Rethinking the Oversight Conditions of Human-Animal Chimera Research

ABSTRACT

New discoveries are improving the odds of human cells surviving in host animals, prompting regulatory and funding agencies to issue calls for additional layers of ethical oversight for certain types of human-animal chimeras. Of interest are research proposals involving chimeric animals with humanized brains. But what's motivating the demand for additional oversight? I locate two, not obviously compatible motivations, each of which provides the justificatory basis for paying special attention to different sets of human-animal chimeras. Surprisingly, the sets of animals that actually get flagged for special scrutiny by research and funding guidelines don't correlate with either of the sets of animals that arise when we think about what's motivating additional oversight. What this shows is that existing research policies and funding guidelines are disconnected from their motivation: the rationale for flagging certain types of human-animal chimeras as requiring special oversight is ignored in execution.

Keywords: animal welfare; human-animal chimera; public policy; research ethics;

INTRODUCTION

Although scientists have been making human-nonhuman chimeras[1] for some time, it has proven difficult for human cells to survive in their host for very long. As a result, most chimeras seem to be nothing more than animals hosting human cells, and these cells tend to give way to their host organisms fairly quickly. New discoveries, however, are improving the odds of human cells surviving in host animals indefinitely. As these odds increase and more human cells become incorporated into their hosts, one might naturally wonder whether humanizing animals

[1] When context is sufficient to establish meaning, I refer to human-nonhuman chimeras simply as chimeras. More frequently, however, I refer to them as human-animal chimeras because I find this turn of phrase less cumbersome.

creates new ethical quandaries. Views will of course vary, but the mere possibility of such humanization has prompted regulatory and funding agencies to issue calls for increased ethical oversight (and in some cases to outright ban or prohibit funding) for research involving certain types of human-animal chimeras. But why? What's motivating the demand for additional oversight? My aim in this paper is to answer these questions by locating and fleshing out in the literature two, not obviously compatible motivations, each of which provides the justificatory basis for paying special attention to different sets of human-animal chimeras. This will reveal something rather surprising, which is that the sets of animals that get flagged for special scrutiny by research and funding guidelines don't correlate with either of the sets of animals that arise when we think about what's motivating additional oversight. In other words, existing research policies and funding guidelines are disconnected from their motivation: the rationale for flagging certain types of human-animal chimeras as requiring special oversight is ignored in execution.

The paper begins by using a few experiments to show that the odds of human cells surviving in host animals are improving. Next, I explain the underlying rationale of regulatory and funding agencies for requiring additional oversight (and/or funding restrictions) of some forms of chimera research. As I'll show, there appear to be two, discordant justifications behind requirements for increased scrutiny. The first, which I'll call a 'capacity-based' rationale, argues that some forms of chimera research require additional ethical oversight because humanizing animals may alter their capacities, making them more human-like. On this basis, additional oversight is needed to ensure that animals with new capacities receive corresponding moral respect. The second, which I'll call 'lineage-based', argues that some forms of chimera research need increased scrutiny because injecting human cells into an animal host may serve to establish a lineage relation with human beings, a relation that is itself sufficient to warrant increased levels

of moral scrutiny. As I flesh out these two ways of justifying increased scrutiny of human-animal chimera research, I'll show that current policies and funding guidelines lose sight of them in application.

NEW AND IMPROVED HUMAN-ANIMAL CHIMERAS

Several experiments in the last decade show the potential of human cells to survive in nonhuman hosts. In one, Steven Goldman's team at the University of Rochester discovered that certain human cell types, particularly in the brain, might have a competitive advantage over animal cells. For example, after injecting human glial progenitor cells into immunodeficient neonate mice, Goldman's lab found that human cells were able to outcompete mouse glial progenitor cells (so that the white matter was largely of human origin) and that the engraftment of human cells enhanced synaptic plasticity and learning.[2] In another experiment, Martha Windrem and colleagues injected neonate mice with glial progenitor cells derived from schizophrenia patients. This time, the human-mouse chimeras exhibited schizophrenia-like behaviors, including excessive anxiety, antisocial traits, and disrupted sleep.[3] Glial progenitor cells may be unusual, however, so a number of scientists are trying to increase the survivability of other types of human cells. Current strategies involve "weakening" the host and/or "strengthening" the injected cells. One example of the former comes from Hiromitsu Nakauchi's lab at the University of Tokyo. In 2010, his lab used a technique known as interspecies blastocyst

[2] Han, X., Chen, M., Wang, F., Windrem, M., Wang, S., Shanz, S….Nedergaard, M. (2013). Forebrain Engraftment by Human Glial Progenitor Cells Enhances Synaptic Plasticity and Learning in Adult Mice. *Cell Stem* Cell. 12(3), 342-353.

