A gene therapy strategy to treat spinal and bulbar muscular atrophy

SBMA, or Kennedy’s disease, is an X-linked disease caused by CAG repeat expansions in the androgen receptor (AR) gene, characterized by motor neuron degeneration and primary muscle atrophy. Toxicity is dependent on the presence of dihydrotestosterone (DHT), and cell dysfunction and death ultimately result from profound alterations of cellular processes by a mixed mechanism of toxic gain and loss of function. No treatment is currently available for this condition. Androgen antagonists and AR silencing have long been sought after as attractive therapeutic strategies for SBMA, however the direct and indirect effects associated with long term AR loss of function limit their clinical applicability. Other approaches using small molecules modulating native AR functions may be hampered by lack of full understanding of their pharmacodynamic and pharmacokinetic properties. By harnessing the heterogeneity of the protein-coding transcriptome, we have identified a naturally-occurring AR isoform acting as a decoy receptor for AR and established the feasibility and therapeutic benefit of a gene therapy strategy modulating expression of this variant to treat SBMA and other AR-related diseases.