36

Cells, Animals and Human Subjects

Regulating Interspecies Biomedical Research

Amy Hinterberger and Sara Bea

36.1 INTRODUCTION

The availability of new cellular technologies, such as human induced pluripotent stem cells (iPSCs), has opened possibilities to significantly 'humanise' the biology of experimental and model organisms in laboratory settings. With greater quantities of genetic sequences being manipulated and advances in embryo and stem cell technologies, it is increasingly possible to replace animal tissues and cells with human tissues and cells. The resulting chimeric embryos and organisms are used to support basic research into human biology. According to some researchers, such chimeras might be used to grow functional human organs for transplant inside an animal like a pig. These types of interspecies biomedical research confound long-established regulatory and legal orders that have traditionally structured biomedicine. In contexts where human cells are inserted into animal embryos, or in the very early stages of animal development, regulators face a conundrum: they need to continue to uphold the differences in treatment and protections between humans and animals, but they also want to support research that is producing ever-more intimate entanglements between human and animal species.

In research terms, human beings fall into the regulatory order of human subjects protection, a field of law and regulation that combines elements of professional care with efforts to preserve individual autonomy.[1] Animals, however, belong to a much different regulatory order and set of provisions relating to animal welfare.[2] To this end, animals have been used, and continue to be used, for understanding and researching human physiology and disease where such experiments would be unethical in humans. Researchers can do things to animals, and use animal cells, tissues and embryos in ways that are very different from human cells, tissues and embryos. Traditionally, ethical concerns and political protection have focused on the human subject in biomedical research, with ensuing allowances to address animal welfare and human embryos. However, such divisions are now under immense strain and are undergoing substantial revision. This chapter investigates these transformations in the area of interspecies mammalian chimera. We ask: what forms of regulation and law are drawn on to maintain boundaries between human

[1] For a current discussion of human subject regulation see: I. G. Cohen and H. F. Lynch (eds), *Human Subjects Research Regulation: Perspectives on the Future* (Cambridge, MA: MIT Press, 2014).

[2] For a current discussion of animal welfare regulation see: G. Davies et al., 'Science, Culture, and Care in Laboratory Animal Research: Interdisciplinary Perspectives on the History and Future of the 3Rs', (2018) *Science, Technology, & Human Values*, 43(4), 603–621.

https://doi.org/10.1017/9781108620024.044 Published online by Cambridge University Press

research subjects and experimental animals in interspecies research? What kinds of reasoning are explicitly and implicitly used? What kinds of expertise are invoked and legitimised?

We will begin with a brief overview of the chimeric organisms in the context of new cellular technologies. We will then explore significant national moments and debates in the UK and USA that highlight the tacit presumptions of regulatory institutions to explore where disagreement and contestation have arisen and how resolutions were reached to accommodate interspecies chimeras within the existing regulatory landscape. Through these national snapshots, the chapter will explore how human–animal chimeras become objects of regulatory controversy and agreement depending on the concepts, tools and materials used to make them. The final sections of the chapter provide some reflections on the future of chimera-based research for human health that, as we argue, calls forth a reassessment of regulatory boundaries between human subjects and experimental animals. We argue that interspecies research poses pressing questions for the regulatory structures of biomedicine, especially health research regulation systems' capacity to simultaneously care for and realign the human and animal vulnerabilities at stake within interspecies chimera research and therapeutic applications.

36.2 FROM DISH TO ANIMAL HOST

Chimeric organisms, containing both human and non-human animal cells, sit at the interface between different regulatory orders. The 'ethical choreography' that characterises health research regulation on interspecies mixtures is densely populated with human and animal embryos, pluripotent stem cells, human subjects and experimental animals.[3] Much depends on the types of human cells being used, the species of the host animal that will receive the cells, along with age of the animal and the region where human cells are being delivered. Regulation thus includes institutional review board approval for using human cells from living human subjects. There also needs to be approval from animal care and use committees that assess animal welfare issues. Depending on the country, there might also be review from a stem cell oversight committee, which must deliberate on whether the insertion of human cells into an animal may give it 'human contributions'.[4] There are significant national differences in regulatory regimes, making for diverse legal and regulatory environments at both national and international levels because countries regulate human and animal embryos, stem cells and animal welfare very differently.[5]

In the biological sciences, the term chimera is a technical term, but it does not necessarily refer to one specific entity or process. Generally speaking, chimeras are formed by mixing together whole cells originating from different organisms.[6] It is a polyvalent term and can refer to entities resulting from both natural and engineered processes.[7] Historians of science have explored how species divides, especially between humans and other animals, are culturally

