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Workshop Summary

Public Health Need, Molecular Targets, and Opportunities for the Accelerated Development of Function-Promoting Therapies: Proceedings of a National Institute on Aging Workshop

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Abstract

Background: People ≥ 65 years are expected to live a substantial portion of their remaining lives with a limiting physical condition and the numbers of affected individuals will increase substantially due to the growth of the population of older adults worldwide. The age-related loss of muscle mass, strength, and function is associated with an increased risk of physical disabilities, falls, loss of independence, metabolic disorders, and mortality. The development of function-promoting therapies to prevent and treat age-related skeletal muscle functional limitations is a pressing public health problem.

Methods: On March 20–22, 2022, the National Institute on Aging (NIA) held a workshop entitled "Development of Function-Promoting Therapies: Public Health Need, Molecular Targets, and Drug Development."

Results: The workshop covered a variety of topics including advances in muscle biology, novel candidate molecules, findings from randomized trials, and challenges in the design of clinical trials and regulatory approval of function-promoting therapies. Leading academic investigators, representatives from the National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA), professional societies, pharmaceutical industry, and patient advocacy organizations shared research findings and identified research gaps and strategies to advance the development of function-promoting therapies. A diverse audience of 397 national and international professionals attended the conference.

Conclusions: Function-promoting therapies to prevent and treat physical disabilities associated with aging and chronic diseases are a public health imperative. Appropriately powered, well-designed clinical trials and synergistic collaboration among academic experts, patients and stakeholders, the NIH and the FDA, and the pharmaceutical industry are needed to accelerate the development of function-promoting therapies.

Keywords: Age-related muscle dysfunction, Clinical performance, Functional decline, Mobility disability, Sarcopenia, Skeletal muscle function deficit

People ≥ 65 years are expected to live a substantial portion of their remaining lives with a limiting physical condition. The numbers of older adults living with a physical disability are expected to increase substantially due to the growth of the population of older adults worldwide. The age-related loss of muscle mass, strength, and function is associated with an increased risk of mobility limitations, falls and fractures, loss of independence, disability, metabolic disorders, and mortality ([1],[2]). Recognizing the public health importance of developing effective interventions to prevent, delay, or reverse the age-related functional limitations, the National Institute on Aging (NIA), National Institutes of Health (NIH) U.S. Department of Health and Human Services (HHS) held a workshop on March 20–22, 2022, entitled "Development of Function-Promoting Therapies: Public Health Need, Molecular Targets, and Drug Development."

A diverse group of experts, including academic investigators, representatives from NIH and the U.S. Food and Drug Administration (FDA), professional societies, pharmaceutical industry, and patient advocacy organizations, shared current knowledge and perspectives on how to advance development of function-promoting therapies. A global audience of 397 professionals attended the workshop.

Speakers and discussants reviewed the urgent public health need for function-promoting therapies; advances in muscle biology, molecular targets, and candidate strategies; findings of preclinical studies and efficacy trials; critical issues in the design of efficacy trials; and strategies for accelerating the drug development process. Lessons learned from the successful Operation Warp Speed for coronavirus disease 2019 (COVID-19) Vaccine Development and from oncology drug development programs offer insights that can facilitate strategic planning to accelerate the development of function-promoting drugs. This review offers a synopsis of the topics presented at the workshop and its recommendations; a complete compendium of 16 scientific papers describing in detail the topics presented and discussed at the workshop will be published in an upcoming special issue of the *Journal of Gerontology, Series A: Biological Sciences and Medical Sciences*.

Societal Impact of Aging-Related Functional Limitations: A Looming Public Health Crisis

By 2050, older adults will comprise nearly 20% of the world's population. Due to the increasing life expectancy (3) and the functional decline associated with advancing age (4), the number of older adults living with physical disabilities is expected to increase, profoundly influencing the need for health care resources. The functional limitations associated with aging affect the ability of older adults to live independently in the community, engage socially, and enjoy a meaningful quality of life. Physical activity is currently the only approach demonstrated to prevent disability, but the sustainability of physical activity interventions remains an issue (5). Therefore, function-promoting pharmacologic therapies that can enhance or recapitulate the benefits of physical activity are urgently needed to reduce the burden of physical disabilities and to forestall the looming public health crisis.

Pathobiology of Functional Limitations Associated With Aging and Chronic Disease

Remarkable advances in muscle biology have revealed attractive targets for drug development, some of which have advanced to clinical trials. The leading candidate molecules undergoing investigation are described below.

Neural Mechanisms of Age-Related Loss of Muscle Strength

Impairments in neural as well as muscle-specific mechanisms contribute to the age-related muscle weakness and mobility limitations. Aging is associated with alterations in neural mechanisms at multiple levels including supraspinal (reduced cortical excitability and arousal, dysfunction of dopaminergic neural circuits) (6,7); spinal cord (loss of functioning motor units, diminished motor neuron firing rates) (8); and neuromuscular junction (NMJ) (9). It is possible that failure of anabolic therapies to improve physical performance despite substantial increases in muscle mass may be related to their inability to induce neural adaptations necessary for integrated functions such as walking and stair climbing. An improved understanding of neural mechanisms that regulate complex physical functions can facilitate the identification of neurotherapeutic approaches to enhance muscle performance and physical function.

