Introduction

The promise and significance of greatly enhancing health and possibly even curing some of the most deadly diseases affecting humankind frequently has mitigated diverse bioethical issues associated with stem cell research. The use of embryonic stem cells to generate human-animal chimeras, however, has created unusual and particular ethical dilemmas, in part because the clinical applications derived from this research are less understood.

Chimeras in myth and culture: The chimera, one of several imaginary and symbolically important monsters of ancient Greek mythology, was depicted as a mythical creature resembling a lion, with the body of a goat emerging from it, with a serpent for a tail.

What exactly is a chimera?

In the current world of scientific research, chimeras are defined as organisms composed of cells or genes obtained from two or more different species. Human-animal chimeras can be generated by either transplanting human stem cells into animal fetuses or human genes into the genome of animal fetuses. Thus a human – mouse chimera may contain a human liver in a mouse or may have a liver composed of both human and mouse cells.

Our experience with chimeras is relatively recent as the first modern interspecies chimeras were engineered in the 1980’s. In the last ten years, however, new and challenging contentious issues have emerged regarding human-animal chimeras, creating considerable debate on the appropriateness of generating such chimeras.
Human-animal chimeras will be discussed below in the context of stem cell research conducted with these inter-species creatures.

Aristotle (384 BC – 322 BC)

Aristotle was a Greek philosopher, a student of Plato and teacher of Alexander the Great. He was the earliest major Western thinker to attempt a systematic and universal classification of all living organisms. He proposed, for example, that visible appearances, characteristics, and structures be used to group animals into distinct species. While many of his concepts have long been supplanted, some of his observations about animals were verified as late as the 19th century (Fendrich 2010).

What is a species?

Carl Linnaeus (1707-1778)

Carl Linnaeus’ Systema Naturae is the basis for modern zoology (Ambrose 2010).

The definition of species has a long history. Aristotle was one of the first thinkers to classify organisms based on defined criteria. He refers to similar biological organisms as members of a "natural kind," sharing physical characteristics or properties common to all of them. Carl Linnaeus is viewed as the father of taxonomy whose system for naming, ranking, and classifying organisms is still in use today.
Ernst Walter Mayr (1904 – 2005)

Ernst Walter Mayr was one of the greatest evolutionary biologists of the 20th century. He was also an explorer, naturalist, ornithologist, philosopher-historian of science, and Harvard professor (Rao and Nanjundiah 2011).

In the twentieth century, Ernst Mayr, a noted evolutionary biologist, defined a species according to its members' ability to procreate and their ability to produce fertile offspring. While donkeys and horses can procreate, their progeny are almost exclusively infertile, thus providing proof of principle that donkeys and horses are different species. One of the troublesome problems raised by his definition of species, however, is that asexually reproducing organisms, such as bacteria, or the five percent of interbreeding birds that are taken to be of different species, do not fit into such a classification system. While there are a variety of different genetic, ecological, and behavioral classification schemes to define a species, none has yet provided a definitive definition of a species.

Historically, anthropologists have repeatedly tried to identify what makes us uniquely human, and have pointed to characteristics such as large brain size, opposable thumbs, bipedality, culture, complex language (written and spoken), humor, utilizing makeup, utilizing fire, cooking, and dressing with clothes. Yet, many of these characteristic can also be found in other creatures. Chimpanzees have rudimentary culture, parrots speak, and some rats giggle when tickled.

Incidentally, there is a mouse analogue of FOXP2. Homozygous mice lacking this gene failed to emit ultrasonic sounds when separated from their mothers, had severe motor defects, and died young (White, Fisher et al. 2006). How this mouse analog relates to the human form will be of great interest.

Engineering human-animal chimeras using genomic technology
Research efforts are in progress trying to identify unique genetic sequences in the human genome that may confer human characteristics. Transplanting human genes into animal fetuses provides a viable approach to study how human genes function. There have been many recent articles on identifying and characterizing the FOXP2 gene in human language development (Lai, Fisher et al. 2001; Konopka, Bomar et al. 2009). Mapping how this gene functions in language has emerged from genetic studies of a family with language dysfunction (Fisher and Scharff 2009). This gene that encodes a transcription factor is the first gene, as yet, implicated in Mendelian forms of human speech and language dysfunction. From an evolutionary perspective, the human form of this transcription factor differs in only two amino acids from the FOXP2 transcription factor found in non-human primates and this amino-acid change appeared to occur around the time of language emergence in human evolution.

