What is a humanized mouse?

Remaking the species and spaces of translational medicine

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Abstract

This paper explores the development of a novel biomedical research organism, and its potential implications for the corporeal and experimental practices of translational medicine. The humanized mouse is a complex experimental object in which mice, rendered immunodeficient through genetic alteration, are engrafted with human stem cells in the hope of reconstituting a human immune system for biomedical research and drug testing. These chimeric organisms are yet to garner the same commentary from social scientists as other human-animal hybrid forms. Yet, they are being rapidly positioned as central to translational medicine in immunological research and pharmaceutical development. This paper explores the complex movement between species and spaces they promise to enact. Humanized mice simultaneously move these animal forms towards the intimate geographies of corporeal equivalence with humans, and towards the expansive geographies of global translational research. These contrary cartographies are achieved by the way the humanized mouse functions both as what Rheinberger (1997) calls an 'epistemic thing', as a model for human corporeality, and as what Michael et al (2005) identify as 'collaborative things', articulating mouse genetics with other research, notably stem cell science. In the context of post-genomics, this instability is critical to their collaborative value; their expansive potential follows as much from this biological openness as from specific expectations. Yet, these new research organisms have both accumulative and disruptive capacities. The paper concludes by suggesting there is a link between these processes of 'becoming human' and the extension of the practices of experimentation into clinical contexts.

What is a humanized mouse? Remaking the species and spaces of translational medicine

> 'It was really a question of whether you could sufficiently engraft mice with human cells, or transgenically alter mice with human genes, to get answers to questions that would be predictive of results in human medicine. I think the end of it was, we're not quite there, but we're well on our way.'
>
> (US biomedical researcher, 2009)

> '[T]he animal becomes ... (Becomes what? Human, or something else?)'
>
> (Deleuze and Guattari, 1987: 237)

Introducing the objects of experimental medicine

The paper 'Humanized mice: are we there yet?' was published in 2005 (Macchiarini et al, 2005). This technical review, a report from a workshop on genetically-altered mouse models for immunology in Bethesda USA, gave definition and prominence to the expression 'humanized mice'. It was followed shortly by an international workshop on humanized mice, held in Tokyo at the Central Institute for Experimental Animals (CIEA)[1]. The term has spread rapidly throughout the biomedical research literature, within immunology, cancer research, stem cell development and the study of infectious diseases (Brehm et al, 2010; Shultz et al, 2007). The humanized mouse itself has been taken up as an *in vivo* research model within the United States and Japan, and more recently in Europe and China. Yet, despite their evocative terminology, their swift employment, and the considerable speculative commentary on human-animal chimeras in related fields like embryology and stem cell research (Bonnicksen, 2009; Parry, 2010), these novel research organisms have yet to attract the attention of social scientists. These missing perspectives are important, for these research entities raise questions about the distribution of risks and benefits in biomedicine, the construction of biological boundaries between species and individuals, and the circulation and commodity forms of biomedical research. Humanized mice not only embody novel configurations of human and animal tissue, they also represent specific expectations for the future of biomedical research, especially

translational medicine, expanding the use of mice as experimental models for studying human diseases 'without putting patients at risk' (Brehm, 2010: 120). However, as anthropologists and social scientists have repeatedly shown, one can never change only one thing (Fischer, 2003). These experimental objects have potentially profound implications for remaking the species and spaces of translational medicine

The notion of translational research is increasingly prominent in the landscapes of biomedical research and funding (Mankoff et al, 2004; Curry, 2008). Put simply, translational research refers to efforts to increase the relevance of basic research to populations being studied. Translational medicine means transferring laboratory findings into medical practice; colloquially moving research from bench-to-bedside. However, a single definition is not possible, for the concepts, materials and spaces of translational medicine are being made and contested in practice. For some, translation is about encouraging transdisciplinary exchange through communication and the co-location of research facilities; for others, translation is best effected through the rapid commercialisation of therapeutic drugs; for yet others, community involvement is key. There is much at stake in the idea of translational research for experimental practices, for corporate actors, for patients and for communities. The context for this paper is developments in the use of animal models, which are positioning humanized mice as 'translational objects' to speed the movement of therapeutics from laboratories to clinics. The account is based on ethnographic research, in-depth interviews with researchers developing humanized mice in the USA, and literature review[2]. The paper is a preliminary mapping of the ways in which humanized mice have the potential to reshape both the intimate geographies of corporeal equivalence between species and the expansive geographies of translational research.

The two short phrases of the review article point towards the multiple trajectories or 'becomings' embodied in this animal. These potentialities are enacted simultaneously, but they are presented sequentially here, for there are differences and patterns of interference between them. The first, the term 'humanized mice', inserts these animals into the experimental and institutional practices, which make it possible to model biological processes for one species in another. The desire to 'humanize' an animal simultaneously suggests inadequacies in existing animal models, as well as the possibility of engineering bodies to overcome these boundaries. 'Humanization' raises the question of what it means for an animal to become human, with implications for definitions of animal and human identity and difference. These are also ongoing questions for experimental investigation. At present, the experimental humanized mouse remains what Rheinberger calls an

'epistemic thing', as opposed to a 'technical object' (Rheinberger, 1997)[3]. Conventionally, the movement from experimental to translational medicine would be enabled by the shift, or black boxing, of the immanent epistemic thing into a more stable technical object. This is not yet the case for humanized mice. These animals are a further place from which to explore the complex material relations enacted between species bodies in experimental practices. But more than this, they point to a reconfiguration of corporeal equivalence, for in this context, as I go on to show, the relations drawn between individuals and animals remain contingent to each experimental context.

