The Journal of Frailty & Aging

SPECIAL ARTICLE

DEVELOPMENT OF PHARMACOTHERAPIES FOR THE TREATMENT OF SARCOPENIA

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Abstract: Sarcopenia, the associated loss of skeletal muscle mass and strength and impaired physical function seen with aging, is a growing, global public health challenge in need of accepted, proven treatments that address the needs of a broad range of older adults. While exercise, primarily resistance training, and increased dietary protein have been shown to delay and even reverse losses in muscle mass, strength and physical function seen with aging, proven treatments that are accessible globally, cost effective and sustainable by patients are needed. While no drug has yet demonstrated the substantial safety and clinical value needed to be the first pharmacological therapy registered for muscle wasting or sarcopenia, the field is active. Several approaches to treating the muscle loss and subsequent functional decline are being studied in a variety of patient populations across every continent. We provide a review of the leading programs and approaches and available findings from recent studies. In addition, we briefly discuss several related issues needed to facilitate the development of a safe and efficacious pharmacotherapeutic that could be used as part of a treatment plan for older men and women with sarcopenia.

Key words: Sarcopenia, skeletal muscle, aging, functional impairment, pharmacotherapy.

J Frailty Aging 2019;in press
Published online April 30, 2019, http://dx.doi.org/10.14283/jfa.2019.11

Introduction

Sarcopenia is the age-associated loss of muscle mass and function that result in impaired muscle strength and power, adversely impacting an older persons' functional capability. The results are typically seen as slowed walking speed and difficulty with basic movements of daily life such as rising from a seated position, climbing stairs and continuous walking. The physical consequences of sarcopenia put a person at risk for falls and fractures, hospitalization, loss of independent living and death (1, 2). The etiology of sarcopenia is a constellation of factors involving the aging neuromuscular machinery (motor unit number and efficiency, muscle architecture and orientation, fiber type distribution, excitation-contraction coupling), reduced anabolic hormone levels, muscle disuse, and inflammation, driven by environmental, genetic and behavioral factors, and is still being clarified (3-5). Even with a known etiology, the loss of muscle mass and function is commonly viewed as "normal aging" in many places. The rapid aging of societies and the increasing effectiveness of technology to engineer muscle work out of daily life, make sarcopenia a growing global public health concern that requires proven, accessible, cost effective and sustainable approaches to its prevention, delay, treatment and reversal (6-9).

Treatments for sarcopenia have focused mostly on extrinsic approaches such as exercise and diet, but recent scientific advances have brought greater attention to additional treatment options. There is a substantial body of literature demonstrating the benefits of exercise, primarily resistance training, and physical activity on muscle mass, strength and function in older adults of various levels of baseline physical function (10-14). These studies demonstrate the plasticity of the neuromotor system to adapt to external stress, even into the tenth decade of life, and the transfer of increased muscle function to the improvement of a person's physical capacity (15-17). Similarly, data showing the efficacy of increased dietary protein and other nutrients to support healthy aging and the maintenance of physical function have led to revised dietary recommendations for protein and other nutrients in older people (18-20). Despite these advances and increased public awareness, the widespread adoption of increased exercise, physical activity or healthier eating by older adults generally has been insufficient (21-24). The topics of exercise and nutrition for improved health and function and as contributors to and potential treatment for sarcopenia in older adults have been reviewed recently (3, 25-27).

Advances in understanding of the biology associated with aging, muscle wasting and sarcopenia provide potential targets for drug discovery and are being pursued by the pharmaceutical and biotech industries and academia (28-30). This review briefly summarizes the definition of sarcopenia, commonly used assessments and preclinical studies and clinical trial findings of the more advanced drug development programs for the treatment of muscle wasting, including for sarcopenia. In addition, we discuss several related issues that are needed to facilitate the development of a safe and efficacious pharmacotherapeutic that could be used as part of a treatment plan for older men and women with sarcopenia.