Further studies in both humans and animals reveal that this gene is present in both vocal and non-vocal animals and is important for muscle coordination in vocalization and in many other motor functions (Fisher and Scharff 2009). Mutations in the human form of FOXP2 gene, for example, cause region-specific cellular changes in the developing human cortex and striatum resulting in functional disturbances in language comprehension, grammar, and syntax. Studies, using human-mouse “genetic chimeras” (transplanting genes from one species into another) where the human form of FOXP2 was transplanted and expressed in mice, reveal changes in vocal output and cellular changes in the neural circuitry in their brains. Interestingly, FOXP2 gene is one of several candidate genes associated with autism and schizophrenia (Wang et al., 2015).

What is the difference between a chimera and a hybrid?

It is important to distinguish between a chimera and a hybrid. A hybrid is created when an ovum from one species is fertilized by the sperm of another species. All the cells in a hybrid organism contain the same genetic information that is derived from the two different species. Examples of hybrids include the mule (a cross between a male donkey, Equus asinus and female horse, Equus caballus), and the more exotic male liger (a cross between a male lion, Panthera leo, and female tiger, Panthera tigris).

Further Exploration: Human-embryonic hybrids have also been used in which a human nucleus is transplanted into an enucleated animal oocyte. As of 2009, there has been no successful attempt to maintain human embryonic hybrids for more than a few days but it is unclear whether in the future some of these human-embryonic hybrids could be formed (Skene, Testa et al. 2009) Thought Question: What new scientific knowledge can be gained through this technology?
Figure 3. A male liger (cross between male lion and female tiger)

These hybrids usually are sterile and sometimes exhibit characteristics not seen in the parent species (McCain, Ramsay et al. 2009). For example, for specific genetic reasons, atypical growth is possible in male ligers, which are the largest and heaviest living cats on earth (the current record-holder is the liger Hercules, who weighs more than 900 pounds).

In contrast, human - animal chimeras, generated by introducing human stem cells into an animal embryo, are composed of two genetically distinct types of cells. One cell type contains a complete human genome while the second cell type contains a complete genome of the animal species. While there are a wide variety of chimeras, we will focus on chimeras that are generated by transferring human cellular or genetic material into an animal fetus.

**Recent history of chimeras in medicine**

For decades, scientists have successfully inserted small amounts of human tissue or cells into animals. In the late 1980's, Dr. Irving Weissman of Stanford University transplanted human bone marrow cells into a mouse strain that lacked its own immune system (McCune, Kaneshima et al. 1991). The stem cells from the human bone marrow were not rejected by the host mice and developed into a nearly complete human immune system.

Other researchers have transferred human material, such as embryonic stomachs, intestine, tracheas, and lungs, into the bodies of mice (Angioi, Hatier et al. 2002). Researchers also have inserted human blood and skin stem cells into mice (Kamel-Reid and Dick 1988; Kauffman, Bean et al. 1993; Goldstein, Drukker et al. 2002; Meuleman, Libbrecht et al. 2005) as well as into fetal sheep (Chamberlain, Yamagami et al. 2007; Almeida-Porada, Zanjani et al. 2010).

In addition, there are several reports of transplanting human embryonic stem cells or neural cells into animal embryos or fetuses. For example, Ourednik et al. (Ourednik, Ourednik et al. 2001) transplanted human neural cells into the developing fetal brain of Old World monkeys to generate monkeys containing human brain cells. Other groups have transplanted human embryonic stem cells into chicken embryos and human neural stem cells into fetal sheep (Goldstein, Drukker et al. 2002; Almeida-Porada, Crapnell et al. 2005).
Case study

After Boston native Karen Keegan was in desperate need of a kidney in 1998, doctors tested her three sons for a match. However, astoundingly, they discovered that Keegan's sons did not match her genetic makeup to the extent that offspring should. After further examination, testing revealed Keegan was a chimera, carrying a distinct combination of two different cells, each with a separate genetic makeup. Scientists theorized that the second set of DNA presumably came from a different embryo from the one that gave rise to the rest of her tissues. This may have occurred after fertilization of two separate ova by two sperm, later followed by the fusing of the ova at the blastocyst stage.

