A data-driven approach to match organisms and research problems

What if we could select research organisms that are far more relevant to human biology or more likely to unearth biological solutions not found in humans? With more sequence data, structural prediction, and phylogenetic comparative methods, a richer framework is possible.

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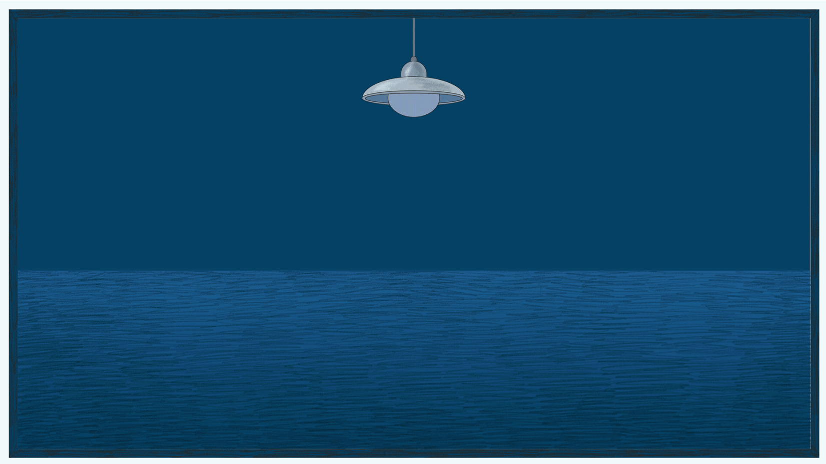
Purpose

It's critical to select the ideal organismal model to use for studying a human disease or biological process faster, cheaper, and easier than can be explored in humans. Scientists often select organisms based on historical precedent, ease of use in the lab, and similarity of genes or phenotypes. While this approach has resulted in many important advancements and certainly has its merits, relying on intuition, convention, and prior studies to select model organisms isn't always optimal for understanding the complexities of human biology, particularly in the context of therapeutic development. Discovery research and preclinical testing in animal models often fail to translate to the clinic [1] and don't take the evolutionary history of mice and humans into account [2].

In this pub, we describe a new framework for thinking about organismal model selection that leverages the vastness of biology, including and beyond traditional model systems. This approach has the potential to accelerate the pace of



We tend to rely on a single set of model organisms, looking "under the lamppost" at the biology we know. What if we shone a light across the whole tree of life? Could we find better models?

biological discovery by highlighting valuable organisms that have been historically overlooked and understudied but have outsized biological relevance to humans.

This pub is meant for a scientific audience and we'd love feedback. Would our organismal selection framework change how you'd select which organism you'd use to solve your research problem of interest? Would you use these tools to identify new research directions based on where your organismal expertise is best leveraged?

- This pub is part of the **platform effort**, "Genetics: Decoding evolutionary drivers across biology." Visit the platform narrative for more background and context.
- Read our **companion pub**, "Leveraging evolution to identify novel organismal models of human biology" [3], for more details on the science underlying our organismal selection pipeline.
- For an **example of this approach in action**, check out "Rescuing *Chlamydomonas* motility in mutants modeling spermatogenic failure" [4].
- Check out our user-friendly **organism selection portal**, Zoogle.

Traditional organism selection

There are many reasons why traditional model organism selection is suboptimal when pursuing *biological conservation*, the context most relevant to humans. Traditionally, this is done by comparing gene or protein sequences between the organism and humans and considering whether the two share relevant phenotypes. Historically, identifying the right system with conserved biology has required deep knowledge of individual organisms and the contribution of an entire field to unearth the dimensions of shared biological context.

Rather than relying on intuition or luck, we wondered if it was possible to more systematically identify properties of organisms across the tree of life that might be redeployed or re-engineered to develop human therapeutics and other useful innovations. Not only might we be able to accelerate the work many organismal biologists have contributed to mechanistic understanding, but we may also be able to improve the accuracy of organismal selection for downstream application.

For example, around 90% of drugs that progress from preclinical testing in organismal models (95% is done in rodents) to clinical trials in humans fail. This failure rate suggests that many researchers are using convention or historical precedent and not fully leveraging available data to optimize the organism they select for their research questions. We asked whether we could use a more rigorous data-driven framework for discovery research to increase the accuracy of insights with respect to human relevance.

Rationally sourcing biological conservation

Beyond proteins and prior mechanistic studies, we've never been in a better position to leverage even more data. We can use protein structural properties inferred from amino acid sequence and take into account evolutionary history to do comparisons between species [3]. Sometimes we find that our intuition about model systems was spot-on, but we can be much more confident in our choices and reach conclusions quicker.

While scientists have long been using *Chlamydomonas* to understand sperm motility due to structural similarities between *Chlamydomonas* and sperm flagella [5][6][7] due to high-resolution electron microscopy, we were able to use our framework to identify an appropriate model and validate its relevance to human biology quickly, cheaply, and with high confidence using little additional context. In this case, the pipeline led us to an existing model, but we got there through an unbiased selection process.

The power of this data-driven approach is more readily appreciated when the results of our analyses lead to unintuitive results, identifying organisms with non-obvious similarities to human biology.

Well-established models like mice aren't just expensive to maintain — they also don't necessarily recapitulate the specifics of the human disease. The conservation of relevant properties in a much simpler system may signal that the etiology of the disease is in a more ancient and conserved biological process that makes muscles and nerves particularly vulnerable. And that more complex tissue-level phenotypes may be a consequence rather than a cause of the disease.

Our strategy lets us rationally and agnostically consider less-studied organisms that may be more biologically relevant to the disease or trait in question.

A call for change

We've developed an approach that allows scientists to rationally identify research organisms for modeling human traits by incorporating genomic data, protein structure, and other biological contexts [3]. Knowing that not all researchers can dynamically spin up new infrastructure for every new research organism they land on, the other major utility of our framework is that for a fly or fish or worm lab, we can help agnostically identify the focus areas where these species are most relevant and can make the most headway. We hope this data-driven approach will increase our ability to leverage the full diversity of the natural world for scientific discovery.

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Weigh in!

Would you use our workflow to identify an appropriate research organism, a biological area the model you have expertise in can best tackle, or use these data to support your choices when seeking funds, in publications, or for drug development? This platform relies on access to high-quality, annotated genomes across a wide range of organisms. What species for which you already have expertise or tools would you like to be integrated into our platform? Did you try Zoogle and test its predictions in the lab? We'd love to hear if it was helpful for your application!

Contributors (A–Z)

- **Prachee Avasthi**: Conceptualization, Supervision, Writing
- **Audrey Bell**: Visualization
- **Megan L. Hochstrasser**: Editing
- **Ryan York**: Conceptualization

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