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Arguably Big Biology: Sociology, Spatiality and the Knockout Mouse Project

Gail Davies

A critical challenge, following the completion of the Human Genome Project, has been how to make biological sense of the sequence data amassed and translate this into clinical applications. A range of large biological research projects, as well as more distributed experimental collaborations, are seeking to realise this through translational research initiatives and postgenomic approaches. Drawing on interviews with key participants, this paper explores the biological assumptions, sociological challenges and spatial imaginaries at play in arguments around one of these developments, which is using genetically-altered mice to understand gene function. The knockout mouse project (KOMP) is a large-scale initiative in functional genomics, seeking to produce a 'knockout mouse' for each gene in the mouse's genome, which can then be used to answer questions about gene function in mammals. KOMP is frequently framed as one successor to the Human Genome Project, emblematic of the ambitions of internationally-coordination biological research. However, the development of new technologies for generating and managing genetically-altered mice, alongside the challenge of asking biologically meaningful questions of vast numbers of animals, is creating new frictions in this extension and intensification of biological research practices. This paper introduces two separate approaches to the future of international research using mutant mice as stakeholders negotiate the biological, sociological and spatial challenges of collaboration. The first centres on the *directed research* practices and sociological assumptions of KOMP, as individual researchers are reorganised around shared animals, databases and infrastructures. The second highlights an alternative vision of the future of biomedical research, using *distributed management* to enhance the sensitivities and efficiencies of existing experimental practices over space. These exemplify two different tactics in the organisation of an 'arguably' big biology. They also critically embody different sociological and spatial imaginaries for the collaborative practices of international translational research.

Keywords: Big biology; functional genomics, Knockout Mouse Project (KOMP); mutant mice; geographies of knowledge; spatiality.

The Knockout Mouse Project

> *"The knockout [mouse] effort is arguably the largest international biological research endeavor since the Human Genome Project" (Grimm, 2006: 1862)*

This sentence is an intriguing invitation to consider the nature of big projects in the contemporary biosciences. That international efforts to produce and characterize a genetically-altered knockout mouse for every gene in the mouse genome is a large-scale undertaking is perhaps self evident[1]. But what does the word 'arguably' signify in this sentence? The alliterative juxtaposition of 'arguably', 'international' and 'endeavour' insert this effort into debates about the changing scope and scale of big biological research (see Davies, Leonelli and Frow, this volume). The adverb opens up questions about the way size is achieved or claimed and the implications of framing internationally distributed research as an identifiable project. It raises questions about the inheritance of the Human Genome Project (HGP) as a model for big biology, and its influence on efforts by contemporary biologists seeking to make biological sense of the genome sequences produced. The hesitation in naming a successor to the Human Genome Project also raises questions about the scientific status of large-scale biological infrastructures and the interrelations between building access to biological resources and furthering experimental understandings. In this paper, I argue these questions not only have implications for the way biology is being organised, understood and practiced; they also indicate the co-existence of different ways of thinking about the operation of scale and the organisation of space in collaborative postgenomic research.

[1] 'Knockout mice' are mice that have had their genome manipulated to eliminate a single gene. This allows researcher to explore the effect this gene has on animal development and phenotype to help decipher gene function. Knockout mice are only one of the many genetically-altered animals now being produced. They differ from transgenic mice, which have had DNA from another species introduced into their genome. Most knockout animals are produced through first generating targeted knockout mutations in mouse embryonic stem cells. Embryos are extracted from mice 4 days after fertilisation, and an inserted sequence of artificial DNA is used to switch off the specified gene. ES cells are used because the gene will then be knocked out of all the adult tissues. The altered ES cells are injected back into a mouse embryo, which is then implanted in an adult mouse uterus and allowed to develop. The National Human Genome Research Institute has a fact sheer on Knockout mice http://www.genome.gov/12514551 (last accessed 27.11.12)

Policy accounts and scientific commentaries following the HGP have stressed two key dynamics of contemporary large-scale biological research: *scale* and *mobility*. The first refers to the scaling-up of DNA sequencing and the challenge of making sense of the huge amounts of genome sequence data generated over the past 15 years. As the commentary by The International Mouse Knockout Consortium (2007) explains 'the great challenge facing biologists today is to ascribe function to the thousands of genes discovered through these efforts' (2007: 9). The second dynamic is that of translational research, which gives renewed attention to the mobility of knowledge and value across domains, notably in developing new architectural and institutional forms which articulate the movement of biological research from experimental to clinical settings (Franklin, 2006; Martin et al, 2008; Leonelli and Sunder Rajan, forthcoming). KOMP is an explicit attempt to address both questions of scale and mobility in large-scale biological research: scaling-up functional genomics by systematically manipulating the whole mouse genome to elucidate gene function and translating research to help understand the contribution of mutant alleles to inherited human diseases.