Received October31, 2018
Accepted for publication January 19, 2019

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Sarcopenia

In 1989, Irwin Rosenberg introduced the term "sarcopenia", to describe the age-associated loss of skeletal muscle mass (31). In the past decade, the operational definition has evolved to include an estimate of total or appendicular muscle mass normalized to body size concurrent with impaired physical function, seen as muscle strength (e.g., isometric handgrip strength) and usual gait speed, with a focus on the individual's quality of life and risk of adverse health events (32-36). Recently, the most widely referenced definition for sarcopenia was updated (37). Of note is the prioritization of muscle weakness as the primary determinant of the diagnosis, based on the view that strength is an important characteristic of the muscle disease, can be measured easily and reliably in the clinic, and is a better predictor of adverse health outcomes than low muscle mass. Low lean mass is used to confirm sarcopenia and distinguish it from other causes of muscle weakness, while gait speed and other measures of performance are used to indicate disease severity. Several cutoff points were modified and new ones added. In addition, age is acknowledged as one of many possible causes of sarcopenia and symptoms could begin before older age (37). Table 1 details the criteria and cutoffs for the various consensus statements. The most advanced operational definition of sarcopenia is being evaluated in the ongoing Innovative Medicines Initiative SPRINTT (Sarcopenia & Physical fRailty IN older people: multi-componenT Treatment strategies) study, which was approved by the European Medicines Agency (38). While no universal definition for sarcopenia exists, the consensus statements provide adequate guidance to identify a sufficiently homogeneous population of older adults with lower than average lean mass and reduced muscle function and physical performance.

Moving beyond aging as the primary cause of sarcopenia, cutoff points for these criteria are being applied to a broad range of populations. This use allows prevalence estimates to be established while considering racial, ethnic and geographical differences (36, 39-44). Increasingly, the term sarcopenia has been used to describe the loss of skeletal muscle mass and function associated with various diseases (45). The range of illnesses include cancer (46), cirrhosis (47), chronic obstructive pulmonary diseases (48), peripheral arterial disease (49), post stroke (50), and heart failure (51), and in those undergoing organ transplant (52) and recovering from hip fracture (53).

Sarcopenia results in mobility disability in approximately 2-5% of older adults (54). Loss of skeletal muscle mass and strength are common consequences of many chronic diseases, of hospitalizations and bedrest, and of normal aging; and are strongly associated with morbidity, mobility impairment, loss of independence, lower quality of life and death (2, 54, 55, 56, 57). Currently, there is no standard, scalable treatment for this loss of skeletal muscle mass, strength, and function seen with aging or other causes.

Determining the occurrence of sarcopenia in a population depends on the definition used, the country or geographical region and the method of assessing lean body mass, a proxy for quantifying skeletal muscle (1, 40, 41, 58-60). Of the three criteria common among the definitions – quantity of muscle for body size, strength and gait speed – total or appendicular lean body mass has the greatest impact on prevalence (1, 61). Moreover, the method of body composition measurement – dual X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA) – affects prevalence even further. Considering the differences between calculations and the range of ages in the various cohorts, current prevalence estimates of low muscle mass range from 1-29% in community-dwelling populations, 14-33% in long-term care populations and approximately 10% in acute care inpatients (1, 40, 41, 59, 60, 62).

In 2016, an ICD-10-CM (International Statistical Classification of Diseases and Related Health Problems, revision 10, clinical modifications) code was introduced for sarcopenia, which acknowledged it as a disease for the first time (63). Recommendations for clinical practice and clinical trials have promoted discussions and knowledge sharing to advance both areas important to developing a proven care plan for this growing patient population (8, 9, 64-66). A universally accepted definition for sarcopenia would facilitate the development of drug treatment for this patient population.

Clinical outcome assessments

No endpoint has been approved for the registration of a drug for sarcopenia or other muscle wasting condition, but health authorities are moving closer to accepting physical performance-based and patient-reported outcome assessments for use in drug trials (67-70). Several measures of physical performance have been validated in older adults (71, 72) and proposed as viable endpoints to assess intrinsic capacity as part of a comprehensive evaluation of health (9, 73, 74). Muscle strength, chair rise ability and gait speed assessment can predict mobility limitation (75-78) and their inclusion could move the field closer to universally accepted assessments of a person's physical capability – the ultimate clinical goal.

