P491 / #1464

Topic: *Theme C: α-Synucleinopathies / C2.a. Therapeutic Targets, Mechanisms for Treatment: Alpha-synuclein*

ZINC FINGER PROTEIN TRANSCRIPTION FACTOR-MEDIATED REPRESSION OF ALPHA-SYNUCLEIN EXPRESSION AS A THERAPEUTIC APPROACH FOR PARKINSON'S DISEASE

Lecture Title:

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Aims: Molecular and genetic evidence implicate alpha-synuclein as a key mediator of PD pathogenesis. Reducing alpha-synuclein expression in neurons thus has the potential to halt or slow PD progression. Zinc finger proteins (ZFPs) are DNA-binding proteins that can be engineered to specifically bind any genomic sequence. When fused to transcriptional regulatory domains to form ZFP transcription factors (ZFP-TFs), they can modulate the expression level of the targeted gene. We engineered ZFP-TFs with human SNCA repression activity for use as potential therapeutics for PD.
Methods: ZFP-TFs were identified in a screen of human neuroepithelial cells. On-target activity was assessed in human iPSC-derived neurons transduced with AAVs expressing the ZFP-TFs (AAV-ZFP-TFs). Transcriptome-wide specificity analyses using Affymetrix microarrays were performed in human iPSC-derived and mouse primary neurons. ZFP-TFs with minimal off-target activity in both human and mouse neurons were administered to PAC synuclein mice, which express the full human SNCA sequence on a mouse SNCA-null background. Animals were euthanized after 3 weeks and their brains were collected for molecular analyses.
Results: The initial screen identified ZFP-TFs with human alpha-synuclein repression activity ranging from ~40% to >99%. Experiments in human iPSC-derived neurons confirmed the on-target activity of the constructs and the durability of the response for 30 days. Alpha-synuclein AAV-ZFP-TFs with a range of repression activity and minimal off-target activity were well tolerated in vivo and led to significant downregulation of aSyn mRNA expression in the mouse brain.
Conclusions: The data presented here support continued development of ZFP-TFs as a potential therapy for PD.