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Much ado about mice: Standard-setting in model organism research

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ABSTRACT

Recently there has been a practice turn in the philosophy of science that has called for analyses to be grounded in the actual doings of everyday science. This paper is in furtherance of this call and it does so by employing participant-observation ethnographic methods as a tool for discovering epistemological features of scientific practice in a neuroscience lab. The case I present focuses on a group of neurobiologists researching the genetic underpinnings of cognition in Down syndrome (DS) and how they have developed a new mouse model which they argue should be regarded as the "gold standard" for all DS mouse research. Through use of ethnographic methods, interviews, and analyses of publications, I uncover how the lab constructed their new mouse model. Additionally, I describe how model organisms can serve as abstract standards for scientific work that impact the epistemic value of scientific claims, regulate practice, and constrain future work.

1. Introduction

This paper is a story about a laboratory of neurobiologists who have developed a new complete genetic mouse model of Down syndrome. They have argued in print, and amongst each other, that this mouse should be used in all genetic research on Down syndrome (DS) as the "gold standard." Specifically, they argue that this mouse should be used instead of the most popular mouse model, which they claim is inferior to their new mouse. The catch is, they are unable to use the mouse they developed and have resorted to using the mouse they have deemed to be inferior. Additionally, in the year following the publication of their paper promoting the superiority of their new mouse, they spent substantial lab resources using the older "inferior" mouse in ways that provided no explanation of any aspect of DS. I will show in this paper that the lab resolved this problem and justified their work with the "inferior" mouse in an epistemically sophisticated way. By discussing how the lab did this, I will also illuminate how, in practice, model organisms can serve as abstract standards for scientific work that impact the epistemic value of scientific claims, regulate practice, and constrain future work. My goal here is *not* to evaluate whether the lab is correct in their determination that the new mouse is the best model for DS research, nor is it to critique the standards which were operant in their determination. Instead, my motivation here is to uncover *how* the lab members set their new mouse as a standard and how this affected their subsequent practices.

This case comes out of a participant-observation ethnography studying the modeling practices of a neurobiology lab that researches cognitive degeneration associated with Down syndrome (DS) and other neurodegenerative conditions. [2] Here I draw on this ethnographic work, supplemented with an analysis of published work, to address issues which are of interest to philosophers of science with a practice focus, namely regarding the norms of actual scientific practice (Rouse, 1996; Chang, 2011; Andersen & Wagenknecht, 2013) and the epistemological functions of model organisms. My guiding questions are: How does the lab justify working with what they believe to be an inferior mouse model? Additionally how does their new mouse line advance their goal of understanding Down syndrome in humans and how does it guide their future work? By answering these questions, I also hope to demonstrate the value of ethnographic methods for philosophical work on scientific practice. Specfically, I aim to show that ethnographic methods can be used to uncover epistemic features of science that are not discoverable by other more traditional means.

To provide an answer, I will examine how this lab (which I will call Lab X) itself has sought to justify (in print and in person) the use of the older, inferior model. The way in which Lab X does this will be surprising for some readers. The lab argues that the old mouse model *is*, in some respects, a suitable model – precisely because (they argue) in some respects the old model can be shown to be functionally equivalent, in a limited sense, with the new model. In the eyes of Lab X, this somewhat convoluted strategy of asserting that their new complete genetic model of Down syndrome should be regarded as a field-wide standard and meeting it indirectly with an "inferior" mouse is

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[2] Even though the lab I will be discussing focuses on the neurobiology of cognition in DS, the research community as a whole has other interests which include: the cardiovascular system, comorbidity, the endocrine system, neuronal pathways, neurotransmitter restoration, drug discovery, sleep, nutrition supplementation, cancer risk, and fertility.

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justifiable. They regard it as justifiable because they have shown that the intracellular behavior of one protein in the inferior mouse is functionally equivalent with that in their new mouse. This allows them to claim that, for the purposes of their work, they have met the new high standards constructed through their new mouse line. However, by doing the work to demonstrate the limited functional equivalency between the two lines, the lab has also reaped several epistemic benefits: i) by doing so, they have afforded the inferior mouse model equivalent epistemic weight; ii) they have established a procedure which other labs could use to overcome the same problem, iii) they have made the new mouse a standard against which all DS mice can be evaluated; iv) the lab has designated what they believe to be the necessary context in which the best and strongest explanations of DS must occur as well as the terms in which these explanations must be.

Before providing the details of the case, I will first (§2) discuss the methodology I used in this paper as well as my site. Second (§3), I will provide a brief review of the literature on model organisms and practice-oriented philosophy of science. (§4), Third, I will provide data from my field notes, interviews, and Lab X's published paper concerning the new mouse as a standard-setter and how the lab is trying to meet those standards. Fourth (§5), I will answer two questions: (§5.1) How does the lab justify working with what they believe to be an inferior mouse model?; (§5.2) how does their new mouse line advance their goal of understanding Down syndrome in humans and how does it guide their future work?