The Short Physical Performance Battery (SPPB) is a series of tasks involving three domains of physical function – static balance, usual walking speed and rising from a chair – used globally to assess and quantify lower extremity function (79). Each section is scored 0-4 based on performance and summed for a total score of 0-12 with a minimum clinically important difference (MCID) of 1 point. Created and introduced in longitudinal aging studies in the United States in the 1970's, a substantial body of literature on SPPB performance is available, documenting test-retest reliability (73); construct validity (79, 80); predictive validity for mortality (79, 81), incident disability (77, 82), institutionalization and hospitalization (73, 79), functional decline after hospital discharge (83); and sensitivity to clinically important change (72, 80, 84). The SPPB has been

Table 1
Summary of key published criteria and cut-offs for defining sarcopenia

Consensus statement	Definition/diagnosis criteria	Lean mass	Mobility/ Performance	Grip strength
European Working Group for Sarcopenia in Older People (EWGSOP) (32)	Low muscle mass plus low muscle strength or gait speed	ASMI: Men ≤7.26 Women ≤5.5	Gait speed <0.8 m/s	Men <30 kg Women <20 kg
EWGSOP2 (37)	Low muscle strength plus low muscle quantity or quality; Severe disease includes low physical performance	ASMI: Men <7.0 Women <6.0	Gait speed ≤0.8 m/s (preferred); SPPB ≤8 points; TUG ≥20 seconds; 400 m walk ≥6 min to complete	Men <27 kg Women <16 kg
Asian Working Group for Sarcopenia (35)	ASMI plus gait speed or grip strength	ASMI: Men ≤7.0 Women ≤5.4	Gait speed <0.8 m/s	Men <26 kg Women <18 kg
International Working Group (34)	ASMI plus gait speed	ASMI: Men ≤7.23 Women ≤5.67	Gait speed <1.0 m/s	
Sarcopenia with mobility limitation (54)	ASMI plus gait speed or 6MWD	ASMI < 2 SD of healthy persons ages 20-30 years	Gait speed ≤1.0 m/s or 6MWD <400 m	
FNIH (36)	Appendicular lean mass/BMI plus grip strength	Appendicular lean mass (kg)/ BMI Men <0.789 Women <0.512		Men <26 kg Women <16 kg

ASMI –appendicular skeletal muscle index (appendicular lean mass (kg)/height (m2)) by dual X-ray absorptiometry; 6MWD – Six-minute walk distance; SPPB – Short Physical Performance Battery; TUG – Timed Up and Go test; FNIH – Foundation for the National Institutes of Health; BMI – body weight (kg)/height (m2);

translated into multiple languages in Europe and Asia and has been administered throughout the world with no known serious adverse consequences. The SPPB has been used as the primary (85, 86) and key secondary (14) outcome in a number of randomized clinical trials involving lower extremity musculoskeletal function and mobility of older adults.

Gait speed or usual walking speed is easy to evaluate in both clinical and research environments, is commonly included in comprehensive geriatric care in many countries and has been called the "5th vital sign" (73, 74, 87, 88). There is a substantial body of epidemiological and intervention-based literature demonstrating a strong association between decreased gait speed (≥ 0.1 m/s) and future adverse physical, psychological and cognitive status, and health outcomes including falls, hospitalizations, mobility disability and death (89-91). Gait speeds of <0.8 m/s and <1.0 m/s over four meters have been recommended to identify older adults at increased risk of functional decline, mobility impairment and adverse health events (32, 34-36, 54, 58).

Skeletal muscle weakness is commonly seen with aging and a reduction in skeletal muscle mass, and correlates with mobility disability and other adverse health outcomes (12, 36, 92). Lower muscle strength, including when assessed by handgrip, is associated with higher risks for falling, chronic disease, impaired mobility and disability (57, 75, 93). Proposed in most consensus statements, grip strength is easy to administer, perform and interpret, does not require motor learning and is relatively inexpensive (32-35, 37, 76). However, as an isometric test, it is not necessarily a reflection of muscle function in the real world, but rather a somewhat artificial construct that gains measurement precision at the cost of direct applicability to daily functional activities. However, the recent focus on muscle weakness as a key characteristic of sarcopenia (37) makes it important to provide a clinic based tool; thus, isometric muscle strength assessed by handgrip dynamometry is being recommended more often.

Looking ahead, digital technologies such as wearable sensors, mobile applications and connected devices, that quantify mobility and other related behaviors and capabilities relevant to patients during daily life, will allow objective evidence to be used to better understand the impact a drug or other intervention has on patients' quality of life (94, 95).

