The increasing threat of treatment-resistant fungal disease is of significant societal concern. Furthermore, with only a limited number of drug classes available for treatment, it is imperative to focus drug discovery efforts on both new compound classes and under-explored fungal protein targets.

Accordingly, in the current project we will employ two innovative high throughput screening technologies, elicitor screening and mRNA display, to discover antifungal hit compounds for development.

Elicitor screening utilises small molecule libraries to unlock suppressed bacterial biosynthetic pathways for producing bioactive molecules. By combining this with a phenotypic fungal growth inhibition assay, we can efficiently explore this natural product “dark matter” for hit compounds.

Our second approach, mRNA display, is target-orientated. It uses cell-free transcription and translation systems to generate RNA-tagged, large peptide libraries for screening against protein targets. The peptide chemical space is expanded by including macrocyclization and adding non-standard building blocks to improve drug-likeness.

In subsequent medicinal chemistry, hits will be optimised for antifungal potency, toxicity and favourable drug-like properties. Furthermore, we will perform target identification and explore mode of action with biochemical assays and crystallography.

Our goal is to generate validated hits corresponding to novel classes of antifungal drugs or those that act against under-explored protein targets, and to push these compounds for further development towards the clinic.