[3] C. Thompson, *Good Science: The Ethical Choreography of Stem Cell Research* (Cambridge, MA: MIT Press, 2013).
[4] As discussed below, the term 'human contributions' is used in the NAS Guidelines for stem cell research oversight.
[5] See, for example, I. Geesink et al., 'Stem Cell Stories 1998–2008', (2008) *Science as Culture* 17(1), 1–11; L. F. Hogle. 'Characterizing Human Embryonic Stem Cells: Biological and Social Markers of Identity', (2010) *Medical Anthropology Quarterly*, 24(4), 433–450.
[6] For a history of the use of the term chimera in developmental biology and stem cell science see: A. Hinterberger, 'Marked 'H' for Human: Chimeric Life and the Politics of the Human', (2018) *BioSocieties*, 13(2), 453–469.
[7] On natural chimerism see: A. Martin, 'Ray Owen and the History of Naturally Acquired Chimerism', (2015) *Chimerism*, 6(1–2), 2–7.

https://doi.org/10.1017/9781108620024.044 Published online by Cambridge University Press

produced and historically situated both inside and outside the laboratory.[8] The regulatory practices we explore in this chapter are not separate, but rather embedded in these larger structures of cultural norms about differences – and similarities – between humans and animals. As the life sciences continue to create new types of organisms, there are currently many groups and regulatory actors in different countries involved in producing definitions and forms of regulation for new human-animal mixtures. As we will see below, it is precisely the debates over the naming and classification of these new entities where the regulatory boundary work between the human and animal categories is illuminated.

36.3 ANIMALS CONTAINING HUMAN MATERIAL

In the following two sections, we will explore national snapshots from advisory and regulatory bodies in the UK and USA. We will examine how they are confronting issues of responsibility and jurisdiction for boundary crossing entities that cannot easily be siphoned into the traditional legal and regulatory orders of either human or animal. We will show that while each country's response via report or guidelines focuses on the human and animal division as primary to maintain in research practices, they each provide different solutions to the problems raised by interspecies mammalian chimera. These two sections of the chapter thus illuminate how interspecies chimera confound long-standing regulatory divisions in health research that challenge the law's capacity to simply encompass new entities.

In 2011, the UK's Academy of Medical Sciences released what is regarded as the first comprehensive recommendations to regulate the creation and use of chimeric organisms, called *Animals Containing Human Material*. The central conclusion of the Academy's report is that research that uses animals containing human material is likely to advance basic biology and medicine without compromising ethical boundaries. The report itself was part of a much longer history of deliberation around the status of the human embryo in the UK where specific forms of human–animal mixtures have been proposed, debated and, in the end, legislated. The UK regulatory landscape is significant in this respect as no other nation has written into law human–animal mixtures – which in UK law are called 'human admixed embryos'. The term human admixed embryo was introduced in 2008 amendments to the Human Fertilisation and Embryology Act 1990 (HFE Act). While it was the 'cybrid embryo' debate that became the most controversial and well-known related to these new legal entities, the legislation outlines a number of different kinds of human and animal mixtures that fall under its remit, including chimeric embryos. According to the Act, a human admixed embryo is any embryo that 'contains both nuclear or mitochondrial DNA of a human and nuclear or mitochondrial DNA of an animal but in which the animal DNA *does not predominate*'.[9]

A 2008 debate in the House of Lords over the revised HFE Act and the term 'human admixed' highlights the classification conundrums of how boundaries between human and animal are drawn. The Parliamentary Under-Secretary of State for the Department of Health explained, regarding the term 'human admixed embryo': 'It was felt that the word "human" should be used to indicate that these entities are at the human end of the spectrum of this research'.[10] Responding to this notion of the spectrum, the Archbishop of Canterbury responded that:

[8] For a recent account see: N. C. Nelson, 'Modeling Mouse, Human, and Discipline: Epistemic Scaffolds in Animal Behavior Genetics', (2013) *Social Studies of Science*, 43(1), 3–29.
[9] Human Fertilisation and Embryology Act 2008 (emphasis added).
[10] UK House of Lords debate, 15 January 2008, Column 1183.

https://doi.org/10.1017/9781108620024.044 Published online by Cambridge University Press

> 'the human end of the spectrum' seems to introduce a very unhelpful element of uncertainty. Given that some of the major moral reservations around this Bill . . . pivot upon the concern that this legislation is gradually but inexorably moving towards a more instrumental view of how we may treat human organisms, any lack of clarity in this area seems fatally compromising and ambiguous.[11]

This lack of clarity referred to by the Archbishop, which may 'be fatally compromising', sought to be addressed by the *Animals Containing Human Material* report.[12] Clarity, in this case, is provided by carefully considered boundaries and robust regulation, to remove elements of uncertainty. In the UK, the Human Fertilisation and Embryology Authority (HFEA) is the central body responsible for addressing proposals for embryo research in the UK. It is the body that licenses human embryonic stem cell research, oversees IVF treatment and the use of human embryos.

