The Ethics of Creating and Using Human-Animal Chimeras

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Pre-Publication Version

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Abstract

Rapid advances in gene-editing and stem-cell technology have expanded the range of possible future applications in human-animal chimera research. Most notably, recent developments may allow researchers to generate whole personalized human organs in pigs for the purpose of transplantation into human patients. Though human-animal chimera research in small animals, such as mice, is routine, human-animal chimeric techniques are now increasingly being applied to larger animals. Moreover, these chimeras include increasing amounts of human material, which is potentially present in more morally significant locations, such as the brain and the reproductive system. These developments raise important ethical questions about whether we should create such chimeras, and if so, how we should treat them. Answers to these ethical questions are needed to inform the development of policies regulating human-animal chimera research and its applications. Here, we provide a review of some of the most important or widespread ethical concerns.

Key Words: chimeras; human-animal chimeras; animal-animal chimeras, human dignity; moral confusion; moral status; human-pig chimeras; human-non-human primate chimera

Scientific Background

Human-Animal Chimeras

A chimera is an organism formed by mixing together whole cells originating from different organisms[1] that are genetically distinct.[2] [3] A chimera can be intraspecific, which means all cells in the chimera belong to the same species (e.g. the introduction of retina cells from a mouse fetus into a blind adult mouse to gain knowledge about treatments for blindness[3])—or interspecific, which means the chimera contains cells belonging to at least two different species.[4] Importantly, it is possible to create interspecific chimeras in which one species is a human and the other a non-human animal (non-human animals will henceforth, for reasons of brevity, be referred to as 'animals'). Such a human-animal chimera can either be (i) an animal embryo or animal at a later stage of development containing some human cells, or (ii) a human embryo or human at a later stage of development containing some animal cells. In this review, we focus on the former type of chimera, since it is likely to receive greater scientific attention than the latter type in the near future.

Human Cells in Human-Animal Chimeras

Human-animal chimeras containing some human cells have been extensively used in biomedical research.[5] For example, human hematopoietic stem cells have frequently been transplanted into immunodeficient post-natal mice to assess their capacity for differentiation,[6] human tumors have been engrafted into mice to create models for human cancer mechanisms and develop therapeutic protocols,[7] and human stem cells have been implanted into embryonic

and neonatal mouse brains and have been shown to differentiate into human neurons, offering the potential to study human neural development, neurodegenerative diseases, and therapeutic drug development *in vivo*.[8] [9] The main scientific attractions of human-animal chimeras are that (i) they allow for the study of human cells and tissues *in vivo* without the need to experiment on humans, and, (ii) they act as better models of human cells and tissues than non-chimeric animals.[10]

Importantly, most human-animal chimera studies to date have involved animals—most often mice—into which human cells have been inserted at later (e.g. fetal, postnatal, or adult) stages of development. In these chimeras, the progeny of donor cells are typically present only in the tissues into which the donor cells were introduced. By contrast, when one or more donor cells from an embryo or embryonic stem cell line are introduced into another early embryo, the resulting chimera potentially has the progeny of the donor cells in many of its tissues.[11] In the few studies where human stem cells have been injected into blastocysts of pigs and sheep, the contribution of human cells to the developing organism has nevertheless generally been limited.[12] However, recent advances in gene-editing and stem-cell technology have allowed scientists to increase the prevalence of human-derived cells in animal hosts, including in larger animals such as pigs and sheep. This raises the prospect of a wider range of applications in human-animal chimera research, including the creation of significantly better models (including human-non-human primate models) for human disease, and the generation of human organs in pigs to help tackle the problem of the worldwide organ shortage in transplantation medicine.[13] Through a combination of gene editing, blastocyst complementation and the use of induced pluripotent stem cells from a human patient, it may become possible to generate personalized human organs in pigs that will not be rejected by the patient's immune system after transplantation.

With these new developments, ethical concerns arise. Some are concerns about the creation and use of human-animal chimeras in general; others are concerns about certain types of human-animal chimeras, including those that may have human cells in their neural tissue or in their reproductive system, and some are concerns about the research that precedes and informs research into human-animal chimeras..

