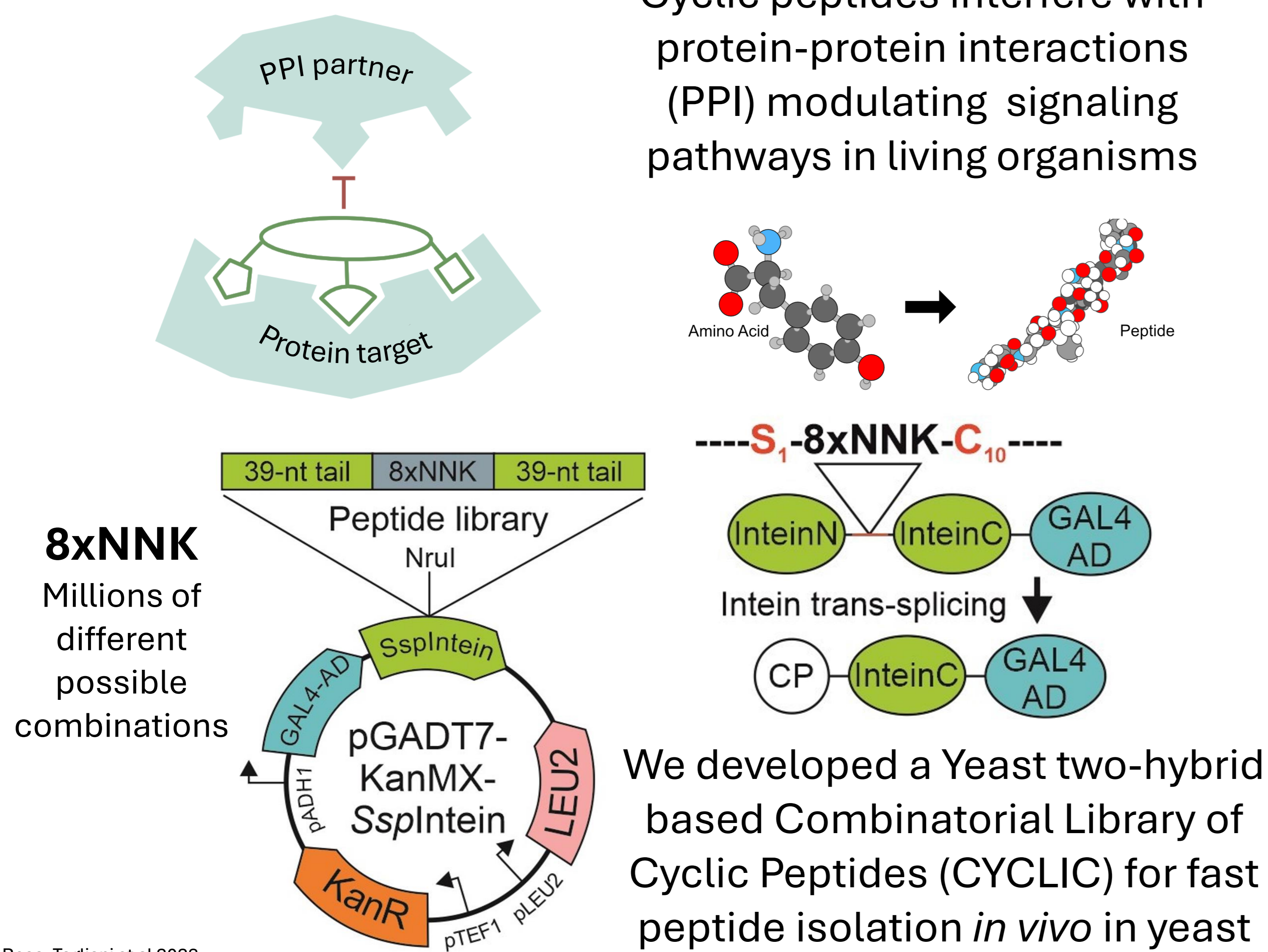


ABSTRACT

Cyclic peptides (CP) are a valuable class of bioactive compounds, also for their ability to selectively target proteins generally considered undruggable. CPs can modulate proteins and enzyme activity by interfering with protein-protein interactions (PPIs). In this context, combinatorial libraries are useful tools for the identification of cyclic peptide binders, due to a cheaper and easier screening pipeline, coupled with quicker isolation of hit molecules when compared with, e.g., DNA-encoded chemical libraries. In this framework, we adapted a combinatorial library of 8 amino acid-long cyclic peptides to the most widely used *in vivo* protein-protein interaction assay, namely the GAL4-based Yeast Two-hybrid system. Our platform (CYCLIC) uses yeast to identify peptides interacting with target proteins of interest, which are then tested for their bioactivity. Peptide cyclization, which increases CPs stability, specificity, and resistance to proteases, is achieved *in vivo* through the post-translational splicing activity of intein protein elements. By exploiting our libraries, we identified cyclic peptides interacting and/or inhibiting target proteins, like cell-wall associated enzymes of plant pathogens, transcription factors regulating sugar metabolism in yeast, and a viral enzyme crucial for the replication of SARS-CoV2. CYCLIC applications can be leveraged to any protein of interest, such as receptors, which are interesting targets for the cultured meat industry. Finally, we envision the production at scale of cyclic peptides employing precision fermentation and synthetic biology.

