Partial Humanity
Ethical considerations in the use of chimeric pigs for human organ transplantation

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Chimera
1a (capitalized): a fire-breathing she-monster in Greek mythology having a lion's head, a goat's ody, and a serpent's tail
b: an imaginary monster compounded of incongruous parts

2: an illusion or fabrication of the mind; especially:
-an unrealizable dream
-a fancy, a chimera in my brain, troubles me in my prayer —John Donne
-His utopia was a chimera.

3: an individual, organ, or part consisting of tissues of diverse genetic constitution
-A hybrid created through fusion of a sperm and an egg from different species is a chimera.
In 2015, there were 122,000 people on the waiting list to receive an organ transplant but only 31,000 transplants were performed, leaving twenty-two people to die every day waiting for a transplant. [1] It is unlikely that this gap between supply and demand will ever be eliminated through human donation alone. Advances in stem cell biology are now raising the hope of a novel but ethically controversial solution to this organ deficit: Growing human organs in animals.

With conceptual roots in Greek mythology describing a chimera as a creature “composed of the parts of more than one animal,” a genetic chimera is “a single organism made up of cells of different embryonic origins.” [2] There is preliminary evidence that it will soon be feasible to induce the growth of human organs within genetically chimeric, otherwise non-human animals. Once current technical limitations and safety concerns are resolved, chimeric organ production could represent a major advance toward interspecies organ transplantation, otherwise known as xenotransplantation.[3] The potential benefits of this endeavor are compelling and could expand the pool of available organs via chimeric production, xenotransplantation would stand to save a great number of lives and could fundamentally change the experience of end-stage organ failure.

Before realizing these potential benefits, however, ethical concerns unique to this nascent area of research must be clarified and addressed. These include issues such as the perceived unnaturalness of blurring species lines and what obligations of moral status are owed to animals with human-like cognition. Here, we critically evaluate these matters and argue that partially-human chimeric organ donors should be granted certain moral protections in accordance with currently accepted principles of transplant ethics.

**Recent Advances in Chimeric Organ Production**

On January 26, 2017, the journal *Cell* published the results of a breakthrough experiment. [4] Researchers at the Salk Institute had injected human induced pluripotent stem cells (iPSCs) into a pig blastocyst (or, a ball of cells early in development). They transferred the mostly-pig, partly-human blastocyst into a surrogate sow. After 21 to 28 days of gestation, the scientists concluded that the human iPSCs had established human cell lines within the originally pig-derived embryos.

Just the day prior to the *Cell* publication, *Nature* reported that Professor Hiromitsu Nakauchi’s team at the University of Tokyo were successful in the use of similar techniques in other animals. Nakauchi and his colleagues were able to grow a functional mouse-derived pancreas within a rat-mouse chimera.[5] The scientists removed the mouse-pancreata from the rat-chimera and transplanted them into mice with chemically-induced
diabetes. The chimeric-organ recipients demonstrated normal glucose regulation over the subsequent year. Even more remarkably, immunosuppressant therapy was discontinued after post-operative day five.

Taken together, these reports suggest it is possible to grow human-derived organs in chimeric pigs using existing methodologies. Researchers hope that chimeric transplants might even improve upon the current long-term risks of transplantation. Scientists could select the human iPSCs based on immunogenicity of the recipient, thereby minimizing the auto-immune reaction of the recipient to the organ. This would render post-transplant immunosuppression unnecessary, relieving recipients of the lifelong risk of organ rejection.

Research into chimeric transplantation has the potential to solve the problem of organ scarcity, conferring vast societal benefits. However, introducing pluripotent human stem cells to non-human embryos could have undesirable consequences. Some commentators argue that chimeric transplantation research is unethical under some circumstances, others may believe that this line of research is inherently unethical, regardless of the consequences. Broadly, these concerns fall into three categories: (1) that partially human chimeras might reproduce and create offspring with novel genome combinations; (2) that human-derived neurons confer chimeras with human-like cognition; and (3) that human-appearing chimeras could seem to gain qualities of human nature. Professor Hank Greely, director of the Stanford Program in Neuroscience and Society. colloquially summarizes the three concerns, respectively, under the epithet “balls, brains, and beauty.”

The Moral Status of Humanlike Cognition

The ethical justification for the use of animals to our own ends relies on the lesser moral status of non-human entities. It is unjustified to treat any living entity in a way incommensurate with its moral status. [6] Whether the introduction of human-derived elements affects the moral status of animals is therefore a salient question. [7] If so, chimeric entities are owed more stringent protections than their animal counterparts.

