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EDITORIAL

Genome editing in non-model organisms opens new horizons for comparative physiology

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For almost 100 years, biologists have made fundamental discoveries using a handful of model organisms that are not representative of the rich diversity found in nature. The advent of CRISPR genome editing now opens up a wide range of new organisms to mechanistic investigation. This increases not only the taxonomic breadth of current research but also the scope of biological problems that are now amenable to study, such as population control of invasive species, management of disease vectors such as mosquitoes, the creation of chimeric animal hosts to grow human organs and even the possibility of resurrecting extinct species such as passenger pigeons and mammoths. Beyond these practical applications, work on non-model organisms enriches our basic understanding of the natural world. This special issue addresses a broad spectrum of biological problems in non-model organisms and highlights the utility of genome editing across levels of complexity from development and physiology to behaviour and evolution.

The study of physiology and genetics has typically been via binary alternative pathways, chosen early in university education. This is a shame because the synthesis of these disciplines is precisely where the most exciting biology is to be found. Physiologists try to understand how the organism works, by painstaking experimental and pharmacological interventions, continually working to minimize artefacts induced by the protocols themselves. Geneticists, by contrast, bring the twin approaches of forward and reverse genetics: forward mutagenic screens allow unbiased discovery of genes that impact a phenotype of interest, whereas reverse genetics uses molecular biology to deduce the function of a gene by mutating it and looking for a detectable phenotype. Until recently, the separation of physiological and genetic approaches has limited the progress that can be made in either of these individual fields. Physiologists have been slow to adopt the gene-based molecular and reverse genetic approaches that were available in 'model' organisms, whereas geneticists have been limited to studying the general problems accessible in model organisms, losing out on the richness of specialized behaviours and developmental mechanisms found in the rest of the tree of life.

Over the past couple of decades, some more intrepid researchers from both camps have worked to close this acknowledged gap by embracing the features and limitations of model organisms. Although these approaches have been fraught with difficulties – fly, worm, zebrafish and mouse are scarcely the biggest representatives of their respective clades – these efforts have generally been transformative in their fields. However, the mismatch remains. Model organisms remain few and far between in phylogenetic space, and it can be hard to convince a salmon specialist that zebrafish is a good model for adaptation to varying salinity, or a mosquito vector biologist that *Drosophila melanogaster* is suitable for studying blood-feeding behaviour.

Hence the excitement that this special issue tries to capture. Here, we assemble papers on the great democratizing technology of genome editing, and in particular CRISPR. Suddenly, the reverse genetic approach becomes accessible in 'target', rather than classical 'model' organisms. Many of the elegant manipulations of modern genetics – single base mutations, gene deletions, GFP fusions and so on, become feasible in a wider array of organisms. This is not the same as 'easy'; it is important to acknowledge that organisms vary hugely in the ease with which gene targeting technology can be applied. However, it is now at least possible, and this special issue illustrates work in organisms as diverse as mosquitoes, cattle, parasitic nematodes, and sticklebacks. The papers further illustrate nicely the versatility of this approach, with topics ranging from molecular evolution to pest control and from control of reproduction to ageing.

Do the advantages of gene editing make our familiar models – yeast, worm, fly, fish and mouse – obsolete? Perhaps the opposite. As nicely documented in Benjamin Matthews' paper (jeb218198), the path to becoming an all-round model requires the development of a huge range of complementary technologies, such as online informatic resources, genomes, transgenic resources, stock centres and cell-specific transgenic interventions like the Gal4/UAS system. Whereas an individual lab can maintain a thousand *Drosophila melanogaster* stocks (and a reference stock centre over 20,000), it is a major undertaking to maintain a stable stock of malaria mosquitoes, let alone more than a few dozen mutants. And, of course, established models come with a prior art that can reach back a century and encompass hundreds of thousands of papers. In this context, 'model hopping' becomes an attractive paradigm. Study of a 'target' organism can be accelerated by referring back to the phylogenetically closest genetic model, finding out what is already known about a gene of interest, and perhaps experimenting with existing mutant or RNAi resources. This relatively quick and inexpensive comparative work can help to frame a strategy for transgenic experimentation in the target species of interest, or even suggest whether such work is needed.

Overall, new technologies associated with genome editing have spawned a new age for comparative physiology. Krogh's famous principle (though uncannily similar to that posited by Claude Bernard in 1865) 'For such a large number of problems there will be some animal of choice or a few such animals on which it can be most conveniently studied', has underpinned modern comparative physiology. Now many more organisms can be 'Krogh organisms', and comparative physiology can ask a whole range of new, truly comparative questions about the logic of life, with access to a hugely expanded toolbox. We hope this special issue will help to convey some of this excitement.

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