There may be a solution, however: Savulescu has argued that in cases of uncertainty, "the genetically modified animal should be accorded the highest moral status consistent with its likely nature" [14] Thus, for example, if we have reason to believe that a human-pig chimera has the same moral status as an ordinary human, we should not use it as a source of donor organs and we should subject it only to forms of research that would be ethically acceptable also if conducted on, for example, human children.

In the US, the 2005 Guidelines for Human Embryonic Stem Cell Research, published by a committee of the U.S. National Academy of Sciences, recommended that ESCRO committees ("embryonic stem cell research oversight committees") review all research involving the introduction of human embryonic stem cells into nonhuman animals at any stage of development and stressed that "particular attention should be paid to the probable pattern and effects of differentiation and integration of the human cells into nonhuman animal tissues". They recommend that research in which human embryonic stem cells are introduced into nonhuman primate blastocyst should not be done. These are only guidelines, but they have nevertheless been influential.[15] The National Institute of Health does not fund research in which

human embryonic stem cells or human induced pluripotent stem cells are introduced in non-human primate blastocysts.

Some have expressed the concern that if human-animal chimeras obtained humanized cognitive capacities, creating them would be an affront to human dignity—that is, would violate the moral requirements that human dignity imposes.[16] [17] [18] [19] [20] Definitions of human dignity vary, as do arguments for the view that the creation of human-animal chimeras with human cells in their neural tissue would be an affront to human dignity. For detailed critique of these definitions and arguments, see Palacios-González[21] and DeGrazia.[22] Here, we present only one general problem that dignity-based arguments against the creation of human-animal chimeras face. This has the structure of a dilemma.

It is uncontroversial that most or all human beings have human dignity. Would human-animal chimeras also have human dignity? This is less clear and has been the object of dispute, but there are only two possibilities: either a given human-animal chimera would have human dignity or it would not.

If it would not have human dignity, then the creation of that chimera would not directly raise issues of human dignity. With respect to dignity, it would be like breeding animals that clearly do not have human dignity—like breeding ants, say. It is possible that creating such a chimera could *indirectly* raise issues of human dignity if, for example, it affected how we would view other creatures that do have human dignity. However, we know of no convincing argument to the effect that this is likely to occur. Perhaps it might be thought that creating human-animal chimeras that lacked human dignity, but outwardly resembled humans, would weaken the link that we tend to make between ‘looking like a human’ and ‘possessing human dignity’. And

perhaps weakening that link might somewhat weaken our tendency to treat a being as possessing human dignity if and only if it looks human. However, it is not clear that weakening this association would be a bad thing. After all, on many views about what confers human dignity—such as those that ground dignity in psychological capacities[23]—appearing outwardly human is a poor indicator of dignity.

If, on the other hand, a given human-animal chimera *would* have human dignity, then creating that chimera would involve creating a being with human dignity. However, in this respect it would be like (most) ordinary human reproduction, yet human reproduction is generally not taken to be problematic with respect to dignity. Why think that creating human-animal chimeras with human dignity would be otherwise?

Perhaps the concern could be that it is problematic to create beings with human dignity *knowing that they will likely not be treated in a way that befits their dignity*, which might be the case if human-animal chimeras were created in the knowledge that they will be used in research. Alternatively, the concern might be that it is problematic to create beings with dignity *while planning oneself to treat them in a way that does not benefit their dignity.* This might be the case if a researcher created a human-animal chimera while planning herself to use it in research. These concerns could be avoided in the same way as concerns about the uncertain moral status of chimeras: whenever we are uncertain as to whether a given chimera has or will have human dignity, we could limit the kinds of research that may be performed to those that are consistent with human dignity—to those that could permissibly be performed on a human child, say. There may, of course, be legitimate doubts about whether such limits will ever be enacted and properly enforced.