Muscle Regeneration in Aging

Studies in preclinical models have documented the loss of resident skeletal muscle stem cells and a reduction in their myogenic potential with aging (10,11). In response to muscle injury, these stem cells in young animals become activated to repair and fully restore damaged myofibers and muscles. However, the satellite cells number and myogenic potential decrease and regenerative response of skeletal muscle precursors following injury are attenuated with aging (11). In aged animals, muscle stem cells exhibit reduced capacity for proliferation, impairment of autophagy, and increased expression of aging-associated senescence markers. Pervasive STAT3 and p38a/β signaling and accumulation of $p16^{mk}$ in aged satellite cells lead to cell cycle exit and senescence (10). Extrinsic changes in the muscle microenvironment also contribute to an impaired regenerative response of aged muscle precursor cells. Skeletal muscles can be reprogrammed to return to a state that fosters restoration, repair, and improved muscle mass and function in old and in dystrophic mice. Pharmacologic agents, cell-based therapies, or a combination of both are being explored for the treatment of people with muscular dystrophies and those with age-related loss of muscle mass (12). It is still unclear whether such interventions will be efficacious as monotherapies or as components of interventions that target multiple pathways.

Mechanisms of Skeletal Muscle Atrophy

The mammalian target of rapamycin (mTOR) is known to control the anabolic and catabolic signaling of skeletal muscle mass, leading to modulation of muscle hypertrophy and atrophy. While anabolic agents that increase protein synthesis have been considered for treatment of sarcopenia, emerging evidence indicates that protein synthesis might be increased due to augmented mTOR complex 1 (mTORC1) activity (13). mTORC1 has been found to be hyperactivated in sarcopenia. Studies have shown that in certain muscles, partial suppression of the mTORC1 increased muscle mass and fiber type (cross-sectional area). The utilization of a low dose of a rapalog has been associated with downregulation of various senescence-linked genes and a reduction in gene expression markers of NMJ denervation. Ongoing efforts to partially suppress mTORC1 with rapamycin and other rapalogs aim to better understand these findings. It is thought that partial suppression of mTORC1 can directly or indirectly control many age-related pathways, likely deferring sarcopenia evolution, and opening a wide array of options for therapeutic targets against this condition. Additional studies are needed to identify age-related alterations in muscle's regenerative response to injury, and to characterize the skeletal muscle adaptations in response to acute atrophy and recovery from it in older animals. Strategies to target multiple pathways associated with inflammation, metabolic stress, and extracellular matrix remodeling are needed.

Pharmacologic Interventions to Prevent and Treat Age-Related Functional Limitations

Although androgens, selective androgen receptor modulators (SARMs), growth hormone (GH) and GH secretagogues (GHS), and inhibitors of myostatin and activins are the farthest along in clinical

development, several other pathways, such as the renin-angiotensin system, peroxisome proliferator activated receptor (PPAR) delta agonists, inflammatory pathways, orphan receptors, mitophagy, and mitochondrial function, also offer useful targets for drug development. There is heightened excitement about drugs that target mechanisms of aging, such as nicotinamide adenine dinucleotide (NAD) boosters, senolytics, and mTOR inhibitors that are in early clinical development. In general, muscle anabolic drugs such as androgens and SARMs have shown excellent safety profile and consistent improvements in muscle mass and strength. Further studies are needed to evaluate strategies such as functional exercise training that can facilitate translation of gains in muscle mass and strength into functional improvements.

Testosterone and Other Androgens

In randomized trials, testosterone treatment has been associated with consistent improvements in lean body mass, maximal voluntary strength, leg power, loaded stair climbing speed/power, and attenuation of the age-related decline in aerobic capacity in healthy older men and older men with chronic conditions and mobility limitation (14–17). Testosterone treatment also improves depressive symptoms, increases areal and volumetric bone mineral density and estimated bone strength, and corrects unexplained anemia in older men with low testosterone levels and 1 or more of sexual symptoms, mobility limitation, and low vitality (18–20). Self-reported physical function is enhanced by testosterone treatment, but randomized trials have not shown clinically relevant improvements in performance-based measures of physical function such as walking speed (21). Strategies to translate increases in testosterone-induced muscle mass and strength gains into functional improvements are needed. Large, adequately powered randomized trials of sufficiently long duration are needed to evaluate the efficacy of a combination therapy that includes testosterone plus multicomponent functional exercise training (22). Testosterone treatment of older men has been associated with relatively low frequency of adverse events in randomized trials; the long-term effects of testosterone on the incidence of major adverse cardiovascular events are being evaluated in a large, randomized trial in older adults with testosterone deficiency and increased risk of cardiovascular events (TRAVERSE Trial NCT03518034) (23).

Selective Androgen Receptor Modulators

SARMs are synthetic ligands that bind to androgen receptor and induce tissue-selective transcriptional activity whose development was motivated by a desire to improve the benefit-to-risk ratio of androgen therapy and spare the prostate. Many SARMs with improved muscle anabolic to prostate activity relative to testosterone have undergone phase 2 trials, and some even phase 3 trials. Increases in lean body mass and muscle size, and the relative prostate sparing have been confirmed in randomized trials of several SARMs. In phase 2 trials in patients with cancer-related weight loss (24) and prostate cancer survivors with testosterone deficiency (25), oral SARMs have increased lean body mass but not measures of physical function. Similarly, in older women, SARM treatment has been shown to enhance lean body mass without increases in measures of physical function (26,27).