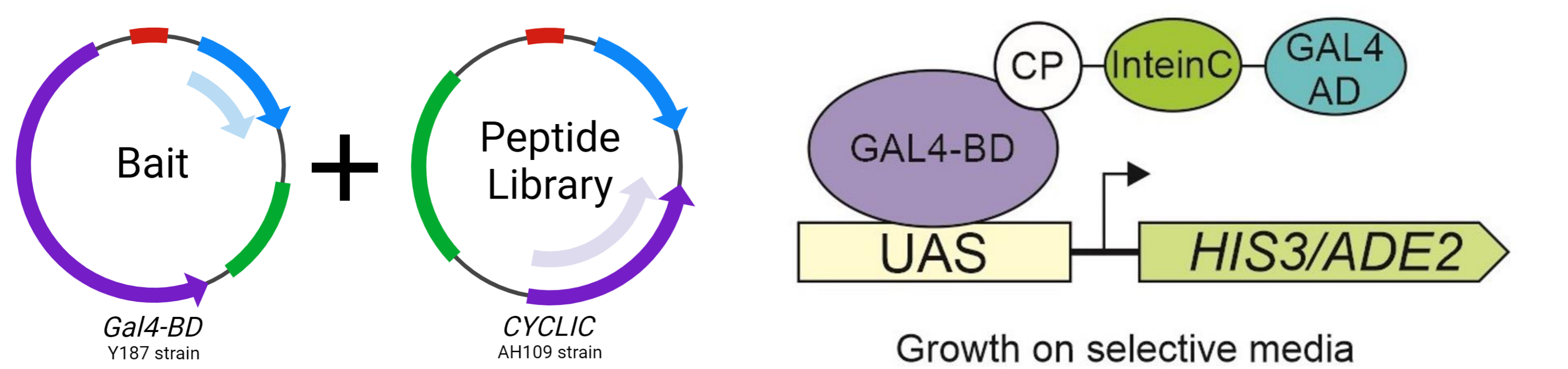
1 INTRODUCTION

CYCLIC: A COMBINATORIAL LIBRARY OF CYCLIC PEPTIDES

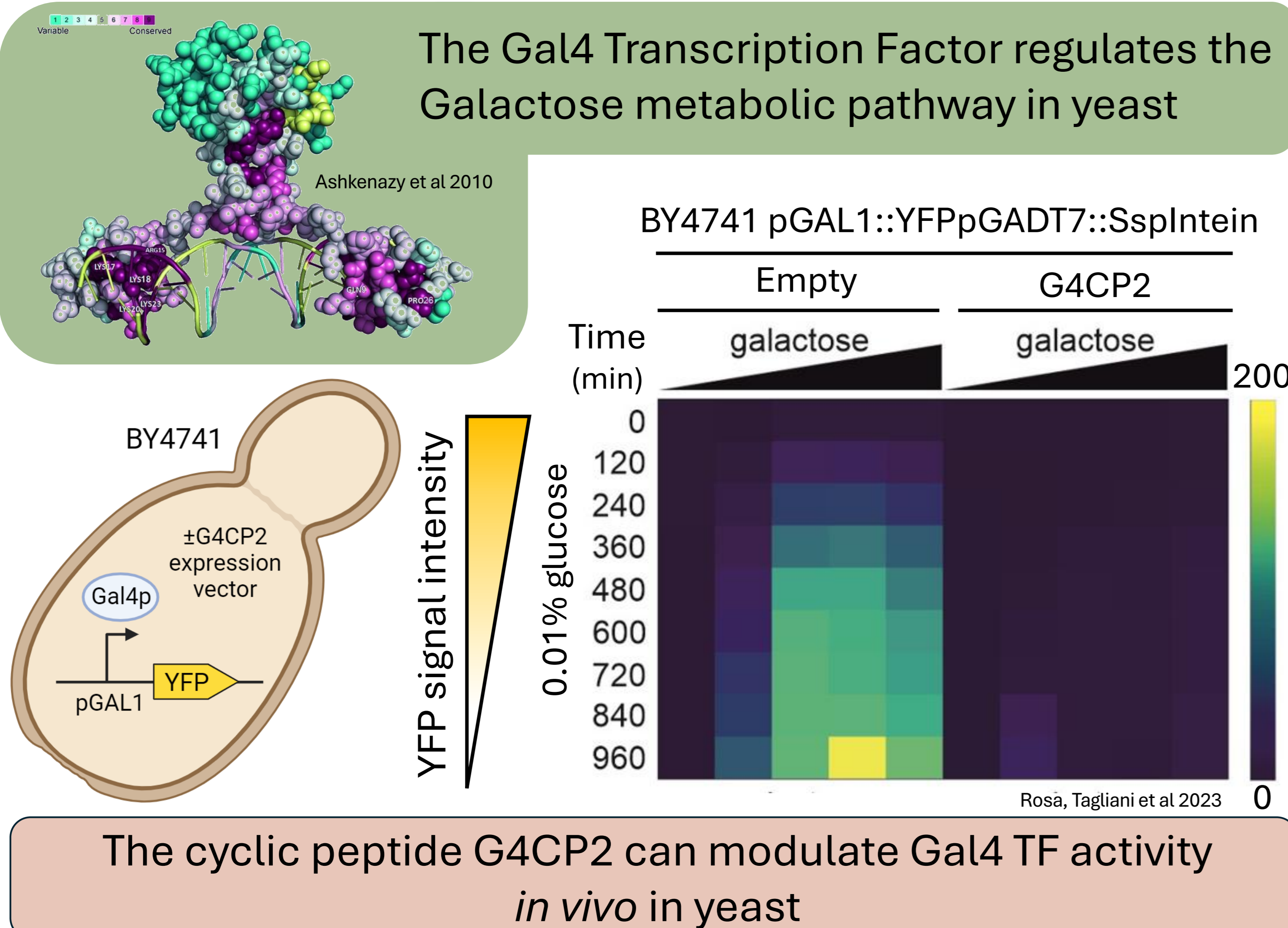


