The Need for New Antifungal Agents

Frank C. Odds

Aberdeen Fungal Group, School of Medical Sciences, Institute of Medical Sciences, Aberdeen AB25 2ZD, UK

The spectrum of infections caused by fungi covers a very wide range, from common diseases of the skin and other superficial sites, such as dermatophytosis and genital thrush, to disseminated, visceral infections in seriously immunocompromised hosts. The niche for superficial infections has been well filled for many years, with a variety of topical and oral agents available, many of them for sale over the pharmacy counter directly to the public. While a case can be made that the dominance of azole and allylamine antifungal agents for treating superficial mycoses suggests there might be clinical benefits from the introduction of drugs with a novel mode of action, the market for this indication is commercially well saturated with inexpensive and effective products, and therefore unattractive to a pharmaceutical industry that needs high prices to justify its high research and development costs.

The need for novel agents to treat life-threatening mycoses is unequivocal. Publication after publication confirms that attributable mortality rates from invasive *Candida* and *Aspergillus* infections are very high. The names of fungi such as *Fusarium* spp., *Scedosporium* spp. and *Rhizopus* spp. are now familiar to every haematologist and represent a threat of untreatable, terminal infections that frustrate normally successful modern approaches to the management of haematological malignancies. The setting for disseminated *Candida* infections has spread from haematology to include other types of severely immunocompromised hosts, typically those who have undergone multiple or protracted surgical interventions, particularly transplantation, so that the intensive care unit is now well recognized as a location where consideration is commonly given to prophylactic and pre-emptive antifungal therapy. While several large studies suggest that the incidence of infections caused by *Candida albicans* has declined through the 1990s, other species such as *C. glabrata*, which is less susceptible than *C. albicans* to widely used triazoles such as fluconazole, may have increased in incidence.

The major clinical problem, then, is management of deep-tissue infections caused by a diverse range of fungal types. One impact of highly active anti-retroviral therapy (HAART) has been to reduce the previously high incidence of opportunistic mycoses associated with AIDS, but even in this setting mycoses are caused by many different types of fungi. This multiplicity of causative species creates a particular problem for the discovery and development of novel antifungal agents: the need has to be for agents with a spectrum as broad as possible. Current approaches to antimicrobial discovery are heavily based on scientific, rational selection of targets that are present in the infecting agent and absent in the host. However, focussing on a single target molecule from one strain of one species of fungal pathogen moves the discovery principle *away* from the need to find agents effective against a broad range of fungal types.

Those who become interested in antifungal discovery read and swiftly learn that *Aspergillus fumigatus* and *C. albicans* are the two most serious fungal threats to survival of patients undergoing chemotherapy or transplantation surgery. Yet the *total* number of all types of serious fungal infections is much lower than that of the

common bacterial septicaemias. Estimates of the incidence of deep mycoses vary enormously, but it is clear that the market for, say, a compound effective only against *A. fumigatus* is small compared to many other medical indications. The problem of small market size is exacerbated by the difficulties of achieving accurate diagnoses of opportunistic mycoses. The most common way in which antifungals are used clinically is empirically — that means an antifungal agent is given in the absence of specific diagnostic evidence for a causative species. For a new agent to be commercially viable it must be effective at least against the most prevalent causes of fungal disease, which means all the common *Candida* and *Aspergillus* species. (It is worth noting that the agents already available cover most of that spectrum, yet they often fail to contribute to patients' survival because of the severity of the patient's underlying disease.)

Target-based antifungal discovery depends on extensive genomic information for many fungal types; the current availability of complete genome sequences for *C. albicans* and *A. fumigatus* heralds a new era in which some 40 fungal genomes have been, or are being sequenced. However, the track record of microbial genome sequences as accelerators of discovery of new antimicrobial agents has not been impressive; in the case of antifungal agents only one of the six targets for the current antifungal chemical classes differs sufficiently from its human equivalent to have been chosen on the basis of genomic information.

Some papers suggest that existing antifungal agents are highly toxic. This is a gross distortion and overstatement that should be laid to rest. Amphotericin B in its long-standing (and cheap) deoxycholate suspension formulation carries an unreasonably high risk of nephrotoxicity. This risk is much reduced in lipid-based formulations of amphotericin B, although the improved safety carries a significant price premium. Flucytosine, which is little used except in combination with amphotericin B, can be the source of severe bone marrow toxicity, but careful management by monitoring blood levels is usually enough to prevent the problem. All of the other systemic antifungal agents have a good to excellent adverse event profile; recorded events tend to be transient and disappear when the agent is no longer used. The real problems that face triazoles such as itraconazole and voriconazole are their extensive interactions with other drugs, which result from their affinity for liver cytochrome P450 enzymes. Caspofungin, the newly introduced echinocandin, has, respectively, very few and no concomitant problems with drug interactions and serious adverse events at all. Safety is therefore a real problem only with the oldest formulations and the oldest antifungal agents.

An ideal antifungal agent would inhibit the growth of (or, better, kill) all types of fungal pathogens, including the uncommon but clinically devastating mould species that resist most current agents. It would be available in both oral and intravenous formulations, to accommodate the changing nature of the typical patient's underlying problems. It would be free of major toxic effects and of interactions with the many other drugs that the typical immunocompromised host is likely to receive. Some of the agents now registered for clinical use approach many of these desiderata; the industry needs to seek new strategies to succeed in finding novel agents, with new mechanisms of antifungal action, that can compete successfully in this small and difficult, but clinically important market.