The second phrase of the title moves in a slightly different direction, towards the expected relations between experimental spaces and translational medicine (Wainwright and Williams, 2008). To ask 'are we there yet?' is to suggest a known experimental endpoint, linking the humanized mouse to specific clinical expectations. The sociology of expectations in science has contributed much to understanding the performativity of the production of futures that are 'concrete, transparent or well articulated' (Michael et al, 2007; Brown and Michael, 2003). Yet, the trajectories through which translation medicine occurs are often uncertain and indeterminate (Rosengarten and Michael, 2009). Expectations around the development of humanized mice are considerable, but, spread across divergent fields of research, they are not singular or fixed. Michael et al (2005) draw on Rheinberger to propose a comparable oscillation within expansive programmes of research between the political reification of translational research, as a predictable and stable 'translational object', and the reality of collaborative associations, which are fraught and emergent, requiring key professionals or institutional arrangements to mediate 'collaborative things'. The insertion of humanized mice into the complex contexts of translational medicine reshapes these relations between experimental spaces and clinical practice. An important corollary to the technical question 'are we there yet?', is the contextual question, what implications does the humanized mouse have for changing relations between laboratory and clinical spaces?

In what follows, I explore these aspirations and oscillations in the development of humanized mice. First, I examine specific expectations for immunological research articulated around these research animals. Secondly, I trace their potential for remaking species and spaces of translational research, developing a vocabulary which considers humanized mice as a contingent assemblage or becoming (Deleuze and Guattari, 1987a). Humanized mice can be considered one response to the challenge of the post-genomic sciences for research using genetically-altered

mice as model organisms. The growing recognition of complexity and contingency in biology destabilises organisational arrangements that sought to translate biological insights across species, through the use of genetically-altered mice and biological grammar of genetic homologues, and extend biomedical research across space, through the patenting of research organisms and the harmonisation of intellectual property rights. The vocabulary of becoming helps conceptualise humanized mice less as an object, even a relational object, and more as a series of overlapping vectors, which have direction and velocity, but no singular identity. There is a theoretical relation here to Barad's concept of intra-action (Barad, 2007), and Mol's work on multiplicity (Mol 2002), but the attention to dynamics and reversals becomings demand is helpful in this context. As I explore, these trends and speeds are not always the ones anticipated, although they can, at times, still be welcomed. In conclusion, I return one final time to the question 'are we there yet?', to develop an alternative spatial imaginary of the future of translational research, one about always being nearly there, but never quite arriving, which sees researchers capitalizes on the expansionary potential immanent in the very idea of a translational gap.

Placing expectations of humanized mice

Nude, immunodeficient, mice have been bred since the late 1930s for use in transplantation studies and cancer research. Using these animals it was possible to transplant cancerous human tissue onto research animals, a process called xenografting; the host animal providing the blood supply to enable cancer development to be studied *in vivo*. Recent research on humanized mice both supplements and supplants this technology. Instead of growing human cancer cells on the surface of the mouse, the aim is to develop human physiological systems within the mouse. This has initially focused on the immune system. The hope is to expand the role of these mice as models for researching infectious diseases, autoimmune dysfunctions, blood cancers, and for the preclinical testing of drugs and vaccines. Developing these animals is contingent upon refinements in mouse genetics, stem cell research, and clinical medicine. Humanized mice are thus not a single technology, or indeed a singular thing. They only appear as such when articulated within institutional hopes for the continuing development of mouse models in translational medicine (Scott, 2007).

The first step towards humanizing mice has been the development of more severely immunodeficient animals (Macchiarini et al, 2005). The full nomenclature for the most

commonly used humanized mouse is written as NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ. It is often called the NOD SCID gamma, or NSG, mouse for short. The name points to the development of a congenic strain of mice, mixing the genetic characteristics of the NOD mouse – the non-obese diabetic strain of the animal, with the SCID mouse – a mouse with a severe combined immune deficiency, and incorporating a targeted mutation of the gamma chain gene, Il2. The final J suffix here is a geographical indicator. It tells us this particular mouse has been developed in The Jackson Laboratories in Maine USA[4]. Animals produced at other sites may be constituted through a slightly different genetic mix, and will have a different suffix indicating their laboratory and geographical origin (Lyon and Searle, 1989).

The second stage in developing a humanized mouse is engrafting the relevant human cells into the immune-suppressed mouse body. The type of injected cells is determined by the context in which the model is to be used. For cancer research, human leukaemia cells may be injected. For other kinds of immunological research, the aim is not to model faulty blood cells, but to reconstitute a functioning human immune system in the mouse, which can be used to study infectious diseases, vaccine development and test for drug safety. In this case, the injected cells will be human haematopoietic stem cells. These are the multipotent stem cells that normally give rise to all human blood cell types. The aim is to enable these human stem cells to colonize the mouse bone marrow and differentiate into the multiple cell lineages that constitute a human immune system. The resulting assemblage is termed a 'humanized mouse'[5].

Outside of the laboratory, humanized mice are being positioned as central to developments in translational research using mice as model organisms. The growing imperative of translational medicine has encouraged the laboratory animal community to position animal models as central to the transfer of biological insights. Model organisms are construed as a Rosetta Stone[6] for translational research, suggesting that animal models can function as simple 'translational objects' (Michael et al, 2005). Yet, despite this strikingly concrete analogy, the application of animal models is increasingly subject to review and refinement. While the mouse may be figured as a standardized translational device, or Rosetta Stone, in public discourse, in practice, the process of reading for human medicine from animal models is subject to constant iteration and transformation. The movement from experimental context to therapeutic intervention is not one way and the boundaries between experimental system and translational medicine are not clear cut; early trials in human subjects can equally be considered by researchers as a test of the validity of the animal model (Lezaun, 2010). In many cases, the precise nature of the biological

equivalence being drawn is still to be determined and scientists are working to understand precisely what is being modelled at the molecular, genetic, cellular or organism scale to improve the transfer of data between species. As one recent commentary states, 'for most, "translational medicine" [...] describes a unidirectional effort to test in humans novel therapeutic strategies developed through experimentation. This would suffice if animal or other experimental models were representative of human pathology, but this remains to be determined' (Mankoff et al, 2004:1; see also Marincola, 2003).