The identification of approved trial endpoints will guide drug development to use relevant assessments that can be compared across treatments (66-68, 96) and answer several critical questions: What is clinically important improvement in a patient with sarcopenia? What domains of physical function are important to patients' quality of life? And, how much improvement in a given parameter is clinically meaningful? Until a standardized set of assessments are

Table 2
Overview of trials evaluating new drugs for sarcopenia and muscle wasting*

Mechanism of action	Drug	Sponsor/ Company	Indications and associated trials	Stage of development
Activin receptor antagonist	Bimagrumab (BYM338)	Novartis	Sarcopenia (NCT02333331);	Phase 2
			Hip fracture recovery (NCT02152761);	Phase 2
			Obesity in type 2 diabetes (NCT03005288)	Phase 2
Myostatin or activin inhibitor	Trevogrumab (REGN1033) and REGN2477	Regeneron	Healthy volunteers (NCT02943239)	Phase 1
	Domagrozumab (PF-06252616)	Pfizer	Duchenne's muscular dystrophy (NCT02310763; NCT02907619)	Phase 2
			Limb girdle muscular dystrophy 2I (NCT02841267)	Phase 2
	BMS-986089	Hoffman-LaRoche	Duchenne's muscular dystrophy (NCT03039686)	Phase 2
	ACE-083	Acceleron	Fascioscapulohumeral dystrophy (NCT02927080)	Phase 2
			Charcot-Marie-Tooth disease (NCT03124459)	
	ACE-2494	Acceleron	Healthy volunteers (NCT03478319)	Phase 1
Selective androgen receptor modulator (SARM)	Enobasarm (GTx-024)	GTx	Stress urinary incontinence (NCT03241342)	Phase 2
			Androgen receptor positive metastatic triple negative breast cancer (NCT02971761)	
	LY2452473	Eli Lilly	Prostate cancer (NCT02499497)	Phase 2
	GSK2881078	GlaxoSmithKline	COPD cachexia (NCT03359473)	Phase 2
	Ligandrol (LGD-4033/ VK5211)	Viking Therapeutics	Hip fracture (NCT02578095)	Phase 2
Troponin activator of fast skeletal muscle	Reldesemtiv (CK-2127107)	Astella Pharma and Cytokinetics	Mobility limitation (NCT03065959)	Phase 1b
			COPD (NCT02662582)	Phase 2
Other	BIO101	Biophytis	Sarcopenia (NCT03452488)	Phase 2

* listed in clinicaltrials.gov as of 1 Jan 2019

approved, established tests of physical function and associated MCIDs will be used in drug development trials. Findings from intervention trials in sarcopenia and from longitudinal studies where adults meeting the criteria for sarcopenia can be identified may provide a more accurate, clinically relevant MCID. Collaboration between health authorities, academia and industry will move the field closer to standardized clinical outcome assessments (70).

Drugs to counter muscle loss

In the past 10 years, significant efforts have been made in the area of developing a pharmacotherapeutic to treat age- and muscle-related loss of physical function. These approaches include the potential expanded use of available drugs registered for other conditions (3, 97, 98), and to a greater extent the development of new molecular entities (Table 2).

The majority of first generation muscle drugs being developed act directly on the main defining characteristic of sarcopenia – the loss of muscle mass. However, drug-induced hypertrophy alone is insufficient as a treatment, unless

Table 3
Overview of active trials evaluating diet, exercise or combination interventions for sarcopenia and muscle wasting*

Approach	Intervention	Lead location of trial	Indications and associated trials
Diet	Oral supplement	Instituto Santa Margharita –Azienda di Servizi alla Persona di Pavia	Sarcopenia rehabilitation (NCT02333331)
	Dietary supplement	Indiana University, US	Sarcopenia (NCT03513302)
	Omega-3-FA	University Sao Paulo, Brazil	Sarcopenia (NCT03462771)
	Vitamin D	Tufts University, US	Sarcopenia with low Vitamin D (NCT02293187)
	Leucine and essential amino acids	The Cleveland Clinic, US	Liver cirrhosis (NCT03208868)
Exercise	High intensity interval training (HIIT)	University of Nottingham, UK	Frailty (NCT03138265)
	Home exercise	University of California, San Francisco, US	Sarcopenia in liver transplant patients (NCT02367092)
Combination treatments	Exercise and protein supplementation	University of Zurich, Switzerland	Sarcopenia (NCT03417531)
	Exercise, protein supplementation, electrical stimulation	University of Maryland, US	Sarcopenia in ICU patients (NCT02509520)
	High velocity resistance training plus creatine supplementation	University of Regina, Canada	Sarcopenia (NCT03530202)
	HMB plus Vitamin D with and without exercise†	Metabolic Technologies, Inc.	Sarcopenia (NCT02043171)
	Aerobic exercise and caloric restriction	Translational Research Institute for Metabolism and Diabetes, Florida, US	Sarcopenia and insulin resistance (NCT02230839)
	Protein supplement with exercise	Copenhagen University Hospital, Herlev, Denmark	Sarcopenia (NCT02717819)
	Whey protein with and without exercise	Coventry University, UK	Sarcopenia (NCT03299972)
	Supervised exercise with testosterone	Washington University School of Medicine, St. Louis, US	Hip fracture, frailty and sarcopenia (NCT02938923)
	Resistance training with testosterone	University of Nottingham, UK	Sarcopenia (NCT03054168)
	Strength training and protein supplementation	University of Vienna, Austria	Aging (NCT01775111)

