Duchenne Distilled: Current DMD Therapies

MDC DMD Masterclass 2023

Treatment Strategy for DMD

- There is currently no cure for DMD, therefore treatment options are focused on improving quality of life and slowing the progression of DMD associated symptoms.
- Treatment strategies currently include glucocorticoids such as Deflazacort or Prednisone as well as physical therapy.
- There has been progress made in the development of gene therapies for DMD in order to target the defect in dystrophin rather than address the secondary manifestations of the disease such as inflammation or fibrosis.
- The treatment landscape for pediatric patients is growing thus emphasizing the importance of early diagnosis to ensure timely access to disease modifying therapies when they become available.

Glucocorticoid Use for DMD

- Glucocorticoids are typically initiated during the early ambulatory stage. The most common steroids prescribed in DMD include **Prednisone** and **Deflazacort.**
- Glucocorticoids have been shown to have several positive effects on DMD patients including:
  - Slowing disease progression and loss of motor milestones
  - Prolonging overall survival
- Glucocorticoid use does have clinically significant side effects when used long term and usage must be monitored closely.
- Deflazacort has been approved for DMD patients aged 5 and older, whereas Prednisone is currently used off-label for DMD patients.
- **Vamorolone** is a novel anti-inflammatory steroid analogue that is currently under investigation for the replacement of traditional glucocorticoids in DMD. It is similar in structure to other glucocorticoids, however it has been created to elicit fewer side effects.