Violations of the licensing requirements of the HFEA are punishable under criminal law, which is both a literal and symbolic marker of respect for the conflicting and contested views on embryo research in the UK.[13] However, the HFEA only has jurisdiction over human embryos (not animal embryos). Research on animal embryos is governed and regulated by an entirely different body, The Home Office, which regulates the use of animals in scientific procedures through the Animals (Scientific Procedures) Act 1986 (ASPA).

Assessing whether the human or animal DNA is most predominant may be harder with chimeric research embryos since their cellular make-up may change over time. Thus, it can become unclear whether their regulation should fall within the remit of the HFEA or the Home Office. Any mixed embryo judged to be 'predominantly human' is regulated by HFEA and cannot be kept beyond the 14-day stage, whereas currently in the UK an animal embryo, or one judged to be predominantly animal, is unregulated until the mid-point of gestation and can in principle be kept indefinitely. Whether or not an admixed embryo is predominantly 'human' is, according to the Academy's report, an expert judgement. However, it recommended that the Home Office and HFEA, two government bodies that had not previously been connected, needed to work together to create an operational interface at the boundaries of their new areas of responsibility.

The Academy report purifies, both through language and regulatory approach, ambiguities raised by chimeric organisms by trying, as best as possible, to compartmentalise research into human or animal regulatory orders. The term 'animals containing human material' itself highlights this goal. According to the report, animals containing human material are animals first and foremost. In this respect, the report places the regulatory responsibility for these new chimeric entities squarely in the already regulated domain of animal research. To this end, the UK remains a highly regulated but permissive research environment for different types of chimera-based research, and is the only country to formerly write into law the protection of biological chimeras containing human and animal cells.

36.4 ASSESSING 'HUMAN CONTRIBUTIONS' TO EXPERIMENTAL ANIMALS

Unlike the UK, in the USA there is no formal legal regulation of interspecies chimera research. The 2005 National Academy of Science (NAS) Guidelines continue to be the cornerstone of

[11] Ibid.

[12] The Academy of Medical Sciences, 'Animals Containing Human Material', (2011).

[13] S. Franklin, 'Drawing the Line at Not-Fully-Human: What We Already Know', (2003) *The American Journal of Bioethics*, 3(3), 25–27.

https://doi.org/10.1017/9781108620024.044 Published online by Cambridge University Press

scientific research involving embryos, stem cell biology and mammalian development. The Academy is not a governmental agency, nor does it have enforcement power but the guidelines are viewed to be binding by governmental and institutional authorities. The NAS guidance acts as the principal reference on the recommendations applicable to research using interspecies chimera involving human embryonic stem cells and other stem cell types.

Stem Cell Research Oversight (SCRO) committees are the localised bodies that put into action the NAS Guidelines. During the stem cell controversies that characterised the USA, the Academy recommended that all research involving the combination of human stem cells with non-human embryos, fetuses, or adult vertebrate animals must be submitted to not only the local Institutional Animal Care and Use Committee (IACUC) for review of animal welfare issues, but also to a Stem Cell Research Oversight (SCRO) Committee for consideration of the consequences of the 'human contributions' to any non-human animal.[14] Thus, SCRO committees need to meet to discuss any experiment where there is a possibility that human cells could contribute in a major organised way to the brain or reproductive capacities particularly.

In late September 2015, the National Institutes of Health (NIH) in the USA declared a moratorium on funding chimeric research where human stem cells are inserted into very early embryos from other animals. However, like other instances where federal research monies were removed from controversial research – e.g. human embryonic stem cell lines – such research continued, but with private monies. The moratorium was met with scepticism and criticism of researchers working in this domain who, in a letter to *Science*, argued that such a moratorium impeded the progress of regenerative medicine.[15] Following a consultation period in 2016, the NIH announced that it would replace the moratorium with a new kind of review for specific types of chimera research, including experiments where human stem cells are mixed with nonhuman vertebrate embryos and for studies that introduce human cells into the brains of mammals – except rodents, which will be exempt from extra review.