* listed in clinicaltrials.gov as of 1 Jan 2019; † HMB = β-Hydroxy β-Methylbutyrate

it translates into an increase in muscle strength and improved patient function. The new field has explored various biological pathways and targets and numerous approaches, including small molecules and biologics. To date, results from trials have shown a range of measurable changes in muscle mass, with less success for improving muscle strength or patient physical function. Observed safety concerns or a lack of sufficient efficacy has thinned the early field of drug candidates; several are in phase II for efficacy and dose range finding.

Selective androgen receptor modulators

Selective androgen receptor modulators (SARMs) are a class of drug that controls the activity of the androgen receptor and are designed to selectively stimulate anabolic effects on skeletal muscle and other tissues (i.e., bone), without the adverse androgenic effects on liver, heart and prostate (99). SARMs have demonstrated efficacy in recovery of skeletal muscle in several preclinical models of muscle wasting, including corticosteroids and hypogonadism (99, 100). Clinically, results have shown moderate increases in lean body mass of adults with sarcopenia and in healthy older adults, without a concomitant increase in strength or improvement in physical function. In a cohort of 170 older women who met the definition of sarcopenia, 6-months' exposure to MK-0773 (Merck, Kenilworth, New Jersey) resulted in a statistically significant increase of approximately 0.6 kg of appendicular lean body mass over placebo at 3- and 6-months, but did not improve muscle strength or physical performance (assessed by the SPPB, stair climb test and gait speed) compared to placebo (101).

In a 12-week study with 120 healthy men and women over the age of 60 years, 3 mg GTx-024 (enobosarm; GTx, Memphis, Tennessee) resulted in a statistically significant mean increase of 1.3 kg (~3%) of total lean body mass and decrease of 0.6 kg body fat (102). A corresponding statistical improvement in stair climb time observed in the GTx-024 group was not clinically meaningful. Both studies reported

the drugs were well tolerated with a small number of adverse events, including elevated transaminase levels that resolved with discontinuation of the drug. Despite a positive proof of concept trial in women with stress urinary incontinence (NCT03241342), GTx-024 did not sufficiently improve outcomes in the extended study with that population (GTx-024; NCT03566290) (clinicaltrials.gov). Currently, SARMs are being evaluated for safety and efficacy in patients with hip fracture (VK5211/LGD-4033/ligandrol; NCT02578095), COPD (GSK2881078; NCT03359473), post radical prostatectomy for prostate cancer (LY2452473; NCT02499497) and in combination treatment for androgen receptor positive triple negative breast cancer (GTx-024; NCT02971761) (Table 2).

Myostatin, activin and ActRII pathway antagonists

The targets for new drugs that have received the most attention are those in the myostatin-activin pathway. Several members of the transforming growth factor beta (TGF-β) superfamily of secreted proteins, including myostatin (growth and differentiation factor 8; GDF8), activin A, and GDF11, negatively regulate skeletal muscle mass in animals and humans throughout the lifecycle (103-106). Ligand signaling occurs via activin receptors, which are heterodimers of a type I receptor (ALK4 or ALK5) and a type II receptor (ActRIIA or ActRIIB); the resulting signal is transduced and activates the Smad 2/3 pathway. These signals inhibit muscle protein synthesis and myocyte differentiation and proliferation (107, 108). The absence of any of these ligands in developing animals and humans results in a hypermuscular phenotype with an increased number and size of muscle fibers (107, 109, 110). Postpartum blockade of myostatin activity in animals and humans by either direct action on the ligand (111-115) or receptor antagonism (108, 109, 116, 117) is associated with varying degrees of muscle hypertrophy, and less frequently with clinically meaningful improvement in physical function (117).

