Drug combinations a good approach for infectious fungus, research shows

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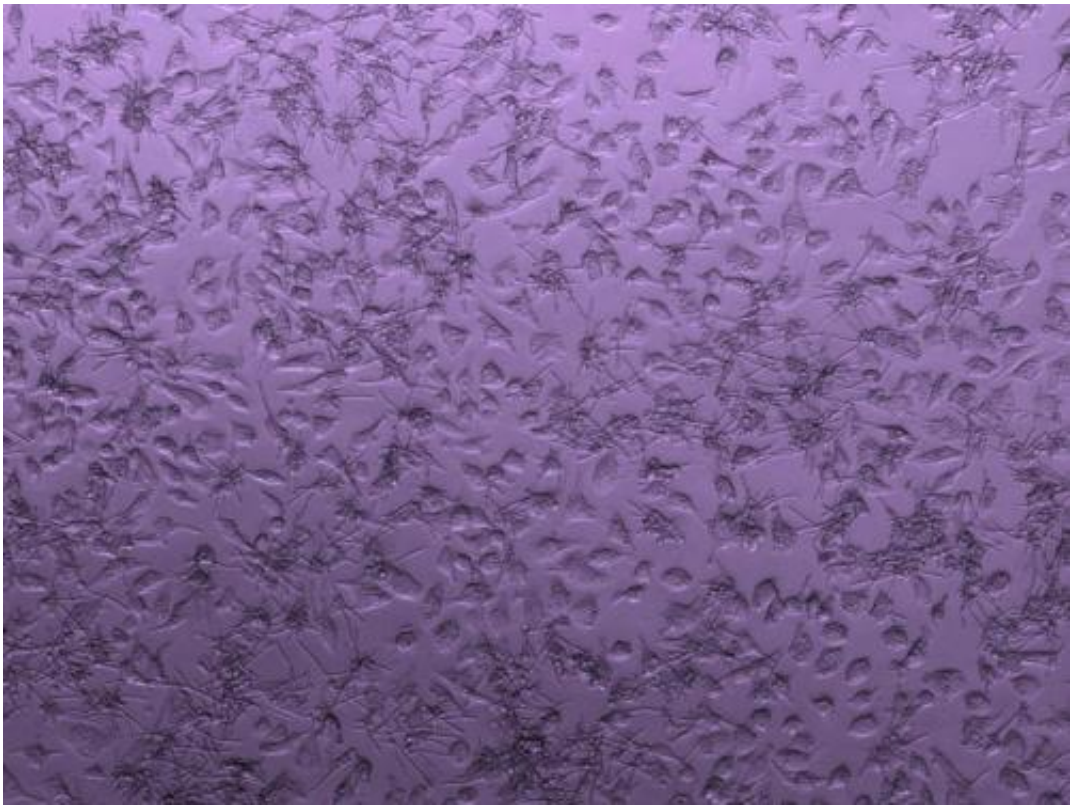

Candida and macrophages. Credit: University of Toronto

Researchers at the University of Toronto have discovered that *Candida albicans*—a leading cause of potentially fatal hospital-acquired infections—rarely develops resistance to combination drug therapy and, when it becomes resistant, it also becomes less dangerous.

The team may also have found a new way to eliminate *Candida albicans* in humans.

Treating fungal infections through a single drug is increasingly ineffective because fungi quickly evolve drug resistance. Combination therapies have shown great promise in overcoming this problem, but scientists are concerned these combinations will spur even stronger resistance.

By testing combination therapies in *Candida albicans*, the U of T researchers found that only a few strains of this fungus became drug-resistant, and that resistance came at a cost to the fungus.

"Drug resistance in fungal infections is a huge problem," says Professor Leah Cowen, the lead researcher on the study who holds the Canada Research Chair in Microbial Genomics and Infectious Disease in U of T's Department of Molecular Genetics. "And if we're going to treat these infections with drug combinations we need to know if they'll readily become resistant. In *Candida albicans* we found a trade-off: a few strains gain some resistance but they become less 'fit' or functional when the drug is not present."

The strains of the yeast that became resistant to drug combinations grew poorly in several stress conditions which are connected to human infections. For example, the resistant strains became weaker when they encounter oxidative stress, which happens when people become sick.

The researchers also found that resistant strains were vulnerable to immune cells called macrophages—further evidence that drug combinations may minimize drug resistance.

Cowen and her colleagues used *Candida albicans* strains they created in the lab, and they compared them to strains that were sensitive to

combination therapy. They also confirmed their findings with yeast that had evolved resistance in a patient. "This was an important step, because what you learn in a test tube often doesn't correspond to what happens in a patient," says Cowen.

The journal Cell Reports published the findings.

Candida albicans is the third-leading cause of intravascular catheter-related infections, and when acquired from implanted medical devices, it kills one-third of people it infects. The number of fungal bloodstream infections has more than doubled over the last two decades, partly because successful treatments for cancer and AIDS have left many patients immune-compromised and vulnerable to infection.

Cowen and her lab have developed a combination therapy for *Candida albicans* that inhibits a protein in the yeast called Heat-shock protein 90 (Hsp90). They're eager to test the therapy in patients, especially given Candida's limited resistance to it. But a big challenge is that Hsp90 is also an important protein in humans, so they need to develop fungal-selective inhibitors that target it in yeast exclusively.

Recently, they found a way to do that.

Cowen's team created and compared detailed maps of the drug-binding structure of Hsp90 in *Candida albicans* and in humans. In the yeast, the Hsp90 protein contains a larger pocket through which drugs can bind to it. So by increasing the size of the drug-like molecules, they engineered a potential therapy that targets Hsp90 only in yeast—the molecules are too big to bind in the Hsp90 drug-binding pocket in people.

"It seems to work," says Cowen. "We have a handful of structures that preferentially inhibit the fungal protein over the human counterpart. With a little more funding we can improve on these molecules and

ultimately test this treatment in patients."

Provided by University of Toronto