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Teaching an old drug new tricks: repositioning strategies for spinal muscular atrophy

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Spinal muscular atrophy (SMA) is a childhood disorder caused by loss of the *SMN* gene. Pathological hallmarks are spinal cord motor neuron death, neuromuscular junction dysfunction and muscle atrophy. The first *SMN* genetic therapy was recently approved and other SMN-dependent treatments are not far behind. However, not all SMA patients will reap their maximal benefit due to limited accessibility, high costs and differential effects depending on timing of administration and disease severity. The repurposing of commercially available drugs is an interesting strategy to ensure more rapid and less expensive access to new treatments. In this mini-review, we will discuss the potential and relevance of repositioning drugs currently used for neurodegenerative, neuromuscular and muscle disorders for SMA.

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Spinal muscular atrophy (SMA) is an inherited neuromuscular disorder characterized by motor neuron loss and muscle atrophy. SMA is the leading genetic cause of infant mortality [1,2]. Approximately 96% of SMA cases have been mapped to deletions and loss-of-function mutations within the ubiquitously expressed *SMN1* gene, which holds several housekeeping functions, including RNA metabolism, small nuclear ribonucleoprotein assembly and spliceosomal regulation as well as numerous cell-specific roles [3,4]. In addition, *SMN1* has an inverted duplicate gene called *SMN2*, which carries out similar functions, although this is limited by an 840C>T polymorphism that causes 90% of expressed proteins to be truncated and non-functional via exon 7 exclusion [5]. While compensated by the fully expressed *SMN1* in healthy individuals, *SMN2* is clinically relevant in SMA as a disease modifier due to an association of increased copy number with reduced severity [5,6].

Presently, the only clinically approved treatment for SMA is nusinersen (Spinraza™), an antisense oligonucleotide that targets *SMN2* to promote the production of higher levels of functional SMN protein through exon 7 inclusion [7,8]. However, as nusinersen is a relatively new therapy, there are no longitudinal studies to assess its long-term effects, although reports suggest its success is dependent upon the treatment being administered as early as possible [9–11]. These limitations, along with others, highlight a host of issues such as limited treatment viability for type 2 and 3 patients, whose symptoms are milder and develop in later years, and elevated costs associated with both newborn screening and treatment (estimated at £450,000 for the first year and £225,000 for subsequent years) [11–13]. As such, National Health Service England and Wales, for example, have only recently approved funding of nusinersen (May 2019), leaving several patients without access to any clinical treatments during a crucial period [13]. While a cohort of additional novel drugs designed to enhance SMN expression are in development, none have yet passed the Phase III clinical trial stages (Table 1) and similar high costs have been predicted (~US$2 million per treatment) [14,15]. Therefore, more cost-efficient drugs are required to ensure accessibility of treatments for all SMA patients.

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Table 1. Status of SMN-dependent drugs in clinical trials for spinal muscular atrophy.

ClinicalTrials.gov ID	Therapeutic	Activity	Current status (as of May 2019)
NCT02268552	Branaplam™	Oral small-molecule stabilizer of U1-snRNP complex and *SMN2* pre-mRNA to promote higher expression of full-length *SMN2* mRNA	Phase II trials
NCT03779334	Risdiplam™	Oral small-molecule promoter of full length *SMN2* mRNA via splicing modification	Phase II trials
NCT02122952	Zolgensma™	Gene therapy delivery of exogenous *SMN1* via adeno-associated virus effector to promote higher SMN abundance	Phase I trials
NCT02240355	R06885247	Oral small-molecule splicing modulator of *SMN2* pre-mRNA to promote higher expression of full length *SMN2* mRNA	Terminated