Thought question

How does this case challenge the traditional notion of motherhood? Are Keegan's sons still technically defined as her offspring? Source: Neng Yu, M.D. et. al. (2002). Disputed maternity leading to identification of Tetragametic Chimerism, N Engl J Med May 16; 6:1545-1552

Human-mouse chimeras have proven to be extremely valuable in studying a variety of human diseases such as Acquired Immune Deficiency Syndrome (AIDS). Human Immunodeficiency Virus (HIV), the virus that causes AIDS, does not normally infect mouse cells but will infect human cells in the immune system of these human-mouse chimeras. From these animal models a great deal of information has been gleaned concerning how the AIDS virus infects and replicates in human immune cells (studied in an animal model). In addition, these human-mouse chimeras have served as an important model to study potential new therapies for fighting AIDS.

Human-mouse chimeras are also being used to study hepatitis viral infections (Turrini, Sasso et al. 2006). Scientists repopulated a mouse liver with human liver cells and are using this animal model to gain a better understanding of liver development and to examine drug metabolism within human livers (Meuleman, Libbrecht et al. 2005).

Potential medical benefits of research with chimeras

Esmail Zanjani at the University of Nevada is attempting to reconstitute human organs in sheep by transplanting human stem cells into specific organ areas of a sheep embryo (Almeida-Porada, Porada et al. 2007; Chamberlain, Yamagami et al. 2007). His research is based on the observations that:

1. foreign stem cells are not necessarily immunologically rejected during sheep embryological development and
2. these transplanted human stem cells can emerge as the dominant cell type of the sheep’s organ
(Almeida-Porada, Porada et al. 2007; Chamberlain, Yamagami et al. 2007; Almeida-Porada, Zanjani et al. 2010; Ersek, Pixley et al. 2010; Goodrich, Ersek et al. 2010).

Figure 4. A human - nude mouse chimera engineered to grow a human outer ear (pinna) for potential transplantation

As of 2010, Zanjani and colleagues have engineered human-sheep chimeras whose livers are composed primarily of human cells that are genetically compatible with the human donor of those stem cells. A human liver developed in such human-sheep chimeras could then be transplanted into an individual needing a liver transplant. Potentially, this transplant technology could increase the number of available transplantable organs, and reduce the need for anti-rejection drugs normally administered to most organ transplant recipients. However, one must view these reports with scientific caution because Zanjani and his colleagues did not absolutely prove that these reconstituted livers contained human hepatocytes or that these human-sheep liver chimeras produced human liver proteins.

Human-sheep chimeras are also being created as a source for human hematopoietic cells (Chamberlain, Yamagami et al. 2007) or human beta cells of the pancreas (Goodrich, Ersek et al. 2010). In all of these results it is important to establish that these human cells in the animals are functioning as the differentiated cells. Thus, a human-animal chimera with a "human" liver should produce the human forms of liver proteins such as albumin.

Despite these impressive advances, there still remain many medical obstacles that must be overcome. Creating human-animal chimeras runs the risk of transmitting animal oncogenes in the human cells. This poses serious risks that must be eliminated before this research can enter clinical trials.

**Thought Question**

Human-animal chimera research has been scientifically informative. But will such research lead to new therapies? Comment on the following video:

Several broad biomedical applications (including a better understanding of how organ development) may emerge from research using human-animal chimeras:

- To understand basic biological principles regarding cellular differentiation, e.g., how precursor stem cells differentiate into the various cells that comprise brain and the nervous system. Creating
novel human-animal chimeras could provide models to study human physiological systems in what would only have been possible previously in human subjects. This will enable scientists to examine all the parameters that regulate human stem cell development within an animal environment (in vivo) rather than within a Petri dish (in vitro). Such information would be extremely helpful in understanding how certain diseases, most notably cancer, develop. There is good scientific evidence that cancer cells lose their capacity to differentiate, and begin to multiply in a prolific and unregulated fashion. Creating a human-mouse chimera that would have a genetic predisposition to specific cancers, such as breast cancer, could be an effective animal model to examine potentially new and effective types of chemotherapies or immunotherapies.