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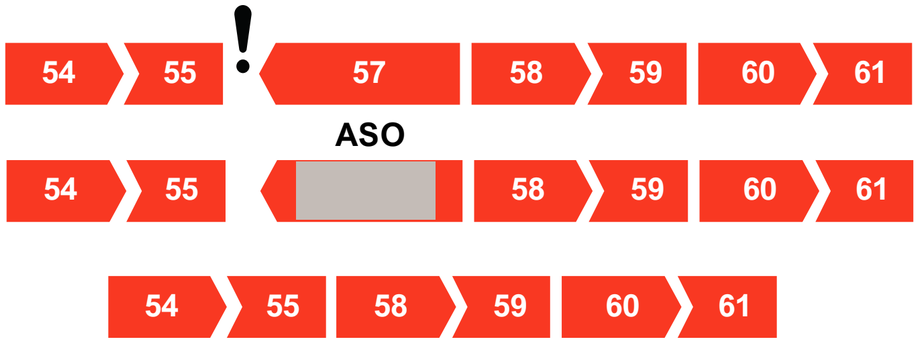
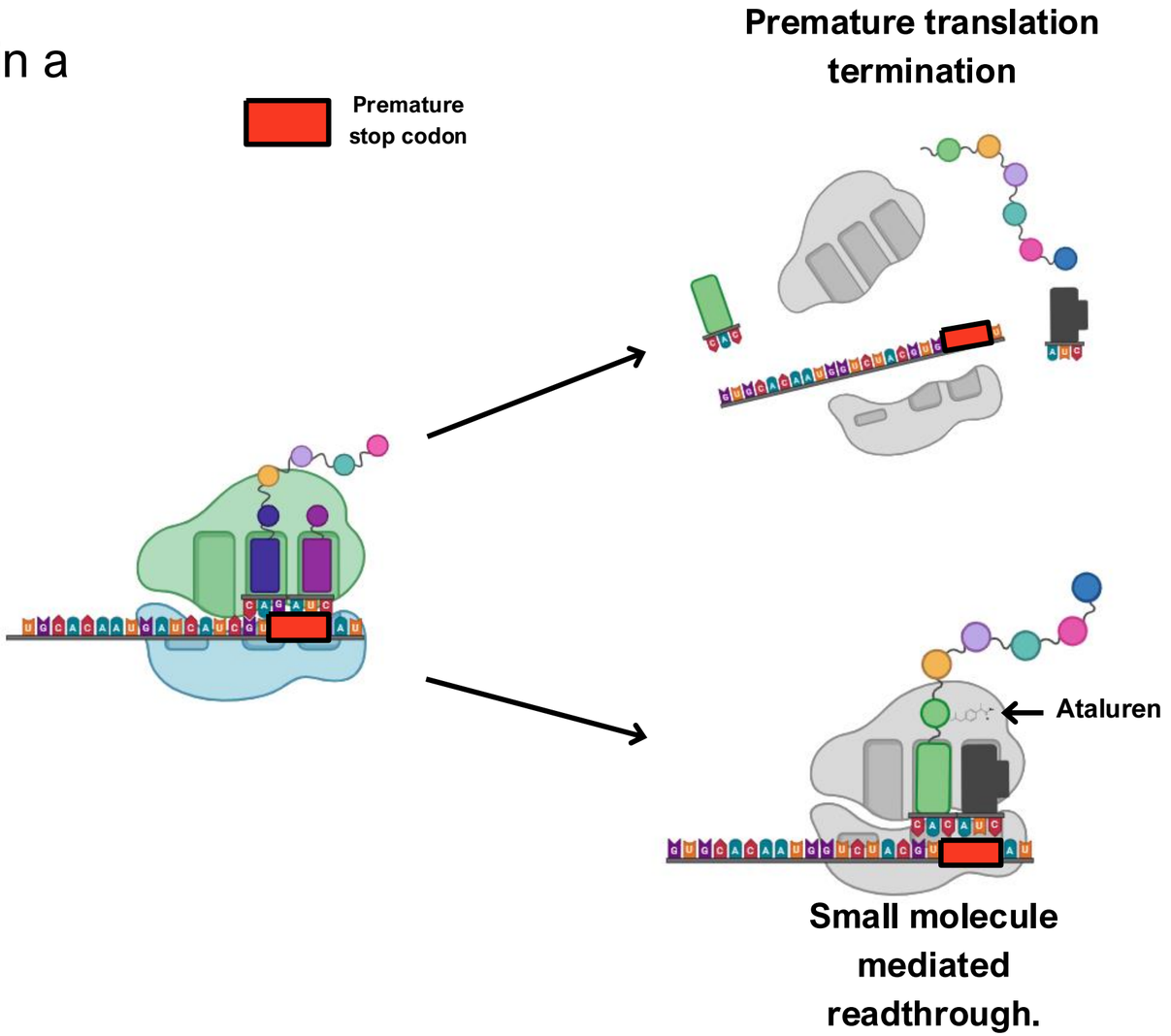
Exon-Skipping/Anti-sense Oligonucleotide Therapies

- Exon skipping therapies target mutated codons within the reading frame of the dystrophin gene using pre-designed anti-sense oligonucleotides (ASO).
- The pre-designed anti-sense oligonucleotides allow for a partially functional dystrophin protein to be generated.
- The U.S. FDA approved Eteplirsen which specifically skips Exon 51 in defective gene variants for DMD. Golodirsen and Viltolarsen have also been approved by the FDA and both drugs have been designed for patients with a mutation in Exon 53.
- These exon skipping therapies have shown significant increases in dystrophin protein expression in the muscles of patients with DMD.



Stop Codon Readthrough

- Certain mutations in the dystrophin gene can result in a premature stop codon inserted into the reading fram This causes a dysfunctional dystrophin protein to be produced.
- Rather than cause a shift in the reading frame, these stop codons prematurely halt translation of dystrophin during protein synthesis.
- There are small molecules like Ataluren (not approved in Canada) that have been designed to combine with premature stop codons and stimulate "stop codon readthrough".
- Stop codon readthrough essentially means that the ribosome will continue past the premature stop codon and continue to translate the functional protein.