Three approaches have been explored to drug this pathway. Initially, a soluble decoy ActRIIb receptor (ACE-031; Acceleron, Cambridge, MA) demonstrated a substantial increase in skeletal muscle mass through hypertrophy of both type I and II fibers in mice (118) and subsequently in thigh muscle volume in humans (119). The single ascending dose study was in effect a proof of concept demonstrating that the skeletal muscle effects seen in mice were translatable to humans. A single dose of ACE-031 in healthy postmenopausal women 45-75 years of age resulted in mean increases in thigh muscle volume (TMV) assessed via MRI of 3.7% and 5.3% over placebo at day 29 with 1 mg and 3 mg doses, respectively. A decrease in total fat mass (assessed by DXA) was seen in the 3 mg dose level. The mechanism of action of ACE-031 caused a reduction of follicle stimulating hormone (FSH) secretion through the inhibition of activin on stimulating FSH release. This effect on FSH is also seen with other drugs perturbing the myostatin-ActRII pathway. The ACE-031 program was stopped following the discontinuation of a study in boys with Duchenne's muscular dystrophy due to the occurrence of epistaxis and telangiectasias (120), thought to be an effect of the drug on other members of the TGF- β superfamily (e.g., BMP9 and BMP10), rather than on activin or myostatin. A follow-up program using a similar approach (decoy receptor to myostatin, activins A and B and GDF-11) is examining the effectiveness of a recombinant fusion protein of modified human follistatin (ACE-083). However, rather than acting systemically, the antibody is designed to act locally and injected directly into a muscle. Studies in wild-type (121) and mdx mice (122) showed localized increases in muscle volume and isometric strength. The first in human study in healthy postmenopausal women showed peak volume increases of 14.5% and 8.9% in the rectus femoris and tibialis anterior muscles, respectively, with no changes in strength (123). ACE-083 is being studied in patients with facioscapulohumeral muscular dystrophy (NCT02927080) and Charcot–Marie–Tooth disease (NCT03124459). Also using a ligand trap approach, ACE-2494 is being studied in healthy volunteers (NCT03478319).

The second and most common approach to stimulating muscle growth via the myostatin-activin pathway has been by targeting the individual ligands, primarily myostatin. Early programs with the myostatin antibody MYO-029 (Wyeth, New York, NY) (124) and anti-myostatin peptibody AMG745 (Amgen; Thousand Oaks, CA) (125) showed an increase in skeletal muscle mass in preclinical studies, but were discontinued due to a lack of sufficient clinical efficacy. PF-06252616 (domagrozumab, Pfizer, New York, NY) a humanized anti-myostatin antibody and its murine analog mRK35, has shown to increase skeletal muscle mass and body weight in cynomolgous monkeys and mice, including the mdx mouse (115). Data from the first-in-human, single ascending and multiple dose study showed increases in total body lean mass by DXA of 2.50%, 5.38% and 3.33% at 15, 29 and 57 days, respectively, following a single 10 mg/kg dose (112). Notable lean mass changes were not seen with lower or higher dose levels. Three doses of 10 mg/kg resulted in a mean difference in thigh muscle volume assessed by MRI of 4.49% from placebo at Day 113 (NCT01616277). Phase II studies in Duchenne's muscular dystrophy and limb girdle muscular dystrophy 2I are ongoing (NCT02310763; NCT02907619; NCT02841267).

LY2495655 (landogrozumab; Lilly, Indianapolis, IN), another humanized monoclonal antibody to myostatin, was evaluated in a group of 201 elderly men and women 75 years and older with a history of at least one fall in the past 12 months and low grip strength and chair rise performance (111). Following 24 weeks of chronic exposure, individuals receiving the antibody saw an increase in appendicular lean body mass (aLBM) of 0.43 kg compared to placebo (+0.303 kg vs. -0.123 kg). No clinically meaningful treatment-associated improvements were seen in muscle strength, usual gait speed or 6-minute walk distance. In a second study with a cohort of men

and women ≥50 years of age who were scheduled for elective total hip arthroplasty due to osteoarthritis, 12 weeks of exposure to LY2495655 resulted in an increase in aLBM compared to placebo of less than 2.5% at 8 weeks of exposure (126). No meaningful difference in muscle strength, physical performance or self-reported measures of physical function compared to placebo was reported.