- To understand basic principles of cancer. Why is it that transplanting human stem cells into mice results in only benign tumors yet when mouse stem cells are transplanted into mice, malignant tumors are formed (Erdo, Buhrle et al. 2003; Bulic-Jakus, Ulamec et al. 2006).
- To examine how specific genes function by transplanting genes across species. If you transfect a human gene into an animal that lacks that gene, then you have a method for analyzing how genes or DNA sequences that are only found in human beings play a role and function in human development. This technology can be used to study how certain genes influence intelligence or human behavior. In addition, enucleated nonhuman oocytes transplanted with human DNA may be useful as human stem cell sources (Chen, He et al. 2003; Solter 2003).
- To help understand how human organs are formed and help identify problems when organ formation becomes defective. While the idea of transplanting human brains into mice is not scientifically feasible within the immediate future, scientists are trying to use chimeras to understand how brain size and neural networks more generally are regulated during development.

There is evidence that transplanted neural cells can transfer behavioral characteristics. Dr. Evan Balaban, at McGill University in Montreal, took small sections of the brain from developing quails and transplanted them into the developing brains of chickens. The resulting chickens exhibited vocal trills and head bobs unique to quails, suggesting that the transplanted parts of the brain contained the neural circuitry for quail vocalizations [i.e., not just calls, also head bobs...]. Furthermore, the research also offered astonishing proof that complex behaviors could be transferred across – in this case -- closely related species (Balaban, Teillet et al. 1988; Balaban 2005).

Dr. E. Balaban (Balaban 1997) clarified the importance of his research: “This is the first experimental demonstration that species differences in a complex behavior are built up from separate changes to distinct cell groups in different parts of the brain and that these cell groups have independent effects on individual behavioral components.”

Could chimeras provide a model to study human neurological diseases?

It remains unclear whether human-animal chimeras will offer a model for examining human neural/behavioral development, yet these chimeras certainly would provide proof of principle that human
cells can contribute to tissue formation or repair of damaged tissue in a nonhuman animal. It is not the primary objective, however, of these experiments to transfer emergent psychological characteristics from humans to animals and certainly not from animals to humans. But we should keep in mind that, similar to the human-mouse blood chimeras, such a model could provide an excellent system to study human neurological diseases.

In 2014 (Windrem et al., 2014), researchers made a remarkable discovery. They implanted human mature astrocytes into the fetus of mice to generate mice whose glial cells in their brains were almost all human in origin. The main objective was to see how astrocytes which are viewed as neural-supportive cells affect behavior. To their surprise, they discovered that the brain signals in these human-animal chimeric animals spread farther and more quickly than what's normally seen in mice – an effect that appeared more similar to human brain activity. In addition, long-term potentiation -- how long neurons are affected by electrical stimulation, occurred more rapidly and was sustained longer in these mice, suggesting that they exhibit improved learning capability and increased memory capacity. In summary, this report is one of the first to present data that non-neural cells (i.e., astrocytes) contribute to cognitive capacity and learning.

Ethical concerns raised by human-animal chimeras

Does chimera technology infringe upon any classical bioethical principles?

Generating a human-animal chimera with human brain cells (referred to here as neural chimeras) is problematic to some bioethicists. As stated earlier, neural chimeras are generated with the scientific intention and objective to “do good” by:

1. examining basic questions in neural development and circuitry and
2. developing new therapeutic protocols for treating various neurological diseases (Behringer 2007).

Recall, scientists do not aim to transfer behavioral characteristics from humans to animals or from animals to humans. Rather, the bioethical concerns regarding the use of human-animal chimeras in neurological research are based primarily on the fear that human brain stem cells or genes transplanted into animal fetuses or embryos may inadvertently trigger the transfer of human characteristics (such as intelligence, consciousness, or speech) into an animal.

Why did the National Academy of Sciences need to consider the bioethical issue of human-animal chimeras?

