Training to Translate: Understanding and Informing Translational Animal Research in Pre-Clinical Pharmacology

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Abstract: We investigate translation in biomedicine by exploring how researchers supported by the British Pharmacological Society's Integrative Pharmacology Fund (IPF) have responded to increasing translational aspirations within pre-clinical animal research. The IPF sought to enhance institutional capacities, collaborative practices, and personal skills within in vivo research in the quintessentially translational fields of pharmacology, physiology and toxicology. We identify three manifestations of the influence of translational aspirations: 1) shifting from the standardisation of animal models to the alignment of research on animals with human therapeutic pathways; 2) expanding relationalities of care in animal research from a focus on the animal body to institutional arrangements around clinical care; and 3) changing training around research ethics, integrity and good statistical practice. Concluding, we discuss the value of working interactively with those involved in the changing practices of animal research and translation as a means to foster reflexivity about what matters when 'training to translate'.

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1. Introduction

This paper reflects on the changing research practices of in vivo pharmacology through the lens of co-produced research carried out with the laboratory animal community. In 2016, the British Pharmacological Society (BPS) funded us to conduct an evaluation of the impact and

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achievements of the Integrative Pharmacology Fund (IPF), a programme that aimed to support animal research and training in pharmacology, physiology, and toxicology in the UK. This involved carrying out interviews with laboratory animal researchers, but also collaborating with BPS members towards developing a framework for understanding the role of in vivo skills and relevant training in the future of pharmacology and related research areas. In what follows, we report our experiences in this project, with the aim of using them as an empirical ground to identify ways in which translational discourse may affect pre-clinical practices of animal research. At the same time, we reflect on how the changing understanding of animal research and translation in Science and Technology Studies (STS) can contribute to the development of laboratory practices within in vivo pharmacology.

Intellectually, this study is located at the intersection of three evolving literatures in STS. The first is work on the practices of laboratory animal research, which since Lynch's classic 1988 study has examined the material transformations and ethical implications of turning animal bodies into scientific data (Lynch 1988). The second is literature on the changing dynamics of translational research. Since the early 2000s, this has challenged linear models of translation, and instead charted the complexities involved in the movement of biomedical research into clinical practice (Sunder Rajan and Leonelli 2013). The third is the growing literature on engagement in STS, which is increasingly exploring when and whether STS should intervene (Martin 2016) and the role of STS in ethics and education (Joyce et al. 2018). What these literatures have in common is an interest in how 'good' science is understood and practiced. Animal research always involves scientific and moral uncertainties, as researchers and regulators work out "the proper relations between the suffering of the research animal and the health of the human" (Dam and Svendsen 2018, 349). The growth of translational imperatives in biomedical research (Harrington and Hauskeller 2014) is reshaping how these relations are understood, adding moral dimensions to the wider collaborations around animal research. These collaborations increasingly include social science scholars (Davies et al. 2016), who are working with the laboratory animal community to understand the practices of laboratory animal science and further both animal welfare and human health. The mutual entwining of scientific and ethical practices in the generation of what Thompson (2013) calls "good science" increasingly features reflexive social science as well.

In this paper, we exemplify these shifts – and the role played by translational imperatives within them – by drawing on our experience in working with laboratory researchers and BPS officers towards the development of discussions around good practice within in vivo research. We start by exploring the existing STS literatures on animal research and translation, drawing out the implications of a growing translational imperative in animal research for the organisational arrangements of animal

research, the roles and relations that are valued, and the changing priorities around reproducibility and validity. We then introduce our collaborative work and reflect on the potential for developing an STS-informed intervention in the practices of translational animal research in pre-clinical pharmacology, detailing the methods used to evaluate and analyse the outcomes of the IPF. On the basis of our sustained interactions with biomedical researchers, we then identify three ways in which the growing translational aspirations have changed pre-clinical animal research practices. Each of these shifts provides a space for productive engagement by STS researchers. They are: 1) shifting from standardising animal models to aligning research on animals with human therapeutic pathways; 2) expanding relationalities of care in animal research from a focus on the animal body to institutional arrangements around clinical care; and 3) the changing focus of training around research ethics and integrity, including different interpretations of statistical good practice. Concluding, we discuss the value of working interactively with those involved in the changing practices of animal research and translation as a means to foster reflexivity about the relations and practices that matter when 'training to translate'.

2. Re-evaluating Animal Research in Translational Pharmacology

Since Lynch's (1988) seminal work on how animals in the laboratory are transformed from naturalistic beings into scientific data, there has been considerable interest in STS concerning the complex practices of laboratory animal research. Ethnographic research inspired by and drawing on Lynch's study has tended to focus on three different dimensions to the work of transforming animals into data, which contribute to what research participants consider 'good' animal research. These can be characterised as: standardisation, care, and training. These dimensions are worth recalling here, for they still describe critically important aspects of the relations between animals, roles, and results that are choreographed in the production of meaningful data from animal research; and they also help to pinpoint how these imperatives have changes over the last thirty years. The organisational arrangements, allocated roles, and nature of affective relations with animals in the laboratory have all shifted slightly with the growth of translational practices in biomedical research. Under UK law, all animal research must be licensed by the Home Office (Animals (Scientific Procedures) Act 1986). Only projects with a positive harm-benefit analysis are authorised and all research must seek ways to replace animals in their research, reduce the number of animals used, and refine methods to reduce suffering and pain – that is, to apply the 3Rs approach of replacement, reduction and refinement (Russell and Burch 1959). The growth of translational research imperatives is now increasing the atten-

tion given to realising research benefits as both a scientific and ethical issue (Davies 2018) and altering the ways by which the 3Rs are applied. This is starting to change the way that standardisation, care, and training are understood and practiced.

