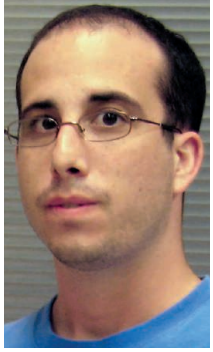

Aaron D. Gitler is an associate professor of Genetics at the Stanford University School of Medicine in Stanford, CA. E-mail: agitler@stanford.edu.

Ruth Lehmann is the Laura and Isaac Perlmutter Professor of Cell Biology and an Investigator of the Howard Hughes Medical Institute at the Skirball Institute of Biomolecular Medicine and the New York University School of Medicine in New York. E-mail: Ruth.Lehmann@med.nyu.edu.

Modeling Human Disease

THE ASTONISHING RECENT ADVANCES IN THE TECHNOLOGY FOR DETERMINING DNA SEQUENCES HAVE made personalized genomics a foreseeable reality for the doctor's office. This technology has started a whole new gold rush for human disease gene discovery and produced an onslaught of information that represents a new challenge in personalized medicine: connecting genotype to phenotype. Experimental organisms such as yeast, worms, fruit flies, zebrafish, and mice have long been critical for discovering the molecular mechanisms fundamental to life, thereby providing a shortcut to understanding human biology. The new developments allow these model organisms to also provide key insights into the association of specific genes with human disease.

Much of what we know about cancer can be traced back to basic studies in yeast cells aimed at decoding cell division. Likewise, studies in the worm revealed the mechanisms of programmed cell death and identified molecular targets that hold great promise for anticancer therapies. The fruit fly, an experimental workhorse in genetics for over a century, has elucidated cellular signaling pathways critical for human development, which often cause disease when dysregulated. And vertebrate model systems such as zebrafish, frogs, rats, and mice have provided insights into basic principles of cell and developmental biology with direct relevance to human disease. Yet despite their indisputable role in fundamental discoveries, some critics are questioning the continued need for model organism research, arguing that new tools such as whole-genome sequencing and patient-derived cells have now made humans and their cells accessible for studies of genes and gene products.

Such arguments ignore the massive amount that scientists have yet to learn in order to understand the function of even a single gene within the context of a living organism. Today, it is not possible to assign a function to at least half of the tens of thousands of proteins in vertebrate cells; moreover, it is the networks of interactions between them that make life possible, and the staggering complexity of these networks will require the innovative use of model organisms to decipher how these networks are used during embryonic development, adapted during aging and when environmental changes occur, and dysregulated in disease. Examples include using inexpensive, readily accessible model systems to tackle very complicated problems, such as how errors in protein folding cause neurodegeneration or discovering and understanding the astonishing and ever-expanding role of noncoding RNAs in regulating almost every aspect of cellular function.

How is work in model organisms valuable to research on specific human diseases? The best recent examples come from genome-sequencing technologies that are being applied to discover possible causes of rare and common genetic diseases. This has led to the surprising finding that there are more variants in the coding regions of genes than previously anticipated. Moreover, there is compelling evidence for a major role of noncoding genetic variation in human disease, associated with changes in gene regulation. How does each of the many variants in genes and gene regulatory regions contribute to the risk for specific diseases or disease outcomes? Insights may come from modeling these variants in genetically more amenable organisms.

We suggest a future in which model organisms will be deployed to work out the basic biology of newly discovered disease genes, assign functions to disease-associated variants, and even to uncover previously unknown disease genes. Remarkably, a goal to define all genetic contributors to a human disease is now fathomable. Some genes will be straightforward to find, but others (perhaps most) will require creative strategies. For example, unbiased genetic interaction screens in model organisms can be combined with human genetics to discover and validate disease genes. It is not time to abandon tried-and-true model organisms but rather to embrace the traditional model systems, develop new models, and forge collaborations between human geneticists and model organism researchers. Let's combine the powerful advances in human genetics with the versatility of model organisms to fulfill the promise of personalized medicine.

– Aaron D. Gitler and Ruth Lehmann

10.1126/science.1227179

Published by AAAS