C O N F É R E N C E


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**Multiplexed Characterization of Protein Families with DropSynth Gene Synthesis and Broad Mutational Scanning**

**LE JEUDI 14 juillet 2022 À 12 H 30**

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***Abstract:***

Metagenomic sequencing has given us a huge number of genes of unknown function. Similarly, our ability engineer new protein function is often dependent on the number of designs which can be tested. Overcoming these problems will require the ability to functionally characterize genes at much larger scales than previously possible. DropSynth is a simple method for multiplexed gene synthesis which can assemble large libraries of diverse genes at low cost. By coupling these gene libraries with multiplex functional assays, where many DNA encoded hypotheses are barcoded and tested together, we can quickly characterize and engineer entire protein families. We used DropSynth to successfully build >7,000 synthetic genes that encode phylogenetically-diverse homologs of two essential genes in E. coli. We tested the ability one enzyme's homologs to complement a knockout E. coli strain in multiplex finding that while the majority of homologs complement, those that do not are broadly distributed across the phylogenetic tree. Synthetic errors in our assemblies allow us to explore the local landscapes around the designed homologs revealing constrained mutations for complementing homologs as well as gain-of-function mutations for low-fitness homologs, which together provide information on core functional motifs and the reasons underlying homolog incompatibility. This broad mutational scanning approach helps us understand proteins by probing evolutionarily divergent sequences that share function. DropSynth coupled with multiplexed functional screens allow us to rationally explore sequence-function relationships at an unprecedented scale.


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