

Expanded View Figures

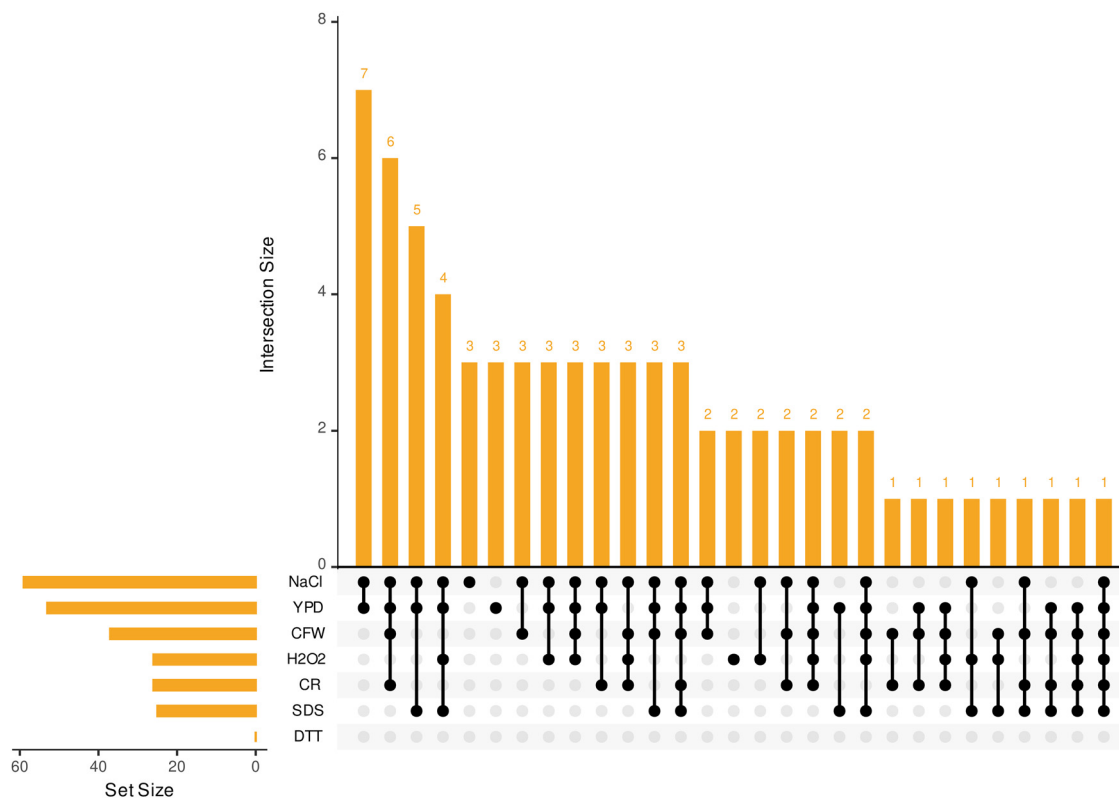


Figure EV1. Trade-off combinations observed in collection phenotyping.

Upset plot showing statistically significant negative trade-off (median fAUCR < 0.9, one-sided t-test (compared to 1) $p < 0.05$, Dataset EV4). Source data are available online for this figure.

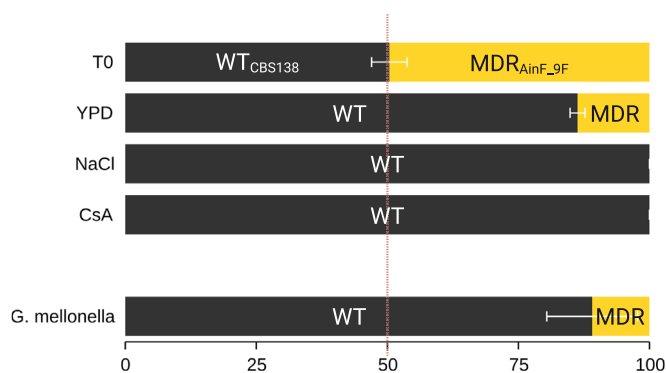


Figure EV2. Fitness trade-offs affect competitiveness of drug-resistant strains.

Results of a competition experiment of the wild type reference strain CBS138 and an multidrug resistant (MDR) strain (AinF-9F) evolved from it. Stacked bar plots showing the percentage of colonies counted after 48 h YPDa plates for each strain at the initial mix of containing 50% of each strain (T0), after 24 h growing in YPD (YPD), in YPD + 1.5 mM NaCl (NaCl), YPD + 20 μ M CsA (CsA) and inside the invertebrate model of fungal infection *Galleria mellonella* (*G. mellonella*). Source data are available online for this figure.