[3] Windrem, M. S., Osipovitch, M., Liu, Z., Bates, J., Chandler-Militello, Zou, L….Goldman S. A. (2017). Human iPSC Glial Mouse Chimeras Reveal Glial Contributions to Schizophrenia. *Cell Stem Cell*. 21(2), 195-208.

complementation to modify the host in order to help injected cells thrive. Their initial experiment[4] involved growing a rat pancreas in a rat-mouse chimera, but scientists are working on using a similar technique to grow human organs inside large animals. The procedure requires genetically altering the embryo of a large animal (e.g., a pig) to prevent the development of a specific organ (or organs) and then injecting human pluripotent stem cells (derived from the patient in need of the organ) into the altered embryo to fill the vacant developmental niche. Weakening the host, however, isn't always the best strategy for increasing the survivability of human parts in a nonhuman host.[5] An alternative to weakening the host is to strengthen the injected cells. To do so, Nakauchi's team at Stanford injected cells with a "survival-promoting gene" that inhibits cell death.[6] So far, they've only tested this strategy on animal-animal chimeric embryos, but Nakauchi has submitted proposals to a government committee in Japan (which now allows culturing human-animal chimeras past 14 days and putting them into a uterus) to create human-mouse, human-rat, and human-pig chimeric embryos. What we see in all this, then, is a trend toward improving the ability of human cellular material to survive in animal hosts.

CAPACITY-BASED RATIONALE FOR ADDITIONAL OVERSIGHT

Experiments like those just mentioned raise their own ethical concerns (e.g., conducting harmful, invasive, nontherapeutic, and nonconsensual research on animals for the sake of

[4] Kobayashi, T., Yamaquchi, T., Hamanaka, S., Kato-Itoh, M., Yamazaki, Y., Ibeta M…. Nakauchi, H. (2010). Generation of rat pancreas in mouse by interspecific blastocyst injection of pluripotent stem cells. *Cell*. 142(5), 787-99. doi: 10.1016/j.cell.2010.07.039.
[5] Wu, J., Platero-Luengo, A., Sakurai, M., Sugawara, A., Gil, M. A., Yamauchi, T….Izpisua Belmonte, J. C. (2017). Interspecies chimerism with mammalian pluripotent stem cells. *Cell*. 168, 473-486.
[6] Servick, K. (2019). Embryo experiments take 'baby steps 'toward growing human organs in livestock. *Science*. Retrieved from https://www.sciencemag.org/news/2019/06/embryo-experiments-take-baby-steps-toward-growing-human-organs-livestock

humans, treating animals as factories for human parts, and so on), but they are for the most part familiar, and animal welfare committees have been trained to navigate them. But if we assume that such training is adequate, how do we explain the push by regulatory and funding agencies for additional ethical oversight of experiments involving human-animal chimeras? The answer is found in the observation that moral intuitions rely on different types of justification, that these justifications give rise to different moral categories, and that chimeric research tends to obscure these categories. Let me explain. It is broadly assumed that differences in organisms' capacities justifies differences in their moral status. For example, organisms that can feel pain are treated differently than organisms that cannot. Similarly, animals that possess the capacity for higher level cognitive functioning warrant moral consideration not merited by organisms that lack it. Tied to this assumption is the further one that such capacities are species specific. But although these two assumptions often travel together, they are distinct. If it is the capacity for higher order cognition that warrants additional moral protection, the category of things to receive that protection will be different than the category protected under the assumption that only human beings exhibit higher order cognition. In light of that fact, we should notice that lineage-based considerations frequently ground ethical deliberations. That an animal is, say, the direct descendent of a mouse justifies treating it differently than one that is the descendent of a horse, sheep, or human. Indeed, even if we go along with the assumption that moral concern for certain animals tends to be tied to their possession of certain species-specific capacities, it's rather obvious that this assumption frequently plays no role in moral deliberation. The human with unresponsive wakefulness syndrome doesn't receive moral protection because of his capacities, but rather because he is human. Here, then, the lineage relation serves as the basis of his moral status.