The first dimension that has characterised the study of laboratory animal research in STS are the practices of standardisation in the production of 'good' laboratory animals. Historical studies on the development of animal research throughout the twentieth century and contemporary ethnographies of practices in animal research often stress standardisation as the route to reliable animal research[1]. Lynch noted that researchers designated particular laboratory animals as 'good' or 'bad', observing that "[t]he 'goodness' of the animal referred to the readability, clarity, congruence with anticipations of what the data should look like, and the ease with which it could be treated as a standardized member of a cohort" (Lynch 1988, 271). Standardisation remains an important consideration in animal research, but the scientific literature is increasingly concerned with questions around the standardisation fallacy (Würbel 2000) or how certain forms of standardisation intensify issues around validity (Richter et al. 2010). STS accounts increasingly talk about how translation is achieved through "balancing standardisation and individual treatments" (Dam and Svendsen 2018, 349). The unstable experimental humanised mouse model generates value as it becomes a "collaborative thing" around which new translational conversations can accrue (Davies 2012).

The second dimension, evident in Lynch's work and advanced subsequently, has been the STS attention to how animal research is co-dependent on the provision of 'good' animal care (Lynch 1988, Holmberg 2011, Bischur 2011, Viteritti 2013). Care is understood as a bodily and affective skill that underpins the validity of the data by reducing animal stress and ensuring that animals perform in the requisite and desired way. However, for much of the last thirty years, discussion of the role of animal care has been premised on a division of labour between care practices and research practices. Responsibility for care has normally been practiced by animal technicians who work in the animal research facility, and who provide specialised care for laboratory animals and support for the work of principal investigators. There were inevitable tensions between these roles, but as Birke and colleagues (2007, 117) suggest, "animal technicians and high-ranking scientists […] are bonded by shared understandings of what counts as 'good' animal care". Animal care remains critically important, but its scope is expanding in the context of translational research and changing regulation. Researchers, as well as animal technicians, are having to attend more carefully to animal experience to facilitate translation (Friese 2013). There is a growing attention by regulators of animal research to the "culture of care" of an organisation, which is concerned with how communication between roles happens within institutions, as well as the extent to which wider societal expectations of humane animal care are reflected in practice (Davies et al. 2018).

The third aspect of work on animal research in STS has been a focus on what it means to train people to work well with laboratory animals. Despret's (2004) work has been inspirational in drawing attention to how training generates the expectations and affects that authorises a good experimental performance and what it means to become an experimentalist (Holmberg 2008). Despret recounts the work of Rosenthal (1966), who used students enrolled in a laboratory course in experimental psychology to explore how their expectations of what kind of rat they were working with shaped the rat's performance in the maze. Despret explores how "the expectations of a good experimenter have authorized the rat to become competent" (2004, 120), whilst also noting how the rat authorises the student to become competent. Despret's work has informed subsequent studies of how becoming a good experimenter involves learning to "become with" animals. Yet, this too is changing as the expectations of 'good' experimental outcomes shift from the performance of the animal in the apparatus to clinical outcomes. Learning with animals remains a vital component of translational research practices. Friese has observed how training for translational research involved developing the "right 'touch' for surgery" (Friese 2013, 133), so that the researcher could now move between the parts and the whole of the mouse appropriately. The movements required for translation are now more complex: animals may have to be made, unmade, and remade as complex circuits of translation seek to match the performance of the animal to the human experience or mechanism it seeks to model (Svendsen and Koch 2013; Nelson 2018). This happens within experimental practices, but also through increasing contestations over the design of experiments and their statistical inferences (Würbel 2017).

As suggested above, these questions around standards, care and training are not only dominant strands in the STS literature on animal research, but are also growing discussions in the scientific literature. These discussions are particularly evident in the literatures around translational research and in pharmacology in particular. Pharmacology is quintessentially translational in its objectives and practices, as it explicitly seeks to bridge the gap between biological knowledge and drug development for humans and non-human animals. Yet this purported translational achievement is increasingly questioned. Discussions of the pharmaceutical 'pipeline' are frequently couched in terms of a crisis (Sunder Rajan 2017; Murphy 2017), referring to the failure of potentially promising new drugs to progress through the different stages of drug discovery and development from pre-clinical laboratory research (whether in vivo, in vitro or in silico), through safety and efficacy testing in animals and humans, to clinical trials in human patients. To date, this process of attrition has been most visible when drugs have failed to show efficacy in human clinical trials, for this is where 'failures' are most public and costly (Freedman, Cockburn and Simcoe 2015).

