

GUEST EDITORIAL



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Model Systems for Studying the Biology of Filamentous Fungi: Rumors of Their Death Should be Postponed

If judged by the almost doubling of the number of publications concerning fungal-related topics during the past decade, fungal research is flourishing. The motivation that fuels the study of filamentous fungi ranges from the use of fungi as model systems for the study of eukaryote biology in general and fungal biology specifically, to facing plant, animal and human fungal-based health threats and to the harnessing of fungi (or their traits) for industrial applications (19).

The availability of the complete genome sequence of an organism provides an invaluable tool for hypothesis-driven research as well as setting the basis for comparative analyses. Coupled with the technological advances that allow for genetic and environmental manipulation of a growing number of fungi, a genome database can be used for functional analysis of almost any conceivable fungal trait. Furthermore, with the proper efforts invested, almost any fungal species can be rendered amenable (with various limitations) to genetic manipulations. One of the outcomes of the technological progress made is the raising of doubts concerning the future validity, potential contribution and, subsequently, justification for continued support for research of so-called 'fungal model systems' (and, more specifically, filamentous fungi). Model systems are usually chosen on the basis of amenability to growth, manipulation and analysis (including the capability to

use defined media and environments to control metabolism, growth and development on the one hand, and classical genetics on the other), along with the expectation that discoveries made in the model organism will provide insight into the workings of other organisms. The accumulating technological advances made over the past decade have significantly improved our capabilities of dissecting traits in fungi of economic importance, raising the question: are the model systems still needed? Here, I argue for the continued support for basic research of fungal biology and contest the tendency to retire fungi not exhibiting immediate economic relevance from the focus of scientific – be it basic or applied – interest. Furthermore, combining model systems with those of economic relevance is advantageous from scientific, educational as well as research-funding investment viewpoints.

The harnessing of increasingly available and more user-friendly ‘X-omics’ approaches by many scientists has resulted in the production of an abundance of new data. Without underestimating the value of large datasets, the massive efforts currently invested in such approaches might also result in diffusing intellectual and material resources. Realizing that experiment-based data analysis, rather than data acquisition, is becoming the rate-limiting step in our era of mycological research (18) implies that production/collection of new data for a large variety of fungal species, without the appropriate experimental follow-up, does not necessarily guarantee our better mechanistic understanding of fungal biology. Perhaps combining the use of some of the available model systems with work on other fungi should be favorably reconsidered at this time. Based on my personal experience, I can testify that I have found cross-species complementation and comparative cell biology to be useful tools in determining fungal gene function, especially in the case of genes whose products (*e.g.* COT1 kinase, NIT3 transcription factor and Calcineurin phosphatase) are involved in the regulation of fundamental process (3,6,9,16), yet the prospects of heterologous genome-wide microarray-based analyses are even more intriguing (12,15). Combining the progress in understanding fungal evolution, development (‘classical’ models), pathogenicity (*e.g.* *Magnaporthe grisea* and *Ustilago maydis*) along with the new bioinformatics and wet-bench tools at hand, strongly supports the likelihood for success of such approaches (13,14,17). An important prerequisite for promotion of such advances is improving the scientific dialogue among mycologists, as well as between mycologists and researchers involved in the study of related organisms, be they other pathogens – such as oomycetes, or hosts – ‘model’ or ‘economic’.

Following the deciphering of the complete genome sequence of the first eukaryotic genome, that of the budding yeast, the genomics initiative has neglected the fungal kingdom for a relatively long time. However, during the past few years increased interest accompanied by financial support in fungal genomics has culminated in the sequencing of approximately 30 fungal genomes to date and this number will surely rise significantly in the near future. Some of the conclusions already reached on the basis of these recent studies include the genomics-based realization of the immense diversity of the fungal kingdom, which is estimated to include approximately 1.5 million species (1,10). For example, a comparison of three species of *Aspergillus* – *A. nidulans*, *A. fumigatus* and *A. oryzae* – revealed only 68% average amino acid identity between any pair of species (8), an evolutionary distance comparable to that between human and fish. Nonetheless, many of the fundamental traits, including some of the regulatory networks, are highly conserved among members of this diverse kingdom. Would such an evolutionary distance diminish the relevance of information obtained by studying *A. nidulans* with regard to other

fungi? Hardly. It is the culmination of efforts invested by a large scientific community that, in many cases, contributes most to advancing our general understanding of fungal biology. For example, establishing a functional link between the regulation of asexual development and secondary metabolite production in *A. nidulans* was very much dependent on decades of classical and molecular genetic analyses of these processes by a large number of researchers (20). The implications to fungi of economic relevance can now be addressed in a significantly more detailed manner, and the specifics of toxin or antibiotic production in other species can be probed. Diverse research programs centered on model organisms have yielded an enormous amount of information relevant to many fungi. This has ranged from formal population and molecular genetics, biochemistry, physiology, and molecular cell biology to more recent studies of development, photobiology, circadian rhythms, gene silencing, ecology, and evolution. Thus, the information obtained by studying the model system can prove an invaluable starting point for analyzing other systems, even if the eventual outcome will prove the model different from the economic subject. Furthermore, the technical capabilities involving gene identification, isolation, manipulation and heterologous expression can make the parallel use of model and applied systems a rational and advantageous one.