Myostatin

A member of the transforming growth factor (TGF)-β superfamily, myostatin, is a negative regulator of skeletal muscle growth. Naturally occurring mutations in several vertebrate species including humans are associated with hypermuscularity. Genetic disruption of the myostatin gene in mice and pharmacologic inhibition of myostatin in model organisms and humans increase skeletal muscle mass. Myostatin signals by binding initially to a type 2 receptor (ACVR2 or ACVR2B)—followed by engagement of either type 1 receptors (ALK4 or ALK5) (28). Targeting both receptor types simultaneously can lead to substantial muscle growth in male and female mice, with greater increase in muscle mass than that associated with the inhibition of the myostatin gene itself. Several strategies have been employed to block the effects of myostatin or activin including targeting of (i) mature myostatin or its pro-peptide; (ii) ligand traps such as a decoy soluble form of ACVR2B receptor, or a portion of follistatin fused to an Fc domain that prevents the binding of myostatin and related ligands to their receptors; (iii) monoclonal antibody directed against ACVR2 subtypes. Candidate molecules utilizing each of these strategies have been evaluated in human studies and shown to increase lean body mass; however, none has shown meaningful improvements in physical function. Inhibiting myostatin in preclinical models increases bone mineral content and density. Skeletal muscle is a major regulator of metabolism; increasing muscle mass by blocking myostatin results in reduced fat mass, improved insulin sensitivity, and attenuation of the development of proatherogenic dyslipidemia and aortic atherogenesis in mice (29). Bimagrumab, a monoclonal antibody against activin type 2 receptor, increases lean body mass, and reduces fat mass, body weight, and hemoglobin A1c in adults with type 2 diabetes (30). Therefore, the therapeutic application of myostatin and activin blockers for the treatment of obesity and type 2 diabetes in older adults with sarcopenic obesity is appealing.

GH Secretagogues

Human aging is accompanied by a reduction in GH and sex steroids. The isolation of growth hormone secretagogues (GHS), and GHS receptor (ghrelin, the natural ligand for the receptor) created new possibilities to investigate GH physiology, pathophysiology, and therapeutics. Orally active GHS restore pulsatile GH secretion in older adults to levels seen in young people without excessive GH overstimulation because of the IGF-1 feedback resulting in augmentation of fat-free mass and fat redistribution to the lower extremities. These agents may have applications in promoting growth restoration in children with GH deficiency or in treating nonalcoholic fatty liver disease, frailty, anemia, and osteoporosis in older adults. Side effects (increase in blood glucose, fluid retention, and worsening heart failure) may be an issue with these drugs (31).

Orphan Nuclear Receptors

Orphan nuclear receptors (ONRs) are important regulators of muscle fitness and potential therapeutic targets for muscle disorders. Skeletal muscle expresses high levels of an estrogen-related orphan receptor (ERR). An overexpression of ERR-γ in muscular dystrophy X-linked mice decreased the markers of muscle damage and improved exercise tolerance. ERR-γ also promotes recovery after exercise. Future research should focus on the translational value of ONRs in skeletal muscle dysfunction in aging and other chronic conditions (32).

Fast Skeletal Muscle Troponin Activation

Fast skeletal muscle troponin activators amplify the response of the sarcomere to neural input and improve muscle force generation by increasing the calcium sensitivity of the troponin-tropomyosin

regulatory complex. Small-molecule fast troponin activators reduce fatigue in normal, atrophied, and hypoxic muscle, and may have utility for neuromuscular diseases (amyotrophic lateral sclerosis [ALS]) and for age-related muscle weakness and frailty. Reldesemtiv, a small-molecule fast skeletal muscle troponin activator, has been reported to increase muscle force generation in a phase 1 trial. Reldesemtiv also has shown some benefit in reducing the decline of slow vital capacity and self-reported function in patients with ALS in a phase 2 trial, but the differences between placebo and reldesemtiv arms were not statistically significant (33).

Mas Receptor Agonists

The binding of angiotensin$_2$ (Ang$_2$) to Ang$_2$ receptor type 1 (AT1R) upregulates nuclear factor-kappa B (NF-κB), which mediates transcription of pro-inflammatory cytokines and adhesion molecules, and induces vasoconstriction, inflammation, and fibrosis. Ang$_2$ is converted by angiotensin-converting enzyme to Ang$_{1-7}$, an agonist for Mas receptor (MasR) that counteracts many of the harmful effects of Ang$_2$ mediated through AT1R. These data suggest that a MasR agonist could restore this balance between AT1R and MasR signaling, attenuate inflammation and fibrosis, and potentially reverse age-related loss of muscle mass and function. The SARCONES (BIO101; 20-hydroxyecdysone purified from the plant of the *Cyanotis* species) is an activator of the MasR (34) that has undergone a phase 2 trial to evaluate its safety and efficacy in improving mobility in older adults ≥ 65 years with sarcopenia. The BIO101 350 mg twice-daily regimen was associated with trends toward improved gait speed for those at risk of functional decline. BIO101 is also being investigated for the prevention of respiratory deterioration in patients with COVID-19 pneumonia (34,35).