2 PROOF OF CONCEPT

INTERFERING CYCLIC PEPTIDE MODULATING TRANSCRIPTION FACTOR ACTIVITY IN YEAST

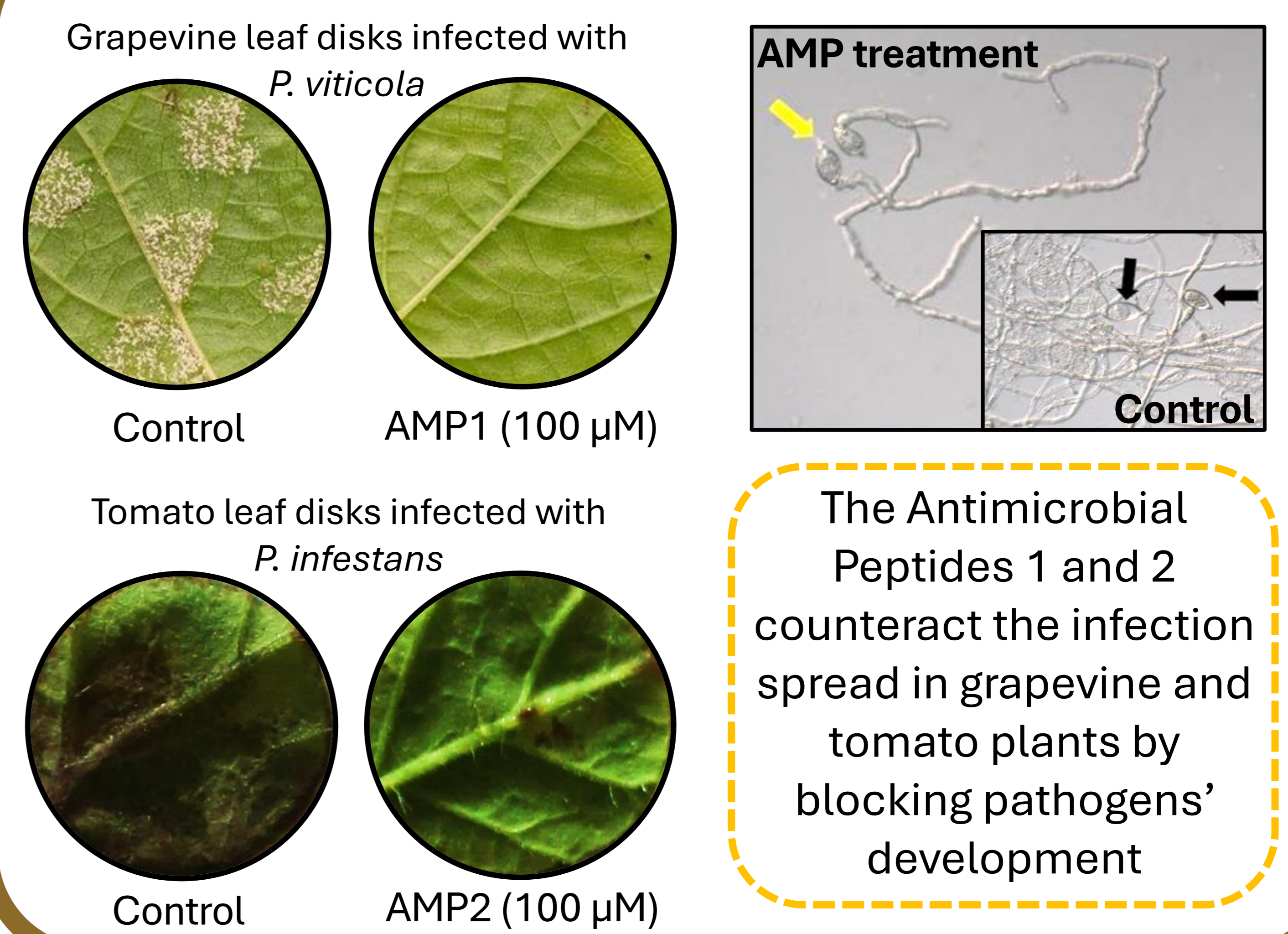


CYCLIC is a Yeast Two-Hybrid based combinatorial library of cyclic peptides (CPs). CPs are isolated based on their ability to interact with a given target protein