At the same time, there is a growing sense that these problems may also be identified and addressed through re-evaluating the practices of pre-clinical animal research. While in vivo research has long been positioned as vital to translational research, detailed discussion of the specific value and limitations of animal models in furthering clinical advances is more recent (for example, Collins 2011). Managing failures sooner in the drug discovery process may be less expensive and have ethical gains in terms of more effective human clinical trials and less animal wastage (Ioannidis et al. 2014). Growing debate over the reproducibility of many studies using animals in research (Academy of Medical Sciences 2015) and the failure of drugs tested on animals that subsequently enter human trials is further seen by some as a fundamental challenge to the ethical justification of biomedical research in animals (Pound and Bracken 2014). Researchers and learned societies are thus increasingly reviewing the different phases of in vivo research to look closely and critically at the practices for translating knowledge of disease mechanisms and treatment between species, including around validity of animal models, experimental design, reporting conventions and forms of animal husbandry and care (Begley and Ellis 2012; Concordat on Openness on Animal Research in the UK; Davies et al. 2017; Nuffield Council on Bioethics 2005; Osherovitch 2011). This raises questions about the operation of animal models, and also about the organisation and implementation of institutional models of translational research.

The opening up of discussions around animals used as models within the research community offers an opportunity to integrate STS studies of animal research with STS work on translation. Earlier models of translation, which viewed the process of producing tangible outcomes from scientific research in terms of a path – bench to bedside – strewn with obstacles to be overcome (e.g. Pober, Neuhauser and Pober 2001), have now largely been superseded. Many scientists and funders acknowledge the complex trajectories involved in translation and the challenges of fostering collaborative relations required to sustain interactive research (Collins 2011; Collins and Tabak 2014; Moher et al. 2016; Zerhouni 2003). Within STS, translation has increasingly been tracked and reinterpreted through attending to how knowledge moves: developing laboratory research with therapeutic outcomes relevant to humans requires organising and managing translational processes so that "biomedical claims, objects and practices" can "move across boundaries" between institutions, disciplines, and species (Sunder Rajan and Leonelli 2013, 466). This promotes certain forms of collaboration, standardisation and regulation. Furthermore, these movements are not only one-way. The movement between research, safety and efficacy testing and clinical trials is increasingly understood as non-linear and recursive, constituting what Lewis and colleagues (2014) characterise as "circuits of translation", which involve both material flows and conceptual transformations at each iteration (see also Crabu 2016 and 2018).

There is a significant body of work within STS focusing on patterns of translational research in genomics (Maienschein et al. 2008), meta-genomics (Levin 2014), stem cell research (Maienschein et al. 2008; Martin, Brown and Kraft 2008; Fagan 2013), neuroscience (Brosnan and Michael 2014) and plant science (Leonelli 2013). The complexity of translation they indicate can help in developing new ways of thinking about the role that animals play in translational research and the training required for researchers to facilitate these practices. Standardisation is no longer the overriding imperative in animal research. Translational animal models need to be stable enough to move, but also sufficiently adaptable to be able to encompass the changing understandings of disease that happen through circuits of translation (Davies 2012; Dam and Svendsen 2018; Nelson 2018). Care for the animal is increasingly seen as not only a shared ethical value, but also an essential component of research, when translation is dependent on stress-linked immunological and other responses (Friese 2013; see also Seok et al. 2013). Training has to be opened up to multiply the "the body we care for" (Despret 2004), to include attuning to and transforming humans as well as animals. In translational research "scientists calibrate animals against the medical phenomena which they are intended to represent. In turn, human medical conditions and the patients who manifest them have to be calibrated against the rodent models" (Lewis et al. 2013, 776).

The question for this study is how far the changing understanding of animal research and translation in STS can contribute to shaping these practices in productive ways. In the next section, we discuss the methods and context for research that we carried out in collaboration with the British Pharmacological Society (BPS) as part of their processes for evaluating past funding and developing future training for pre-clinical animal research.

3. Evaluating the Integrative Pharmacology Fund

This research emerged from a commission, by the BPS, for the authors to evaluate the outcomes of the Integrative Pharmacology Fund (IPF). The BPS are a membership charity, whose mission is to promote and advance pharmacology. They have played a role in the development of in vivo skills in the UK by driving long-term collaborative partnerships and providing funding. The BPS launched the IPF in 2004 as part of its efforts to address a perceived in vivo skills gap (ABPI 2005). It was run between 2004 and 2014 by a consortium involving the BPS and three major pharmaceutical companies: AstraZeneca, GlaxoSmithKline, and Pfizer (see Collis 2006, 2009; Lowe et al. 2016). The IPF was led by a steering group comprising representatives of the funders. It worked with national funding bodies (the Biotechnology and Biological Sciences Research

Council, BBSRC; the Medical Research Council, MRC; and the Higher Education Funding Council for England, HEFCE) to support in vivo education and training. The initial £4 million investment in the IPF was used to leverage total support of £22 million for in vivo research, education, and training. The IPF thus constituted a significant focus for the BPS for over 15 years; was a substantial investment of both public and commercial funding; and has played an important role in shaping the practices, skills and training that have defined pharmacology in the UK over the last 15 years.

The authors were approached to provide an evaluation of the IPF because of past experience in working collaboratively with the laboratory animal community (Davies et al. 2016). The overall scope and organisation of the evaluation project was co-produced between Davies, Lowe, and Leonelli as independent researchers, Anna Zecharia and David Lewis as representatives of the BPS, and BPS member Michael Collis as an independent consultant (following former leadership of the IPF). The project was given ethical approval through the University of Exeter. Research started with a review of the current literature on in vivo skills training through academic and grey literature. Two questionnaires were delivered to those who received IPF support as a Master's or PhD student (25 were returned) and those who were appointed to fellowships or staff positions as a result of IPF support (17 were returned). These were used to gather basic information and recruit participants for semi-structured interviews. Lowe conducted 19 interviews with 20 participants. All participants had been, and many still were, engaged in work using in vivo research. They were asked about how the BPS had supported their work and invited to reflect on the changes they made to the design and conduct of experiments through this training, including around ethical practice, public outreach and research translation. The transcripts of these interviews were coded using the qualitative data analysis software NVivo. The evaluation was completed through two stakeholder meetings organised by the BPS, which provided feedback on the initial findings and enabled the whole evaluation team to develop recommendations in conversation with key stakeholders.

