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The Latest on Antifungal Vaccines: Updates from IDWeek 2023

Dr. Turck:
Fungal infections can be a serious health threat, and they cause more than 1.5 million deaths worldwide each year. And while there are currently no effective vaccines to protect vulnerable patients from these infections, researchers are working on developing them. So what are the latest updates on antifungal vaccines that we should be aware of?

Welcome to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and joining me today to help answer that question is Dr. Stuart Levitz. Dr. Levitz is a Professor at the UMass Chan Medical School in Massachusetts. He also spoke about this exact topic at the 2023 IDWeek conference.

Dr. Levitz, thanks for joining me today.

Dr. Levitz:
Thanks for having me.

Dr. Turck:
So if we start with some background, Dr. Levitz, what could you tell us about the current treatment options for fungal infections?

Dr. Levitz:
Well, we have a lot more treatment options than we used to, but they're still limited; and traditionally, antifungal development has been difficult, and it's difficult because fungi in humans are eukaryotics. And eukaryotic cells have very similar cellular structures in terms of having nuclei RNA, DNA synthesis, and protein synthesis. They share very similar molecular mechanisms and very similar organelles. Thus, a lot of drugs that are active against fungi also inhibit human cells and therefore are too toxic for use. But fortunately, there are differences between fungi and humans; first of all, humans, of course, have cholesterol as their major cell membrane sterol. Fungi, on the other hand, have ergosterol, and targeting ergosterol pathways, such as with the azole class of antifungal drugs or with terbinafine that inhibits ergosterol synthesis, can inhibit and even sometimes kill the fungal cell. Amphotericin B is a fungicidal drug that directly targets ergosterol. So most of our antifungal drugs in use today either target ergosterol or beta-1, 3 glucan.

Dr. Turck:
And what are some challenges clinicians run into when treating fungal infections?

Dr. Levitz:
Well I think first of all, diagnosis can be very difficult. Fungi grow slower than most bacteria. Sometimes you need special media in order to grow fungi. Our diagnostic tests that are available are limited, and often clinicians don't think to order these diagnostic tests; so as an infectious disease physician, by the time I'm called to see the patient, if a diagnosis has been made, a lot of times the patient already has an advanced infection. And as with any infection, once the infection is far advanced, it becomes more difficult to treat. Secondly, most patients with serious fungal infections have significant comorbidities, particularly severe immunocompromise, so you don't have the host immune system that's able to work with the antifungal drugs to help fight off the infection. Thirdly, the antifungal drug armamentarium is limited as I mentioned, and resistance, unfortunately, is increasing and becoming a bigger problem. We're seeing more and more candida infections, such as Candida auris, which is almost always resistant to fluconazole, one of our mainline antifungal drugs. Even with fungi that used to be almost uniformly susceptible, we're now starting to see more and more resistant strains in clinical isolates.

It is important to know the fungus that you're treating and what antifungal drugs usually work against it, and in many cases, to get resistance testing; you know, get your fungal susceptibility testing so that you know which drugs are the drugs of choice. That said, in

many hospitals, the susceptibility testing, especially against molds, is a send-out test, and it can take a week or even longer for the results to come back.

Dr. Turck:
Now as I understand it, there's been some progress on immunotherapeutic and vaccine strategies being tested, so what progress has been made in the development specifically of antifungal vaccines?

Dr. Levitz:
We have had three fungal vaccines that have made it to clinical testing, including two that have actually undergone clinical trials. There are a lot of vaccines in preclinical development that are quite promising, particularly in mouse models of infection. Obviously, we want to advance these now beyond preclinical testing and into human arms. In terms of the progress with fungal vaccines, you can categorize vaccines in general and fungal vaccines in particular in different ways. One way to categorize them is by looking at them as a whole organism vaccine versus a subunit vaccine. So a whole organism vaccine is a vaccine that generally would be an attenuated fungus or sometimes a killed fungus, such as E-killed or formalin-killed. A subunit vaccine would be similar to, let's say, our COVID vaccines or flu shots or tetanus shots.

Another way that you can categorize fungal vaccines is what I like to call a pan-fungal vaccine versus a targeted vaccine. So a pan-fungal vaccine would be a vaccine that would work against all or most medically important fungal species. Unfortunately, this vaccine never got tested in clinical trials, so we don't know whether it would have been effective or not.

The other type of vaccine would be targeted to specific fungi. So, for example, there are vaccines that are being developed against a fungal infection called coccidioidomycosis, and that's a fungal infection that's endemic to certain regions mostly in North America—for instance, in the United States, in the Southwest and parts of California. So this type of vaccine would be administered to people who live in endemic areas, especially people that might be at higher risk of developing severe disease.

The last thing I'd like to highlight in terms of progress is that there's been remarkable advances in adjuvant development, with newer adjuvants that promote stronger immune responses and also adjuvants that direct immune responses not only toward antibody responses but also toward T cell responses. And without getting too much into the weeds of immunology, T cell responses are very important for controlling many of the fungal infections that we see in our patients.

Dr. Turck:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Stuart Levitz about the latest updates on antifungal vaccines.

So given everything we've discussed so far, Dr. Levitz, what are the challenges in getting an antifungal vaccine developed and approved?

Dr. Levitz:
There are both scientific challenges and logistical challenges. I think the number one scientific challenge is that most patients with severe fungal infections, you know, systemic fungal infections—I'm not talking about athlete's foot or jock itch or those sorts of fungal infections. Let's say cryptococcosis in somebody with AIDS or aspergillosis in somebody who has profound neutropenia from leukemia treatment. For immunocompromised populations, vaccines generally don't work as well, so a big challenge is getting vaccines that elicit enough immunity that they're going to work in immunocompromised individuals. The other real issue is that even with the increased numbers of fungal cases, the target population is relatively small, so it's not something like a COVID vaccine where it's going to be recommended for almost the entire population or a flu vaccine where everybody should get an annual flu shot. You're talking about a relatively small target population.

Clinical trials are very expensive, and follow-up to demonstrate efficacy can take years. With the COVID vaccine, within a few months we knew that it was a protective vaccine, but for a vaccine against fungal infections that may take years before developing, you would have to have a large patient population that would be followed for a long period of time. So for this reason and others, vaccine manufacturers often view fungal vaccines as products that are unlikely to be profitable and that would be difficult to study.

Dr. Turck:
Now if we look ahead for just a moment, where do you see the future of antifungal vaccines going?

Dr. Levitz:
I follow the fungal vaccine literature and the vaccine literature in general very closely, and there are a lot of promising vaccines that are close to being ready for at least phase 1 clinical trials. And as I mentioned before, there have been a few vaccines that have actually been tested in humans with promising results. I see fungal infections increasing as our immunocompromised population and our at-risk

population increases, so I think with that increased need, I'm hopeful that companies will be willing to take chances on at least the most promising of the vaccines and that we can get some of them tested in human clinical trials.

Dr. Turck:
Well, this is such an important topic and timely as well. And I want to thank my guest, Dr. Stuart Levitz, for sharing his valuable insights with us today. Dr. Levitz, it was a pleasure speaking with you.

Dr. Levitz:
OK. Thank you.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit *Clinician's Roundtable* on ReachMD.com where you can Be Part of the Knowledge. Thanks for listening.