Periodically, an event dramatically reveals the gap between experimental model and human corporeality. The most recent was the catastrophic failure of pre-clinical safety trials at Northwick Park, North London, in 2006 (Suntharalingam et al, 2006). The trial was testing a drug, itself a humanized monoclonal antibody, being developed to treat leukaemia and rheumatoid arthritis. The drug had been tested on mice, with no adverse consequences. Yet, the first introduction of a small dose of this compound into humans produced sudden and systemic organ failure in all six trial participants not taking the placebo. Monoclonal antibodies are biotherapeutics that bind to specific cells in the patient's body. They are not the therapeutic agent themselves, but stimulate the patient's own immune system to attack the targeted cells. In this trial, the participants' immune systems overreacted, attacking the body indiscriminately in a so-called cytokine storm. The drug was removed from development, the failure of the trials investigated, and the six men warned to expect a life time of health problems. The key question for investigation was why did a drug, which cleared safety tests in laboratory animals, cause such an adverse reaction in humans (Duff, 2006). Reports identified several differences in the way the immune systems of research animals and trial participants reacted to the TGN1412 treatment, and criticized the lack of knowledge of the immunological mechanism being tested (St Clair, 2008). There were other contextual issues too (Fleming, 2008). The mice used for safety testing, kept in sterile laboratories, had not had the same immune challenges as the human trial subjects. Their inexperienced immune systems did not react. In humans, the memory of past infections contributed to the detrimental response. The species, but also the spaces, were not representative.

This is the context in which expectations for the potential of humanized mice are most often articulated. It is hoped that humanizing mice will aid translation between species with divergent immune systems, developing the understandings of immunology required by biotherapeutics (Scott, 2007). At the same time, there is the expectation that these research animals can

themselves be stabilized to speed up the movement of research between experimental spaces and clinical practice, forming part of the future global landscapes of translational science. The expectations circulating around the humanized mice are considerable and multiple. They are potentially important for scientific breakthrough in basic research and clinical medicine (Brown, 2000), they have promise to pharmaceutical companies for high-throughput efficacy and safety testing, and they are already of value for those resource centres involved in their manufacture and distribution. There are expectations around the role of species and spaces in translational medicine; yet, these are not quite the same.

The changing species and spaces of translational medicine

Translation requires the possibility of connecting across multiple biological species, the model organism in the laboratory and the person in the clinic, as well as across disciplinary spaces, between research environments and clinical practices[7]. The way this is figured depends, amongst other things, on the changing way we understand and enact biology. For earlier research using genetically-altered mice as models for human genetic disorders, translation could be figured as an apparently linear process. Genes had homologues in different species, and translation could be construed as a relatively simple process if gene, rather than context or environment, was the key causal agent. The metaphor of the Rosetta Stone has purchase here. It stresses the informational qualities of biology and understands the correspondence between human and animal bodies through the agential properties of genes or proteins (Maleszka et al, 1998). Expectations for the value of genetics in translational medicine can be found in the large number of patents taken out on genetic technologies in the late 1980s and 1990s (McAfee, 2003). It can also be found in the way social scientists began talking about the link between the processes of molecular biology and the processes of mobilization, figuring translational medicine as both a linguistic and geometrical operation through which biological entities could be deterritorialized and reterritorialized. As Rose puts it, molecular biology enabled biological materials 'to be regarded, in many respects, as manipulable, and transferable elements or units, which can be delocalized – moved from place to place, from organism to organism, from disease to disease, from person to person' (2007: 15). In this context, the pursuit of translational research was articulated with a range of other regulatory and commercial practices, including the standardization of model organisms, the conformity of biological nomenclatures and the harmonization of intellectual property regimes (Rader, 2004; Shostak, 2007).

Yet, even as the genome was finally mapped, the limitations of the biological grammar of genetics were being revealed. The complexities of post-genomics, with its focus on gene/gene, gene/epigenetic and gene/environment interactions, challenge the assumed symmetry between deterritorialization and reterritorialization. The post genomic sciences are increasingly characterised by complexity, multiplicity and emergence (Wynne, 2005; Braun, 1998). The hope for gene therapies for anything other than single gene disorders has stalled (Jones, 2009), and the patenting of research organisms as models for genetic disease is slowing (Einhorn and Heimes, 2009). The work on mouse models of human disease has contributed to this emerging picture of complexity. A mutation to a gene, considered a good genetic homologue between mice and humans, may not produce similar clinical symptoms in the different species, raising questions about the involvement of species-specific pathways. Post-genomics is engaged in different ways with attempts to understand these cellular, epigenetic and environmental contexts. Franklin identifies in this a 'de-geneticization' of biology; a shift from coding to context. Returning to Haraway, she characterizes a move away 'from 'the translation of the world into problem of coding' (Haraway, 1991: 165), as in early genetics, towards 'a translation of the problem of coding into one of context' (Franklin 2006: 179).