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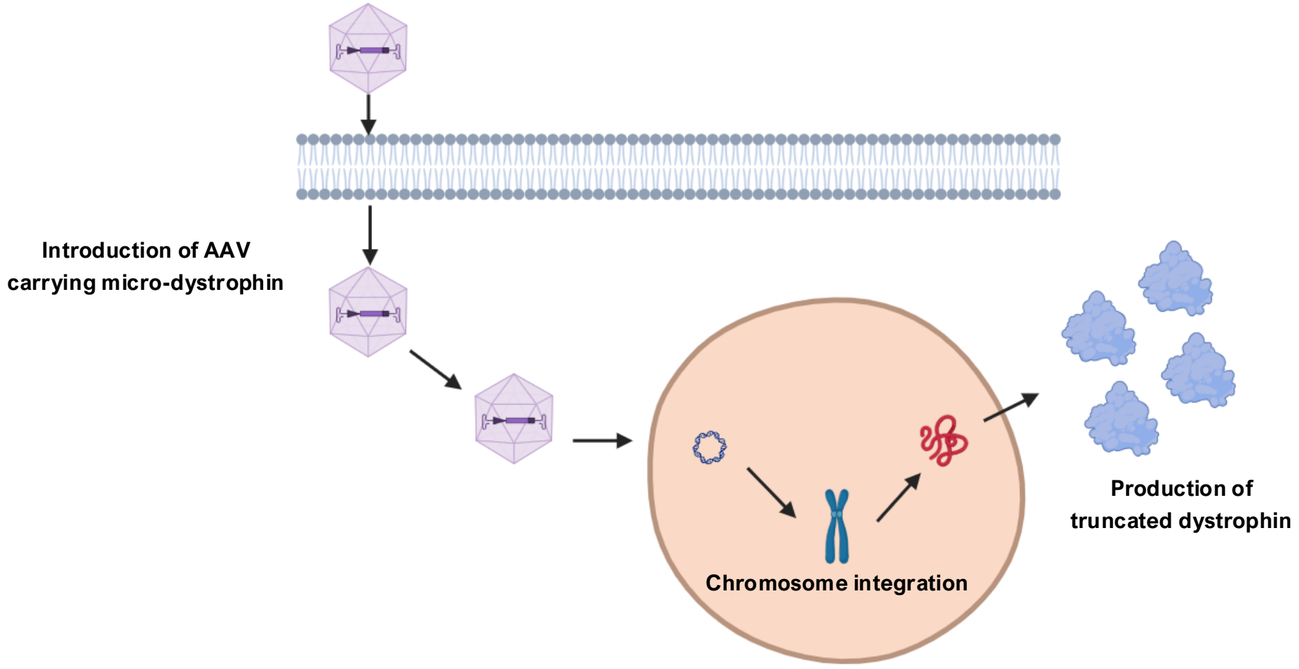
Gene Addition

- The root cause of DMD is the mutations within the DMD gene. A therapy option considers completely replacing the dysfunctional DMD gene with a normal gene.
- This particular therapeutic works to package a partially functional "micro-dystrophin" into an adeno-associated viral delivery vector (AAV) due to its ability to infiltrate skeletal muscle at high efficiency.
- Elevidys (*delandistrogene moxeparvovec-rokl)* is an AAV mediated gene addition therapeutic that was approved by the U.S. FDA but has not been approved in Canada.



