

Editorial overview

Model organisms and new tools: Choose your weapons wisely

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Twenty years ago, yeast was a highly used model system to understand the basic biology of processes such as cell signaling. Before the advent of tools such as antisense, double-stranded RNA and transgenic mice, yeast was the only eukaryotic system that could be genetically manipulated, making it an important model for drug discovery. Using a relatively simple molecular construct, one could knockout a gene of interest [1] and measure whether a signaling pathway would still function, or if it

were perturbed in any way. Whole signaling systems could be replaced by their mammalian systems counterparts and, sometimes, they would still work!

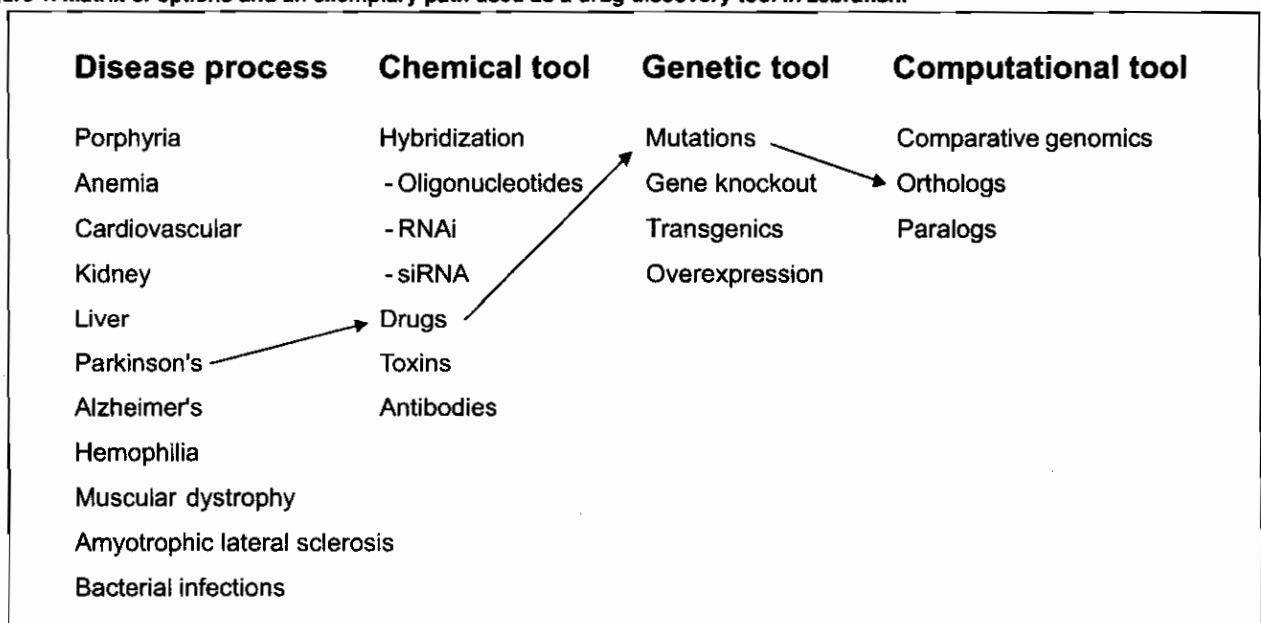
Wealth of new options

While yeast remains a valuable model organism to understand biology, applications to complex multicellular organisms are limited. A broader range of model organisms now exist that can be genetically manipulated, and the complete genome sequences of the most popular model organisms are known. In addition, techniques are available that allow the manipulation of model organisms. Among the interesting reviews of this issue of *Current Opinion in Drug Discovery & Development* is the article by Amy L Rubinstein on the use of the zebrafish as a model organism, which exemplifies how several new tools in our arsenal can be used to dissect complex cellular systems. The current matrix of model organisms, genetics, genomics, computational tools and chemical probes provides a broad range of options that give new insights in our understanding of problems relevant to diseases, and to the therapeutic approaches to treat them.

Exploring the matrix

One of the most effective new tools for drug discovery is comparative genomics, through which orthologous genes, proteins and pathways in different organisms can be identified. The way the components interact can be deduced by observing which component parts are conserved or dispensed with as a whole. Genetic tools can then be used to modulate the level of specific proteins of interest, whereas chemical tools allow the inhibition of the function of specific proteins, or the inhibition of their production by interfering

Figure 1. Matrix of options and an exemplary path used as a drug discovery tool in zebrafish.



with the mRNA encoding them. The Rubinstein review nicely exemplifies how some of these tools are effectively matrixed, with the zebrafish as a model organism (Figure 1). Zebrafish are excellent models for human systems. Although relatively simple, zebrafish are prototypical vertebrates that retain a high percentage of the relevant developmental and functional pathways of higher vertebrates (some researchers in the field of zebrafish are offended by the term 'higher', and prefer 'larger'). The zebrafish reproduce rapidly, and have many offspring; as the embryos develop outside of the mother and are transparent, one can actually visualize the organs, as well as monitor function and viability.

Zebrafish also seem to be amenable to manipulation of specific genes by antisense oligonucleotides. Antisense oligonucleotides are effective tools for drug discovery due to their specificity, and also because they mimic drugs. Unlike most types of genetic manipulation, in which long-term physiological equilibration can occur, drugs and oligonucleotide inhibitors have a relatively sudden onset, and a short duration of action. Antisense formats are more or less effective, depending on the animal model: morpholino-based antisense oligonucleotides are effective in zebrafish, whereas RNA interference by double-stranded RNA is less effective in specific gene inhibition. Double-stranded RNA has been successfully used in a number of model organisms, especially *Caenorhabditis elegans* [2]. When

choosing a system to study, the relative success of different chemical tools in different model organisms is also a parameter to consider.

Many choices, little time, few excuses

Tools currently available to aid biologists or practitioners of drug discovery are numerous, considerably more than what was available two decades ago. Has this resulted in a commensurate increase in the quality and quantity of new drugs being discovered and developed? I think we all know that the answer to this question is, no. The missing part of this equation is time. Ironically, as the matrix of tools becomes richer, the complexity of the options available will partially offset their value until we learn how to use them effectively. However, it is fair to say that we have fewer excuses for failure and that, by using better models, effective new drugs should be developed.

Suggested reading

1. Ecker DJ, Butt TR, Sternberg EJ, Neeper MP, Debouck C, Gorman JA, Crooke ST: **Yeast metallothionein function in metal ion detoxification.** *J Biol Chem* (1986) **261**(36):16895-16900.
2. Montgomery MK, Xu S, Fire A: **RNA as a target of double-stranded RNA-mediated genetic interference in *Caenorhabditis elegans*.** *Proc Natl Acad Sci USA* (1998) **95**(26):15502-15507.