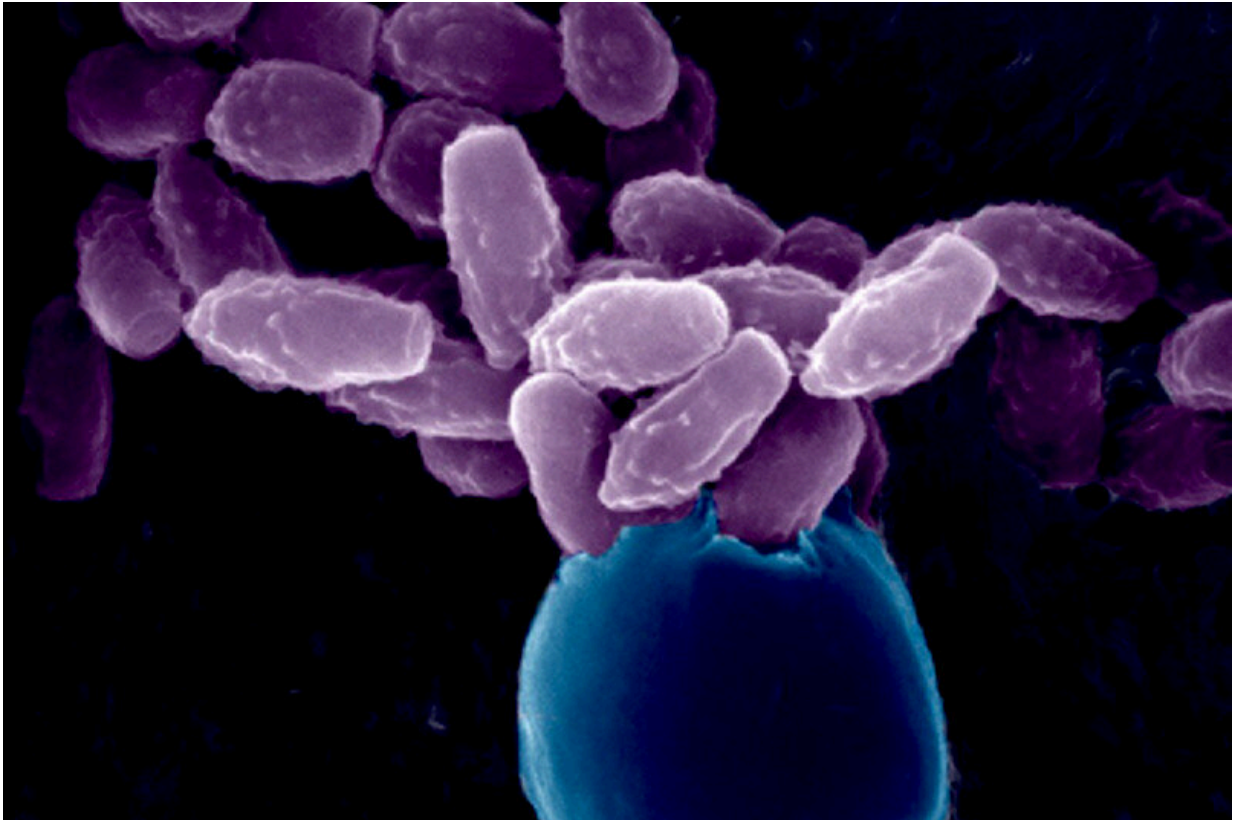


# How highly resistant strains of fungi emerge

August 3 2022

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Scanning electron micrograph of infectious yeast spores (purple) on the surface of the structure where they are produced following sexual reproduction (in blue, the basidium). Credit: Chaoyang Xue, Kasey Carroll, and Joseph Heitman (Duke University Department of Molecular Genetics and Microbiology); and Valerie Knowlton (North Carolina State University, Center for Electron Microscopy)

An international research team has deciphered the mechanism by which

the fungus *Cryptococcus neoformans* is resistant to fungus-specific drugs. It is a yeast-like fungus that can infect humans. Specific drugs, named antifungals, are available for treatment, but they don't always work—a phenomenon similar to antibiotic resistance. A team from Duke University in the U.S. and Ruhr-Universität Bochum (RUB) has used genetic, bioinformatic and microbiological techniques to decipher the mechanism underlying this resistance. They describe it in the journal *Nature Microbiology*, published online on 2 August 2022.

"The results are highly relevant for combating [fungal infections](#) in [clinical practice](#), [veterinary medicine](#) and agriculture," says Professor Ulrich Kück, Senior Professor in General and Molecular Botany at RUB. He cooperated for the project with the Bochum researcher Dr. Tim Dahlmann and the team headed by Professor Dr. Joe Heitman, who is currently based at Duke University in North Carolina and has been a visiting professor at RUB on several occasions.

## **Number of fungal infections on the rise**

"In the [western hemisphere](#), the number of people with a lowered immune defense is increasing, because life expectancies are rising rapidly and treatment with immunosuppressants after [organ transplants](#) is becoming more common," explains Ulrich Kück. "This is associated with an increase in fungal infections."

*Cryptococcus neoformans* is one of the most significant human pathogenic fungi responsible for so-called cryptococcosis. It triggers acute infections in immunocompromised patients; and the mortality rate may be as high as 70 percent. This is because fungal strains that are resistant to the drugs often evolve in hospitals, which makes treatment more difficult. So far, it was unclear which cellular and genetic mechanisms lead to this resistance.

So-called transposons, however, were known to play a role in the resistances. Transposons are jumping genes, i.e. DNA segments that can change their position in the genome and thus affect the function of genes. If a transposon jumps into a gene that's critical for susceptibility to a drug, it's possible for resistance to emerge. The mobility of the transposons is controlled by regulatory RNAs, so-called small interfering RNA, or siRNA for short.

## **RNA mechanism causes resistance**

In their current study, the researchers discovered gene mutations in resistant isolates that led to siRNA control being switched off. By introducing an intact copy of the gene, it was possible to restore siRNA control; as a result, the researchers were able to prevent the transposons from jumping and shed light on the cause of resistance. Due to their [small size](#), the gene segments that code for siRNAs are not easy to find in the genome. Tim Dahlmann managed to locate them with special bioinformatic analyses. By identifying the resistance mechanisms, it will be possible to use them for the treatment of mycoses in humans in the future.

**More information:** Shelby J. Priest et al, Uncontrolled transposition following RNAi loss causes hypermutation and antifungal drug resistance in clinical isolates of *Cryptococcus neoformans*, *Nature Microbiology* (2022). [DOI: 10.1038/s41564-022-01183-z](https://doi.org/10.1038/s41564-022-01183-z)

Provided by Ruhr-Universitaet-Bochum

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