As the UK's predominant predicament demonstrated, currently it is difficult to predict how and where human cells will populate in another species – when cells are added at the embryonic or very early fetal stages of life. This predicament was recently characterised as the problem of 'off-target' humanised tissues in non-human animals.[16] Currently, animal embryos with human cells are only allowed to develop for a period of twenty-eight days – four weeks – in the USA. As we explained above, animal embryos fall under a separate legal and regulatory structure from human embryos, which traditionally have been allowed to develop for fourteen days, though this number is subject to increasing debate (see McMillan, Chapter 37 in this volume).[17] In practice, this means that assessments of human contributions to an animal embryo are restricted to counting human cells in an animal embryo. Current published research puts the human contribution to the host animal embryo at 0.01–.1.[18] This is primarily because a chimeric embryo is only allowed to gestate for twenty-eight days.

[14] National Academy of Sciences 'Final Report of The National Academies' Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to The National Academies' Guidelines for Human Embryonic Stem Cell Research', (National Academies Press, 2010).

[15] A. Sharma et al., 'Lift NIH Restrictions on Chimera Research', (2015) *Science* 350(6261), 640.

[16] I. Hyun, 'What's Wrong with Human/Nonhuman Chimera Research?' (2016) *PLoS biology*, 14(8).

[17] See: B. Hurlbut, *Experiments in Democracy: Human Embryo Research and the Politics of Bioethics* (Columbia University Press, 2017); G. Cavaliere, 'A 14-day Limit for Bioethics: The Debate over Human Embryo Research', (2017) *BMC Medical Ethics*, 18(1) 38.

[18] T. Rashid et al., 'Revisiting the Flight of Icarus: Making Human Organs from PSCs with Large Animal Chimeras', (2014) *Cell Stem Cell*, 15(4), 406–409.

https://doi.org/10.1017/9781108620024.044 Published online by Cambridge University Press

In 2017, privately funded researchers in the US published findings from the first human–pig embryos. While labs have previously created human–animal chimeras, such as mice transplanted with human cancer cells or immune systems or even brain cells, this new experiment was unique because the researchers placed human stem cells — which can grow to become any of the different types of cells in the human body — into animal embryos at their earliest stages of life. Broadly, the making of these human–pig chimeras included collecting pig zygotes (eggs), that were then fertilised *in vitro* to become blastocysts – a progressive phase in embryonic development. Human induced pluripotent stem cells were then pipetted into the developing pig embryo that had been genetically modified. That embryo was then put into a female pig and left to develop for twenty-eight days. After twenty-eight days the animal was sacrificed, and the entire reproductive tract of the animal removed and studied to see where the human cells developed and grew in the embryo.

This study, and others like it, raised ethical concerns relating to 'off-target' humanised tissue with concern for an animal's central nervous system (brain) and reproductive capacities. In the below excerpt, the study leader explains how these concerns of 'off-target' humanisation can be handled in the development of human-pig chimeric embryos:

> . . . we must pay special attention to three types – nerves, sperm and eggs – because humanizing these tissues in animals could give rise to creatures that no one wants to create . . . We can forestall that problem by deleting the genetic program for neural development from all human iPSCs before we inject them. Then, even if human stem cells managed to migrate to the embryonic niche responsible for growing the brain, they would be unable to develop further. The only neurons that could grow would be 100 percent pig.[19]

Scientists are developing a variety of techniques to ensure 'on target' organ complementation so that a fully human organ can be grown inside an animal, and to avoid any 'off-target' problems that could potentially confer human qualities to the non-human experimental animal.

Possible ethical breaches relating to human research subjects and chimeras have been intensely discussed by scholars; however, until recently, concerns over animal welfare have largely taken a back seat in the regulatory and ethical debates over interspecies chimera. When we turn from the regulation of stem cells to the regulation of the organism – or animal – a new set of concerns open. The overwhelming emphasis on avoiding risky humanisation by measuring and counting the number of human cells in a non-human animal can obfuscate the crucial discussion about how animal welfare staff members might monitor changes in behaviour and attributes of experimental chimeric animals. For example, bioethicist Insoo Hyun[20] has argued that people tend to assume the presence of human cells in an animal's brain might enhance it above its typical species functioning. This 'anthropocentric arrogance' is, he points out, completely unfounded.[21] Why, he asks 'should we assume that the presence of human neural matter in an otherwise nonhuman brain will end up improving the animal's moral and cognitive status?'[22] The much more likely outcome, he suggests, of neurological chimerism is not a cognitive humanisation of the animal but 'rather an increased chance of animal suffering and acute biological dysfunction and disequilibrium, if our experience with transgenic animals can be a guide'.[23]