Dr. Irving Weissman of Stanford University proposed in 2002 to insert human neural stem cells into the brain of a mouse embryo whose own neural stem cells were dysfunctional. He did this in an attempt to understand how human neurons develop in the brain and in hopes of developing stem cell therapies that could lead to curing Parkinson's or Alzheimer's disease.
The National Academy of Sciences (NAS), a self-elected group of notable scientists, advises the United States government on a broad variety of health and scientific issues (Final-report 2010). While the Academy’s recommendations are nonbinding, they nonetheless are taken quite seriously within scientific and governmental sectors.

Weissman’s research team and other scientific groups had already succeeded in developing mice with one percent of their brains containing human cells. Before continuing, however, Dr. Weissman asked Stanford University to convene a group to advise him on the ethics of these types of experiments. (Final-report 2010). Stanford University in turn presented this issue to the National Academy of Sciences.

The first ethical guidelines for human-animal chimera research

In April of 2005, the NAS established ethical guidelines for scientists who want to transplant human embryonic pre-neural stem cells into animal fetuses. This landmark report (Final-report 2010) lists more than thirty major guidelines covering everything from accurate record-keeping to prohibitions against certain experiments, as well as outlining the need to establish a system of local and national oversight panels for reviewing stem cell research. The guidelines are intended to enhance the integrity of all human embryonic stem cell research, regardless of who allocates the research funds. Some of the positions taken by the NAS are as follows:

- The Academy advised against growing normal or chimeric embryos past 14 days in culture. The fourteen day limit was chosen since it is the time when the fertilized zygote implants into the uterus and concomitantly, it is the time when nervous system development initiates in the fetus.
- The Academy advised against inserting human stem cells into non-human primate embryos, at least for the time being, until science gains a better understanding of the risks and benefits of this new biotechnology.
- The Academy recommended that no chimeric animals should be allowed to mate in order to avoid the remote possibility of human-like creatures being conceived.

With respect to Dr. Weissman’s proposal, the NAS advised him to go ahead with the first part of his experiments to see whether the architecture of the human-mouse brain was mouse-like or human-like after implanting human neural stem cells into a mouse fetus. Dr. Weissman’s proposed experiments, it was thought, would be valuable in beginning to understand how the human brain is formed during development. The National Academy of Sciences agreed to revisit Dr. Weissman’s proposal after he obtained his initial results (Bearden 2009). The NAS updated their review in 2010 (Final-report 2010).

Specific bioethical concerns related to human-animal chimeras
Creating a human-animal chimera generates a classical ethical dilemma: studying human-animal chimeras may enhance our understanding of human evolution and provide great medical advances, but the number of ethical concerns gives us pause. Specific ethical concerns with respect to human-animal chimeras include:

1. tampering with natural law
2. violating the integrity of species: defining Homo sapiens as a unique species
3. disrespecting human dignity
4. unnecessary cruelty to animals
5. unknown consequences
6. concerns raised by xenotransplantation

1. Tampering with natural law

From a scientific perspective, tampering with natural law is unethical when it results in doing harm to animal life, the environment, human individuals, or to society. Some ethicists also believe in the Aristotelian theory which asserts that every living thing has an inner tendency to reach its appropriate end or goal (telos) by exercising certain characteristic biological functions. According to traditional natural law theorists, the very fact that a living entity pursues a particular kind of life through certain biological processes is its own justification (Crowe 1977). Thus, transplanting human cells, tissues, and organs into nonhumans in ways that change their normal function would violate the natural teleology of these beings.

The appeal to the “unnatural” argument was the stance taken by the administration of George W. Bush and the panel he appointed. The President’s Council on Bioethics indicated in 2003 that the creation of such chimeras would be contrary to the orderly way in which the natural world functions. (Karpowicz, Cohen et al. 2005)

In science, however, experiments often are conducted that do tamper with or create biological situations not normally found in nature. The purpose of engaging in these types of experiments is to:

- develop a greater understanding of basic biological principles
- subsequently apply these principles to develop new therapies
- to expand basic knowledge in scientifically purposeful and often highly significant ways not otherwise obtainable.

Expressing the human gene for human speech in transgenic mice, for example, is an artificial system, as is reconstituting a human immune system in transgenic mice. Nonetheless, the creation of artificial biological systems to examine how specific genes or cells function within a whole animal can be extremely important and is generally considered ethically acceptable.
There was no public outcry in response to human-mouse chimeras expressing a human immune system because of the importance of enlarging our understanding of how this mouse model could be used to study a variety of human diseases such as AIDS.

