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Ultra-compact TIGRa platform for multiplexed gene activation and single-AAV delivery

Stanford researchers have developed a next-generation programmable transcriptional activation platform, TIGRa, that addresses key limitations of CRISPRa technologies, including large size, limited multiplexing capacity, and delivery constraints.

Programmable gene activation systems such as CRISPRa enable precise control of gene expression but remain difficult to translate due to their large size and limited ability to regulate multiple genes within compact delivery systems. These limitations are particularly critical for therapeutic applications, where coordinated activation of multiple genes is required and delivery platforms such as adeno-associated virus (AAV) impose strict size constraints.

TIGRa introduces a mechanistically distinct and ultra-compact solution based on an engineered, nuclease-inactive effector protein fused to optimized activation domains. The resulting activator is less than half the size of conventional dCas9-based systems, enabling efficient packaging within a single AAV vector. Uniquely, TIGRa leverages a native RNA array architecture to process multiple guide RNAs from a single promoter, enabling simultaneous activation of up to 12 endogenous genes within a compact genetic payload.

This integrated design enables single-AAV delivery of both the activator and multiplexed guide array, supporting scalable in vivo gene regulation. In proof-of-concept studies, TIGRa demonstrated robust multi-gene activation, efficient cell reprogramming, and enhanced neuronal survival and function in vivo.

By combining ultra-compact design with intrinsic multiplexing capability, TIGRa establishes a scalable platform for coordinated, multiplexed gene regulation across research, biotechnology, and therapeutic applications.

Applications

- Multiplexed gene activation for cell reprogramming and differentiation
- In vivo gene therapy for retinal diseases, neurodegeneration, and polygenic disorders
- Scalable gene-regulation platforms for functional genomics and pathway engineering
- Development of compact, AAV-deliverable transcriptional activation systems

Advantages

- Ultra-compact activator enabling efficient single-AAV delivery
- Intrinsic multiplexing via native RNA array architecture (up to 12 targets)
- Eliminates the need for multiple promoters or complex processing elements
- Enables coordinated regulation of gene networks rather than single targets
- Flexible platform with engineered variants optimized for size, potency, and delivery

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