Targeting Inflammation to Improve Health in Older Persons

The maladaptive activation of the immune system and chronic inflammation are a key factor in age-related functional decline and incident disability (36,37). Organ-specific and systemic alterations of the immune cell populations have been identified in aging. Alterations in a distinct subset of clonal GZMK$^+$ CD8$^+$ T cells are a conserved hallmark of inflammaging (38). Circulating interleukin (IL)-6 levels are cross-sectionally linked with increased risk of multimorbidity. Signaling molecules that regulate immunosenescence and inflammaging may offer therapeutic targets to prevent age-related loss of muscle mass, strength, and function. The ENRGISE trial evaluated the effects of losartan and fish oil to reduce IL-6 and improve physical function. However, neither losartan nor fish oil were efficacious in reducing IL-6 or in improving walking speed (39). The Canakinumab Anti-Inflammatory Thrombosis Outcome Study trial tested the hypothesis that targeting inflammation without affecting lipid levels reduces the risk of cardiovascular diseases (40). Canakinumab treatment was associated with lower rate of recurrent cardiovascular events than placebo, even though the drug did not affect lipid levels. Tumor necrosis factor (TNF)-α functions as the gate to many pro-inflammatory cytokines and inflammatory signals. Its pharmacological blockade by weekly subcutaneous injection of etanercept in mice prevented atrophy and loss of type II fibers, and improved muscle function and life span (41). In animal models, senolytics like dasatinib and quercetin have been reported to facilitate removal of senescent cells and reduce cytokine levels in tissues (42). The beneficial effects of aspirin, sodium salicylate, losartan, fish oil, and canakinumab in improving physical function or preventing

age-related functional decline in humans have not been demonstrated. Furthermore, there is concern that nonspecific suppression of inflammatory pathways could increase the risk of infections and cancers in older adults. An improved understanding of the mechanisms that trigger inflammaging is needed to enable the development of targeted interventions to suppress specific inflammatory pathways without inhibition of body's defense mechanisms against cancer and infection.

Urolithin-A

Because aging impairs the body's ability to eliminate poorly functioning mitochondria, inflammation develops with consequent impairment of muscle strength and energetics (43). Urolithin-A is a gut-microbiome-derived metabolite of ellagitannins, reported to improve mitophagy and mitochondrial function in preclinical models. Daily dosing of urolithin-A for 4 months in overweight participants (40–64 years) with low endurance improved aerobic capacity and 6-minute walking speed; increased mitophagy proteins and decreased inflammatory markers (NCT03464500). In another trial, urolithin-A treatment of healthy older adults for 4 months improved muscle endurance and inflammatory markers but did not improve 6-minute walking distance (44). These data provide the rationale for larger trials to evaluate the efficacy of urolithin-A in older adults with functional limitations.

Gerotherapeutics: Drugs Targeting the Mechanisms of Aging

Age is a major risk factor for most chronic diseases and functional decline. Current approaches to prevent or treat single disease eventually lead to polypharmacy and its adverse consequences. The geroscience hypothesis posits that targeting the mechanisms of aging could prevent or treat several age-related conditions (45–47). Despite advances in understanding the mechanisms of aging, substantial work is still needed to determine the safety and efficacy of interventions targeting the aging mechanisms and whether these drugs can extend health span. There is also a need to identify the appropriate indications, target populations, and end points for clinical trials of gerotherapeutics.

NAD Augmentation

NAD plays an important role in energy production and regulation of mitochondrial function, metabolism, inflammation, innate immune response, DNA repair, chromosomal integrity, axonal integrity, and regeneration during aging (48–55). NAD levels are reduced in many tissues with aging (51–53) due to increased activity of the NAD-consuming enzymes CD38 and poly (ADP-ribose) polymerase 1 (PARP1) (54) decline in nicotinamide phosphoribosyl transferase activity. NAD levels can be increased by stimulating NAD production through its precursors (nicotinamide mononucleotide [NMN], or nicotinamide riboside [NR]), or by inhibiting its degradation. Administration of NMN and NR in preclinical models prevents or reverses several age-related conditions (adiposity, diabetes and its nephropathy, nonalcoholic fatty liver disease, retinal disorders, and Alzheimer's disease), attenuates weight gain and fat accumulation in response to high-fat diet, and delay vascular aging (56). NMN administration to old mice is associated with increased muscle capillarity, improved blood flow to the muscle, and longer running time to exhaustion than young mice (57). Repeated administration of NMN or NR daily is safe and increases blood NAD levels (48–53), prevents kidney injury in acutely ill patients, and shortens the length of stay in

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (57–59). Other short-term studies of NMN and NR have reported reduction in blood pressure, total and low-density lipoprotein (LDL) cholesterol, and aortic stiffness, and improvements in muscle insulin sensitivity. The changes in physical performance measures in early-phase trials have been inconsistent. Larger trials of longer duration are needed to determine whether NAD augmentation by administration of its precursors improves physical performance and whether the effects of NAD augmentation on physical performance are enhanced by physical exercise in older adults. Future trials should evaluate whether increasing NAD levels can protect against multiple age-related conditions, in line with the geroscience hypothesis.

