Nuclear transfer: an example of responsive epistemologies*

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Keywords: Epistemologies, embryonic stem, mammalian cloning, nuclear transfer.

Introduction

IN this article I will focus on some recent developments in the field of mammalian cloning (nuclear transfer). In particular, I will trace the emergence of experimental practices and laboratory artefacts that have been developed with the explicit aim of solving some of the ethical dilemmas posed by cloning and embryonic stem (ES) cell research. My aim is not a bioethical critique of these approaches to test whether they do solve the ethical problems they are supposed to address. Rather, I am interested in the implications of these practices for the development of molecular biology as a discipline and for its role in contemporary society. For the past two decades, the conflation of genetic engineering with molecular developmental biology has started to generate across all model organisms novel entities that reflect our increased ability to reshape living forms. The potential application to humans of this same technology has attracted increased attention from the public at large and from a variety of institutions that have been called upon to regulate and tame altogether the plurality of options arising at the intersection of assisted reproduction, regenerative medicine and molecular genetics.

Here I discuss the genesis and implementation of altered nuclear transfer (ANT) as a revealing example of these emerging experimental practices and laboratory artefacts in which political and ethical considerations are intermingled with the experimental practices in ways that are much tighter and deeper than in the past, raising both social and epistemological questions about the place of molecular biology today. But let me first start by outlining the relevance of nuclear transfer (NT) and the reason why it can be a productive place to look at the dynamics of the joint work through which life science, law and politics make and shape order in technological societies.

*This article was originally published in the *Proceedings of the Max Planck Institute for the History of Science* (G. Testa, Nuclear Transfer: An Example of Responsive Epistemologies, *Preprint 310 of the Proceedings of the Max Planck Institute for the History of Science*, 2006, pp. 205–214) and is reprinted here with kind permission from the Max Planck Institute for the History of Science.

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Why nuclear transfer?

There are two reasons for choosing NT as a significant topic for this analysis. First, and most obviously, cloning has polarized the debate on the possibilities and limits of scientific inquiry like few other topics in the history of life sciences. It is significant because, quite simply, political communities worldwide have thought and cast it as highly significant, devoting substantial efforts to its regulation as testified most recently by the UN resolution on cloning[1]. Thus, through its high-profile political career, cloning joined a 'club' of scientific objects, from climate change to the ozone hole, that are of concern for the whole planet.

The second reason why cloning is significant is less political and touches the epistemological level. If we look at the discourse on cloning across a wide range of contexts, from the way in which scientists themselves describe it, to the way in which the topic appears in the public debate, we can easily identify a clear line of demarcation between the 'reproductive' and the 'therapeutic' aspects of the technology. Basically all discussions about cloning eventually resort to the same set of distinctions: generative versus regenerative, reproductive versus therapeutic. Faced with an experimental result deemed till then impossible by the overwhelming majority of the research community, it is as if both practitioners and observers of this 'impossible' development tried to make sense of it by looking at its potential application. But the fact that a scientific object or an experimental practise is defined according to its application is not simply a sign of its technological maturity, but a distinctive feature shared by many entities of modern biology. It points to what Rabinow identified as a hallmark of modern rationality: 'The object to be known – the human genome – will be known in such a way that it can be changed'. In the case of cloning, we could actually say that the object is known only because it can be changed, making the artefact arising from nuclear transfer, perhaps an even stronger example of Rabinow's conflation through which 'representing and intervening, knowledge and power, understanding and reform, are built in, from the start, as simultaneous goals and means'[2]. Thus, if we look at NT as a way to reprogramme the mammalian genome towards a variety of possible fates (cloned cells, cloned embryos, cloned individuals, etc.), our ways of ordering all these

fates, of telling them apart, of enabling some while disabling some others, speaks to the impossibility of defining the NT thing independently from our intervention. What is the NT 'thing'? Is it an extension of a patient's body or is it an embryo? It is certainly a prototype for so many artefacts in modern biology which, quite physically, do not exist in 'nature' prior to our intervention but which, once created, force us to reassess life and its developmental trajectories from within, sorts of distorted mirrors that are able to interrogate nature exactly because of their being technologically manipulated. Marcus Aurelius' suggestion to 'ask of each particular thing what it is in itself, what is its nature' would not bring us very far in the case of NT, as indeed with many products of the molecular life sciences. The NT thing does not have an essence, it is, quite literally, nothing 'in itself'. That is to say that it does not have an essence so long as we do not decide what counts to define it. Is it important where it is coming from? In this case, it could well be thought of as a pure act of human ingenuity. Or is it important where it is going? But what does it mean 'where'?