In this context, the word 'arguably' opens up consideration of whether the painstaking, time-consuming and sometimes uncertain practices of generating, characterising, archiving and distributing knockout mice actually coheres in a way that allows its identification as a singular project of translational research. The organisation of KOMP is complex and overlapping with other initiatives, involving researchers in many different institutions[2]. At the highest level, KOMP is running alongside EUCOMM (the European Conditional Mouse Mutagenesis project) and NorCOMM (the North American Conditional Mouse Mutagenesis project) in international efforts to generate mouse gene knockouts. Within KOMP there are a number of elements which articulate 'to enhance the availability and utility of mouse knockout strains' (Collins et al, 2007: 9). Scientists developing the ES cell precursors to new mouse model development are based in the University of California Davis (UCD), Children's Hospital Oakland Research Institute and the Wellcome Trust Sanger Centre in the UK, with additional support from the private pharmaceutical company Regeneron. Distribution of these biological resources is facilitated by the KOMP

[2] For further information see http://www.knockoutmouse.org/. Last accessed 16.03.2012.

Repository at UCD, the European Mouse Mutant Cell Repository (EuMMCR) and the European Mutant Mouse Archive (EMMA). There are some further 19 US health institutes and other international centres helping understand the value of these mouse models for human biology. Data coordination is centred on the Mouse Genome Informatics Database, developed and curated by the Jackson Laboratories in Maine USA. Funding has been provided by the US National Institutes of Health (NIH) for work in both the USA and Europe, with additional resources from the European Union and The Wellcome Trust. Together and separately, they are working to add biology back into genomics; breeding mice from a known background strain with a known gene knocked-out, using these to explore the links between gene and gene function, with the hope of developing new understandings of mouse biology of value for human therapeutic applications. On the one hand, this is large-scale functional genomics. On the other hand, it is a series of still-emerging international and interdisciplinary initiatives, seeking economies of scale to reduce the costs of animal model production and speed up the translation of genomic research from basic biology to clinical application, but without a clear sense of the most effective routes for achieving either reduction or translation.

There are thus further social scientific questions about how to understand the emergence and coherence of these big biological projects, in ways which are attentive to their complex dynamics and the disparate biological, social and other imaginaries which animate them. In conversation with scientific researchers, some of whom are directly involved in KOMP and some of whom are not,[3] it is clear there is a critical third dimension to such large-scale biology: that is the *spatial* imaginaries and logics shaping the ambitions and achievements of large-scale biological research. These rarely feature in scientific commentaries, but are

[3] This paper is based on research carried out for the ESRC fellowship 'Biogeography and Transgenic Life'. This traced the different ways mice are 'on the move' in contemporary biomedical research: internationally, in the establishment of large-scale mutant mouse resource centres; corporeally, in the development of further mouse models of human disease; and affectively, in the changing ways these animals are figured in different scientific, regulatory and ethical cultures. This paper is based on ethnographic research, literature review and in-depth interviews with key scientists involved in and critiquing the development of KOMP, carried out in the UK, USA and Singapore from 2008-2009. It is further informed by over 80 interviews with research scientists, animal welfare scientists, regulators, patient groups and others involved in the changing use of mouse models, as well as participation in research meetings and conferences. All research participants were offered anonymity.

increasingly the focus of social scientific research. Pioneering work by Parry (2004) on the global trade in bio-information shows how the circulation and commodification of genetic plant resources are layered onto spaces central to the earlier dynamics of plant collecting (Parry 2004). Cooper has shown how the epistemologies of the life sciences are increasingly being reshaped alongside the regulatory logics and economic spaces of neoliberal economics (Cooper 2008). Further studies have explored the uneven geographies at stake in the globalisation of biomedical experimental practices (Sunder Rajan 2006), as well detailing the architectures which shape materiality and ethics within and between specific laboratory and clinical spaces (Franklin 2006). In different ways these studies demonstrate the complex intersections between the biological, sociological and spatial, at a time when both postgenomics and the globalisation of science are opening up new questions around the contextualisation of biological processes and the spatialisation of bio-value.