Chimeric animals promise to obscure both capacity-based and lineage-based categories. If transferring one organism's parts to another type of animal might enhance its cognitive functioning, we must be sensitive to that fact in order to ensure it ends up in the appropriate moral category. Similarly, if such transfers could alter an animal's lineage, and (for example) literally humanize it, we must consider that fact as well. Either way, chimeric research threatens to obscure moral categories used in ethical deliberation.

It will help to show how such categories are used to justify increased scrutiny of human-animal chimeras. As we work through the examples, I'll be fleshing out each rationale (i.e., capacity-based versus lineage-based) in a way that makes clear that regulatory bodies are losing sight of it when considering which sets of animals (chimeric and otherwise) warrant increased scrutiny. Turning, then, to the role of capacity-based judgements in our moral deliberations about human-animal chimeras: Committees are sensitive to the fact that different types of animals have different types of capacities and that these features are significant for determining how they should be treated. However, ethicists worry that some human-animal chimeras may exhibit subtle changes in capacities that fall outside the range of what's typical for the host species.[7] For example, suppose a human-mouse chimera exhibits a capacity for problem solving well beyond that exhibited by mice typical of its species. Given such an oddity, we might (I think rightly) worry that we've made the chimeric animal susceptible to new kinds of wronging not ensconced in or accommodated by current principles of regulatory bodies.[8] Since it may be hard to anticipate the needs of a mouse with a humanized brain or to recognize that a humanized mouse

[7] Hyun, I. (2016). What's Wrong with Human/Nonhuman Chimera Research? *PLoS biology*. 14(8), e1002535. doi:10.1371/journal.pbio.1002535; Hyun, I. (2018). The Ethics of Chimera Creation in Stem Cell Research. *Current Stem Cell Reports*. 4, 235-239.
[8] Streiffer, R. (2005). At the edge of humanity: human stem cells, chimeras, and moral status. *Kennedy Institute of Ethics Journal*. 15(4), 347-70.

is in distress, it seems reasonable to recommend additional oversight of some types of human-animal chimeric research.

In fact, a recent advisory report from the International Society for Stem Cell Research (ISSCR) reflects just this sort of thinking. It recommends building on existing Institutional Animal Care and Use Committees (IACUC) standards (or their equivalents outside of the U.S.) by paying special attention to changes in behavior outside of the typical range for the host species. Insoo Hyun describes the recommendation as follows:

> [C]himera review committees must add additional ethical standards only if something specific to stem cell research makes it necessary to do so. For example, current IACUC evaluations of animal welfare are conducted at a species-specific level … Past experience with genetically altered laboratory animals has shown that reasonable caution might be warranted if genetic changes carry the potential to produce new behaviors and especially new defects and deficits.[9]

Hyun is here saying that if review committees are going to ramp up their ethical standards, it needs to be on the basis of something specific that justifies doing so. He goes on to suggest that the potential of research projects to produce "new behaviors and especially new defects and deficits" in host animals is the sort of thing to be worried about. But surely that kind of potential is much too broad. Animals are regularly used as models of human diseases (or as models on which they test therapies for human diseases) and most of them display behaviors, defects, and deficits atypical of their species, yet we do not insist that they receive added regulatory

[9] Hyun 2018, op. cit. note 7, p. 237

oversight. We need narrower criteria, then, if we are to make sense of the idea that human-animal chimeras require special moral scrutiny.