Typically, clinical drug development is a very long overhaul with some drugs taking up to 20 years before being approved [16]. Due to the limited availability of treatments for SMA and the urgency in getting them to patients, a valid alternative is the repositioning (or repurposing) of drugs originally designed to treat other conditions [17]. Compared with novel drugs, most repositioned drugs have passed safety efficacy tests for human administration, thus allowing a complete omission of Phase I trials [17]. Furthermore, information such as efficacy dosage, side effects and formulation costs are already known, making trials of repositioned drugs more cost and time effective [17]. Drug repositioning is not a new concept in the fields of non-neurodegenerative diseases and has opened several novel avenues of research [17–19]. Indeed, the Type 2 diabetes drug metformin is now being evaluated in clinical trials for breast and endometrial-based cancers, while the controversial morning sickness drug thalidomide is a possible candidate for Alzheimer's disease (AD) [20–26]. However, very little research on drug repositioning has been conducted in the context of inherited neurodegenerative diseases. This review will discuss how commercial drugs originally designed for other neurodegenerative, neuromuscular and muscular disorders have the potential to be repositioned to treat the central nervous system (CNS), neuromuscular junction (NMJ) and skeletal muscle pathologies observed in SMA.

Repositioning drugs to target CNS pathologies in SMA

The loss of motor neurons in the anterior horn of the spinal cord is the canonical feature of SMA [27]. While the genetic basis behind SMA is now well understood, it has not yet been elucidated how and why loss of SMN affects and causes motor neuron degeneration [27]. Besides its ubiquitous localization within nuclear Gemini of coiled bodies (Gems), SMN is also specifically abundant in the axon and synaptic regions of motor neurons where it regulates mRNA transport, actin dynamics and vesicle release [28–31]. This is supported by studies showing neurite outgrowth, differentiation and synaptic defects in SMN-depleted neuronal cells, suggesting that CNS-specific functions of SMN are dysregulated in SMA [31–33]. Commercial drugs that modulate similar regulatory pathways in the CNS might therefore be beneficial in SMA patients.

One plausible repositioning strategy may be through identifying drugs that are currently used to treat other motor neuron diseases such as amyotrophic lateral sclerosis (ALS). Indeed, the ALS drug riluzole (Rilutek™ or Teglutik™), a pharmacological compound thought to promote neuroprotection through Ca^{2+}-activated K^{+} channel-mediated glutamate reduction, has already been evaluated in clinical trials for SMA, albeit with limited success in improving survival rates (ClinicalTrials.Gov ID: NCT00774423) [34–38].

While the repositioning of riluzole for SMA is ongoing, other ALS drugs have not yet made that leap, including rasalgiline (Azilect™), an irreversible MOA-B inhibitor (Figure 1) [39]. The MOA-B isoform is expressed in the outer membrane of mitochondria with a neuron-specific role in oxidative deamination of monoamine neurotransmitters [40–43]. Based upon evidence of MOA-B upregulation in rodent models of Parkinson's disease (PD), rasalgiline was initially evaluated in clinical trials for PD (ClinicalTrials.Gov ID: NCT00203138) and received EMA and US FDA approval in 2005 and 2006, respectively [43].

Recently, rasalgiline underwent Phase II clinical trials in ALS patients, either alone or in combination with riluzole, with the latter demonstrating moderate success, which is thought to be due to rasalgiline's neuroprotective role through promoting mitochondrial stability (ClinicalTrials.Gov ID: NCT01786603; NCT01879241; NCT01232738) [44–46]. Indeed, increased MOA-B activity could contribute to mitochondrial dysfunction and neurodegeneration via accumulation of its aldehyde and reactive oxygen species by-products [47–50]. Given that mitochondrial instability has been reported in pre-symptomatic SMA motor neurons, rasalgiline could be a treatment option to improve mitochondrial stability and delay motor neuron degeneration (Figure 1) [51].