This shift to context in biology has potentially profound implications for the practices of translational research using genetically-altered models. It does not rule out making statements about biological equivalence between animal model and human biology, but it does make the achievement of translation more contingent. Whilst genetics promised a stable transfer of coding strategies across species and spaces, post-genomics points to spatialities and species kinds that are emergent and contextual. There are still contexts in which symmetry can be demonstrated, for example, in the translation of IVF techniques from one species to another (Franklin, 2006). In this context, biological multiplicity can be managed, temporarily tamed the 'symmetry of species parts', allowing the simultaneous engineering and improvement of animal models and human biology. As Sarah Franklin explains, 'biology exists in multiple forms – digitally, virtually, synthetically, mimetically, algorithmically and so forth – that are endlessly combined. It is a world of cyborgs, but also of mixtures in which it is the symmetry of parts that allows translation, so that the mouse, the sheep, the cow, the pig and the dog move together as animal models susceptible to re-engineering and improvement' (Franklin, 2006: 176). The oscillation between biological multiplicity and symmetry can be managed, and the hatch between

the laboratory and IVF clinic illustrates the ideal of proximity as one spatiality of translational medicine.

Yet, as the Northwick Park trials suggests, the return to context is a significant challenge for immunological research (Aderem and Hood, 2001). The reductionist practices of molecular biology have to work alongside the combinatorial outcomes of the multiple entities which constitute a functioning immune system at the level of the individual organism. There is symmetry, but there is also the emergence of individuality from this multiplicity. This is captured in Haraway's earlier discussion of immunology, which draws attention to the way immunology inserts an asymmetry between processes of deterritorialization and reterritorialization, or in her terms 'disassembly and reassembly'. As she puts it, 'any objects or persons can be reasonably thought of in terms of disassembly and reassembly; no 'natural' architectures constrain system design. Design is nonetheless highly constrained. What counts as a "unit", a one, is highly problematic, not a permanent given' (Haraway, 1993: 208). She locates this with the immune system, which acts as 'a chief witness for the irreducible vulnerability, multiplicity, and contingency of every construct of individuality' (Haraway, 1993: 217). Moving between species and spaces in translational research is more tricky when the precise object of enquiry is the immune system, which gives rise to 'every construct of individuality', as well as species difference itself.

Haraway's work in the early 1990s, and in the context of HIV/AIDS, focused on the immune system as an icon for principal systems of symbolic and material difference in late capitalism. As she suggests, the immune system became 'the iconic means of maintaining the integrity of the one in the face of the many' (Haraway, 1993: 216). The development of humanized mice suggest a shifts away the associations of immunology with closure and defence, towards the more open-ended communicative and collaborative expectations of translational research. Rather than protecting the singular human from multiple others, this makes use of the permeability between species boundaries, given by genetics, to incorporate traces of the human within the animal other. The communication systems of the immune system, through which it is possible to read the human body 'as a coded text, organized as an engineered communications system, ordered by a fluid and dispersed command-control-intelligence network' (Haraway, 1993: 207) become multispecies, engineered to speak in the languages of different kinds. The animal model in immunological research moves from the metaphoric figure of the Rosetta Stone, to something more metamorphic, an experimental becoming human, which is materially complex, intricately

emplaced and potentially expansive. As Deleuze and Guattari suggest, 'metamorphosis is the contrary of metaphor' (1987b: 22). The implications of metamorphosis function as a guide to the openings and oscillations inherent in the development of humanized mice. 'There is no longer man or animal, since each deterritorializes the other in a conjunction of flux, in a continuum of reversible intensities [...] There is no longer a subject [...] Rather, there is a circuit of states that forms a mutual becoming, in the heart of a necessarily multiple or collective assemblage' (Deleuze and Guattari, 1987b: 22). Becoming human, and the associated implications of becoming collaborative, enables the humanized mouse to move simultaneously towards the intimate geographies of corporeal equivalence and the expansive geographies of globalized biomedical research, even whilst they remain in flux, and never quite arrive.

'The human body writ small'[8]

Becoming human

Perhaps unsurprisingly to 'humanize' another mammal is not an easy process. There is a delicate balance in developing an animal that is 'mouse' enough to survive as a viable host for the engraftment of human cells, which is not too 'mouse' so that the transferred human cells are eliminated, or too 'human' such that the engrafted cells launch an immune response against the 'mouse' host. The process of 'becoming human' is narrated by researchers through a series of spatial metaphors, drawing attention to the literal deterritorialization of the animal, the configuring of space within the animal, and the animal's reterritorialization by human stem cells. Yet, there is the ever present potential for human and animal to deterritorialize each other. Talking to researchers, there is uncertainty about whether they are involved in model development or basic research, and indeed about where these boundaries now lie. In Rheinberger's (1997) formulation, there is a fundamental instability in the identity of these mouse models as technical objects or epistemic things. What the humanized mouse is not is an easily bounded object, an inert receptacle, or simply 'the human body writ small'.

The initial task is to remove species markers defining the mouse's immunological identity. The genetically-altered NOD-SCID strain cannot produce immunologically active T and B cells, so creating space for human stem cells within the mouse. As Researcher 1 explains, 'T and B cells of course would reject a human tissue, by eliminating them [in the mouse] you then have a host

which is a much better receptacle for human tissues'. Yet, this is only the first stage of the process. The immune system is not a static process, simply determined by this mutated genetic inheritance; it is also constantly interacting with the bodily structures of the animal, and in relation to the animal's internal and external environment. A second stage has been exploration of ways of halting any reconstitution of immune function. This requires a further mutation to knock-out the gamma chain gene. This helps hold open the 'space in the mouse', interrupting cytokine signalling between mouse cells, preventing them re-territorializing. As Researcher 1 explains,

> 'The absence of this chain eliminates any residual inefficient rearrangement of T and B cells. It eliminates natural killer cells, which otherwise mediate a non-specific rejection. And it also makes space in the mouse because if the receptors are available, cytokines are consumed as well as generated. If they're not available, cytokines are generated, and they're then available for the human cells and that allows the human cells to develop better'.

