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Supplement Article: Function-Promoting Therapies

Synergistic Strategies to Accelerate the Development of Function-Promoting Therapies: Lessons From Operation Warp Speed and Oncology Drug Development

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Abstract

Background: Functional limitations and physical disabilities associated with aging and chronic disease are major concerns for human societies and expeditious development of function-promoting therapies is a public health priority.
Methods: Expert panel discussion.
Results: The remarkable success of Operation Warp Speed for the rapid development of COVID-19 vaccines, COVID-19 therapeutics, and of oncology drug development programs over the past decade have taught us that complex public health problems such as the development of function-promoting therapies will require collaboration among many stakeholders, including academic investigators, the National Institutes of Health, professional societies, patients and patient advocacy organizations, the pharmaceutical and biotechnology industry, and the U.S. Food and Drug Administration.
Conclusions: There was agreement that the success of well designed, adequately powered clinical trials will require careful definitions of indication/s, study population, and patient-important endpoints that can be reliably measured using validated instruments, commensurate resource allocation, and versatile organizational structures such as those used in Operation Warp Speed.

Keywords: Age-related skeletal muscle dysfunction, Function-promoting therapies, Mobility-disability, Sarcopenia, Skeletal muscle function deficit

Due to the remarkable increase in human life expectancy across the globe, a greater proportion of adults today are ≥ 65 years and the oldest old, those ≥ 85 years, constitute the fastest growing segment of human populations in many countries. While these trends toward aging of human societies have been apparent in the developed countries for some time, the emerging economies are witnessing some of the fastest demographic transitions in the population pyramid with increasing proportions now composed of middle-aged and older adults. Increased life expectancy together with decreasing fertility rates have already inverted the population pyramid (greater number of older people compared to young people) in some countries and many other countries are rapidly transitioning toward this inversion. While the steady progress in improving life expectancy over the past two centuries is a remarkable human accomplishment worthy of celebration, the aging of human societies also has been associated with the emergence of the attendant health and health care delivery challenges associated with old age. As people age, they experience increasing risk of functional limitations and physical disabilities (1–4) that limit their ability to perform activities of daily living (ADLs), engage socially, live independently in the community, and increase their risk of falls and fall injuries, healthcare resource utilization including hospitalizations, and death. A substantial fraction of older adults has one or more disabilities; the rates of physical disability increase from ~30% in adults 65–74 years, to 75% of adults over age 85 (2–6). In addition to the impact of aging on the health, wellbeing, autonomy, and finances of each individual, the functional limitations and physical disabilities associated with aging profoundly impact health care and other resources needed to care for the increasing numbers of older people, economic growth, and the social contract of human societies (7–9). Therefore, the development of function-promoting therapies that can prevent or treat functional limitations and physical disabilities associated with aging and chronic diseases is a societal and health-economic imperative. In recognition of the urgent public health need for the development of function-promoting therapies, the National Institute on Aging (NIA) at the National Institutes of Health (NIH), U.S. Department of Health and Human Services (HHS) convened a workshop of experts to review the state of current knowledge and research, identify gaps in our knowledge as well as opportunities for further research to catalyze the development of function promoting therapies. The discussion in the final session of the workshop focused on the remarkable success of the Operation Warp Speed that led to the approval of the SARS-CoV-2 vaccines within less than a year of the emergence of the pandemic. Similarly, the laudable progress in the development and approval of many oncology drugs during the past decade was hailed as another success story. This narrative review summarizes the major gaps in knowledge, challenges in clinical trial design, and regulatory processes that have hindered the development and approval of function-promoting therapies. The narrative also highlights the lessons learned from the success of Operation Warp Speed and how these lessons can be applied to accelerate the development and approval of function-promoting therapies.

As people get older, they experience a slow but progressive decline in skeletal muscle mass, muscle strength, and muscle power (10,11). Age-associated loss of skeletal muscle mass is associated with declining metabolic rate, insulin resistance, osteopenia, cognitive decline, weakness, and most importantly, mobility issues. The loss of skeletal muscle mass with advancing age also is strongly related to functional decline and to the increased risk of physical disability, falls, hip fracture, and mortality (12,13). During periods of immobilization, older adults lose more muscle than do young people resulting in substantially reduced functional capacity (14,15). In addition, age-associated changes in muscle quality due to alterations in mitochondrial function, neuromuscular function, and fat and fibrous tissue infiltration affect muscle performance and function, and energy and glucose metabolism (16–18). Extraordinary advances in muscle biology have improved our understanding of the regulation of muscle growth and the causes of age-related loss of muscle mass and function and facilitated the development of targeted pharmacological interventions that may improve muscle mass by slowing muscle breakdown, stimulating muscle protein synthesis, or by directly improving muscle contractility.

