Considerable ferment over antifungal agents

Several developments involving drugs for combatting fungal diseases are worth noting. Early last month, an advisory panel of the US Food and Drug Administration (FDA) met to consider liposome-encapsulated antifungal agents. Moreover, Pfizer Inc. of Groton, Connecticut, which markets a leading antifungal drug, announced late in March that it is investing up to $50 million in Myco Pharmaceuticals Inc., a small biotechnology company in Cambridge, Massachusetts, focusing on the development of novel antifungal agents.

Fungal diseases were once about as interesting as athlete's foot. What explains this recent activity and such high-level investments? In a word, opportunism — at the microbial level. AIDS and immunosuppressive treatments allow opportunistic fungal infections to develop, for example, after organ and bone marrow transplantation and with the use of high-dose chemotherapy to combat malignancies. Often, fungal infections strike after an individual has already experienced several rounds of bacterial infections and been treated aggressively with antibiotics, but by then the patient is weakened.

According to recent clinical data, fungal infections continue to rise exponentially, with *Candida albicans* still the "major culprit," says Michael Rinaldi from the University of Texas Health Sciences Center in San Antonio, Texas, who spoke in March in San Francisco, California, at Fungal Focus 5, an annual meeting of clinicians and researchers in his field.

During the 1980s, *C. albicans* became the fourth most frequent cause of nosocomial infections. Although this continues to be true, fluconazole-resistant strains of *C. albicans* are turning up with increased frequency. Disease caused by other 'non-albicans' yeast species and by moulds is also on the increase. Moreover, some of these rarer fungal pathogens are not susceptible to fluconazole or other members of the azole family of antifungal drugs. For patients who develop such infections, the situation could soon become critical.

For instance, a few years ago, infections caused by the fungus *Torulopsis glabrata* were found rarely but nearly exclusively in the urinary tract. Now, it is frequently found at other sites. Moreover, this pathogen is popping up as the cause of nosocomial infections in many hospital critical-care units across the United States, according to a recent multi-site survey conducted by Richard Wenzel of the University of Iowa Hospital.

Resistance of fungal pathogens to antifungal drugs is a serious and complicating factor particularly in the case of disseminated fungal infections, partly because of the effect of the prophylactic use of antifungal agents, as well as the increase in non-albicans species. A different problem is *C. lusitaniae*, which, although still very rare, not only resists azoles but also sometimes amphotericin B.

Clinicians continue to debate the best approach to the treatment of fungal infections and usually prescribe the drugs amphotericin B (given intravenously) or the newer azoles, usually fluconazole (administered orally) in less severe cases. Although amphotericin B has a broader range of action and tends to be more effective, it also is more toxic, often causing kidney damage.

One new approach to therapy being developed and evaluated is lipid-encapsulated formulations of amphotericin B. When used to treat neutropenic patients with fungal infections, they are more effective than amphotericin B by itself. Although these newer formulations require higher doses, they appear to cause less long-term kidney damage than conventionally administered amphotericin B.

Earlier this year, another FDA panel recommended approving a liposome-encapsulated drug for the treatment of Kaposi's sarcoma, doxorubicin-containing DOX-SL (Liposome Technology, Menlo Park, California). Several panel members voiced misgivings about this approach, however, suggesting that liposomal formulations of amphotericin B may face similar difficulties at FDA.

Another approach to combatting fungal diseases is showing promise. Granulocyte colony-stimulating factor (G-CSF) is a cell-growth stimulating factor, made by using recombinant DNA techniques, that helps restore immune system activity. Early results indicate that G-CSF-treated neutropenic patients develop higher levels of neutrophils and thus do better in overcoming fungal infections.

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Shake-up of London hospitals goes ahead

The British government ran into a new political storm last month over its efforts to restructure the provision of medical care in London in a way that, it hopes, will enhance the national capital's reputation in biomedical teaching and research.

The trigger was an announcement by Virginia Bottomley, the health secretary, that the government has given the go-ahead to a number of new projects to be implemented as part of a strategy to reorganize London's hospitals around four multi-faculty colleges, each equipped with high-class research facilities.

These moves — originally proposed in the so-called Tomlinson report of 1992 — have been broadly welcomed by London's biomedical research community, not only because they remove uncertainty over the future organization of the teaching hospitals, but also because they are recognized by many as a sensible response to the declining need for long-term hospital beds in the Nation's capital.

But Bottomley came under sharp criticism for her handling of the decisions, both in the national press and in Parliament (even from some members within her own party representing London constituencies) for overriding with apparent insensitivity the vocal objections of groups that will see local hospital facilities either reduced or eliminated completely as part of the overall rationalization strategy.

The new projects will allow teaching and research in London to develop along lines already favoured by the University of London. For example, the Higher Education Funding Council for England, is to provide £20 million (US$32 million) towards a new basic and medical science building at Imperial College, which will become the core of a West London medical college.

The new building is a central element in Imperial's planned merger with the