One way to conceive of the narrower criteria is by looking at experiments with the potential to cause more harm to chimeric animals than similar experiments done using standard, non-chimeric animals. One such experiment consists of human-animal chimeras with enhanced cognitive capacities, or more specifically, "animals with chimeric brains [that] might develop human-like cognitive capacities."[10] Such an experiment would have the potential to create organisms susceptible to types of suffering not characteristic of their unmodified conspecifics. It is one thing to be sentient and thus capable of perceiving and responding to features of one's environment, it is another to be self-conscious. When poked, sentient animals sense pain and respond by trying to avoid it. Self-conscious creatures, in contrast, sense pain, respond by trying to avoid it, and are aware that they are in pain. They have a pain experience.[11] If an experiment enhanced a sentient animal's cognitive functioning by humanizing it, we might worry that it could acquire a capacity for self-consciousness, making it susceptible to new forms of suffering. Similarly, we might worry that the humanization of a chimeric animal's brain could result in the animal acquiring the capacity for mental time travel.[12] That is, we might worry that by humanizing an animal, we grant it the ability to anticipate future events, to reflect on past events, and to be harmed in virtue of these enhancements.[13] The pain of being poked is no longer here-and-now then gone; it is here, in the future, and in the past. In addition to suffering immediate

[10] Koplin, J. K., Wilkinson, D. (2019). Moral uncertainty and the farming of human-pig chimeras. *Journal of Medical Ethics.* 45, 440-446.
[11] Smith, J. (2017). Self-Consciousness. *The Stanford Encyclopedia of Philosophy* (Fall Edition). Edward N. Zalta (ed.). Retrieved from https://plato.stanford.edu/archives/fall2017/entries/self-consciousness/
[12] The capacity for mental time travel is thought to be unique to humans. See, for example, Tulving, E. (2005). Episodic Memory and Autonoesis: Uniquely Human? In H. S. Terrance & Metcalfe, J., *The missing link in cognition: Origins of self-reflective consciousness* (pp. 3-56). Oxford University Press.
[13] Varner, G. E. (2012). *Personhood, Ethics, and Animal Cognition: Situating Animals in Hare's Two Level Utilitarianism*. Oxford University Press.

pain, we might worry about creating creatures that—as a result of their capacity for mental time travel—will suffer anxiety, post-traumatic stress, and other mental hardships. Thinking about the possibility of creating organisms with sophisticated cognitive capacities, then, provides a more constrained rationale for increasing oversight of human-animal chimeric research.

In fact, the National Institutes of Health (NIH) used this line of reasoning to justify their 2015 funding moratorium on research involving various types of human-animal chimeras. When the NIH was pressed about the moratorium (which has not yet been lifted), it expressed its hesitation with interspecies blastocyst complementation as follows:

> Various types of chimeric animals have been used in research for a long time, but this new approach raises the question of whether human cells could contribute to or affect off-target organs. That outcome could be problematic from ethical and animal welfare perspectives, particularly if there are significant alterations of the animal's cognitive state.[14]

Public policy groups abroad have expressed similar worries. The National Academy of Sciences, UK Academy of Medical Sciences, Japanese Expert Panel on Bioethics, and German Ethics Council have all recommended that research involving chimeric animals with humanized brains should be subject to greater restrictions than other forms of chimera research.[15]

[14] The National Institutes of Health. (2017). Frequently Asked Questions on Chimera Proposal. *Office of Science Policy.* Retrieved from https://osp.od.nih.gov/wp-content/uploads/QA_Chimera_Policy_updated_1_Feb_2017.pdf

[15] See Koplin, J. K., Savulescu, J. (2019). Time to rethink the law on part-human chimeras. *Journal of Law and the Biosciences*. Retrieved from https://doi.org/10.1093/jlb/lsz005 for a table of international legislation on part-human chimeric embryos.

Notice that the rationale being offered by the NIH is capacity-based: it justifies the funding moratorium by appealing to the possibility of altering cognitive states that may affect the animal's welfare. And if the capacities possessed by an organism are in fact the basis of our moral concern, then this rationale makes perfect sense. Research oversight committees ought to ramp up their concern for post-transfer behavioral patterns that indicate the emergence of new cognitive capacities. That said, it's not obvious (on a capacity-based rationale) why merging or transferring peculiarly human cells matters. After all, on the capacity-based view, moral concern arises from the capacities possessed by an organism, not the source of the biological material that makes up that organism. And there is simply no obvious reason to believe human cell transfers are uniquely (or even more probably) capable of altering the cognitive capacities of animals to a degree that would require an appropriate adjustment in their ethical treatment. Consequently, if we use the capacity-based rationale for increasing oversight of chimeric research, it seems that the increased oversight ought to extend to all animal cell transfers, not just those involving human cell transfers.[16]