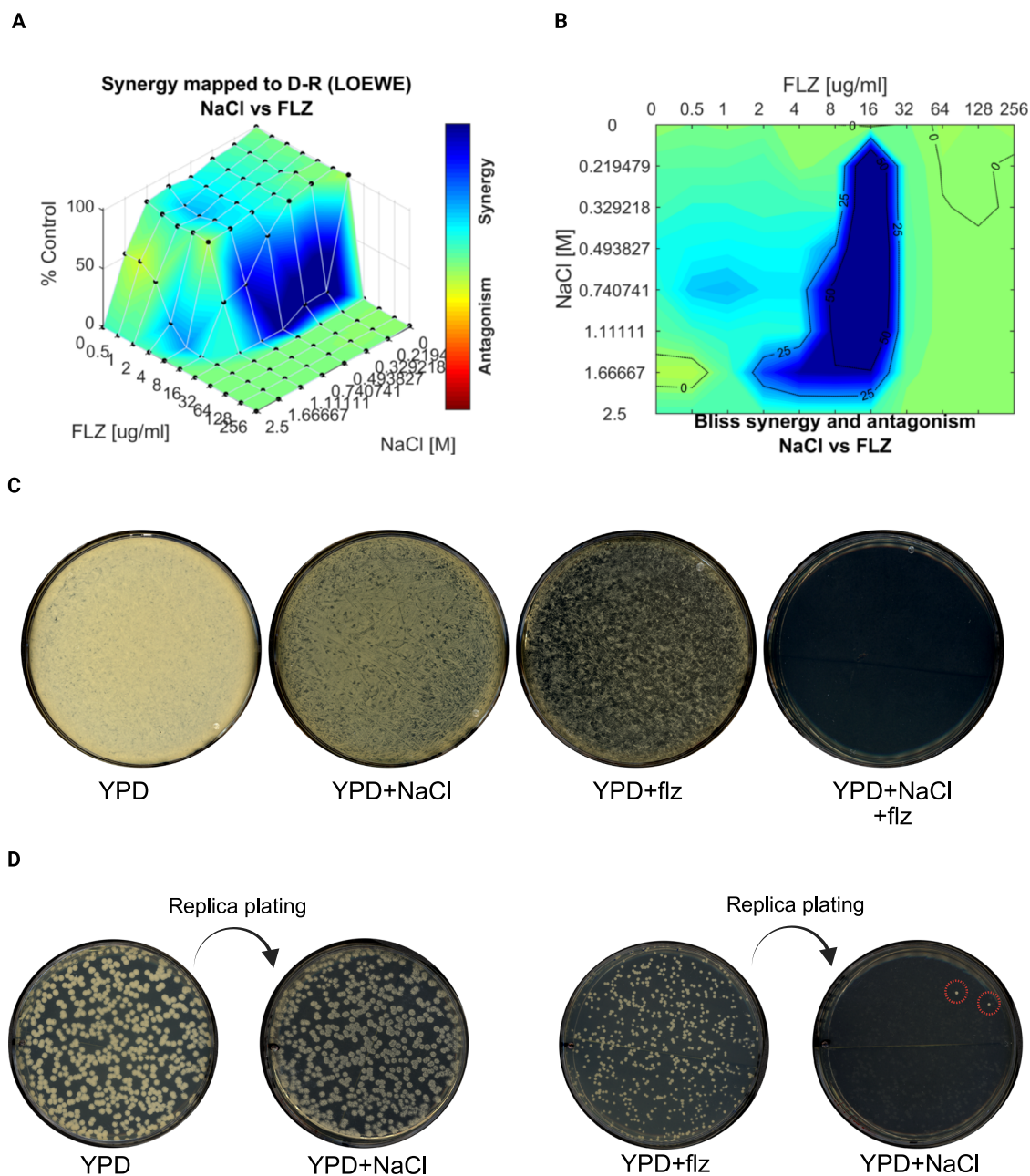


Figure EV3. Synergistic effect of NaCl with fluconazole on *N. glabratus* growth inhibition.

(A) 3D representation of the synergy matrix between different concentrations of fluconazole (flz) and NaCl using the Loewe synergy model. (B) Contour plot showing the synergy values calculated from the Bliss model. Both plots were generated by Combenefit software. (C) Images taken after 72 h of incubation of 10^7 cells on YPD, YPD + 1.25 M NaCl, YPD + 128 $\mu\text{g}/\text{mL}$ flz, and YPD + 1.25 M NaCl + 128 $\mu\text{g}/\text{mL}$ flz plates; no colonies were observed under the combined treatment. (D) Images of plates obtained after 72 h of replica plating onto YPD + 1.25 M NaCl (shown after the arrow) from source plates (shown before the arrow) containing ~500 colonies of YPD adapted or YPD + flz (128 $\mu\text{g}/\text{mL}$) adapted strains. On the YPD + NaCl plate replicated from YPD + flz, only two colonies were observed, marked with red circles. Source data are available online for this figure.

