Title: Chemical genomic profiling of hydrolysates and toxins: implications for yeast strain engineering

Authors: Elena Vanacloig Pedros[1]* (vanacloigped@wisc.edu), Kaitlin Fischer[1,2], Lisa Liu[1], Derek Debrauske[1], Michael Place[1], Chris Todd Hittinger[1,2,3], Trey K. Sato[1] and **Audrey P. Gasch**[1,2,3]

Institutions: [1] DOE Great Lakes Bioenergy Research Center, Univ. of Wisconsin-Madison, Madison, WI; [2] Laboratory of Genetics, [3] Center for Genomic Science Innovation, Univ. of Wisconsin-Madison, Madison, WI

Project Goals: We used chemical genomic profiling of yeast gene deletion strains to better understand the mechanisms of toxicity of hydrolysates and their inhibitors, as well as to identify engineering targets to generate hydrolysate tolerant strains more efficient in production of biofuels.

Abstract text: Budding yeast *Saccharomyces cerevisiae* has been extensively used in fermentative industrial processes, including biofuel production from sustainable plant-based hydrolysates. A myriad of toxic compounds and stressors are generated during biomass deconstruction, inhibiting biofuel and biochemical production by microbes. Here, we studied how these compounds affect yeast cells, both to understand the mechanisms of toxicity of hydrolysate inhibitors and to improve efficiency in conversion by engineering more tolerant yeast cells. To do so, we used chemical genomics by exposing a gene deletion library to each of 34 inhibitory chemicals, including solvents used in pre-treatment, toxins generated during hydrolysis of plant material, and biofuel products that induce stress at high levels. The results identified classes of toxins based on similarities and differences in their chemical genomic profiles and revealed surprising insights into the mechanisms of cellular defense. Our results also revealed widespread antagonistic effects of gene deletion strains across specific classes of inhibitors, pointing to conflicting strategies of cellular defense that may pose difficulties for engineering universally tolerant yeast strains. We further propose strategies designed to overcome these engineering challenges.

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