Metformin

Commonly used for type 2 diabetes mellitus, metformin extends life span in *Caenorhabditis elegans*, nematodes, and mice (60). In humans, metformin is associated with lower incidence of cancer, cardiovascular disease, dementia, frailty, and all-cause mortality (61–64). Metformin activates adenosine monophosphate activated protein kinase (AMPK), modulates several pillars of aging, such as PPAR gamma coactivator 1α, a master regulator of mitochondrial function; nrf2, a transcription factor that controls antioxidant programs; and the mTOR (65). Metformin also reduces inflammation (local, systemic) and insulin/IGF-1 signaling, and inhibits NF-κB activation (66,67). Metformin treatment reduces reactive oxygen species in an AMPK-dependent manner, and attenuates DNA damage induced by Ras expression (67). Metformin-induced AMPK activation upregulates autophagy and suppresses senescence and senescence-associated secretory phenotype (SASP) in some cell lines and induces transcriptomic changes in animals similar to those seen with caloric restriction (66). A randomized placebo-controlled trial is examining the effects of metformin on frailty and several hallmarks of aging in older adults with frailty and impaired glucose tolerance (68). Metformin could be quickly translated to clinical use if clinical trials show evidence of efficacy in preventing age-related diseases.

Senolytics

Senescent cells accumulate with age and clearance of these cells in mice has health benefits (69). Two key triggers of senescence are the cyclin-dependent kinase inhibitors, CDKN2A (p16[Ink4a]) and CDKN1A (p21[Cip1]); activation of these pathways leads to growth arrest, resistance to apoptosis, and the SASP, which consists of inflammatory cytokines, chemokines, and metalloproteinases (69,70). At least 2 approaches have been used to target senescent cells (71): (i) senolytics aimed at the anti-apoptotic pathways these cells rely upon for their survival; (ii) senomorphics that do not kill senescent cells but inhibit the SASP. Genetic approaches to target senescence as well as pharmacologic senolytic and senomorphic agents have shown some beneficial effects on age-related changes in multiple tissues in mice, consistent with the predictions of the geroscience hypothesis (69,72). Some senolytic compounds have advanced into early-phase clinical trials. Although targeting senescent cells has shown promise in preclinical studies, substantial work is needed for development of new senolytic compounds and biomarkers to identify individuals most likely to benefit from these therapies, and monitoring of treatment response.

Table 1 summarizes research gaps and opportunities for the development of function-promoting therapies.

Physical Exercise Interventions to Enhance Mobility in Older Adults

Physical exercise interventions are the most efficacious function-promoting therapies for older adults with mobility limitation (5). The

Table 1. Summary of Research Gaps and Opportunities for Function-Promoting Therapies Development

Translational biology	Clinical trials of function-promoting therapies
Improved understanding of the neural mechanisms that regulate integrated muscle performance and complex physical functions (walking, stair climbing, and other ADLs) to facilitate development of neurotherapeutic approaches to enhance muscle performance and physical function. Strategies targeting multiple mechanisms/signaling pathways associated with muscle energetics, regeneration, inflammation, metabolic stress, and extracellular matrix remodeling.	Adequately powered randomized efficacy trial/s of multicomponent intervention/s that combine a promyogenic pharmacologic agent with other strategies to translate muscle mass gains into clinically meaningful functional improvements in older adults with a recognized functional limitation/s using a model study protocol and validated end points. Adequately powered randomized efficacy trials of 1 or more geroscience function-promoting molecules/drugs representative of leading geroscience mechanisms (NAD boosters, senolytics, rapalogs, Mas receptor agonists) that have shown promise in early-phase studies.
Targeted studies to identify druggable pathways and mechanisms that contribute to age-related impairments of muscle's regenerative response to injury and maladaptation in response to acute muscle atrophy. Additional studies to evaluate translational value of promising novel molecular targets (orphan nuclear receptors, fast skeletal muscle troponin activators, Mas receptor agonists, apelin, and other pathways) in appropriate preclinical models, preferably in higher mammals (eg, dogs) that display physical functional limitations similar to humans. Harmonized methods for the measurement of geroscience biomarkers (eg, NAD and its metabolites, senescence markers and SASPs, other geroproteins) in biological fluids and in situ in the tissues, and reference ranges to facilitate subject selection and serve as end points and improve scientific rigor in preclinical and early-phase human trials of gerotherapeutics.	Studies of clinical pharmacology, metabolism, and pharmacokinetics of leading geroscience drugs/molecules in humans to guide dosing and design of intervention trials. Consensus-based model study protocol/s to provide guidance on framing indications, inclusion and exclusion criteria, selection of end points including PROs, and defining meaningful change and efficacy of pharmacologic function-promoting therapies in efficacy trials of function-promoting therapies.

Notes: ADLs = activities of daily living; NAD = nicotinamide adenine dinucleotide; PROs = patient reported outcomes; SASPs = senescence-associated secretory phenotypes.

goal of the Molecular Transducers of Physical Activity Consortium (MoTrPAC) is to assess molecular changes in response to physical activity in animals and humans. with a particular focus on the role of exosomes in integrating the exercise response across organ systems (73). Exercise training induces sex-specific alterations in the white adipose tissue in male rats but not in female rats. Training-induced alterations in metabolite levels at rest are smaller in magnitude than those observed in response to acute exercise. Initial analyses of the metabolomic data reveal that exercise training induces alterations in sphingolipids, fatty acids, and aromatic amino acids.