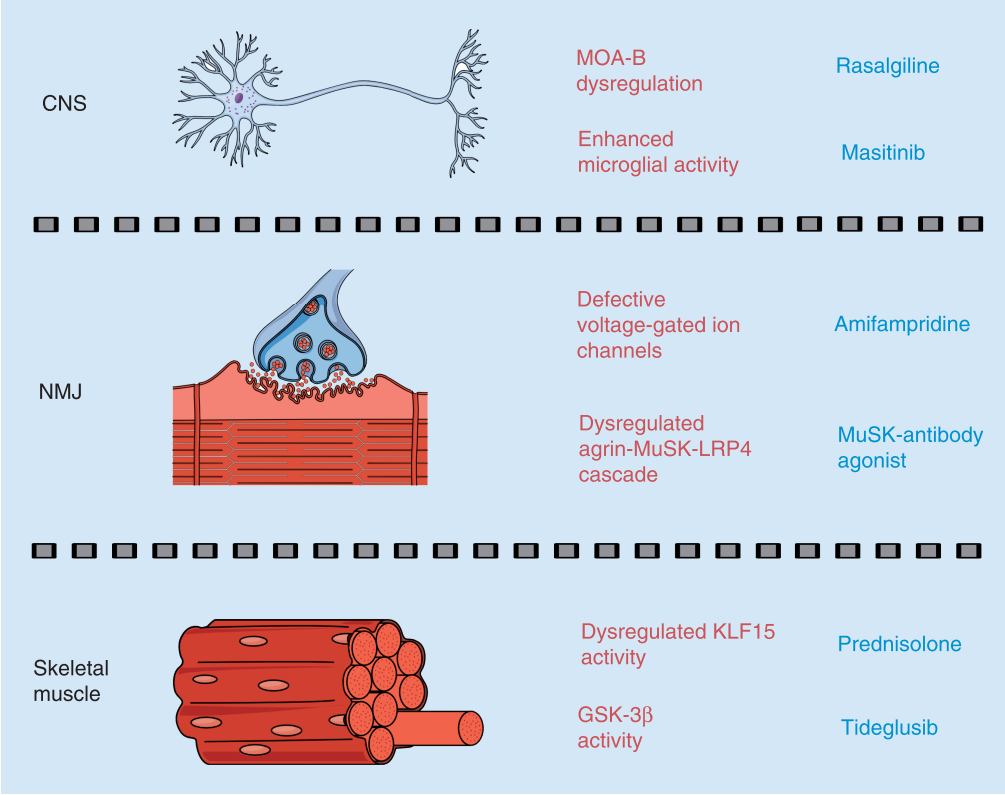

Figure 1. Targets for survival motor neuron-independent drug repositioning strategies for spinal muscular atrophy.
Overview of pathological molecular effectors or biological pathways (in red) that could be therapeutically modulated by commercially available drugs (in blue) to treat CNS, NMJ and skeletal muscle pathologies in spinal muscular atrophy.
NMJ: Neuromuscular junction.

Modulating the aberrant inflammation of nervous tissue (neuroinflammation) can also help minimize motor neuron death. The pathological impacts of neuroinflammation, predominantly mediated by astrocytes and microglia, have been associated with several neurodegenerative diseases such as AD [52]. Microglia are specialized macrophage cells that regulate the removal of damaged neurons, plaques and infectious agents [53]. However, the chronic release of pro-inflammatory factors by M1 microglia can result in neuroinflammation-induced neuronal loss [54–57]. Studies in rodents identified the colony-stimulating factor 1 receptor, a member of the RTK family, as a key promoter of microglia proliferation and viability [58–61]. The RTK inhibitor masitinib (Masivet™) has been demonstrated to reduce the levels of microglia via colony-stimulating factor 1 receptor inhibition (Figure 1), thus decreasing neuronal degeneration in clinical trials for AD (ClinicalTrials.Gov ID: NCT01872598) [62–64]. Masitinib has recently been evaluated in *SOD1*^{G93A} ALS rats, where administration of the drug delayed disease progression as well as reduced both microglial activity and neuroinflammation [65]. Furthermore, emerging results from Phase III clinical trials of masitinib in ALS patients are promising, with reports of delayed neuronal degeneration, although the extent of the delay remains unclear (ClinicalTrials.Gov ID: NCT02588677) [66]. Recent reports also support a role for neuroinflammation in SMA pathogenesis [67]. Indeed, increased microgliosis and release of the pro-inflammatory IL-6 cytokine by microglia have been described in SMA mice [33,68]. In addition, astrocytosis was observed in the spinal cord of SMA mice at early symptomatic stages, when motor neuron loss is first detected [69,70]. The role of astrocytes in SMA pathology was further supported by experiments demonstrating that astrocyte-specific restoration of SMN expression in SMA improves disease phenotypes [70]. Recent work has also identified the Notch pathway as a mediator of neuroinflammatory activity in SMA mice [71]. Thus, drugs that reduce neuroinflammation such as masitinib may provide significant therapeutic benefits for SMA (Figure 1).

