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The Unknown of Human Animal Chimera Research

Alessandro Luna
Stanford University

Abstract

Human-animal chimera research has potential benefits for physiological modeling, neural analyses, and organ harvesting, the last of which is particularly relevant for the organ donor market in the U.S. However, ethical debates have scrutinized the necessity of such research while 119,000 people await organ transplants in the U.S. alone. Beyond ethical interpretations, a pressing issue of public safety not previously considered is the likelihood of introducing diseases that can jump across species. Research needs to address how cross-species diseases can propagate. Human-animal chimera researchers need to understand and prevent such unintended outcomes, making exploration into the mechanisms and factors determining disease jumps across species of primary concern moving forward.

Human-animal chimera research has potential benefits for physiological modeling, neural analyses, and organ harvesting, the last of which is particularly relevant for the organ donor market in the U.S. The ability to study and model human functions *in vivo* opens up a new realm of possibilities for scientists and clinicians to serve patients better with new therapies that could far surpass current medicines and treatments.

The benefits of human-animal chimera research are marked by potential dangers: its implications beckon a bioethical analysis across a clinically applicable paradigm. Indeed, since the purpose of studying human-animal chimeras is to ultimately benefit humankind, the analysis requires specific attention to future benefactors while acknowledging the necessity of animals ceded for the cause. Expanding on the Belmont Report's framework of respect for persons, beneficence, and justice is necessary in addressing the novel challenges posed by human-animal chimera research (Department of Health, Education, and Welfare, 1979). Thus, ethically grounded questions of medicine are categorized in the following four categories: medical indications, patient preferences, quality of life, and contextual features (Jonsen, Siegler, and Winslade, 2010). Specific ethical questions can be addressed within these organized divisions.

First, medical indications concern how a treatment improves the welfare of a patient. This category is further defined by the principles of beneficence and nonmaleficence: pursuing helpful actions and avoiding those that cause harm (UCSF School of Medicine Office of Educational Technology, 2008). In the case of research with human-animal chimeras, the purpose is to understand human patients better so that medicine and therapies can treat them more efficiently and efficaciously, minimizing unnecessary efforts while optimizing desired outcomes. In this sense, the ethical dilemma is a question of whether or not human-animal chimeras can improve patient lives. The answer is difficult, because such research is still being developed and is not currently funded by the NIH (National Institutes of Health, 2016). A significant patient need that could be addressed by developments in human-chimera therapies would be growing organs for transplantation. Surprisingly, in January 2017 researchers at the Salk Institute confirmed the viability of human pluripotent stems cells surviving and proliferating in pig embryos (Wu et al., 2017). However, the embryos were smaller than normal; the limited contribution of human cells presented a technical barrier to embryo success in pig models. The "evolutionary distance" between humans and animals currently hinders

creation of true human-animal chimeras (Vogel, 2017). The jury is still out, but research charges forward.

Second, patient preference will play a major role in the acceptance of human-animal chimerism. Patient autonomy stands as the overarching premise for which ethical positions are made. For example, should a patient be informed if the medical therapies they receive have been developed through human-animal chimera research? If organ transplantation becomes possible through chimerism, would a patient be receiving a suboptimal treatment if they opt out? For example, Catholic moral teachings justify "xenotransplantation" to benefit mankind, but preclude "unnecessary animal suffering" and "genetic modifications that could significantly alter the biodiversity and balance of species," terms which may elicit rejection of chimeric organs on an individual basis (Vatican, 2001). Furthermore, if a patient opts out, would they receive any treatment at all? More than 119,000 people are waiting for organ transplants in the U.S. alone; organs from chimeras could benefit these people, but only if they choose to accept it (U.S. Department of Health and Human Services, 2015). Chimeras could have a positive effect on organ transplant availability, but further implications include chimeras wholly supplanting organ donors. Patient preferences are tied to beliefs and values that will affect the rate at which chimeras provide transplantation opportunities for the organ donation market. Relatedly, NIH also released guidelines regarding the technicalities behind future human-animal chimera research in attempts to eventually lift the moratorium (National Institutes of Health, 2016). The details are less important than the implications of revisions to previous ethical boundaries. Organizations may continue to refine the limits of research in order to achieve a perceived good that misaligns with the ethical principles of communities.

Third, determining the ethics behind changes to quality of life intricately builds upon previous medical indications and patient preferences. Knowing the principles of beneficence, nonmaleficence, and respect for autonomy—what are the prospects for individuals benefitting from human-animal chimeras? Will this research exclude certain communities based on predispositioned barriers? If therapies produced from human-animal chimerism become sanctioned medical services, how does their effectiveness rank them on a costs versus benefits scheme? Dr. Sean Wu, Associate Professor of Cardiovascular Medicine at Stanford University, predicts that this research may need $500 million in further funding to produce clinically significant chimeras for organ harvesting (Wu, 2017). However, compared to the $2 billion average cost to develop

immunosuppressant drugs for transplant recipients and an estimated $100,000 annual cost to the patient, chimeric organ harvesting presents strong financial and clinical advantages (Wu, 2017). If the drug route is selected, patients can expect a lifetime of medications. Conversely, the $80,000 procurement cost for a single heart transplant could be decreased with an alternative chimeric transplant, and there would be no need for immunosuppressants, saving patients and healthcare providers money in the long run (United Network for Organ Sharing, 2017). If chimera organ transplantation reaches a level of clinical applicability, it could address a well-documented need. On the other hand, it is an ethical disservice to offer therapies that do not improve patient quality of life above a statistically significant level. This problem is compounded by the ethical implications of implementing such services in the first place.