There are yet more contextual and relational issues. It is not enough merely for human and mouse cells to co-exist within the mouse model; they also need to be able to 'see' each other. The parts need to reconstitute into some sort of communicative system. Effective communication between human and mouse cells within the NOD-SCID gamma mouse is now a limiting factor in the development of the model. For Haraway, the fluidity of the immune system was symbolized by the circulatory qualities of blood, but the mammalian immune system is not just constituted through the differentiated immune cells within the blood; it has important structural elements too, the thymus and other organs, and epithelial and other cells, which take part in the interacting processes of an immune response. These elements of the mouse cannot be seen by the human blood cells; the multispecies immune system communicates only partially. As Researcher 1 describes,

> 'All of the components are there but they aren't communicating perfectly and you [the human blood cells] just can't see the mouse tissues at the moment [...] It potentially points to some incompatibility between human and mouse cells'.

Contextual differences remain, as do the asymmetries which hinder easy movement of research insights between species. There are new patterns of absence and presence, of visibility and

invisibility. The translational gap remains, but the communicative issues between human and animal biology are relocated within the animal body. Inserting more genes that are human might enable key structural elements of the mouse to be seen by human blood cells. However, as yet, these models are not simple 'translational objects'. Expert judgement about function of the experimental model is critical for each context. This is part of the contingency of 'every construct of individuality' in immunology (Haraway, 1993: 217). Nonetheless, the inherent multiplicity of this assemblage means that each iteration of the research model is a new opening in the process of becoming human, or becoming something else.

Becoming something else

There is the ever present potential for these models to become something else. As Researcher 2 puts it, 'people have dirty animal rooms, import these mice, try to do experiments and they generally fail 'cause their mice are dead'. Rather than becoming humanized, there the risk of becoming microbialized. In laboratory environments, which are not totally sterile, the immunodeficient animals suffer the unchecked proliferation of their own internal flora and will perish. Even in sterile laboratories, the level of immune deficiency can be such that the microbes present in all animals will overwhelm their hosts. Researcher 2 cites one example of an animal, whose composition appeared to have 'genetic potential', but which did not survive long.

> 'We made one model that is the NOD SCID Gamma and it's got the MyD88 knockout. […] This poor mouse, even in our cleanest, cleanest, squeaky-clean mouse room can't survive. It gets killed by its own flora, so in that particular cross we just, we made a mouse that is just too immunodeficient for its own good.'

There are also challenges raised by the introduction of human cells into the immunodeficient mouse body. While suppressing the mouse immune system is vital for allowing the engraftment of human stem cells, experimental procedures with the injection of adult human blood cells reveal the potential for a reverse problem. The adult cells are able to mount an immune response that attacks the mouse body.

> 'If you take human […] peripheral blood cells, so peripheral blood lymphocytes have mature cells. You put them in a mouse environment, and even though the mouse is

> immunodeficient and can't recognise and deal with the human cells you're putting in, the human cells are immunocompetent and they'll attack against mouse antigens' (Researcher 2).

Not all unexpected becomings are unwelcome. In this case, the research trajectory bifurcates; the instability of one research model becomes the basis for another. The 'failed' experiment is not a negation, but allows the continued expansion of experimental practices; subject and object are reversed. As Researcher 2 continues, 'in that case we developed a nice model for graft-versus-host disease'.

Yet, such complications do reinforce the inadequacy of biological symmetry for considering the humanized mouse as a translational object. The complexities of immunology, and the role of microbial agencies in shaping the immune system, prevent a simple exchange of insights between animals in the laboratory and humans in the clinic. Microbes have shaped, and continue to shape what it means to be human, as opposed to mouse or microbe (Hird, 2010). Moving research insights between mice and humans is interrupted by the additional agency of these microbial environments. This was one challenge in the Northwick park trials. Microbial challenges had already shaped these human bodies; their understanding of self and other was different to that of the sterile mice. This is a further complexity for the model. While humanized mice incorporate elements of the human immune systems, they appear even less able to cope with the microbial elements of their environment.

This begins to question why these mice have become so highly valued and widely circulated. The humanized mouse remains an experimental process, with uncertainties about precisely what is being modelled, and under what conditions. The animal bodies are constantly interacting with the laboratory space, with their own internal flora and the engrafted cells; the species parts constituting a complex matrix of presence and absence amidst partial signalling between human and murine genes and cells. They are 'a conjunction of flux, in a continuum of reversible intensities' (Deleuze and Guattari, 1987b: 22). This is a model organism composed through the potential for difference, rather than through singular identification with a known gene, molecular pathway or disease. Yet, this lack of a clear definition enables their potential for expansion (Deleuze and Guattari, 1987a: 239). The humanized mice constitute an experimental space in which new things can happen. They are closer to what Mike Michael et al (2005) call 'collaborative things' in the contexts of translational research. Their benefits accrue from

maximising the potential for exchange across disciplinary spaces, rather than for their specific expectations. In the context of the post genomic sciences, their underdetermined characteristics are beneficial to becoming collaborative.

'Today the mouse, tomorrow the world'[9]

Becoming collaborative

For collaborative things, processes of encompassment are more important than the achievement of specific expectations (Michael et al, 2005). The way in which scientists' work encompasses and is encompassed by others is critical to the often indefinite practices of translational medicine. This is reflected in the experience of those developing research on humanized mice. As Researcher 2 suggests, collaboration defines his role: 'I'm not sure if it's fair or not or whether I should be bothered by it but I think that I may be considered as much a facilitator as anything else'.