As discussed in earlier chapters in this special issue, several pharmacological strategies to prevent or treat aging-associated functional limitations have been studied; these strategies include anabolic drugs that increase muscle mass and strength (eg, androgens, selective androgen receptor modulators, growth hormone, growth hormone secretagogues and ghrelin mimetics; myostatin and activin antagonists) (19,20); drugs that directly improve muscle contractility and muscle strength (eg, troponin activators) (21); drugs that target the mechanisms of aging (eg, nicotinamide adenine dinucleotide boosters; senolytics) (22,23); and drugs that target other mechanisms. Although several candidate molecules have undergone phase 1 and 2 trials and some have even advanced to phase 3 trials, none has been approved by the U.S. Food and Drug Administration (FDA). The numerous challenges in translating the advances in muscle biology into approvable drugs are discussed below.

Challenges in Translating Advances in Muscle Biology Into Approvable Drugs

Many anabolic drugs such as androgens, selective androgen receptor modulators, and myostatin and activin antagonists increase whole body and appendicular lean mass. Historically, lean body mass has been measured typically by dual-energy x-ray absorptiometry (DXA). However, lean body mass, measured using DXA is not associated with incident mobility disability, falls, fractures, or limitations in instrumental activities of daily living (24,25). The age-related loss of muscle strength and slowing of walking speed is very weakly or not related to changes in DXA-derived lean mass. In contrast, estimates of skeletal muscle mass derived using D3 creatine dilution method are robustly related to strength, physical performance, and disability outcomes in older adults (26,27). These data support efforts to evaluate muscle mass using the D3 creatine dilution method in future definitions of sarcopenia and in randomized trials of anabolic drugs (12).

Careful framing of indications and the eligibility criteria, and the selection of appropriate study endpoints is critical in efficacy trials of function-promoting therapies. The inclusion of both performance-based as well as patient-reported outcome (PRO) measures of physical function is needed to demonstrate that the intervention improves physical performance and that improvements in physical performance are associated with beneficial effect on how a person "functions or feels" that can be assessed using validated PRO measures.

The measurements of skeletal muscle mass (using heavy water labeling) or size (using computed tomography or magnetic resonance imaging) and muscle protein synthesis (using steady state infusions of stable-isotope-labeled amino acid) (28) may be useful pharmacodynamic markers in early phase 1 and proof-of-mechanism trials of anabolic drugs. However, demonstration of increase in skeletal muscle mass by itself may not be sufficient to demonstrate efficacy of anabolic drugs; it is necessary to provide evidence that improvements

in muscle performance and physical function are having a meaningful beneficial downstream effect on the person's life as it relates to physical ADLs. While testosterone and some other androgens have been shown to improve whole body lean and appendicular soft tissue mass, maximal voluntary strength, and stair climbing power (19), and myostatin-activin antagonists have been reported to increase lean body mass and muscle size along with some measures of muscle power, these drugs have not yet been shown to improve how a person "functions and feels."

Innovative strategies are needed to translate muscle mass and strength gains induced by anabolic drugs into functional improvements. Resistance exercise training augments the anabolic effects of androgens on muscle mass and performance (29–31). However, strength training alone may not be sufficient especially in older adults; adjunctive multi-dimensional functional exercise training that combines strength building exercises, improved nutrition, endurance training, task-specific training to improve mobility and balance, and cognitive and behavioral training to increase physical activity and adherence and reduce disability might be required to induce the neuromuscular and behavioral adaptations that are necessary to translate the gains in muscle mass and strength into clinically meaningful functional improvements and to reduce physical disability (32).

Lessons Learned From Operation Warp Speed and the Successful Development of COVID-19 Vaccines

In May 2020, at the height of the COVID-19 pandemic, the Operation Warp Speed, a private-public partnership, was established by the U.S. government to coordinate efforts among biopharmaceutical companies and several U.S. government agencies including the NIH, the Department of Defense, the FDA, the Centers for Disease Control and Prevention, and academic experts (33). The program catalyzed the successful development and emergency use authorization of 3 COVID-19 vaccines in less than a year; an unprecedented historical accomplishment in vaccine development to address a new infectious agent. There was agreement that several aspects of the Operation Warp Speed's processes contributing to its speedy success despite its complexity and the involvement of many government agencies could be emulated and applied to the development of function-promoting therapies.