The distinct roles of the University of Exeter researchers and BPS representatives were negotiated at the start of the project to establish boundaries that protected the independence of key aspects of the research and the identity of research participants. A firewall was constructed between the University of Exeter and the rest of the team, ensuring only the University researchers had access to the full results of the questionnaires, including the identity of the respondents. Participants for the qualitative research interviews were recruited from the lists provided by the BPS and sampled by the authors to encompass a diversity of thematic research areas, institutional positions, and personal experiences with the IPF. Of the interviewees, for example: one was the head of an Integrative Mammalian Biology centre (an IMB, discussed in section 4), eight were

researchers working as fellows or permanent research staff members at IMBs, four encountered the IPF as postgraduate students, three worked in senior technical positions at IMBs, two were recipients of 'pump priming awards', and a further two were well-established figures in animal research who were not based at IMBs. To enhance the integrity of the data collected, participants were promised full anonymity and only anonymised quotes from interview transcripts were shared with the BPS. It was agreed at the outset that the data generated in the project would be owned by the BPS but could be used by the authors in subsequent publications independent of the BPS.

The final evaluation report was jointly agreed. The main body of it detailed the empirical material generated, analysed and drafted by the University researchers. The introductory material and final recommendations in the report were guided by the requirements of the BPS, drawing on the interviews and workshops, and agreed in consultation with the BPS council. For the authors, this project constitutes a constructive engagement and intervention into science policy in an area for which the BPS assumes professional responsibility. It is notable that this 'serviceable STS' was for an organisation with little executive power itself (Webster, 2007), but with an established role in guiding norms and standards for its field. The outcomes of the study thus focus on how the organisation and practices of translational pharmacology can be enhanced through education, training, and reflexive conduct by practitioners. The intervention is shaped by the aims and activity of the BPS itself, but also the restricted and specific scope of the power and influence of that organisation within a wider context of education, skills, research and industrial policy and activity. The report was launched in December 2016. One of the initial outcomes from this work has been the development of an undergraduate core curriculum for pharmacology courses in the UK, which was launched in 2018 and now has over thirty organisations signed up[2].

This paper has been developed subsequently and separately from the commissioned work. The interview transcripts used for the evaluation were further analysed to explore how researchers manage the different accountabilities and changing aspirations in translational pharmacology, drawing on coded responses to questions around 'best practice', 'translation' and 'the 3Rs'. In the next section, we draw on this material to explore how translational aspirations are changing the practices of standardisation, care, and training indicated by earlier studies in STS. We show how the work of transforming animals into data sources is being recalibrated at an institutional level, changing what is valued as 'good' science from standardising animals to aligning experiments, expanding institutional interactivity, and in deliberations around balancing research design with the 3Rs.

4. Training to Translate: The Recalibration of Animal Research in UK Pharmacology

A key element of the IPF initiative was the establishment of four Integrative Mammalian Biology centres (IMBs) across six UK universities. These brought together the different disciplines involved in pharmacological research, and were involved in employing staff, awarding PhDs and establishing Master's degree courses to build future capacity for in vivo skills in pharmacology. The IMBs were intended to form centres of excellence, with responsibilities for promulgating high standards of animal welfare and developing innovative forms of research. An important aspect of this was advancing the translational potential of research. This involved a series of changes to practice that we identify below.

4.1 From Standardising Animals to Aligning Pre-Clinical and Clinical Experiments

Different forms of pre-clinical animal research use animal models in different ways. While standardised strains are still used for regulatory toxicity and safety testing, research into specific human diseases or injuries involves the use of 'bespoke' animal models created to model particular aspects of a disease[3]. This dual use of animal models leads to a diversity of proposed solutions to the problem of enhancing translation through in vivo research. Some commentators demand greater standardisation in research, for example through standardised reporting of animal research (Kilkenny et al. 2010), the reduction of bias in publications through experimental randomisation and blinding, the publishing of negative results (van der Worp et al. 2010), and the development of standards for recognising the importance of genetic background effects in animal models (Crusio et al. 2009). Others stress enhancing sensitivity to local experimental situations and individual disease trajectories, including incorporating animal care and environmental enrichment into translational research (Richter, Garner and Würbel 2009; Friese 2013), developing more personalised disease models (Davies 2012), or using biomarkers and so-called reverse translation methods to move in non-linear ways between animal models and individual disease trajectories (Garner 2014). These are not mutually-exclusive, since standardised reporting and greater experimental variability can work together, but these debates do indicate the tensions researchers face in striving for translation in their work.

In our interviews, researchers talked about how they had increasingly moved away from established 'gold standard' models in animal research, instead seeking to match experimental and clinical treatment regimes. This happens, for instance, when seeking to align in vivo research with clinical trial protocols, and model patient experiences alongside disease characteristics. In other words, there has been a sustained attempt to shift

research focus beyond the animal body and related forms of standardisation and control, and towards the circumstances and requirements of clinical care and related institutional arrangements.