Collaboration is essential to the engage the complex technologies and areas of expertise for developing and circulating the humanized mice. For the moment, much of this distribution is centred on The Jackson Laboratory in the US. There are alternative sources of related animals, notably the CIEA in Japan, but they are more difficult to get hold of. The Jackson Laboratory is part biomedical research institute, and part service provider, selling inbred and humanized mice strains. They are not-for-profit, but sales of their mice subsidize their research. The humanized mouse is currently their most expensive item, costing around $300 for commercial use, compared to ten dollars for an ordinary inbred strain. The wide distribution of the model is thus valuable to The Jackson Laboratory as the main supplier, it supports their research in other arenas, and this circulation has been important for model development too. Rather than seeking to limit the distribution of the animal and confine the intellectual property embodied within it through patent restrictions, they have been trying to circulate it as far as possible, so as to benefit from the collective and distributed inventiveness characterizing the post genomic sciences[10]. As Researcher 1 puts it,

> 'They [The Jackson Laboratory] have been pushing very, very hard to get this model into as many hands as possible. My feeling is that it's probably the right time for them to

> start pushing, I think there are going to be a series of incremental improvements over the next few years, and I think there probably needs to be one more breakthrough before it's really going to become a standard tool.'

These breakthroughs are likely to come from engagements with other research communities beyond those using genetically-altered mice. Work on humanized mice brings a research community, predominantly using mice as genetic tools, into collaborative engagements with high profile and well-funded research agendas around stem cell science, infectious diseases and pre-clinical testing.

In particular, the model has strong links to stem cell research. This is the most costly element of model development, involving access to expensive foetal or other human biological materials, as well as the expertise and support of stem cell researchers. These are pursued through external collaborations and persuading stem cell researchers of the fundamental value of these techniques to their field. Such encompassments are essential to the development and further circulation of the model.

> 'I think things will happen much quicker once more people start using this, rather than as a model development thing, start using it for science. There was actually a really big break point for that just a few months ago. There was a paper published by Irv Weissman's Group. So they're very interested in stem cells, and they were the first out and out stem cell people to publish a paper using the NOD-SCID gamma chain mice. [...] And that's a tipping point because he is an influential figure in his field and people will start using this model, it's like 'okay, it's got the Irv Weissman seal of approval' and that needs to happen with more fields for the model to spread.' (Researcher 1)

The technical developments and approval of stem cell scientists have been vital to the development of the model (Serafini et al, 2007; Bernard et al, 2008). Yet, researchers are still looking to expand these collaborations, for the model to be encompassed by more fields, to build more relations, and for the model to spread. Yet, such collaborations also introduce the potential for becoming disruptive as these expansive spatialities loop back into the intimate geographies of corporeal equivalence.

Becoming disruptive

Humanized mice not only embody the potential to compose new research relations, they could also decompose relations, as new constructs of individuality re-emerge. By incorporating human stem cells into the mouse model, the regulatory and ethical regimes, which support the extrapolation of data from inbred animal populations to human medicine, are challenged. The model organism shifts from a metaphoric surrogate for human populations to a metamorphic becoming, which is materially related to one person. The relationship between animal and human changes from species resemblance to intimate kinship. The animal becomes a better model for human medicine, through forging relations with one particular human, affecting a movement between research and clinic, which may collapse space and time for some, whilst distancing it for others. The development of the humanized mouse is closely linked to the promises and pitfalls of personalized medicine (Epstein, 2007; Fullwiley, 2007). As Researcher 2 explains, 'at least in terms of the genetics, all the mice are the same and in terms of the human cells you put them in, they're never going to be the same, especially with haematopoietic stem cells, they're always going to be person specific'.

This specificity has been an issue in the development of the model, for each source of human cells is both unique and costly. This specificity also challenges the regulatory relations between basic research and clinical medicine. Experimental research and clinical practice are already linked, albeit it by processes which keep them apart. Basic research is connected to clinical medicine through regulatory mechanisms, which use statistics and agreed ethical protocols to extrapolate acceptable levels of efficacy and safety from known animal strains to human populations. These divisions slow the transfer of data and biological entities from basic to applied research. Indeed, the inefficiency of this process is one driver for the development of humanized mice. Yet, established regulatory mechanisms are by their nature risk averse, slow to change, and incorporating complex data from humanized mice is likely to take a long time.

There is the additional challenge of incorporating the increasingly personalized nature of these research entities into regulatory thinking based on population risks. Humanized mice raise new ethical dilemmas for researchers, doctors and patients. The development of a humanized mouse model of leukaemia, for example, opens up the potential to make a model of one person's cancer, testing treatment in the animal before transferring this to the clinic. The animals have yet to be used in this way, but for these people, the experimental and therapeutic exchange would become

a 'real time thing' (Researcher 1); their individual treatment choices linked to the experimental experiences of their personalised humanized mouse. This raises new questions for translational medicine: 'how can information be transferred to the researcher and how the researcher's findings then should be transferred back to the patient', especially given ongoing issues in understanding 'quite what it is you are modelling' (Researcher 1). It also challenges the very notion of humanization, for the mouse is not humanized in any generic way. Rather, the research animal becomes tied to the patient, in what Deleuze and Guattari characterize as a 'block of becoming', which, for that person and that animal, 'runs its own line' (1987a: 263).