Operation Warp Speed refined existing processes and technologies to expedite the development of the vaccines. The vaccine development processes are described in the FDA's guidance documents—Development and Licensure of Vaccines to Prevent COVID-19 (June 2020), available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19; and the Emergency Use Authorization for Vaccines to Prevent COVID-19 (Originally Oct. 2020, last updated May 2021), available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19. During Operation Warp Speed, the combination of the availability of formal guidance along with informal interactions between the FDA officials and manufacturers facilitated ongoing dialogue to resolve potential challenges that might have otherwise stymied the clinical development or the evolving manufacturing processes. Informal interactions brought the kind of catalytic force necessary to break barriers among agencies and enabled multiple experiments to be conducted while minimizing risk for academic investigators, the government, and the industry. The simultaneous engagement of a diverse group of experts in different vaccine development strategies allowed the pharmaceutical manufacturers to evaluate and apply a variety of different promising vaccine development strategies and platforms.

The success of Operation Warp Speed offers several lessons that can help guide similar efforts for expedited development of function-promoting therapies, given their public health importance. The most important lesson is that coordination among academic investigators, the NIH, the biopharmaceutical industry, and the regulatory agencies such as the FDA is necessary for expeditious execution of drug development programs of public health importance. Government funding is necessary, but funding alone may not be sufficient to increase the likelihood of advancement to drug approval. In the relatively new therapeutic area of function-promoting therapies in which there is little prior guidance or a roadmap from previously approved drugs, an FDA regulatory workshop in collaboration with the stakeholders to discuss the regulatory framework for product development including indications and endpoints could be very beneficial and may be necessary. Input from various stakeholders early in the course can build consensus that can facilitate the development of guidance and accelerate product development. A vigorous dialogue among the academic investigators, industry and regulatory agencies can also result in products getting breakthrough therapy or advanced therapy designation for unmet medical needs.

Lessons Learned From the Development of Oncology Drugs: Critical Ingredients for Success

Numerous factors embedded in the Pharmaceutical Cancer Drug Development Programs at the NIH National Cancer Institute and the FDA's Oncology Center of Excellence (https://www.fda.gov/about-fda/fda-organization/oncology-center-excellence) have contributed to the success of these programs. These factors that have catalyzed the development of many oncology drugs should be taken into consideration in the development of plans for the accelerated development of function-promoting therapies and include the following: (i) Clear regulatory guidance on well-defined clinical trial endpoints for both phase 1 and 3 trials that are reproducible, easily measured, clinically meaningful, and relevant to patients; (ii) An enhanced understanding of cancer biology and the molecular therapeutic targets; (iii) An enhanced understanding of the host response through the discovery that cancers are immunogenic; and (iv) Improved selection of patient populations for clinical trials using biomarkers for patient stratification (34). Adequate clinical trial bandwidth supported by generous NIH funding has enabled over 2,000 cancer clinical trials to be conducted each year. This has increased the number of treatments found to be effective and expanded the pool of drugs that can be developed. The publicly supported clinical trial infrastructure for cancer trials has been pivotal in enabling the study of uncommon conditions as well as efficacy trials for conditions that were deemed high risk. Public support can also de-risk the development of agents for small populations or for populations that are considered risky for other reasons.

Prevention trials also are an important means of addressing a disease if they can be conducted in a cost-effective manner with a good safety profile. Success stories for cancer prevention include smoking cessation in lung cancer, human papillomavirus vaccination for preventing cervical cancer, hepatitis B vaccination for

hepatocellular carcinoma, and colonoscopy screening for colorectal cancer. Prevention trials typically require larger sample sizes, longer intervention durations, and substantially larger budgets than treatment trials, although our ability to identify non-disabled populations at high risk of becoming disabled can reduce needed sample sizes. Because of these constraints, initial efforts to develop function-promoting therapies should focus on treatment trials rather than prevention trials.

Operation Warp Speed as well as the success of cancer trials has demonstrated that flexible and diverse funding mechanisms are needed to increase the speed of execution as well as to increase accountability, early identification of bottlenecks, and facilitate mid-course corrections.

Expert Panel Discussion on the Development of Function-Promoting Therapies: The Need for Synergistic Partnerships of Stakeholders

The final panel discussion of the workshop expert panel underscored the need as well as a commitment of all stakeholders to work together toward faster development of function-promoting therapies to enable older adults around the globe to live better, live longer and live independently. The professional societies can provide leadership in the development of consensus definitions of geriatric indications for function-promoting therapies.