Genome Editing

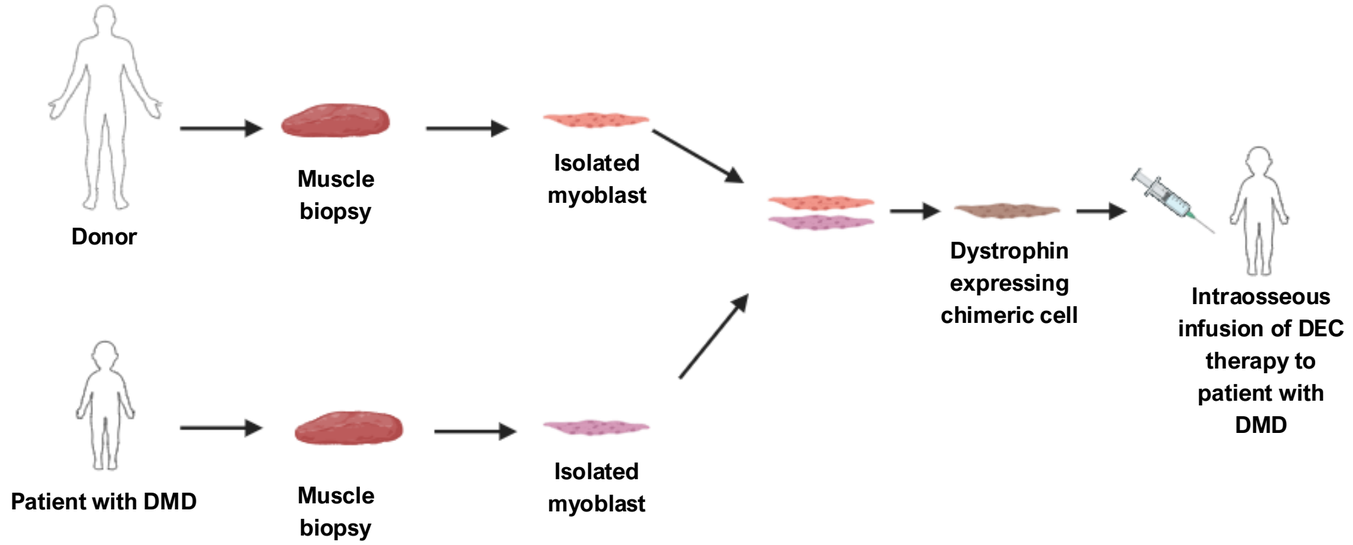
- CRISPR/Cas9 mediated gene editing has been used as a powerful tool to modify genetic abnormalities including correcting mutations in the DMD gene.
- In the CRISPR/Cas9 system, specific double stranded breaks in a gene can be introduced which will activate the DNA repair systems.
- For DMD specifically, there have been studies investigating the correction of exon deletions using the CRISPR/Cas9 system that cause a dysfunctional dystrophin to be produced.
- Further studies in-vivo are required to investigate the long term efficacy and safety of CRISPR mediated gene editing systems as a therapeutic for DMD before it can be implemented clinically.

Protein Replacement

- Utrophin is a functional paralog of dystrophin and shares similarities in both structure and function.
- The similarity between utrophin and dystrophin has caused researchers to propose utrophin as an alternate for dystrophin.
- Upregulating utrophin levels in DMD patients is a promising strategy and there have been research studies investigating small molecule utrophin modulators in mice.
- While the studies in mouse models were promising, a phase 2 clinical trial on C1100 (Ezutromid - utrophin up-regulator) showed that C1100 did not provide any significant benefit for DMD patients.
- The combination of utrophin based therapies and other dystrophin targeting therapies for DMD has been proposed though this requires further investigation.