Spatial questions have shaped my own ethnographic research on the changing production, circulation and regulation of mice as model organisms in international biology (Davies 2011a, 2011b; 2012a; 2012b). In this paper, I explore how the spatial imaginaries underpinning international research using mutant mice figure the sociological challenges of collaboration and the emergence of biological insights in different ways. These are more implicit than questions of scale or mobility, but they emerge when respondents reflect on what a geographer might be doing researching a world of mice. This perhaps exploits the ethnographic truism that respondents assume you are there for the same reasons they are, but is intended as a generous engagement with spatial, social and biological assumptions articulated as researchers reflect on the challenge of coordinating research practices across infrastructures, disciplines and spaces. Here, I want to outline just two of these. The first draws attention to the *directed practices* of KOMP and the emergence of sociological challenges as researchers are rearticulated around uniform animals and shared databases. The second highlights arguments for the more *distributed management* of biological resources through questions about the efficiencies of monitoring practices and understanding differences across space. These two modes of imagining and spatialising research are not exclusive or exhaustive, but characterise a central tension between

standardisation and heterogeneity, the articulation of community norms and the management of biological excess, in the contexts of international translational research.

The Directed Practices of KOMP

> *The opportunities are huge. […] The challenges are getting the community to buy into such an approach. It's a little bit like the human genome project: it's expensive; it deflects resources into bigger centres. So, there's all of those negatives associated with it, and you have to convince people that the ultimate value is going to be much greater if it happens (Scientist 1, UK 2008).*

One of my interviews starts with the observation the only mouse this researcher works with operates his computer. We probe the complexities of biological databases before talk turns to the intersections of science, sociology and space. This researcher is integrating information from the diversity of work done with mutant mice, through a database storing gene expression data, for both wild-type mice and mutant mice. The gene expression database is part of the larger mouse gene informatics system or MGI. This is a public database aiming to assimilate information from ongoing mouse research and make it available to the wider scientific community. This publicly accessible repository incorporates data from existing scientific literature and other databases. It also helps the extended parts of KOMP coordinate priorities across institutions. This is central to KOMP's aim of reducing the costs of using animals in research – costs to funders and to the animals themselves – whilst speeding up research for those animals with most potential as models for translational research. As he explains, 'coordination means avoiding redundancy of work and making informed decisions in terms of prioritisation' (Scientist 2, USA 2009). Reflecting on this, he suggests it makes a good case study for someone interested in the geography, or international coordination, of science: 'The KOMP data coordination centre is a really nice example that works because there are a lot of things that do not necessarily work as they are supposed to' (Scientist 2, USA 2009). I prompt him to develop this analysis for me. The resulting narrative takes the conversation back to the founding of KOMP.

The core aims of KOMP are detailed in an article collectively written for *Nature Genetics* by the Comprehensive Knockout Mouse Project Consortium (2004)[4]. From the start, the composite authorship makes clear a community is being forged alongside a biological research project. The authors were involved in a series of meetings, commencing 2003 at the Banbury Conference Centre at Cold Spring Harbor Laboratory in the USA, which articulated an ambitious vision for the future of research using knockout mice. After reviewing the patchy availability of fully characterised knockout mice in academic literature, the paper lays out the objectives of KOMP as a coordinated initiative for the generation of mouse ES cells and subsequent characterisation of mutant animals. Centralisation is argued to produce benefits in terms of financial savings – the 'economies of scale in an organized and carefully planned project' (The Comprehensive Knockout Mouse Project Consortium, 2004: 921) – and in terms of biological standardisation – the 'uniform use of knockout methods, allowing for more comparability' (2004: 921). Yet beyond these centralising practices, the overall aim of KOMP is outward looking and more centrifugal – to 'accelerate the translation of genome sequences into biological insights' (2004: 921). It is also ultimately global in its language and aspirations. The paper concludes: 'this ambitious and historic initiative must be carried out as a collaborative effort of the worldwide scientific community, so that all can contribute their skills, and all can benefit' (2004: 923).

There are thus two assumptions embedded in KOMP. The first is the epistemic and ontological supposition that accelerating translational biomedical research is best achieved through centralising biological resources. The second is the sociological presumption of a worldwide scientific community, willing to share skills and benefits via a project led largely by Euro-American scientists. Both are susceptible to a characteristically spatial ambivalence, around what is gained from being gathered together and what is lost for those places, people and practices finding themselves on the margins. There is also the complex, but equally spatial, question about whether the most valuable insights for translational

[4] There is an overlapping area of debate on establishing protocols for mouse sharing (Einhorn & Heimes 2009). This is an important component to the realisation of KOMP, but full consideration of changing property regimes for research animals exceeds the scope of this short paper.

research, connecting laboratory research to clinics or communities, are going to emerge from standing at the centre of things.