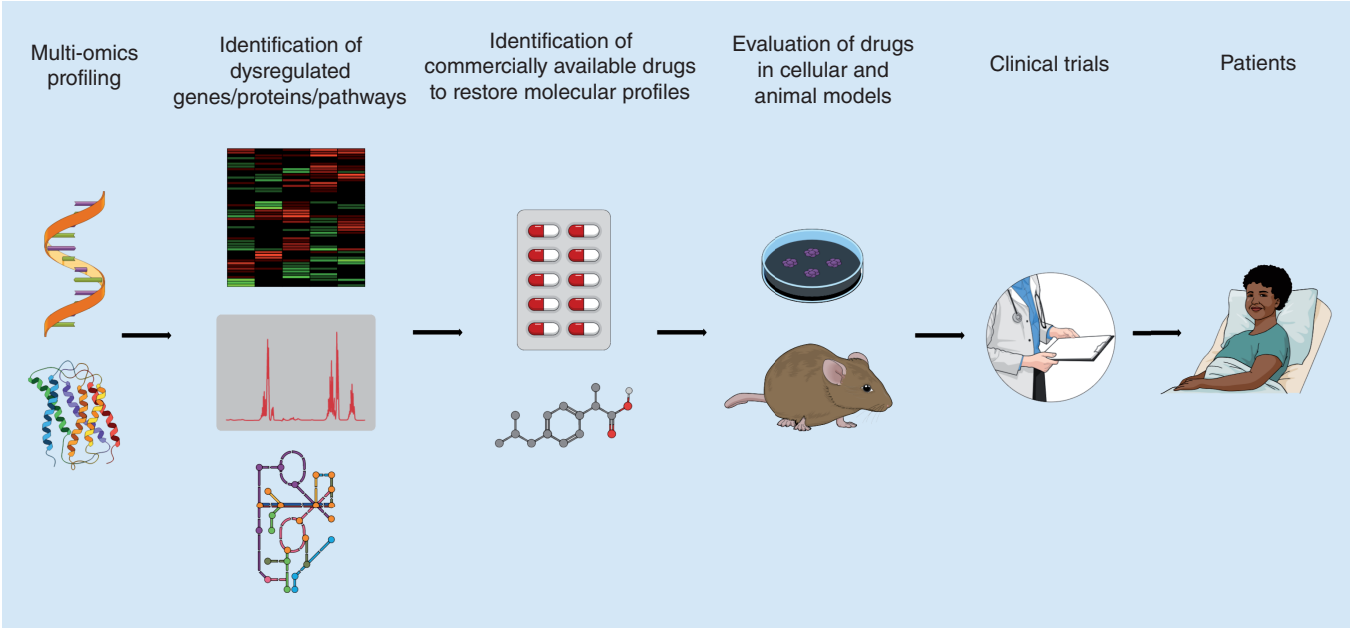

Figure 2. Proposed experimental model for drug repositioning strategies. Proteomic and transcriptomic approaches can be used to define the differential expression patterns of genes, proteins and biological pathways between diseased and healthy states. Published literature or integrated publicly available drug databases allow for the uncovering of commercially available drugs that can restore the aberrant molecular profiles in the diseased state. The drugs then require to first be validated for safety and efficacy in relevant *in vitro* and *in vivo* models. Successful drug candidates can then be evaluated in clinical trials, with Phase I usually bypassed as information regarding safety and dosages are known. Finally, the drug is approved for patient use if it demonstrates benefits in clinical trials.

Preventing and/or delaying motor neuron death in SMA is a therapeutic priority and repositioning neuroprotective drugs such as rasalgiline and masitinib for SMA has the potential to rapidly expand the number of available CNS-specific treatments.