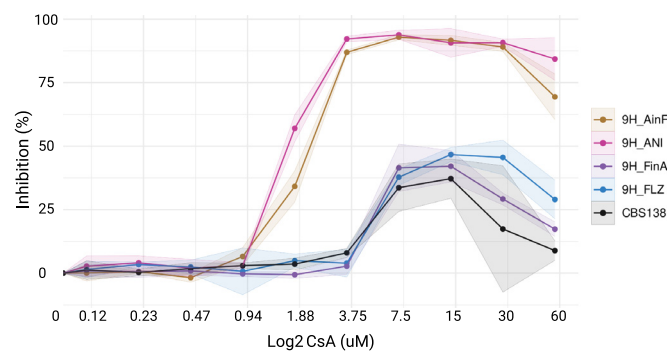


Figure EV4. Selective inhibition of Cyclosporine A to certain drug resistant strains.

Dose-response assay for Cyclosporine A (CsA) in evolved strains under different treatment of the CBS138 wild type reference strain. The y-axis indicates the percentage of growth inhibition versus control based on OD600 measurements, and the x-axis indicates CsA concentrations on a logarithmic scale. Source data are available online for this figure.

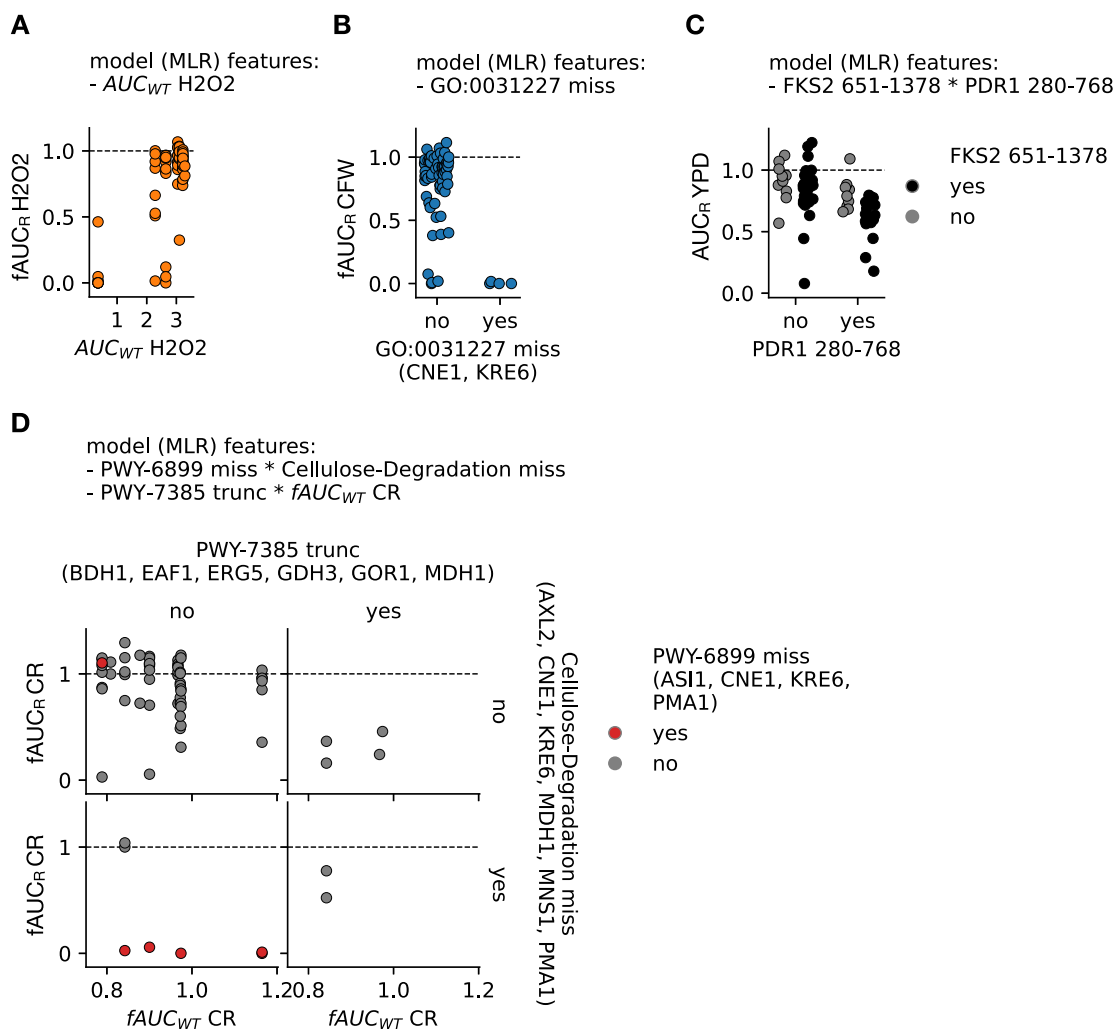


Figure EV5. Top model results for phenotypes with lower predictive accuracy.