In seeking uniformity across knockout methods, a critical challenge for KOMP has been agreeing the use of in-bred mouse strains and developing shared bio-ontologies for describing genes and phenotypes. This standardisation is important for KOMP to contribute experimental results, as well as research animals, to endeavours in functional genomics. Tracing the effect of knockout genes on animal development requires a consistent and well-characterised genetic background. Without, KOMP becomes a rather elaborate mechanism for facilitating off-the-shelf access to a range of knockout mice; a potentially important function, but arguably not science. Inbred mouse strains provide animals with known genotype and phenotype, allowing researchers to identify experimental outcomes from genetic alterations. But there are many different kinds of inbred mice. An initial decision had to be made over which strain to use. The knockout mouse project is organised around the mouse strain C57Black6. This was not an immediately obvious choice and it has some consequences.

Proposed image here

The ES cell precursors used in KOMP were originally developed in the mouse strain 129 (Evans and Kaufman 1981). Yet its genetic background is complex and 'messy', the animals have known neuro-anatomical abnormalities, and as adults they are slow to breed. The C57Black6 had already become the favoured strain for researchers using transgenic, rather than ES cell, techniques to genetically-alter mice. These animals are more resilient breeders, and their widespread use means their phenotypes are better characterised[5]. At the start of KOMP it was not known if it was possible to produce ES cell lines from the C57Black6 mouse. The assumption was made that it was, but it was a risk. As one scientist reflects: 'sometimes we can get so full of ourselves, that we think we're so good and

[5] Much of this ubiquity comes from the simple fact they were the animal favoured by Elisabeth Russell in the 1930s, who backcrossed many early genetic experiments onto this background strain (Scientist 7, USA 2009). For further information on the history of making laboratory mice in the USA see (Rader, 2004).

everything works so well on paper, that of course the biology will agree' (Scientist 3, USA 2009). In the event, and in this case, the biology agreed. Markers of success are emerging in papers suggesting 'investigators are on the home stretch of the largest international biological research initiative since the Human Genome Project' (Dolgin 2011: 262). Figures on the KOMP website[6], show the expanding numbers of DNA vectors, ES lines and mutant mice available from each centre. Yet, there are potential costs to this focus on a single strain. Some of these derive from known issues with C57Black6 mice: they lose hearing early; they may have behavioural issues; they also methylate DNA rapidly, changing gene expression. There is also the risk of over-centralisation, such that research on other strains is left undone and biological insights lost due to what one researcher called these 'Black6 blinkers'.

Further complexities emerge in standardising gene terminologies, bio-ontologies, husbandry standards and phenotyping protocols used by different researchers. If centralisation of data is the aim, then unambivalent knowledge of terms and practices is required in advance. As my respondent suggests 'we need to have a clear understanding of what we actually mean before we do any coordination, otherwise it would create a huge mess' (Scientist 2, USA 2009). He explains how terminologies and practices change over time and vary over space, with new generations of sequencing technologies and different gene models in different databases. There is the challenge of standardising vocabularies to codify phenotypes, such as three dimensional anatomical structures. There is also the growing complexity of the animals themselves. KOMP is increasingly working with conditional mutants, where genes can be switched on and off at different stages of development, so vocabularies are required for a 'genotype that is mosaic, and there is a time-space aspect of the mutation' (Scientist 2, USA 2009). These biological complexities extend beyond the animal, as gene function is increasingly understood in relation to its many environments, raising the tricky question of where to stop when key factors are still unknown. He admits this is potentially irresolvable: 'we were involved in a project where we studied the impact of diet and drugs and environment. But where do you stop this

[6] For updates see http://www.knockoutmouse.org/about/geneprogresssummary. Last accessed 16.3.12.

collecting? Where do you? It could make a difference if there's one or two mice in the cage, it might depend on the mood of the animal caretaker. I'm serious! You have to do something that's reasonable, but it's always …' (Scientist 2, USA 2009).

In addition to these biological complexities this is the growing realisation 'the main problems we have to deal with are sociological' (Scientist 2, USA 2009). While trying to resolve internal complications, they are also working to secure the external participation of scientists. There are several issues here (see also Leonelli and Ankeny 2012). Some are the immediate and well recognised ones to do with encouraging researchers to submit data electronically. Scientists do not get credit for the electronic submission of data as they do for publication, so incentives are low. The barriers can also seem high, as submission requires initial investments in learning to format data for databases, something he suggests researchers resent, even if they would spend significant periods learning new biological techniques. Even when depositing data is a funding requirement, he suggests agencies are hesitant to enforce data submission for fear of a backlash. Those building databases recognise these sociological challenges and do their own market research: keeping weblogs and posting surveys to ask how researchers are using their services and how they might be improved.