2. Model organisms and practice-oriented philosophy of science

Model organisms that are intended to serve as genetic representations of their targets are a relatively new feature of the biological sciences. The practitioners pursuing humanistic and social scientific studies of science have taken note of this phenomenon and have inquired into how these particular kinds of models are produced and how they figure into scientific practice, including explanatory practices. The community of researchers working on these topics is an interdisciplinary one comprising philosophers of science, science and technology studies (STS) scholars, and historians of science. My case of the GCDS mouse is similar in its aims to illuminate how model organisms function in practice and how they are involved in the construction of explanation. However, this case presents a less tidy story of how a particular line of a model organism was developed and how it serves the function of being an epistemological constraint and standard for current and future work. This is not to minimize the value of the literature on model organisms, but to illuminate the philosophical payoffs for employing ethnographic methods to delve into the less straightforward reality of everyday scientific practice. In order to show how ethnographic approaches in the philosophy of science can be of value, I will situate it in the context of several foci of practitioners interested in scientific practice.

Notably, the philosophical literature on model organisms seeks to provide practice-friendly accounts that are applicable to my case. The literature is in agreement that a successful model, including model organisms, must have the capacity to serve as an "indirect representation of the world" in some relevant way (Giere, 1988/2010, pp. 82; Godfrey-Smith, 2006, pp. 726).[3] This definition leaves debatable what standard a model should meet in order to be the *best* and allows a modeler's own standards to be taken into consideration. This does leave room for critical inquiries on how extrapolation ought to work when there are significant differences between model and target (Steel, 2007, p. 86). However, it would be a challenge to arrive at a general principle for what counts as a good model organism and successful extrapolation.[4] In the literature on model organisms, there is a move away from trying to arrive at an overarching principle of success for all organismic models in biology. Instead, philosophers have taken case-based approaches to discussing what *standards* determine the *best* model organism. There is some agreement that the questions practitioners are pursuing in the context of their given fields determine the standards for what counts as the best model (Ankeny & Leonelli, 2011; Bolker, 1995, p. 451; Burian, 1993, p. 360, pp. 314). In approaching the case of the GCDS mouse, I do not seek to provide any critique of the Lab X's standards (in particular that of the genetic "gold standard"), but join the practitioners focused on uncovering the modeler's own standards and how they operate in biological practice.

Scholars in STS and the history of science have also taken a case-based approach to model organisms. They have also focused on how scientists chose and standardized them as well as the social and cultural practices surrounding their use. Although the case of the GCDS mouse does not include discussion of the greater social and cultural factors involved in the line's development, it pursues STS's and the history of science's goal of telling the story of the development of a particular model. For example, Karen Rader traced the history of *mus musculus* (aka. The "Wild Type" or WT mouse) focusing on how biologists standardized it (2004). Other historical works in STS have similarly shown how scientists developed other organisms , focusing on their socio-pragmatic justification for doing so (Creager, 2002; Kohler, 1994).[5] Yet, the story of the GCDS mouse is less straightforward perhaps because it does not have the vantage point of the historian. It will take decades before one could determine how the GCDS mouse has affected, and will affect, DS research. I will show, however, that there is value in determining the intentions of Lab X and the standards they have set with their mouse prior to the clarity a future historical analysis could provide.

I would also argue that participant-observation ethnography is suitable for discovering epistemic features of modeling practice and is not at odds with current practice-oriented trends in the philosophy of science. One group that has inquired into what scientists actually do and, in particular, how explanation works in biological practice are the New Mechanists (See Bechtel & Abrahamsen, 2005; Craver, 2007; Craver & Darden, 2013). This research program moved away from viewing explanations as "subsumption of phenomena to be explained under a theory or law" (Bechtel & Richardson, 1993/2010, pp. xvii) Instead, the New Mechanists have looked at how biologists give, and epistemically value, "mechanistic" explanations and have used this to guide their work.[6] In their seminal paper, Machamer, Darden, and Crave strongly state that the biological concept of "mechanism" is "central to an adequate philosophical understanding of the biological sciences" (Machamer, Darden, & Craver, 2000, p. 3) My discussion here is in the same spirit of looking to actual practice to determine what is necessary for a philosophical understanding of aspects of the biological sciences. Although the case of the GCDS mouse is not an instance of explanation, Lab X is explicit, as I will show in §5, that their aim is to be able to use their mouse models to ultimately find and explain the mechanisms involved in DS.

The philosophy of science has not only developed an interest in the topic of practice (Soler, Zwart, Lynch, & Israel-Jost, 2014), but it has incorporated a variety of methods to uncover what scientists are doing

[3] For discussions focused on how model organisms represent targets through phylogeny or developmentally related cells, see: (Ankeny & Leonelli, 2011; Ankeny, 2001; Leonelli, 2007; Weber, 2004).

[4] As Tudor Baetu has shown, there are many different kinds of models in contemporary biology that serve multiple functions and are evaluated by different standards. To complicate things further, practitioners use multiple models in coordination to meet particular scientific aims (Baetu, 2014).

[5] See also Carrie Friese and Adele Clarke's work on human reproductive sciences (2012) as well as Nicole Nelson's work on how scientists make inferences using animal models (2013).

[6] The New Mechanistic movement has produced a diverse body of literature and my treatment here does little justice to it. I am making note of it here as a way of demonstrating the current practice-focused currents within the philosophy of science that give support to employing ethnographic methods.