COMMENT

There's more to life than rats and flies

The tiny number of model organisms constrains research in ways that must be acknowledged and addressed, warns **Jessica Bolker**.

For most experimental biologists, life revolves around a handful of species: the mouse (*Mus musculus*), the nematode worm (*Caenorhabditis elegans*), the fruitfly (*Drosophila melanogaster*) and the thale cress (*Arabidopsis thaliana*). We assume that model organisms offer universal insights, and funding agencies largely support work on a shortlist of favoured species (www.nih.gov/science/models).

Scientists who submit grant proposals for a project using a standard model organism need not use up space to explain their choice. By contrast, choosing a less common model that is uniquely suited to the research demands a lengthy justification to convince sceptical colleagues. Proposals for projects in unusual species are often returned with the suggestion that the applicant use a standard organism instead, because any worthwhile question should be accessible in a well-established model.

Investments in research with a handful of models have returned rich dividends in basic knowledge and medical progress. And many careers, labs and journals are built on the primacy of the fly, mouse and worm[1].

But studying only a few organisms limits science to the answers that those organisms can provide. The extraordinary resolving power of core models comes with the same trade-off as a high-magnification lens: a much reduced field of view. For instance, traditional models for developmental biology — such as the fly — were chosen because their phenotypic traits directly reflect their genotype, with minimal environmental input. These models are poorly suited to questions asked by scientists in emerging fields such as ecological developmental biology — 'eco-devo' — which focuses on external influences on developing phenotypes. ▶

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Such limitations have serious consequences. Disparities between mice and humans may help to explain why the millions of dollars spent on basic research have yielded frustratingly few clinical advances[1–4]. Narrowing the research focus too far limits basic understanding, in ways that can lead directly to clinical failures. For example, an experimental treatment for multiple sclerosis that, in inbred mice, improved symptoms of induced disease produced unpredicted — and sometimes adverse — responses in human patients. The inbred mouse model failed to represent the genetic and immunological diversity of human cells, a shortcoming that was obvious in retrospect[2].

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It is time to think more critically about how we use models. This means articulating tacit assumptions, such as the adequacy of rodent models to fully represent specific human diseases. It means looking hard at how we select and use our favoured model species, and acknowledging both their strengths and their limitations. And it means mainstream funders and journals welcoming work in non-standard organisms.

MODELS OF CONVENIENCE

How did a handful of species become central models? Sometimes it was more about convenience than strategic planning. *Drosophila* rose to prominence in the early 1900s in part because its short generation time was handy for student projects and its four pairs of large chromosomes were ideal for the study of eukaryotic genetics[5]. Yeast, mice, chickens and other domesticated species became lab favourites because they were already familiar and accessible. The existence of lab populations of frogs (*Xenopus laevis*) for use in pregnancy tests led to their recruitment as a model for developmental research.

As model-based science grew, these few species became increasingly dominant, despite the sometimes haphazard way that they had initially been chosen. We have now reached a point where, if researchers cannot tackle a problem using a familiar species, they may not study it at all[1].

Take modern developmental biology. The field has centred on small, rapidly developing organisms with short generation times — most typically, *Drosophila* and *C. elegans*. Much of our current understanding of developmental principles is based on experiments in these species. However, evolutionary selection for rapid development has broad implications. It seems to favour stronger genetic control during development and less plasticity (or flexibility). Compared with related species, development in the models is less responsive to external signals, whether adaptive or disruptive. Because plasticity and the role of the developmental environment are particularly hard to study in key models, these areas receive comparatively little attention[6].

A similar narrowing has occurred in biomedical research. In the case of Parkinson's disease, potential treatments are often assessed by measuring motor function in a lesioned rat. But the rat model does not clearly represent other significant symptoms of Parkinson's that occur in human patients, such as cognitive decline. This may steer some researchers away from these aspects of the disease.

Similar biases rooted in the use of particular models may also contribute to the 'translational disconnect' with regard to neurodegenerative diseases such as Alzheimer's and amyotrophic lateral sclerosis[3,4]. The inability of highly inbred and often genetically modified rodent strains to fully represent the diversity of human patients and symptoms has called the power of such models into question, even within the research communities they serve[1–4,7].

At the same time, the effects of apparently trivial environmental variations, such as the details of mouse handling, are often overlooked[8]. Aggression is the key behavioural phenotype in male mice lacking the enzyme neuronal nitric oxide synthase. This was not observed — and could not be seen — until animals were housed in groups rather than in standard individual cages[9].

Few lab models explicitly account for the environment of organisms, despite increasing recognition that this may affect the outcome and replicability of experiments[7].

