

# Ethical issues of creating human- animal chimeras



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To the public the term “ chimera” elicits images of mythical creatures, often composed of body parts from different animals. In popular culture, chimeras are often displayed as monsters, which stems from Greek mythology in which a chimera is a creature that has the head of a lion, the body of a goat, and the tail of a serpent<sup>13</sup>. However, in the realm of science and medicine a chimera may not be easily recognizable. The medical definition of a chimera is an organism that is made up of two cell types that are genetically distinct from each other. Humans may become chimeras in instances when they receive transplants from other humans or when they are pregnant, and cells migrate outside of the womb<sup>14</sup>. In research laboratories, chimeric mice are commonly used and often created by researchers inserting human cells into mice in order to examine specific diseases or test potential treatments<sup>11</sup>. They have also been used to study organ regeneration<sup>12</sup>. With increasing scientific advances and discoveries, the ethical lines of this research are becoming more and more blurred. Creating human-animal chimeras presents a variety of ethical concerns that have had to be addressed by research funding bodies including the National Institutes of Health (NIH).

In September of 2015 the NIH released a notice, NOT-OD-15-158, which was an announcement that implemented a moratorium, or temporary prohibition, on funding a specific type of research. The moratorium was announced because the NIH saw that the field of regenerative medicine was advancing to the point where researchers were looking to use early stage animal embryos to grow human organs and tissues for transplant<sup>1, 15</sup>. The title of the announcement was “ NIH Research Involving Introduction of Human Pluripotent Cells into Non-Human Vertebrate Animal Pre-Gastrulation

Embryos” 15. This moratorium pertains specifically to human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) and their uses. These human cell types are capable of dividing for an extended period without differentiating. When they do differentiate, they can become cells that make up any kind of tissue<sup>8</sup>. Under the moratorium, research projects in which hESCs or hiPSCs are introduced into non-human vertebrate blastocysts, or early stage embryos were not able to be funded. Research projects that involved breeding animals in which hESCs and hiPSCs were introduced and may contribute to the germ line, or reproductive cell lines, were also not eligible for NIH funding<sup>15</sup>.

The production of human-animal chimeras presents a complex ethical problem. The moratorium allowed the NIH to step back and examine the guidelines surrounding this type of research. The overarching ethical issue leading to this moratorium is that the researchers doing this work may not know exactly what they are creating<sup>9</sup>. In terms of human-animal chimera models, the animals being created may be altered in a variety of unexpected ways. For instance, an animal’s level of consciousness may be altered, it may gain a more human-like appearance, or produce human gametes<sup>3</sup>. An ethical concern is that introducing human cells into animal blastocysts lead to the human cells majorly contributing to the brain of that animal in a way that could humanize the animal’s brain and therefore change its moral status and legal status<sup>3, 5, 6</sup>. There are also concerns that the physical appearance or attributes of an animal may be altered in a way to become more human-like, which introduces concerns about our identity as humans. Another

ethical concern is that a human-animal chimera may produce human gametes and go on to breed further blurring the line between species.

After the NIH introduced the moratorium on human-animal chimera research, they held a workshop to evaluate the issues surrounding the moratorium including the current state of the research and animal welfare. After the workshop, the NIH decided to move forward with lifting the 2015 moratorium on human-animal chimera research. The NIH announcement following the workshop, NOT-OD-16-128, revealed that even though there are challenges surrounding making human-animal chimeric models there is interest and potential in pursuing this research<sup>16</sup>. One change that the NIH decided to implement as a result of the workshop was creating a steering committee to provide more oversight over the field while allowing the field of research to still move forward. The steering committee would be tasked with thoroughly reviewing human-animal chimera research proposals prior to issuing a funding decision. In addition to providing input on funding decisions for grants this steering committee will also be monitoring the field of human-animal chimera research and scientific advances in order to provide advice for future NIH decisions on this topic<sup>16</sup>. Throughout the review of relevant grant proposals this committee will examine five different criteria including the characteristics of the human cells being introduced to the animal and the characteristics the animal recipient for the cells. The committee will also examine any changes to the recipient animal, provide an assessment of animal welfare, and provide an assessment of the outcomes of the research that has been done before more research begins<sup>10, 16</sup>.