To have moral status is to be entitled to be treated as a being whose existence is morally relevant and therefore must be respected. A species’ moral status is often equated with its capacity for mental life. This would be problematic if chimeras have brains that are partially human because moral status is assigned in degrees based on the capacities and experiences that an organism is capable of enjoying. Bugs, for example, are hardly sentient and thus have few interests or experiences that can be wrongfully thwarted. By extension,
they are owed few obligations. Humans, by contrast, are capable not only of feeling pain, but also of relationships, of generating knowledge and culture, and of harboring plans and aspirations.

Some argue that such mental capacities, in particular, underlie humankind’s heightened moral standing over animals with lesser cognition. This sentiment is reflected in the ethical guidelines for animal research. For example, the primates have the most human-like cerebral cortices in the animal kingdom and are therefore afforded the most stringent protections from harm. The Academy of Medical Sciences in the United Kingdom permits research on primates only if there are no other means of achieving a valuable scientific objective, but its criteria for use of non-primate animals are more permissive.[8] Accordingly, insofar as chimeras develop human-like brains and consciously experience the world as humans do, it stands to reason that chimeras are also entitled to mankind’s moral protections.

The morally-salient cognitive capacities of chimeras might be affected if human-derived stem cells differentiate into neural tissue. In 2013, Steve Goldman’s lab showed that chimeric mice engrafted with human-derived glial progenitor cells performed significantly better on tests of learning and cognitive function than non-engrafted chimeric mice.[9] Thus chimeric donors with partially human neural architecture could merit a special moral standing relative to their wild-type counterparts.

Some might respond that aspects of cognition which might confer chimeras with a moral status similar to that of humans—capacities such as sentience, self-awareness, sociality, memory, executive functions, language, or abstract thought—would likely require a substantial proliferation of human-derived neural progenitor cells. However, the effect of human iPSCs on chimeric cognition is not well understood; less so in cortically-sophisticated mammals like the pig. It is far from clear how anyone would demonstrate that the presence of human iPSCs have no effect on the phenomenological experience of chimeric pigs. Presuming that partially human chimeric pigs have a heightened moral status would show appropriate humility considering this epistemic limitation.

These issues might be partially addressed by the development of a method to restrict the fate of pluripotent stem cells to non-neural cell lineages.[10] Another method further constrained the fate of stem cells by knocking out another pathway involved in neural differentiation.[11] A combination of such approaches could help manage the risk that human neural progenitor stem cells are present during embryogenesis, weakening this line
of ethical concern. However, cells migrate around the body throughout life, and some types of stem cells are programmed to periodically migrate across the blood-brain-barrier. Assumptions about chimeric pigs’ mental life are still far from certain.

**Caution in Crossing a Natural Divide**

A second source of ethical concern relates to the possibility that chimeras give birth to human offspring. In theory, at least, only two human-derived gametes are sufficient for two partially-human chimeras to conceive a fully-human zygote. If this were to occur, how would the transplant community respond? There is no ethically-obvious answer, and the situation could invite public backlash. This concern can be addressed proactively through laboratory measures which prevent human iPSCs from differentiating into germ line cells or taking developmental trajectories that lead to their incorporation in reproductive organs. Insofar as no human-derived cells become viable gametes in chimeras, this ethical objection is empirically unsubstantiated.

This threat is compounded by our limited *a priori* understanding of the relevant biology. Human-derived cells capable of reproduction could be sustained in chimeras through unanticipated mechanisms. For example, the Beltsville pigs—engineered to express a human gene associated with growth—suffered multiple unforeseen symptoms including diarrhea, lethargy, skin and eye problems, and constant arthritic pain.[12] The risks of human gamete formation should be ameliorated or eliminated before chimeric experimentation is allowed to further develop.

Finally, this field of research might seem to violate the biological boundary that distinguishes our species from all others. These human-defining characteristics or genes may seem to have a special sanctity, whether because they exist naturally or were created by God. Crossing interspecies boundaries appears to usurp divine authority or artificially intervene in the natural order.[7]

Questions of naturalness have been probed in bioethical debates ranging from in-vitro fertilization to genetic enhancement. These arguments have led many ethicists to conclude that the property of naturalness, considered on its own, is not directly relevant to moral worth. After all, artificial light is unnatural and yet society understands electricity as a common good. Likewise, it is natural that some human pancreata catastrophically fail, yet the synthesis of artificial insulin was a monumental and ethically-uncontroversial discovery. Medicine itself has been praised as “the comprehensive attempt to frustrate the course of nature.”[13] Worries over naturalness might reflect deeper anxieties about the proper limits of human intervention into our own nature.
Morally Salient Considerations in Procurement Versus Allocation