Many researchers report making changes to experimental design, especially strategies around dosing techniques and levels, to enable them to scale up to human clinical studies. Some have suggested that there has been a recent shift away from using dose levels in animal research that would generate a statistically meaningful – and thus publishable – effect, towards asking whether the doses and methods of drug application could translate meaningfully to humans, as exemplified by the following quote:

> Are they using the animal model that they are working with in the correct way? Are they dosing at a dose that you could think of translating to a human equivalent that would be actually realistic? Are they thinking about what route of administration would you be giving it in humans in order to actually think about bio-distribution and those sort of things quite early on? (Senior researcher at a small university, 2016)

As pointed out by the same interviewee, sometimes addressing these questions means changing experimental protocols in animal research 'upstream', to match the likely downstream mode and dose of clinical application:

> I've become increasingly convinced that if you are going to do a drug IV [intravenously] then it's got to be IV in the mouse. […] And within the literature I work in, the [mouse model that the interviewee works on] is just littered with examples of mice being fed, or whatever, huge quantities of a drug of some sort which is completely unfeasible in man, completely unfeasible. That's very disappointing because what we've seen historically is clinical trials being developed on the basis of the mouse work, but a disconnect where the human receives a fraction of the scaled dose that the mouse got and it's not surprising that it's not a very successful trial. (Senior researcher at small university, 2016)

Further interviewees discussed how the design, validation, and use of animal models are themselves modified to produce results of greater translational potential. One researcher described a change in use of mice models to simulate the human experience of neurodegenerative disease, where drug treatment follows diagnosis rather than preceding the onset of symptoms:

> We wanted to use an animal model and a time course that was going to be translational. What a lot of previous work does is set up an animal model, of Alzheimer's or Parkinson's for example, but they'd pre-treat it with the drug before the model was initiated. So translating that to people is effectively like treating anyone over 50 with a drug in the hope that a few of them get Alzheimer's disease. They won't get Alzheimer's disease because you've given them the drug. So that was one of the prob-

lems in what we were doing. So we sort of worked quite hard to design a study so that you set-up the model, wait a certain period of time to make the animals how a person would be when they get to clinic with Parkinson's or Alzheimer's, for example, and then that's when you start the drug treatment. (Postdoctoral researcher at large research university, 2016)

Another researcher talked about moving from using adult rats to using elderly rats, and small focal lesions to larger ones, to better model important characteristics of people affected by stroke. As well as changing the experimental temporalities through matching older animals to older patients, they also changed the treatment period to match median hospital admissions and facilitate the organisation of later clinical trials:

In one of our experiments we were infusing the protein into the muscles of the animals for a month after stroke, starting 24 hours after stroke. He [the clinician] challenged me on it. And he said, that's really interesting, but why would you choose a month, because in practical terms it's really hard to run a clinical trial like that, as the majority of our patients discharged, the median stay is 13 days. […] So he said, you've got to find a way to compress this down into a timeframe that's compatible with our patients. (Mid-career researcher at a large research university with a neighbouring hospital, 2016)

This search for a more 'translatable' animal model is recognised to have trade-offs. The time involved in allowing disease aetiologies to develop may be expensive, and there may be welfare implications if animals with disease symptoms are used in procedures for longer periods (as, for instance, in the case of diet-induced obesity in mice). In addition, outcomes are still uncertain even using the 'best' available models. Some researchers explained how they were including aspects of patient experience in their pre-clinical studies. Examples involved modelling comorbidities in experimental stroke research by using hypertensive rats; and using analgesics on animal models, which better represents patient experiences while also promoting animal welfare.

The increasing interactivity fostered by aspirations for translational research is promoting the alignment of drugs, doses, models, and temporalities between pre-clinical research with clinical trials and clinical application. The interviews indicate growing acceptance that the evaluation of animal models requires revision to include their potential translational value (as argued by van der Worp et al. 2010 and Garner 2014, among others). The specifics of this vary by disease area, and researchers stress how improving translational in vivo research is complex and iterative, rather than a one-way linear process. Several interviewees described collaborations as vital for changing both the experimental design and pharmaceutical agent, so that a viable compound can be taken from the laboratory into a clinical trial or clinical setting:

A lot of the drugs I was using in my PhD were quite unstable. So I couldn't give them in drinking water or in their food, for example. I had to make up the drug fresh each day and give the animal an injection. In some of the work we're doing here, with the help of [the pharmaceutical company funding the laboratory] we've been able to mix the drug for example into the mouse food so that they can eat it without having an injection twice a week. (Postdoctoral researcher at a large research university, 2016)

Indeed, this trend towards context-specific alignments and equivalences increases the complexity of pre-clinical research data and may work against those who view standardisation as a solution to the translation gap (Lewis, Hughes and Atkinson 2014). This increasing complexity demands renewed attention to how care is practiced in translational research, both for animals and for people.

4.2   Caring for Animals; Caring for People

Pre-clinical pharmacologists sit at a critical juncture between basic and clinical research. In addition to the experimental realignments presented above, this also involves working in new organisational configurations and incorporating new relations of care for research subjects, whether they be humans or non-humans. Interviewees talked about needing to be more responsive to the multiple responsibilities involved in developing interdisciplinary research collaborations, thus reflecting on the new forms of accountability brought about by bringing laboratory and clinical practices closer together. As Crabu suggests, in translational research "the laboratory itself can be re-framed and adjusted to render laboratory facts and scientific phenomena congruent with the processes of care and the clinical management of patients" (Crabu 2016, 3). This changes where problems are defined, how they are framed, and how they might be addressed.

