Human, nonhuman, and chimera research: considering old issues with new research

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Abstract (137 words)
Chimera research – research on nonhuman animals that contain human cells – is being used to understand human disease and development, and to create potential human treatments such as transplantable organs with the proposed advantage that such models better represent humans. Emerging ethical issues are being explored such as at what point chimeras are "human enough" to have human rights and thus benefit from higher standards of research protection. However, this question and others related assume that the ethics of experimenting on nonhuman animals have been settled, which they have not. In this article, we argue that it is imperative to give adequate attention to familiar questions about nonhuman animal research as well as new questions about chimera research, and that failure to do so will result in a distorted understanding of the ethics of chimera research.

Key Words: animal experimentation, genetically modified organisms, human subjects research, IRB, IACUC

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1. Introduction

Whenever a new kind of research emerges, bioethicists consider the ethics of that kind of research. We ask: What are the distinctive features of this new kind of research, and what are the ethical questions that these distinctive features raise? We then produce an ethical literature meant to guide the thinking and behavior of a variety of stakeholders.

As natural as it might seem, this way of framing the ethics of new kinds of research can lead to two related problems. First, it can lead us to focus on new and distinctive ethical questions, when in fact we should also be considering old and familiar ethical questions. Second, it can lead us to consider ethical questions in ways that take already-existing practices for granted, when in fact we should also be considering them in ways that challenge these practices. Thus, to the degree that we frame the ethics of new kind of research in terms of its new and distinctive features, we risk missing important issues and distorting our analyses.

In this article, we will illustrate this phenomenon by discussing the ethics of human-nonhuman chimera research. Chimera research is research on nonhuman animals that contain transplanted human cells. It is potentially useful for understanding human development and disease, and is being explored as a source of organs that can be transplanted into humans (Hyun, 2016). The value of this research rests on the premise that we can learn more about human health and development, and create treatments for humans, by using nonhuman animal models that better approximate human biology without risking harm to humans.

This research raises many new ethical questions, which have dominated discussion so far. However, the most important ethical questions that it raises are old questions about the ethics of harmful, invasive nonhuman subjects research. Moreover, our assessment of new questions (for example, about whether to regulate chimera research on the model of human or nonhuman subjects research) requires an appreciation of old issues (for example, that our distinction between human and nonhuman subjects research is, itself, problematic). Thus, insofar as we frame the ethics of chimera research in terms of its new and distinctive features, we risk missing the most important ethical questions and distorting our analyses of the questions we consider.

Before we start, we should emphasize that we are not suggesting that everyone focuses only on new questions in ways that take already-existing practices for granted. However, we do think that this is a risk, and that insofar as it is, we should work to mitigate it.

2. The ethics of animal research

When people ask what concerns us about chimera research, our answer is simple: Chimera research is animal research, and animal research is often deeply morally problematic. In particular, many animal studies are harmful, lethal, non-consensual, non-therapeutic studies conducted on vulnerable populations with the aim of benefiting less vulnerable populations. This kind of research is generally highly morally problematic. Insofar as chimera research will take this form, it will likely be highly morally problematic as well.

We want to emphasize that the claim that this kind of research is morally problematic is not a minority position that follows only from an "extreme" animal rights position. Instead, it is a plurality position that follows from any reasonable set of assumptions about the moral status of animals and the ethics of research. There is now broad agreement that sentience, that is, the ability to experience pleasure and pain, is sufficient for moral status, and there is also broad agreement that all vertebrates and at least some invertebrates are sentient (Proctor 2012).

Thus, the question that concerns research ethicists now is not whether lab animals morally matter, but rather how much and in what ways they morally matter. But while experts still disagree about the answers to these questions, any reasonable set of views about these issues imply that our current treatment of most lab animals is deeply morally problematic. For example, consider two ethical issues about which experts still disagree, one concerning the nature of moral status and the other concerning the nature of right action.

First, experts still generally disagree about whether or not moral status exists in degrees. Some people think that it does not. We should assign equal weight to the interests of everyone,

independently of who they are or what social or biological category they occupy. On this view, we can say that some individuals have more well-being at stake than others, but we cannot say that the well-being of some individuals matters more than the well-being of others.