In this respect, NT appears paradigmatic for what has been identified as one of the key features of modern biology, namely the fact that living forms are studied from and become themselves living laboratories[3]. In a sense, this turns upside down, and eventually obliterates, the *in vivo*/*in vitro* distinction that has characterized so much of modern biology. The *in vitro* experiment interrogates nature from the outside, through a process of controlled imitation that aims at understanding the naturally given through levels of increased approximation. The *in vivo* experiment on the other hand, especially with the options of genetic engineering, is modern in the 'Rabinowian' sense, it interrogates nature from within, aiming at understanding the naturally-given through the creation of a parallel nature. And this parallel nature, these engineered living forms defy traditional attempts of classification exactly because they arise from precise interventions, and as we shall see, the more subtle and precise the intervention, the less certain becomes the classification.

Furthermore, these are not exotic questions for scholarly contemplation. It is exactly by giving answers to such questions that courts and parliaments around the world regulated the science and technology of cloning, and the answers were expectedly different and varied, reflecting differences in the institutions and in the discourse in which these answers developed[4,5].

Thus, it is against the backdrop of the inherent malleability of modern biological artefacts that I now turn my attention to new entities that are called upon to solve ethical problems through technological means.

Altered nuclear transfer

In December 2004 William Hurlbut, a physician and ethicist from Standford and member of the President's Council on Bioethics presented to the Council a proposal that would enable to harness the power of cloning and embryonic stem cell technology while circumventing the ethical quandaries associated with the destruction of human embryos. His explicit aim was to provide a 'technological solution to our moral impasse', since 'a purely political solution will leave our country bitterly divided, eroding the social support and sense of noble purpose that is essential for the public funding of biomedical science'[6]. His diagnosis of a bitterly divided country was certainly correct, and can be dated at least as far back as Roe v Wade. And against the backdrop of these seemingly irreconcilable weltanschaungen Hurlbut situates the need for a technological solution. His proposal (referred to as ANT for Altered Nuclear Transfer) is straightforward enough. If, prior to the transfer of the somatic nucleus into the enucleated egg, we could inactivate, in the somatic nucleus, a gene known to be essential for development, after the transfer has taken place, this biological entity we have created (which has been creatively named ANTity) would 'lack the attributes and capacities of a human embryo', being 'biologically and morally more akin to the partial organic potential of a tissue or cell culture'. We have crippled it so that it could never become a fully developed human, hence its moral status ought to change accordingly. Obviously, the crippling must still enable this entity to arrive at the blastocyst stage required for the derivation of ES cells, and in fact the ideal gene to inactivate, as we shall see, is a gene that allows development up to that point but not further.

But what were the cultural and technological resources that enabled the shaping of this proposal? In terms of cultural resources, the ANT idea draws heavily from the emerging science of systems biology, upon which Hurlbut grounds his framing of the organism as a living whole, which is 'more than the sum of its parts, and the parts are dependent on the integrated unity of the whole'. This holistic interpretation of life allows him to distinguish between the whole, that is to say the human embryo, in which 'this principle of organismal unity is an engaged and effective potential-in-process', and the bits of the whole, that Hurlbut calls 'subsystems with partial trajectories of development…that ultimately fail to rise to the level of coordinated coherence of a living organism'.

But when it comes to the technological resources used to think, and as we shall see, implement ANT, we find the molecular representation of development with its reductionistic focus on genetic switches supported by the most advanced technologies in mouse genetic engineering. In this sense, ANT is also representative of the inevitable tension of today's biology between the aim to understand living forms as complex systems (hence the emphasis on system biology and computer models) and the need to go out in the field–genome and do the laborious harvest of picking gene by gene the causal relation-

ships and tie them, in ways that are yet to be found, to the emergent properties of the system.

In referring to the product of ANT as 'biologically and morally akin to the partial organic potential of a tissue or cell culture', Hurlbut refers to a paper published in *PNAS* by one of the leading molecular embryologists that had established that the gene Cdx2 is required for the formation of the trophectoderm (the part of the mammalian embryo which gives rise to the placenta and the other support structures, in the absence of which implantation in the uterus cannot occur)[7]. And his presentation at the Council on Bioethics already lays out, following the testimony to the Council by Rudolph Jaenisch, one of the leading experts on cloning, the practicalities of such an approach. Anticipating that many scientists could question the quality of ES cells harbouring a mutation in a gene, like for example Cdx2, essential for development[8], Hurlbut envisions an experiment of conditional mutagenesis, in which Cdx2 is shut off in the somatic nucleus prior to the transfer into the egg, and once the ES cells have been derived, the gene is switched back on again to ensure that the cell line and its derivative lineages will not be affected by its absence.