Throughout the interviews, participants highlighted their efforts to develop new relations between basic, pre-clinical and clinical researchers, so as to create the interactive and recursive mobilities between disciplines that facilitate translation. One interviewee used the terminology of 'back-translation' to identify this shift. This highlights the reversion of the stereotypically linear, bench-to-bedside direction of translational research, and acknowledges how researchers are now seeking to answer questions coming from clinical care in pre-clinical research. In their words:

In the past, mainly my research was based on research which was done on animal models and problems that people identified in more molecular problems. Now it's also directed by problems in the clinic. So […] I'm more thinking about how problems identified in the clinic can be back-translated and how animal models can help answer the question. (Early career researcher at a medical school, 2016)

Beyond answering questions generated across basic, pre-clinical, and clinical research contexts, the translational mobilities of in vivo research also require understanding how answers are given value and statistical significance within different experimental systems. Statistical measures of biological significance have tended to be domain-specific and to some extent incommensurable with each other. Given this context, informal dialogue between pre-clinical and clinical researchers aids further understanding of the criteria by which answers will be deemed to be biologically significant across other domains. Being involved in translational research means adopting statistical standards that will protect patients in clinical trials, which are not necessarily the same as those meeting the thresholds for publishing in basic research, as highlighted by the following interview quote:

> I am more aware of the clinical research and the types of designs for clinical trials, which maybe I wasn't aware of before. So it's widened my knowledge and my circle of reading and I am aware of the very stringent criteria there are for clinical trials which there isn't in basic science […] There's this fallacy that exists where people tend to think that an n of 6 is enough for a significant experiment in the animal world, whereas that's a ridiculous way of thinking now. The group on stroke, they are far further down this line than I am, so they have the pre-clinical stroke models and they work very closely with the clinicians, so they have much more dialogue. And so being involved with their lab meetings and in just general tearoom discussions, I've become more and more aware of how stringent we need to be when, first of all, designing experiments and then doing power calculations but also in interpreting our data as well and determining what is or what isn't biologically significant. (Senior lecturer at a large research university, 2016)

This exchange can also go the other way, with clinicians being trained in animal use and care. One interviewee, who was appointed within an IMB centre to help share expertise on animal research, talked about how they were able to introduce clinical researchers to the required skills to conduct animal research. Clinicians were guided through the process of initiating a project, matched up with potential collaborators, and given training to design and conduct experiments with them. In their words:

> In terms of marrying up clinicians to any in vivo research side, things have certainly progressed. Those individuals had never had any experience of working in an animal model, but [want to] in order to progress their work […]; essentially, they'll ask, 'I want to do some animal work. Who do I talk to?' Then they end up talking to me. (Research and technical support at a large research university, 2016)

Some collaboration focused around formal roles allocated via the IMB centres, such as the research management role above. Other forms of interactivity were brokered through jointly-supervised PhD studentships,

which were "always highly favoured where there were two supervisors for different faculties […] which could bring together basic and translational skills" (senior manager at a large research university, 2016). Other collaborations were more informal, facilitated by the co-location of IMB centres near large teaching hospitals. As one researcher suggested, informal meetings with a clinical researcher with everyday experience of patient care had provided advice that would not have been available from the literature, but which had affected how they designed and conducted their experiments:

> We probably meet once or twice a year on average, and he asks me what I've been doing, and I tell him what I've been doing, and he explains what the challenges are in translating this kind of thing. He's given me a couple of really good bits of advice which made me think about how to do the work that I do. It's these kinds of little gems of information that you can't get from the literature and from chatting with your friends. It needs to be someone that works with stroke patients every day that can tell you the realities of it. (Mid-career researcher at a large research university with a neighbouring teaching hospital, 2016)

These informal collaborations do not involve formal working relationships and typically they do not result in the clinician being involved in co-authoring publications. Nevertheless, our interactions with IPF researchers show that informal collaboration plays an important role in facilitating access to clinical knowledge that comes from day-to-day interactions with patients. Informal collaborations supplement the technical and experimental knowhow developed through circuits of translation, by helping to identify matters of care in both clinical settings and animal research.

4.3   Reporting, Reproducibility, and the 3Rs

In this final empirical section, we explore how translational expectations in animal research are increasingly intertwined with policy and training on research integrity, reproducibility, and applications of the 3Rs. Training to become a 'good experimenter' today means conforming to multiple expectations, whilst navigating a shifting methodological landscape in light of the so-called crisis in the reproducibility in biological research (Academy of Medical Sciences 2015). Researchers in pre-clinical academic settings are often working in environments where there are career pressures to "win a place in a select few journals" (Horton 2015, 1380). However, top-ranking journals have been criticised for poor reporting of animal research, with few articles containing information on randomisation, blinding, and sample size estimation (Macleod et al. 2015). Training students in pre-clinical pharmacology means teaching them to negotiate the pressures and policies around research integrity, research reproducibility, and the 3Rs. This sort of training rarely appears in the literature on animal research in STS but is an increasingly significant

part of becoming a good experimenter (Leonelli 2017). Producing 'good' results may not involve working directly with animals but will require making 'good' calculations to get sample sizes right, avoid bias, and be transparent about the relationship between hypotheses and data.