At this time, scientists are not proposing to use human-animal chimeras to study human behavioral characteristics. They do propose to use chimeras to study early human neural circuitry. The mechanism by which early neural precursor cells differentiate and form the first circuits is a critical issue in the neurosciences.

So it is appropriate at this time to accept recommendations from the National Academy of Sciences prohibiting the implantation of animal fetuses or embryos containing human neural stem cells into animals to prevent development into whole organisms. Rather, scientists can study early human neural circuitry in an animal embryo in vitro, within the confines of a Petri dish.

2. Violating the integrity of species: defining Homo sapiens as a unique species

How scientists define a species is another obstacle in elaborating the underlying ethical issues related to human-animal chimeras. There is great debate over how to establish scientific criteria for species classification because many essential physical and behavioral characteristics are often non-unique to a particular species. Science also is developing the capacity to alter, via genetic engineering, the physical and behavioral characteristics of plants, animals, and human beings, in such a way as to possibly change the definition of a species.

At least 50% of the human genome consists of mobile elements more commonly called “jumping genes”. Barbara McClintock won the Nobel Prize in 1983 for predicting the existence of “mobile elements” - pieces of DNA that translocate from one location in the genome to another. These jumping genes could account for developmental differences among individuals of a given species. These mobile elements may play a critical role in creating the uniqueness of individuals within a population because they are active in neural differentiation and could affect neuronal development and diversity of brain function in humans and some species of animals.

The controversies associated with establishing defined criteria to identify a Homo sapiens complicate how ethicists and scientists debate the generation of chimeras. Nonetheless, the outward characteristics may play a primary role. Generating an animal with any visibly recognizable human characteristics will
probably be universally targeted as defining whether a chimera is human or animal, irrespective of the underlying genetic composition.

3. Disrespecting human dignity

Any discussion of the ethics of reconstituting a human brain in animals has to address the role of human dignity. Human dignity concerns the worthiness of embodied human life, and the worth of our natural desires and passions, our natural origins, our sentiments and aversions, our loves and longings. Human dignity is manifested in all persons’ capacities to set goals for themselves and to act to achieve them in the practical sphere. Human beings are autonomous, and possess the right to legislate laws, formulate models of conduct, and create ethical standards. A violation of human dignity in part includes the loss of control over one's own choices but also threatens that infringe on the infinite value of human beings. Kant proposed that human beings have unconditioned and incomparable worth (or dignity) because they are moral agents who are capable of and responsible for their own volition (Kant 2008).

Immanuel Kant (1724 - 1804) Immanuel Kant was a German philosopher from Königsberg (today Kaliningrad), Russia and a major exponent of the 18th Century Enlightenment, researching, lecturing, and writing on philosophy and anthropology. He hoped to bring an end to an age of speculation and what he saw as futile, ungrounded theories that were in opposition to the skepticism and idealism of innovative thinkers such as Descartes, Berkeley, and Hume.

Most major religions emphasize the infinite value of human life and assert that human life must be preserved almost at all cost.

Producing animals with human characteristics, such as human-like intelligence or human gametes raises concerns about the dignity of such organisms. If an organism is created that potentially infringes on human dignity, it is likely to create religious and secular public controversy even if medical benefits could emerge from these organisms.

The moral status of a chimera with inserted genes that enhance mental development, or encode for human-like behavioral characteristics, also might be unclear. Astronomy pioneer Carl Sagan has said, “How smart does a chimp have to be before killing him constitutes murder?”

- What if chimpanzee also contained some human cells or genes?
- Will adding human genes or cells to non-primate mammals somehow alter their moral status?
- With respect to moral status, does the nature of the introduced human genes or cells, and their target organs in the chimeric animal, matter?
- Is it unethical to generate mice that produce human eggs (see Cyranoski, 2014)?
The International Society for Stem Cell Research commented on such issues, in its 2006 Guidelines for the Conduct of Human Embryonic Stem Cell Research (Knowles 2003) [http://www.isscr.org/GuidelinesforhESCResearch/2917.htm]:

There is widespread belief that it is highly unlikely that human neurons could proliferate and structure themselves in an animal brain in such a way as to create, for example, human consciousness in a mouse. Yet, most consequences and outcomes of creating these chimeras remain unexplored.