Taking a similar approach, REGN1033/SAR391786 (trevogrumab, Regeneron Pharmaceuticals Inc., Tarrytown, NY) is a human monoclonal antibody targeting myostatin. In vivo, REGN1033 demonstrated the ability to increase muscle size by increasing fiber cross-sectional area resulting in improved maximum isometric force production (strength) in young and aged mice (113). Dosing before and during hind-limb suspension (7-days) and during and after 14-days of casting or dexamethasone administration resulted in the prevention of muscle loss and enhanced recovery of muscle mass in mice compared to placebo. In addition, muscle hypertrophy and improved endurance running in old mice was observed without exercise training. REGN1033 was evaluated for safety and efficacy in 253 sarcopenic older adults (NCT01963598) (127). Twelve weeks of exposure to three dose levels of REGN1033 (100 mg and 300 mg monthly and 300 mg every two weeks) resulted in increases in lean body mass with all doses (1.2%-1.8% vs. -0.5% PBO; $p<0.05$) and a decrease in total fat mass in the high dose (-2.67% vs. -0.08%) in men and women 70 years and older. Modest, inconsistent, non-significant improvements were seen in strength and function (127).

Activin A, another ligand that signals through the ActRII, has recently been proposed to have a greater effect on regulating muscle mass in primates than myostatin (113). In a recent phase I study (NCT02943239), 48 healthy postmenopausal women received a single dose of either placebo, the anti-myostatin antibody (REGN1033), an anti-activin antibody (REGN2477; garetosmab), or one of three dose levels of the combination of the two antibodies (128). Findings reported at the 2018 International Conference on Frailty and Sarcopenia Research showed that inhibiting the action of both myostatin and activin A with the two antibodies resulted in a dose dependent increase in TMV and aLBM. The group receiving the highest dose level of the combination treatment showed an increase from baseline at 8 weeks of 7.73% compared to 0.88%, 2.85% and 4.85% in the groups receiving placebo, REGN2477 and REGN1033, respectively. A reduction in total fat mass was also seen in the high dose combination group.

The above anti-myostatin antibodies work by blocking the interaction of mature myostatin with its receptor. Recently, a different approach was reported that uses human monoclonal antibodies to selectively bind to the precursor (pro- and latent) forms of myostatin inhibiting the proteolytic steps required for extracellular activation of the growth factor (129). Data with SRK-015 (Scholar Rock, Cambridge, MA) in a mouse model, reported a 27% increase in total cross sectional area and a 20% increase in mean cross sectional area of type IIB fibers of the plantar flexor. Given concurrently with dexamethasone, the antibody attenuated the drug-induced atrophy of skeletal muscle in the mice.

Receptor blockade is the third treatment strategy being explored to perturb the myostatin-ActRII pathway. BYM338 (bimagrumab, Novartis, Basel, Switzerland) is a human, monoclonal antibody to both ActRIIA and ActRIIB that prevents ligand binding to the receptor and promotes differentiation of human myoblasts by inhibiting downstream phosphorylation of Smad 2/3 (108). The affinity for both receptor types enhances the drug's efficacy (109). Bimagrumab increased body weight and muscle size in mice by expanding myofiber cross section in slow, fast and mixed fiber type muscles in a dose dependent manner. The effectiveness of blocking all ligand activity at the ActRII vs. inhibiting myostatin alone was evaluated two ways in vivo. A mouse version of the bimagrumab antibody (CDD866) was compared to a myostatin inhibitor and resulted in greater increases in body weight (36% vs. 15%) due to muscle hypertrophy. Subsequently, CDD866 administration to both wild type and myostatin mutant mice, resulted in increased body weight, lean body mass and muscle weight in both groups, confirming that inhibiting multiple ligands of the ActRII with bimagrumab could induce greater hypertrophy than blocking myostatin alone (108). In addition, CDD866 prevented muscle loss and maintained isometric muscle strength in dexamethasone-induced atrophy (unpublished results).

In humans, bimagrumab has demonstrated consistent increases in total lean body mass and concomitant decreases of fat mass in healthy volunteers and those with insulin resistance (+1.6-2.0 kg LBM and -0.97 to -2.3 kg fat mass with 8-10 weeks of exposure) (129) and expedites the recovery of skeletal muscle volume following 14-days in a cast (116). Concomitant with the body composition changes in adults with insulin resistance, a single dose of bimagrumab resulted in a reduction of HbA1c (-0.21%) and improvement in insulin sensitivity of 20-40% (130). The mechanism of action of bimagrumab results in suppression of FSH secretion in women that is reversible with drug discontinuation (130). Other than FSH, exposure to bimagrumab results in no clinically relevant effects on the pituitary-gonadal or pituitary-adrenal axes in either men or women.