This block of becoming challenges the identification of a unitary human subject for translational medicine (Epstein 2007). Much of this is yet to come, but will raise ethical questions for some individuals, as experimental systems become intricately intertwined with clinical spaces. And presumably, though I have seen nothing about this yet, the corollary will also be true. There will be communities, whether defined geographically, socially, genetically, epidemiologically, or even microbially, who are excluded from collaborative efforts to translate between spaces and species. Humanized mice promise to tease open new opportunities, but they have what Haraway (1992) and Franklin (2006) identify as trickster elements as well. Their biological and disciplinary multiplicity enables new forms of biological co-presence and interdisciplinary collaboration, but their associated constructs of individuality bring forth new forms of absence and new axes of difference.

Reflections on being always nearly there

In concluding, I want to return one final time to the opening question 'are we there yet?' In terms of the specific answer to whether researchers using humanized mice have been able to reproduce the cytokine storm seen at Northwick Park, the answer is no. As Researcher 2 explains,

> 'One of the things that we're not completely successful at, but are almost there now, is being able to engraft these mice with human cells and give them the same kind of treatment that caused a cytokine storm and caused near death of people in the UK. So the mouse model doesn't work.'

As before, they are nearly there, but not quite. There is a constant deferral of the achievement of translation. This may be due to communication between species parts within the space of the mouse; the challenge of managing complex interactions between humans, mice and microbes; the need for more disciplinary collaborations to complete the model; or the specificity of the human stem cells used. Yet, even whilst never arriving, each stage of development sets in train a spiralling pattern of experimentation and expectation, based on expanding collaborations and the increasing use of this particular model organism. Perhaps, humanized mice are intriguing answer to a question researchers and institutions do not ask, but appear to enact. Given the collapse of the reductionist assumptions of genetics, and the move away from patenting genetically-altered animals, how do you generate and circulate an experimental and biologically reactive space itself. Or, how can you commodify a becoming?

This interpretation is borne out by one further, ongoing, disruption to the circulation of the humanized mouse. In 2008, the Japanese non-profit biological resources centre, the CIEA, filed a lawsuit against The Jackson Laboratory, for patent infringement; the first time in its history that the laboratory has been sued (Abbott, 2009). The legal action revolves around the property rights embedded in the Japanese version of the humanized mouse. According to the lawsuit, the CIEA applied for a patent in 2001, published their genetic characterization in 2002, and were awarded a US patent in 2006. The lawsuit is being contested in the courts. The Jackson Laboratory argues the original patent should not have been granted, being too broad and insufficiently novel, and furthermore that the immunodeficient animals, although similarly named, are not genetically equivalent[11]. Researchers have also faced considerable barriers in obtaining the Japanese animals, in verifying and building on their research. The genome from The Jackson Laboratory mouse is certainly more widespread and is the animal around which collaborations have been secured and experiments planned. The new Jackson Laboratory West Coast facility was opened in May 2009, primarily to supply these fragile animals to the biotechnology markets in California[12]. Although still to be settled, the Japanese decision to pursue a patent on the genetic make-up of their animals appears to have isolated their research. The anomaly functions to elucidate the nature of this experimental animal, defining more clearly what is at stake. The very biological mutability of these animals, which in the 1990s was seen as a threat to the coherence of patents on genetically-altered organisms (Lezaun, 2006; 2007), is now being used to proliferate opportunities to develop, circulate and commodify these emergent forms. As Deleuze and Guattari suggest, becomings are always political affairs (1987a: 292).

The humanized mouse offers a deterritorialization, a means of escape, from the biological grammar of genomics and the limitations of the gene patent as a commodity form (Calvert, 2008). It offers a new arena of commodification, which makes use of, rather than denies these animals' potential for biological surplus. In recent reflection on the practices of rendering and animal capital, Shukin (2009) is critical of the work of Deleuze and Guattari for understanding the enrolment of animals into such capitalization processes. She goes back to Žižek's critique, emphasizing the 'features that justify calling Deleuze the ideologist of late capitalism' (Žižek, 2004: 183-184; Shukin, 2009: 29). Yet, the point here is not so much ideological as ethnographic. Their emphasis on becoming means that, in this arena of the biological sciences and in this concretization of biocapital, Deleuze and Guattari are a useful guide. This is what biocapital looks like from this partial perspective (Sunder Rajan, 2006). The value of never arriving, of always being one iteration away from the achievement of translation, articulates more people and incorporates further intellectual capital into the animal model. The distributed expertise of these collaborations is centralized, and widespread circulation secures it as the universal standard, affecting what can be seen as a 'privatization of the 'general intellect' itself' (Žižek, 2009: 145), within the animal body.

Translational medicine here is not based on the same spatial imaginaries as genetics, with its assumptions of delocalized biological material moving easily from place to place. Instead, the multiplicities, the constructs of individuality and the consequent lack of symmetry in immunological research remake the corporeal, experimental and clinical spaces in which the biological is enacted. With its emphasis on context and diversity, post-genomics is inherently topological compared to the geometric imaginaries of genetics. This is something hinted at throughout narration of the development of humanized mice, with the focus on opening up space within the mouse, and always increasing the sphere of circulation and collaboration. The process of 'becoming human' opens these model organisms to biological relations, which are not only interior, but also external, remaking relations between experimental subjects and objects, laboratory spaces and clinical contexts. Their instability as 'epistemic things' turns out to be critical to their value as 'collaborative things', as their expansive potential follows as much from their experimental openness as from any specific expectations. These instabilities spiral outwards, gathering pace, generating potentiality and patterning new topologies of difference. The corporeal, material and ethical cartographies are complex and remain to be mapped. There are many humanized mice in the world, and there are many worlds in the humanized mouse.

Endnotes

[1] See http://www.ciea.or.jp/English/History.htm, last accessed 28/05/2010.

