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AI-driven design of mini-USH2A and gene electrotransfer for mutation-independent therapy of Usher syndrome type 2

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Usher syndrome type 2 (USH2) is the most common form of syndromic retinitis pigmentosa, with mutations in the USH2A gene representing its leading genetic cause. Current retinal gene therapy approaches are limited by mutation-specific strategies or by the restricted cargo capacity of viral vectors. To overcome these limitations, we propose a mutation-independent therapeutic strategy that combines AI-driven protein design with non-viral gene electrotransfer (GET). Using molecular dynamics–based computational modeling, the USH2A protein was rationally miniaturized by approximately 50 % while preserving key structural and functional domains. GET was selected as a localized delivery method, enabling enhanced cellular uptake of plasmid DNA while minimizing systemic immune responses. Three pEFS plasmids were generated: a full-length wild-type USH2A construct (∼16 kb) and two mini-USH2A variants (∼8 kb). Preliminary in vitro experiments in HEK293T cells demonstrated successful GET-mediated transfection of all constructs. Quantitative RT-PCR analysis revealed that transfection efficiency was independent of plasmid size. This study demonstrates the feasibility of combining computational protein engineering with GET as a scalable, mutation-independent gene therapy platform for inherited retinal diseases.