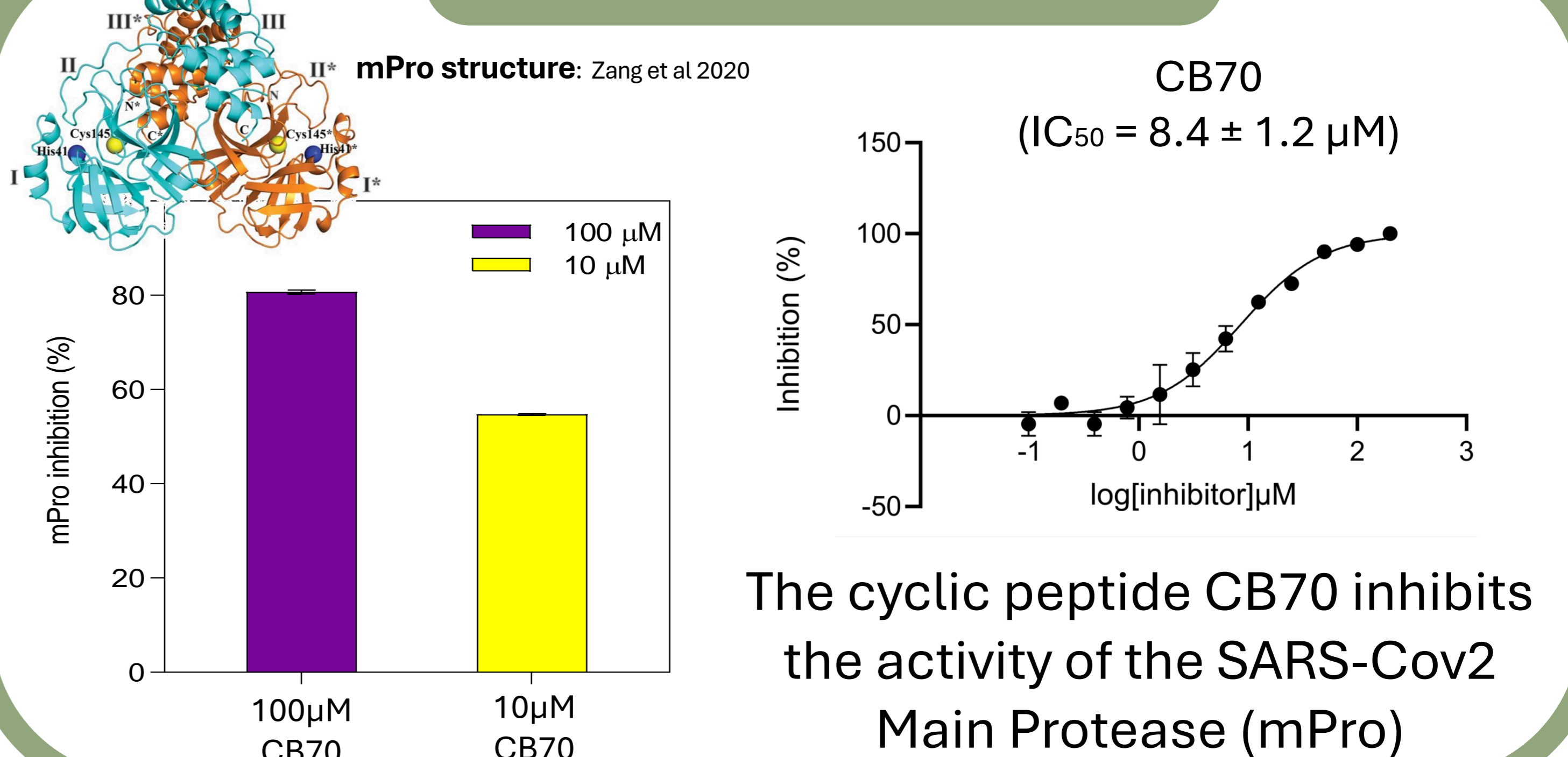


3 RESULTS

ANTIMICROBIAL PEPTIDES (AMPs)



ANTIVIRAL PEPTIDES



4 FUTURE PERSPECTIVE

BIOMANUFACTURING OF CYCLIC PEPTIDES