Let me illustrate this point with a hypothetical example.[17] Imagine two chimeric mice created by injecting cells into a host during early embryogenesis. The first is a human-mouse chimera and the second an elephant-mouse chimera. Assume further that each injection is expected to affect the brains of each chimeric mouse and that, indeed, both acquire a heightened capacity for empathy as a result of the transfer (the capacity is inferred by researchers after observing the abnormally empathetic behavior exhibited by the chimeric mice). Now, according

[16] DeGrazia, D. (2014). Persons, Dolphins, and Human-Nonhuman Chimeras. *The American Journal of Bioethics.* 14(2), 17-18; Piotrowska, M. (2014). Transferring Morality to Human-Nonhuman Chimeras. *The American Journal of Bioethics.* 14(2), 4-12; Sagoff, M. (2007). Further Thoughts About the Human Neuron Mouse. *The American Journal of Bioethics.* 7(5), 51-52.

[17] This is a modified version of my (Piotrowska, op. cit. note 16) *mouse*$_d$ and *mouse*$_h$ example.

to recommendations for additional oversight that we've looked at, even though both chimeric mice acquire the same capacity, making them both vulnerable to new forms of suffering, only the human-mouse research proposal would qualify for an additional layer of review. This, it seems to me, is straightforwardly incompatible with the idea that what warrants increased scrutiny of chimeric research proposals is the possibility of an animal acquiring new, morally relevant cognitive capacities. Instead, the general worry about chimeric animals developing new, enhanced capacities is being traded out for a different worry, which bottoms out in the fact that some chimeric animals have parts that originate from human beings and that may alter their lineage relations in morally relevant ways, as I will argue below.

What seems obvious, then, is that the rationale for increased scrutiny of some chimeric research is coming apart from its application: we're making appeals to enhanced capacities in order to justify increased scrutiny of chimeric research but ignoring those capacity-based considerations when deciding which sets of chimeric animals require increased scrutiny. If we believe that we ought to consider a creature's capacities when deliberating about how it should be treated, then it shouldn't matter if the creature in question is a human-animal chimera or an animal-animal chimera.[18] The consideration of paramount importance is what capacity the animal exhibits and that is what should figure most prominently in our moral deliberation, not the origin of the parts that may be responsible for the acquisition of that capacity. Consistency requires that the comparable interest of organisms, whatever those organisms may be, should be given comparable weight in our moral deliberations. This means that if both mice stand to acquire a heightened capacity for empathy post transfer, which might make the chimeras susceptible to new forms of wrongdoing, both research proposals ought to go through an

[18] Although see Piotrowska, op. cit. note 16, for a discussion of the epistemic role that the source of the cells might play, even if what one fundamentally cares about is their effect, and not their source.

additional layer of review. And it's worth noting that the same conclusion applies to human and animal gene transfers. If the justification for increased oversight rests on the possibility of a research project's likelihood of enhancing the cognitive capacities of its subjects, that oversight ought to extend to various chimeric and transgenic animals.

LINEAGE-BASED RATIONALE FOR ADDITIONAL OVERSIGHT

We've looked at one rationale for increased ethical scrutiny of chimeric research. Given this rationale, it's a mistake to focus exclusively on research involving human-animal chimeras. Or, rather, to do so is to fail to give application to the principles used to justify the added scrutiny. Even so, more often than not, existing oversight involving chimeric research seems guided by a rather rigid focus on human-animal chimeras. Let me put the capacity-based rationale to the side then in order to ask whether there are legitimate reasons for this preferred focus. One rationale for focusing exclusively on human-animal chimeras can be fleshed out by looking at an asymmetry in what oversight committees consider relevant when establishing guidelines for the ethical treatment of research subjects. Consider, on the one hand, an animal welfare committee such as an IACUC. Typically, IACUCs recognize the relation between a creature's capacities and the way the creature ought to be treated, which is why they already encourage researchers to use experimental subjects with less sophisticated cognitive capacities whenever possible. Even so, IACUCs allow even very cognitively sophisticated animals to be subject to research not permissible on human beings. It is an institutionalized fact that animal research oversight committees consider a very wide range of research objectives to justify sacrificing even the most fundamental interests of animals. The interests of elephants, mice, and