It is fascinating to see how deeply the conceptual and practical framework of conditional mutagenesis has permeated the categories of bioethical and political reasoning. Conditional mutagenesis, endorsed by the Volkswagen Foundation as a specific field of inquiry in 1992 with a major 10-year long funding effort that was instrumental both for the development of the technology and for the positioning of this field at the cutting edge of molecular biology, emerged as a field and derived its main force from the main limitation of classical genetic approaches: the need to infer the function of a gene from the phenotype of the mutant animal forced to develop in the absence of that particular gene, with two possible outcomes. In the worst case, one had no mutant organism to look at, because the gene was necessary for the organism to develop in the first place. But even in the case that one did have a mutant organism to analyse, it was difficult to trace the phenotype unequivocally to the introduced mutation as opposed to the variety of unknown adaptive and compensatory mechanisms that would be set in motion during abnormal development. Hence the vision to pursue a system in which genes could be turned off and on where one wanted (tissue specificity) and when one wanted (time specificity). So when Hurlbut conceived his proposal and discussed it with the leading molecular biologists, conditional mutagenesis stood available as a powerful resource, both cultural and practical, to articulate ANT.

We have so far seen, in a remarkable display of co-production[9], how scientific understandings and experimental practices (system biology, molecular embryology and conditional mutagenesis) are taken up by the political system (in this case through Hurlbut and the endorsement of the Council on Bioethics) and fit onto an existing framework of values and norms. The language of system biology, with its emphasis on the 'whole' and the 'integration of the parts' is cast into a pre-existing notion of human life starting at fertilization. And the coalescence of scientific arguments and moral convictions results in the view of the human embryo containing from the moment of fertilization 'the organizing principle of the full human organism', something which is not 'an abstract or hypothetical potential in the sense of mere possibility (rather) an engaged and effective potential-in-progress, an activated dynamic of development in the direction of human fullness of being'. But it is not only at the theoretical level that scientific concepts (in this case, system biology) are taken up according to pre-existing moral commitments. The conceptual and practical framework of conditional mutagenesis, with its ability to shuffle around genes and to regulate them at will, is inserted by Hurlbut into a larger discourse about human artefacts. He views the product of ANT as a 'biological artifact – a human creation for human ends', and he describes the technology as 'the harnessing of partial developmental trajectories apart from their full natural context in order to produce embryonic stem cells'[10].

On 16 October 2005, the idea of ANT materialized as a new experimental object on the pages of *Nature*. Faithful to the original proposal, the paper by Rudolf Jaenisch and co-workers at the Whitehead Institute of the MIT[11] describes the creation of ES cells through ANT. The technology of RNA interference (a quick method of inactivating genes) was used to inactivate – in a reversible manner through the conditional approaches described above – the Cdx2 gene in the original donor nucleus prior to transfer into the enucleated egg. In the third figure, the main scientific and moral argument of the paper takes the shape of two dissected mouse uteri. The uterus on the left is empty because the embryos produced by ANT and lacking Cdx2 did not implant. The uterus on the right shows normal implantation sites of embryos produced by 'standard' NT.

In an editorial accompanying the article in the 'News and views' section of *Nature*, Irving Weissman, one of the world's leading experts on stem cells, refers tellingly to the ES cells produced through ANT as 'politic stem cells'. And in fact the co-production in this example is so intimate that one almost wonders why Hurlbut is not among the co-authors of the *Nature* paper or at least why the ethical reasoning outlined in the Committee session of 3 December does not figure in the section of the paper on the materials and methods, on a par with the technologies of cell culture and genetic engineering.