The second major outcome of the workshop and of the decision to lift the moratorium was a revision of the guidelines surrounding human-animal chimera research. They decided to expand the current guidelines by prohibiting funding for the research that includes the introduction of human stem cells into non-human primate blastocyst stage embryos and the breeding of animals where the introduction of any human cells could contribute to reproductive cells<sup>16</sup>. They also added that they would not provide funding for obtaining stem cells from human embryos and that they would not fund research using human embryonic stem cells from other sources. These types of research proposals could still be funded through private funding sources, just not with NIH funds<sup>8</sup>. They also asked the public to comment on whether or not funding should be allowed of research where human stem cells are introduced into non-vertebrate embryos up until the end of the gastrulation stage, where the cell layers begin to form and if funding should be considered for research where human cells are introduced into non-human mammal embryos, not including rodents, where they may contribute or modify the animals brain<sup>16</sup>. Consideration of the ethical issues surrounding human-chimera research allowed for revised review processes and funding guidelines with more oversight.

Examining the ethical concerns surrounding human-chimera research allows us to examine the pros and cons of lifting the funding moratorium. There are a variety of arguments against the NIH funding human-animal chimera research. One of the arguments originates through the source of the human cells being used. Using human embryonic stem cells presents a moral dilemma involving the duty to prevent suffering and the duty to respect

human life<sup>7</sup>. The answer of which duty has the upper hand is dependent on how each individual views a human embryo because in order to obtain human embryonic stem cells a human embryo must be destroyed. If an individual does view a five-day old embryo as having significant moral standing because it has the capability to develop into a human being, then research involving human embryos is not ethical<sup>7</sup>. Based on these arguments, an individual who views an embryo as having the same moral status as a fully developed human being would not support the destruction of this embryo and use of its cells in human-chimera research.

Another argument against human-animal chimera research is that we are not entirely certain of what effects this research would have on the animals. When human cells are incorporated into animal embryos, a species barrier is crossed. We are uncertain of exactly what cell types they will become or where they will be incorporated. The results of the transplantation of human cells into an animal embryo may be dependent on the number of stem cells and the stage of the animal host as well as the species of the host. The main ethical concern is that by performing this research we may, in a way, humanize animals that we use for laboratory research either through changing physical characteristics or through increasing their sense of self-awareness. In doing this, we may create an organism with an ambiguous moral status<sup>3</sup>. This would blur the lines between human and animal rights, and it is unclear at what point that organism would gain the rights that we have. Some also feel that the creation of human-animal chimeras poses a threat to human dignity. Human dignity is the concept that one is worthy and is respected because they are human. Therefore, it has been argued that

when human-animal chimeras are created we risk denying them human dignity<sup>2, 5</sup>. There are also concerns that by introducing human cells into the embryo may lead to these humans producing human gametes, or reproductive cells. If these animals were to go on to breed, they could potentially produce more human-animal chimeras and the results would be unpredictable. This would further blur the lines between species and moral status of the chimera created.

There are also major concerns about animal welfare. We want to perform research where the potential benefits outweigh the risks. In performing human-animal chimera research where there is uncertainty in what the results may be, we may not know what the effects on the host animal are. We do not want animals to suffer and it is possible that hundreds of animals may suffer even before the right human-animal chimera model is created<sup>4</sup>. The effects of growing the human organs are also unknown and may cause the host animal pain and discomfort. The concern of animal welfare is also accompanied by the concern of animal sacrifice. Along with this for each organ grown, one pig would be sacrificed to obtain the organ for transplant. Research would be ongoing, and pigs would continue to be sacrificed for future research. In drug testing studies, once the drug passes clinical trials animals are no longer sacrificed. Unlike in drug clinical trials, the success of transplantation of human organs grown in animals would mean that more animals would be used to create more organs<sup>4</sup>.

Other concerns surrounding this type of human-animal chimera research is that this research may lead to the development that are dangerous and could potential harm humans as well. While the chimeras that would be

created would be growing human organs, the cellular environment within an animal is different than humans. There are concerns that these human organs grown in animals may contain residual animal proteins or cells that could lead to severe immune reactions in the receiver of the organ<sup>6</sup>. One other concern is that creating these human-animal chimeras could potentially lead to zoonoses<sup>5, 9</sup>. This is because there are retroviruses that are incorporated into an animal's genome. Creating chimeras may result in these viruses being transferred to humans. If this occurred the effects of the virus in humans may be unpredictable<sup>6</sup>.