elephant-mouse chimeras, then, may all be sacrificed. This might well explain why no one is requesting additional layers of oversight for animal-animal chimeric research (or animal transgenic research) even when it has the potential to enhance the cognitive capacities of research subjects. Animal welfare committees already take into account what seems morally salient in these cases (i.e., the capacities of the animal subjects) and they seem well equipped to look out for the welfare of animals in research. And even if the welfare of some cognitively enhanced animal-animal chimera is trodden upon, it may nonetheless be justified. Why? Because it isn't human. It doesn't have the appropriate lineage.

Indeed, merely being human seems to accord research subjects special moral status. If the wrongs done to some animals were done to human subjects, it would be considered a significant oversight failure and would likely be met with rather swift and severe retribution. This fact demonstrates a fundamental asymmetry in the moral basis of oversight committees: the ethical basis of research involving animals is ultimately guided by what capacities a thing demonstrates, whereas research involving humans is fundamentally constrained by the fact that it involves humans. The institutionalized view (that of an Institutional Review Board (IRB) or its equivalent outside of the U.S.) is that human beings have special moral status, which provides them substantial moral protections, including very stringent prohibitions against research that may be harmful. To put it plainly, we cannot do to even the most incapable humans what we do to the most capable animals. No research objective can justify sacrificing the most fundamental interests of human beings.[19]

[19] The focus by regulatory bodies on human-animal chimeras might be mere anthropocentric bias, another expression of the type of speciesism that has worried people like Peter Singer. Perhaps. If so, it's worth emphasizing the controversial nature of such views: they tend to be fraught with philosophical difficulties. Be that as it may, I'm not going to engage those difficulties, choosing instead to focus on the considerations actually used by regulatory and funding agencies to justify asymmetrical treatment of different research programs. For a discussion of

This asymmetry marks the distinction between the capacity-based and lineage-based rationales used in moral deliberation. And it is this distinction that seems to weigh on oversight committees when thinking about chimeric research. It's not that human-animal chimeric research might produce new capacities that is ultimately worrying (because if it were, we'd extend moral protections to very capable animals[20] and remove them from very incapable humans), it's that such research may establish a lineage relation between the chimeric animal and human beings and with that relation would come an increased demand for moral attention. Given this difference in the moral status granted human research subjects versus their animal counterparts, the lineage-based rationale provides the justification needed for additional oversight of human-animal chimeras. This fact is sometimes obscured by concerns about the humanization of animal brains,[21] but those concerns ignore the fact that the cognitive capacities of human beings just don't influence their moral standing. Human beings don't have to have "human-like thought or consciousness" to warrant their higher moral status and benefit from the stringent protections of an IRB. They're given that status by default. From Robert Streiffer:

---

anthropocentric views for grounding moral status and alternative ways to do it see the relevant entry in *The Stanford Encyclopedia of Philosophy* and its extensive bibliography.

[20] Chimpanzees are one notable exception here. In recent years, they've gained additional protections from research, although still not equivalent to the protections granted to even the most incapable humans. See, for example, Nature. (2011). Great Ape Debate. *Nature*. Retrieved from https://www.nature.com/articles/474252a

[21] As an example of this, consider the reasoning used by the Animal Legal Defense Fund (Animal Legal Defense Fund. (2016). Urging the NIH to recognize that chimeric should be protected as human research subjects. *Animal Legal Defense Fund*. Retrieved from https://aldf.org/case/urging-the-nih-to-recognize-that-chimeric-should-be-protected-as-human-research-subjects-comments-to-nih-re-chimeras-and-transgenic-animals/) to urge the NIH that "chimeric should be protected as human research subjects." They write:

> In 2016, the Animal Legal Defense Fund submitted comments to the National Institutes of Health (NIH) urging the agency to recognize that chimeric and transgenic animals with humanized cognition should be protected as human research subjects, and ensure regular oversight by Institutional Review Boards (IRBs) in all NIH-funded research where enhanced cognitive ability in such animals is a possibility.