In short, if we frame a research model or system too narrowly, leaving out key causal elements such as environmental influences, we cannot hope to construct a complete picture of the mechanisms that underlie crucial variations, for example in development and disease. To study environmental influences, we need to study species in which such factors matter. So the traits that define a successful model must shift as the questions for which we use them evolve.

BEST FIT

Choosing a research model should be more than a matter of convenience or convention. Scientists need to ask more questions — about the goals of a specific experiment, how suitable a given model is to reaching those goals, and what environmental or other external factors might be relevant to how well the model works. For a given question, it is crucial to determine which aspects of human biology are essential (for example, our genetic diversity, unique characteristics of our immune system or particular disease symptoms) and assess how well they are represented in a candidate model (see 'Choosing the right candidate'). Where mismatches appear, we must limit our inferences from animal studies accordingly, and consider when and how to move to research in humans. For some kinds of biomedical

MODEL PROBLEMS

Choosing the right candidate

1 Matching between the model and what it represents

Example: Does studying immunology in highly inbred mouse models shed useful light on the diversity of human immune function and disease[1]?

Key questions

- What do we need to know about a disease to develop treatments?
- What mechanisms link disease origin to symptoms?

Research objectives

- Discover aetiology of symptoms.
- Compare disease initiation and progression between models and humans.
- Assess whether therapeutic targets are well represented in specific models.
- Identify gaps between models and patients that may be significant with respect to basic knowledge and to treatment approaches.

2 Need for additional models

Example: Where there are known obstacles to translating results from mice to humans, how do we develop alternative routes to find new treatments for human diseases[3]?

Key questions

- What aspects of human disease are poorly represented in current models?
- How might the utility of current models be expanded?
- What potential new models are available, or could be developed?

Research objectives

- Develop strategies to assess other aspects of human disease in current models.
- Identify new candidate models for specific questions.
- Develop criteria for selecting new models.

research, it may not matter that the damage or symptoms in the model developed by a different pathway to that which occurs in patients — orthopaedic injuries are one example. But in other areas, such as epidemiology, it matters a great deal.

Recognizing that standard models have limitations does not mean we should give them up. Rather, we should deliberately account for their limitations as part of study design — for example, by analysing the role of a gene in mouse strains with different genetic backgrounds. No single species, no matter how highly engineered, can ever serve as a universal model: every species has unique features that may be assets or faults, depending on the question being asked. For instance, the lack of developmental plasticity in *Drosophila* and of genetic variability in inbred rats limit what these models can tell us about ecological effects on development, but make them powerful tools for studying gene function during development.

We also need to broaden our range of models to include species such as Antarctic icefish, comb jellies, cichlids, dune mice and finches that are naturally endowed by evolution with features relevant to human diseases[10]. Studying the basis of unique adaptive traits in these animals may yield insight into human disorders such as osteoporosis, cataracts and cancer.

Immediately and practically, the US National Center for Advancing Translational Sciences in Bethesda, Maryland, should support the development of new systems for investigating problems that are not tractable in currently favoured models. It should also fund investigations into fundamental questions about model-based research (see 'Choosing the right candidate'). The resulting insights would help scientists to select the best models for advancing basic and applied research, and strengthen the bridges between them. ■

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Pro-choice and pro-life activists clash outside the US Supreme Court in Washington DC.

Politics and fetal diagnostics collide

Without better regulation, non-invasive prenatal genetic tests will be targeted by US anti-abortion lobbyists, argues **Jaime S. King**.

In the United States, pro-life advocacy groups, notably Americans United for Life, based in Washington DC, have been making headway in their mission[1] to limit women's access to abortions "state by state, law by law and person by person". In 2011, 24 US states enacted 92 new provisions restricting abortion — nearly triple the previous record of 34 in 2005 (see 'Clamping down'). One of the strategies of pro-life advocates is to target the reasons for which a woman can have an abortion. Meanwhile, a major development in prenatal care, called non-invasive prenatal genetic testing (NIPT), promises to increase the genetic information available to women early during their pregnancy.

The US Food and Drug Administration (FDA) cannot control how people use information from genetic tests. But by developing a clear regulatory framework for NIPT and improving public understanding of NIPT's benefits and limitations, the agency could help to allay fears that the tests will lead to a drastic increase in selective abortions.

NIPT has the potential to improve women's reproductive autonomy. But if it is not integrated cautiously into prenatal care, the technology could be targeted to support burgeoning strategies to restrict abortion.

In recent years, two blood tests combined with an ultrasound have been the most common method for determining a fetus's risk of having a congenital disease such as Down's syndrome. Results from this type ▶