Innovative therapeutic strategy for Duchenne Muscular Dystrophy by AAV mediated delivery of artificial transcription factor genes

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Up-regulation of the dystrophin-related gene "utrophin" represents a promising therapeutic strategy for the treatment of Duchenne Muscular Dystrophy (DMD). In order to re-program the utrophin expression level in muscle, we engineered artificial zinc finger transcription factors (ZF-ATFs) that target the utrophin promoter "A". In dystrophic "mdx" mice by systemic Adeno-associated viral vector delivery, the prototype artificial gene "Jazz" or its up-graded version "JZif1" induces significant muscle functional rescue. These encouraging results are producing several international patents owned by CNR and financially supported by CNR and Zingenix Ltd Company (Tel Aviv, Israel). To investigate the molecular mechanisms underlying Jazz and JZif1 induced muscle rescue, we focused on utrophin related pathways. In particular, on-going studies aim to characterize the neuromuscular junction (NMJ) in Jazz and JZif1 mAAV8-treated wt and mdx mice. We have analysed, in skeletal muscle, pre- and post-synaptic structures by staining the neurofilaments and acetylcholine receptor (AChR) clusters, respectively. We provided evidence that our ZF-ATF genes induce beneficial effects on NMJ morphology, improving the post-synaptic clustering of AChRs. In summary, the development of ZF-ATF technology, coupled with the mAAV delivery, highlights the potential of this novel therapeutic strategy for DMD and other neuromuscular diseases.

References:
- Pisani et al. Utrophin up-regulation by artificial transcription factors induces muscle rescue and impacts the neuromuscular junction in mdx mice. Biochim Biophys Acta Mol Basis Dis. 2018 Apr;1864(4 Pt A):1172-1182.

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