Professional Societies

The Gerontological Society of America is the largest interdisciplinary organization devoted to aging research, education, and clinical practice and is well-positioned to convene all relevant stakeholders for consensus building on the operational definitions of geriatric conditions and the development of guidance clinical trials endpoints selection. The representative from the American Geriatrics Society (AGS) emphasized that AGS members include clinicians of all varieties who provide care to older adults and their input is critical in drug development. It is likely that a combination of therapies (eg, an anabolic drug plus multi-component exercise training, or combination of drugs that target different mechanisms) may be necessary to treat different categories of functional limitations. A host of public health campaigns by professional societies could facilitate behavior change at a population level. Clinical trials should not have any upper age limit and should include a diversity of older people of different backgrounds, races, ethnicities, gender, and functional status. Geriatricians' involvement is critical.

Patient Advocacy Organizations

The representatives from Patient Advocacy Organizations underscored the urgent public health need for further research and substantially increased public investment in the development of function-promoting therapies. They emphasized that the availability of function-promoting therapies to help prevent functional limitations may also prevent and/or improve other common chronic conditions in older adults: diabetes, hypertension, heart disease, osteoporosis, osteoarthritis, chronic pain, and Alzheimer's disease. A survey from the West Health Institute revealed that people's concerns about aging are less about chronological age and more about independence and being able to take care of oneself—functional ability (https://www.norc.org/Research/Projects/Pages/WHI-NORC-Aging-Survey.aspx). It is critical to determine what functions are the most important to older people because people's concerns about aging-associated decline can be leveraged to develop messaging about function and independence. The representatives from Patient Advocacy Organizations encouraged the stakeholders—researchers, NIH, the industry, patients, and the professional societies to agree on prioritizing one or more targeted areas and a plan to advance expeditiously along that trajectory because that could greatly accelerate progress in this field.

The Pharmaceutical and Biotechnology Industry

The representatives from pharmaceutical and biotechnology industry identified several critical actions needed to advance the field including: (i) Collaboration among academic experts, industry, and regulatory agencies to identify specific disease endpoints. The muscle dysfunction spectrum is broad and is more of a syndrome; therefore, it is advisable to develop specific endpoints for specific subsets of patients. (ii) Addition of physical function to physicians' vocabulary. Reimbursement for validated physical function measures, such as the Short Physical Performance Battery and gait speed by the Centers for Medicare and Medicaid Services and third-party payers could encourage clinicians to evaluate and address functional limitations in older adults. (iii) Partnering with big technology companies to develop and validate digital health technologies that will increase participants' adherence and researchers' ability to learn how a certain intervention is adding value to participants' daily lives. (iv) Rely on biotech startups and academic investigators to guide innovation in a focused and mechanism-driven manner, attending to specific target indications. Researchers must start with a functional endpoint, because demonstrating that the drug affects how a patient feels, functions, and survives is what gets a drug approved by a regulatory agency. In the selection of primary endpoint for a clinical trial, it is important to pick a functional measurement that everybody has agreed to. There are drugs today that build muscle mass and increase muscle strength. The challenge is how to demonstrate that increased muscle mass and strength improve how a person functions or feels in the clinical trial setting. Notably, the decline in muscle function is a gradual process associated in the psyche of individuals as part and parcel of the aging process. As shown in Figure 1, the progressive decline ultimately poses a challenge to identify the target patient best suited for such interventions. Interim endpoints such as d3 creatinine changes that can be correlated with muscle function and independent ADLs are required to be endorsed by regulatory agencies to help create a clinical trial design paradigm which can be leveraged to test the utility of specific pharmaceutical interventions.

The fact that there is not an agent approved today for any indication in this field demonstrates how big the challenge is. Meaningful functional endpoints are the key issue in the field of aging. A composite clinical endpoint aligned with the biology of aging may be useful in older adults with many comorbid conditions. One or more biomarkers of aging biology could facilitate early phase trials of drugs that target mechanisms of aging. Additionally, skeletal muscle has many functions beyond the generation of force, and metabolic functions are one of the most important ones. Even relatively modest increase in muscle mass could have an important effect on insulin sensitivity and glucose tolerance. Therefore, glycemic remission or preventing progression from pre-diabetes to diabetes could be important targets for a muscle anabolic agent.