Fourth, contextual features concerning the bioethics of human animal chimera research focus on the principles of justice and fairness. Consider the previous conflicts of interest behind funding this type of research; the NIH currently holds a moratorium whereas private organizations can choose to fund it (Kaiser, 2016). Research developments then depend on private interests that may not align with public interests. Public interests could reject projects such as chimera organ harvesting or neurological enhancement studies. However, contention between public versus private funding is not a new development. For example, nearly 70% of U.S. clinical trials are funded by private companies ("Who Pays For Science?", 2017). Furthermore, public interests may not always align with public investments in research. For example, people may not agree with publicly funded research of ancient literature at an academic institution if they feel there is more value in reallocating funds towards cancer care. Taxpayer funds can support a wide spectrum of research that some individuals might ethically reject for a number of reasons ("Who Pays For Science?", 2017). Private funding does face the risk of supporting research advancements in dangerous directions. Since science has been historically supported by private entities, the research itself must adhere to bioethical principles regardless of the funding mechanism. This stipulation also applies to human-animal chimeras. Regarding the principle of justice, religious issues often reach the forefront of the debate (Jonsen, Siegler, and Winslade, 2010). Certain groups may find that the sanctity of human nature is interrupted; other ethical concerns include violation of human dignity, disregard for interspecies mixing, and possible moral confusion regarding the organisms produced as a result of chimerism (Hermeren, 2014).

One paramount issue of public safety not previously considered is the likelihood of introducing diseases that can jump across species. These zoonotic diseases are defined as infectious diseases transmitted from animals to humans (Minnesota Department of Health, 2017). Indeed, Dr. Wu states that cross-species diseases are the main concern for researchers studying human animal chimeras. Beyond determining the humanness of a chimera, fully comprehending the possibility of disease propagation will be the most pressing issue researchers face. Along the principles of beneficence and nonmaleficence, stakeholders in human-animal chimera research will need to verify that such transplantation scenarios do not carry with them the vehicle for zoonotic diseases traveling into the human domain. The unintended consequence of a cross-species disease jump presents itself as the most immediate problem of human-animal chimeras, both ethically and epidemiologically. Nonetheless, humans can also harm animals in the process of chimera research.

From a different perspective, the animals that are part of chimera research are subject to the will of the researchers. Researchers impose objectives on animals without much regard for their rights and consciousness. Currently, humans rank their cognition and sentience as highest among the animal kingdom, making animals "lower" species. However, what happens when the integrity of species alters due to changes in their perceived intelligence? If chimera research extends into the intertwining of human and animal neural capacities, the lines between human and animal may become blurred (Hermeren, 2014). When cognition and self-awareness are large factors in our defining characteristics, the implications of sharing these unique qualities with other species has vast impacts on the role and distinctness of humankind. Dr. Haiyan Lee, Professor of East Asian Languages and Cultures at Stanford University, compares the current state of human-animal chimerism to a philosophical fable. "If you have a ship, and you replace each of its planks one by one, eventually all of the old planks will be replaced. Do you still have the same ship?" (Lee, 2017). Relating this example to chimeras, Dr. Wu says that scientists are still deciding how many cells an organism needs to be deemed a human. The fact that we experiment on animals for human benefit speaks to our similarity, but we reject their moral and emotional capacities as dissimilar (Lee, 2017).

Nonetheless, humans have always relied on animals throughout history. "We have never been 100% human," says Dr. Lee. Indeed, humans have used animals for food, livestock, hyde, transportation, and

work (Lee, 2017). Chimera research is pushing the boundaries of our animalian dependencies amidst the biomedical possibilities of neurorestorative therapies and organ transplantation. Although true human-animal chimeras fit for organ harvesting are far off, the serious implication that needs to be considered by all stakeholders, beyond human-animal dichotomy interpretations, is preventing cross-species diseases. Preventing the spread of cross-species diseases becomes paramount when considering the bioethical principles of beneficence, nonmaleficence, and patient quality of life; human-animal chimera research will need carefully planned safety regulations and testing in the coming years.

This conclusion leads to two specific recommendations. First, a specific research question that should be addressed is how cross-species diseases can propagate. Some of the most prominent examples include Ebola, H5N1 influenza A, and the emergence of HIV/AIDS in humans from primates nearly 70 years ago (Parrish et al., 2008). Previous research has shown disease transmission can occur when interspecies proximity is reduced and external physiological barriers are inhibited (Parrish et al., 2008). In the case of human-animal chimeras, both proximity and physiology are sidestepped when mixing stem cells. Further exploration into the mechanisms and factors determining disease jumps across species is of primary concern moving forward. Second, investments made into studying these mechanisms and factors must be concomitant with research advances in human animal chimeras. Transmission and adaption of diseases must be understood to interpret the epidemiological implications for disease propagation resulting from human-animal chimera research. In line with the bioethical analysis, human-animal chimera researchers need to understand and prevent unintended outcomes with foresight derived from these recommendations to eliminate any uncertainty surrounding human animal chimeras. The safety and success of this biomedical revolution depends on it.

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