Physical Activity SPRINT-T

The Sarcopenia and Physical fRailty IN older people: Multicomponent Treatment Strategies was conducted in 16 clinical sites in 9 European countries, with the goal of recruiting 1500 community-dwellers > 70 years. The intervention focused on physical activity, nutritional assessment with personalized diet, and remote monitoring of physical activity. The physical activity included an aerobic exercise, strength, flexibility, and balance trainings. Aerobic and strength components gradually increased in intensity during a 1-year adoption phase. Adherence with the center- and home-based exercise was >70%. The multicomponent intervention was associated with a reduction in the incidence of mobility disability in older adults with physical frailty and sarcopenia and short physical performance battery (SPPB) scores of 3–7. Investigators concluded that physical frailty and sarcopenia may be targeted to preserve mobility in vulnerable older people (74).

Prehabilitation to Improve Functional Recovery After Orthopedic Surgery

The prevalence of osteoarthritis (OA) is increasing due to the aging of human population and increasing rates of sarcopenic obesity. Lifestyle modification and exercise are as effective as orthopedic surgery in managing painful OA in middle-aged and older adults with hip or knee OA (75). Yet less than one third of patients undergoing joint replacement receive adequate nonsurgical interventions (eg, nutrition and exercise training) prior to surgery. Despite high-quality evidence that exercise and weight reduction reduce pain and improve function, implementation strategies and systematic approaches to incentivize these behaviors are lacking. Robust trials to determine the value of prehabilitation programs prior to total knee and hip arthroplasties are lacking. Larger trials are also needed to examine the effects of multimodal interventions (eg, exercise, nutrition, and muscle anabolic therapies) for OA in older adults with obesity. Strategies to delay the onset and progression of OA through lifestyle modification and function-promoting therapies have the potential to significantly affect the management of OA and health care costs.

Behavior Change Strategies to Increase and Maintain Physical Activity

Despite the proven benefits of physical activity for functional health, <20% of adults engage in recommended levels of exercise. The annual health care costs of inadequate physical activity are estimated at $117 billion, with 1 in 10 premature deaths in the United States related to inactivity. The Midlife in the United States longitudinal study measured functional health at midlife and later life and found that functional decline starts early in life and the slope of decline is significantly steeper for those without a college education compared to those with a college education. Studies of self-regulatory and motivational strategies to increase physical activity in sedentary adults

by The Boston Roybal Center for Active Lifestyle Interventions show that social support and interaction with other participants using social engagement technologies increase physical activity and social engagement (76). Future approaches to improve physical activity and functional health should include technology use, intergenerational programs, and preventive interventions during midlife.

Nutritional Interventions to Support Aging Muscles

The Influence of Dietary Protein Quantity, Quality, and Timing During Aging

Aging is associated with substantial alterations in nutrient metabolism and the efficiency of the uptake of amino acids in the splanchnic region, insulin resistance, protein anabolic resistance, and inflammation. A review of the effects of the timing of protein intake found that the primary benefit of these strategies is to help older adults consume sufficient total protein to meet their needs, rather than any specific timing effect (77). Habitual protein intake less than the recommended daily allowance (RDA) is associated with reduced muscle mass and immune response in postmenopausal women (78,79). Older adults with daily protein intake in the highest quintile lost 40% less whole body and appendicular lean mass than those in the lowest quintile (80). A systematic review and meta-analysis of controlled feeding studies found that the RDA for protein is adequate to support lean mass in adults in nonstress states and protein intake greater than the RDA had no influence on lean body mass (81,82). Both appendicular lean mass and grip strength were lower in middle-aged adults who ate less than the RDA. It is possible that protein intakes above the RDA may be needed during periods of catabolic stress. Further research on dietary protein as a modifiable sarcopenia risk factor in older adults is warranted (83).

Optimen Trial

The Optimen Trial compared the effects of protein intake equal to the RDA versus 1.3 g/kg/day without and with a regimen of testosterone administration in older adults with mobility limitation who were consuming less than the RDA (84,85). Changes in lean body mass, muscle strength and power, and physical function did not differ between men who consumed controlled diets (RDA for protein) and men who consumed the higher amounts of protein (84). Protein intake exceeding the RDA did not augment anabolic response to testosterone. Protein intake greater than the RDA was associated with greater loss of whole-body fat mass than the RDA but higher protein intake did not improve insulin sensitivity or lipids (86). High-quality interventional trials are needed to determine the effects of the quantity, quality (source), and timing of dietary protein, especially in older adults with chronic disease and functional limitations. Data on protein requirements and muscle's adaptations in response to higher protein intake are lacking in the oldest old and in older adults with chronic disease. It also remains unknown whether animal- or plant-based proteins are more efficacious in improving muscle mass and function. Long-term studies are needed to further evaluate the effect of protein intake and visceral adipose tissue and metabolism. The effects of combinations of higher protein, anabolic agents, and resistance exercise on body composition, muscle strength, and function, and metabolism should be investigated.