To date, the only trial with bimagrumab to see an increase in skeletal muscle mass translate to improved patient function was in a proof of concept study in older adults with sarcopenia. Participants administered bimagrumab, saw significant increases in TMV of 7.72% to 8.01% and total LBM of 5.2% to 6.0% (1.8 kg – 2.0 kg) with a corresponding decrease in total fat mass of -1.5 to -3.0 kg with 8 to 16 weeks of exposure. In patients with gait speeds <0.8 m/s at baseline, gains in lean mass seen with bimagrumab translated to clinically meaningful improvements in usual gait speed (+0.15 m/s) and six-minute

walk distance (+82 m) over placebo at 16 weeks, with an improvement in distance walked (+66 m) seen at 24 weeks (117). In patients with sporadic inclusion body myositis, an increase in muscle mass with bimagrumab treatment did not sufficiently improve patient function and the program was discontinued in this disease (NCT01925209; clinicaltrials.gov). Three phase II studies are ongoing in sarcopenia (NCT02333331), hip fracture recovery (NCT02152761) and obesity in type II diabetes (NCT03005288).

Other pharmacological approaches

CK-2127107 (reldesemtiv; Cytokinetics, San Francisco) is a selective fast skeletal muscle troponin activator (FSTA) designed to increase the force of contraction of type II (fast) muscle fibers. CK-2127107 and its predecessor (tirasemtiv; CK-2017357) act by increasing the sensitivity of fast skeletal muscle fibers to calcium by extending the time calcium is bound to the troponin complex, resulting in greater force production with submaximal nerve stimulation. This approach has been explored in several neuromuscular disease populations and is currently in phase 3 with tirasemtiv in patients with amyotrophic lateral sclerosis (ALS) (NCT02496767). Data on CK-2127107, a second generation FSTA, showed sufficient safety, tolerability, pharmacokinetics and initial pharmacodynamics in healthy volunteers (131) and is being studied in patients with spinal muscular atrophy (NCT02644668), ALS (NCT03160898), chronic obstructive pulmonary disease (NCT02662582) and in older adults with limited mobility (NCT03065959).

BIO101 (Sarconeos; Biophytis, Paris) is an oral medication based on the active ingredient 20-hydroxyecdysone (20E), which is an extract from the herb Stemmacantha carthamoides (Maral root). A phase II trial to evaluate safety and efficacy of six-months of exposure to BIO101 is ongoing in community-dwelling men and women with sarcopenia and sarcopenic obesity 65 years of age and older at risk for mobility disability (NCT03452488).

Conclusion

Sarcopenia is a growing socio-economic burden due to the ongoing demographic shift and the aging of most societies, with no viable treatment to meet the global need. While not yet successful in leading to an approved drug, significant progress has been made in the past 10 years to develop drugs for treating age- and muscle-related loss of physical function. The first generation of muscle drugs directly address the original defining characteristic of sarcopenia – the loss of muscle mass – with the expectation that a resulting muscle hypertrophy would translate to an increase in muscle strength and improved patient function. This translation of muscle mass to improved patient function remains the major challenge for current experimental drugs that target skeletal muscle anabolism. To date, results from trials have shown a range of measurable muscle hypertrophy, with limited success for improving muscle strength or patient physical function. The new field is exploring various pathways, targets and mechanisms of action based on the evolving science around skeletal muscle biology. Drug development focuses on new molecular entities and novel biology. While observed safety concerns or a lack of sufficient efficacy has thinned the early field, several drug candidates are in phase II to evaluate efficacy and dose range finding for numerous conditions with associated muscle wasting, including sarcopenia. The next generation of drugs to improve physical function will likely target muscle function directly, with less or no effect on muscle mass, which would align well with strength and patient function based diagnostic criteria for sarcopenia. Currently, available study findings hold out hope that phase III studies with drugs for the treatment of sarcopenia will begin within the next few years. As with the consensus statements defining sarcopenia, collaboration among drug development organizations and other industries, academic experts, patient advocacy groups, and health authorities will drive progress in the field of understanding the pathophysiology, medical and societal consequences and effective interventions for sarcopenia, including where a pharmacotherapeutic would be most beneficial to patients.

Conflict of interest: Both authors are full-time employees of Novartis Institutes for BioMedical Research.

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