There are further sociological challenges, which relate to securing scientists' investment in the more abstract scale and value of KOMP. Given the everyday costs of contributing to centralised databases, scientists have to buy in to the vision that this is the best way to progress research in functional genomics. The importance of 'selling scale' is emphasised on both sides of Atlantic. As a UK scientist suggests, 'the impediments are financial, political, sociological to some degree. […] I think that probably the hardest one is to convince the community that a big project of this scale is going to be hugely beneficial for understanding what a genome is about' (scientist 1, UK 2008). The extent to which scientists value such big projects depends upon their research, their experiences and their location. The importance of place emerges in comparison between the way European and North American parts of KOMP are progressing: the difference between having central funding or soft money available for data integration. In Europe, the emphasis has been on

developing large-scale resources to integrate research from the outset, with the ultimate aim of phenotyping the full-range of mutants; an inductive, open-ended empirical exploration which seeks to encompass the whole mammalian genome[7]. In the US, the project had to fit within the disease funding structures of the NIH, so phenotyping efforts were initially more fragmented. With its focus on centrally funded research, and what one respondent identifies as a commitment to furthering the 'European project' through science, integration between databases has progressed more quickly in Europe. During my research there was a suggestion the USA was playing catch up, albeit increasingly rapidly. However, these international differences, and their divergent imaginaries of research community, ownership and output, raise questions, for some, about the feasibility of full integration.

> I think the whole model organism community and specifically the mouse community in Europe, has over the past five years, really coalesced under these European Union group projects. They've really focused on advancing the use of mouse as a model system. So I think a lot of the data we're getting from Europe is because of that focus. There probably will be parallel types of resources developed in Europe and elsewhere cooperatively, if not collaboratively. I mean so maybe [X] will build something like the mouse phenome database but if he does that, then the data that gets submitted to his database would also be shared in a way that we could also access it and vice versa, even if we can't get people to all buy in. This is to me one of the stresses of globalisation. How many databases do we need and who manages them? There's always this thing about, where is this resource going to live and be housed? I think human nature is such that you kinda want to have something of your own to point to. If you know what I mean? (Scientist 4, USA 2009)

[7] The European Commission has provided Sixth Framework Programme funds to integrate data emerging from the variety of mouse projects in CASIMIR (Coordination and Sustainability of International Mouse Informatics Resources). Although KOMP is a trans-NIH initiative, the larger amount of funding for the integration of gene and phenotype data for mutant mice has come through Europe.

The potential of KOMP is underpinned by the visions of a big biology, unfolding through the co-production of a global scientific community, which shares data and biological resources, centred around large research centres. For its proponents, this centrally organised project is still the best way of accelerating insights from genetic resources for translational research. In this sense, it is framed as a successor to the HGP. It may never 'capture the imagination, the way of "I can sequence a whole genome", but I do think it's how we're going to learn what each gene does' (Scientist 5, Singapore 2009). The central assumption of KOMP is that organisation is ultimately better than serendipity; biological complexity or 'mess' is inevitable, but standardisation and central organisation is essential for the effective utilisation of genetic resources. However, even its proponents acknowledge it is not the only route. There are opportunities, but there are recognised costs. For the diversity of biological researchers making up the mouse community, with a history one respondent compares to a cottage industry, it represents a significant and not always welcome shift. Furthermore, as the complexities of characterizing and defining genes, phenotypes, animals and environments across complex time-space patterns mount up, so do questions about the overall value of centralisation, and whether massing animals and amassing data in this way is the most efficient, effective and ethical way to further biological understanding of genetic resources for translational research. There are biological, sociological and spatial challenges, and there is not one solution.

The Distributed Management of Biological Resources

> *'We spend a lot of time on management because we see opportunities in this industry, that haven't yet been realised on how management can improve how we do things faster, better, cheaper, like you see in almost every other industry, but it's been very late coming to ours' (Scientist 6, USA 2009).*

In another interview, within the biological resource centre of a large American university hospital, I encounter a different understanding of my research. The meeting starts in an unexpected way. Uniquely, I am not asked to explain why a geographer is researching the production and circulation of mutant mice. I have seen this researcher talk at conferences,

and sent some explanatory sentences on my interests. In our opening conversation, he reflects back to me the importance of geography in identifying challenges and opportunities for contemporary laboratory animal science, much of which remains trapped in local frame and scale.