Vitamin D Supplementation

The VITamin D and OmegA-3 TriaL (VITAL), a large randomized controlled trial of supplemental vitamin D versus placebo, revealed

that 2 000 IU/day of vitamin D_3 did not reduce the risk of incident falls or bone fractures, nor improved body composition, bone density, or structure in men and women not selected for vitamin D deficiency (87,88). These findings do not support the use of vitamin D to improve musculoskeletal health in healthy adults. The vitamin D3-omega 3-home exercise-healthy ageing and longevity trial (DO-HEALTH Trial) determined the effects of 3 strategies—2 000 units vitamin D/day, 1 g of omega-3 fats/day, and home exercise—on bone, muscle, cardiovascular, immunological, and brain health in adults ≥ 70 years (89). No significant benefits of vitamin D were found on lower extremity function measured by the SPPB or falls incidence. Vitamin D, omega-3 fatty acids, and exercise individually showed no significant reduction in the risk of frailty but the combination of all 3 revealed a significant reduction in the odds of becoming prefrail (89).

Nutraceuticals for Frailty

Malnutrition continues to be a problem for some older adults worldwide. In older people who are malnourished, providing sufficient nutrition reduces mortality (90). In critically ill hospitalized patients, β-hydroxy-β-methylbutyrate (HMB) did not significantly improve the composite end point of 90-day post-discharge incidence of death or nonelective readmission, but HMB decreased mortality and improved indices of nutritional status during the 90-day observation period (91). In the Effect of Early Nutritional Support on Frailty, Functional Outcomes, and Recovery of Malnourished Medical Inpatients Trial (EFFORT) (92), the use of individualized nutritional support in hospitalized patients at nutritional risk improved survival, compared with standard hospital food. These findings suggest that nutritional screening of hospitalized patients and individualized nutritional intervention in those at risk can improve health outcomes.

Effect of Calorie Restriction and Time-Restricted Feeding on Muscle and Bone Health

Obesity exacerbates age-related decline in physical function. Calorie restriction has been shown to extend health span and life span in some but not all model organisms. In Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) phase 2 trial, an average 12% reduction of caloric intake—substantially less than that achieved in model organisms to improve life span—improved plasma lipids, insulin sensitivity, inflammation, and oxidative stress (93). Long-term adherence and loss of muscle mass and bone associated with caloric restriction also are a concern (94). There is a need for nutritional strategies such as intermittent fasting, periodic fasting, and time-restricted eating (TRE) that can achieve the benefits of caloric restriction with greater likelihood of sustainability over long periods. TRE refers to the restriction of food intake to specific time windows during the 24 hours, typically <10 hours. A restricted eating window of 8–10 hours early in the day frequently leads to modest calorie restriction (94,95), to which the addition of a moderately increased protein intake could possibly minimize loss of lean mass. Randomized trials of time-restricted feeding, however, have yielded inconsistent results (96,97). Dietary interventions in older adults with obesity should consider quality, quantity, and timing of food intake, perhaps starting with time restriction.

Optimizing the Design of Clinical Trials of Function-Promoting Therapies

No pharmacologic function-promoting therapy has been approved to date; many aspects of clinical trial design including the framing of indications, selection of patient populations, and primary and secondary end points have been recognized as major barriers to the development and approval of these therapies. Many problems of aging do not fit well into regulatory guidelines for a medical indication. Mobility disability associated with aging and chronic diseases is a highly prevalent condition and an appealing indication for function-promoting therapies. Mobility disability is a validated marker of disablement commonly seen in older adults and linked to elevated risk of incident instrumental activities of daily living (IADLs), disability, hospitalization, and mortality (98,99). Older individuals hospitalized for an acute illness who have mobility disability or ADL disability during recovery from an illness; persons with burns or massive trauma, who have functional limitations during recovery; and cachexia associated with some types of cancer also represent attractive indications for function-promoting therapies.

Sarcopenia is a multicomponent syndrome associated with age-related changes in the skeletal muscle (100). Over 15 definitions of sarcopenia have been published; these definitions have substantial overlap in their conceptual framework but differ in the specific tests and the associated cut points for defining this condition. The Sarcopenia Definitions and Outcomes Consortium (SDOC) funded by NIA to develop diagnostic cut points for sarcopenia analyzed data from 8 prospective observational studies using classification and regression tree analysis (101,102). Both low grip strength and low usual gait speed independently predicted falls, self-reported mobility limitation, hip fractures, and mortality in community-dwelling older adults (101). Lean mass measured by dual energy X-ray absorptiometry (DXA) with or without adjustment for body size was not associated with incident health outcomes (101). Based on these comprehensive analyses, the SDOC definition of sarcopenia includes low grip strength (<35.5 kg for men, <20 kg for women) and slowness (walking speed <0.8 m/s) (101,102). Although in the SDOC analyses, DXA-derived lean mass was not associated with health outcomes, recent studies have found that low muscle mass measured using D3 creatine dilution is predictive of incident falls, disability, fractures, and mortality (103,104). Anabolic drugs that increase muscle mass induce loss of fat mass and improve metabolic outcomes. Therefore, anabolic drugs should be investigated for the treatment of older adults with sarcopenic obesity and functional limitations, or as adjuncts to caloric restriction or weight loss drugs to minimize loss of muscle and bone mass.

Inclusion/Exclusion Considerations for Clinical Trials

Carefully defined inclusion criteria are necessary for reconciling the dual goals of recruiting people with the condition with objectivity and ensuring that the study participants are representative of the general population. Eligibility criteria also should enable exclusion of people who are unlikely to respond or might respond differently to the intervention or are at increased risk of being harmed by the intervention than the general population. In older adults, attention must be paid to polypharmacy, drug interactions, and other potential adverse events.