Human-animal chimeras with human gametes

Although debate surrounding human-animal chimeras has focused on human neural tissue, the potential for human stem cells to contribute to the reproductive system of non-human animal hosts, either intentionally or unintentionally, has also sparked concerns. The UK Academy of Medical Sciences and the US Committee on Guidelines for Human Embryonic Stem Cell Research have recommended against the creation of human-animal chimeras capable of human gamete production, and against allowing human-animal chimeras to breed.[24] [25] These advisory bodies, however, have not provided ethical grounds for these recommendations. We will now discuss some ethical considerations that bear on the creation of human-animal chimeras containing, or capable of producing, human gametes. This has been analyzed at length by César Palacios-González,[26] [27] and our discussion draws heavily on his.

One reason to worry about the creation of human gametes within a human-animal chimera is that this might in some way undermine or fail to respect the value of human gametes. It has generally been acknowledged that the value of human gametes derives not from the properties that they possess, as gametes, but from what they can become or produce.[28] For example, we might think that human gametes have instrumental value by virtue of their ability to produce valued offspring. The question, then, is whether this value of human gametes might be undermined if they were generated in a human-animal chimera. Palacios-González contends that as long as the goals of chimeric-generated human gametes are achieved, whether that be research or reproduction, then those gametes would retain their instrumental value.[29]

Another potential argument against human-animal chimeras capable of producing human gametes might be based on an appeal to intuitive moral responses, also known as the "yuck factor" approach. The idea would be that we should take people's intuitive disdain for human-animal chimeras as evidence that there is something wrong with creating them, even if we cannot articulate what the problem is.[30] However, there are several problems with this approach. First, different people have different intuitive moral responses to the same issue. Secondly, if we settle for accepting our own moral intuitions, regardless whether they can be given any rational basis, then we might find ourselves with no basis for rejecting the moral intuitions of those who condone, for example, racism and slavery.[31]

On the other side of the moral ledger, there are also reasons in favor of creating human-animal chimeras capable of human gamete production. Palacios-González identifies three: first, to relieve the shortage of human eggs in regenerative medicine and embryonic stem cell research; second, to reduce the number of women subject to the risks that donating eggs for research entails; and finally third, to restore fertility in patients who have become infertile due to medical treatments or trauma.[32]

A further issue to consider is the *reproduction* of human-animal chimeras capable of producing human gametes. One argument against creating these beings might be that theoretically, it is possible that if a human-animal chimera with human gametes were to reproduce, the fertilization of a human gamete and a nonhuman gamete might take place and form a hybrid embryo with unintended or unexpected characteristics. However, this scenario appears highly unlikely due to the significant differences in human and animal species. Furthermore, even if a hybrid embryo is formed, it is likely that it would not be viable. Moreover, Hank Greely has suggested several solutions to the potential outcome of human-animal chimera reproduction,

such as sterilizing chimeras, ensuring that they are segregated by sex, or only creating one sex of chimera.[33]

Creating and using animal-animal chimeras

Some, if not all, of the aforementioned concerns, may also apply to research that precedes and informs human-animal chimera research: research using *animal*-animal chimeras. In 2019, scientists in China created the first monkey-pig chimeras.[34] They injected early piglet embryos with monkey stem cells to study cell migration in the piglet's bodies. (The two monkey-piglet chimeras died within a week after birth, though probably as a result of the IVF procedure through which they had been created and not the mixing of cells from different species.) The goal of the research was to gain knowledge about interspecies chimerism and human organ growth in pigs. Though this research received significantly less attention than the human-animal chimera research it is meant to inform, it seems that many, if not all, of the concerns raised by the creation of human-animal chimeras could also be raised by this sort of research. Concerns about unnaturalness evidently apply to any kind of chimera research, including research using animal-animal chimeras. (And objections based on these concerns are, evidently, equally problematic.) What about concerns regarding moral confusion? Since no human material is involved, there won't be any confusion about what moral framework to apply to determine how to treat the chimeras: it will be the moral framework people normally apply to animals. But as we pointed earlier, the 'moral confusion' argument, as formulated by Robert and Baylis and is not very strong anyway.