While there are these arguments against human-animal chimera research there are also an equivalent amount of counter arguments for doing this research. Regarding the argument about using human embryonic stem cells for chimera research, embryonic stem cells don't have to be the only source of stem cells used in this type of research. Induced pluripotent stem cells can also be used. These cells are adult cells that have been reprogrammed to an embryonic-like stem cell. Like embryonic stem cells, induced pluripotent stem cells can differentiate into specialized cell types<sup>3, 7</sup>. Using induced pluripotent stem cells in chimera research means that no human embryos will be destroyed for human-animal chimeras to be created.

Many of the ethical arguments against human-animal chimera research concern creating more human-like animals. Arguments for this type of research indicate that creating animals that are more human-like is highly unlikely. For an animal to develop the consciousness that humans have, that would first require the development of a more human-like brain. Research has shown that cells that develop into many of the cell types in the brain

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need more time to develop and go through divisions in primates. Human-chimera research has a focus on producing human organs in pigs and pigs have a shorter gestation time than humans do. For comparison a human pregnancy lasts nine months while a pig's gestation period is only three months<sup>6</sup>. With the gestation period being one third of the time of human pregnancy it is unlikely that there would be enough time to produce a human-like brain in a non-human animal host. This scenario is also unlikely due to competition of cells within the host organism. The cellular environment within a pig is different than within a human, therefore it would be expected that the pig cells would be more competitive than human cells, making it more likely for more pig cells to colonize the brain than human cells<sup>6</sup>. Based on this, it is unlikely that the introduction of human cells into a pig embryo would result in an animal with more human-like brain leading to an increased level of self-awareness and self-consciousness.

Other concerns pertaining to the uncertain effects of this research and creating human-like qualities are the concerns over producing animals with human-like appearances and creating animals that produce human-like gametes. Based on previous studies, it has been shown that when donor cells are introduced to a different species there is a lower contribution to the organism than when the species are the same. For example, in mouse-mouse chimera studies the contribution of the donor cells was around fifty percent, but in mouse-rat chimera studies the donor cell contribution was only around twenty percent<sup>1</sup>. For human-pig chimera studies it has been estimated to be even lower than this at one percent donor cell contribution<sup>6</sup>. This percentage indicates that the human cells introduced in the embryo

contribute little to the entire organism and it is therefore unlikely that a pig would be born with human physical features like human hands or feet. In terms of reproductive concerns, the argument for doing this research is that the reproductive barrier is very strong<sup>6</sup>. It is unlikely that a pig producing human sperm would be able to produce a viable embryo with another pig based on crossbreeding attempts that have previously occurred between humans and apes. There are other ways to address this concern as well. These include that the pigs being used to grow human organs could be sterilized to prevent further reproduction and that the induced pluripotent stem cells being introduced could be genetically modified so that they are unable to differentiate and become reproductive cells<sup>5, 6</sup>.

One of the most compelling arguments for human-animal chimera research aimed at producing transplantable organs is the unfortunate lack of alternatives. Every day, around twenty-two people die while waiting for organ transplants<sup>1</sup>. This is due to the organ shortage. This field of research has the potential to produce transplantable organs capable of saving lives. Although there are fears of rejection and diseases, doing more research on this topic will allow these concerns to be addressed. One way researchers are trying to address these concerns is by examining if potentially harmful retroviruses can be inactivated using CRISPR/Cas9<sup>6</sup>. While the benefits of this research may potentially be five to ten years away, there are currently not many alternatives<sup>9</sup>. While many animals may be utilized for this specific field of research and for growing transplantable organs, this doesn't mean that other alternatives will not be discovered. If other alternatives are developed, such as functional and transplantable human organs grown from

organoids, then the number of animals being used in this research could be reduced and animal suffering could be limited.

Based on everything that I have researched regarding ethical concerns surrounding human-animal chimera research, I do believe that this research should continue to be funded, within reason. I think the NIH was correct in introducing the funding moratorium because it allowed them to step back and gain a better idea of how this type of research should be regulated. I like how the steering committee can not only give feedback on individual proposals but also oversee the field altogether. Based on the research that I have done I believe that the ethical concerns are valid. We don't necessarily know what the research could produce or what the results will be. Even though it is unlikely that creating a human-animal chimera will humanize the animal, I believe that there should be tight regulation of this research and that any concerning results should be addressed right away. I also think this regulation should always be evolving as the field does, so ethical concerns can be addressed as they arise. Overall, I believe that this research should be done due to the lack of current alternatives because it does have the potential to save lives. If better alternatives are developed that limit the number of animals used and would prevent potential animal suffering, then I believe this research should be stopped at that time.

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