Fungal pathogens are ubiquitous in the environment, and it has been estimated that up to 10 fungal spores are inhaled into the human organism with every breath. The incidence and lethality rates of fungal infections have increased dramatically over the recent years. Every year, about 1.4 million people worldwide die from the complications of organ and systemic fungal infections, matching the number of deaths caused by tuberculosis. A major difficulty in the search and design of new groups of fungicidal drugs is the fact that, as eukaryotic organisms, fungi employ few metabolic pathways distinct from those in human cells. Currently available antifungal agents act by inhibiting the synthesis of the ergosterol, or the cell wall formation. Most of these formulations have fungistatic, but not fungicidal effect, leading to the emergence of an increasing number of resistant fungal strains. In recent years, drug and multi-drug resistant strains are increasingly isolated in biological samples from patients, and therefore a fungal infection can be associated with high mortality.

Amphotericin B (AmB) is the gold standard in treatment of serious systemic mycoses with a broad spectrum of activity and very rare resistance. Therefore, a key and indispensable task is the development of new formulas of antifungals based on AmB. The greatest limitation in the application of AmB is its high toxicity, therefore, efforts should be made to reduce its dose. Scientists are still working to obtain less toxic formulations of AmB, but no optimal solution has yet been found that effectively reduces the toxicity of this drug while maintaining high antifungal efficacy. It seems that a good solution would be the use of combination therapy, in which two drugs acting via different metabolic pathways would accumulate their antifungal effects. However, in the case of AmB, this combination therapy encounters many difficulties, because the main groups of antifungal drugs act by inhibiting the ergosterol biosynthesis pathway, and AmB elicits its effect by forming complexes with ergosterol in the fungal cell membrane. Therefore, there is often a phenomenon of antagonism or lack of positive interactions of AmB with other antifungal drugs.

A new and poorly explored group of antifungals are 1,3,4-thiadiazole derivatives. Preliminary studies have shown that some compounds from this group exhibit a strong synergistic interaction with AmB against fungal pathogens (the combination activity is higher than the sum of activities of the single compounds), allowing a reduction of AmB dose by up to several times (Fig. 1). Further research has shown that selected 1,3,4-thiadiazoles do not show toxic effects on human cells *in vitro* in a wide range of concentrations. The mechanism of the antifungal activity of the 1,3,4-thiadiazoles has not been elucidated yet; however, preliminary studies have shown that these compounds do not reduce the level of ergosterol in fungal cells. These results allow a hypothesis that fungal pathogens resistant to azoles will not show the cross resistance to 1,3,4-thiadiazole derivatives. We assume that the developed composition of AmB and selected 1,3,4-thiadiazoles will be an effective agent against fungal pathogens, including drug resistant ones and non toxic to human body.

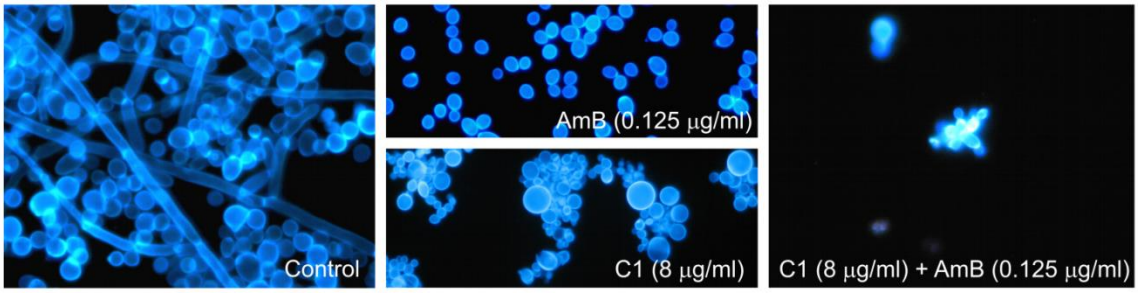

Fig. 1. Morphological image of control *C. albicans* cells and treated with Amb or the C1 compound separately or with a combination of the C1 with AmB. Fluorescence microscope image; staining with calcofluor; magnification 600 x.

Another important problem in the practice of diagnosing and treating fungal infections is determination of the susceptibility of the isolates responsible for the infection. Currently, this requires the performance of a classical antibiogram, which is time-consuming and delays the beginning of the appropriate treatment. As a part of the project, we plan to carry out the susceptibility testing of isolated strains to routinely used antifungals (fluconazole, itraconazole, voriconazole, flucytosine, and echinocandins) and the composition of AmB with selected 1,3,4-thiadiazole derivatives, using Fourier transform infrared (FTIR) spectroscopy. In the FTIR method, each biomolecule gives a specific spectral "fingerprint", which is a reflection of a set of specific vibrations of its covalent bonds. This method can also provide a characteristic spectrum of cells in their intact states, which shows the general molecular composition of the sample. A new approach proposed in our project is to study characteristic changes in the FTIR spectrum of fungal cells after a short time of treatment with an antibiotic. This approach will allow development of a rapid test for detecting the sensitivity/resistance of the isolated strain to a particular antibiotic using the FTIR method.