What's in a name? Broadening the biological lexicon to bolster translational research

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So-called model organisms have long been at the core of biomedical research, allowing scientists to study the ins and outs of human disorders in non-human subjects.

In the ideal, such models accurately recapitulate a human disorder so that, for example, the Parkinson's disease observed in a rat model would be virtually indistinguishable from that in a human patient. The reality, of course, is that rats aren't human, and few models actually faithfully reflect the phenotype of the disease in question. Thus, in the strictest sense of the word, many "models" aren't truly models at all. To developmental biologist and Whitehead Institute Member Hazel Sive, this is no small matter.

"The term model is used very loosely," says Sive. "That was a problem to me: Everything's a model!"

Sive sees the need to adopt a new term to expand the language of biological research to encompass systems that, although not technically models, can still offer tremendous utility in studying the etiology of human disorders. In this setting, she proposes the use of the word "tool."

Sive formally states her case in the March issue of Disease Models *&* *Mechanisms*. In an editorial entitled "'Model' or 'Tool'? New definitions for translational research," Sive calls for using 'tool' as a way to define a biological system that, though failing to recapitulate a phenotype, can, by virtue of its molecular makeup, provide important insights into a human

disorder.

"This is not semantic—there really is a difference," says Sive. "Mice have a cachet and are thought of as similar to humans, but obviously they're really quite different from humans. Frogs, flies, fish, and yeast, are serious systems for understanding fundamental biological questions, but they're seen as less valuable when it comes to studying human disease.

Although the publicity around Sive's proposal is new, she conceived of this construct nearly eight years ago for her own research with zebrafish. She uses zebrafish as a something of a test tube in which to study human mental health disorders, including schizophrenia, bipolar disorder, and autism. Knowing full well that zebrafish don't get autism, Sive nonetheless has employed the fish successfully as tools because she also knows that mental health risk genes in humans have homologs in zebrafish and that these genes are active during brain development. Because of this, Sive and her lab are able to conduct loss-of-function studies on these genes, examine what happens to the developing brain, and screen for chemicals that can alter the genes' activity. Such work could help identify potential therapeutic targets.

Having heard Sive discuss this 'tool-model' construct several years ago, Vivian Siegel, editor of *Disease Models & Mechanisms*, encouraged Sive to share it with the scientific community at large.

"She did exactly what I was hoping she would do." Siegel says of Sive's editorial. "We wanted to emphasize that you can find utility without the disease being recapitulated, as long as you know the limitations of the system."

Both Sive and Siegel, whose journal focuses on publishing basic research with translational impact, believe increased but judicious adoption of the

term 'tool' should encourage researchers to consider new uses for their systems of choice, help educate grant reviewers evaluating related applications, and ultimately lead to greater understanding of human disorders.

"If you adhere strictly to the term 'model', you can be misled by your own system," says Siegel. "This approach has a lot of benefits. My hope is that by publishing this in *Disease Models & Mechanisms*, it reaches out to people interested in translational research, and lets others know that they needn't be so dismissive of certain aspects of looking at organisms. This offers a new way to help recognize the potential contributions of organisms that aren't necessarily traditional 'models'."

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