Panels A–D are scatterplots equivalent to those in Fig. 5E–G, but for H₂O₂, CFW, YPD, and CR, respectively See Fig. 5D for reference about the pathway-related figures. Source data are available online for this figure.

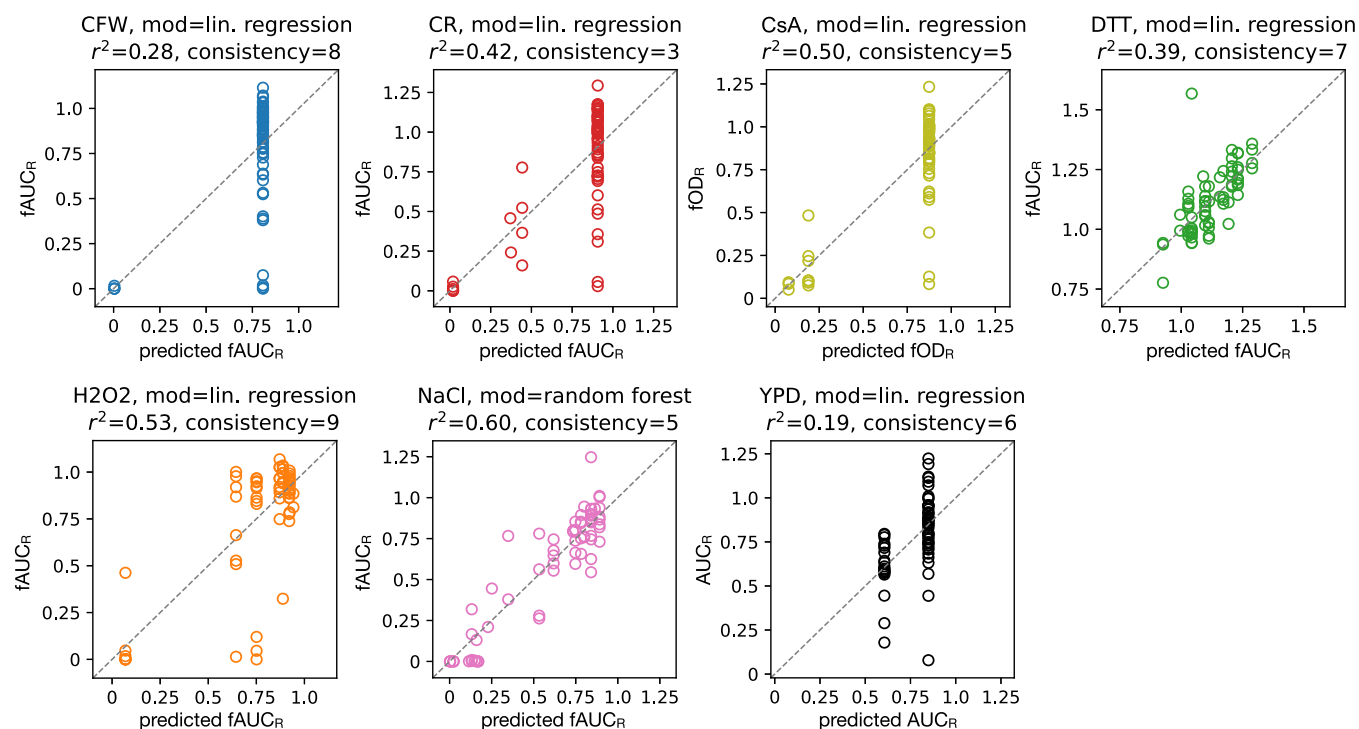


Figure EV6. Predictive performance of the top models.

Across all different strains, in each condition, the predicted trade-off intensity (x-axis) vs the actual one (y-axis) for the top models (see Fig. 5C). The title indicates the condition, type of model used (linear regression or random forest), the model performance (r^2) and the model consistency. Source data are available online for this figure.