As well-intentioned as these recommendations may be, I believe the inclination to appeal to the potential enhanced cognitive capacities of research animals as the justificatory basis for treating human-animal chimeras as if they were human is a red herring. As things stand, the cognitive capacities of human beings have no bearing on their moral standing.

> [W]hen faced with an organism that has some human cells and some non-human cells, how is one to decide whether the organism is human, and hence, whether it is a human being? It is overly narrow to focus on transplants that affect neural tissue, since it is not plausible to suppose that an individual must have a human brain to be a human being: an anencephalic infant is a human being…[22]

Human beings are entitled to stringent protections in research not because they have one or another cognitive capacity, but because of a relational property. All human beings, regardless of their cognitive sophistication, are protected because they are appropriately connected to other members of the species *Homo sapiens*. And David Hull emphasizes what that connection amounts to in the following way:

> If species are taken to be the things which evolve, then they can and must be characterized in terms of ancestor-descendant relations, and in sexual species these relations depend on mating. The organisms that comprise sexual species form complex networks of mating and reproduction. Any organism that is part of such a network belongs to that species even if the characters it exhibits are atypical or in some sense aberrant.[23]

[22] Streiffer, R. (Summer 2019 Edition). Human/Non-Human Chimeras. *The Stanford Encyclopedia of Philosophy*. Edward N. Zalta (ed.). Retrieved from https://plato.stanford.edu/archives/sum2019/entries/chimeras/
[23] Hull, D. L. (1986). On human nature. In A. Fine & Machamer, P. K., *PSA 1986: Proceedings of the 1986 Biennial Meeting of the Philosophy of Science Association*, Vol. 2. (pp. 3-13) Philosophy of Science Association, East Lansing, Michigan.

We are part of the same species because of the way in which we are genealogically related to one another. It is this relational property, this lineage-relation that serves as the basis for the superior moral standing of human beings. At least, this is the basis of the institutionalized view that guides oversight committees to give research involving human subjects special scrutiny.

If I've fleshed out the actual rationale for many of the demands for additional oversight of human-animal chimeric research, we need to ask when (or whether) transfers of biological material might establish the morally worrying lineage relation, the relation that could elevate the status of an animal to that of a human being. This is a very difficult problem, but if we are going to give coherent application to the rationale motivating the demand for increased scrutiny of human-animal chimeric research, it is increasingly important that we find an answer to it. As things stand, there is no principled way to give application to the lineage-based rationale for demanding increased scrutiny of human-animal chimeras. That's probably because most of the experiments involving the transfer of human parts to nonhuman animals seem to have no chance of establishing a lineage relation between human beings and nonhuman research subjects. Consequently, chimeric researchers haven't thought very hard about when (or whether) transferring parts between animals establishes a lineage relation. But this could change if they begin to perform experiments that involve transferring parts between human and nonhuman animals in a way that could establish such a relation. Is that possible?

Intuitively, transferring biological material between organisms can be a process of either transplantation or reproduction. When part of an organism is transferred to another without producing a parent-offspring relation, on organism's part has been transplanted to another; when transferring parts establishes a parent-offspring relation, however, reproduction has occurred and a lineage relation has been established. Increasingly this intuitive distinction is being undermined

by advances in biological technology and what is becoming apparent is that 'transplantation' and 'reproduction' are not mutually exclusive, but rather, constitute two ends of a spectrum. At one end are material transfers that result in something akin to transplanting one animal part into another. At the other end are material transfers that result in parent-offspring relations, something akin to reproduction. Chimeric research frequently provides cases that don't clearly fall on either end of the spectrum, but some cases fall closer to the 'reproduction' end, providing insight into what it would take to establish a lineage relation between humans and chimeras.