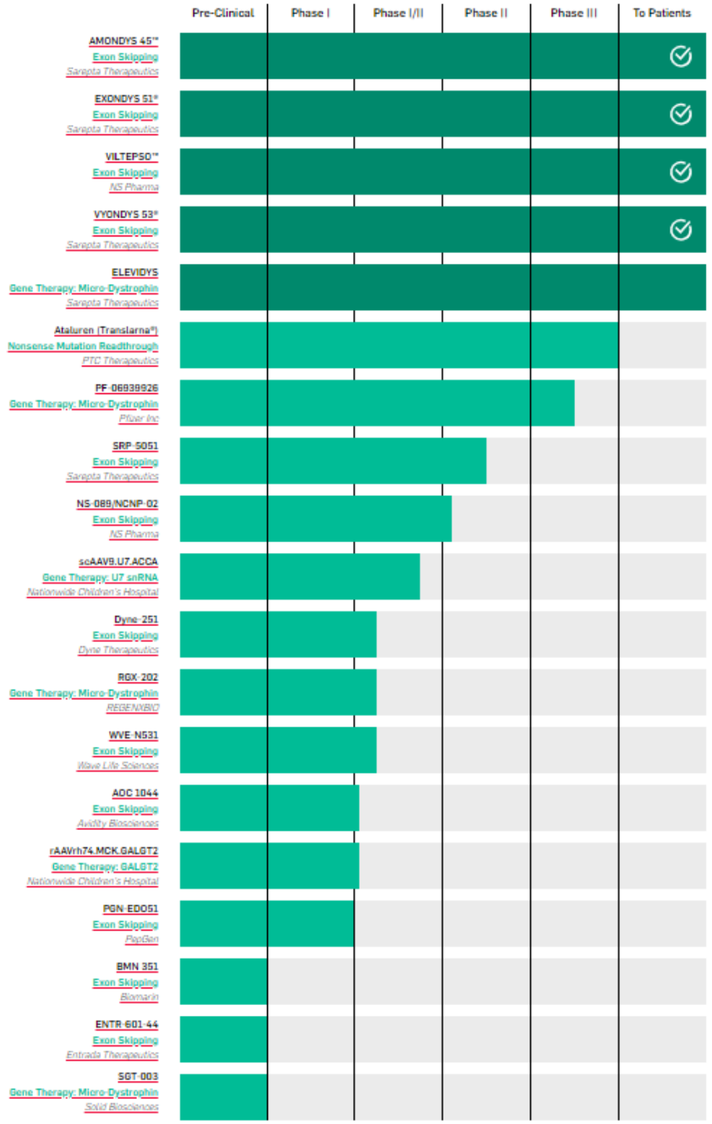
Stem Cell Therapy/Myoblast Transplantation

- Stem cell based therapies are an alternative treatment option to gene based therapies. The goal of these therapies is to restore dystrophin expression within the cells.
- Dystrophin Expressing Chimeric cell (DEC) therapy involves the fusion of DMD patient myoblasts with myoblasts of normal donor origin. The fused chimeric cell can then be introduced to the DMD patient intravenously to restore dystrophin expression.
- Results from a study on DEC therapy safety and functional outcomes published in 2023 reported that ambulatory patients with DMD showed improvements in functional tests and improved strength in both ambulatory and non ambulatory patients with DMD.