> ‘Geography, in your definition of geography, is extremely important and biomedical science is experiencing a geographical shift today. Whether they know or care, it is going to have pretty big implications on how science gets done.’ (Scientist 6)

Questions of space permeate our conversation, ranging across scales from the potential for the international offshoring of biological resource centres to the growing use of radio frequency information devices (RFID) to monitor movements within laboratory spaces. This individual is involved in managing the provision of specialised mouse strains within his organisation, a task both providing services and shaping biological approaches. He is also working internationally and is well respected, but he is not directly involved in KOMP. Instead of looking to imitate European databases, he is seeking to emulate the spatial practices of successful industries. Alongside biological research, he is reading management theory, citing journalist Thomas Friedman on globalisation. He suggests the reorganization of biological and experimental practices across space is essential to maximising the value of genetic resources. He recognises this might be radical given the reluctance of scientists to explore sub-disciplines down the hallway, which is ‘the next and obvious step for people to take before they go across town, much less across the ocean’. But, he is confident the international reorganisation of research is vital for translational research using genetically-altered animal models, in the light of biological complexity and the potential for personalised medicine. In this imaginary, the spatialities are flat rather than hierarchical, expertise is mobile rather than nationally organised, differences incorporated into experimental systems rather than standardised, and costs saved through management at the margins rather than coordination at the centre. The spatial dimensions to this enterprising logic are intriguing and despite their clear articulation with the spatial logics of neoliberal economics, their biological and ethical implications are not so easily categorised.

First, reducing costs is related to enhancing the ability of research to cope with the growing scope of biological enquiry, not only by standardisation but also by taking difference seriously. This is not the search for economies of scale through the uniformity of biological resources. Rather their work with genetically-altered mice has been central to a growing recognition of complexity. As he suggests, 'we're no longer simply interested in an animal living or dying [...] now we're focusing on specific receptive molecules, we're focusing on gene activation, and we're focusing on genetic differences between individual animals'. The need to produce data at a higher resolution, and for more animals, is seen as essential to reaping potential rewards of genetic understandings for translational research and personalised medicine[8]. As the complexity of biological understanding increases, so does the value of research animals, and the requirements for information about their care and their environment, especially their husbandry, microbiology and health. This challenge is shared in KOMP, but here demand for detailed data puts the whole organism in its environment, rather the gene itself, at the centre of attempts to utilise the value of genetic resources. There is some standardisation; contemporary biological research still requires a well-characterised genotype, but this is not standardisation around one inbred strain in a single project. It also extends consideration to the life experiences of the individual animal. Pressure from humane societies, in raising awareness throughout the laboratory animal community, is welcomed as a means to support forms of care that might extend the lives of animals and aid translation of data between animal model and clinical practices. This point is explained to me in detail, and on more than one occasion.

> 'If you want to talk about personalised medicine models [...] that requires a lot more investment in the care and the environment of that animal. So we as lab animal care providers, are giving to our customers, the scientists, as well-defined and as least variable an organism or a model or an entity as possible, so that you avoid a lot of the statistical noise that you might see otherwise.

[8] Developments in personalised medicine are changing the way model organisms are being used in experimental and translational research. Whereas conventional biological research using model organisms relies on statistical models to make judgements about the safety and efficacy of new therapeutic interventions at the level of populations, personalised medicine seeks to examine the wide range of data relevant to the genetic profile of individuals being treated. See for example Davies (2012a).

> Coupled with that is much more public awareness, concern, scrutiny of how animals are used and how they're cared for in the lab. So there's a lot more attention being paid on things that 10 or 20 years ago, weren't very common. Post operative analgesics for mice, routine today, wasn't even considered critical 20 years ago […] There's a much greater investment in time and money into these animals, to give scientists the evolving detailed data that they need.' (Scientist 6)

The growing importance of attention to both animal genotype and environment, and the investments of time and money into research animals, is shared in discussions of KOMP. However, what is different in this spatial imaginary is that doing things 'faster, better and cheaper' is not about managing biological resources through centralised projects in the USA and Europe, but about redistributing research practices across space, to reduce costs and enhance sensitivity to biological difference. He reckons about 25-30% of the mouse capacity at any major research institute today is devoted to breeding. Animal facilities are expensive to maintain in the USA. They are also costly to build, and facilities are running out of room. In his institution, they are searching for places, overseas, 'that are doing things acceptably well for a whole lot less money'. He is looking to locate mouse facilities overseas, building a satellite breeding and holding facility in China, which would operate under the supervision of the US resource centre. Most experimental practices would remain in the USA, but breeding and cryopreservation would take place elsewhere, with frozen embryos shipped back to be re-implanted into animals in the USA. There are still questions to be resolved: over reliability, protection of intellectual property and veterinary competency and authority. Vets have final authority on animal procedures in the USA; in China, the scientist is in charge in the final instance. But he praises the pragmatism he finds outside the USA and Europe. Overseas laboratories who want to collaborate are rapidly seeking AAALAC accreditation[9], which requires them to adopt US animal care guidelines, so for him trust and understanding are slowly being built.