[19] J. C. I. Belmonte, 'Human Organs from Animal Bodies', (2016) *Scientific American*, 315(5), 32–37, 36.
[20] Hyun, 'What's Wrong with Human/Nonhuman Chimera Research?'
[21] Ibid., 3.
[22] Ibid.
[23] Ibid., 4.

https://doi.org/10.1017/9781108620024.044 Published online by Cambridge University Press

Animal care and use committees are less interested in cell counts and more interested in whether potential 'human contributions' may cause unnecessary pain and distress in an animal. Further, the question of how 'human contributions' might be measured in the behaviour of non-human animals is difficult and requires expert knowledge related to the species in question. If highly integrated chimeras are allowed to develop, the role of animal husbandry staff will be crucial in assessing and monitoring the behaviours and states of experimental animals – thus, animal behaviour and animal welfare knowledge may be a significant emerging component of measuring 'humanisation' in health research regulation.

36.5 SHIFTING REGULATORY BOUNDARIES BETWEEN CELLS, HUMAN SUBJECTS AND EXPERIMENTAL ANIMALS

As a domain of science that is continually reinventing and reconceiving the human body and its potentials, the futures of stem cell science and its regulation is not easy to predict or assess. However, it is in this context of ambiguity and change that we situate our discussion. First, theoretically and conceptually, chimera-based research has given rise to new living entities, from 'animals containing human material' to 'human contributions to other animals' that challenge assumed regulatory boundaries, rights, and protections provided for human subjects in contemporary societies. By tracing out how the categories human and animal are enacted in health research regulation we have shown that interspecies chimera requires a double-move on the part of regulators and researchers: animals must be kept animals, and humans must be kept humans. From this vantage point, we can see that interspecies chimera are not so marginal to health research regulation. The regulatory deliberations they elicit require re-examining the most basic and foundational structures of contemporary biomedical research – both human subjects research regulation, and animal care and welfare.

In health research regulation, animals are often defined in law; however, what constitutes or defines a human subject is generally not written down in law or legislation. What constitutes the human is, almost always, taken for granted or tacit regulatory knowledge. The national snapshots we examined here encompass Euro-American political and cultural contexts where regulatory containers, such as the human research subject, are shown to be potentially variable – or at least, drawn into question. For example, deliberations in the USA over what constitutes a 'human contribution' to another animal brings to light how the human subject is not a universal given, but a legal and regulatory designation that has the potential to be made and remade. Scientists, policy-makers and regulators approach the category human and animal differently across cellular and organismal levels, showing that these categories do not precede health research regulation but are actively co-produced within it.

Second, on the technical front, our review of current scientific practice shows how life scientists increasingly work according to the consensus that life is a continuum where species differences do not travel all the way down to the level of cells and tissues, thus destabilising assumed species differences and raising new questions about cell integration and containment across species. Third, politically, we are witnessing increasing agitation around both human and animal rights, in a context where bioscience is taking a significant role in the public sphere by not only informing debates about what life is, but also what life should be for.[24]

The stem cell techniques we have discussed above were first developed not with human materials but with animal. While dilemmas over the humanisation of other animals may appear

[24] S. Jasanoff, *Can Science Make Sense of Life?* (Cambridge, UK: John Wiley & Sons, 2019).

https://doi.org/10.1017/9781108620024.044 Published online by Cambridge University Press

to be new, these technical possibilities only exist because of previous animal research, such as the creation of mice–rat chimeras. For example, rat embryonic stem cells were injected into a mouse blastocyst carrying a mutation that blocked the pancreas development of a mouse, resulting in mice with a pancreas entirely composed of rat cells. These rat–mouse chimeras developed into adult animals with a normal functional pancreas, demonstrating that xenogeneic organ complementation is achievable.[25] Recent media coverage of the first human—pig interspecies chimera can conceal from view these longer and less discussed histories of biological research. To come to grips with the regulatory dilemmas elicited by interspecies chimera then, we must be attentive to biomedical research itself and the many kinds of living organisms used to advance scientific knowledge and to develop therapeutic applications for human health problems.