In previous work[24], for example, I considered an experiment that involved pushing three young rhesus monkey embryos together to form one aggregate embryo.[25] The outcome was the birth of a rhesus monkey whose initial composition was the product of three different populations of cells, which contained the genetic material of six individuals. Intuitively, the offspring of this experiment bear a genealogical relation to all six individuals, thus being an instance of a rather peculiar sort of reproduction. Similarly, if scientists were to combine early embryonic material of different species to produce a new chimeric embryo, the resulting experimental subject would seem to bear genealogical relations to both species, thereby acquiring the moral protections (assuming there were any) established by both relations. Whether this would be the case, however, requires clarity about the concept of 'reproduction' and when (or whether) reproduction has occurred. There are a number of scholars that have offered

[24] Piotrowska, M. (2019). Why is an Egg Donor a Genetic Parent, but not a Mitochondrial Donor? *Cambridge Quarterly of Healthcare Ethics.* 28, 488-498.
[25] Tachibana, M., Sparman, M., Ramsey, C., Ma, H., Lee, H. S., Penedo, M. C., & Mitalipov, S. (2012). Generation of chimeric rhesus monkeys. *Cell*. *148*(1-2), 285–295. doi:10.1016/j.cell.2011.12.007

accounts of 'reproduction'[26] but none of the existing accounts are being used to ground lineage-based considerations for oversight of chimeric research.

But even if they were, the lineage-based rationale for increased scrutiny of some chimeric entities still seems to be inconsistently applied. If the justification for increased moral scrutiny of some chimeric animals is that they bear a certain relation to human beings (whatever that comes to), then singling out research that transfers biological material with the potential to affect the brain is a mistake. Such transfers are no more likely to be lineage-altering than other types of transfers. At least, according to our best theories of reproduction, there's no reason to believe that potentially-brain-altering transfers are more likely to produce a lineage relation than other kinds of transfers. Relying on the lineage-based rationale, then, chimeras with humanized brains shouldn't get flagged for special scrutiny. Instead, the transfers that ought to be flagged are the lineage-altering ones.[27]

CONCLUSION

Let me conclude with a summary of my argument. Experiments that have increased the odds of human cells surviving in animal hosts have prompted regulatory and funding agencies to

[26] Babcock, G. (2019). Are Synthetic Genomes Parts of a Genetic Lineage? *The British Journal for the Philosophy of Science*, axz046, https://doi.org/10.1093/bjps/axz046; Griesemer, J. (2000). Development, Culture, and the Units of Inheritance, *Philosophy of Science* 67 (Supplement. Proceedings of the 1998 Biennial Meetings of the Philosophy of Science Association. Part II: Symposia Papers), S348–S368; Mertes, H., Pennings, G. (2008). Embryonic Stem Cell-Derived Gametes and Genetic Parenthood: A Problematic Relationship. *Cambridge Quarterly of Healthcare Ethics.* 17/1, 7-14; Piotrowska, M. (2018). Is 'Assisted Reproduction 'Reproduction? *The Philosophical Quarterly.* 68(270), 138-157.

[27] It might seem reasonable to include chimeras with human gametes in the set of research proposals requiring additional oversight on the lineage-based justification. However, I don't include them for the reasons offered by Hank Greely. According to Greely, the idea that human and animal gametes could form an embryo or that two chimeras could mate, each with complementary human gametes, and produce viable human offspring inside an animal uterus is highly unlikely, if not "scientifically bizarre" (Greely, H. T. (2011). Human/Nonhuman Chimeras: Assessing the Issues. In T. L. Beauchamp & Frey, R. G. *Oxford Handbook of Animal Ethics* (pp. 671-98). Oxford: Oxford University Press).

issue calls for additional layers of ethical oversight. Of interest are research proposals involving chimeric animals with humanized brains. I have located two not obviously compatible motivations driving the requirements for increased scrutiny of chimeras. On the capacity-based rationale, additional oversight is needed to ensure that the possible development of new capacities receives corresponding moral respect. But this rationale is ignored in execution. Animal-animal chimeras and transgenics are as likely to acquire new capacities as human-animal chimeras but the former are not flagged for special oversight. On a lineage-based rationale for increasing oversight of chimeras, injecting human cells into an animal host may serve to establish a lineage relation with human beings, a relation that is itself assumed to be sufficient to increase moral scrutiny. But this rationale is also ignored in execution because transfers that are likely to humanize the brain (i.e., the ones currently under the radar of regulatory and funding agencies) aren't any more likely to produce a parent-offspring relation between the human donor and the animal recipient than other types of transfers. What I hoped to have shown, then, is that the set of animals that actually get flagged for special scrutiny don't map onto either set of animals arising by thinking about the rationale of increased oversight of human-animal chimeric research. Consequently, existing research policies and funding guidelines are disconnected from their motivation.