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‘Model’ or ‘tool’? New definitions for translational research

Hazel Sive

Summary
The term ‘model’ often describes non-human biological systems that are used to obtain a better understanding of human disorders. According to the most stringent definition, an animal ‘model’ would display exactly the same phenotype as seen in the relevant human disorder; however, this precise correspondence is often not present. In this Editorial, I propose the alternative, broader term ‘tool’ to describe a biological system that does not obviously (or precisely) recapitulate a human disorder, but that nonetheless provides useful insight into the etiology or treatment of that disorder. Applying the term ‘tool’ to biological systems used in disease-related studies will help to identify those systems that can most effectively address mechanisms underlying human disease. Conversely, differentiating ‘models’ from ‘tools’ will help to define more clearly the limitations of biological systems used in preclinical analyses.

Defining a ‘tool’
I define a ‘model’ as an animal or other biological system that precisely recapitulates a human disorder, exhibiting what seems to be an identical phenotype to that seen in affected humans. Applying this stringent criterion, models of human disorders are rare, because the biology of a given animal or other biological system and a human is not identical, and/or because the molecular players underlying the disorder have not been fully defined. However, a specific term applying to biological systems that do not completely recapitulate a human disorder, yet are still relevant for studying it, is currently lacking. In order to address this deficit, I therefore define a ‘tool’ as a biological system that gives insight into a human disorder, without obviously recapitulating the phenotype that is diagnostic of that disorder. In order to be useful, the tool must have attributes that are not accessible in other systems – for example, it might provide the opportunity to perform rapid and inexpensive analysis of changes in the activity of human genes (or homologs) that are associated with the disorder, genetic modifier screens to identify interacting players, and/or chemical screens to identify potential therapeutic targets. However, the overarching notion is that similar or identical molecular pathways should underlie the phenotype observed in either tool or model as are affected in the human disorder. Therefore, both tools and models are relevant for dissecting some of the mechanisms underlying that disorder.

Is it a tool or a model?
Some biological systems are clearly models, whereas others are clearly tools. Since the crucial consideration in determining whether a given system is a model or a tool is the specific phenotype observed, even a simple animal can be a precise model. For example, in studies of memory and learning, the sea snail Aplysia can be considered a model for human memory, because the final output – memory formation – is the same in both species (for a review, see Bailey and Kandel, 2008).

Animal systems used to analyze the etiology of cancer include those that appear to accurately copy the human tumor phenotype. For example, non-small cell lung carcinomas (Kim et al., 2005) and some cases of soft tissue sarcoma in which the human disorder shows simple karyotypes (Dodd et al., 2010) appear to be phenocopied in mice, which would therefore be termed ‘models’. However, for other cancers, mouse phenotypes do not precisely copy the human tumor, often because the full cohort of genes contributing to the human cancer is not known, and/or because the methods used to develop the tumor do not reflect the human case (Frese and Tuveson, 2007). For example, this is the case for soft tissue sarcomas with complex karyotypes (Dodd et al., 2010), or for any cancer using xenografts of human tumor cells transplanted into ectopic sites of immunodeficient mice, where a human tumor forms, but in an environment that is quite different to that of the normal tumors in humans (Frese and Tuveson, 2007). These cases would be classified as ‘tools’.

Even in cases where genetic players have been conclusively identified, the phenotypic outcome of disrupting specific genes may be different in different animal species. For example, the pathology of Fanconi anemia (FA) is caused by abnormalities in a complex of 13 human proteins, each encoded by a different gene, many of which have been studied at the level of their molecular function (all are involved in DNA interstrand cross-link repair) (Kee and D’Andrea, 2010). Although almost all human FA homologs are found in most multicellular animals, and several are present in yeast, the final outcomes of disrupting their function in these systems does not precisely recapitulate the human outcome. For example, the Caenorhabditis elegans genome definitively encodes four of the 13 human genes associated with FA, and may include several other homologs (McVey, 2010), but worms do not have a hematopoietic system equivalent to that of humans, and so cannot develop anemia nor display the complex FA-associated developmental defects seen in humans with the disorder. Therefore, although C. elegans is an excellent genetic tool with which to study the...
function of some individual FA genes, it cannot be defined as a precise phenotypic model of the disorder.