Repositioning drugs to target NMJ pathologies in SMA

SMA pathology also affects the NMJ, a specialized synaptic region between the motor nerve terminal and skeletal muscle fiber that contributes to contraction via an ACh and nicotinic AChR interaction [72]. In both severe and intermediate SMA mice, NMJ defects include neurofilament accumulation, axonal sprouting, immature motor endplate development, impaired synaptic regions and dysregulated AChR clustering, the latter being a crucial step in NMJ development [72,73]. Thus, drugs currently aimed at modulating NMJ activity (pre- and post-synaptic) are an interesting avenue for SMA.

Lambert-Eaton myasthenic syndrome is an autoimmune disorder caused by antibodies that target motor neuron voltage-gated Ca^{2+} channels, resulting in a pre-synaptic NMJ pathology [74]. Amifampridine (Firdapse™) has been used to treat this disorder by blocking pre-synaptic K^+ channels to allow an increased duration of ACh release (Figure 1) [75,76]. Interestingly, impairments in neuronal excitation of SMN-deficient motor neurons were similarly caused by defective voltage-gated Ca^{2+} channels, suggesting that amifampridine could provide therapeutic benefits in SMA (Figure 1) [77]. Furthermore, with successful use in the post-synaptic NMJ disorder muscle-specific kinase-myasthenia gravis (MuSK-MG), amifampridine could potentially modulate both pre- and post-synaptic defects observed in SMA NMJs (ClinicalTrials.Gov ID: NCT03304054) [78–80].

MuSK-MG is caused by an antibody-mediated breakdown of MuSK, a specialized RTK that regulates motor endplate development, maturation and AChR clustering through an agrin-MuSK-LRP4 cascade [81–84]. Although there are limited studies of MuSK regulation in SMA, agrin dysregulation contributes to impaired AChR clustering, suggesting that the agrin-MuSK-LRP4 cascade may be a suitable target for SMA treatments [85,86]. Although not yet in clinical trials, preliminary work is currently ongoing to evaluate the therapeutic potential of MuSK-specific antibody agonists aimed at increasing MuSK activity (Figure 1) [87,88]. Increasing MuSK activity either genetically or pharmacologically in *SOD1*^{G93A} ALS mice resulted in reduced NMJ denervation and improved motor function [89,90]. Although the MuSK antibody agonist did not influence survival rate or disease progression

in ALS mice, its ability to maintain NMJ integrity and innervation makes it an interesting candidate that could potentially be combined with amifampridine to reduce NMJ pathology in SMA (Figure 1).

From a repositioning approach, one limitation in the use of NMJ-specific drugs for SMA treatment is that they were originally designed to treat disorders that display either pre- or post-synaptic NMJ defects. However, both compartments are affected in SMA and studies in ALS mice indicate that these pharmacological compounds may not be as effective when administered individually. Instead, future research endeavors in SMA could adopt a combinatorial approach when trialing NMJ targeting drugs to ensure optimal benefits.

Repositioning drugs for skeletal muscle pathologies in SMA

Reduced SMN levels also affect skeletal muscle development and function [91–94]. A new avenue for SMA therapeutic development could therefore involve drugs currently used for muscular disorders. Indeed, shared treatment paradigms have recently been identified for SMA and Duchenne muscular dystrophy (DMD), an inherited X-linked recessive muscle disorder [95]. Currently, the most commonly used drug to treat DMD is prednisolone, a synthetic glucocorticoid, which was originally prescribed to reduce fibrotic development in skeletal muscle via its anti-inflammatory properties [96,97]. Research in DMD *mdx* mice has recently demonstrated that when dosed intermittently, prednisolone also displayed ergogenic benefits in skeletal muscle by increasing its repair [98,99]. The molecular mechanism behind the prednisolone-induced muscle repair is thought to be through restoration of Klf15 expression, a transcription factor involved in muscle homeostasis via regulation of glucose, lipid and amino acid metabolism (Figure 1) [99–102]. Subsequently, Klf15 levels were also observed to be low in skeletal muscle of pre-symptomatic SMA mice [103]. Importantly, prednisolone treatment in SMA mice increased Klf15 expression and led to amelioration of muscle-specific phenotypes, weight and survival [103]. Evidence of common pathological targets and treatment strategies between SMA and DMD supports further investigations into the repositioning of additional muscle-specific drugs not previously considered for SMA.