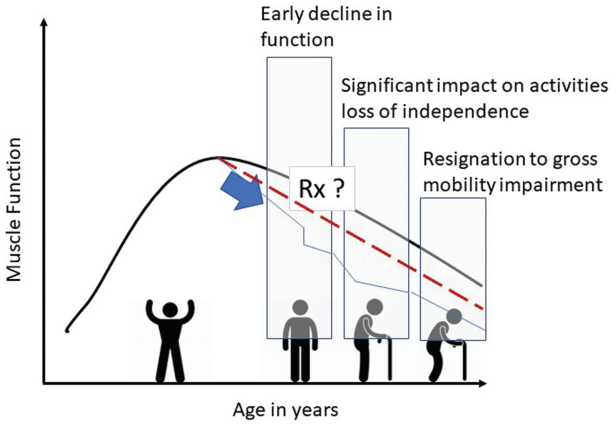

Figure 1. Progressive decline in muscle function tends to be gradual and is associated with a natural process of aging. Targeting the early decline offers a potential window to stem this progressive mobility impairment. The dashed red line and the blue lines illustrate the variable trajectories of age-related decline in muscle function. Rx, prescription .

Agencies of the U.S. Department of Health and Human Services

The representatives from regulatory and research agencies under the HHS re-emphasized that one of the key things that has held back the field is a lack of a clearly defined endpoints for clinical trials to support drug approval. A clinical outcome assessment is needed that is validated for use in a specific population with functional impairment, with an understanding of the magnitude of change in the clinical outcome that is associated with a meaningful clinical improvement. Pharmaceutical companies need to understand what constitutes efficacy for their products. This can be achieved through measure qualification and through direct interaction between companies and the FDA. There have been efforts in the past to qualify performance outcome measures for functional impairment in older adults. More needs to be learned about what additional evidence would be needed to get clinical outcome assessment validated. Building consortia are an important part of the solution because they can bring together academia, industry, patient groups, and regulatory bodies in a constructive collaborative environment. They can also bring resources, pull data, and conduct clinical trials that can serve to validate clinical outcome assessments. In addition, trying to draw more product developers into the area will be helpful to get more potential products into clinical trials. The FDA can engage with these consortia to facilitate development.

The NIA representative called attention to the fact that while the advances in basic muscle biology have been impressive, the challenge in translation is not having clearly defined indications and endpoints for clinical trials. Consensus on endpoints and criteria for success are necessary to carry out efficacy trials. The development of digital technologies to remotely ascertain outcomes will facilitate speedy execution of multiple clinical trials. An appropriate consensus must be reached about how to translate the pathophysiology that may have multiple upstream etiologies into useful endpoints that can be used in efficacy trials of function promoting therapies.

The NIAMS representative reminded us of this workshop's greatest potential to engender collaboration to address important challenges, such as defining the right patient population and indication, defining the right outcome, and working closely with the regulatory agency (FDA). Aging is an area where NIAMS and NIA already work together closely, and these collaborations create important new opportunities. There is a pressing need within the population of older adults to select well-defined subgroups that would be more homogeneous and to study endpoints important to patients. The field is just starting to appreciate the functions of muscle as an endocrine organ. Considering those pathways with targetable ways of improving the overall health of a person is important. The Molecular Transducers of Physical Activity Consortium provides a wealth of data that will be a goldmine if researchers can figure out how to translate those outcomes that are induced by exercising the muscle and lead to improved health. There are multiple patient populations with different muscle diseases such as Duchenne muscular dystrophy that have more defined outcome pathways without the confounders of comorbidity and frailty in older adults. The challenge is finding not only the right target, but the right scope and scale of disease that will be the most effective to get interventions to market.

Conclusion

With the aging of the populations globally, functional limitations and associated physical and cardiometabolic disorders are growing; consequently, physical disabilities associated with aging are a major concern of human societies. Expeditious development of function-promoting therapies to prevent and treat functional limitations associated with aging and chronic disease is a public health priority. The remarkable success of Operation Warp Speed for the rapid development of COVID-19 vaccines, and of the NIH and FDA oncology drug development programs have taught us that complex public health problems such as the development of function-promoting therapies will require collaboration among many stakeholders including academic investigators, the NIH, professional societies, patients and patient advocacy organizations, the pharmaceutical and biotechnology industry, and the FDA; appropriate resource allocation with flexible funding mechanisms; and versatile processes for speedy execution. There was agreement that the success of well designed, adequately powered clinical trials will require careful definitions of indication/s, study population, and patient-important endpoints that can be reliably measured using validated instruments. Additional benefit may result from drawing on findings of relevant international efforts and engaging in global collaboration in future initiatives targeting accelerated development of function-promoting therapies.

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Conflict of Interest

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