

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Top of Page

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Top of Page

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Top of Page