[9] Association for Assessment and Accreditation of Laboratory Animal Care International http://www.aaalac.org/ Last accessed 16.03.2012.

This vision of the future of international research using genetically-altered animals configures the intersection of the sociological, biological and spatial differently. As in KOMP, there are opportunities and there are potential risks, but these are rather differently distributed. Managing research across different places, rather than centralising research practices, removes some of the sociological challenges. It is less dependent on the co-construction of a shared global scientific community, treating scientists as specialised customers rather than a single community. Collaboration and trust are sought through quality assurance rather than through creating collective identities. It is also more agnostic about the experimental biological practices through which new insights might emerge. Biological differences encountered in other places become potentially relevant for developing personalised medicine and furthering the scope of translational research. In this sense, space, or geography, is not only a resource managed to reduce costs, it can also add value for US and Chinese partners. As he reflects,

> ‘Ethnic minorities in China have very different rates of cancer [...] Is it diet, is it genetics, is it a combination of both? And combine with that a lot of these ethnic minorities have their own traditional medicines specific for this. So one of the research programmes we’re discussing with our Chinese contacts, is to establish in combination with this mouse breeding service [...] I don't know what the right phrase is, a localised cancer research initiative for each one of these outlying populations. Then can we start looking at extracts of all these traditional medicines that have been evolving for centuries with those cultures, to see if there’s any gold in some of the elements that go into those concoctions. And then treat those xenograft mice bearing those tumours with extracts, to see if we can find a new cancer drug. It may be active only to those genotypes or it may be active to all humans, we don't know. But this is where we see geography now contributing to medical science. ‘(Scientist 6)

The imaginaries of this research are more spatially extensive and biologically distributed. The previous focus on European and North American research is widened as Asia enters the conversation. The response of research to biological differences is more distributed than

in the central integration of KOMP. This is science framed through biological emergence and economic imperatives, realised through management at a distance; a conjuncture of practices resonating with other accounts where transnational neoliberalism meets biocapital (Cooper 2008). It is still underpinned by a central political vision, of science as an international endeavour, regulated through quality assurance mechanisms, but without the centralizing practices for animals, people and places in a project like KOMP. In the end, this individual is fairly scathing about the potential of centrally directed 'big biology', to maximise understandings in functional genomics or improve animal welfare.

> 'People are now looking for ways to justify the huge costs that have been made in these large lists, as opposed to letting nature tell us […] on an ad hoc, case by case basis. Because if you went back to these large centres for phenotyping cores and asked them what was their yield, what was their return on investment, how many surprises did they discover that were actually either of major animal welfare impact or of additional scientific value? I'm guessing that percentage is very low. It was a very logical edifice to construct earlier and a very logical concept to emerge, but in a performance based mentality, is it still adding value? It's very expensive and so let's move on' (Scientist 6)

In this framing, new biological understandings emerge from being open to surprise (Braun 2008). Biological complexity is not seen as amenable to the logics of centralised engineering. Rather the management and understanding of experimental excess, for both human and animal health, has to be negotiated on asking on a case-by-case basis: 'have we created an animal that clearly is in a worse state than it was before and do we need to provide additional veterinary accommodations for that animal? Or have we now created an animal where the accident is of scientific value?' Answering this question requires the spread of surveillance technologies of both animals and animal care-takers. There is a link between the internationalization of science and the monitoring of space at the smallest scale, in laboratory, even the cage. Being able to answer questions about animal welfare or scientific value requires skilled technicians to work with animals, wherever they are to be housed. Our conversation ends with a discussion about the emerging use of RFID

technologies to track laboratory animals, providing biological data on animal behaviour or monitoring institutional processes as cages and people move around[10]. Conformities can be achieved through such devices without requiring technicians or researchers to invest in a central biological project or share the same notions of a global scientific community. This is arguably not 'big biology', but an assemblage of international technoscientific practices, animated by the language of customers and the distributed management of animal and human life.