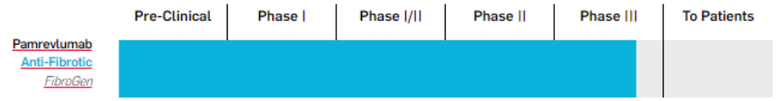


DMD Therapeutic Overview

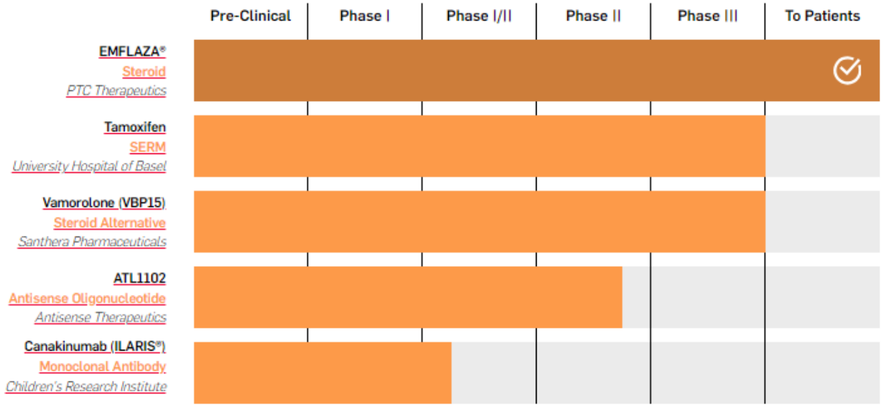
Restoring or Replacing Dystrophin



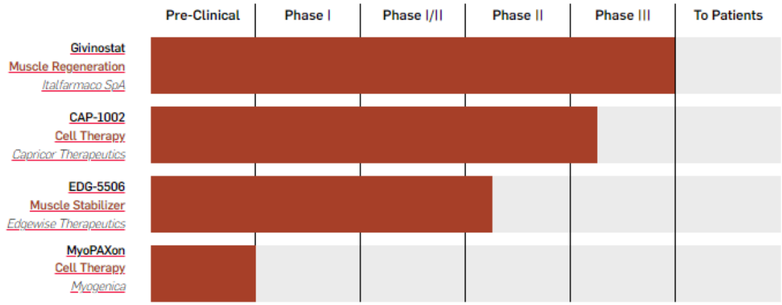
Combating Fibrosis



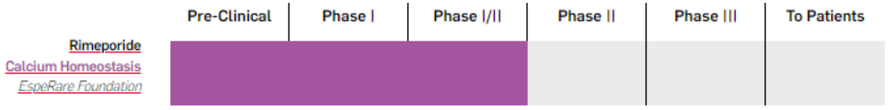
Reducing Inflammation



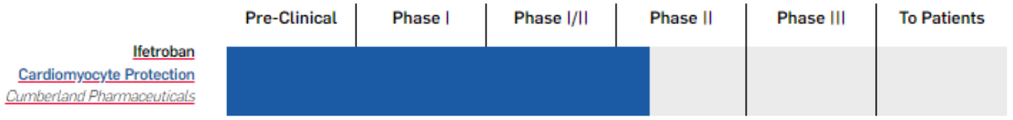
Improving Muscle Growth & Protection



Regulating Calcium Balance



Improving Heart Function



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DMD Therapeutic Overview

There are numerous DMD therapies in the pipeline, with some that have received FDA approval for use. Health Canada approvals are currently still pending and clinical trials in Canada continue.

Therapeutic strategies	Mechanism of action	Chemistry	Drug route	Current stage
Exon skipping				
Golodirsen	Exon 53 skipping	Antisense oligonucleotides	Intravenous	Approved (FDA)
Eteplirsen	Exon 51 skipping	Antisense oligonucleotides	Intravenous	Approved (FDA)
Viltolarsen	Exon 53 skipping	Antisense oligonucleotides	Intravenous	Approved (FDA)
Casimersen	Exon 45 skipping	Phosphorodiamidate morpholino oligomer	Intravenous	Phase II/III
SRP-5051	Exon 51 skipping	Peptide-conjugated phosphorodiamidate morpholino oligomer	Intravenous	Phase II
DS-5141b	Exon 45 skipping	2 ENA antisense	Intravenous	Phase I/II
Stop codon readthrough				
Ataluren	Readthrough strategy of nonsense mutations	Small molecule	Oral	Approved (EMA), confirmatory Phase III,
NPC14(Arbekacin Sulfate)	Readthrough strategy of nonsense mutations	Small molecule	Intravenous	Phase II
Gene addition				
PF-06939926	AAV9 gene therapy	Recombinant adeno-associated virus and codon-optimized human micro-dystrophin	Intravenous	Phase III
rAAVrh74.MHCK7	AAV9 gene therapy	Recombinant adeno-associated virus and codon-optimized human micro-dystrophin	Intravenous	Phase I/II
SGT-001	AAV9 gene therapy	Recombinant adeno-associated virus and codon-optimized human micro-dystrophin	Intravenous	Phase I/II
Genome editing				
CRISPR-Cas9	Removes DNA encoding a specific target exon	AAVs- CRISPR-Cas9 system	–	Pre-clinical
Protein replacement				
C1100 (Ezutromid)	Upregulation of utrophin	Small molecule	Oral	Phase II
rAAVrh74.MCK.GALGT2	Upregulation of utrophin	Recombinant adeno-associated virus and GALGT2 gene	Intravenous	Phase I/II
Myoblast transplantation				
Donor-derived myoblasts	Fuse with host muscle fibers	Myoblasts grown	Intravenous	Phase I/II

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DMD Therapeutic Overview

There are also a number of small molecule therapeutics currently in the pipeline for management and treatment of DMD.

