

## Review

# New and Improved Techniques for the Study of Pathogenic Fungi

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**Fungal pathogens pose serious threats to human, plant, and ecosystem health. Improved diagnostics and antifungal strategies are therefore urgently required. Here, we review recent developments in online bioinformatic tools and associated interactive data archives, which enable sophisticated comparative genomics and functional analysis of fungal pathogens *in silico*. Additionally, we highlight cutting-edge experimental techniques, including conditional expression systems, recyclable markers, RNA interference, genome editing, compound screens, infection models, and robotic automation, which are promising to revolutionize the study of both human and plant pathogenic fungi. These novel techniques will allow vital knowledge gaps to be addressed with regard to the evolution of virulence, host–pathogen interactions and antifungal drug therapies in both the clinic and agriculture. This, in turn, will enable delivery of improved diagnosis and durable disease-control strategies.**

## The Persistent and Expanding Threat of Fungal Disease

The past decade has seen the emergence and persistence of fungal diseases in humans, animals and plants. Human fungal infection accounts for more deaths annually than either tuberculosis or malaria [1]. Emergent fungal pathogens have meanwhile led to widespread population declines for terrestrial and marine species, with significant impacts at the ecosystem level [2]. With regard to global food security, fungi consistently reduce crop yields, alongside a geographic expansion of fungal crop pathogens driven by climate change [3]. These alarming events are occurring at the same time as continued reports of antifungal resistance, both in agriculture and in the clinic [4,5]. New biological leads for pathogen identification and therapeutics are therefore urgently required, and, accordingly, researchers have developed new *in silico* resources and experimental tools for the study of pathogenic fungi. In this review, we highlight these new techniques and resources in order that they are maximally exploited to combat the persistent and expanding threat of fungal disease.

## *In silico* Resources and Bioinformatic Tools for Analysis of Fungal Pathogens

### Comparative Genomics

Until recently, variations in data archiving and the lack of user-friendly, publicly available analytical tools greatly limited comprehensive bioinformatic analyses of pathogenic fungi. Now, large-scale fungal sequencing projects have resulted in an explosion of genomic data that have been integrated into several well-curated, interactive tools for web-based analyses (Table 1, Key Table). Genomic sequences of numerous model and pathogenic fungi populate these datasets, making comparative genomics of persistent and emergent disease agents possible. These tools are improving understanding of the genetic mechanisms underpinning fungal virulence framed

### Trends

New online bioinformatic portals enable novel analysis of host–pathogen interactions, antifungal drug interactions, functional annotation of ‘omics data and comparative genomics *in silico*.

Molecular tools, including inducible promoters, recyclable markers and genome-editing, facilitate more sophisticated functional genomic analysis.

Recent use of compound library screens, heterologous expression systems, and experimental pipeline automation offer the promise of ultrahigh throughput evaluation of antifungal drugs and cognate targets.

There is an unprecedented opportunity to understand fundamental aspects of pathogen biology, enabling development of improved diagnostics and antifungal therapy in the clinic, agriculture, and natural ecosystems.

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## Key Table

Table 1. Selection of Online Bioinformatics Tools and Databases for *in silico* Analysis of Fungal Pathogens

Description	Name	URL	Highlights	Refs
<b>Functional and comparative genomics</b>	Comparative fungal genomics platform	<a href="http://cfgp.riceblast.snu.ac.kr/main.php">http://cfgp.riceblast.snu.ac.kr/main.php</a>	<ul style="list-style-type: none"> <li>• &gt;390 fungal/oomycete genomes plus numerous animal and plant hosts</li> <li>• Analyse data using numerous hosted bioinformatic tools, e.g., sequence search, phylogenetic analysis, identification of signal peptide/functional domain/subcellular localisation</li> <li>• Integration of gene family databases, including fungal transcription factors, cytochrome P450, secreted proteins and cell-wall degrading enzymes</li> <li>• Taxonomy and genome browser functions</li> <li>• BLASTMatrix tool for identification of homologous genes across multiple species</li> </ul>	[84]
	ENSEMBL	<a href="http://fungi.ensembl.org/">http://fungi.ensembl.org/</a>	<ul style="list-style-type: none"> <li>• &gt;400 fungal genomes from numerous species/strains</li> <li>• Curated functional annotation of genomes through UniProt and InterProScan</li> <li>• Numerous user data upload features, (e.g., RNAseq/transcriptomic datasets, plotting genomic coordinates on genome viewer)</li> <li>• BIOMART data warehouse system for easy retrieval of attributes for user-defined gene lists, including homologues, paralogues, chromosomal coordinates, exon/intro boundaries, gene flanking sequences, external gene identifiers</li> <li>• Search genome of choice via keyword, gene identifier, or chromosomal locus</li> </ul>	[85]
	FungiDB	<a href="http://FungiDB.org">http://FungiDB.org</a>	<ul style="list-style-type: none"> <li>• &gt;70 fungal/oomycete genomes</li> <li>• Contains functional genomic datasets, such as EST data, cell-cycle microarray/yeast two-hybrid <i>Saccharomyces cerevisiae</i> data, RNA seq</li> <li>• Genomes annotated with InterPro domains, signal peptide predictions, gene ontology terms, transmembrane domain predictions</li> <li>• 'Search Strategy System' enables construction of user-defined multistep data analysis pipelines, based on numerous parameters (e.g., GO (Gene Ontology), orthology, transcriptomics); data analysis pipelines can be saved as a specific URL and shared</li> <li>• Genomic collocation function</li> </ul>	[86]
	MycCosm	<a href="http://jgi.doe.gov/fungi">http://jgi.doe.gov/fungi</a>	<ul style="list-style-type: none"> <li>• &gt;250 fungal genomes</li> <li>• Users can nominate new fungal species/strains for sequencing, genome annotation and integration into MycoCosm</li> <li>• Genomes can be grouped into PhyloGroups or EcoGroups, which share similar phylogenies or lifestyles respectively</li> </ul>	[30]

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