

It's time to exploit your favorite quirky organism with new technologies

Haruhiko Siomi

We live in a competitive world where, at any given moment, our peers might achieve the very discoveries we hope to make with our own research. This reality creates butterflies in the stomachs of those who are engaged in risky experiments. Any hesitation or setback, even momentary, can make you feel that by the time you are in a position to pursue your own direction, every novelty will already have been discovered. But don't worry, for many years to come there will be plenty of biology waiting to be investigated with many questions we haven't yet thought of asking.

I think that the most important field in biology today is developmental biology. During development, it is thought that each event or structure is consequential to a preceding event or structure and that the layering of subsequent processes ultimately brings the phenotype into being. This process is also studied by those in the field we now call epigenetics, which, I believe, is modern developmental biology armed with state-of-the-art genomics tools and systems bioinformatics. I want to know how a fertilized egg with one genome can give rise to a dazzling variety of cell types in which all genomes are the same as that of the egg, and how these cells are organized to form a functional whole at the end of ontogeny. I very much want to decode where and how in the genome or cell the storage and retrieval of the 'memory' of ordered sequences of events that contribute to the elaboration of complex developmental patterns is achieved. I have learned that if we ask the right questions, we can learn fundamental truths about how and why life is the way it is. Unfortunately, however, I don't know the right questions that can be refined and tested experimentally by the broader scientific community that will

unlock the mysteries of development. I am, nevertheless, optimistic.

In the past three decades, we have discovered the striking wholesale conservation of molecular mechanisms across the world of eukaryotes. My favorite paper is by Halder, Callaerts, and Gehring, published in 1995, in which they show that ectopic expression of mouse *Pax6* cDNA under the control of GAL4 induces the formation of ectopic eyes on a fly leg [1]. We have also learned that what is learned in one species will lead to new approaches and principles that can be transferred to more complicated cells and animals. I particularly like the RNAi paper by Tuschl and colleagues, published in 2001, which demonstrates that 21-nucleotide siRNA duplexes specifically suppress expression of endogenous and heterologous genes in different mammalian cell lines [2]. The realization that the number of genes does not increase proportionally with developmental complexity has led to the conclusion that regulation of gene expression is more important than simply the number of genes in a genome. We are also well aware that special elaborations and exaggerations of certain basic eukaryotic mechanisms in unusual organisms have often facilitated discoveries opening the door to major new fields of fundamental research. Elizabeth Blackburn thoughtfully used *Tetrahymena* to study the function of telomeres and, thereby, identified telomerase [3]. David Allis also used *Tetrahymena* to study histone modifications. This eventually led to the first identification of a nuclear histone acetyltransferase (HAT) as the homolog of the yeast transcriptional factor, GCN5, and, thereby, the realization that transcriptional regulators can act by modifying chromatin [4]. *Tetrahymena* is a single-celled organism and exhibits nuclear

dimorphism; each cell has two nuclei, the micronucleus, which contains the germline genome and is transcriptionally silent, and the macronucleus containing the somatic genome, which becomes transcriptionally active, hyperacetylated, and highly fragmented—that is, many chromosomes requiring telomeres. These scientists clearly had the open minds needed to ask the right questions of the right model organism.

We live in an era where advances in DNA sequencing technology allow an individual scientist to determine the whole-genome sequence and the entire transcriptome of any organism in a matter of days. Methods for manipulating gene expression—RNAi, TALENs, and CRISPR/Cas9, for example—are also increasingly employed. With these new technologies, the constraints of relying solely on traditional model organisms are released. Rather, any favorite animal or plant that is best studied to resolve the problems under scrutiny can be adopted as a model organism. Thus, the suitability of a model organism has to be redefined in terms of how developed and elaborated is the basic eukaryotic feature that you want to resolve. Progress in biology is driven by new scientific questions, which demand not only new technology, but often new model organisms. The beginning of the molecular biology era—the 1950s and 1960s—was stimulated by many physicists who moved into the field; hence, we perhaps now need people who bring with them a happy ignorance of classical model organisms.

How can we identify new model organisms? Just like development, science progresses not by creating anything wholly *de novo* by chance, but by integrating the preceding knowledge with the new. As the old Chinese proverb goes: "he that would

know what shall be must consider what has been". A conservative approach, therefore, is to go to the library and search through old journals. I used to love walking through silent alleys of book shelves to occasionally find very strange but interesting papers, such as 'Planarians and memory', which describes the transfer of learning by the injection of ribonucleic acid (now, that, I think, is cool!) [5]. Alternatively, an exploration of the plethora of wild species may yet yield your favorite quirky organism.

By the way, if you are wondering whether I have a favorite odd organism, the answer is

yes: it's the naked mole rat [6]. They look really quirky *and* cute, and they can live for more than thirty years without any sign of cancer. But they are already popular, so I should go out to the library or out into the wild to hunt for new peculiar organisms. Oh, I nearly forgot that I should identify the problems I want to solve before I leap. For me: the organic memory of ordered sequences of events.

Conflict of interest

The author declares that he has no conflict of interest.

References

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