Therapeutic strategies	Mechanism of action	Chemistry	Drug route	Current stage
Anti-fibrotic				
Pamrevlumab	Monoclonal anti-CTGF antibody	Antibody	Intravenous	Phase II
Losartan	Angiotensin II type 1 receptor blocker	Small molecule	Oral	Phase II
Halofuginone	Inhibitor of collagen a1 and MMP2	Small molecule	Oral	Phase I/II (Suspended)
Infliximab	Antibody to human TNF-α	Antibody	—	Pre-clinical
Suramin	Inhibits TGF-β	Small molecule	—	Pre-clinical
Imatinib Mesylate (Gleevec)	Inhibits TGF-β	Small molecule	—	Pre-clinical
Anti-inflammatory				
Corticosteroids (Prednisone, Prednisolone, and Deflazacort)	NF-κB inhibition	Small molecule	Oral	Phase III
Edasalonexent	NF-kB inhibition	Small molecule	Oral	Phase III
Vamorolone (VBP-15)	NF-kB inhibition	Small molecule	Oral	Phase II
Increlex (R)	Recombinant IGF-1	Fusion protein	Subcutaneous	Phase II
TAS-205	Hematopoietic prostaglandin D synthase inhibitor	Small molecule	Oral	Phase II a
Flavocoxid	NF-kB inhibition	Small molecule	Oral	Phase I
Givinostat	Histone deacetylase (HDAC) inhibitor	Small molecule	Oral	Phase I/II
Tamoxifen	Estrogen receptor modulator	Small molecule	Oral	Phase III
Reduction of muscle damage				
Ca^{2+} dysregulation				
Rimeporide	Sodium–hydrogen exchanger 1 inhibitor	Small molecule	Oral	Phase Ib
AT-300	Blocks mechanosensitive Ca^{2+} channels	Small molecule	—	Pre-clinical
Recombinant Mitsugumin 53	Facilitates membrane repair at sites of injury	Recombinant proteins	—	Pre-clinical
BGP-15	Hsp72 inducer	Small molecule	—	Pre-clinical
Streptomycin	Nonspecific Ca^{2+} channel blocker	Small molecule	—	Pre-clinical
Oxidative stress				
Coenzyme Q10	Electron acceptor for NADH and succinate dehydrogenase	Small molecule	Oral	Phase III
Idebenone	Antioxidant	Small molecule	Oral	Phase III
N-acetylcysteine	Endogenous antioxidant	Small molecule	—	Pre-clinical
Muscle ischemia				
Sildenafil	PDE5 inhibitor	Small molecule	Oral	Phase I/ II
L-Arginine	Metabolic support	Recombinant proteins	Oral	Phase I
Tadalafil	PDE5 inhibitor	Small molecule	Oral	Phase III (Terminated)
Muscle atrophy				
GLPG0492	β2-Agonist, increases cAMP	Small molecule	Oral	Phase I
Urocortin	Increases cAMP	Ca^{2+}-independent phospholipase A2 type β	—	Pre-clinical
rAAV1.CMV.huFollistatin344	Delivery of follistatin using adeno-associated virus	AAV1-Follistatin	Intramuscular	Phase I/II
Bone homeostasis				
Zoledronic acid	Inhibits bone resorption	Small molecule	Intravenous	Phase III
Alendronate (ALN)	Improves bone mineral density	Small molecule	—	Pre-clinical