**Thought Question**

If an organism contains human cells, does this confer a higher level of dignity on the animal containing those cells? Currently, science does not have sufficient experience generating chimeras to assess whether they suffer. Several human-mouse chimeras with a reconstituted human hematopoietic (blood stem cell) system have developed life-threatening tumors (Kroon, Thorsteinsdottir et al. 2001).

### 4. Unnecessary cruelty to animals

Concern for the welfare of animals also is raised because of the potential to create chimeras with implanted human neural cells. These chimeras, if allowed to develop, might manifest conflicting behavioral or emotional tendencies that could also cause suffering to the animal.

The following types of problems have been reported by those managing these cats:

- it has been reported that hybrid big cats have behavioral or emotional problems. They inherit different and sometimes conflicting behavioral traits from the two parent species;
- the mother of one species may become confused by her hybrid offspring's atypical behavior;
- ligers, a lion/tiger hybrid (see Figure 3) may inherit both the social, pride-living habits of the lion, and the solitary habits of the tiger, which would inherently be in conflict.
- similarly, a chimera with introduced human genes or brain cells that might affect behavior and emotion might experience such behavioral conflicts.

The National Academy of Sciences has advised against chimeras being allowed to grow in vitro beyond 14 days gestation, and recommended that adult chimeras be prohibited from mating. Hopefully guidelines will protect the basic welfare of chimeric animals, and ethically questionable manipulations of animals will not be allowed. In the future, however, the possibility exists that they might be allowed, for example if significant medical discovery is deemed to be at stake.
Animal experiments involving creation of chimeras must take into account the full range of experimental circumstances, as well as the likelihood of unintended consequences, which could give rise to animal suffering. Scientific teams must seek to mitigate animal suffering whenever possible.

5. Unknown consequences

Most importantly, we must weigh whether our scientific curiosity about the potential benefits of chimeras as research models can justify the known and unknown risks and concerns that may emerge.

6. Concerns raised by xenotransplantation

Raising transgenic or chimeric animals to grow organs in them for eventual transplantation into humans (xenotransplantation) requires that these animals also lead highly-restricted, if probably well-cared-for, lives. From the animal welfare point of view, is growing a heart valve in a pig that has human genes inserted for greater tissue compatibility, or growing a reasonable facsimile of the cartilage for a human external ear (pinna) transplant in a nude mouse (see Fig.4 above), inherently harmful, or neutral, for the animal? Animal species such as pigs, currently raised for xenotransplantation organ harvesting, are also raised for food.

Compelling questions:

- Should we be concerned about raising animals to kill them to harvest specific organs?
- Does it matter if the animals used for organ-production are or are not normally food or laboratory animals, or possibly neither?
- Are there ethical issues in using them to harvest one piece of them?
- Is it wasteful to harvest one organ from a pig and discard the rest?
- Could a human-pig chimera also be eaten, so as not to waste the creature?
- Can we raise human-pig chimeras without the risk of transmitting unwanted pig oncogenes into humans?

One more frequent bioethical concern with xenotransplantation is that the human recipient might have concerns about the tissue source, for example, for reasons of religious faith. If a transplanted heart valve might come from a pig – even a chimeric pig with some human genes, to make the valve more bio- and immuno-compatible – Jewish and Muslim patients might not wish to have inserted a valve from a pig, and probably should be notified of all available options.

These are just some of the diverse questions that can arise concerning use of animals for xenotransplantation in the 21st century.

For more information on regulation of research involving chimeras, see the Empire State Stem Cell Board (ESSCB) Statement Regarding the Conduct of Human Embryonic Stem Cell (hESC) Research Involving Chimeras.
Conclusion

Scientists are trying to create chimeras to benefit humankind, to gain a better understanding of human disease, and to develop novel therapies. We have described many examples of human-animal chimeras that have provided significant advances in scientific and medical benefits and that, so far, do not appear to encroach on human dignity. It is up to scientists to continue to act responsibly and to respect human dignity and all animal life. Many ethicists believe that in science and medicine, research should be guided not by what you can do, but rather what you should do.

References

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