Docket #: S22-054

Compositions for Activating and Silencing Gene Expression

Stanford researchers have developed an expanded catalog of compact transcription effector domains and fused them onto DNA binding domains to engineer synthetic transcription factors. These synthetic transcription factors perform targeted and tunable gene expression regulation in eukaryotic cells, with applications in gene and cell therapy, synthetic biology, and functional genomics. Previously, a limited number of effector domains were available for engineering synthetic transcription factors. In response, Bassik Lab and Bintu Lab researchers applied a high-throughput approach to discover and characterize effector domains at a 1000-fold larger scale than previous efforts. Their approach has enabled the discovery of hundreds of short effector domains (?80 amino acids; advantageous for delivery) that can upregulate or downregulate transcription in a targeted manner when fused onto a DNA binding domain.

Stage of Development – Research *in vitro*
The large, diverse domain collection expands the catalog of effectors that can be used to create synthetic transcription factors with new properties. Their systematic analysis of the effectors' sequence-function relationships provides a resource for further engineering compact tools for controlling gene expression, and refines predictive computational models of effector domain function.

Applications

- **Gene and cell therapy**
- **Targeted repression/activation of endogenous genes**
- Synthetic transcription factors can be used to perturb the expression of multiple genes simultaneously (e.g., **high-throughput genetic interaction mapping with CRISPRi/a screens** using multiple guide RNAs).

- Use in synthetic transcription factors in **genetic circuits**, e.g., inducible gene expression or more complex circuits

Advantages

- High throughput
- Compact sequences (? 80 amino acids) advantageous for delivery via viral vector
- Domains extracted from human proteins reduce immunogenicity in compared to viral effector domains
- Most of the domains generated have NOT previously been reported as transcriptional effectors

Publications

- DelRosso, N., Tycko, J., Suzuki, P. et al. "Large-scale mapping and mutagenesis of human transcriptional effector domains." Nature 616, 365–372 (2023).
- Josh Tycko, Mike V. Van, Aradhana, Nicole DelRosso, David Yao, Xiaoshu Xu, ConnorLudwig, Kaitlyn Spees, Katherine Liu, Gaelen T Hess, Mingxin Gu, Adi Xiyal Mukund, Peter H. Suzuki, Roarke A. Kamber, Lei S. Qi, Lacramioara Bintu, Michael C. Bassik. "Development of compact transcriptional effectors using high-throughput measurements in diverse contexts." bioRxiv 2023.05.12.540558.
- Mukund, A.X., Tycko, J., Allen, S.J., Robinson, S.A., Andrews, C., Ludwig, C.H., Spees, K., Bassik, M.C. and Bintu, L. (2022). High-throughput functional characterization of combinations of transcriptional activators and repressors. *bioRxiv*, 2022-12.

Patents

- Published Application: WO2023173012
- Published Application: 20250387517

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