As we have shown, the USA established new private committees where members must assess whether an experiment might give 'human contributions' to experimental animals. Whereas governance in the UK clearly defines and names new legal and regulatory categories such as 'human admixed embryo' or 'animals containing human material'. In contrast, the phrasing 'human contributions' in the USA is suggestive of more of a spectrum rather than new legal and regulatory containers for boundary-crossing biological objects, such as in the UK. Chimeric organisms embody new articulations about the plasticity of biology and the recognition that assumed species differences do not travel all the way down to the molecular level. Consequently, explicit deliberations for regulation and governing procedures are also pushed and pulled in new directions. This remodelling of boundaries in biological practice and state governance has consequences for humans and animals alike.

36.6 CONCLUSION: REALIGNING HUMAN AND ANIMAL VULNERABILITIES

With the advent of new and sophisticated forms of human and animal integration for the study of disease, drug development and generation of human organs for transplants, keeping the human separate from the animal, in regulation, becomes increasingly difficult. The disruptions posed by interspecies chimeras give rise to growing conundrums as disparate regulatory actors try to accommodate chimeric entities within existing health research regulation structures that enact a clear division between the human/animal opposition.

In Europe and North America, the regulation of therapeutically oriented biomedicine has historically been split into two vast and abstracted categories: human and animal. Numerous legal and regulatory processes work to disentangle human material, bodies and donors from organisms and parts categorised as animal. Regulators and policymakers thus find themselves in a tricky situation needing to sustain the regulatory and legal estrangement between humans and other animals, while facilitating basic and applied research on human health – such as the kind described above – that relies on the incorporation of human and animal material in new biological entities.

Our explorations above suggest that health research regulation will need to be sufficiently reflexive on the limits of boundaries that reify the foundational human/animal division and be flexible enough to allow a re-consideration of classificatory tools and instruments to measure the extent and consequences of prospective interspecies chimera research. If human/animal chimeras provide to be an efficient route to engineering human organs, as opposed to genetically

[25] T. Kobayashi et al., 'Generation of Rat Pancreas in Mouse by Interspecific Blastocyst Injection or Pluripotent Stem Cells', (2010) *Cell*, 142(5), 787–799.

https://doi.org/10.1017/9781108620024.044 Published online by Cambridge University Press

modified pigs or organoids,[26] then the humanisation of experimental animals will likely develop further. An ethical and effective health research regulation system will need to be simultaneously reactive and protective of both human and animal vulnerabilities at stake.

In practice, this implies that regulatory efforts could be directed at fostering and maintaining dynamic collaborative relationships between regulatory actors that often work separately, such as stem cell research oversight, human subjects and animal care and use committees. Establishing efficient communicative pathways across disparate regulatory authorities and institutional bodies will demand a mutual disposition to consider and incorporate divergent and emerging concerns. The collaborative relationships should also be invested in the development of novel regulatory tools capable of addressing the present and coming challenges raised both at the level of the cell and at the level of the organism by interspecies research. This means going beyond the existing instruments to measure 'human contributions' at the cellular level to monitor 'on target' human organ generation as well as 'off-target' proliferation of human tissue in experimental animals. Collaboration between regulatory actors that have traditionally operated separately would also need to integrate the knowledge and expertise from animal behaviour and welfare professionals, such as animal husbandry staff.

A learning health research regulation system that operationalises the multi-level collaborative relationships across regulatory actors complemented by the introduction of animal care experts would be better prepared to engage in the disruptions that interspecies chimera research poses to existing regulatory mechanisms, actors, relations and tools. The direction and increased traction of stem cell biotechnologies clearly signposts that the development and growth of human health applications of interspecies chimera research requires a gradual intensification of entanglements between animals and humans. Health research regulation will thus need to reflect on the ethical and practical consequences for experimental animals' and human research subjects' vulnerabilities and address the shifting boundary between experimental animals and human subjects in biomedicine to make room for the new life forms in the making.

[26] S. Camporesi, 'Crispr Pigs, Pigoons and the Future of Organ Transplantation: An Ethical Investigation of the Creation of Crispr-Engineered Humanised Organs in Pigs', (2018) *Etica & Politica/Ethics & Politics*, 20(3), 35–52. Latest predictions are that a combination between genetically modified pigs and interspecies chimera organogenesis could deliver regenerative medicine solutions for transplantation, see F. Suchy and H. Nakauchi, 'Interspecies Chimeras', (2018) *Current Opinion in Genetics & Development*, 52, 36–41.

https://doi.org/10.1017/9781108620024.044 Published online by Cambridge University Press