Other people think that moral status does exist in degrees. We should assign greater moral weight to the interests of some individuals, such as more "cognitively advanced" individuals, than to other individuals, such as the interests of less "cognitively advanced" individuals. On this view, we can say not only that some individuals have more well-being at stake than others but also that the well-being of some individuals matters more than the well-being of others.

Second, experts still generally disagree about whether or not we should be in the business of respecting rights or maximizing good outcomes. Some people think that we should be in the business of respecting rights (Regan, 2004). There are certain things that we should simply never do to each other, no matter how much good we can do in the world as a result.

Other people think that we should be in the business of maximizing good outcomes (Singer, 1977). We should attempt to bring about the greatest good for the greatest number by any means necessary. Thus, if we need to sacrifice some individuals for the greater good, we are not only morally permitted but also morally required to do so.

Importantly, many people seem to accept a non-scalar, rights-based conception of research ethics for humans and a scalar, consequentialist conception of research ethics for nonhumans. That is, many people seem to assign equal weight to the interests of all humans and think that humans have rights that we need to respect no matter what. Meanwhile, they assign greater weight to some nonhumans than to others and think that nonhumans do not have rights that we need to respect no matter what. These assumptions lead to higher ethical standards for human subjects research than for nonhuman subjects research, as reflected by the fact that Institutional Review Boards, which oversee human subjects research, apply higher ethical standards than Institutional Animal Care and Use Committees, which oversee nonhuman subjects research.

Some philosophers attempt to justify these different ethical standards. For example, Shelly Kagan argues that, while we should accept a scalar conception of moral status for everyone in theory, we should accept a non-scalar conception of moral status for people in practice and a scalar conception for animals in practice (Kagan, 2019). Similarly, Robert Nozick considers, as part of a thought experiment, the idea of "Kantianism for people, utilitarianism for animals." On this view, we should treat people as having rights that we should respect no matter what, and we should treat animals not as having rights but rather only as having interests that we should consider in a harm-benefit analysis (Nozick, 2013).

We do not believe that such views are promising. In our view, we need to apply a consistent set of ethical standards to our treatment of everyone, human and nonhuman alike. With that said, our present claim is only that, *even if* we accepted such views, it would *still* follow that the vast majority of harmful, lethal, non-consensual, non-therapeutic nonhuman subjects research is morally wrong. There are simply too many research subjects experiencing too much suffering, without nearly enough counterfactual benefit. Thus, even on the combination of views that most

justifies a moral divide between human and nonhuman subjects research, this moral divide should be much narrower than it currently is.

3. The ethics of chimera research

All the issues discussed so far are old concerns that people have about animal research in general, rather than new concerns that people have about chimera research in particular. We suggest here that the old questions are the most important ones, and are also essential context for proper consideration of the new questions.

To see why we make this suggestion, consider some of the new questions that chimera research raises. This list will not be exhaustive, but it will be enough to illustrate our point.

First, many people are concerned that chimera research involves playing God (Robert and Baylis, 2003). When we create chimeras, we are creating new beings and disrupting traditional species boundaries. In the process, we are violating the inherent dignity of the human form.

These are not particularly good reasons for opposing otherwise useful research. We already disrupt the species boundaries when we create plants through hybridization or implant nonhuman heart valves in humans, and we accept these ways of "playing God" because we see them as useful (though, of course, we should seriously consider the animal welfare questions raised in the latter case). It might be that we should accept other ways of "playing God" for similar reasons, provided that it treats all relevant stakeholders with respect and compassion. Granted, insofar as the public cares about disrupting species boundaries, we might need to address this issue to engage with the public and maintain public trust in science. But we should not be too concerned about this issue independent of the importance of public engagement and approval.

Second, many people are concerned that chimera research involves difficult classificatory questions. Suppose that we create an individual with 50% human and 50% nonhuman biological material. Should we classify this being as a human or nonhuman and, therefore, should we regulate this research according to human or nonhuman subjects research standards?

These questions are important, since current human and nonhuman subjects research standards are very different. We protect human subjects much more than nonhuman subjects. As a result, we would protect chimeras much more if we classified them as human subjects than if we classified them as nonhuman subjects for purposes of ethical review. However, as we noted in the previous section, the fact that we protect human subjects much more than nonhuman subjects is, itself, a moral problem. If we had a more consistent, species-egalitarian set of regulations that treated like cases alike (while still making distinctions across species insofar as different animals have different interests, needs, and vulnerabilities), then these classificatory questions would be revealed as much less important than they currently appear to be.