[2] This paper is based on research carried out for the ESRC fellowship, Biogeography and Transgenic Life, Grant no RES-063-27-0093. This fellowship is tracing the different ways in which mice are 'on the move' in contemporary biomedical research: firstly, internationally, in the development of large-scale mutant mouse resource centres and functional genomics; secondly, corporeally, in the development of further mouse models of human disease; and thirdly, affectively, in the changing ways these animals are figured in different scientific, regulatory and ethical cultures. Translational research is only one part of the changing use of these genetically-altered organisms, and humanization only one part of the more general processes of translation. However, humanization is interesting in the way it encapsulates these global, bodily and ethical global developments. The paper focuses on the way these animals are narrated in the expectations and disruptions of experimentation and translational medicine. The account is based on ethnographic research, literature review and two in-depth interviews exploring the development of humanized mice, both carried in the NE USA in June 2010. It is informed by over 80 interviews with research scientists, animal welfare scientists, regulators, patient groups and others involved in the changing use of mouse models in the UK, Singapore and USA, as well as participation in research meetings and conferences in the USA, Europe, and SE Asia. All research participants were offered anonymity.

[3] Rheinberger suggests experimentation involves an oscillation between what can be held constant in the context, what he calls technical objects, and what forms the focus of current inquiry, that is epistemic things. This allows experimenters to simultaneously hold two forms of expectation about the future in concert. Epistemic things are necessarily underdetermined; they embody what one does not already know; they are 'absent in their experimental presence' (Rheinberger, 1997: 28); 'graspable only in the moment of emergence' (Michael et al, 2005: 376). Technical objects in contrast embody concrete futures; they are the instruments, inscription devices and biological entities, with given standards of purity and precision, whose stable linear temporalities allow researchers to make sense of the immanence of epistemic things.

[4] For further information on this specific model organism see http://jaxmice.jax.org/strain/005557.html, last accessed 27/05/2010.

[5] Also included within the broad definition of humanized mice are techniques for taking blood that has developed in a human and inserted into a mouse for experimentation (Macchiarini et al, 2005). In this context, experiments with blood are, to quote one researcher 'a little more physiological than they are in a test tube'.

[6] For example, see the PowerPoint Grieder, F. and Harding, J. (2007) 'Animal Models: the Rosetta Stone of Translational Research', NIH. Available at http://www.ncrr.nih.gov/about_us/advisory_council/presentations/2007/Animal_Models_The_Rosetta_Stone_of

_Translational_Research_Grieder_Harding_5-22-2007.ppt, last accessed 24/05/2010. The Rosetta Stone is an ancient Egyptian stone, inscribed with two languages in three scripts. Its discovery at the end of the Eighteenth Century was instrumental to deciphering Egyptian hieroglyphic scripts, and the term Rosetta stone has emerged as a metaphor to refer to anything that is a critical key to processes of decryption or translation, especially in science. The stone is currently on display in the British Museum. Also relevant to this paper, it has long been a focus of struggles over national ownership, shifting from French to British control, and more recently emerging as central object of concern for the repatriation of Egyptian antiquities.

[7] There is of course a relation between the two. Species appear in Michael et al's paper on translational research and stem cell science as different disciplinary kinds: the 'clinicians and scientists are seen to be rather different professional species' (Michael et al, 2005: 385). That they work on different species is part of this divergent professional identity.

[8] This title, and the subsequent one, are both taken from the novel *Intuition* by Allegra Goodman, first published in the USA in 2006. The book is a drama about scientific integrity, publicity and controversy, set in a research institute in Cambridge, Massachusetts, which is using mice to develop experimental interventions into tumour development. The quotes usefully sum up the two directions in which researchers using model organisms have to face: towards the intimate geographies of corporeal equivalence - 'here was the human body writ small' (Goodman, 2006: 69) - and towards the expansive geographies of globalized research 'Today the mouse, tomorrow the world' (Goodman, 2006: 49). This is not unique to humanized mice, but these challenges are particularly evident in an unfolding research arena.

[9] See note 12 above.

[10] The Jackson Laboratory no longer patents research animals, although it holds and distributes the controversial Dupont oncomouse and other animals developed using patented Cre-lox technologies. The Jackson Laboratory is supporting the move towards mouse commons, but it not against patenting per se, and is pursuing patents on techniques to cryopreserve valuable research animals. According to The Jackson Laboratory news archives, it has two patents pending, one for an effective way to freeze and thaw mouse sperm and one for a process to stabilize the genome of laboratory mice to increase the consistency of derived animals http://www.jax.org/news/archives/2009/mainebiz1109.pdf, last accessed 26/05/2010.

[11] The nomenclature for the related Japanese NOD mouse is commonly written NOD/Shi-*scid*/IL-2rγ^{null}. This similarly points to the NOD – non-obese diabetic strain of the animal, with the SCID – severe combined immune deficiency – mutation, with a targeted mutation of the IL2 family common cytokine receptor gamma chain gene. As outlined above, the nomenclature for the Jackson NSG mouse is more fully transcribed as NOD.Cg-*Prkdc*^{scid} Il2rg^{tm1Wjl}/SzJ. The extent to which this fuller nomenclature – including the suffix 'J' detailing that the mouse is held at the Jackson laboratory and the fuller description of the gamma chain mutation - indicates an animal which significantly differs from the NOD mouse is the substance of the lawsuit. Reports from the latest stages of this case indicate that questions of

nomenclature are still being settled, http://www.wolfgreenfield.com/newsstand/press-releases-253, last accessed 27/05/2010.

[12] See http://jaxmice.jax.org/jaxnotes/513/513a.html, last accessed 28/05/2010.

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