Debates over rigour and reproducibility are particularly acute in in vivo research, where underpowered experiments and p-hacking result in animals' lives being wasted (Ioannidis et al. 2014)[4]. Several initiatives are seeking to enhance the conduct of biomedical research through improving reporting in academic journals, ensuring rigorous grant review, and supporting institutional leadership (Begley and Ioannidis 2015). The ARRIVE guidelines refer to the reporting of animal research and are increasingly incorporated into journal submission processes (Kilkenny et al. 2010). The PREPARE guidelines are intended to be used prior to research taking place (Smith et al. 2018). The National Centre for the 3Rs (NC3Rs) is developing resources to help in vivo researchers in the UK meet legal requirements to replace, reduce, and refine the use of animals in their research. These attempts to standardise and harmonise the conduct of experiments and programmes of research mirror international efforts on care and welfare of laboratory animals (see Bayne et al. 2015). They also change the attunement between expectations, animals, and affects that go into training animal researchers (Despret 2004). These are now mediated through written guidelines, checklists, and protocols. These document what matters in communicating research quality and animal care, but they do not resolve tensions for researchers who have to work out how to articulate their research to meet these expectations.

Our interactions with IPF staff revealed widespread support for the 3Rs, accompanied by a recognition that overall efforts to reduce animal use in research should not be at the expense of the statistical power of each experiment. Many had been involved in both teaching and outreach activities that prompted them to think about relations between research translation and the 3Rs. One researcher had contributed to the development of the Experimental Design Assistant[5], an online tool developed by the NC3Rs to assist the design of experiments. Nevertheless, divergence in practice remains. In interviews, we found that researchers talking about the requirements for reporting, reproducibility and the 3Rs held different views on the most appropriate experimental design for translating in vivo research.

One researcher, who otherwise sought reduction in the use of animals in education, argued for increased sample size as a way to improve a study's statistical significance:

> If I decide that a study's worth doing, I do my sample size calculations. But then in most cases, for a four-month study I'm talking about where you have a significant investment in time and energy, we do as many animals as we can in that timeframe. So, we don't attempt to reduce the number of animals, because when we do our sample size calculations, we realise that for all the additional animals we put in we increase our abil-

ity to detect a benefit of a drug and you reduce the chances of getting a false positive by accident. So I don't actually try to minimise my animal use, I just decide which experiments are really worth doing well, and doing them properly. And the reason for that is I think a lot of the low-hanging fruit is gone now, there are no easy stroke therapies that are out there. They're all going to be most likely small effect sizes, modest effect sizes, so you just need to power your studies as fully as possible. (Mid-career researcher at a large research university, 2016)

Another researcher preferred instead to use smaller numbers of animals, thus shifting focus to the magnitude of experimental effects:

So if you do an experiment in an animal model with a human condition and you get a small change for the better, that shouldn't be used as a rationale for going into man. You need to see a big change. A big change at a rational dose. I do quite a lot of consulting now in the neuromuscular field and I'm seeing datasets where I tell the company on the basis of this, that drug is not going to be clinically effective because the change is too small, and yet I've seen these programmes go through to full clinical development. (Senior researcher at a small university, 2016)

Both of the above researchers are concerned with the potential value of their experiments for future drug development and with ensuring that their results are reproducible and useful. Their experimental design is guided by their understanding of how data deriving from the drug achieves translational value in their field. If only marginal effects are thought to be possible, then larger sample sizes are used. If larger experimental effects can be anticipated, then using smaller sample sizes constitutes better practice. Even for people working in similar fields, on similar organisms, there are different understandings of what constitute good statistical practices for interpreting results in translational research. The extent to which experimental practices are sensitive to the concrete translational goals depends not only on the biology, but also on the prior history of investigation and therapeutic development in the relevant area of research, and the historical constitution of that research itself. The expectations between researcher and animals that Despret (2004) identifies as vital to producing "good experiments" are supplemented by researchers' interpretations of the technical requirements of translation.

While the two approaches discussed above come from established investigators, there are important lessons here for training early-career researchers. Future efforts to improve experimental design and statistical power would benefit from a better understanding of how researchers interpret the overlapping imperatives around the 3Rs, reproducibility, and translation in their everyday research practices. Again, our research suggests that standardised prescriptions of good practice should be approached with caution. Checklists and standards need to be supplemented with explicit discussions among pre-clinical researchers about the as-

sumptions that they make in their experiments, as well as discussions between pre-clinical and clinical researchers to ensure the applicability of findings across domains. Innovation around translational practices from animal research will not be achieved through compliance with reporting policies alone, but also requires discussion around the validity and mobility of the data that results. Minimum standards in check-boxes at the point of submission of a journal article need to be augmented by opportunities to encourage dialogue and reflexivity around research practice. This is exemplified by the very exchanges between STS and animal researchers that characterised our collaboration with BPS, and the uptake of the recommendations produced through these interactions, as discussed below.

5. Discussion and Conclusion

Our research with representatives from the four IMB centres funded by the BPS suggests widespread identification with current translational research imperatives. It also indicates that translational research practices are multi-dimensional and, at times, contested. In this paper, we identified and discussed three kinds of ways in which researchers who use animals in pre-clinical research are responding to imperatives to make their work more translatable. These include moving from the standardisation of animals to the alignment of experiments, connecting practices of animal care and patient care, and reflexivity in the calculation of statistical power and the 3Rs. Collectively, these constitute different dimensions through which the researchers with whom we interacted conceived of striving towards translatable science. These supplement the ways in which STS scholars talk about animal research and translation. They can also be used to inform the future training of animal researchers. In closing, we briefly discuss the practical implications of these findings for the improvement of in vivo research, and reflect on how, through sustained dialogue and reciprocal learning across STS and animal researchers, co-produced qualitative research can contribute to a productive reframing of how scientific practice is enacted, understood and evaluated.