For human mental health disorders, most non-human animal systems do not yield a phenotype equivalent to the human behavioral changes associated with the disorder. In the case of autism, for example, several risk genes have been identified in humans (e.g. Weiss et al., 2008), and homologous genes are present in the zebrafish. However, in analyses of these genes, the zebrafish should be defined as a tool, as fish do not have the behavioral repertoire, or perhaps even the brain regions, that are responsible for the human autistic phenotype (Blaker-Lee et al., 2011). Nonetheless, if perturbing a zebrafish homolog of a gene known to confer autism risk in humans results in a specific measurable phenotype in zebrafish, and expression of the human gene rescues the phenotype, then the zebrafish is useful for assaying the activity of human variants associated with autism. Furthermore, the modified zebrafish can be used to carry out chemical screens to define factors that modulate the function of autism risk genes, and thereby help to define potential therapeutic targets. The fish is thus a valuable tool for autism research.

**Importance of the tool definition**

The 'tool' definition is useful for two related reasons. First, the definition may encourage investigators to develop their biological system for experimental analysis of a specific disorder, which was not considered previously because the system was not an obvious model. Second, the tool definition allows an honest and rigorous assessment of both the useful characteristics and the limitations of an experimental system in studying a human disorder.

Together, the above points are relevant for justifying grant applications pertaining to translational research, in which the applicability of an animal-based or other biological system is crucial. On the one hand, the tool definition allows the applicant to suggest that a particular system is useful for addressing the etiology or treatment of a human disorder without feeling the need to claim that the system recapitulates the disorder itself. For example, mutations in the α-synuclein protein are tightly associated with Parkinson's disease, leading to formation of fibrillar plaques in human cells, and abnormal ER-to-Golgi trafficking in both yeast and human cells expressing proteins with the same mutation (for a review, see Auluck et al., 2010). Since yeast cells do not get Parkinson's disease, they would be classed as a tool; however, as a tool they have great potential to identify genes and small molecules that can modulate plaque formation at the cellular level. On the other hand, successful preclinical use of a biological tool requires a stringent level of justification for the proposed use of the tool. This includes a thorough analysis of how it will be used to examine the disorder – and some systems are better than others for certain approaches. For example, *Drosophila* might be excellent for genetic modifier screens, to identify suppressors of a lethal phenotype caused by mutation of a human disease gene homolog (e.g. Kucherenko et al., 2008), but might not be useful for identifying behavioral or anatomical brain phenotypes associated with a specific mutation found in human patients, as the fly brain differs so significantly from the vertebrate brain.

**A tool-model continuum**

Here, I have proposed that the tool versus model definition can identify the relative utility of specific biological systems in translational studies. However, in some cases it will not be clear whether to label a system a tool or a model, because sufficient comparative data might not be available. The purpose of these definitions is not to box a given system as a model or tool, but rather to highlight more accurately where and how a system might be valuable. The most useful framework may therefore be a tool-model continuum, whereby the systems at one end are clearly tools (showing no phenotypic resemblance to the human disorder, except with respect to homology to the underlying gene or molecular pathway) and those at the other end are clearly models (which so closely resemble a human disease as to be indistinguishable from it). Between these two endpoints is a continuum – perhaps the ‘tool-model index’, although this would be difficult to quantify. A biological system that lies at any point along the continuum can be useful in studying a human disorder, as long as the application of the system is carefully considered and justified. Formalizing the previously unstated notion of an animal ‘tool’ in analysis of human disease will diminish constraints on which non-human biological systems are considered useful for translational research, which will be enriched through extending the repertoire of systems and approaches that are available.

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