A Yeast Synthetic Biology Platform Generates Novel Pharmacological Scaffolds for Drug Discovery

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Synthetic biology has been heralded as a new bioengineering platform for the production of bulk and specialty chemicals, drugs and fuels. In this presentation we describe a completely new use of synthetic biology, the biosynthetic formation of novel chemical compounds using a combinatorial genetics approach in baker's yeast. Either cDNA libraries or various metabolic pathways were integrated into yeast artificial chromosomes and the resulting yeast transformants exposed to a functional pharmacological screen, usually resulting in a survival phenotype of yeast clones in the presence of novel chemistry. Based on the concept of 'co-evolution' with target proteins in such an intracellular primary survival assay, the identified, mostly scaffold-sized (200-350 MW) compounds, which displayed excellent biological activity, can be considered as pre-validated hits. Of the molecules found, >75% have not been described previously; 20% of the compounds exhibit novel scaffolds. Their structural and physicochemical properties comply with established rules of drug- and fragment-likeness and exhibit increased structural complexities compared to synthetically produced fragments. In summary, the synthetic biology approach described here represents an innovative, complementary strategy for hit and early lead identification that can be easily integrated into the existing drug discovery process.

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