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Comment on: "Myostatin inhibition in combination with antisense oligonucleotide therapy improves outcomes in spinal muscular atrophy" by Zhou *et al*.

We read with interest the article by Zhou *et al*.[1] The concept that a combination of different therapeutic strategies for spinal muscular atrophy (SMA) could maximize the benefits for SMA treatment is quite attractive, especially entering the era of increasingly approved SMA therapeutics. In general, the therapeutic strategies in SMA can be categorized into either SMN-dependent or SMN-independent approaches, which can be subsequently divided into eight different therapeutic approaches (*Figure* 1). Deletion or mutation of *survival motor neuron 1* (*SMN1*) in all SMA patients is partially compensated by limited expression of SMN protein produced by variable *SMN2* copies. With the proof of concept, the initial SMA treatment strategies mostly aim to target *SMN2* in the treatment of SMA. However, emerging evidence extend the pathogenic effect of SMN deficiency beyond MNs to include additional cells both within and outside the CNS, whereby numerous peripheral tissues, including muscles and neuromuscular junction (NMJ), demonstrate pathological changes in both preclinical models and patients.[2] Therefore, the precise characterization of SMN-dependent and

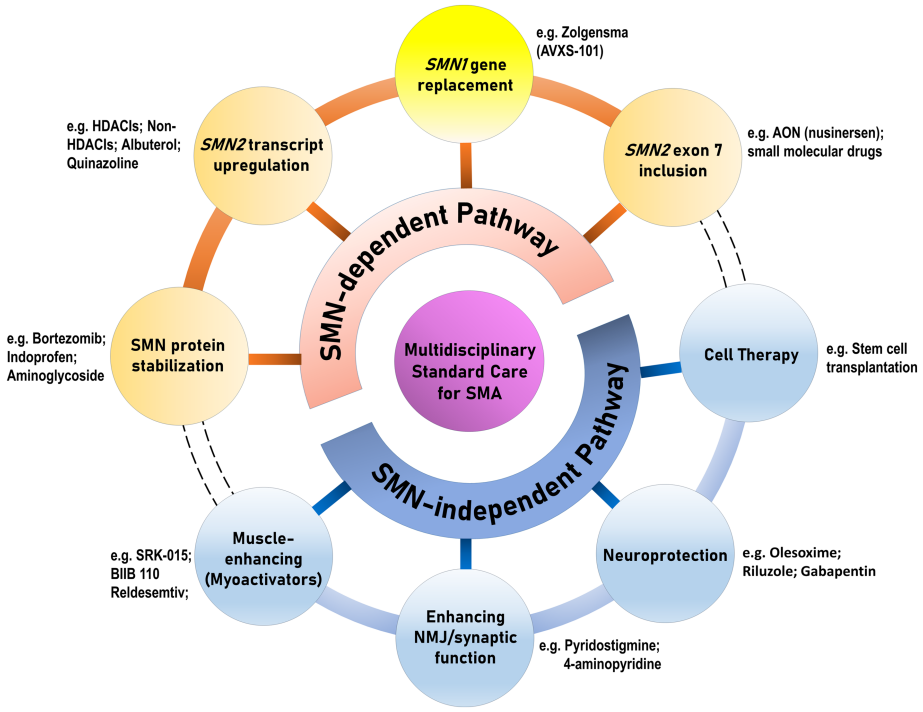

Figure 1 Therapeutic approaches for SMA. The therapeutic approaches are generally categorized into SMN-dependent and SMN-independent therapies, which can be further divided into four branches of development, respectively. The dashed lines of outer rims connecting the SMN-dependent and SMN-independent approaches imply the potential for combinatory effect as a 'cocktail therapy' for SMA. HDACIs, histone deacetylase inhibitors.

SMN-independent pathways that are both affected and underlying the disease remains a critical aspect of therapeutic development for SMA.

Excitingly, Zhou *et al*. demonstrated a promising result of combined SMN-dependent strategy of antisense oligonucleotide (AON)-inducing *SMN2* exon inclusion and SMN-independent strategy of myostatin inhibition on an SMA animal model. However, we still concern several issues that might be addressed in current SMA preclinical and clinical trials. Inhibition by adeno-associated virus (AAV)-mediated expression of myostatin propeptide (MPRO) seems an efficient and safe approach; however, an off-target effect due to systemic delivery of viral particles and likely immunogenicity to the recipient host remains a concern for AAV-based gene therapy.[3] On the other hand, several non-viral-mediated myostatin inhibitors are under investigation clinically and preclinically, such as SRK-015 and BIIB 110 (ALG 801),[45] which may also have potentials for combined SMA therapies. Furthermore, because thrombocytopenia has been reported as an adverse event in association with AON therapy, extreme caution is required when AAV-based gene therapy is combined.[6]

As the first SMN-dependent therapies are emerging into the clinical arena, other approaches beyond SMN augmentation are also under active investigation. However, SMN-dependent approaches pose a particular challenge for patients with chronic forms (types 3 and 4) of SMA, who are often diagnosed beyond the critically therapeutic window.[7] For the chronic form of SMA patients with a substantial number of motor neuron loss, it would be more crucial to target the SMN-independent pathways disrupted downstream of SMN. Identifying non-SMN targets to develop combinatorial therapeutic approaches is imperative because a comprehensive whole-lifespan approach to SMA therapy is required that includes both SMN-dependent and SMN-independent strategies that treat the CNS and periphery together.

Author contributions

All the authors conceived the scientific ideas and critically reviewed and approved the final version of the manuscript.

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