



Olorofim, now in phase II trials, has shown promise against *Lomentospora prolificans* (above), a fungus that mostly infects patients with weakened immune systems.

DRUG DEVELOPMENT

New drugs target growing threat of fatal fungi

Well-stocked pipeline could yield new tools to treat intractable infections

By Kai Kupferschmidt, in Nice, France

Martin Hoenigl, a specialist in fungal infections at the University of California, San Diego, sees half a dozen patients a year infected with a rare mold called *Lomentospora prolificans* that is resistant to all available antifungals. Doctors use combinations of two or three drugs in high doses to try to stop the infection, but usually to no avail. “Most of these patients die,” Hoenigl says.

That may be about to change. Hoenigl just started to enroll patients in a phase II trial of a new drug called olorofim that holds promise against *Lomentospora*. It is one of several compounds now in trials that could give doctors much-needed new tools against these intractable infections. “We have got several drugs with new mechanisms of action and they look really good,” says Tom Chiller, who heads the mycotic diseases branch at the U.S. Centers for Disease Control and Prevention in Atlanta. “It’s exciting times,” Hoenigl says.

Of the millions of fungal species on Earth, only a few dozen regularly cause human disease; fungi don’t grow well at mammals’ high body temperature, and a healthy human immune system is adept at dealing with the ones that do. But the HIV/AIDS epidemic and modern medical interventions such as chemotherapy and transplantation have led to a growing number of people with compromised or suppressed immune systems whose bodies can be overrun by a fungal invader. Symptoms vary widely depending on which organs are affected; a lung infection, for example, can lead to shortness of breath and cough. An

estimated 1.5 million people die worldwide every year of invasive mycoses.

New drugs have been slow in coming because research funding has been scarce and investors prefer drugs against chronic diseases that patients take for life over ones that cure an infection. “There’s not a huge incentive, there’s not a big market,” Chiller says. The urgency is growing, however, as cases have increased and once-treatable fungi are becoming resistant. About one-quarter of recent Indian isolates of *Candida auris*, a fungus that’s on the rise globally, were resistant to two or more classes of antifungals, for instance. (For some other species, drugs have yet to be found.) And there are other problems: Only one class of drugs, the azoles, can be taken orally. The others must be injected, and many have side effects or interact with other drugs, a problem for patients who have a fungal infection on top of another illness.

At a medical mycology meeting here earlier this month, scientists presented promising phase II clinical data for rezafungin, a new member of an existing class called the echinocandins developed by Cidara Therapeutics in San Diego. Like other echinocandins, it acts by inhibiting synthesis of the polysaccharides that make up the fungal cell wall, but it has a much longer half-life, allowing it to be given once a week instead of daily. It might one day become the standard prophylaxis for patients receiving transplants, Hoenigl says.

Doctors are eager to have new classes of drugs—which have a new target or a new way to attack an existing target—because it allows them to try new combinations that may work synergistically and help avoid resistance. Olorofim, the compound

Hoenigl is testing, is one example: It blocks the synthesis of pyrimidine, the precursor of DNA building blocks. Developed by U.K.-Austrian biotech F2G, olorofim can be taken orally and kills not only *Lomentospora*, but also *Scedosporium*, another rare and usually fatal mold infection. Further along is ibrexafungerp, developed by Scynexis in Jersey City, New Jersey, and now in a phase III trial. Like the echinocandins, it attacks the fungal cell wall but does so by latching onto another part of a key enzyme.

On these drugs’ heels is fosmanogepix, a new broad-spectrum antifungal developed by Amplyx in San Diego that is now in phase II trials. Last month, the U.S. Food and Drug Administration gave it “fast-track” status, an expedited review procedure for urgently needed drugs.

Because fungal diseases are relatively rare and diagnosis is difficult, the current clinical trials are small. But Oliver Cornely, an expert on fungal infections at the University of Cologne in Germany who is involved in trials of all four drug candidates, hopes that even a limited amount of positive data will persuade regulators to approve these drugs, which address fatal diseases with few treatment options. “If this were HIV, we would see people protesting in front of the convention center for these drugs to become available.”

Chiller says new diagnostics are also needed. Fungi often lead to unspecific symptoms and are hard to culture, and rapid, accurate diagnostic tests are scarce. That means patients may die without ever receiving a proper diagnosis. For the new drugs to have their biggest impact, that has to change, Chiller says. “If you can’t diagnose it, it doesn’t exist.” ■

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