

Correspondence

Functional genomics does not have to be limited to a few select organisms

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A response to Whither genomics? by Andrew W Murray, *Genome Biology* 2000, **1**:comment003.1-003.6

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In response to Andrew Murray's article 'Whither Genomics' (*Genome Biology* 2000, **1**:comment003), I would like to take issue with the assertion that "genomics will accelerate the migration of biologists to...humans, mice, fruit-flies, worms, yeast and *Arabidopsis*". Functional genomic studies attempt to relate genome sequences to functional changes in an organism. If we are seeking to understand the functional importance of DNA sequences and how patterns of mRNA expression affect the biology of organisms, one of the more productive approaches is to follow August Krogh's principle [1]: for many problems there will be an animal in which it can be most conveniently studied. Thus, functional genomics will be enhanced by a comparative approach: studying a diversity of organisms, in which physiological, developmental or biochemical traits are more readily determined. Unfortunately, many believe that functional genomics is only suited for 'model species' or, more accurately, species that are well defined genetically.

The strength of the comparative approach lies in the use of species or groups of species best suited to address specific physiological or biochemical processes. For example, Hans Krebs's

research depended on muscle tissue from the common dove to elucidate the 'Krebs' cycle [2]. Krebs's Nobel Prize winning (1953) research used this non-model species because the breast muscle was rich in mitochondria and these organelles were 'tough' [3]. Warburg (Nobel Prize, 1931) used a wide range of species in his elucidation of metabolic principles [4,5]. The Nobel Prize for the fundamental work on neural conduction by Hodgkin and Huxley depended on the use of the giant nerve fiber of the squid *Loligo* [6,7]. The basic research on sodium transport was done using toad bladder [8]. The elucidation of acetylcholine esterase's role in neural impulses used the electric organ of the fish *Electrophorus electricus* [9]. Isolation of influenza virus used the ferret [10]. Studies of nuclear and cytoplasmic interactions used the giant unicellular alga *Acetabularia* [11]. The studies of prion proteins, for which the Nobel Prize was awarded in 1997, used a diversity of mammals [12-14]. The recent Nobel Prize for the biological importance of nitric oxide used endothelium from rabbits. These studies are but a few of the biological endeavors that relied on non-model species to elucidate fundamental principles of human biology.

Non-model species offer a complementary method (relative to model species) to begin to understand how genome-wide patterns of gene expression alter physiological, biochemical and developmental traits. Using a diversity of species also identifies general or common principles rather than molecular traits that can be specific for one or few species [15]. By exploring the variation in mRNA expression among non-standard organisms, we should gain a better understanding of which genes effect an adaptive change in physiological processes. For example, the brine shrimp *Artemia* has virtually no metabolic rate during diapause. Which genes are involved in this process? Is the level of one, a few, or all gene products down-regulated? Toadfish are unusual for teleosts in that they are capable of producing urine. Are there unique sets of genes expressed in this species as compared to other similar species not capable of producing urea? Among extreme hypotherms such as Antarctic species, are there unique patterns of gene expression? In fish living in estuaries, which genes are differentially expressed when the fish are subjected to different salinity or different environmental pollutants? In ectothermic organisms where differences in incubation temperatures affect sex ratios, what

are the changes in gene expression associated with the establishment of one or the other sex? Among social insects, what patterns of gene expression are associated with different caste? What makes a large soldier versus a minor worker? These problems may represent qualitative differences in gene expression (on/off) but are more likely to reflect quantitative differences in gene expression. Thus, they would be better studied using microarrays. There is an opportunity to study the functional genomics of a wide diversity of organisms and thus to learn more about the biological solutions to adaptation, solutions that are unlikely to be obtained by the application of standard molecular techniques to model systems.

Many developmental biologists study a diversity of organisms [16] to discern the genes involved in pattern formation. Until recently, only the presence and absence of a gene product were readily determined (for example, by subtractive hybridization, differential display or *in situ* hybridization). Microarray technologies would allow developmental biologists to study quantitative differences in gene expression. This approach could begin to address the importance of quantitative differences in gene expression in the establishment of, for example, dorsal-ventral axis formation, bilateral symmetry, or limb development. Evolutionary developmental biology would benefit from the ability to use microarrays in a wide diversity of organisms. Molecular ecology is a relatively young field (the first journal devoted to this subject is less than a decade old), but it offers insights into how ecological factors affect the biochemistry and molecular biology of an organism and how molecular attributes affect the interactions among organisms. Should the most powerful tools for the analysis of gene expression be denied to this and other fields because of the cost and time required to develop them? My response is that there is no need to limit microarray technologies to a few genetically well described species. Importantly, this type of research

could provide a perspective that is unlikely to be obtained by studying only model species.

The problem is how to provide the necessary tools to study this diversity of organisms. It is possible to generate thousands of unique cDNAs from any organism simply and inexpensively [17]. These cDNAs can then be used for microarray analyses. Thus, functional genomics, specifically quantifying the expression of many, if not most, of the genes expressed, does not have to be limited to a few select organisms.

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Andrew Murray responds:

I agree with Crawford that studying a wide variety of organisms is good and should be encouraged. I was not arguing that biologists should concentrate on a small number of model organisms, but was simply pointing out that the development of genome-based tools has a strong element of positive feedback, and as a result the rich (widely studied organisms) get richer and the poor get poorer. There are also two important points about how data from microarrays leads to statements about biology. First, if the thousands of arrayed cDNAs aren't sequenced, they don't tell us what is encoded by the transcripts that are found to rise and fall in interesting ways; and the process of both generating and sequencing such collections is still non-trivial. And second, even if one knows what an interesting gene on an array encodes, not much can be done to determine its role in an organism or ecosystem unless the gene can be manipulated - so genetically tractable organisms remain likely to be favored.

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