Third, many people are concerned about the long-term, indirect effects of engaging in chimera research. For example, suppose that we create knowledge about how to create a particular kind of chimera. Suppose that somebody then creates that kind of chimera and allows these individuals to escape the lab. What might the ecological effects of this series of events be?

These questions are important as well, since genetically modified plants and animals do escape controlled environments and enter wild populations, with pervasive and unpredictable impacts on ecosystems (Ellstrand, 2003; Kimman, Smit and Klein, 2008). As noted above, we do not always consider these kinds of long-term risks when we engage in harm-benefit analysis. If we took a more comprehensive approach to harm-benefit analysis, then we would rightly treat these kinds of long-term risks as important. Yet if we did that, then we would need to be open to the possibility that we should not pursue *in vivo* chimera research at all, since this kind of research imposes substantial risks and harms on humans and nonhumans alike, and it might not produce enough counterfactual benefits to justify these expected impacts.

As these examples illustrate, if we ethically assess new kinds of research in ways that consider only new questions and take for granted already-existing practices, there is a risk that we will (a) miss many important questions entirely and (b) distort our answers to the questions that we do consider. For example, if we ethically assess chimera research in this way, then we risk focusing more on, say, whether or not chimera research disrupts traditional species boundaries than on, say, whether or not chimera research involves serious welfare and rights violations. We might also miss the opportunity to consider other important issues, such as whether we should collapse the distinction between human and nonhuman subjects standards, and whether we should expand our application of harm-benefit analysis to consider a wider range of expected impacts.

This leads to a further risk, which is that our ethical assessment of new kinds of research will "humane-wash" these kinds of research. That is, there is a risk that we will extend the appearance of ethical legitimacy to fundamentally illegitimate practices. For example, if we ethically assess chimera research in a way that focuses on new issues and takes for granted already-existing practices, our assessment will probably conclude that chimera research is more or less ethically acceptable. If so, this would be deeply misleading. If chimera research is ethically unacceptable primarily because of features that it shares with other kinds of animal research, and if our assessments ignore these features, then our assessments will miss most of what makes chimera research ethically unacceptable.

4. Conclusion: Striking a balance

In light of these considerations, when a new kind of research emerges, we should attempt to strike a balance in our assessment of that kind of research in two related ways. First, we should strike a balance between discussing new issues and discussing old issues. Second, we should strike a balance between discussing short-term goals – that is, what to do given current, non-ideal practices – and discussing long-term goals – that is, what kinds of practices would be ideal and how to make incremental progress towards this ideal set of standards.

In the case of chimera research, a commitment to striking a balance between discussing new issues and discussing old issues means several things. First, we should discuss the problems with harmful, invasive animal research, and the reality that chimera research will inherit those problems. Second, we should discuss the problems with the distinction between human and nonhuman research standards, and the reality that current solutions – for instance, a policy that specifies which chimeras should be treated as "humans" and "nonhumans" for the sake of ethical

review – are only band-aid solutions. Third, we should discuss the limits of our current approach to harm-benefit analysis, and the reality that this approach will undervalue some of the risks of chimera research, including but not limited to the risk of ecosystem disruption.

Moreover, and relatedly, a commitment to striking a balance between discussing short-term goals and discussing long-term goals means several things as well. First, we should consider what our ideal research system might look like. In our view, this is a system that involves no harmful, lethal, non-consensual, non-therapeutic, nonhuman subjects research at all. Second, we should find solutions to our current problems that make incremental progress towards this long-term goal. In our view, this means at least not expanding the amount and variety of harmful, lethal, non-consensual, non-therapeutic, nonhuman subjects research. It might also mean unifying oversight of all research on living beings under one framework, with much higher ethical standards for harmful non-consensual research on sentient beings.

These considerations are especially important in the case of chimera research, given its formative stage of development and the path-dependence of research programs. It can take time to reduce harmful research that people are currently doing, since careers and institutions depend on it. However, it can be easier to stop a new kind of harmful research before it starts.

We currently have the opportunity to curb the development of harmful, lethal, non-consensual, non-therapeutic in vivo chimera research, but doing so requires more than attending to its new and distinctive features. We should prioritize attending to its old and familiar features, since this is where the vast majority of the harms and rights violations would be occurring.

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Conflict of Interest

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