Tideglusib, a small heterocyclic thiadiazolidine-based non-ATP competitive inhibitor of GSK-3β, could potentially ameliorate SMA muscle pathology (Figure 1) [104]. GSK-3β is a ubiquitously expressed isoform of GSK-3, which acts as a serine/threonine kinase in many cellular processes such as proliferation, survival and metabolism [105,106]. Tideglusib was initially developed for AD, with initial trials deeming the drug safe for human use [107,108]. The ubiquitous and multipurpose activities of GSK-3β thus enabled repurposing opportunities for tideglusib. In skeletal muscle, GSK-3β is a negative regulator of growth through dysregulation of the myogenic regulator factors [109]. When GSK-3β was inhibited in C2C12 myoblasts and C57BL/6 mice, myogenic regulator factor activity, myotube formation and muscle growth were enhanced, confirming its usefulness as a potential drug candidate for impaired muscle development [109–111]. As such, tideglusib is being evaluated in Phase II clinical trials (ClinicalTrials.gov ID: NCT03692312; NCT02858908) for congenital myotonic dystrophy, an autosomal polyQ-dominant disorder characterized by myotonia, muscle dystrophy and weakness [112]. Although the trial results are not fully published, early results are promising, suggesting that a Phase III approval is in the near future [113]. In addition to promotion of muscle growth, tideglusib may have a further advantage in SMA by restoring SMN levels. Indeed, chemical screens in human SMA fibroblasts exposed to GSK-3β inhibitors or GSK-3β short-hairpin RNAs revealed an increased SMN expression [114]. With positive effects in congenital myotonic dystrophy and on SMN, tideglusib could be a potential therapeutic candidate for SMA, ameliorating SMN-dependent and -independent muscle atrophy.

The shared dysregulation in pathways related to muscle growth, differentiation, function and homeostasis between muscular disorders and SMA highlights the contribution of intrinsic muscle defects to SMA pathogenesis. The parallel continual development of pharmacological compounds for muscle disorders suggests that several potential muscle-specific treatments could potentially lead to significant benefits for SMA.

Conclusion

Despite being the leading cause of genetically caused infant deaths, there is presently only one clinically approved drug for SMA that is not accessible to all SMA patients and is unfortunately not a cure. Additional SMN-specific drugs may be approved in the future, thus increasing treatment options (Table 1). However, molecular and functional pathological similarities between SMA and other neurodegenerative, neuromuscular and muscular disorders highlight potential novel non-SMN treatments (Figure 1). Indeed, the existence of shared dysregulated pathways between diseases offers a therapeutic solution in the form of drug repositioning. Pharmacological compounds that are either approved or in clinical trials could provide SMA patients more affordable and accessible treatment

options that could be used in combination with SMN-dependent therapeutics. Furthermore, while the present review focuses on the potential of repurposing drugs currently in use for neurodegenerative, neuromuscular and muscular disease, repositioning strategies for SMA should not be limited to these groups of disorders as pathological overlaps may also exist between SMA and unrelated disorders such as cancer (e.g., RTK signaling) [115]. With several published multi-omics SMA studies identifying a multitude of dysregulated pathways and molecular effectors, the opportunities for drug repositioning are many and should be a key component of future therapy development for SMA (Figure 2) [116–118].

Future perspective

It is clear that the SMA therapeutic landscape has drastically changed since the approval of nusinersen/Spinraza™. In the next few years, it is likely that most, if not all, SMA patients will have been administered one form or another of an SMN-enhancing therapy (antisense oligonucleotide, gene therapy, small molecule). Our role as researchers and clinicians is to support the SMA community by anticipating additional therapeutic needs as these presently young children reach adolescence and adulthood. SMN-dependent therapies will without a doubt have to be accompanied by complementary treatments aimed at ameliorating and/or preserving neuromuscular health in SMA patients. Our goal should be to develop these drug entities well ahead of them being required, which can be ensured by understanding the pathological similarities between SMA and other diseases and by using this information for drug repositioning strategies.