Of greater importance, however, is whether concerns raised in the context of human-animal chimeras about increased cognitive capacities and the production of gametes carry over to the use and creation of animal-animal chimeras. It seems most plausible that they might do so in

the case of pig-monkey chimeras, given that monkeys are cognitively sophisticated and often thought to have significantly greater moral status than other non-human animals.

There is a growing consensus that non-human primates (henceforth 'primates') have sophisticated psychological capacities, including sophisticated cognitive capacities.[35] Of all primates, great apes have the most sophisticated psychological capacities, which led some jurisdictions to extend personhood, and the legal protections that personhood brings with it, to great apes. The European Union, for example, banned great ape scientific experimentation in 2013. If great apes are indeed persons, then all concerns about human-animal chimeras discussed above, equally apply to the creation and use of animal-great ape chimeras. But what about other primates, like the monkeys used in the recent pig-monkey chimera experiment?

Other primates also have sophisticated psychological abilities, be it somewhat less sophisticated than those possessed by great apes and humans. As a result, we cannot exclude the risk that, for example, pig-monkey chimeras may possess enhanced cognitive abilities that could affect how we ought to treat them, and whether we ought to create them at all. Because of their sophisticated psychological capacities, some countries and regions, including the U.S., Europe and New Zealand, legally protect all primates in the context of scientific research. For example, the 1985 amendment of the animal welfare act in the U.S. (Sec.43(a)(2)(A)) requires that special steps be taken to ensure the psychological well-being of non-human primates. It seems then that, if, for example, pig-monkey chimeras had cognitive (and other high-level psychological) abilities normally possessed by monkeys, they too ought to be protected by these laws and should receive special care in research settings. If we are uncertain about their psychological capacities, and hence their moral status, we should err on the side of caution and protect the chimeras as we would protect primates (just like we should err on the side of caution

when using human-animal chimeras). This may imply that we cannot use them for certain types of research. Perhaps special committees, comparable to ESCRO committees overseeing research involving human embryonic stem cells should evaluate, on a case by case basis, experiments involving primate embryonic stem cells. This could reduce the risk of maltreatment of pig-monkey chimeras (or other chimeras involving primates).

What about concerns regarding the creation of chimeras capable of producing gametes? Animal gametes not normally thought to have any great moral significance, suggesting that, in relation to animal-animal chimeras, there would be no analogue of the concern about undermining or failing to respect the value of human gametes. It also seems unlikely that people would have the same 'yuk factor' reactions to gametes created by an animal-animal chimera. Moreover, since the sterilization of animals to prevent their reproduction is widely accepted, it would arguably be easier to prevent animal-animal chimeras from reproducing, should it be deemed necessary to do so. On the other hand, however, if some primates qualify as persons, it would presumably follow that we should be as concerned about the reproduction of chimeras involving those species as we would be about the reproduction of human-animal chimeras, and we should perhaps also be more prepared to sterilize such primates than we currently are.

Concluding Remarks

The ethics of creating and using human-animal chimeras will continue to evolve as technology advances and the potential applications of human-animal chimeras grow. There remain empirical uncertainties surrounding the off-target contribution of human stem cells, and whether these cells could 'humanize' cognition or become functional human gametes in animal hosts. The typical arguments against creating human-animal chimeras, such as the

unnaturalness argument and the moral confusion argument, are generally unconvincing. Now, the focus of ethical discussions surrounding human-animal chimeras is the unintentional or intentional contribution of human stem cells to the host's neural tissue. The most serious concerns are that researchers may create human-animal chimeras that have higher moral status than their non-chimeric animal counterparts, and perhaps even possess human dignity. These concerns could in principle be dealt with by erring on the side of caution, assuming that a chimera has the highest level of moral status—or dignity—that it might plausibly be thought to possess, and permitting only research that would be appropriate for beings at that level. The same applies to pig-monkey chimeras. However, it remains a legitimate question whether this strategy would be sufficiently effective in practice.

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