Concluding remarks

I would like to propose that the ANTities[12] and related experimental systems that I have discussed constitute an

example of responsive epistemologies. Responsive in the sense that the experimental process and the biotechnological object respond to a variety of social, ethical and legal concerns and accommodate them within their epistemological texture. Does this represent the emergence of a new phenomenon in the history of molecular biology? After all, one could argue that there were already many instances in which experimental systems were encouraged or devised simply in order to align with a specific political request, as in the case, for example, of cell culture systems developed for drug screening in order to avoid the use of experimental animals. There are clearly similarities between such an example and the ANT case. However, I would like to suggest that the ANT points to an altogether deeper level of contamination between the scientific and the political levels. It is not only a question of endorsing generically a certain research direction over another, because this is after all in the very nature of the relationship between research and its funding and could hardly be a significant development. Rather, in the case of ANT, we observe an intimate connection not only between the actors of the project (the prominent representative of a politically influential ethics council and a leading cloning researcher) and their institutions, but also between the practice and discourse of the two systems of knowledge they refer to. We observe, quite literally, the quintessential co-production of things and meanings by the simultaneous activity of science and politics. *De facto*, politics is recruiting science and technology to depoliticize a bioethical conflict and deliver morally neutral biological artefacts. But in so doing, moral and religious commitments about the beginning of human life and the source of its dignity, political commitments about the necessity of consensus and a social understanding of science as a public enterprise (that therefore requires consensus) conflate with the molecular explanation of life and the most sophisticated tools for its genetic engineering. The moral status is cast as a question of potential to achieve the mature form (organismic unity), and that potential is assessed, and interfered with, within the conceptual and practical framework of molecular genetics; hence the moral status of the embryo also becomes predicated upon the technical reversibility of conditional mutagenesis; the attribution of moral status, understood within the experimental paradigm of molecular switches, becomes itself a switch to be turned off and on.

And if we look at the trajectory of molecular biology in the last three decades, we realize that the emergence of such 'responsive objects' is not at all surprising. The inquiry into the practice of molecular biology has convincingly shown that model systems are not simply tools to answer pre-existing questions, but that they contribute in a decisive way to define and shape the questions themselves[13]. In this sense it has been argued that model systems and scientific problems are co-constructed[14]. If this was always true, at an epistemological level, for model systems in general, it has become more evident with our increased ability to change the living model systems from within. When the epistemic thing becomes itself the living laboratory in which to ask questions and interpret answers, the embodiment of the gain of knowledge through representation and intervention, it also becomes open, by definition, to the modulation of this intervention for a variety of goals, including those goals that explicitly reflect ethical, political, religious or social commitments.

1. http://www.un.org/News/Press/docs/2005/ga10333.doc.htm
2. Rabinow, P., *Essays on the Anthropology of Reason*, Princeton, 1996, p. 92.
3. Rheinberger, H. J., *Toward a History of Epistemic Things: Synthetizing Proteins in the Test Tube*, Stanford, 1997.
4. Jasanoff, S., *Designs on Nature*, Princeton, 2005, pp. 247–271.
5. Testa, G., Reprogramming Genomes and Reframing Rights forthcoming (ed. Jasanoff, S.), Reframing Rights.
6. Hurlbut, W. B., *Altered Nuclear Transfer as a Morally Acceptable Means for the Procurement of Human Embryonic Stem Cells*, The President's Council on Bioethics, December 2004; http://www.bioethics.gov/background/hurlbut.html
7. Chawengsaksophak, K. *et al.*, Cdx2 is essential for axial elongation in mouse development. *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 7641–7645.
8. Melton, D. *et al.*, Altered nuclear transfer in stem-cell research – a flawed proposal New England. *J. Med.*, 2004, **351**, 2791–2792.
9. Jasanoff, S. (ed.), *States of Knowledge the Co-production of Science and Social Order*, London, 2004, pp. 1–45.
10. Hulbut, W., Altered nuclear transfer as a morally acceptable means for the procurement of human embryonic stem cells, National Catholic Bioethics Quarterly, 2005.
11. Meissner, A. and Jaenisch, R., Generation of nuclear transfer-derived pluripotent ES cells from cloned Cdx2-deficient blastocysts. *Nature*, 2005.
12. Devolder, K., What's in a name? Embryos, entities, and ANTities in the stem cell debate. *J. Med. Ethics*, 2006, **32**, 43–48.
13. Clarke, A. E. and Fujimura, J. H. (eds), What tools? Which Jobs? Why right? In *The Right Tools for the Job. A Work in Twentieth-century Life Sciences*, Princeton University Press, 1992.
14. Burian, R. M., How the choice of experimental organisms matters: epistemological reflections on an aspect of biological practice. *J. History Biol.*, **26**, 351–367.

ACKNOWLEDGEMENTS. I thank Sheila Jasanoff, Hans Joerg Rheinberger and Soraya De Chadarevian for discussions and insightful comments that helped nourish this work.