Applying insights from STS scholarship within the initial evaluation of the IPF helped us to contribute concrete recommendations for the BPS. Many of these recommendations relate to the increasing complexities found in "circuits of translation" charted above, and sought to avoid being prescriptive, focusing instead on ways of enhancing reflexivity and learning across organisations and for individuals. The final evaluation report included key recommendations for supporting and assessing in vivo education, strengthening networks for sharing good practice, recognising the diversity of activities and careers involved in translational biomedical research, and enhancing collaboration between them (Lowe et al. 2016). It also details practical examples, including the emergence of new roles

for managing and facilitating the increasingly complex modes of dialogue and collaboration required for translational research.

The evaluation report also identified some specific challenges and opportunities for change. Some of the challenges relate to how translational research is changing career structures for scientists. There are potential barriers in the credit structures in science which value publication within discipline-specific journals. The researchers interviewed here do not exhibit strong disciplinary affiliations; they conduct problem-focused research, and some were members of more than one learned society. Work tracing the pathways taken by translational research indicate that these results are rarely in the highest impact factor journals (Cambrosio et al. 2006). However, regimes of scientific credit are evolving to accommodate new forms of publication and patent applications (see Rasmussen 2014), which are more aligned with translational researchers' interests. Some of the opportunities relate to how translational research is relocating animal research within a wider context of organisational practices and research skills. The new BPS core curriculum concerning the use of research animals includes training that puts knowledge, skills and attitudes about animal research into context. However, it no longer requires undergraduate students to undertake hands-on research with animal in education settings[6]. This decision was part of the harm-benefit analysis around the use of animals in education that the report facilitated, suggesting that learning outcomes at this stage could be achieved through observation, using simulations or videos, or through working with an animal facility where research is ongoing.

Our study adds further dimensions to the accounts of what constitutes 'good' animal research in STS with which we started. Striving for good translation can be understood through the notion of "good science" developed by Charis Thompson, in which scientific and ethical practices are understood to be "mutually entwined" (Thompson 2013). Thompson's articulation of good science centres on stem cell research, where she argues that "ethical concern lies at the heart of innovation" (Thompson 2013, 221). In the case of pre-clinical animal research, striving towards translation involves raising questions about model reproducibility and validity, rather than standardisation; connecting care for animals with care for patients; and balancing the reduction in harms to animals with the potential benefits in clinical practice. These questions about the planning, conduct, and outcomes of scientific research are important in driving innovative practices but cannot be resolved by adhering to (external) ethical guidelines and norms. Training for 'good' animal research requires attuning experiments to complex contexts, learning what matters to different bodies, and interpreting statistics and ethics in situ. Many researchers valued taking part in this research as an opportunity to reflect on their experiences of being trained, developing research careers, and informing the next generation of pre-clinical pharmacologists. Their accounts of what makes good pre-clinical animal research links science and ethics,

encompasses policy and politics, and draws on individual beliefs and conduct. Good translation is enhanced by this reflexivity. The recommendations to the BPS aim to generate researchers able to construct their research practice and collaborations in ways that support the multi-directional forms of attention that support translational research. Working collaboratively with social scientists has helped to identify and enhance these opportunities in future training for translation.

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[1] See for example Rader (2004) and Kirk (2008). For a detailed overview of the historiography of animal research, see Ankeny and Leonelli (2018).

[2] https://web.archive.org/web/20191016093215/https://www.bps.ac.uk/-educati-on-engagement/research-animals/curriculum-for-the-use-of-research-animals/ab-out-the-curriculum-for-the-use-of-research-anima, retrieved 16th October 2019.

[3] These kinds of animal models can be produced by surgical intervention (for example, removal of most of the pancreas, a pancreatectomy, to induce hyperglycaemia and symptoms of type 1 diabetes in pigs, dogs and non-human primates; King 2012); chemically-induced (the injection of the neurotoxin MPTP

into cats to simulate Parkinson's disease, Schneider and Markham 1986; Schneider, Yuwiler and Markham 1986); naturally-occurring (e.g. homozygous mutations resulting in obesity in mice, as a model of obesity; Lutz and Woods 2012); environmentally-induced (e.g. raising mice in obesogenic environments to make them obese; Lutz and Woods 2012); and produced by genetic modification by knockout of genes or transgenesis, the introduction of DNA into the genome (e.g. the transgenic mouse with mutant SOD1, a model of amyotrophic lateral sclerosis; Julien and Kriz 2006).

[4] P-hacking involves generating a large amount of data then conducting statistical analyses to find statistically significant relationships between variables without an a priori hypothesis.

[5] https://web.archive.org/web/20191016095130/https://www.nc3rs.org.uk-/expe-rimental-design-assistant-eda, retrieved 16th October 2019.

[6] https://web.archive.org/web/20191016094917/https://www.bps.ac.uk-/educati-on-engagement/research-animals/curriculum-for-the-use-of-research-animals/ab-out-the-curriculum-for-the-use-of-research-anima, retrieved 16th October 2019.