The ethics of organ procurement highlights the moral obligations owed to organ donors. The permissibility of organ procurement is considered independent of the potential benefits of transplantation because donors do not stand to gain personal health benefits from surgically-invasive organ procurement. As a result, organ procurement must respect a donor’s autonomous preferences in order to justify the harms realized in the absence of proportional medical benefit.[14]

The transplant system operationalizes these ideals through strict adherence to the doctrine of informed consent and the dead donor rule (DDR). The DDR stipulates that it is always impermissible to cause the death of a donor through organ procurement.[15] This is meant to respect the principle of nonmaleficence. [16] Similarly, standards for informed consent ensure that organ donation occurs only when this honors the donor’s preferences, reflecting respect for the dignity and autonomy of donors.[17]

In sum, organ procurement is framed by deontological duties to the donor, not the consequential benefits of transplantation. Nonmaleficence and dignity are particularly salient to the ethics of human organ donation and procurement. But these are principles meant for the fully human. What changes when the donor is chimeric?

Procurement in the Case of Chimeric Donors

How does the prospect of chimeric xenotransplantation fit within current ethical frameworks for organ transplantation? Should ethical standards for the DDR and the doctrine of informed consent apply to chimeric donors? While partially-human chimeric donors are entitled to fewer moral protections than competent adults, they share morally-salient characteristics with humankind.

Although the standards for informed consent applicable to human organ donors are poorly suited to these circumstances, we suggest that chimeric organ procurement should nevertheless adhere to the dead donor rule. Enhanced cognition notwithstanding, chimeric pigs would lack the capacity to make complex medical decisions. When human patients are incompetent, healthcare proxies make decisions based on what patients would normally choose for themselves. If an incompetent human’s preferences are unknown, requirements for informed consent are replaced by a best-interest standard wherein decision makers seek to promote the presumed interests of the individual.[18] This model attempts to respect the dignity of individuals who lack capacity to make decisions concerning their welfare.
Even if chimeric pigs cannot express granular preference in, say, an advanced directive, a population of chimeric pigs would certainly share some basic interests. After all, we can infer that as a living being, a chimera’s set of interests include that of continued life with respectable living conditions; realizing this interest is foundational to the pursuit of all other interests.[19] Similarly, chimeras have an existential interest in not suffering from intolerable environmental exposures or inadequate perioperative analgesia. The duty to promote these interests derives directly from the moral status of the chimeric donors. While the doctrine of informed consent as applied to chimeras fails to operationalize the principle of autonomy, adherence to the best-interest standard would promote the same ethical imperative: that organ procurement should promote or at least protect donor dignity.

The principle nonmaleficence is particularly salient to organ procurement. Chimeric pigs stand to gain even less than humans from transplantation. Without benefit, the principle of nonmaleficence holds greater comparative stringency.[20] Insofar as the DDR operationalizes the duty not to harm, and insofar as this obligation is owed to beings with moral status, the norm ought to be respected for chimeric organ donors. In other words, animals should not be intentionally killed through organ harvesting in accordance with the DDR. This could delay the societal benefits of this technology because researchers would have to develop techniques so that human-derived vital organs like the heart have not simply taken the place of endogenous organs. However, respecting this ideal helps ensure that chimeric organ procurement promotes human flourishing in a way that is not predicated on carrying out atrocities on the beings who enable our lives to be saved or extended. In other words, observing this ideal enables us to flourish on a morally sound foundation.

To knowingly allow chimeric donors to die post-donation would violate the spirit of the DDR. Therefore, chimeric donors also ought to be housed in a responsible manner and must not be deprived of the conditions required for a decent post-donation existence. Likewise, in light of the stringent *prima facie* duty of nonmaleficence under the circumstances of donation, the transplant community is morally obligated to make every effort to minimize chimeric suffering, pain, or other forms of harm.

**Conclusion**

It may soon be feasible to derive organs of human origin from chimeric animals. Currently, safety concerns preclude such operations, yet the time is ripe to consider associated ethical issues. We have argued that crossing species boundaries is not inherently unethical and that questions of enhanced moral status do not arise unless substantial cognitive
capacities are conferred to the chimeras. Nevertheless, it is of utmost importance that the welfare and interests of chimeric donors be respected to the highest degree possible throughout their life, including peri- and post-operatively. Finally, we have stressed the importance of observing the DDR in the context of chimeric xenotransplantation. Should these conditions be met conscientiously, such chimeras may yet grant many transplant candidates the gift of life, without having to lose theirs in the process.

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