Executive summary

Spinal muscular atrophy

- Spinal muscular atrophy (SMA) is an inherited neuromuscular disorder and the leading genetic cause of infant mortality caused by homozygous loss of the *SMN1* gene.
- Disease severity is dependent upon the copy number of *SMN2*, a duplicated but mutated copy of *SMN1*, which only produces 10% of full-length protein.
- The benefits of the only currently available treatment for SMA (nusinersen/Spinraza™), an antisense oligonucleotide that promotes expression of full-length SMN from *SMN2*, are limited by its accessibility and age-dependent efficacy.

Drug repositioning

- There is currently a gap in treatment availability for SMA patients.
- Drug repositioning provides a shorter and more cost-effective transition to the clinic as pre-clinical and clinical dosage and safety assessments have already been performed.
- Molecular and functional similarities between SMA and other neurodegenerative, neuromuscular and muscle disorders present opportunities for drug repositioning strategies.

Rasalgiline

- Rasalgiline (Azilect™) is an irreversible MOA-B inhibitor that promotes neuroprotection in Parkinson's Disease through increased mitochondrial stability.
- Mitochondrial instability has been reported in pre-symptomatic SMA and amyotrophic lateral sclerosis (ALS) motor neurons, which has led to rasalgiline Phase II clinical trials in the latter.

Masitinib

- Masitinib (Masivet™) is a CSF1 receptor inhibitor, which reduces microglia- and neuroinflammation-induced neuronal loss.
- A Phase III clinical trial of masitinib in ALS patients revealed delayed neuronal degeneration, with similar results in ALS mice that were associated with reduced microglial activity.
- Although masitinib has not been trialled in SMA, neuroinflammation-induced neuronal loss has been reported, suggesting potential benefits of the drug in SMA.

Amifampridine

- Amifampridine (Firdpase™) is a pre-synaptic K^+ channel blocker used in neuromuscular junction disorders such as Lambert-Eaton myasthenic syndrome to promote ACh release, which is impaired due to defective voltage-gated Ca^{2+} channels.
- Similar voltage-gated Ca^{2+} channel defects have been reported in SMA motor neurons, suggesting amifampridine could be effective in SMA.

Muscle-specific kinase antibody agonist

- The agrin-MuSK-LRP4 cascade is important for ACh receptor remodeling at the post-synaptic motor endplate.
- ACh receptor remodeling is dysregulated in a variety of neuromuscular disorders such as SMA, ALS and MuSK-myasthenia gravis.
- A MuSK antibody agonist, previously designed to promote MuSK activity in MuSK-myasthenia gravis, improved motor function in ALS mice, suggesting it could have similar benefits in SMA.

Prednisolone
- Prednisolone is a synthetic glucocorticoid used in Duchenne muscular dystrophy that demonstrates anti-inflammatory and ergogenic properties.
- In both Duchenne muscular dystrophy and SMA mice, prednisolone improves muscle health through restoration of Klf15 activity, an important regulator of muscle metabolism.

Tideglusib
- Tideglusib is a small heterocyclic thiadiazolidine-based non-ATP competitive inhibitor of GSK-3β.
- In skeletal muscle, GSK-3β negatively regulates myogenic regulatory factor activity and its inhibition is associated with muscle growth.
- Tideglusib is currently showing promising results in Phase II clinical trials for the muscle disorder congenital myotonic dystrophy.
- Tideglusib could potentially ameliorate SMA skeletal muscle through both SMN-dependent and -independent pathways.

Second-generation SMA therapies
- There is increasing evidence that future treatments need to incorporate both SMN-dependent and -independent therapies that affect both neuronal and systemic tissues.
- The increasing number of multi-omic studies will allow for the identification of drug target similarities between SMA and different disorders.

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