Selection of End Points in Clinical Trials

Careful selection of end points is essential for establishing proof of efficacy and securing treatment approval. Muscle mass measured with an accurate method, such as D3 creatine dilution, could provide proof of mechanism for anabolic drugs in early-phase studies. Muscle protein synthesis might also be a good pharmacodynamic marker for anabolic therapies. In efficacy trials, performed-based as

well as self-reported measures of physical function are needed to determine whether improvements in performance-based measures of muscle performance and physical function are associated with enhancements in how a person lives, functions, or feels. The end points should be well-aligned with the attributes of the disease or condition, meet some minimal metrics of reliability and validity, and have sufficient precision and accuracy in the range of functional ability of the study population. Estimates of meaningful treatment effect in the context of the study population are required for interpreting their clinical relevance. The measures of mobility, such as walking speed using standardized procedures (6-minute walking distance, 4-m walking speed, SPPB, or 400-m walking speed) and stair climbing speed and power, can be useful as end points in studies of older people with mobility limitation. Mobility can also be ascertained reliably by self-report. The end point should be aligned with the mechanism of drug action (98,99,105–107).

Clinical Outcome Assessments

Clinical outcome assessment should measure the way a patient functions, feels, or survives. The clinically meaningful threshold may not be a single threshold for all patient populations. Triangulation of evidence is a good way to ensure that several lines of evidence point to a range of thresholds that would define what is clinically meaningful. Patient-generated health data collected from digital health technologies also allow researchers to understand patient behavior in the context of their daily lives.

Adjunct Multicomponent Functional Exercise Training

Pharmacologic function-promoting therapies, such as androgens, have shown consistent improvements in fat-free mass and maximal voluntary strength, but the increases in muscle mass and strength have not translated into consistent improvements in performance-based measures of physical function. Adding progressive resistance training to the pharmacologic regimen might produce an additive effect. Functional training aims to develop movement patterns with resistance specific to a targeted activity and integrates whole-body, multiplanar movement; includes training in balance and stability, strength, and power; and is intended to improve performance in specific tasks. Well-designed and executed functional exercise training, appropriate to ability, followed by progression to increasingly larger doses of exercise specific to the targeted task could facilitate the translation of muscle mass and strength gains into improved ability to perform task-specific functions required in ADLs; improve balance; and reduce fall risk. There was strong agreement that well-designed, large, randomized trials of a multicomponent intervention that combines an anabolic drug, multidimensional functional exercise training, and cognitive and behavioral strategies are urgently needed and have the best potential to improve function and health outcomes (108,109).

Standardizing Nutritional Intake

Appropriate attention to nutritional status and intake is important when designing clinical trials of function-promoting therapies. While rigorous standardization of protein and energy intake may not be feasible in large, randomized trials of function-promoting therapies, baseline assessment of nutritional status to exclude those with involuntary weight loss or severe malnutrition as well as specific guidance to the study participants to minimize the risk of major changes in energy and protein intake during trial are necessary and feasible.

A baseline assessment of physical activity can help identify people who are engaged in progressive exercise training or those who are severely disabled and may not be able to undertake tests of physical performance (110).

Strategies to Expedite the Translation of Extraordinary Advances in Muscle Biology Into Approvable Drugs

Lessons From the Extraordinary Success of the COVID-19 Vaccine Development

The Operation Warp Speed was established by the U.S. government to coordinate efforts among pharmaceutical companies, several U.S. government agencies, and academic experts. The success of Operation Warp Speed was based in part on optimizing existing processes and technologies to support expedited vaccine development. Formal guidance and informal ongoing interactions between the FDA and manufacturers facilitated rapid resolution of issues that might have otherwise delayed the project. The historical success of Operation Warp Speed in expediting the development of COVID-19 vaccines in less than a year offers useful lessons that can guide the development of function-promoting therapies.

Lessons From the Oncology Drug Development Programs

Numerous factors have contributed to the success of cancer drug development programs, such as having well-defined clinical trial end points for phases 2 and 3 trials; enhanced understanding of cancer biology, therapeutic targets, and the host response; improved selection of patient populations using biomarkers; and availability of a publicly supported clinical trial infrastructure. These factors should be considered in the development of strategic plans to accelerate the development of drugs to treat age-related functional limitations.

Conclusions of the Expert Panel Discussion

The aging of human populations and the imminent increase in the numbers of older adults with aging-related physical disabilities would greatly affect the ability of older people to lead meaningful independent lives in the community, as well as the health care needs and economies of human societies. Therefore, expedited development of function-promoting therapies to prevent and treat functional limitations and physical disabilities associated with aging and chronic diseases is an urgent public health need. The success of the Operation Warp Speed and the oncology drug development programs holds useful lessons that can be applied to accelerate the development of function-promoting therapies. Such an effort to advance the field would require synergistic collaborations among academic investigators, the NIH, professional societies, patients and patient advocacy organizations, the pharmaceutical industry, and the FDA, and expeditious trial execution. In addition, well-designed, adequately powered clinical trials will require careful definition of indication/s, and reliably measured patient-important end points to ensure successful execution and outcome.

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