The input of an expanded research community is essential not only for establishing large-scale projects in fungal biology, but a critical mass of scientists involved in the study of multiple facets of an organism can better reap the offerings that large projects such as genome sequencing can provide. This has been clearly demonstrated in the case of the first filamentous fungus whose genome was entirely sequenced: *Neurospora crassa* (2,4,7). It is no coincidence that *N. crassa* was chosen to lead the public fungal genome initiative; the seminal contributions of this organism in the past (5) made it a prime choice. Other ‘model’ organisms have followed suit, including plant pathogens, providing an environment for genomic comparative biology that will be unsurpassed for studies of genome evolution (for the phylogenetic relationship of model fungi, see ref. 11). The soon-to-be-sequenced species related to *N. crassa*, such as *N. discreta* and *N. tetrasperma*, will significantly enhance our abilities to study fundamental fungal traits, relevant to a wide range of fungi (*e.g.* genome defense against mobile elements, evolution and genetic consequences of fungal mating strategies, pseudohomothallism, and fungal mutation), and these prospects are exciting.

It is only natural that the lure of combining cutting-edge technology with our personal research affects many of us. Indeed, the implications that novel techniques/equipment have in many fields of fungal research are enormous. It is only natural that our students are among the first to embrace new technologies. Nonetheless, one of our missions is to teach our students how to harness technology to answer scientific questions, rather than direct our science to fit the technique. Here, again, model systems can be of help in setting the example. The concerted use of biochemistry, physiology and classical genetics as traditional approaches for dissection of fungal traits should be emphasized – rather than phased-out – in our training programs. Model systems are extremely convenient for such purposes and can not only provide for actual training and increased awareness in the mentioned topics (acquiring a feel for the organism), but also fuel the imagination with the unique possibilities fungi (models and others) offer in terms of research, in a convincing and hands-on manner. Furthermore, providing a historical perspective of the progress made in fungal biology and the general scientific contributions arising from research on fungal

systems may provide an additional means to implant an appreciation of fungal research upon our next generation of scientists.

Model organisms certainly provide an advantage, yet as data accumulate (especially with regard to the diversity within the fungal kingdom), it is becoming clear that the definition of a model, in the context of the possibility to extrapolate from our findings to other fungal species, also has limitations. Nonetheless, for the most part, past reasons for choosing many of the model organisms are still relevant today. Abandoning them now for the sake, or rather hope, of quick returns by focusing on immediate problems related to specific organisms, might prove to be counterproductive. The prime example is the non-filamentous fungus *Saccharomyces cerevisiae*. Even though differences between the most genetically dissected eukaryote and other organisms are increasingly accumulating, eliminating this yeast as a foundation, resource and tool would not be a productive move. Perhaps similar appreciation of the virtues of studying model systems from other kingdoms (e.g. *Escherichia coli*, *Arabidopsis thaliana*, *Caenorhabditis elegans*, *Drosophila melanogaster*, etc.) has also contributed to the continuous scientific enthusiasm and support for their exploitation. Details concerning economic species, or even strains, can – and should – be eventually challenged on a case-by-case basis, perhaps with an emphasis on problem solving, or analysis of unique traits, rather than a ‘me-too’ approach (involving the generation and analysis of very large datasets), which is a major and alluring pitfall, given the feasible technical possibilities facing fungal biologists today. One rational approach is to carry out research on fungi of economic importance along with appropriate model fungal systems, in a complementary fashion, which may prove to be significantly more advantageous than appears at first. Thus, the *a priori* branding of model fungi as irrelevant on panels considering funding of applied research is premature, to say the least, and their relevance to a given project should be considered on the basis of their contribution to the scientific merit and chances of success of the project in mind.

In this editorial I argue that ‘model fungi’ should be continuously embraced in current mycological research. The advantages and potential scientific gains to be harvested by exploiting model systems have only expanded in the wake of the technological advances being made. The rationale for combining model and applied systems is based on scientific and economic pragmatism. In addition, the educational value of model systems for securing the quality of our next generation of mycologists should not be underestimated. Thus, the call for continued exploitation of model fungal systems is directed at researchers, educators and funding decision-makers alike.



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