Conclusions

This paper has presented two distinct visions for the future of international collaborative biology as research with mutant mice gathers in pace and scale. The two approaches embody different biological assumptions, sociological challenges and spatial imaginaries in the search for effective means of developing mouse genetic resources for translational research. These are not the only ones, and they are not exclusive, but I argue they are instructive for considering what is at stake in the contemporary intersection of the biological, sociological and spatial. The first centres on the integrative practices of KOMP, as animals and researchers are reorganised around shared animals, databases and infrastructures. The second highlights an alternative vision, using distributed management to reduce costs and enhance the potential for biological insights to emerge across space. These international visions cannot be explained by attending only to the local assemblage of technological and biological artefacts through which research is mobilised and scale emerges. Rather, these assemblages are composed and animated in part through such biological, sociological and spatial imaginaries from the outset, with implications for the individual scientists, national institutions and research animals involved. These different

[10] There are emerging discussions about how RFID technologies might be used to train animal caretakers to work with animals in standardised ways, by training bodily movements, rather than disseminating written instruction. Attach sensors and transmitters to the room, cage-racks and sleeves of staff, set the standard operating procedures for a given task, for example handling micro-isolator cages, and each person can then be evaluated, for efficiency and precision, against the programmed sequence of movements. This development is still nascent but has the potential to transform discussions about the value of tacit knowledge in relation to both the geographies of scientific knowledge and embodied practices of animal care.

spatialisations are simultaneously political-economic and techno-scientific (Parry 2004; Braun 2006). Both indicate a different settlement in the oscillation between the centripetal practices of standardisation in experimental biology and the more centrifugal demands of translational research, and the value of centralisation and the valorisation of difference in economic organisation and scientific research. For both, their spatial imaginaries come at a complex conjuncture of late capitalist economic organisation, the internationalisation of science and the postgenomic sciences, whose intersecting contours are currently hard to pull apart.

In the early 2000s, influential work by Franklin et al (2000) drew attention to the emergence of the 'global biological' in relation to international developments in stem cell research and genomic technologies. The spatial and biological forms underpinning the global reach and ambition of these technologies were 'predicated on the reduction of nature to the molecule or the gene' (Braun 2006, p.650). This conceptualisation draws attention to the 'double reductionism' involved in earlier battles over biotechnology (McAfee, 2003). First, biological reductionism extracted genes and molecules from their 'cellular, environmental and cultural contexts' (Braun, 2006, p.650). This genetic reductionism enabled the economic reductionism through which genes were circulated as tradable commodities, enclosed via property rights. Through such means genes were constructed as essentially 'placeless', susceptible to de-localization and circulation. The informationalisaiton of biology around genetics was seen to herald a particular mobilisation and globalisation of molecular life (Rose 2007).

In conclusion, I want to suggest the postgenomic sciences are reopening the spatial assumption of the 'global biological'. Of course this transcendence of space was never achieved, and only sometimes claimed, but the return of attention to the spatialisation of biology and value in the experimental and management practices of the postgenomic sciences demands detailed consideration. This can be exemplified in the challenge of centralising animals and data in KOMP, which not only involves uniform animals and gene ontologies, but also careful considerations of environment, from the scale of the body to the located practices of animal husbandry. In many ways, KOMP inherited the genetic

reductionism from the early Human Genome Project, working sequentially and logically through the genome of a single animal. The subsequent 'respatialization' of biological research, partly emerging out of projects like KOMP, thus presents a challenge to its directed organisation. The registers of centralisation in play, which are simultaneously biological, geographical and sociological, are tricky to align and to that extent do challenge the idea of KOMP as an obvious successor to the HGP.

The alternative presented above is an economic reorganisation, epistemic agnosticism and increased surveillance. It is possible to see in this attentiveness to biological emergence conceptual confirmation of a 'neoliberal biological' science, with its rolling back of central state-based organisation and rescaling of regulatory capacities around audit cultures. However, here too, these biological, sociological and spatial imperatives do not map neatly onto one another, and there is more space to articulate alternative ethical and postcolonial perspectives in this distributed management of mutant mouse resources. Collapse questions of biological organisation and neoliberal economics too quickly and there is a risk of spatial reductionism too, extrapolating from the historical experience of western science and closing down the questions about the operation of biological contextualisation within postgenomics. If we are to understand the emerging contours of this arguably big biology I suggest we need careful mapping of its spatial complexities and reflexivity about the role of sociological abstractions in our own social science research as well (Castree 2005).

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