Model Organisms: Nature's Gift to Disease Research

Read the related commentary in The American Journal of Human Genetics (Boycott *et al*. 2020; doi: 10.1016/j.ajhg.2020.01.009).

The diversity of life on our planet is astounding. If that were the result of processes unique to each organism, understanding the basis of life would have been unreachable, because it would have required studying an almost limitless variety of species.

But we've known for over 150 years that all living things are related, giving us confidence that what we learn about one organism will likely inform how others are born, live, and die. Thus, we learned that DNA is the carrier of inheritance in all organisms from the study of a simple bacterium (Avery *et al.* 1944). We learned much about the nature of the code embedded in DNA from studies of even simpler bacteriophages (Crick *et al.* 1961). We learned universal rules of inheritance from studies of a fruit fly (Bridges 1916). And we learned fundamental principles of how cells grow and divide by studying unicellular yeasts (Hartwell 1991). Studies of relatively few select organisms brought us the answer to Schroedinger's (1944) question: "What is Life?".

Fundamental research on "model organisms" continues to reveal the workings of life. And this research also helps us understand how things go wrong. Human disease phenotypes caused by a defective gene are often recapitulated in model organisms when the orthologous gene is made similarly defective, providing an experimentally tractable model of the disease. Numerous examples of how studies in model organisms have informed human disease, in some cases leading to development of a treatment, are nicely described in a review published in this journal (Wangler *et al.* 2017).

Pursuit of the genetic basis of disease increased dramatically over the last 10 years owing to sharply reduced costs of genome sequencing. Variants potentially responsible for rare and undiagnosed diseases are now identified by whole-genome or whole-exome sequencing. But thousands of variants are identified. Which one causes the disease? Model organisms often point to the answer by offering candidate genes whose function can be tested.

The potential for model organism research to speed diagnosis, mechanistic understanding, and treatment of human disease took a great leap forward with the organization of networks that connect clinicians with model organism geneticists. The Undiagnosed Disease Network (UDN) in the United States connects several clinical centers to, among other resources, a Model Organism Screening Center for functional exploration of candidate genes and variants (Ramoni *et al.* 2017). In Canada, the Rare Diseases Models and Mechanisms (RDMM) Network has taken a novel distributive approach that identifies and seeds collaborations between model organism researchers and clinicians who have discovered a new disease gene variant. A Commentary published in the February 2020 issue of The American Journal of Human Genetics describes how the RDMM has, over the past five years, connected model organism geneticists with clinicians through a national registry, and summarizes outcomes that include validation of disease gene discovery, identification of possible therapies, and success in obtaining subsequent funding (Boycott *et al.* 2020).

It's fair to say that progress in identifying disease genes has been spectacular. Disease-gene associations are now being discovered at a rate of 300 per year (~5 per week!); ~5400 diseases caused by variants in 3800 genes have already been solved. There are estimated to be ~5000 rare diseases for which disease gene variants have yet to be discovered. It's not unreasonable to expect that essentially all Mendelian disease genes will be identified over the next 10 years.

But disease gene discovery is just the beginning of the quest to improve the lives of those living with genetic diseases. Understanding the function of those genes is necessary to develop rational approaches to disease prevention, management, and treatment. We are far from understanding the function of humans' ~20,000 genes, or how they are organized and regulated in pathways and networks. Due to their experimental power and the evolutionary conservation of gene function, research on model organisms will surely continue to provide answers far into the future. The success of the RDMM and UDN should attract more model organism geneticists to human disease research, resulting in more disease genes being the focus of dedicated research programs.

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The Genetics Society of America strives to support and promote that work. The Allied Genetics Conference (TAGC) this April will showcase the ways model organisms are informing human disease. *GENETICS* has featured several such stories (*e.g.*, Brooks *et al.* 2014; Hamza *et al.* 2015; Pena *et al.* 2017; Lansdon *et al.* 2018), and we look forward to publishing more of them. And there are sure to be many more of these stories, because model organisms are nature's gift to science (Brenner 2003) that keeps on giving.

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